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Extended Research Article

Clinical and cost-effectiveness of detailed anomaly ultrasound screening in the first trimester: a mixed-methods study

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This article

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Abstract

Background: In the United Kingdom, pregnant women are offered two scans: at 11–14 and 18–20 weeks' gestation. Current guidance supports fetal anatomical screening at the second scan, but evidence suggests earlier detection is possible.

Objectives: To determine clinical and cost-effectiveness of a detailed two-dimensional ultrasound scan in the first trimester for detection of fetal anomalies, in addition to usual practice.

Design:

1. Systematic review and meta-analysis.
2. Nationwide survey.
3. Analysis of National Congenital Anomaly Disease Registry data.
4. Consensus procedure.
5. Prospective survey of parental opinions.
6. Probabilistic decision-analytic model for cost-effectiveness.
7. Value-of-information analysis.

Setting: United Kingdom National Health Service.

Participants: Pregnant women and partners.

Interventions: Detailed anomaly ultrasound at 11–14 weeks' gestation, in addition to usual practice.

Main outcome measures: Diagnostic accuracy, protocol development, health economic modelling and value-of-information analysis.

Data sources: MEDLINE (OvidSP), EMBASE (OvidSP), Science Citation Index and Conference Proceedings Citation Index-Science (Web of Science Core Collection); National Congenital Anomaly Disease Registry; European Congenital Anomalies Registry; Surveys of National Health Service Trusts; screening sonographers, midwives and doctors; and parents; National Schedule of National Health Service Costs (2019–20).

Review methods: Systematic review and meta-analysis for diagnostic accuracy.

Results: First-trimester ultrasound detects 93.3% (95% confidence interval 90.4% to 95.7%) of a pre-selected group of eight major anomalies with specificity of 99.99% (95% confidence interval 99.98% to 99.99%) and positive predictive value of 96.5% (95% confidence interval 93.3 to 98.8, 416,877 fetuses, 40 studies). For major cardiac anomalies, the respective data are 55.8% (95% confidence interval 45.9% to 65.5%), 99.98% (95% confidence interval 99.97% to 99.99%) and 94.85% (95% confidence interval 91.63% to 97.32%, 306,872 fetuses, 45 studies). Of NHS trusts surveyed, 77% currently perform first-trimester anatomy assessment, with evidence of inequity of care; earlier screening resulted in more diagnoses before 16 weeks' gestation. A consensus procedure (n = 172) developed an anatomical protocol and minimum targets for diagnosis. Parental survey (n = 1374) indicated that over 90% would opt for such screening. Modelling of singleton pregnancies undergoing earlier anomaly screening using two-dimensional ultrasound was associated with increased mean healthcare costs per woman (£11, 95% confidence interval £1 to £29) and maternal quality-adjusted life-years (0.002065, 95% confidence interval 0.000565 to 0.00358), an incremental cost per quality-adjusted life-year of £5270, with likelihood of being cost-effective at £20,000 per quality-adjusted life-year of over 95%. Additional modelling predicted reductions in infant healthcare costs and quality-adjusted life-years. Decision uncertainty was low. Value-of-information analysis of cost-effectiveness results showed no groups of parameters for which further research to reduce uncertainty would likely prove cost-effective.

Limitations: Study heterogeneity; the lack of a universal reference standard; simplifying assumptions relating to economic model structure; and estimation of some parameters are documented and justified. The rarity of the conditions made estimation of longer-term maternal and infant costs and quality-adjusted life-years challenging, resulting in likely under-estimation of healthcare costs.

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Conclusions: With standardisation and training, first-trimester ultrasound screening for fetal anomalies is clinically effective with over 90% detection for eight major conditions and low false-positive rates. Decision uncertainty around implementation is low and a prospective study would not be an efficient investment. Adding first-trimester anomaly screening to the current screening likely represents a cost-effective use of resources and is acceptable to parents.

Future work: Focus on developing an implementation framework to modify the current United Kingdom Fetal Anomaly Screening Programme.

Study registration: This study is registered as PROSPERO CRD42018111781 and CRD42018112434.

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List of supplementary material

Report Supplementary Material 1 Literature searches conducted to support health economics work (*Chapters 10* and *11*)

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/NLTP7102).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ALARA	as low as reasonably achievable
AUS	anatomical abnormality of undetermined significance
CEAC	cost-effectiveness acceptability curve
CF	colour flow
CRL	crown–rump length
CVS	chorionic villus sampling
D&E	dilatation and evacuation
DQASS	Down syndrome screening quality assurance support service
DV	ductus venosus
EUROCAT	European network of population-based registries for the epidemiological surveillance of congenital anomalies
ENBS	expected net benefit of sampling
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
EVSI	expected value of sample information
FASP	Fetal Anomaly Screening Program
FMU	fetal medicine unit
FN	false negative
FP	false positive
GA	gestational age
HC	head circumference
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ISUOG	International Society of Ultrasound in Obstetrics and Gynaecology
LUTO	lower urinary tract obstruction
NCARDRS	National Congenital Anomaly Disease Registry
NIHR	National Institute of Health and Care Research
NIPT	non-invasive prenatal testing
NT	nuchal translucency
OTV	outflow tract view
PHE	Public Health England
PPI	personal and public involvement
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
PTSD	post-traumatic stress disorder
QALY	quality-adjusted life-year
QUADAS-2	quality assessment of diagnostic accuracy studies
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised control trial
SHINE	Spina Bifida, Hydrocephalus, Information, Networking, Equality Charity
TA	transabdominal
TOP	termination of pregnancy
TN	true negative
TP	true positive
TR	tricuspid regurgitation
TV	transvaginal
UK NSC	United Kingdom National Screening Committee
VoI	value of information analysis
VSD	ventricular septal defect
WTP	willingness to pay

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Plain language summary

In the National Health Service, all women are offered two ultrasound scans during pregnancy: at 11–14 weeks, which confirms the baby is alive, takes measurements, and checks if there is more than one baby; and at 18–20 weeks, which checks whether the baby is developing as expected. Unfortunately, in about 2–3% of pregnancies, a serious physical condition (anomaly) is found at this second scan.

With improvements in scanning equipment, almost half of these anomalies can now be picked up on the early scan. This has advantages for parents: extra time for testing, to speak to specialists or to prepare for the baby's birth. For parents deciding on termination, having this done earlier can be safer. But there may be disadvantages: early scanning could suggest the baby has a condition which further testing shows not to be the case. This could cause worry and further unnecessary tests. Our research looks at whether earlier scanning would be the right approach, and if so, how this should be done. We conducted several studies to answer this question.

First, we reviewed the experiences of hospitals who already offer this early scan. This identified which serious physical conditions can be found, and that the number of parents given a false alarm is relatively low.

Second, we surveyed every National Health Service trust in England. Approximately 75% already perform an early anatomy scan, but with a lot of variation of what options are available to women.

Next, we asked 172 doctors, midwives and sonographers to work together to plan how early scanning could be introduced. They recommended that every woman be scanned between 12 and 14 weeks, to look for one of eight major physical conditions.

We then surveyed over a thousand parents to hear what they think. Over 90% felt that this earlier scan would be beneficial.

Finally, we built a computer model to help us calculate the costs of this earlier scan. This suggested early screening would lead to fewer live births of babies with anomalies. It showed that an early scan would be associated with a small increase in healthcare costs, but also in positive health outcomes for each woman. The additional maternal benefits were considered worth the additional healthcare costs. We identified that there is already sufficient evidence to support this new policy of screening, and that it would not be a good use of money to carry out further research in this area.

Scientific summary

Background

In the UK, all pregnant women are currently offered second-trimester ultrasound screening at 18–20^{+6} weeks of gestation for the detection of congenital fetal anomalies. However, many severe and lethal anomalies can be detected earlier and routine first-trimester anomaly screening at 11–14 weeks may be a valuable addition to prenatal care.

Objectives

The objectives of this study were:

1. To assess the diagnostic accuracy of first-trimester ultrasound for major structural anomalies through systematic reviews and meta-analyses of the literature and to understand how this screening should be optimally performed (i.e. anatomical protocol, anomalies to be targeted, gestational age window, ultrasound modality used and referral pathways).
2. To undertake a survey of the current first-trimester screening environment in England.
3. To perform an analysis of UK-based data currently held by the National Congenital Anomaly Disease Registry (NCARDRS) to determine the impact of performing a routine first-trimester anomaly scan on the timing of fetal congenital anomaly diagnosis.
4. To conduct a Delphi consensus procedure for the development of a protocol including technical and logistical aspects of first-trimester anomaly screening, based on expert opinions of healthcare providers from across the UK (sonographers, midwives, obstetricians and fetal medicine specialists).
5. To determine the acceptability of the early anomaly scan among women and their partners.
6. To conduct an economic analysis to estimate the expected costs and outcomes associated with current practice and with prospective first-trimester anomaly screening protocols identified by the work described above.
7. To undertake a value-of-information (VoI) analysis to determine whether there is economic value in undertaking additional future research.
8. To draw together the findings and recommendations from the project, and, if appropriate, outline the design of plausible studies or clinical trials.

Methods

The systematic reviews and meta-analyses of studies were designed to evaluate the diagnostic accuracy of two-dimensional ultrasound for the detection of a pre-selected group of major anomalies at 11–14 weeks' gestation, based on Fetal Anomaly Screening Program (FASP) priorities and the consensus group: anencephaly, holoprosencephaly, encephalocele, body stalk anomaly, ectopia cordis, exomphalos, gastroschisis, lower urinary tract obstruction (LUTO) and major cardiac anomalies. The protocols for the reviews were developed and registered with the International Prospective Register of Systematic Reviews prior to undertaking the search, selection of studies and data extraction (PROSPERO, CRD42018111781 and CRD42018112434). A systematic electronic search strategy was designed with the help of a specialist librarian using free-text terms and subject headings related to prenatal screening, early pregnancy and congenital abnormalities and conducted using four databases (MEDLINE, EMBASE, Web of Science Core Collection and Cochrane Library) for studies published between January 1998 and July 2020. Prospective and retrospective studies evaluating pregnancies of low, mixed or uncertain a priori risk and in any healthcare setting were eligible for inclusion. We excluded studies only evaluating high-risk pregnancies. The reference standard used was the detection of a major abnormality on postnatal or post-mortem examination. Data were extracted from the included studies to populate 2 × 2 tables. Meta-analysis was performed using a random-effects model to determine the performance of first-trimester ultrasound for the detection of the individual pre-selected congenital anomalies, for major cardiac abnormalities overall and for the major non-cardiac anomalies overall (n = 7). Pre-planned secondary

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analyses were conducted to assess factors that may impact screening performance, including the imaging protocol used for assessment, ultrasound modality, year of publication, and the index of sonographer suspicion at the time of the scan. Risk of bias and quality assessment were undertaken for all included studies using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool.

The nationwide survey of NHS practice was developed and undertaken in collaboration with the FASP. Thirty-six questions covered domains including current first-trimester ultrasound protocols; local policies regarding screening logistics (e.g. time allocated for scan, mode of scan, equipment) and referral pathways; inclusions of a routine early fetal anomaly scan and resource availability. After validation and piloting, the survey was distributed electronically in January 2019 to all NHS maternity trusts in England (n = 132). Anonymised data were analysed using descriptive statistics for the group of responding trusts; survey responses from trusts in different regions [as defined by Public Health England (PHE) at that time] were compared using chi-squared tests.

Data obtained from the nationwide survey of NHS practice regarding the first-trimester anomaly screening protocols of different NHS trusts were linked to retrospective data held by the NCARDRS from pregnancies with estimated delivery dates between April 2017 and 2019. Ethics approval for this work was obtained after full review by the North West – Preston Research Ethics committee (21/NW/0173) in March 2021 and by the National Disease Registry Project Review Panel on behalf of PHE. Data from NHS Hospital trusts who responded to the nationwide survey were aggregated into one of four groups based on the reported type of first-trimester anomaly screening protocol used routinely: (1) no formal assessment; (2) basic anatomical assessment (routine evaluation of fetal head, limbs and/or cord insertion only); (3) advanced anatomical protocol (basic + either stomach and/or bladder); (4) extended anatomical protocol (advanced + fetal heart, spine and/or face). The primary objective of the study was to determine the proportion of anomalies (a pre-designated group) which are currently identified prior to 16 weeks in England and to compare the early detection rates of these anomalies based on the first-trimester screening protocol used (Group a vs. Group b vs. Group c vs. Group d). The pre-designated anomalies of interest were based on current FASP second-trimester guidance and on several anomalies of interest in the first trimester which included anencephaly, alobar holoprosencephaly, encephalocele, exomphalos, gastroschisis, spina bifida, facial clefts, congenital diaphragmatic hernia, bilateral renal agenesis, megacystis, lethal skeletal dysplasias, limb reduction defects, hypoplastic left heart syndrome (HLHS), atrioventricular septal defect (AVSD), tetralogy of Fallot (TOF) and transposition of great arteries. Pre-specified subanalysis of each type of anomaly by ultrasound protocol was also assessed. Analysis of data at individual trust level was not undertaken.

The Delphi consensus procedure took place entirely online over two rounds using RedCap software (Vanderbilt, Nashville, TN, USA). The study was open to all UK healthcare professionals with an interest in this area of research, with invitations to participate circulated to a list of UK-based sonographers, midwives and doctors with known interests in this area, and to the membership of the British Medical Ultrasound Society and the British Maternal Fetal Medicine Society. All data collected from participants were kept confidential, analysed anonymously and in aggregate form. A literature search conducted from 1991 to 2021 identified (1) all published first-trimester ultrasound protocols evaluating fetal anatomy; (2) a list of anomalies detectable at 11–14 weeks; and (3) relevant screening factors; this formed the basis for round one of the Delphi questionnaire. Participants were asked to identify those fetal anomalies and anatomical views which should be routinely evaluated in the first trimester, and determine logistical aspects. Items receiving ≥ 80% support and < 60% support were included and excluded, respectively, from the protocol. In round two, results were fed back to the participants for confirmation, and items receiving between 60% and 80% support were reconsidered. Subgroup analysis was performed to determine whether responses differed by stakeholder group.

The ACceptability of the first trimester Anomaly Scan (ACAS) Study was a multicentre prospective, questionnaire-based study designed to explore parental views towards routine anomaly screening at 11–14 weeks in the UK. It included two distinct study cohorts. In Cohort A, parents attending routine antenatal ultrasound at 1 of 10 participating NHS hospitals in England and Wales were eligible for recruitment. In Cohort B, parents with a previous pregnancy or child with a congenital anomaly were invited to participate via two national charities: Antenatal Results and Choices and Spina Bifida, Hydrocephalus, Information, Networking, Equality Charity. All participants received a briefing guide explaining the potential benefits and risks of an 11–14 week anatomy assessment and were asked to complete a validated, structured questionnaire on their views regarding screening for anomalies.

For the health economic evaluation, a detailed decision-analytic model was developed to simulate the impact upon healthcare costs and maternal quality-adjusted life-years (QALYs) of a policy to add a first-trimester anomaly scan to the current antenatal screening pathway. Assessments of the impact of the screening policy upon pregnancy outcomes and infant costs and QALYs were also made and are reported separately. Costs included additional time for consent and scanning, sonographer training, as well as additional fetal medicine and echocardiographic scans, and other follow-up investigations offered following an initial screen-positive scan. The implications for maternal quality of life of screening outcomes, further investigations, pregnancy continuation decisions, and fetal losses during the first and second trimesters were also modelled. The model was run for a period of 20 years using an NHS perspective, and populated using data from the project's systematic reviews and surveys, administrative databases, the National Schedule of NHS Costs (2019–20) and the published literature. Parameters were entered using distributions to facilitate probabilistic sensitivity analysis. VoI analysis, conducted on the cost-effectiveness results generated using maternal healthcare costs and QALYs, was used to identify uncertainty present in groups of key model parameters and whether investments in further research are needed to reduce such uncertainty before a policy decision can be made about the implementation of first-trimester anomaly screening.

Results

Based on systematic review of low-risk and unselected pregnancies (416,877 fetuses in 40 studies), for the group of major anomalies prioritised by FASP and the consensus procedure, a first-trimester anomaly scan will detect 93.29% [95% confidence interval (CI) 90.37% to 95.71%] of anomalies with a specificity of 99.99% (95% CI 99.98% to 99.99%) and a positive predictive value (PPV) of 96.54% (95% CI 93.27 to 98.76). False-positive (FP) rates are low, and this is consistent with findings from several individual studies examining this issue. Within our review, there were 49 reported FP cases identified, of which 47 were described as findings of bowel-only exomphalos on first-trimester ultrasound in euploid fetuses which were labelled as having subsequently 'spontaneously resolved'. It should be noted that FP screening will result in additional referrals for fetal medicine assessment, and this has been taken into account within the health economic analysis. For major cardiac anomalies (306,872 fetuses, 45 studies), a first-trimester anomaly scan will detect 55.80% (95% CI 45.87% to 65.50%) of anomalies with a specificity of 99.98% (95% CI 99.97% to 99.99%) and a PPV of 94.85% (95% CI 91.63% to 97.32%). Individually, the first-trimester detection rates for seven of the non-cardiac anomalies in question (acrania, exomphalos, gastroschisis, body stalk anomaly, holoprosencephaly and ectopia cordis) exceed 85% of cases, with fetuses affected by LUTO identified in 65% of cases. We compared studies using a formal anatomical protocol to those not doing so. This showed no statistically significant differences in the detection rates for these eight anomalies combined, nor in the detection of the anomalies individually, with the exception of screening for holoprosencephaly. For major cardiac anomalies, we found strong evidence that the imaging protocol used for examination impacts screening performance ($p < 0.0001$), with a significantly higher detection rate observed in studies using at least one outflow tract view or colour flow Doppler imaging (both $p < 0.0001$). Different types of cardiac anomalies were not equally amenable to detection, though first-trimester detection rates exceeded 70% for the following anomalies: complex cardiac defects, left and right hypoplastic syndromes, arterio-ventricular septal defects, tricuspid atresia, truncus arteriosus and heterotaxy syndromes.

Despite an absence of national recommendations, approximately 75% of units in the UK already perform some form of early anomaly screening, and the majority of trusts do this within the current time allocation of 25–30 minutes. However, significant variations in practice were seen with 64% of trusts using a locally developed anatomical protocol of varying detail, 36% offering in-house sonographer training and 24% giving patients local written pre-scan information specific to first-trimester anomaly screening. There were important differences seen between the services offered across different geographical regions of the UK, resulting in inequity of care.

Data from NCARDRS suggest that NHS hospitals undertaking first-trimester anomaly screening provide significantly more patients with an early diagnosis (before 16 weeks of gestation). The highest detection rates were seen in those centres performing detailed first-trimester ultrasound scans routinely, using formalised protocols (Group d, 40%), but a sizeable proportion of anomalies are also being diagnosed at early gestations in units where no first-trimester anatomy assessment is formally declared (Group a, 28%). A significant association was demonstrated between the sensitivity of early ultrasound at a population level and the use of an anatomical protocol for screening. This suggests that higher detection rates for the pre-designated group of major anomalies are achieved in those centres with the most detailed protocols for screening ($p < 0.001$).

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Based on a Delphi consensus procedure, an anatomical protocol for first-trimester screening was developed with the expert opinion of 172 UK healthcare providers recommending that early anomaly screening should be performed at 12–14 weeks' gestation, primarily using transabdominal ultrasound. At a minimum, this screening should target the diagnosis of eight major anomalies: anencephaly, body stalk anomaly, ectopia cordis, encephalocele, exomphalos, holoprosencephaly, gastroschisis and LUTO.

The ACAS Study included participation from 1374 parents (1199 in Cohort A and 174 in Cohort B.) The vast majority of parents felt that first-trimester anomaly screening would be beneficial and would opt for an 11- to 14-week anomaly scan in a future pregnancy (A: 91%, B: 95%). This includes couples who would opt against screening for chromosomal abnormalities and those who would not consider termination of pregnancy. Of note, many parents wish to be informed of a suspected anomaly in the first trimester, even if it cannot be confirmed until a later gestation (A: 74%, B: 82%).

Health economic analysis showed that first-trimester anomaly screening was associated with a small, per woman, mean cost increase of £11 (95% CI £1 to £29) on account of increased scanning times. A mean maternal QALY gain of 0.002065 (95% CI 0.000565 to 0.00358) was driven largely by the temporary reassurance provided by a negative first-trimester anomaly scan to around 90% of all women. The incremental cost-effectiveness ratio was £5270 per maternal QALY and the likelihood of first-trimester anomaly screening being cost-effective at a willingness to pay of £20,000 per QALY was 95%. The model predicted an increase in first-trimester terminations, and reductions in second-trimester terminations and live births of infants with anomalies. These changes led to reductions in infant healthcare costs and QALYs. Maternal and infant costs and QALYs were not aggregated for methodological and ethical reasons, and because of a general lack of guidance around how to interpret the overall implications of such antenatal screening programmes.

The VoI analyses indicated the expected value of perfect information (i.e. the value of removing all uncertainty across all 175 model parameters) for England over a period of 20 years to be £3,461,151. Parameters for the extra costs of anomaly screening (encompassing sonographer training and additional screening time) and the screening performance for the eight anomalies (sensitivities and FPs) accounted for most uncertainty but the value likely to be realised from reducing the uncertainty around these parameters was considered to be lower than the costs of the research needed to achieve this.

Conclusions

Given a framework of standardisation and training, first-trimester ultrasound screening for fetal anomalies is clinically effective and acceptable to parents. Analysis modelling maternal healthcare costs and QALYs indicate that the addition of first-trimester anomaly screening to the current antenatal screening pathway is likely to represent a cost-effective use of resources. Fewer live births of babies with anomalies are predicted and this raises complex and ethically sensitive issues previously documented by analysts evaluating antenatal screening programmes for fetal anomalies. VoI analysis on maternal costs and QALYs suggests that decision uncertainty is low, and that investing in new research to further reduce this uncertainty would not be a cost-effective use of resources. Overall, our report suggests that first-trimester ultrasound screening for fetal anomalies is clinically effective and cost-effective, and that further prospective studies would not constitute an efficient investment.

Study registration

This study is registered as PROSPERO CRD42018111781 and CRD42018112434.

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Chapter 1 Background

Antenatal ultrasound

Women in the UK receiving standard antenatal care are currently offered two routine ultrasound scans in pregnancy as recommended by the National Screening Committee (NSC): the first at 11–14 weeks of gestation, and a further scan at 18–20 weeks.[1,2]

The 11- to 14-week scan ('first-trimester scan') aims to confirm fetal viability, establish accurate gestational age (GA) from the measurement of fetal crown–rump length (CRL), identify multiple pregnancies, and determine chorionicity in these pregnancies.[2,3] In addition, fetal nuchal translucency (NT) can be measured as part of a 'Combined Screening Test', which uses maternal age, serum-free beta-human chorionic gonadotropin, pregnancy-associated plasma protein A and fetal NT to determine fetal risks for trisomies 21, 18 and 13.[2,3] The screening test offers a sensitivity of approximately 85–90% for Down syndrome and other aneuploidies, with a false-positive (FP) rate of 5%.[4] Based on these objectives, the first-trimester ultrasound scan has become a cornerstone of prenatal care and central to antenatal screening for fetal aneuploidy in women who opt for this.

The second ultrasound scan is offered to women at 18–21 weeks of gestation. The main objective is to detect major congenital abnormalities and specifically to identify fetuses with anencephaly, open spina bifida, cleft lip, diaphragmatic hernia, gastroschisis, exomphalos, major cardiac anomalies, bilateral renal agenesis, lethal skeletal dysplasia and chromosomal anomalies (trisomy 13 and 18).[1]

This model of care is being challenged due to a number of reasons. Firstly, the distinction between anomaly screening at the first and the second scans is artificial, because the majority of organogenesis is complete by 10 weeks GA.[5,6] Secondly, many chromosomally abnormal fetuses will have structural malformations, and early anomaly detection is complementary to the current aneuploidy screening model.[7,8] Thirdly, recent technological improvements in ultrasound image quality now allow earlier visualisation of the fetal anatomy;[9,10] studies suggest that this results in many severe and lethal anomalies being detectable at 11–14 weeks.[11,12] As a result, some NHS centres are offering such screening routinely to patients, despite the absence of formal national recommendations.

Screening for fetal anomalies

Fetal congenital abnormalities occur in 2–5% of the fetal population and represent a significant cause of fetal, neonatal, childhood and adult morbidity and mortality.[13,14] An accurate prevalence is difficult to estimate as this value can only be based on live births and stillbirths that have undergone autopsy. As the overwhelming majority of fetuses that miscarry is not examined, the true prevalence of fetal structural abnormalities is impossible to determine. However, among liveborn and stillborn infants and fetuses that underwent pregnancy termination, data from the European Surveillance of Congenital Anomalies register suggest a prevalence rate of 261.41 non-chromosomal anomalies per 10,000 births [95% confidence interval (CI) 260.02 to 262.79].[15]

In the UK, ultrasound screening to detect congenital anomalies is offered to all pregnant women in the second-trimester ultrasound as part of the Fetal Anomaly Screening Program (FASP).[1,2]

However, studies have shown that many major anomalies can be detected earlier, between 11 and 14 weeks of gestation, in both low-risk and high-risk populations.[12,16–18] A recent meta-analysis has shown that first-trimester screening can accurately diagnose over half of all major anomalies detected prenatally.[19] In addition, the use of an anatomical protocol for screening is associated with improved detection rates for fetal anomalies in the first trimester. This highlights the importance of a systematic approach to screening and suggests that detection rates could potentially be optimised with a focus on a standardised anatomical protocol, directed sonographer training, clear guidelines

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with respect to the GA at time of screening and modality of ultrasound, and a structured referral pathway for the investigation of screen positive results.

As routine ultrasound is already carried out at 11–14 weeks, additional screening for structural anomalies at this gestation may be valuable as detection rates are now relatively high.[19] This justifies assessing the utility of such a screening approach. This assessment needs to be balanced, as there is little consensus as to whether first-trimester anomaly screening is clinically reliable enough for routine use in low-risk and unselected populations. Furthermore, there is currently no UK guidance recommending how first-trimester anomaly screening should be optimally performed, what anatomical structures and planes of visualisation should be obtained as a standard of care, which anomalies should be targeted and how positive or suspicious findings should be managed in practice. Thus, the specific objectives and role of early anomaly screening as a part of prenatal care, particularly in relation to its second-trimester counterpart, remain unclear. This is a critical point if the healthcare system is to consider amending current screening to include early anomaly screening as part of routine practice.

The feasibility of detecting fetal structural abnormalities in the first trimester means that some NHS hospitals have been undertaking ultrasound for detailed anatomical assessment in the first trimester, resulting in a lack of equity and access to care around the country. In addition, many private providers offer detailed anatomical assessments in the first trimester and when problems are identified, attendance in the NHS for the subsequent management of findings is common. There is, therefore, anecdotal information suggesting that ad hoc screening is taking place across the UK, but with little evidence available to patients and practitioners regarding the balance of risks and benefits of such screening; and critically, no structured management pathways exist for the care of screen-positive pregnancies.

In light of these uncertainties, we answered this commissioned call to undertake a detailed, reasoned and quantitative assessment of the potential for clinical benefit and harm in relation to early anomaly screening using ultrasound; to assess cost-effectiveness; and to determine what future studies are needed.

Potential advantages of first-trimester anomaly screening

Over the past decades, much of the focus in obstetrics research has been on the early risk stratification and diagnoses of maternal and fetal conditions in pregnancy.[20] There are clear advantages to early diagnostics in obstetrics medicine and, in particular, in the diagnosis of fetal structural anomalies.

The majority of parents undergoing a first-trimester scan will be carrying an unaffected pregnancy. For these individuals, particularly those with a previous experience of fetal anomaly, first-trimester screening provides early reassurance regarding the health of their fetuses.[21]

However, it is for the relatively small number of parents carrying a fetus affected by a major congenital anomaly, where the clear benefits to early screening will be most pronounced. An early diagnosis allows additional time for genetic testing; and for multidisciplinary specialist input from fetal medicine experts, geneticists, neonatologists, paediatricians (e.g. neurologists, cardiologists), paediatric surgeons, counsellors and parent support organisations, as appropriate.[22] The diagnosis of a major fetal congenital anomaly will be difficult and overwhelming news for most parents carrying a wanted pregnancy. Allowing additional time for an accurate diagnosis with a clear prognosis (and critically, the discussion around this) is important, so that parents can develop a comprehensive and balanced understanding of their baby's condition, prior to making any decisions regarding pregnancy management. The increasing possibility for parents to be offered in utero surgical management aiming to improve the postnatal outcome of certain major conditions must also be acknowledged and is reliant on the early identification of fetuses who might benefit from such treatment.[22–26] As we look towards building a screening strategy for the future, it is clear that genetic testing is also evolving rapidly, and the possibility of undertaking next-generation sequencing techniques at an earlier stage of pregnancy will increase the likelihood of presenting parents with meaningful genetic information (beyond fetal karyotype) about their child's condition antenatally.[27–29] The prospects of being able to offer fetal gene therapy to fetuses with monogenic conditions remains firmly at the research stage, but promising early results may well make this a future therapeutic option for parents to consider prenatally.[24,30] Most importantly, an early diagnosis provides parents with additional time to process

the information presented to them and to make the best possible decision for their family, allowing time to properly consider and prepare for the birth of an affected child. A screening strategy which focuses on the early detection of fetal anomalies would support this important process of informed and considered decision-making for parents.

Termination of pregnancy in the setting of a lethal or severe fetal anomaly

In the setting of a lethal or severe fetal congenital anomaly diagnosis in the UK, the option of termination of pregnancy (TOP) may be discussed, within the legal framework set out by the 1967 Abortion Act [Section 1(1)(d); Ground E] and the 1990 Human Fertilization and Embryology Act.[22] The majority of women would consider a termination in this context,[31,32] and UK data show that over 50% of parents who are given an antenatal diagnosis of fetal aneuploidy or neural tube defect will opt for termination.[33] Therefore, a discussion regarding the implications of antenatal screening practice on pregnancy termination is relevant and will impact a significant proportion of parents carrying a pregnancy affected by a major congenital fetal abnormality in this country.

Although the terminology of 'termination of pregnancy' refers to the practice of ending a pregnancy at any GA, it is important to recognise that the process by which this is undertaken, the options in terms of where and how this takes place, and the implications, both in terms of physical and psychological maternal risks are different based on GA.[22,34,35] TOP can be offered using one of two methods, distinguished as either a surgical or medical. A surgical termination involves use of a transcervical procedure with the patient usually under sedation or with local anaesthesia, and can be performed with vacuum aspiration prior to 14 weeks (in some units up to 16 weeks) or using dilatation and evacuation (D&E) at later GAs. The high level of specialist training and equipment required for D&E, means that there is a considerable shortage of doctors who are able to perform this procedure. As a result, the majority of women requesting TOP beyond 14 weeks in the UK will only be given an option for medical termination.[22,36] A medical termination involves the use of misoprostol (either alone or in combination with mifepristone) for the induction of labour, stimulating the onset of uterine contractions resulting in vaginal delivery of the fetus. Prior to 12 weeks GA, a medical termination may be performed at home, usually with the support of prescription pain medication. Beyond this point, medical termination is performed in hospital, as there is an increasing risk of complications requiring medical intervention and requirement for non-oral analgesia (including epidural) for pain management.

The maternal risks associated with TOP increase with GA, regardless of the method used.[34,35,37] Based on UK data, the overall risk of complications, including risk of severe bleeding requiring blood transfusion, uterine perforation and/or maternal sepsis increase from 1 per 1000 terminations at 10–12 weeks, to 5 per 1000 terminations at 13–19 weeks, to 11 per 1000 terminations beyond 20 weeks' gestation (an 11-fold increase from the first trimester). This increase in complications is most striking for women undergoing a medical termination, where the risk increases from 3 per 1000 at 10–12 weeks, to 11 per 1000 at 13–19 weeks, to 21 per 1000 beyond 20 weeks GA (a seven-fold increase from a first-trimester medical termination and a 21-fold increase from a first-trimester surgical abortion).[35] In a recent, large retrospective review of cases where medical termination was conducted at or beyond 20 weeks GA, severe maternal morbidity affected 1 in 81 women undergoing the procedure and complications included cardiac arrest, major obstetric haemorrhage, amniotic fluid embolism, uterine rupture and intensive care admission.[37]

It should be highlighted that after any medical pregnancy termination, a second procedure may be required to allow for removal of retained fetal or placental tissue and this increases from 7% prior to 14 weeks to 13% thereafter.[34] Women undergoing termination at later GAs are also more likely to require hospitalisation and to have an increased length of stay, with over 50% requiring hospitalisation for one or more nights following termination after 20 weeks compared with 5% at 10–12 weeks and 15% at 13–19 weeks GA.[35]

When a decision has been reached to terminate a pregnancy for fetal abnormality after 21^{+6} weeks, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends that an additional procedure of fetal feticide be offered to all women.[22] This procedure most often involves an injection of potassium chloride into the fetal heart to induce fetal asystole (fetal death) prior to the onset of labour and delivery. While this process is understandably stressful for patients and practitioners, failure to perform this procedure may lead to postnatal survival of the fetus, in effect contradicting the aim of the termination. In the UK, retrospective data analysis demonstrates that at 22 weeks' gestation and

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later, 95% of terminations were preceded by feticide or conducted in a manner to stop the fetal heart prior to delivery.[35] For abortions conducted under Ground E justification, feticide has been performed as early as 20 weeks with increasing incidence with later GAs.[22] The fetal feticide procedure is not performed at all centres across the UK and women may need to travel some distance for this procedure to take place.[22] Therefore, while TOP for severe and lethal anomalies remains legal beyond 20 weeks, the additional procedure of fetal feticide may cause an additional element of emotional distress.

Beyond the medical risks, the psychological impact of this life event must also be recognised. The decision around whether to proceed with termination is complex and conflicting, and while seemingly a voluntary act, it has been described by parents 'as an almost inhuman decision to make'.[38] Consequently, women may show life-impacting levels of psychological morbidity following termination for fetal anomaly at any GA;[39,40] this reaction will be unique to individuals, but may be impacted by factors including the previous experiences of the woman, level of partner support, educational status and the lethality of the fetal anomaly.[38] Levels of grief, post-termination doubt and post-traumatic psychological distress (including post-traumatic stress disorder, PTSD) have been shown to be associated with advancing GAs at time of termination and may last for many years following the event.[38,40] Advanced GA and the method by which termination is performed (with its associated risks) are closely related, and therefore it may be difficult to ascertain which is causing the greatest impact on psychological symptoms. It has been suggested that over time, the burden from PTSD experienced by some women may be more impactful than their symptoms of grief, indicating that they may experience TOP 'more as a trauma, than (they do) as a loss'.[38] The earlier diagnosis of fetal anomalies may not impact the sense of loss experienced by these women and their partners. However, it may help with feelings of post-procedure doubt by allowing more adequate time for supported decision-making around termination (allowing less pressurised, reactionary decision-making). Furthermore, by giving women options for safer, less physically and emotionally traumatic methods of termination, there may well be an opportunity to reduce the incidence of long-term PTSD.[38,40] Finally, allowing women autonomy of choice regarding the method of termination undertaken (medical vs. surgical), which is more readily available at earlier gestations, has been shown to have a positive impact on long-term psychological morbidity and acceptance of this difficult life event.[36,41]

Potential disadvantages of first-trimester anomaly screening

Any advantages of first-trimester screening for fetal abnormalities need to be balanced against disadvantages.

First, there are certain major anomalies which remain difficult to diagnose at 11–14 weeks: anomalies considered undetectable include those relating to structures which have not yet fully developed at this gestation (e.g. cerebellar anomalies, echogenic lung lesions), or those which are diagnosed on the basis of changes in physiology (e.g. duodenal atresia, bowel obstruction).[16] Consequently, the early anomaly scan cannot be considered a replacement for the formal second-trimester anomaly scan.

In addition, the small size of certain anatomical structures in the first trimester (notably heart and kidneys) and the evolving nature of fetal pathology also indicate that certain anomalies may only be suspected in the first trimester and require follow-up scans at later gestations for confirmation and to understand prognosis. This may lead to a period of increased anxiety and uncertainty for parents as they wait for confirmation and the possibility of unnecessary additional scans and testing (with the associated costs to the health service).

The possibility of a FP result after first-trimester screening is also a risk. This will differ depending on the anomaly in question and has been poorly defined in most previous studies (also for second-trimester screening).[19] When major fetal anomalies are diagnosed after first-trimester screening, early termination is offered. Surgical termination may preclude post-mortem examination and therefore physical confirmation of ultrasound findings will not always be possible. FP rates can also be impacted by anomalies that evolve: for example, a significant proportion of megacystis or bowel-only exomphalos resolve spontaneously in euploid fetuses with advancing gestation. Therefore, understanding FP rates and the types of anomalies that are most likely to resolve spontaneously is a crucial aspect of this work.

The health economic implications of first-trimester ultrasound screening

A critical consideration in relation to first-trimester anomaly screening is whether it represents value for money for finite NHS resources (i.e. is it cost-effective compared with other uses for those same funds?). It is possible that earlier screening for the pregnant mother leads to improved outcomes, but at additional costs to the healthcare system. It is important then to assess whether these additional resources are justified by the associated improved outcomes. In a healthcare setting with limited resources like the NHS, this becomes crucial because adopting early anomaly screening translates into a potential reduction of resources to invest elsewhere within the NHS. These questions are addressed quantitatively in the modelled health economic analyses presented in *Chapter 10*.

Chapter 10 also describes in detail the model's consideration of the potential quality-of-life implications for women of events arising along the screening pathway. These include, for the first and second trimesters, the detrimental utility impact of a true-positive (TP) anomaly screen, a FP anomaly screen, a fetal loss following invasive testing, a decision to terminate, and the spontaneous loss of a baby. The positive impact of reassurance received from a negative anomaly screen is also modelled for both trimesters. These utility adjustments facilitate the estimation of quality-adjusted life-years (QALYs) for the duration of the pregnancy. QALYs are also used when modelling the longer-term implications of changes to pregnancy outcomes brought about by early anomaly screening, for both mothers and infants.

Adding a detailed anatomical assessment to the existing first-trimester pregnancy ultrasound scan will clearly incur some additional direct costs, such as implementation of a protocol, training of sonographers and potentially longer scanning times. Other elements may be cost-neutral: for example, the pathway of care for women with a positive screening test may be similar regardless of whether the positive screening finding is at 12 or 20 weeks – the pathway simply starts earlier. Finally, costs may also be reduced in relation to QALYs gained by the mother because of being screened. The individual elements required for these calculations, and their associated uncertainty, are based on a synthesis of the information generated by the various components of this project, some of which are detailed in the chapters that precede *Chapter 10*, and other evidence obtained from the published literature.

Within *Chapter 10*, we detail the identification of an appropriate modelling framework, model structure, key study parameters and potential measures of outcome. The model developed allows estimation of the healthcare costs and outcomes of first-trimester structural fetal anomaly screening, compared to current practice. It attempts to take into account the main potential outcomes, which are complex, multifaceted, ethically sensitive, and have implications for both parents and infants.

Value-of-information analysis

The health economic analyses described above answer the question of whether there is an economic case for implementing a programme of first-trimester anomaly screening given the current evidence base and levels of uncertainty. Our decision-analytical model utilises parameter values that encompass relevant measures of uncertainty and facilitates a probabilistic sensitivity analysis (PSA) to assess the implications of joint parameter uncertainty. Value-of-information (VoI) analysis addresses whether our cost-effectiveness results are robust enough to inform the adoption of earlier screening now or whether further research is warranted before such a recommendation is made. Using the model's facility for PSA, we first calculate the expected value of perfect information (EVPI) to assess whether there is value in obtaining additional research and second, the expected value of partial perfect information (EVPPI) to identify groups of parameters where reducing uncertainty would represent an efficient investment. These works are described in detail in *Chapter 11*.

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Chapter 2 Objectives

The objectives of this study were:

1. To assess the diagnostic accuracy of first-trimester ultrasound for major structural anomalies through systematic reviews and meta-analyses of the literature and to understand how this screening should be optimally performed (i.e. anatomical protocol, anomalies to be targeted, GA window, ultrasound modality used and referral pathways).
2. To undertake a survey of current first-trimester screening practices in England.
3. To perform an analysis of UK-based data currently held by the National Congenital Anomaly Disease Registry (NCARDRS) to determine the impact of performing a routine first-trimester anomaly scan.
4. To conduct a Delphi consensus procedure for development of a protocol including technical and logistical aspects of first-trimester anomaly screening based on expert opinions of healthcare providers from across the UK (sonographers, midwives, obstetricians and fetal medicine specialists).
5. To determine the acceptability of the early anomaly scan among women and their partners.
6. To conduct an economic analysis to estimate the expected costs and outcomes associated with current practice and with prospective first-trimester anomaly screening protocols identified by the work described above.
7. To undertake a VoI analysis to determine whether there is economic value in undertaking additional future research.
8. To draw together the findings and recommendations from the project, and, if appropriate, outline the design of plausible studies or clinical trials.

Chapter 3 Identifying the research questions

As this was a commissioned call, the primary research question was set by the Health Technology Assessment (HTA), namely 'What is the value of undertaking a study to determine the clinical and cost-effectiveness of a detailed ultrasound scan in the first trimester, in addition to usual practice, for the earlier detection of fetal anomalies?'

The intervention under investigation is a detailed anomaly ultrasound scan at around 12 weeks' gestation, in addition to usual practice. A protocol for detailed anomaly scans was to be defined and justified as part of this research for pregnant women in UK maternity services.

The comparator is usual practice (i.e. ultrasound scan at around 12 weeks' gestation to date the pregnancy and a detailed ultrasound scan at around 20 weeks for detection of anomalies), and the brief was to (1) define and protocolise the 12-week detailed anomaly scan including the method of scanning, and (2) perform economic modelling of the proposed intervention and a VoI analysis to inform plans for future research.

Prior to the start of this project, we conducted a large systematic review and meta-analysis of first-trimester screening for major fetal anomalies in pregnancy, which largely informed the development of the clinical research questions addressed in this project (see below). We showed that the sensitivity, in the first trimester, for the detection of major anomalies in unselected populations (19 studies, 115,731 fetuses) is 46.10% (95% CI 36.88% to 55.46%), representing 53.47% (95% CI 43.42% to 63.37%) of all antenatally diagnosed ultrasound abnormalities. A statistically significant association ($p < 0.001$) was found between the sensitivity of first-trimester ultrasound and the use of an anatomical protocol for screening, with a trend suggesting that the more detailed the protocol, the greater the detection rate. In addition, we conducted a systematic review of all available screening protocols within the literature.

Based on the commissioning brief, our previous work, and input received from our personal and public involvement (PPI) group we developed the following research questions to be addressed in this project:

1. What is the diagnostic accuracy of ultrasound in the early detection of fetal abnormalities?
2. How is first-trimester ultrasound screening currently performed in the UK?
3. How do different screening pathways followed by individual NHS trusts across England impact the timing of fetal congenital anomaly diagnosis?
4. What anatomical protocol should be used for routine first-trimester screening in low-risk and unselected populations? And is there consensus among UK-based sonographers, midwives and doctors on what protocol for the first-trimester scan should be used?
5. What is the best GA to screen?
6. Is there a preferred method of scanning [transabdominal (TA)/transvaginal (TV)]?
7. What are the parental opinions around first-trimester anomaly screening?
8. What are the costs and outcomes of the proposed protocols for first-trimester fetal anomaly screening, compared to current practice?
9. What are EVPI and EVPPI and can these help determine whether there is economic value in undertaking additional future research?
10. If there is value in undertaking additional future research, what should the study design be?

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Chapter 4 Systematic review of the diagnostic effectiveness of early anomaly screening in the prediction of congenital anomalies

Introduction

Women in the UK are currently offered a second-trimester ultrasound screening assessment, under the aegis of the FASP. This scan aims to detect congenital anomalies and specifically to screen for a group of designated conditions including anencephaly, open spina bifida, cleft lip, diaphragmatic hernia, gastroschisis, major cardiac anomalies, bilateral renal agenesis, lethal skeletal dysplasia as well as trisomy 13 and 18.[1,2] Recent studies, however, have shown that a significant proportion of major anomalies can be detected earlier, between 11 and 14 weeks of gestation in both low-risk and high-risk populations.[16–19]

The objective of this study was to systematically review the current literature to determine the screening characteristics of first-trimester ultrasound for the detection of specific, individual congenital anomalies in low-risk, unselected or mixed-risk pregnancy populations. This was done with a view to informing any future first-trimester screening strategy and protocol. The specific aims of this chapter were to understand (1) which anomalies can be reliably detected in the first trimester and expected detection rates, (2) the likelihood of a FP diagnosis and (3) the impact of logistical screening decisions, such as GA, mode of ultrasound and use of an anatomical protocol, on screening outcomes.

Methods

The study protocol for this systematic review and meta-analysis was developed and registered with PROSPERO (registration number: CRD42018111781) prior to undertaking the search, selection of studies and data extraction. The review of all studies included in the meta-analysis and the reporting of results were based on the Meta-Analysis of Observational Studies in Epidemiology, the Synthesizing Evidence from Diagnostic Accuracy Tests guidance and the Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies.[42–45] The Cochrane Collaboration Systematic Reviews of Diagnostic Test Accuracy handbook was also consulted.[46]

The primary outcome was the diagnostic accuracy of two-dimensional ultrasound at 11–14 weeks for the detection of a pre-designated selection of abnormalities comprising acrania/anencephaly, body stalk anomaly, encephalocele, exomphalos, holoprosencephaly, gastroschisis, lower urinary tract obstruction (LUTO) and ectopia cordis. Secondary outcomes were factors that might impact screening performance (see *Statistical analysis* for details). The included anomalies were based on a Delphi consensus procedure (see *Chapter 8*), as well as priorities outlined by the FASP in the UK.

Search strategy

A systematic electronic search strategy was designed with the help of a specialist librarian (N.R.) to identify studies evaluating the diagnostic accuracy of two-dimensional ultrasound in the detection of fetal congenital abnormalities at 11–14 weeks' gestation (see *Appendix 1*). The search was developed initially using free-text terms and subject headings related to prenatal screening, early pregnancy and congenital abnormalities as described previously.[19] In order to increase sensitivity, free-text terms and subject headings for specific congenital anomalies were incorporated. The search was conducted in MEDLINE (OvidSP), EMBASE (OvidSP), Science Citation Index and Conference Proceedings Citation Index-Science (Web of Science Core Collection) and the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) from 1 January 1998 to 17 July 2020. Articles written in a language other than English, single case reports, commentaries, and animal studies were excluded within Endnote X9 after full deduplication of references (N.R.).

Study selection was performed in stages by two independent reviewers (J.N.K. and D.D.). Titles and abstracts of citations obtained from the systematic electronic search were reviewed to identify potentially relevant studies. Full texts were subsequently evaluated to determine their eligibility for inclusion. The reference lists of all eligible studies were screened manually for additional citations not identified by the initial electronic search. Agreement regarding inclusion and exclusion of studies was achieved by consensus between the two reviewers or by consultation with a third reviewer (A.T.P.).

Study selection

Studies reporting on the detection of fetal abnormalities using two-dimensional TV or TA sonography or a combination of both approaches in the first trimester of pregnancy were included. Prospective and retrospective observational studies and randomised controlled trials were eligible for inclusion. Studies evaluating pregnancies with all levels of a priori risk were eligible for inclusion. However, given the context of the work (i.e. population-based screening), only low-risk, unselected or mixed-risk pregnancy populations will be included in this chapter.

Every attempt was made to identify publications from the same research groups that shared screened subjects, and in such cases, only the study judged to be the most relevant to the aims of the present study or the one with the largest cohort was included. Literature reviews, conference abstracts, case reports with fewer than five subjects, editorials, letters, personal communications and non-English language publications were excluded.

The review included studies that focused exclusively on first-trimester ultrasound detection of the pre-designated non-cardiac abnormalities and studies screening for all types of structural fetal abnormalities, as long as (1) the abnormalities of interest were included in the reported cohort and (2) an individual breakdown for each abnormality was reported. Studies that exclusively investigated the use of first-trimester ultrasound for the detection of fetal chromosomal abnormalities were excluded.

Based on the previous work of our group,[19] the reported GA is often not clearly defined in first-trimester screening studies, and the GA interval of 11–14 weeks could be interpreted as 11^{+0}–13^{+6}, 11^{+0}–14^{+0} or 11^{+0}–14^{+6} weeks of gestation. In order to ensure a systematic approach, an a priori decision was made to include all examinations completed within the 14th week (up to 14^{+6} weeks of gestation). Prospective studies were included based on their intention to perform screening prior to 14^{+6} weeks, with the understanding that, in real-life clinical practice, a small proportion of scans may have been performed outside the intended GA window.

The reference standard for determining the accuracy of first-trimester ultrasound assessment was the detection of an abnormality on postnatal or post-mortem examination. Studies that did not state an intention to perform a postnatal or post-mortem examination as part of their aims, for the purposes of confirming first-trimester screening results, were excluded. However, a pragmatic approach was taken: studies that aimed to, but did not always achieve, complete follow-up of their patient cohort were still eligible for inclusion in the meta-analysis. Similarly, post-mortem examination was not a requirement for inclusion of individual cases, as this is not always achievable and depends on parental wishes.

Data extraction

All data-included reviews were derived from tables or main text on two independent occasions from each study to reduce the risk of error in data collection.

For each study, the following variables were extracted: first author's name, year of publication, sample size, GA window at the time of screening, population characteristics, study type, patient recruitment details, healthcare setting, index test (i.e. TV or TA or both), time allocated to ultrasound assessment, the number of sonographers participating in the study and their level of experience, the type of malformations assessed and information regarding postnatal follow-up. Details regarding the ultrasound protocol used by each study and the anatomical structures specifically evaluated were recorded.

Data were extracted to populate 2 × 2 tables and to calculate TP, FP, true-negative (TN) and false-negative (FN) rates to determine the diagnostic accuracy of first-trimester ultrasound for the detection of each of the congenital anomalies which were designated as being of interest.

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Owing to the anticipated heterogeneity of the included studies, considerable efforts were made to ensure that the results from the studies were comparable. In this chapter, only studies reporting non-high-risk populations are included, defined as cohorts of patients described by authors as low risk, unselected or mixed risk. Studies in high-risk populations (by author definition), including those with previously affected pregnancy, personal or family history of anomaly, increased fetal NT, other fetal abnormalities and multiple pregnancies were analysed separately but are beyond the scope of this work.

Defining screen positives

A screen-positive result following anatomical ultrasound assessment in the first trimester might reflect one of three possible situations based on index of suspicion: (1) the diagnosis of a specific anomaly in the first trimester; (2) the suspicion of a specific anomaly in the first trimester; or (3) the finding of an anatomical abnormality of undetermined significance (AUS).

All three situations represent a 'screen positive' test result, and, for the primary analysis, detection rates were calculated regardless of the index of suspicion.

We also recognised that a specific diagnostic 'label' in the first trimester may be modified later in pregnancy. The anomaly initially identified in the first trimester may evolve or may be reclassified. These cases could not be fairly considered as either a TP or a FP and were therefore documented separately as 'a change of first-trimester diagnosis'.

Estimation of false-positive rate and specificity

False-positive rates (and therefore specificity) of first-trimester ultrasound screening are difficult to determine because many fetuses with severe or lethal abnormalities undergo early TOP without post-mortem confirmation.[19] In order to estimate specificity, reported TP results were assumed accurate when these led to TOP, even if post-mortem confirmation was not available. This is consistent with previous studies in this area, although we acknowledge that this practice may lead to under-ascertainment of the FP rate. In order to address this, a subanalysis of individual screen-positive fetuses with subsequent diagnostic confirmation (on postnatal examination or post-mortem) was undertaken.

Quality assessment of studies

Risk of bias and quality assessment was undertaken for all included studies based on the quality assessment of diagnostic accuracy studies (QUADAS-2). This evaluates studies within four key domains: patient selection, index test, reference standard and flow of patients through the study. Each study was graded as having either a low, high or unclear risk of bias for each domain and the first three domains for applicability, based on a series of signalling questions developed specifically for this review (see *Appendix 1*).

Statistical analysis

Meta-analysis of data extracted from eligible studies was performed in two steps. First, summary statistics with 95% CIs were derived for each study for sensitivity, specificity, and positive and negative predictive values of first-trimester ultrasound anomaly screening for the detection of individual anomalies. Second, individual study statistics were combined to obtain a pooled summary estimate using a random-effects model. A Haldane–Anscombe correction was used, in which a value of 0.5 was added to cells in any 2 × 2 table, when required, to avoid a division by zero error. Heterogeneity between studies was estimated using the I^2 statistic. In the meta-analysis for the primary outcome, all patients with any type of screen-positive result (diagnosed or suspected) were included. Pre-planned secondary analyses were then conducted to assess the factors that might impact screening performance in subgroups stratified according to the following: (1) the imaging protocol used for assessment; (2) ultrasound modality (TA vs. TV vs. both); and (3) publication year of the study. The impact of GA at the time of first-trimester screening on test sensitivity was planned but not undertaken due to insufficient data. We made a decision not to undertake a formal assessment of publication bias as, unlike methods to assess publication bias in meta-analyses of therapeutic interventions, assessing publication bias in meta-analyses of diagnostic tests may not be reliable (Sotiriadis, 2016 #2204). Significance was set at $p < 0.05$. All statistical analyses were performed using StatsDirect statistical software version 3.3.0 (StatsDirect Ltd, Altrincham, UK).

Results

The electronic search yielded 4928 citations following removal of duplicates, of which 193 underwent full-text review, resulting in the inclusion of 40 studies reporting on non-high-risk populations (*n* = 416,877 fetuses) in the meta-analysis (*Figure 1*).[11,12,16,47–83]

The included studies were published between 1999 and 2021. Studies were performed in a variety of healthcare settings, although the majority (*n* = 31) took place, at least in part, in either a university hospital or a tertiary-care-affiliated centre (see *Appendix 1*, *Table 28*). Seven studies performed multicentre data collection. Thirty-five studies examined patients in the first trimester using a systematic anatomical protocol (in at least one study cohort). There were six study cohorts included in the meta-analysis where no standardised, routine approach for screening in the first

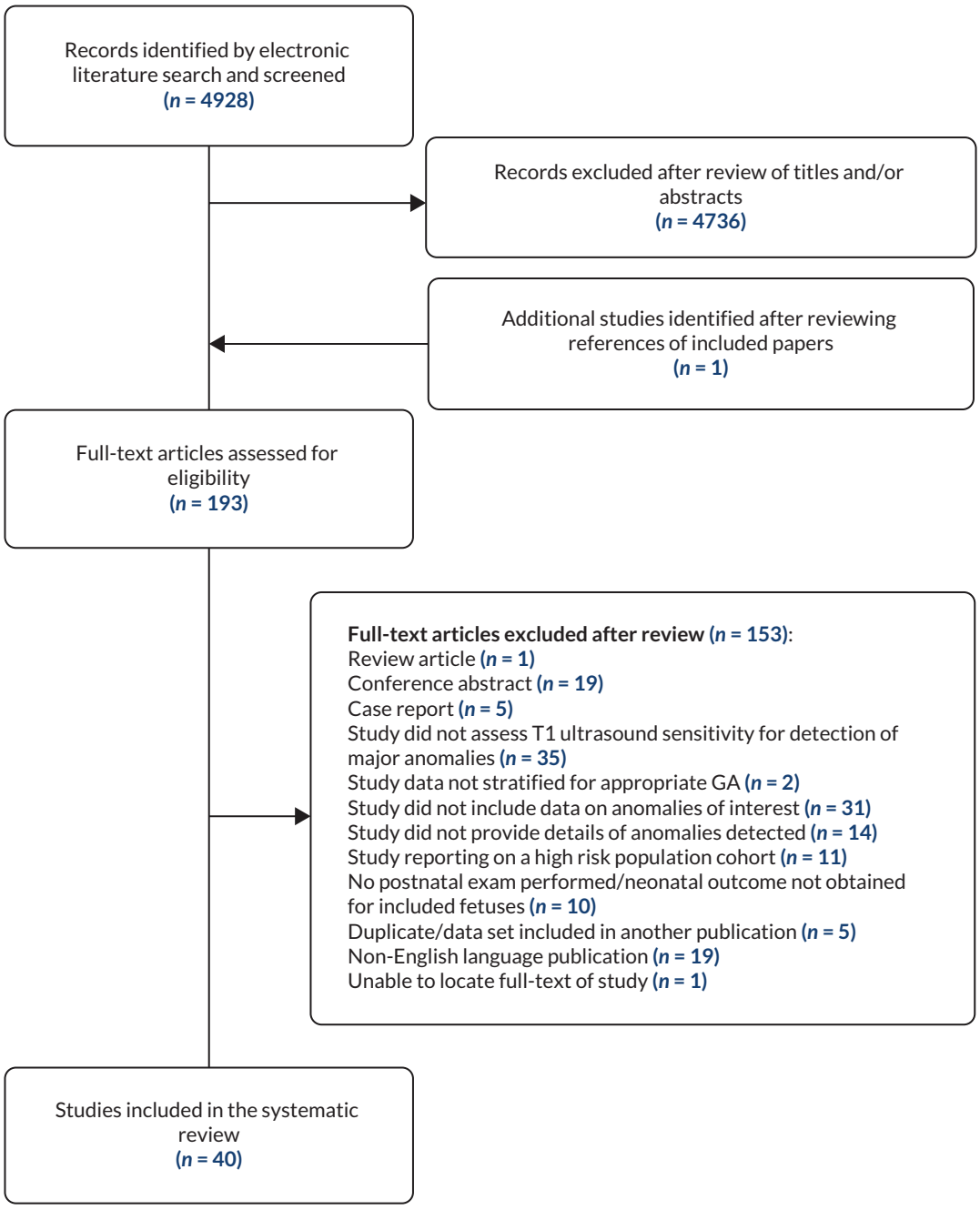

FIGURE 1 Flow chart of search strategy and selection of studies for inclusion in systematic review and meta-analysis. T1, first trimester.

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trimester was reported. The details of the imaging protocols of each study are summarised in *Appendix 1*, *Table 29*. The methodological quality assessment of included studies is summarised in *Appendix 1*, *Figures 24* and *25*.

Screening performance for major abnormalities (composite)

In non-high-risk populations, a total of 416,877 fetuses were screened and a combined 1128 anomalies belonging to 1 of the 8 targeted anomalies were identified, yielding a prevalence of 0.25% (fixed-effects model, 95% CI 0.24% to 0.27%). Of these, 1068 were detected on first-trimester ultrasound, while the remaining 60 were not detected; a further 49 cases were FP. Based on the pooled analysis, first-trimester ultrasound screening had a sensitivity of 93.29% (95% CI 90.37 to 95.71%) (see *Figure 2*), specificity of 99.99% (95% CI 99.98% to 99.99%) and positive predictive value (PPV) of 96.54% (95% CI 93.27% to 98.76%).

Screening for individual major anomalies

Screening performance of first-trimester ultrasound for each of the eight individual major anomalies is shown in *Table 1*. For five of these anomalies (acrania, exomphalos, gastroschisis, body stalk anomaly and ectopia cordis), the first-trimester sensitivity was well above 90%. For encephalocele and holoprosencephaly, reported pooled detection rates were just below 90%. The sensitivity for the detection of LUTO in the first trimester was approximately 65%.

Factors affecting screening performance

Imaging protocol

Studies included in the review were classified into two groups based on whether a formal anatomical protocol was used for first-trimester screening. Detection rates from studies using a formal anatomical screening protocol (n = 35 study cohorts) were compared against those which did not report a standardised screening approach (n = 6 study cohorts) (see *Appendix 1*, *Table 29*). Our analysis demonstrated no significant differences in pairwise comparisons using a chi-squared test (and/or Fisher's exact test, where appropriate) for the combined detection of the eight anomalies (p = 0.1583) or for the first-trimester detection of the individual anomalies, with the exception of screening for holoprosencephaly (see *Table 1*).

Ultrasound mode

An evaluation of the impact of mode of ultrasound was also assessed. The vast majority of studies used a combination of both TA and TV (n = 31; 387,081 fetuses), while a minority of studies used solely TA (n = 6; 15,351 fetuses) and three studies did not report on the mode of ultrasound used for screening (see *Appendix 1*, *Table 28*). Fisher's exact test showed no statistical difference when comparing detection rates of the two modalities (p > 0.99).

Publication year

Analysis by year of study publication (≤ 2004, 2005–9, 2010–4, ≥ 2015) in the non-high-risk population group demonstrated improved screening sensitivity with increasing years of publication (p < 0.0001).

Discussion

The eight anomalies investigated as part of this systematic review were a combination of those prioritised by the UK FASP and those selected by a Delphi consensus (see *Chapter 8*) to be a diagnostic focus for the 'basic' first-trimester anatomy protocol offered routinely to low-risk and unselected women presenting for care. In this review, we have shown that 93.29% of fetuses affected by one of these eight anomalies were identified within the first trimester of pregnancy, with a screening specificity of 99.99%. These findings support the feasibility of introducing screening for these eight anomalies to routine first-trimester ultrasound practice and highlight the impact that such a policy would have on the GA at which these anomalies are diagnosed.

One of the key objectives of this review was to understand the likelihood of parents facing a FP result following first-trimester screening. Our best estimate based on available data, is that the FP rate for these conditions remains low and this is consistent with findings from several individual studies examining this issue. Within our review, there were 49 reported FP cases identified, of which 47 were described as findings of bowel-only exomphalos on first-trimester

TABLE 1 First-trimester sensitivity and specificity for the detection of eight pre-designated major anomalies in all studies, in those not using a formal anatomical protocol and in those using a formal anatomical protocol for screening

	All				No protocol		With protocol		
Anomaly	Prevalence (per 10,000)	T1 sensitivity (%)	T1 specificity (%)	FP (*n*)	Studies (*n*)	T1 sensitivity (%)	Studies (*n*)	T1 sensitivity (%)	*p*-value
Acrania/anencephaly	8.87 (6.78–11.25)	98.26 (96.57–99.39)	100.00 (100.00–100.00)	0	6	93.13 (77.85–99.84)	28	97.96 (96.10–99.23)	0.6409
Exomphalos	6.74 (4.96–8.79)	94.73 (91.17–97.41)	99.99 (99.98–100.00)	47	3	75.75 (21.53–99.66)	25	95.68 (92.75–97.88)	0.1911
Gastroschisis	3.00 (2.36–3.72)	95.64 (91.54–98.43)	100.00 (100.00–100.00)	0	4	91.02 (66.78–100.00)	19	95.95 (91.77–98.69)	0.6422
Body stalk anomaly	1.85 (0.90–3.14)	98.51 (95.62–99.89)	100.00 (100.00–100.00)	0	1	100.00 (2.50–100.00)	12	98.59 (95.74–99.91)	ND
Holoprosencephaly (alobar, semilobar and not defined)	3.42 (2.15–5.00)	88.20 (79.75–94.60)	100.00 (100.00–100.00)	0	2	41.96 (2.89–99.97)	20	91.75 (86.15–96.00)	0.0152
Encephalocele	1.55 (0.96–2.28)	89.94 (81.63–95.95)	100.00 (100.00–100.00)	2	1	100.00 (15.81–100.00	16	89.90 (81.40–96.02)	0.6953
LUTO	1.28 (0.71–2.01)	65.70 (55.66–75.08)	100.00 (100.00–100.00)	0	1	50.00 (1.26–98.74)	12	66.13 (55.96–75.59)	0.6128
Ectopia cordis		93.26 (76.03–99.98)	100.00 (100.00–100.00)	0	1	100.00 (2.50–100.00)	4	93.94 (76.11–99.98)	ND

ND, analysis not performed; T1, first trimester.

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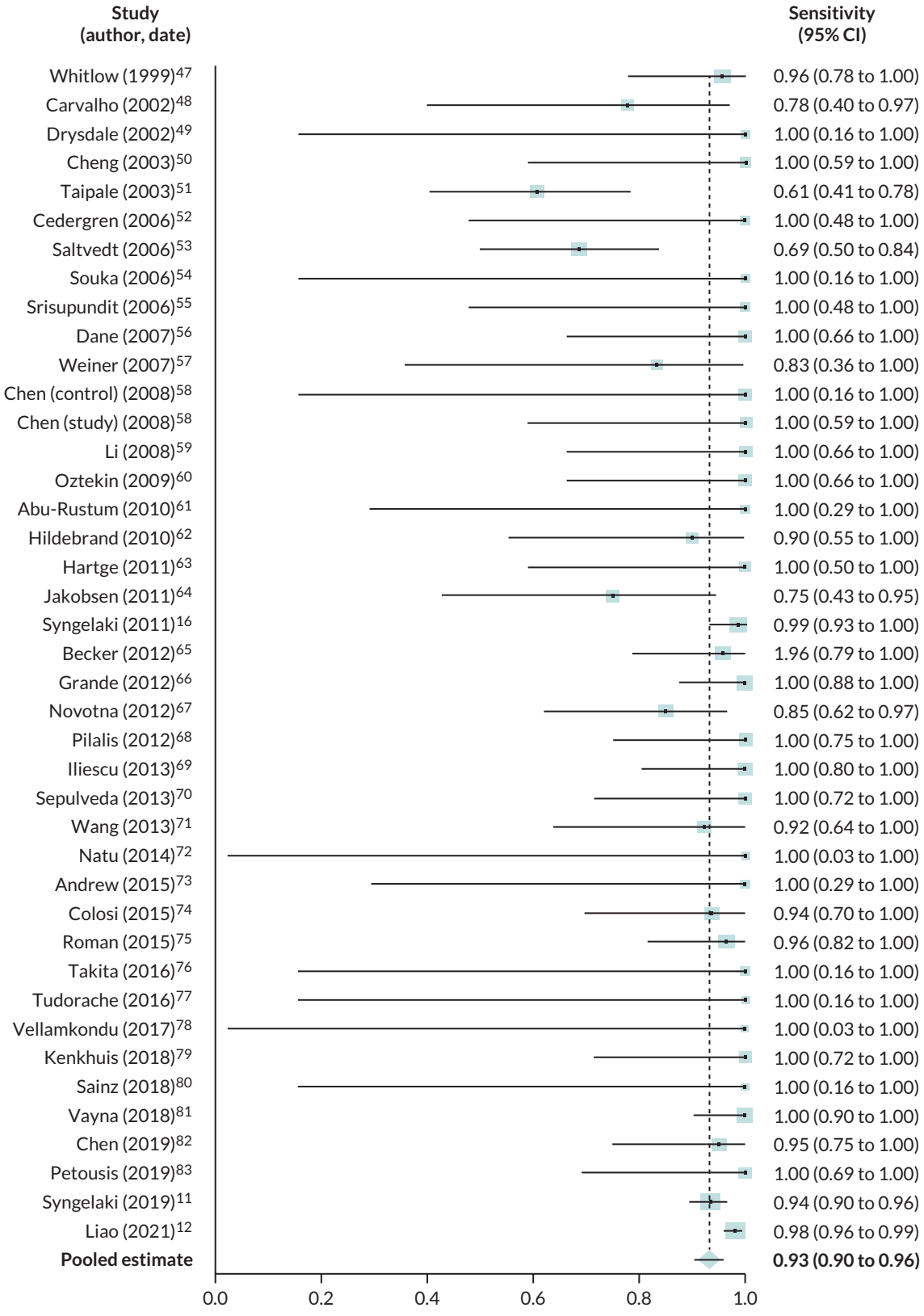

FIGURE 2 Forest plot of sensitivity of first-trimester ultrasound for the detection of eight pre-designated major anomalies by study (see text for details). I^2 = 49.8% (95% CI 23.1% to 64.4%).

ultrasound in euploid fetuses which were labelled as having subsequently 'spontaneously resolved'. It is widely accepted that anomalies will often evolve throughout pregnancy and that a significant proportion of bowel-only exomphalos and megacystis (≤ 15 mm) cases identified in the first trimester in euploid fetuses will be found to have resolved on scan at a later GA. It is not clear whether these cases should formally be considered to be 'FPs', although they have been classified as such for the purposes of this review.

First-trimester ultrasound findings need to be placed in context for patients and the implications of an abnormal finding are not fixed. In the case of bowel-only exomphalos and megacystis diagnosed in the first trimester, healthcare providers should be well informed of the possible fetal outcomes to provide parents with appropriate counselling regarding the natural history of these pathologies.

Screening for individual major anomalies

The first-trimester detection rates for seven of the anomalies in question (acrania, exomphalos, gastroschisis, body stalk anomaly, holoprosencephaly, and ectopia cordis) exceeded 85% of cases, with fetuses affected by LUTO identified in 65% of cases.

There were considerable challenges in determining the first-trimester screening characteristics for the detection of LUTO. LUTO is an umbrella term encompassing a series of different conditions with varying aetiologies, which may include obstructive uropathy, distended and/or dilated bladder, posterior urethral valves, urethral atresia, megacystis micro-colon and cloacal plate dysgenesis. These anomalies were specifically included in the development of the search strategy (see *Appendix 1*) and through the process of data extraction, though the complex and varying terminology across different studies may have resulted in some cases being missed from inclusion in the review. It is widely acknowledged that a first-trimester diagnosis of LUTO will be made on the basis of a finding of megacystis, which is a sonographic sign identifying an enlarged bladder with a longitudinal length > 7 mm in a sagittal plane. Megacystis in the first trimester (in particular of length > 15 mm) suggests a severe form of LUTO, allowing early identification of these fetuses. Megacystis in the first trimester is also strongly associated with chromosomal aneuploidy (in particular in those with bladder length between 7 mm and 15 mm). In those fetuses with normal karyotype and an enlarged bladder between 7 mm and 15 mm, the most likely outcome is spontaneous resolution of the megacystis without any long-term residual impact on fetal outcome. Thus, the finding of megacystis is a sonographic marker which allows for the stratification of fetuses at high risk of structural or chromosomal anomaly but does not in itself, represent a congenital abnormality. In this review, the detection rate for megacystis was 65.70% (95% CI 55.66% to 75.08%) based on 84 cases of LUTO reported. It should be noted, however, that our data collection identified an additional 92 cases of first-trimester fetal megacystis for which no formal diagnosis or outcome was reported (i.e. spontaneous resolution of megacystis, diagnosis of a progressive LUTO and/or confirmation of abnormal fetal karyotype). A proportion of these fetuses may have been affected by LUTO, but could not be included within the review due to a lack of available information. The first-trimester screening characteristics in this study represent our best estimate based on the available literature, but we encourage future study authors to provide more transparent reporting around the outcomes of fetuses affected by megacystis to allow more accurate screening statistics to be ascertained.

Strengths and limitations

The primary strength is the size of the cohort of 416,877 fetuses, screened in the first trimester of pregnancy. The study was undertaken using a prospective and registered protocol and involved manual and detailed data extraction. It focused on screening outcomes from women presenting as low-risk or unselected pregnancies for antenatal care and therefore is representative of a patient population presenting for routine care.

Our review does have some expected limitations. It should be noted that the majority of the studies included within this review were undertaken within tertiary-care centres and by the most experienced sonographers. As a result, our findings likely represent the highest level of care and may not reflect outcomes achievable in routine, daily practice. There may also be an element of publication bias by authors wishing to publish positive findings. Evaluation of the studies using the QUADAS-2 tool found that most studies had 'high' or 'unclear' risk of bias in relation to the index test, reference test, study flow and timing. Methodologically speaking, an ideal study design for evaluating first-trimester anomaly screening would involve population-based screening which avoids the referral bias seen in tertiary-care centres; blinding of sonographers to patient history; non-disclosure of ultrasound findings to avoid treatment paradox;

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post-mortem analysis of every pregnancy loss or termination and blinding of neonatal assessors to antenatal ultrasound results. Clearly, such a rigorous examination of first-trimester anomaly screening would be very challenging to achieve in practice and unlikely to be considered ethical. Nevertheless, it is important to recognise the limitations of the data available within the existing literature.

The vast majority of the studies evaluated used a protocol which examined at a minimum, basic anatomical structures such as the fetal head, abdomen, cord insertion and bladder. Previous work has shown that use of such structured anatomical protocols is associated with higher detection rates. In our analysis, other than for holoprosencephaly we did not show a difference in detection rates between centres using a screening protocol and those that did not. However, the vast majority of included studies used a standardised protocol, making subgroup comparison analysis less robust. In addition, given the severity of the conditions assessed here, it is plausible that many are identifiable even to those not following a structured anatomical evaluation. Relevant information can be inferred from Chen *et al.* (2008), the only randomised control trial (RCT) included within the review. In this study, over 8000 women were randomised to receive either a basic dating scan at 10–14^{+6} weeks (control) or a detailed anomaly scan at 12–14^{+6} weeks (study group). Within the control group, major anomalies were diagnosed in the first trimester, though these were primarily lethal conditions such as anencephaly, body stalk anomaly and amniotic band syndrome, which is in keeping with our findings. An analysis of the study group showed that, in addition to these lethal conditions, a large number of severe anomalies such as holoprosencephaly, spina bifida, and major cardiac anomalies could also be identified after a detailed, protocolised scan in the first trimester.

The impact of mode of ultrasound on first-trimester fetal anomaly detection was another secondary outcome. The vast majority of studies within this review (n = 31) used a combination of TA and TV ultrasound, making a meaningful comparison against those using only TA (n = 6) difficult to achieve. The findings, however, suggest that for these eight conditions, there were no significant differences between those centres using only TA compared with those using a combination of both TA and TV. Studies examining visualisation of fetal organs in the first trimester suggest that the modalities offer advantages and disadvantages, and it is likely that a patient-tailored approach will yield the highest detection rates.

Conclusion

In this systematic review, we evaluated the use of first-trimester ultrasound for the detection of eight anomalies of interest (acrania/anencephaly, body stalk anomaly, encephalocele, exomphalos, holoprosencephaly, gastroschisis and LUTO). First-trimester anatomical ultrasound has the potential to identify over 90% of these conditions with high specificity and at an earlier GA than is our current standard of practice.

Chapter 5 Systematic review of the diagnostic effectiveness of early anomaly screening in the prediction of fetal cardiac anomalies

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Presentations

Data in this chapter were presented at the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) World Congress (October 2019).

Publications

Karim JN, Bradburn E, Roberts N, Papageorghiou AT; ACCEPTS study. First-trimester ultrasound detection of fetal heart anomalies: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2022;**59**(1):11–25.

Karim JN, Papageorghiou AT. Cardiac anomaly screening in the first trimester – a systematic review and meta-analysis of ultrasound sensitivity and factors impacting detection. *Ultrasound Obstet Gynecol* 2019;**54**(S1):289–9.

Introduction

Congenital cardiac abnormalities are the most prevalent structural malformation, affecting 8 per 1000 fetuses. While the majority of these abnormalities are minor, 3 per 1000 fetuses suffer from severe forms of cardiac pathology.[85,86] The associated mortality remains high, with recent research linking congenital cardiac abnormalities to over 50% of all infant deaths in England.[86] Importantly, the risk of morbidity and mortality of these neonates may be impacted favourably by prenatal diagnosis.[87–91]

The detection of cardiac abnormalities represents a distinct challenge for prenatal screening, and most occur in patients deemed to be at low a priori risk.[92,93] In many countries, the gold standard involves a second-trimester evaluation of cardiac anatomy. However, there is widespread variation in how this screening is performed, and detection rates vary due to different factors, such as the anatomical views routinely obtained and sonographer training.[93–96] Specialist prenatal echocardiography can diagnose at least 80% of all congenital cardiac abnormalities, but during routine second-trimester screening a large proportion of them are still missed.[95]

Reports of successful fetal echocardiography in the first trimester were first described over 30 years ago.[97–100] Since then, cnsiderable improvements in technology have fuelled increasing interest in early anomaly detection.[5,16,18,19] As in the second trimester, routine first-trimester screening for cardiac anomalies varies between centres and may involve any of the following: an assessment without cardiac examination beyond demonstrating a heartbeat; routine visualisation of the four-chamber view; detailed examination involving outflow tract visualisation and Doppler evaluation or early risk stratification of patients using, for example, NT, tricuspid regurgitation (TR) or ductus venosus (DV) measurements. Thus, there is little international consensus as to how first-trimester cardiac anatomy assessment should be performed routinely.[3,101,102]

Apart from the value of detecting a cardiac abnormality in itself, the finding is associated independently with fetal aneuploidy, genetic conditions and additional extracardiac malformations.[103,104] Thus, the first-trimester detection of

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cardiac abnormalities is complementary to the overarching objective of diagnosing chromosomal abnormalities earlier and will often constitute an indication for invasive prenatal testing rather than screening using cell-free DNA.

The aim of this chapter was to determine the diagnostic accuracy of two-dimensional ultrasound at 11–14 weeks' gestation in the detection of fetalfoetal cardiac abnormalities and to evaluate factors that impact the screening performance.

Methods

The study protocol for this systematic review was developed and registered with PROSPERO (registration number: CRD42018112434) prior to undertaking the search, selection of studies and data extraction. The review of all studies included in the meta-analysis and the reporting of results were based on the same methodology as previous systematic reviews undertaken for this report (see *Chapter 4*).

The primary outcome of this systematic review was the diagnostic accuracy of two-dimensional ultrasound at 11–14 weeks for the detection of major cardiac abnormalities. Secondary outcomes were factors that might impact screening performance (see *Statistical analysis* section for details).

Search strategy

A systematic electronic search strategy was designed with the help of a specialist librarian (N.R.) as previously described (see *Chapter 4*), to identify studies evaluating the diagnostic accuracy of two-dimensional ultrasound in the detection of fetal cardiac abnormalities at 11–14 weeks' gestation (see *Appendix 1*). The search was conducted from 1 January 1998 to 17 July 2020. Study selection and full-text evaluation were performed in stages by two independent reviewers (J.K. and E.B.).

Study selection

Studies reporting on the detection of fetal cardiac abnormalities using two-dimensional TV or TA sonography or a combination of both approaches in the first trimester of pregnancy were included. Studies evaluating pregnancies with all levels of a priori risk were eligible for inclusion in the review; however, only the results from low-risk, mixed-risk or unselected pregnancy populations will be included in this chapter, as this is most relevant to the question of population screening. Prospective studies were included based on their intention to perform screening prior to 14^{+6} weeks.

The review included studies that focused exclusively on first-trimester ultrasound detection of cardiac abnormalities and also studies screening for all types of structural fetal abnormalities, as long as cardiac abnormalities were included in the reported cohort and an individual breakdown for each cardiac abnormality was reported. Studies that exclusively investigated the use of first-trimester ultrasound for the detection of fetal chromosomal abnormalities and those that evaluated sonographic markers of cardiac abnormalities, such as raised NT, TR and abnormal DV flow, were excluded.

The reference standard for determining the accuracy of first-trimester cardiac ultrasound assessment was the detection of a cardiac abnormality on postnatal or post-mortem examination. Studies that did not state an intention to perform a postnatal or post-mortem examination as part of their aims, for the purposes of confirming first-trimester screening results, were excluded. However, a pragmatic approach was taken: studies that aimed to but did not always achieve complete follow-up of their patient cohort were still eligible for inclusion in the meta-analysis. Similarly, post-mortem examination was not a requirement for inclusion of individual cases, as this is not always achievable following TOP.

Data extraction

Data extraction was performed using the same methodology as for the previously reported systematic review (see *Chapter 4*).

Manual counting of each cardiac abnormality was undertaken and recorded separately from the number of affected fetuses. This was done to enable the assessment of screening characteristics of individual cardiac conditions. For example, if one fetus was affected by atrioventricular septal defect and coarctation of the aorta, we would be able to distinguish between a scenario in which both abnormalities were identified on first-trimester ultrasound (two TP abnormalities diagnosed; one affected fetus identified correctly in the first trimester) and one in which only the

atrioventricular septal defect was identified on first-trimester ultrasound, with the coarctation of the aorta detected only postnatally (one TP diagnosis and one FN diagnosis; one fetus affected by cardiac anomaly identified correctly in the first trimester). The exception to this procedure was in the case of a known cardiac syndrome, such as tetralogy of Fallot (TOF), which was considered as one major cardiac anomaly. In addition, a number of studies described the diagnosis of a 'complex cardiac defect', which was not defined further, and this was considered as 'one major cardiac abnormality' for the purposes of this study.

The commonly used definition of a major cardiac abnormality as a malformation assumed to be lethal, or requiring surgery or interventional cardiac catheterisation during the first year of postnatal life, was followed. Anomalies that are not considered to be structural in nature, but which may require treatment, such as pericardial effusion, hydrops and fetal heart block, were excluded.

Defining screen positives

A screen-positive result following cardiac anatomical ultrasound assessment in the first trimester might reflect one of three possible situations based on index of suspicion: (1) the diagnosis of a specific cardiac anomaly in the first trimester; (2) the suspicion of a specific cardiac anomaly in the first trimester; or (3) the finding of an anatomical AUS following assessment of the four-chamber view or the outflow tracts (e.g. ventricular and/or outflow tract disproportion or unclear spatial relationship of the vessels).

All three situations represent a 'screen positive' test result, and, for the primary analysis, detection rates were calculated regardless of the index of suspicion. As the different screen-positive situations may lead to different patient counselling, management and follow-up strategies, all cardiac anomalies were recorded as diagnosed, suspected or classified as 'AUS', and TP/FP rates were also calculated separately.

We also recognised that a specific diagnostic 'label' in the first trimester may be modified later in pregnancy. The anomaly initially identified in the first trimester may evolve (e.g. progression of severe aortic stenosis to hypoplastic left heart) or may be reclassified [e.g. a ventricular septal defect (VSD) that is subsequently found to be part of TOF]. In this situation, the fetus was identified correctly as having a major cardiac anomaly, but the initial diagnosis was revised. These cases could not be fairly considered as either a TP or a FP and were therefore documented separately as 'a change of first-trimester diagnosis'.

Estimation of false-positive rate and specificity

False-positive rates (and therefore specificity) of first-trimester ultrasound screening are difficult to determine because many fetuses with severe or lethal abnormalities undergo early TOP without post-mortem confirmation.[19] In order to estimate specificity, reported TP results were assumed to be accurate when these led to TOP, even if post-mortem confirmation was not available. This is consistent with previous studies in this area, although this practice may lead to under-ascertainment of the FP rate. In order to address this, a subanalysis of individual fetuses that were assumed screen-positive and which subsequently received diagnostic confirmation on either post-mortem or postnatal examination was undertaken.

Quality assessment of studies and statistical analysis

Risk of bias, quality assessment of studies and statistical analysis were performed as described in *Chapter 4*, using a questionnaire developed especially for this review (see *Appendix 2*).

In the meta-analysis for the primary outcome, all patients in both population groups with any type of screen-positive result (diagnosed, suspected or AUS) were included. This allowed us to determine the overall performance of first-trimester ultrasound in the detection of major cardiac abnormalities in high-risk and non-high-risk populations. For the purposes of the primary analysis, a major cardiac anomaly detected in the first trimester that subsequently changed to a different major cardiac anomaly was considered a TP.

Pre-planned secondary analyses

Pre-planned secondary analyses were then conducted to assess the factors that might impact screening performance for major cardiac abnormalities in subgroups stratified according to the following: (1) the imaging protocol used for cardiac assessment, such as four-chamber assessment only, addition of colour flow (CF) Doppler and examination of

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outflow tracts; (2) ultrasound modality (TA vs. TV vs. both); (3) publication year of the study; (4) the index of diagnostic suspicion, with cardiac abnormalities diagnosed, suspected or classified as AUS. For all types of cardiac abnormalities, a secondary analysis was conducted according to the type of individual cardiac anomaly. For this subanalysis, an a priori decision was made to perform meta-analysis only when at least 10 cases of a specific anomaly were present in the pooled sample. The impact of GA at the time of first-trimester screening on test sensitivity was planned but not undertaken due to insufficient data.

All statistical analysis was performed using StatsDirect statistical software version 3.3.0.

Results

The electronic search yielded 4108 citations following removal of duplicates, of which 223 underwent full-text review, resulting in inclusion of 67 studies[11,16,47,52,54–56,58,59,61,63–69,71,73,74,76–82,99,105–143] reporting on 328,214 fetuses in the meta-analysis (see *Figure 3*). Forty-nine studies[11,16,47,52,54–56,58,59,61,63–69,71,73,74,76–82,105–123,141–143] reported on non-high-risk populations (*n* = 306,872 fetuses), while 18 studies[100,124–140] assessed high-risk women (*n* = 21,390 fetuses). Only the results from non-high-risk pregnancy populations will be included in this chapter (see *Appendix 2*, *Table 30*).

The included studies were published between 1998 and 2020. Studies were performed in a variety of healthcare settings, although the majority took place, at least in part, in either a university hospital or a tertiary-care-affiliated centre (see *Appendix 2*, *Table 30*). Five studies performed multicentre data collection. The methodological quality assessment of the included studies is summarised in *Figures 4* and *5*. The details of the imaging protocols of each study are summarised in *Appendix 2*, *Table 31*.

Screening performance for major cardiac abnormalities

In the non-high-risk population, a total of 306,872 fetuses were screened and 1445 major cardiac anomalies were identified, yielding a prevalence of major cardiac anomaly of 0.41% (fixed-effects model, 95% CI 0.39% to 0.43%). Of these, 767 were detected on first-trimester ultrasound, while the remaining 678 were not detected; a further 43 cases were FP. Based on the pooled analysis, first-trimester ultrasound screening had a sensitivity of 55.80% (95% CI 45.87% to 65.50%), specificity of 99.98% (95% CI 99.97% to 99.99%) and PPV of 94.85% (95% CI 91.63% to 97.32%) (see *Table 2* and *Figure 6*). Abnormalities diagnosed in the first trimester represented 63.67% (95% CI 54.35% to 72.49%) of all antenatally diagnosed major cardiac abnormalities (*Table 2*).

TABLE 2 Screening performance of first-trimester ultrasound imaging in the detection of major cardiac abnormalities in non-high-risk populations

Fetuses screened (*n*)	306,872
Studies included (*n*)	45
Total number of major cardiac abnormalities (*n*)	1445
TP (*n*)	767
Sensitivity [%, (95% CI)]	55.80 (45.87 to 65.50)
Specificity [%, (95% CI)]	99.98 (99.97 to 99.99)
PPV [%, (95% CI)]	94.85 (91.63 to 97.32)
Proportion of all antenatally detected major cardiac abnormalities[a] [%, (95% CI)]	63.67 (54.35 to 72.49)

a Proportion of all major cardiac abnormalities identified antenatally (i.e. excluding anomalies detected postnatally) detected on first-trimester ultrasound.

Note
The values reflect the global detection rate calculated and refer to any screen-positive result following cardiac anatomical assessment in the first trimester based on the index of suspicion: diagnosis of a specific major cardiac abnormality, suspicion of a specific major cardiac abnormality or detection of an abnormality of unknown significance in the four-chamber or outflow tract view.

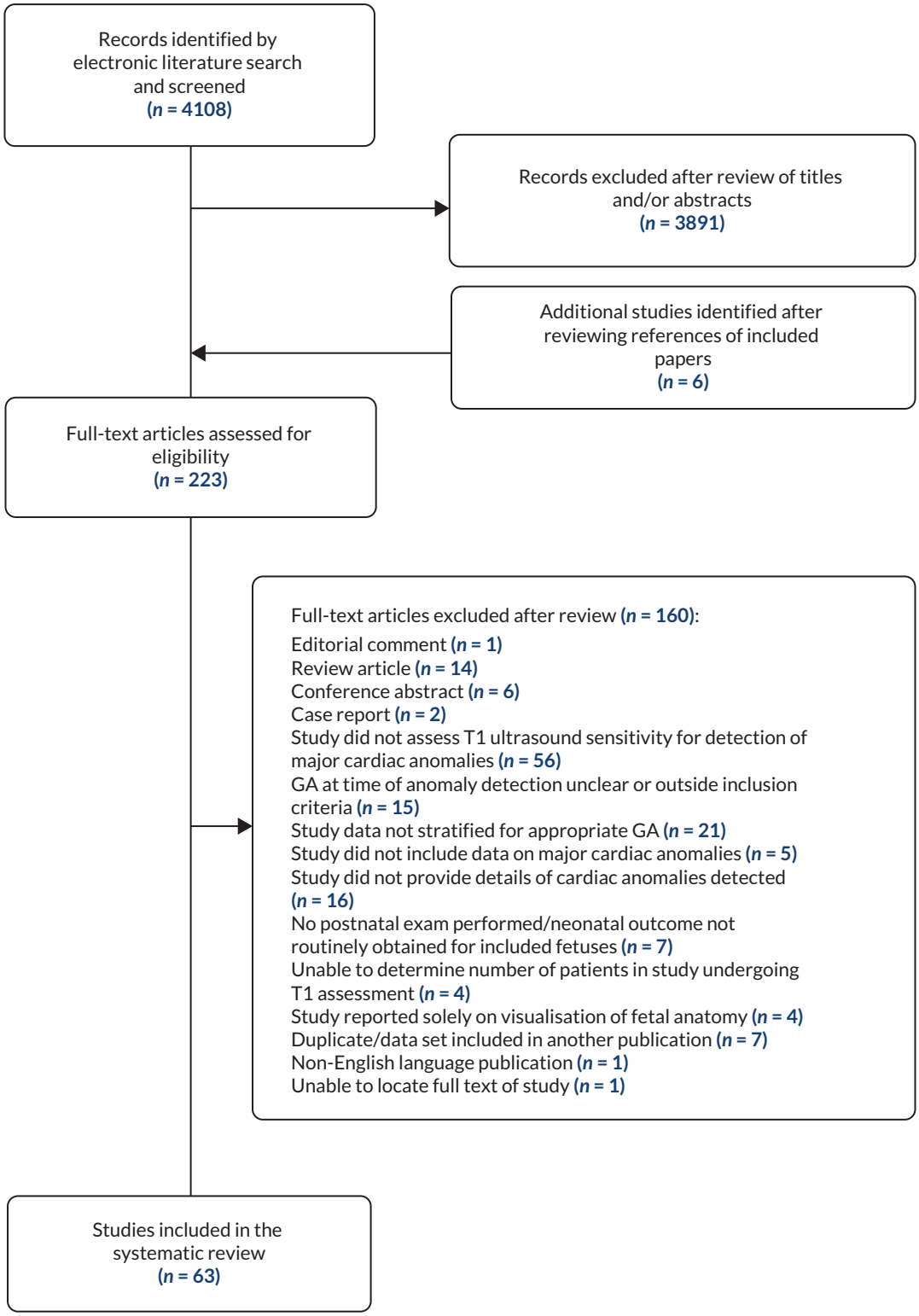

FIGURE 3 Flow chart summarising search strategy and study selection in systematic review and meta-analysis of first-trimester ultrasound screening for major fetal cardiac abnormalities. US, ultrasound.

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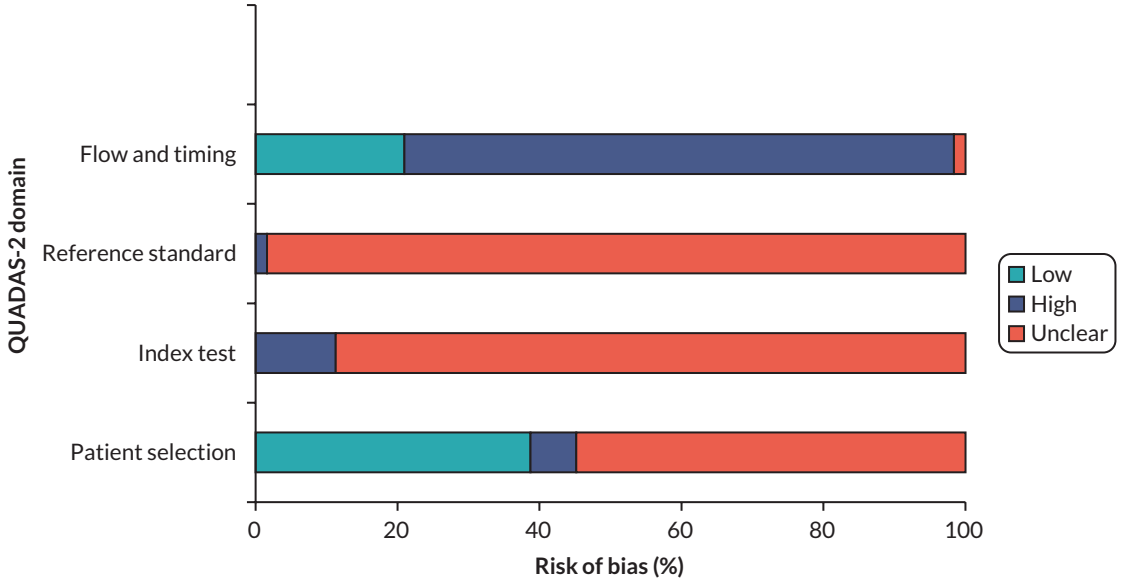

FIGURE 4 Quality assessment of studies included in systematic review, for risk of bias based on QUADAS guidance.

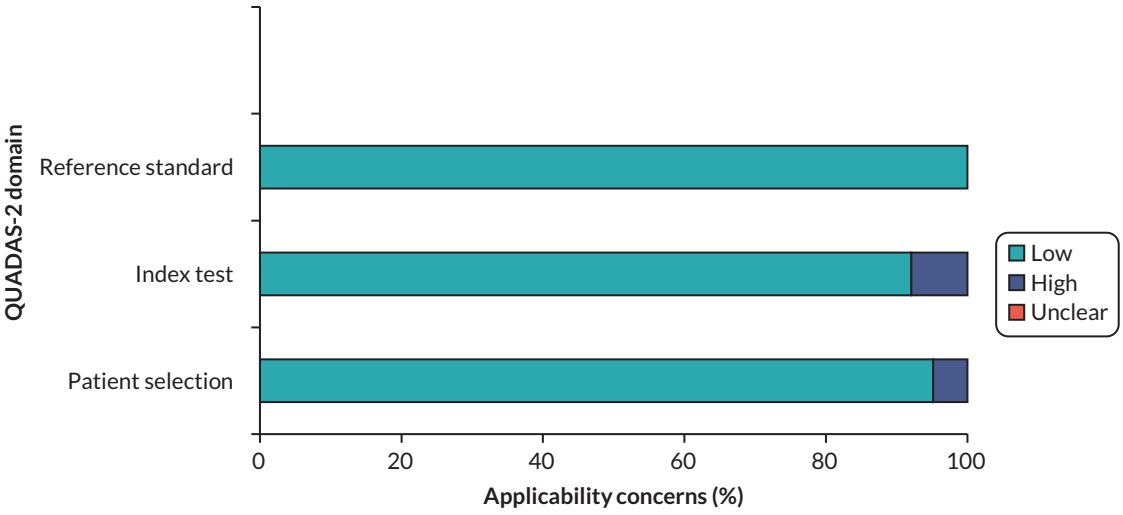

FIGURE 5 Quality assessment of studies included in systematic review, for study applicability based on QUADAS guidance.

On analysis per fetus (26 studies, 99,621 fetuses), 340/585 fetuses with a major cardiac abnormality were identified on first-trimester ultrasound [pooled sensitivity, 63.78% (95% CI 51.21% to 75.45%), pooled specificity, 99.98% (99.97% to 99.99%)].[16,47,52,56,59,63,69,71,77,78,80,106–120,123]

Of the 699 major cardiac anomalies that were diagnosed (*n* = 683) or suspected (*n* = 16) on first-trimester ultrasound and assumed to be TP, 155 (22.17%) were confirmed by post-mortem or postnatal examination (see *Appendix 2*, *Table 32*).

Factors affecting screening performance

Imaging protocol

Studies were classified into five subgroups, according to the imaging protocol used: (1) systematic protocol not reported; (2) assessment of the four-chamber view without CF Doppler; (3) assessment of the four-chamber view with CF Doppler; (4) assessment of the four-chamber view and at least one outflow tract view (OTV) without CF Doppler;

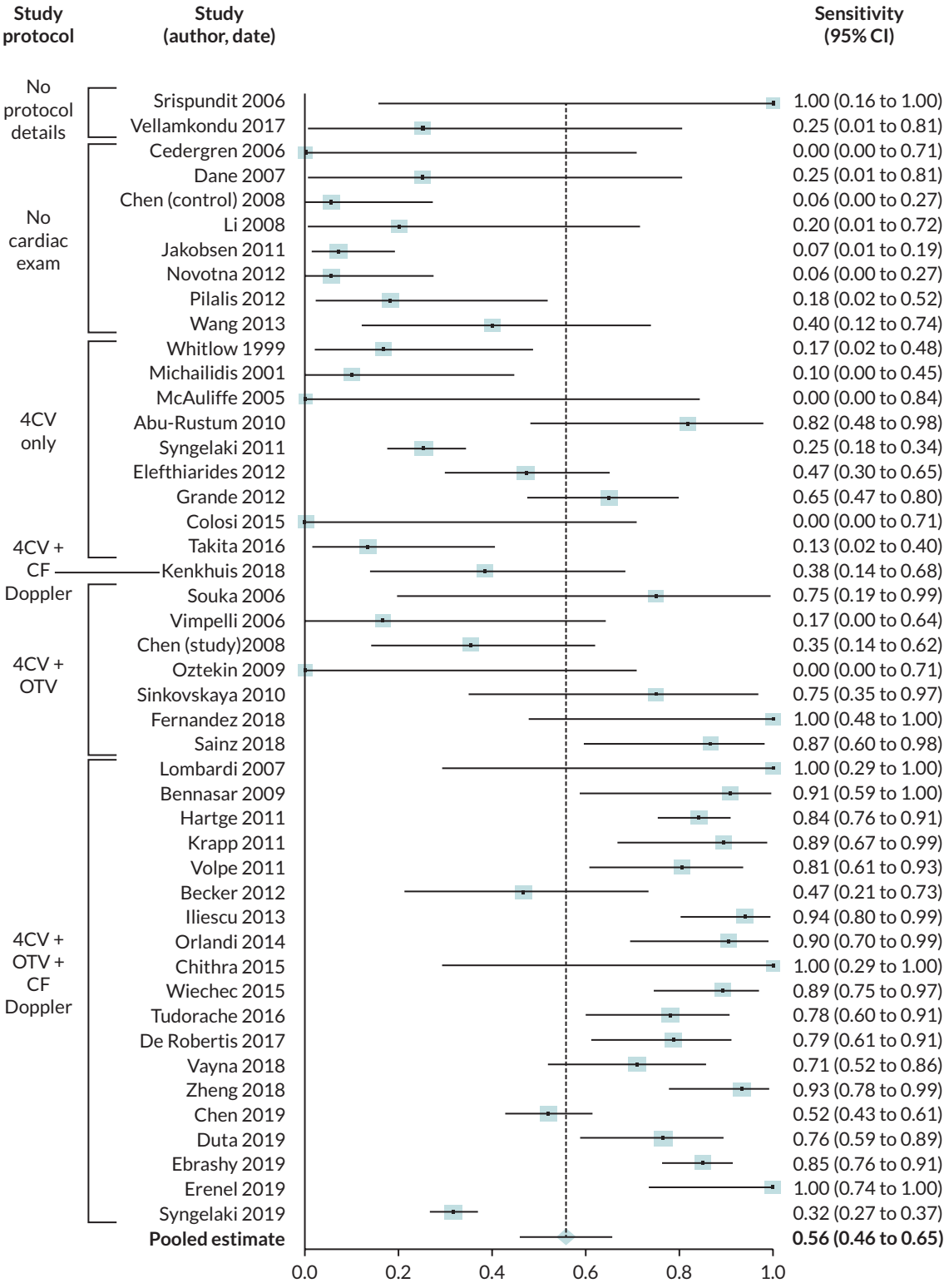

FIGURE 6 Forest plot of sensitivity of first-trimester ultrasound in the detection of major fetal cardiac abnormalities in non-high-risk populations, which included low-risk, mixed-risk and unselected populations. Only the first author of each study is given. I^2 = 91.8% (95% CI 90.3% to 93.0%). a 'No formal protocol' was defined as the absence of a dedicated ultrasound checklist or a protocol without a dedicated cardiac assessment. 4CV, four-chamber view; OTV, outflow tract view.

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and (5) assessment of the four-chamber view and at least one OTV and CF Doppler examination (see *Appendix 2*, *Table 31*).

Analysis of these protocol subgroups demonstrated significant differences in sensitivity in pairwise comparisons using chi-squared and linear trend testing (both $p < 0.0001$). This analysis showed an increase in first-trimester screening sensitivity with increasing level of detail in the anatomical protocol used (see *Table 3*). Evaluation of at least one OTV and use of CF Doppler in addition to the four-chamber view assessment were associated independently with a significantly higher rate of detection (both $p < 0.0001$) (see *Table 4*).

Ultrasound mode

Evaluation of the impact of the mode of ultrasound was also performed. The vast majority of studies used both TA and TV ($n = 36$; 294,185 fetuses), while a minority of studies used solely TA ($n = 9$; 17,444 fetuses) or TV ($n = 2$; 648 fetuses). Chi-squared test (2 by k) showed no statistical difference when comparing the detection rates of the three modalities ($p = 0.4662$) (see *Table 5*).

Publication year

Analysis by year of study publication (≤ 2004, 2005–9, 2010–4, ≥ 2015) demonstrated improved screening sensitivity with increasing year of publication ($p = 0.0006$).

Diagnostic certainty

Screening performance of first-trimester ultrasound examination according to diagnostic certainty is shown in *Table 6*. In the non-high-risk population, there were 767 anomalies detected on ultrasound, of which 683 were given a diagnosis, 16 were suspected and 68 were considered AUS. Among the cases given a label of (diagnosed and suspected), 10 had a change of diagnosis. Detailed information is provided in *Appendix 2*, *Tables 33–36*.

Screening performance of first-trimester ultrasound for individual cardiac anomalies that affected at least 10 cases was assessed (see *Appendix 2*, *Table 37*). Cardiac anomalies were grouped into those with a detection rate of > 60%, 25–60% or < 25% (see *Table 7*). VSDs were associated with higher rates of FP findings and change of diagnosis compared with other anomalies assessed in the study (see *Appendix 2*, *Table 37*).

Discussion

In this meta-analysis, we show, firstly, that the majority of cardiac anomalies can be identified at the 11- to 14-week scan; secondly, that imaging protocols have an important impact on screening performance, with significantly higher detection rates observed in the studies using OTVs and CF Doppler imaging; and thirdly, that the type of cardiac anomaly under evaluation has a strong impact on detection rate.

In non-high-risk populations, which were unselected or had an a priori low or mixed risk, first-trimester ultrasound assessment identified just over half (56%) of major cardiac abnormalities, which constituted two-thirds (64%) of all anomalies detected antenatally. The PPV of an abnormal first-trimester cardiac assessment was approximately 95%.

Clinical implications

After a first-trimester cardiac evaluation, possible outcomes are (1) the diagnosis of a major cardiac anomaly, (2) the suspicion of a major cardiac anomaly, (3) an AUS, (4) an inconclusive result secondary to inadequate imaging and (5) early reassurance in the context of normal findings. Many studies have concentrated on treating the scan as a diagnostic test. In our analysis, we evaluated the diagnostic accuracy as a screening test, considering women in categories 1–3 described above as screen positive, those in category 5 as screen negative and those in category 4 as 'no-call'. We believe that greater clarity in future reporting will better inform future screening strategies.

If we are to screen in the first trimester, how should this be done? Directly relevant is the finding that use of an anatomical protocol is associated with increased detection of fetal cardiac abnormalities. A 'dose-response'

TABLE 3 Impact of first-trimester imaging protocol on screening performance in the detection of major cardiac anomalies in non-high-risk populations

	Anatomical protocol				
	No formal protocol[a]	4CV only	4CV + CF Doppler	4CV + OTV	4CV + OTV + CF Doppler
Studies (*n*)	8	9	1	7	19
Fetuses (*n*)	35,121	85,287	5534	8033	171,860
Pooled sensitivity (%) (95% CI)	13.51 (7.05 to 21.67)	32.96 (18.18 to 49.71)	38.46 (13.86 to 68.42)	57.54 (31.41 to 81.58)	80.04 (67.94 to 89.84)

4CV, four-chamber view.
a No formal protocol was defined as absence of a dedicated ultrasound checklist or a protocol without a dedicated cardiac assessment. This table includes only studies with protocols available for analysis (see *Table 31*). The protocol was not available in two studies.[55,78]

Note
The chi-squared test (2 by *k*) comparing the five protocol types showed a significant difference in their sensitivity ($p < 0.0001$), while chi-squared test for linear trend suggested a statistically significant increase in screening sensitivity with increasing level of detail in the imaging protocol used ($p < 0.0001$).

TABLE 4 Impact of CF Doppler and OTV on sensitivity of first-trimester ultrasound in the detection of major cardiac anomalies in non-high-risk populations

	Additional value of CF Doppler			Additional value of OTV		
	Without CF Doppler	With CF Doppler	*p*-value[a]	4CV only (± CF Doppler)	4CV + OTV (± CF Doppler)	*p*-value[a]
Studies (*n*)	16	20	—	10	26	—
Fetuses (*n*)	93,320	177,394	—	90,821	179,893	—
Pooled sensitivity (%) (95% CI)	42.49 (28.41 to 57.24)	78.38 (66.39 to 88.32)	< 0.0001	33.79 (20.12 to 49.00)	75.37 (64.31 to 84.95)	< 0.0001

4CV, four-chamber view.
a Chi-squared test (2 by *k*).

TABLE 5 Impact of ultrasound mode on sensitivity of first-trimester ultrasound in the detection of major cardiac anomalies

	Ultrasound mode		
	TA only	TV only	TA and TV
Studies (*n*)	9	2	36
Fetuses (*n*)	17,444	648	294,185
Pooled sensitivity (%) (95% CI)	57.82 (36.72 to 77.53)	57.06 (1.76 to 99.99)	56.13 (45.30 to 66.67)

Note
Data are given as *n* or % (95% CI). Chi-squared test (2 by *k*) showed no significant difference between the three approaches ($p = 0.4662$).

improvement in the detection rate with increasing detail of the anatomical study protocol was seen. The strength of this association, clinical plausibility and similar findings from previous studies further support the notion that this is not a chance finding.[19,144,145] Our data suggest that when undertaking routine screening for fetal cardiac anomaly at 11–14 weeks, an OTV and CF Doppler should be included, as both have a statistically significant impact on the detection rate.

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TABLE 6 Screening performance of first-trimester ultrasound in the detection of major cardiac anomalies, according to diagnostic certainty

	Index of suspicion			
	Major cardiac anomaly diagnosed (Analysis 1)	Major cardiac anomaly suspected (Analysis 2)	AUS in 4CV and/or OTV (Analysis 3)	Studies screening exclusively for AUS of 4CV and/or OTV (Analysis 4)[a]
Studies evaluated	42	9	1	3
Fetuses evaluated	299,075	34,125	5534	7997
Screen positive[b]	698	36	1	75
TP	674	15	0	68
Change of diagnosis	9	1	-	-
FP	15	20	1	7
Pooled sensitivity[c]	51.20 (40.92 to 61.43)	44.60 (15.08 to 76.41)	0.00 (0.00 to 36.94)	83.10 (74.30 to 90.35)
Pooled specificity	99.99 (99.99 to 100.00)	99.96 (99.88 to 100.00)	99.98 (99.90 to 100.00)	99.90 (99.81 to 99.96)
Pooled PPV	96.58 (93.95 to 98.48)	67.81 (27.84 to 96.37)	0.00 (0.00 to 97.50)	91.27 (71.81 to 99.84)

4CV, four-chamber view.

a Studies[44,60,63] in Analysis 4 screened exclusively for abnormalities of the 4CV or OTVs (e.g. ventricular and/or outflow tract disproportion, abnormality of the spatial relationship of vessels, etc.) with the objective of providing a formal and specific diagnosis at a more advanced GA. Therefore, these three studies were excluded from Analyses 1, 2 and 3.

b Number of anomalies identified in the first trimester refers to all screen-positive anomalies that were diagnosed, suspected or labelled as AUS, which included TP and FP diagnoses and cases in which the initial first-trimester diagnosis was subsequently changed.

c For the calculation of sensitivity for diagnosis of major cardiac anomaly, a FN case was defined as any anomaly that was not diagnosed, suspected or labelled as AUS in the first trimester in each study. Similarly, for the calculation of sensitivity for suspected major cardiac anomaly in the first trimester, a FN case was defined as any anomaly that was not diagnosed, suspected or labelled as AUS in the first trimester in each study.

Note

Data are given as *n* or % (95% CI). This table provides a breakdown of screen-positive results obtained by first-trimester ultrasound screening according to the index of suspicion of the sonographer: (1) diagnosis of a specific major cardiac anomaly in the first trimester, (2) suspicion of a specific major cardiac anomaly in the first trimester or (3) finding of an AUS in either the 4CV or the OTV. Screening for individual cardiac anomalies

Barriers to implementation of such protocols include the high level of sonographer training required as well as appropriate allocation of time and use of high-resolution ultrasound equipment. It is likely that the combined impact of these factors contributed to the overall increased detection rates seen in studies with more detailed protocols, although it was not possible to examine this given the limitations of data. Another consideration is the safety of Doppler before 14 weeks,[3,145] although CF Doppler is considered safe at 11–14 weeks as long as reasonably achievable (ALARA) principles are followed.[102,147,148] Studies assessing the use of Doppler during first-trimester cardiac screening have demonstrated that this assessment is consistently feasible with a thermal index and mechanical index well below the maximum levels recommended for practice and that a satisfactory assessment is possible within 3–4 minutes of exposure time, not only for experienced sonographers but also through the learning curve.[149–151] Finding the balance between (demonstrated) benefits of improved diagnostic accuracy and (theoretical) risk needs to be considered when undertaking screening.

There is no consensus on whether TA or TV should be used for primary screening.[18,152] This analysis did not demonstrate a difference in screening performance for cardiac anomalies when comparing TA alone, TV alone or a combination of the two. However, very few studies relied on a single ultrasound modality, with the majority of studies using a

combination of both TA and TV, most commonly beginning with TA followed by TV when visualisation with the former was insufficient. We believe that the choice of ultrasound modality will continue to be tailored to patient preference, clinician expertise and other factors, such as obesity.[153]

Detection of individual cardiac anomalies

It was possible to categorise cardiac abnormalities based on our ability to detect them in the first trimester on ultrasound (see *Table 7*). The variation seen is logical: for some anomalies, for example, stenotic valvular pathologies or narrowing of the pulmonary artery and aortic arch, pathophysiological mechanisms involve gradual changes in utero, meaning that such abnormalities may only be amenable to diagnosis at a more advanced GA or even postnatally.[95,154] For other anomalies, such as VSDs, their size may be below the resolution of ultrasound imaging. It is therefore unlikely that first-trimester ultrasound will ever be able to detect every fetus affected by these types of abnormality. We must acknowledge that the focus of first-trimester screening should be primarily on the detection of anomalies that might

TABLE 7 Screening performance of first-trimester ultrasound in the detection of individual cardiac anomalies in the non-high-risk population

Anomaly	Sensitivity [% (95% CI)]
Detection rate > 60%	
Ectopia cordis	93.26 (76.03 to 99.98)
HRHS	91.65 (77.23 to 99.21)
Tricuspid atresia/dysplasia	88.63 (76.00 to 96.94)
Atrioventricular septal defect	77.24 (63.62 to 88.42)
Truncus arteriosus	76.73 (58.94 to 90.62)
Complex cardiac defect	76.31 (57.46 to 90.92)
Hypoplastic left heart syndrome	73.28 (59.86 to 84.82)
Heterotaxy syndrome	72.59 (55.75 to 86.63)
Single ventricle	71.21 (52.11 to 87.03)
DORV	63.11 (44.90 to 79.59)
Detection rate of 25–60%	
Pulmonary atresia	59.68 (23.63 to 90.53)
TGA	45.05 (29.29 to 61.35)
TOF	40.95 (30.16 to 52.20)
Aortic valve stenosis	38.81 (15.77 to 64.90)
Coarctation of the aorta	37.23 (23.96 to 51.56)
Ebstein's anomaly	25.03 (4.83 to 54.08)
Detection rate < 25%	
VSD	23.92 (14.41 to 34.97)
Atrial septal defect	21.53 (6.78 to 41.66)
Pulmonary valve or artery stenosis	19.45 (8.99 to 32.74)
Rhabdomyoma	4.87 (0.19 to 22.09)

ASD, atrial septal defect; DORV, double-outlet right ventricle; HRHS, hypoplastic right heart syndrome; TGA, transposition of the great arteries; TOF, teralogy of Fallot.

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impact prenatal decision-making and care, as patients affected by those anomalies are the ones who will benefit the most from an early diagnosis. Our review has shown that a comprehensive first-trimester cardiac evaluation can detect a very high proportion of certain cardiac anomalies, including complex cardiac defects, single ventricle pathology, ectopia cordis, heterotaxy, atrioventricular septal defect and valvular atresia.

Strengths and limitations

In this systematic review, we have assessed the totality of the existing evidence regarding the diagnostic accuracy of first-trimester cardiac screening. The study was undertaken using a prospective and registered protocol and involved detailed extraction of individual data on cardiac anomalies. Pre-planned subgroup analyses based on a priori risk of the population group, index of suspicion at the time of scan, anatomical protocol and mode of ultrasound allowed an in-depth understanding of first-trimester cardiac screening and yielded evidence-based recommendations for future work.

Our study had some expected limitations. Many of the studies analysed as part of this systematic review were performed in centres of excellence and often by a small group of highly experienced experts (see *Appendix 2*, *Table 30*). There may also be an element of reporting bias from authors wishing to demonstrate positive results. As a consequence, pooled first-trimester detection rates in this review are comparable (if not higher) to those reported in second-trimester cardiac screening initiatives. This means that our findings reflect the highest standards available in our field, which may not be achievable on a larger scale.[86,95,155–158] Useful data come from one of the largest multicentre studies, involving 476 sonographers, which may provide a more realistic estimate of what can be achieved by a high-quality, first-trimester population-based cardiac screening programme (see *Appendix 2*, *Table 33*).[11] In addition, considerable heterogeneity between the included studies was observed. These were mitigated by subgroup analysis and strict definitions regarding the types of cardiac anomalies included in the analysis. Variation remains among studies in their inclusion and exclusion criteria, sonographer experience, level of detail of postnatal examination, length of postnatal follow-up and outcome reporting. In addition, differences in case-mix between the studies could lead to a positive bias in estimated detection rates. Variation also exists in the nomenclature as defined by individual study authors: for example, hypoplastic right heart syndrome (HRHS), tricuspid atresia, pulmonary atresia with intact septum and univentricular heart may all be overlapping diagnoses. However, we believe this is a secondary issue, as the detection of a cardiac abnormality is more important than the precise anatomical diagnosis. Finally, there is a risk of differential ascertainment of abnormalities. As an example, VSDs may often be too small to detect in the first trimester.[77] When ascertainment is low, two effects will be observed: firstly, this will lead to a lower than expected prevalence of VSD, and secondly a higher overall detection rate will be seen, in contrast to those studies with good ascertainment. Wherever possible we have undertaken analysis stratified by prior risk; and also per anomaly, but cannot exclude the possibility that detection rates are inflated due to under-ascertainment. Nevertheless, this is less likely for major cardiac defects as second-trimester scans and postnatal assessment would be expected to detect the majority. Despite the limitations described above, we believe that the pooled data provided us with the best estimate of first-trimester ultrasound screening performance and the factors that affect it.

An important challenge faced in this study was the determination of FP rates. As with other major anomalies in the first trimester, early surgical termination may preclude post-mortem examination. In this study, we found that only approximately 22% of all assumed TP results had a reported physical secondary confirmation (see *Appendix 2*, *Table 32*), resulting in a relative uncertainty regarding the exact FP rate of first-trimester cardiac ultrasound evaluation. We attempted to quantify this uncertainty by assessing each individual first-trimester cardiac diagnosis in relation to secondary confirmation. A large proportion of the FP cases were cases with low diagnostic certainty [i.e. suspected and AUS cases (see *Table 6*)]. Our best estimate is that the FP rate is low: in the most relevant group (non-high-risk group), there were 674 TP diagnoses, 9 changes of diagnosis and 15 reported FPs. Therefore, only 15/698 (2.1%) diagnoses were FP. This low rate is reassuring, but we call on researchers to report reference tests (post-mortem, subsequent imaging or postnatal examination) clearly and comprehensively in future screening studies, including a clear statement of the proportion of cases in which this was not available.

Conclusion

This study provides strong evidence that first-trimester examination of the fetal heart allows effective stratification by identifying a cohort of fetuses at high risk of a cardiac anomaly. Based on the available data and uncertainty regarding FP rates, the action after a positive screening scan should be expert fetal cardiac ultrasound follow-up. The development of information and support for parents will also be a key consideration. Future first-trimester screening programmes should follow a standard anatomical assessment protocol and recognise that not all anomalies are amenable to detection and that some evolve through pregnancy based on their natural history. Combined with appropriate training and implementation of referral pathways, this would be expected to have an important positive impact on the earlier detection of fetal cardiac anomalies.

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Chapter 6 National survey of first-trimester ultrasound screening practice

Presentations

Data in this chapter were presented to the FASP Bi-Annual meeting (September 2019) and at the ISUOG World Congress (October 2019).

Publications

Karim JN, Pandya P, McHugh A, Papageorghiou AT. Significant variation in practice for first trimester anatomy assessment: results from a nationwide survey [abstract]. *Ultrasound Obstet Gynecol* 2019;**54**(S1):60.

Introduction

The current state of 'what screening already exists' is a crucial piece of information when examining the incremental cost of a change in the screening pathway, and when assessing the feasibility of implementation of protocol-driven screening. In order to gain this information, we undertook a national scoping exercise that identified four broad categories of routine first-trimester ultrasound scans practised in the UK:

1. Basic first-trimester ultrasound: Confirmation that the fetus is alive, accurate dating by measurement of fetal CRL and detection of multiple pregnancy.
2. Basic first-trimester ultrasound and measurement of fetal NT: as above, PLUS screening for chromosomal abnormalities usually in conjunction with first-trimester maternal serum biochemistry.
3. Basic first-trimester ultrasound, measurement of NT and assessment of the fetal anatomy: as above, PLUS purposeful assessment of fetal anatomy with the aim of diagnosing major fetal abnormalities.
4. Detailed fetal first-trimester anatomical ultrasound: often reserved for targeted screening due to a previous abnormality or other risk factor, this is routinely undertaken in some UK centres and includes more detailed anatomical assessment.

Based on these results, the aim of this study was to conduct a nationwide survey of NHS trusts in England to establish how first-trimester ultrasound scan is currently performed.

Specifically, we aimed to:

1. establish current first-trimester ultrasound protocols and policies;
2. explore whether units perform a first-trimester anatomy assessment;
3. determine what resources exist for first-trimester ultrasound and;
4. understand how practices and policies differ between trusts;
5. establish whether first-trimester anatomy scanning is offered irrespective of choice for aneuploidy screening;
6. whether referral pathways exist when an abnormality is suspected (change from the standard antenatal care pathway).

Methods

In collaboration with the Public Health England's (PHE's) Fetal Anomaly Screening Program, a national survey was designed with 36 questions, in the following four domains: current first-trimester ultrasound protocols; local policies; inclusion of an early fetal anomaly scan; and resources (see *Appendix 3*). The format and question style of

the questionnaire was based on previous national surveys of antenatal ultrasound practice commissioned by the UK NSC and FASP ('Ultrasound Survey of England: Mapping of 1st and 2nd trimester fetal screening services in the NHS' in 2002 and update in 2008).[159,160] This was done so staff completing the questionnaire would feel familiar with the approach and ensure consistency.

Questionnaire validation and piloting took place over multiple sequential stages:

1. Document review by core members of the research team.
2. Document review and piloting of survey by a group of research midwives, sonographers and fetal medicine specialists with academic knowledge of the topic and from outside the immediate research team. This allowed the questionnaire to be assessed for face validity and content validity. The questionnaire was completed on multiple occasions by the same individual to ensure reproducibility of results (test–retest reliability). Answers provided by this group were also assessed to ensure inter-rater reliability and internal consistency of the questionnaire.
3. The survey was piloted and validated by JK working with sonographers with an interest in antenatal ultrasound at the British Medical Ultrasound Society's annual conference (Manchester, November 2018; *n* = 17). We asked participants to provide constructive feedback, and analysed data generated from this pilot to ensure understanding of the questions, and maintain consistency with expected results.
4. Final document review and approval by members of FASP (led by AM, PP).

After this piloting was complete the survey was distributed electronically to all NHS maternity trusts in England (*n* = 131) on 25 January 2019. One electronic reminder was sent to all trusts on 12 February 2019 by FASP and we contacted individual trusts with outstanding responses by e-mail in March and April 2019. In cases where first-trimester screening policy was different among units forming part of one trust, we requested a separate questionnaire for each ultrasound department. Survey submission closed in June 2019.

Data were anonymously analysed using descriptive statistics for the group of responding trusts; survey responses from trusts in different regions [as defined by PHE at that time, *n* = 9] were compared using chi-squared tests; responses received from different levels of care (tertiary, secondary, community) were compared using descriptive statistics.

Results

The survey was distributed to 131 NHS trusts currently participating in the NHS Screening programme. There were 118 responses from 110 NHS trusts (response rate 84%), undertaking approximately 445,000 first-trimester scans per year (based on those trusts who provided us with this information). Responses were received from all nine designated PHE regions as defined at the time (see *Figure 7*) and represented a variety of healthcare settings, including district general hospitals (67%), university and academic centres (32%), and tertiary-care units (11%).

Of the responding trusts, 98% suggested they had the capacity and resources to meet current first-trimester screening demands within their units; 94% of units use TA transducers primarily, with an offer of a TV scan when required for improved visualisation, while the remainder offer patients only TA imaging at this gestation.

The survey showed that the majority of units follow current national guidelines: they assess fetal viability, measure CRL and perform NT screening routinely (see *Figure 8*).

National Health Service units performing a first-trimester anomaly scan

We found that 75% of trusts routinely perform some form of first-trimester anatomy assessment (see *Figure 9*): 100% of tertiary-care centres, 80% of university and academic centres and 69% of district general hospitals that responded offer their patients a first-trimester anomaly scan.

Among the units who perform a first-trimester anomaly scan, 64% use a formal anatomical protocol, while 23% of units have a sonographer-dependent protocol. There were variations in the anatomy assessed by each unit (see *Figure 10*) and regional variations in practice (see *Tables 8* and *9*).

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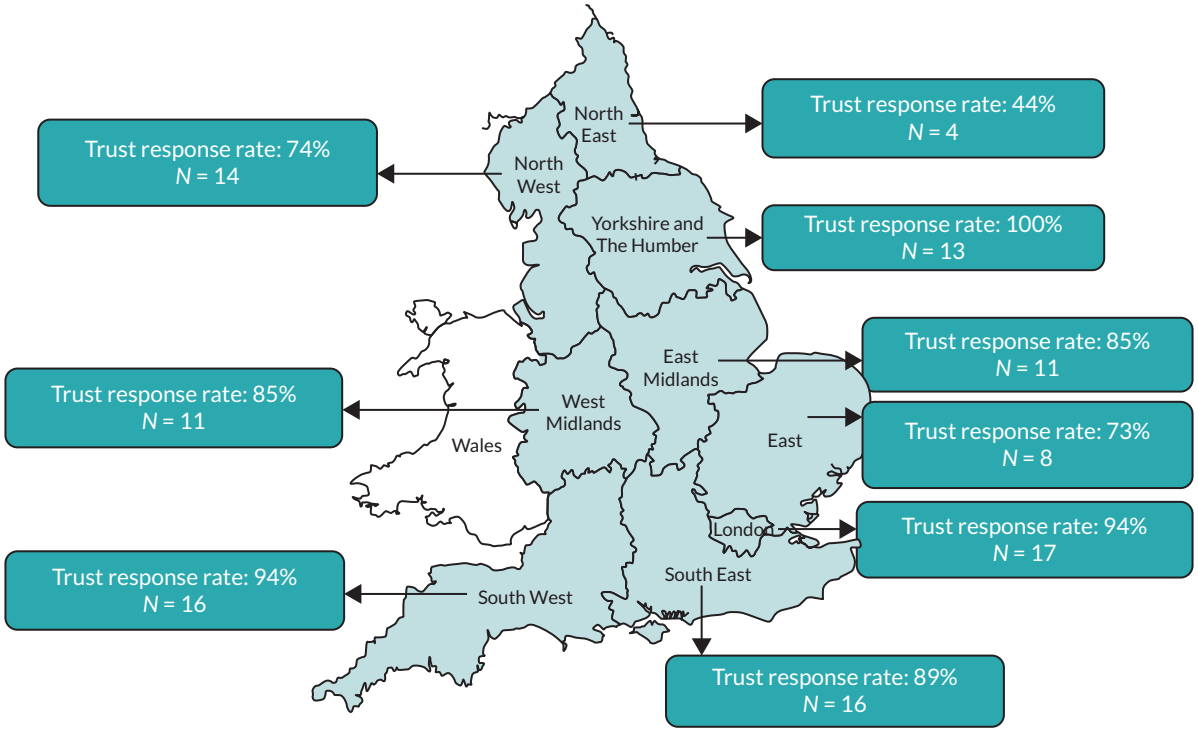

FIGURE 7 Map of England showing nine designated regions as defined by PHE with survey response rates by region. The strongest response rates were in the south of England (South West and South East), East and West Midlands and London (over 75% trusts responded) with the poorest response in the North East England (44%).

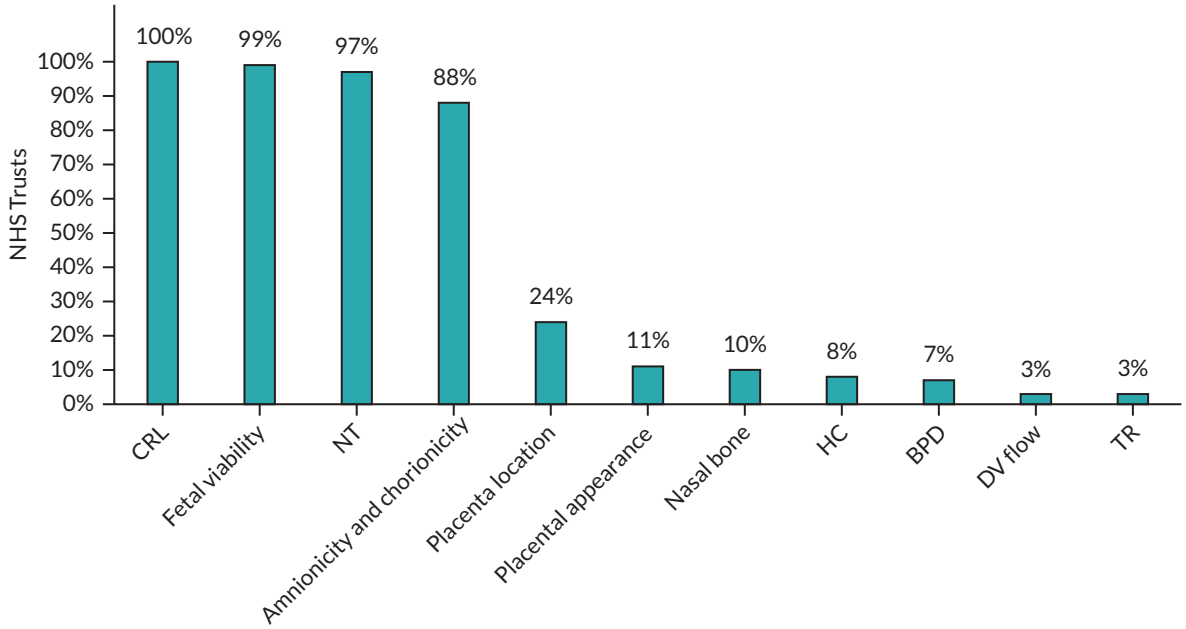

FIGURE 8 Bar chart demonstrating percentage of NHS trusts in England which routinely perform each type of ultrasound assessment in the first trimester of pregnancy. BPD, measurement of bi-parietal diameter.

Results demonstrated that regions where hospitals are more frequently evaluating fetal anatomy are generally more likely to use a formal anatomical protocol when performing their assessment. This can be seen when comparing region A where 88% use a protocol to region 1, where 33% do so.

Logistics of screening

For those trusts undertaking a formal first-trimester anatomy screening approach, in women where this is not possible to complete, a follow-up appointment prior to 18 weeks (to complete the assessment) is offered in 31% of trusts.

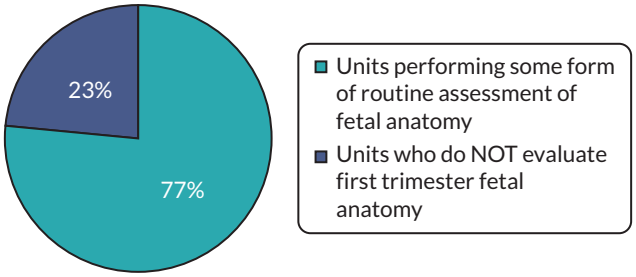

FIGURE 9 Pie chart demonstrating the percentage of NHS units performing some form of routine ultrasound assessment of fetal anatomy in the first trimester of pregnancy.

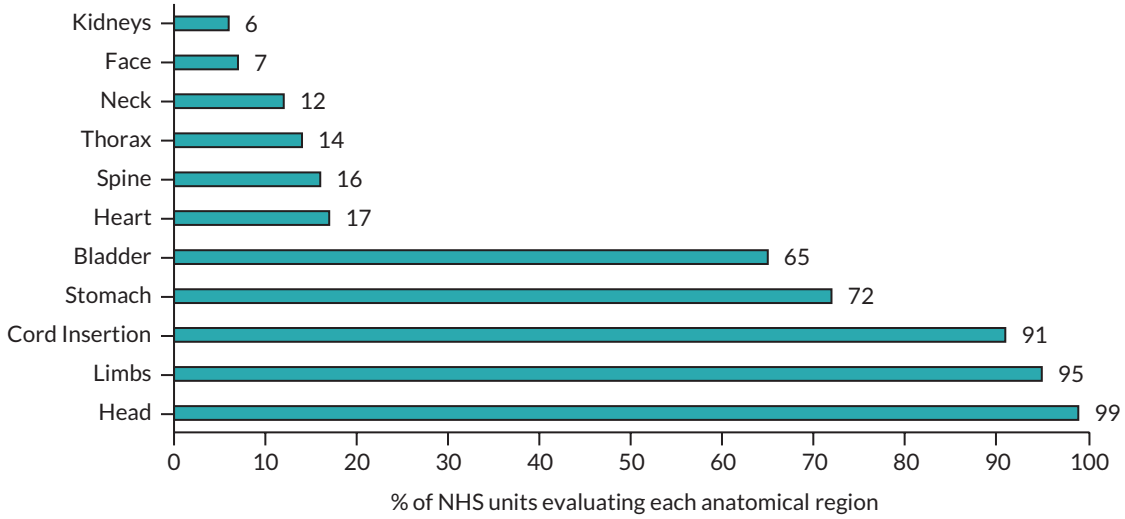

FIGURE 10 First-trimester fetal anatomy assessment performed by NHS units. Bar chart demonstrating the fetal anatomical regions routinely assessed by NHS units using a formal anatomical protocol for first-trimester screening.

TABLE 8 First-trimester fetal anatomy assessment by geographical region (A–I)

	Health region									
	A	B	C	D	E	F	G	H	I	All
Total number of responding hospital trusts in each region (n)	16	17	16	4	11	14	11	8	13	110
Trusts offering early anatomical assessment (n, %)	16 (100)	17 (100)	13 (81)	3 (75)	8 (73)	10[a] (71)	6[b] (55)	4 (50)	6 (44)	83^ (75)
Trusts using a formal anatomical screening policy/ protocol (n, %)	14 (88)	10 (59)	8 (62)	2 (66)	5 (45)	6 (60)	2 (33)	3 (75)	2 (33)	52 (63)

a For one unit in Region D, responses indicated that early anomaly screening was routinely offered with a formal anatomical protocol in use, however this protocol was not made available and therefore could not be assessed. The nine available protocols for Region D were therefore included in the analysis.
b For one unit in Region I, responses indicate that early anomaly screening was routinely offered without a formal protocol in use and this was not made available for analysis. The three available protocols for Region I were therefore included in the analysis. ^Of the 83 units included in this analysis, only 81 protocols were available for analysis.

Note
Table indicating the percentage of trusts offering first-trimester fetal anomaly assessment and the percentage of those trusts who use a formal anatomical screening programme for this purpose. The results from each region (as pre-defined by PHE) are represented anonymously in this table with each region represented by a letter of the alphabet from A to I.

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TABLE 9 Variation in anatomical structures assessed by formal protocol in each geographical region

Anatomical structure assessed by formal protocol	PHE Region									
	A	B	C	D	E	F	G	H	I	All
Head	16 (100)	17 (100)	13 (100)	2 (66)	8 (100)	9 (100)	5 (100)	4 (100)	6 (100)	80 (99)
Limbs	15 (94)	17 (100)	13 (100)	3 (100)	7 (88)	9 (100)	5 (100)	3 (75)	5 (83)	77 (95)
Cord Insertion	16 (100)	14 (82)	13 (100)	3 (100)	6 (75)	9 (100)	5 (100)	4 (100)	4 (66)	74 (91)
Stomach	16 (100)	17 (100)	9 (69)	2 (66)	3 (38)	6 (66)	0 (0)	2 (50)	3 (50)	58 (72)
Bladder	15 (94)	16 (94)	6 (46)	3 (100)	3 (38)	5 (56)	0 (0)	2 (50)	3 (50)	53 (65)
Heart	4 (25)	6 (35)	1 (8)	0 (0)	0 (0)	1 (11)	0 (0)	1 (25)	1 (17)	14 (17)
Spine	4 (25)	6 (35)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (25)	1 (17)	13 (16)

Note
Table indicating which anatomical structures are formally assessed in the first trimester by those units using a protocol in each region. As shown previously, the results from each region (as pre-defined by PHE) are represented anonymously in this table with each region represented by a letter of the alphabet from A to I.

With respect to written pre-scan information for parents (see *Figure 11*), 22% of units have developed a local leaflet specific to first-trimester anomaly screening and 84% routinely distribute to parents the PHE 'Screening tests for you and your baby' leaflet.

In 34% of units, formal sonographer training specific to first-trimester anomaly screening is offered in-house; in 31% of units, sonographers are required to complete an external course for training [e.g. Fetal Medicine Foundation (FMF), Down syndrome screening quality assurance support service (DQASS), etc.].

Storage of ultrasound images is routine in the second trimester; 49% of units store all images related to the first-trimester scan routinely, whereas 21% only store images with suspicious or abnormal findings, 6% do not routinely store any image and 21% allow a sonographer-dependent approach.

A policy for immediate disclosure of suspicious findings was present in 66% of units, while a further 22% refer to a second sonographer within the same unit to confirm findings. Following a suspicious or abnormal finding, 82% of units

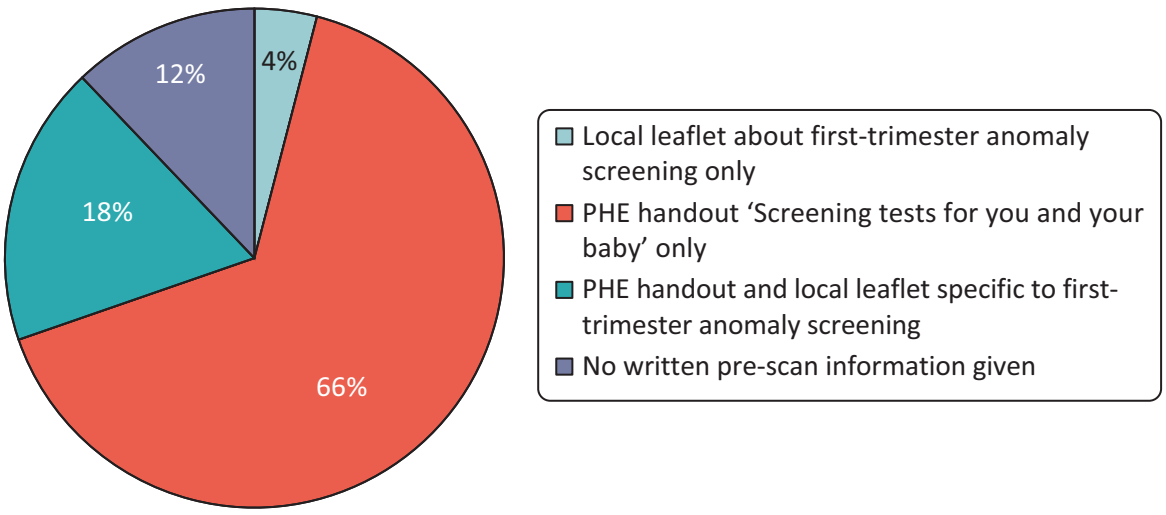

FIGURE 11 Pie chart demonstrating percentage of NHS units performing a first-trimester anatomy assessment who distribute pre-scan written information to parents and the type of information provided.

have a policy for referral to the local fetal medicine unit (FMU). A further 31% will refer to the local obstetrics unit and 2% have no formal referral pathway in place.

Time allocated to the first-trimester anomaly scan

The vast majority of units allocate 20–30 minutes for their first-trimester ultrasound scan appointment, regardless of whether a formal assessment of fetal anatomy takes place and how such an examination is performed (see *Figure 12*). It should be noted that tasks which sonographers are expected to complete within this allocated time, in addition to the ultrasound assessment, vary by unit and may include: pre-test counselling (29%), obtaining informed verbal consent (82%), post-test counselling and disclosure of findings (43%) and other administrative tasks (completing forms, referrals, etc.) (19%).

Policy for women who decline the Combined Screening Test

The majority of units (79%) offer women who decline combined screening a first-trimester scan between 10 and 14^{+1} weeks of GA and 18% will offer one ultrasound scan which may take place at anytime in the first trimester, for assessment of fetal viability and dating with CRL. Of note, 3% of units will not offer a first-trimester scan routinely in this patient group.

Of those who provide patients with a first-trimester scan between 11 and 14 weeks, 11% have a formal policy offering a fetal NT assessment to women who decline the Combined Screening Test. The majority of trusts (96%) have policies in place regarding the disclosure of unexpected and incidental findings on ultrasound in cases where parents have declined this screening.

Open feedback

Responders to the survey (in most cases a screening support sonographer or antenatal and newborn screening co-ordinator), were encouraged to provide open feedback (*n* = 45). Many suggested that a national framework with recommendations for first-trimester anomaly screening standards would be very welcome. Concerns were raised regarding the inequity of service offered to women who present to different trusts within their region and that this might be mitigated by a nationwide strategy for first-trimester anomaly screening. A national framework would also ensure that all sonographers receive clear instructions, adequate training to perform this scan and adequate support when suspicious or inconclusive results occur.

Several concerns were raised regarding the process of patient consent and that parents were not always adequately informed about the nature of their ultrasound assessment. Concerns were also raised regarding a lack of referral pathways, suggesting that women receiving a screen positive result following a first-trimester anomaly scan may not always receive appropriate and timely follow-up.

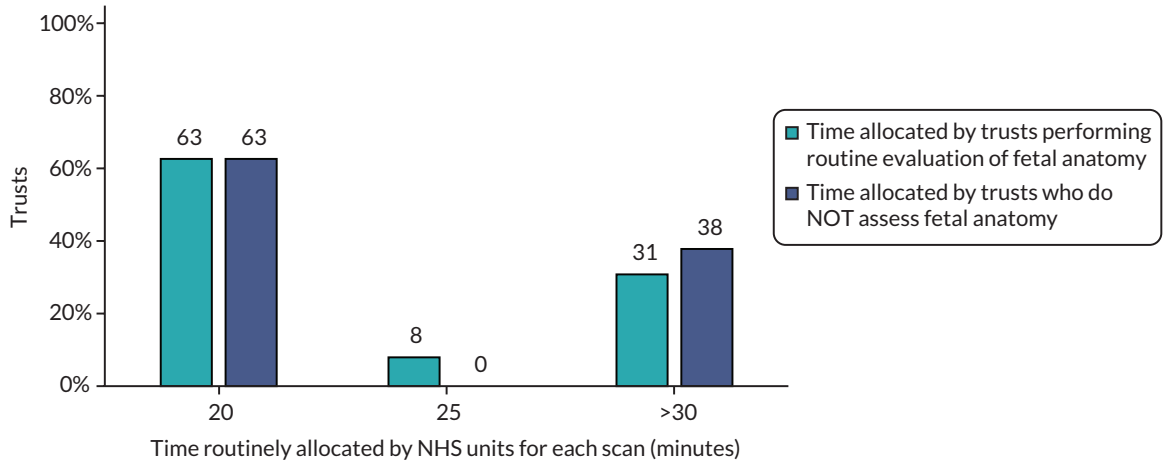

FIGURE 12 Time in minutes routinely allocated by NHS units for the performance of a first-trimester ultrasound scan. Data suggest that units routinely examining first-trimester fetal anatomy can do so in a time slot of 30 minutes or less which is comparable to those units who do not include this assessment.

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Discussion

In this survey, we found that NHS providers follow national first-trimester ultrasound guidance for assessment of fetal viability, GA estimation and measurement of fetal NT as part of combined screening for chromosomal abnormalities. In addition, despite an absence of national recommendations, many NHS trusts perform first-trimester assessment of the fetal anatomy; and most have been able to establish this practice within existing resources (sonographer time, equipment, etc.).

We observed significant variation in practices across England with a large number of units having established independent definitions as to how first-trimester anatomy assessment should be performed within their units. In some cases, anatomical evaluation is dependent on the unit the patient attends, or even the sonographer performing the scan. This results in a lack of consistency even within the same unit.

This evidence suggests significant inequity of care for women in the first trimester, based on the region where they reside. In addition, it is frequently assumed that women who decline screening for chromosomal abnormalities may not want to have first-trimester scans. Thus, they are less likely to receive care in keeping with guidance on assessment of fetal viability and GA estimation, and are also less likely to be offered early pregnancy screening for fetal anatomical abnormalities.

The strength of this study is the high rate of participation of over 80% of NHS trusts in England; and that this was representative throughout the country. Hence, the data have been able to meet the objectives of the study. Although non-responders always remain a limitation, the non-response rate is low. We do not know whether screening leads in trusts that did not respond to the survey may be different to those that did, but it is possible that non-responders had a lower interest in first-trimester anomaly screening; or may be struggling to support first-trimester ultrasound services in their current form. However, even assuming that none of the non-responders undertake any form of first-trimester screening for fetal anatomy still means that this is undertaken in 64%. The data were collected prior to the COVID-19 pandemic, and while there were some changes in antenatal screening pathways during the pandemic, the post-COVID-19 landscape has returned to pre-pandemic practice.

The questionnaire was not designed to request information about how informed consent takes place, which in hindsight would have been useful. The data suggest that over 75% of units do not offer specific first-trimester written pre-scan information to their patients. It therefore remains unclear as to what (if any) information patients are being given and how they are being consented for a process that may be inconsistent, even within the same unit.

Options for early anomaly screening provided to women who decline combined screening also remain unclear.

Conclusions

Our findings clearly demonstrate that a significant proportion of NHS units currently undertake a first-trimester anomaly scan of some form. There are significant variations which can be seen between different trusts; within trusts; and between operators. These differences relate to the type of first-trimester assessment provided to patients; the level of pre-scan information provided; the level of training given to sonographers; and the response to an abnormal result. These findings strongly suggest that there is a degree of ‘ad hoc’ screening, and this supports the need to develop national standards for what first-trimester anatomical assessment is recommended.

Chapter 7 The link between early anomaly screening and detection rates at population level (NCARDRS)

Introduction

The proposed programme of research initially developed in response to this National Institute for Health and Care Research (NIHR) HTA commissioned call relied solely on the systematic review and meta-analysis of published literature, alongside surveys of clinical practice, to understand the potential clinical impact of introducing a first-trimester anomaly scan on antenatal care in the UK. The Nationwide Survey of Practice (see *Chapter 6*) was conducted, with support from FASP, as an exercise to better understand how first-trimester ultrasound is currently practised across England and in essence, to determine a reference point for 'the status quo'. The survey demonstrated that 75% of units already routinely assess fetal anatomy in the first trimester, despite the absence of national policy. There were significant variations in practice between trusts regarding the anatomical structures evaluated in the first trimester, the anatomical image views obtained by sonographers routinely, the amount of time spent on scanning, and the training provided to sonographers. As a result of these findings, our group felt it would be valuable to assess how local policies in individual trusts regarding early fetal anomaly screening have impacted the diagnosis of fetal congenital anomalies in England. Specifically, we wanted to determine whether there was an association between the offer of a first-trimester anomaly scan by trusts across the UK and earlier diagnosis of major fetal anomalies for parents.

The NCARDRS collects data on congenital abnormalities and rare diseases in England (previously under the aegis of PHE, and now under NHS Digital since 1 October 2021).[161] As part of their role, NCARDRS registers and monitors epidemiological information on the prevalence, timing of diagnosis, and outcome of fetal anomaly diagnoses of affected pregnancies (both antenatal and postnatal diagnoses). Reporting of this information to NCARDRS recently became a requirement for all NHS trusts in England in 2017. NCARDRS performs audit at a national level to support the NHS FASP. In this capacity, the organisation provides trust level, regional and national detection rates for the 11 structural conditions audited under the FASP programme and Down syndrome. In addition, the anomaly register collects limited information on the timing of detection for other anomalies as well.

In order to answer the study question, our aim was to link information regarding the first-trimester anatomical screening protocols used by individual NHS trusts (collected as part of the Nationwide Survey of Practice – *Chapter 6*) to data held by NCARDRS on GA of diagnosis for 16 anomalies of interest.

The primary objective of the study was to determine whether NHS trusts currently performing a routine first-trimester anomaly scan are able to provide a larger proportion of patients with an earlier diagnosis (below 16 weeks) when compared to trusts which do not offer this screening. This was achieved by comparing antenatal detection rates between NHS trusts depending on the screening protocol used.

Methods

This is a retrospective study linking data regarding first-trimester anomaly screening protocols obtained from the Nationwide Survey of Practice (see *Chapter 6*) with data collected and held by NCARDRS.

The team from NCARDRS (led by Jennifer Broughan and Nick Aldridge) was initially approached regarding the study objectives with a proposal for collaboration. Over several meetings, the study aims and methodology were further developed with their support. Formal ethics approval was obtained after full review by the North West – Preston Research Ethics committee (21/NW/0173) in March 2021. In addition, approval for the conduct of this research was obtained formally from the National Data Registry (NDR) Project Review Panel on behalf of PHE. Members of the immediate NIHR research group (JK and AP) were granted honorary academic contracts with NCARDRS to facilitate the partnership.

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Data provided from Nationwide Survey of Practice

In order to examine the impact of different screening policies, data from NHS Hospital trusts who responded to the nationwide survey were aggregated into one of four groups based on the reported type of first-trimester anomaly screening protocol used routinely:

1. NHS trusts that do not formally examine fetal anatomy during the first-trimester ultrasound scan (Group A).
2. NHS trusts that perform a basic anatomical assessment (Group B), defined as a formal examination of at least one of the following structures: the fetal head, the fetal limbs and/or cord insertion into the fetal abdomen.
3. NHS trusts that perform an advanced anatomical protocol (Group C), defined as those routinely practising the 'basic' protocol with the additional evaluation of either the fetal stomach and/or the fetal bladder.
4. NHS trusts that perform an extended anatomical protocol (Group D), defined as those routinely perfoming the 'advanced' protocol with the addition of an examination of either the fetal heart, the fetal spine and/or the fetal face. This group included trusts with the most detailed first-trimester screening protocols in the country.

The primary outcome of the study was to determine the proportion of anomalies which are currently identified prior to 16 weeks in England and to compare the early detection rates based on the first-trimester screening protocol used (Group A vs. Group B vs. Group C vs. Group D). Prespecified subanalysis of each type of anomaly was also assessed.

The nationwide survey received 118 responses from 110 NHS trusts. In five cases, the first-trimester protocols in the two units submitting responses from the same trust were identical; in three cases the individual protocols within the same trust were different and for the purposes of this analysis, the most detailed of the two protocols was considered. As a result, each of the 110 ultrasound units with different first-trimester anomaly screening protocols were divided into one of the four groups as defined above.

Data provided from NCARDRS

Data were requested from the NCARDRS database regarding pregnancies affected by the following congenital anomalies (in keeping with the analysis conducted in previous *Chapters 4* and *5*): acrania/anencephaly/exencephaly, alobar holoprosencephaly, encephalocele, exomphalos, gastroschisis, spina bifida, facial clefts (cleft lip and/or palate), congenital diaphragmatic hernia, bilateral renal agenesis, megacystis, lethal skeletal dysplasias, limb reduction defects, HLHS, AVSD, TOF and transposition of great arteries. This list was compiled as a combination of the 12 structural anomalies which are the focus of the current FASP second-trimester screening programme and an additional four anomalies which are considered to be of particular interest to the early anatomy scan.

The NCARDRS analysts (led by NA) extracted available data from the registry on pregnancies in England where one of the fetal congenital anomalies of interest (see above) was confirmed to be present, and either suspected or diagnosed between April 2017 and April 2019. For each pregnancy, the GA at which the diagnosis was first suspected or diagnosed was identified as either: (1) prior to 16 weeks, (2) between 16 and 23^{+6} weeks, (3) after 24 weeks but prior to birth or (4) postnatal (although no postnatally diagnosed anomalies were included in the primary analysis). Pregnancies affected by a fetal anomaly of interest, but where the GA of diagnosis was unknown, were excluded from the analysis. Women who were known to be late bookers (> 112 days GA at time of booking) were also excluded from the data set, as they would not have been offered a first-trimester ultrasound scan as part of their antenatal care.

The NCARDRS team was provided with the list of NHS trusts belonging to each first-trimester protocol group (A, B, C, D). All data were depersonalised by the NCARDRS data analysts; in addition, data were aggregated by first-trimester protocol group prior to being made available to our research group (JK, AP) for analysis. The data provided were restricted to those NHS Hospital trusts who responded to the Nationwide Survey of Practice, as details regarding first-trimester anomaly screening protocols was only available for this group of hospitals.

Analysis of data at individual trust level was not undertaken, as it was felt that the low prevalence of certain anomalies could risk the identification of individual patients. It was thought that this risk would be significantly minimised by keeping the data aggregated in large groups as defined by their scanning protocol, as well as by focusing our analysis on more prevalent congenital anomalies.

Data analysis

First, the prevalence of each anomaly in the study population was calculated using available antenatal and postnatal data in the study population.

The antenatal detection rates prior to 16 weeks (this covers the period of routine screening at 11–14 in addition to referral) and after 16 weeks (until birth) was calculated for each anomaly in the entire data set (i.e. for all included NHS trusts, irrespective of the first-trimester protocol in use). We then repeated this analysis within each protocol group (A, B, C, D): the prevalence of each anomaly was calculated (as above), as were antenatal detection rates prior to 16 weeks and after 16 weeks (until birth) for each anomaly in of the four protocol groups (A, B, C, D).

The primary outcome of the study was to determine the proportion of antenatally detected anomalies which are currently identified prior to 16 weeks in England and to compare the early detection rates based on first-trimester screening practice (Group A vs. Group B vs. Group C vs. Group D). Prespecified subanalysis of each type of anomaly was also assessed using the chi-squared test.

Results

The data extracted by the NCARDRS team over the study period reflect outcomes from an estimated 1,030,224 pregnancies booked in with the NHS trusts in England which were included as part of the study. Data on fetuses affected by alobar holoprosencephaly and/or megacystis are not routinely collected by NCARDRS, and therefore these two anomalies were omitted from any further analysis.

Data were available for analysis of the remaining 14 anomalies. The prevalence in the study population was consistent with the expected prevalence for these conditions based on available data from NCARDRS and European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) (see *Table 10*).

The first-trimester screening protocols of all included NHS ultrasound units (n = 110) were reviewed and on this basis each unit was allocated to one of four protocol groups: Group A (n = 27), Group B (n = 22), Group C (n = 45) and Group D (n = 16).

Within the study population, there were a total of 5895 anomalies belonging to the 14 congenital anomalies of interest. Of these, 1929 fetal anomalies were suspected or diagnosed prior to 16 weeks GA (32.72%).

For the primary outcome, analysis showed that early detections rates for the combined 14 anomalies were lowest in Group A (27.68%), with a stepwise increase in sensitivity in Group B (31.23%), Group C (33.23%) and Group D (40.42%), respectively (*Table 11*). A chi-squared test demonstrated a statistically significant association between the detail level of the protocol and the sensitivity of first-trimester ultrasound for the detection of the 14 fetal anomalies ($p < 0.0001$) with a trend suggesting that the more detailed the protocol, the greater the first-trimester detection rate.

Secondary analysis by type of anomaly could be broadly categorised into three types: (1) anomalies where the majority of affected fetuses are currently identified in the first trimester regardless of whether a formal screening programme is in place, (2) anomalies where detection was higher in centres using a first-trimester anatomical protocol and (3) anomalies which are challenging to detect in the first trimester, even with the use of a formal protocol (see *Table 10*).

Discussion

In this study, we have examined nationally collected data from 110 NHS Hospital trusts on the antenatal detection of fetal congenital anomalies, using the NCARDRS database. Our analysis was centred on 14 major anomalies, of which 12 anomalies are currently a focus of the FASP second-trimester FASP. We found that approximately one-third (32.72%) of these anomalies were detected prior to 16 weeks GA in England. The highest detection rates were seen in those centres performing detailed first-trimester ultrasound scans routinely using formalised protocols (40.42%),

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TABLE 10 Table demonstrating prevalence of each fetal anomaly assessed with the detection rates of these anomalies prior to 16 weeks GA, provided for: those centres using a formal anatomical protocol for first-trimester screening and those without one

Anomaly	Prevalence (per 10,000 births)	Total number of anomalies[a] (*n*)	Anomalies detected prior to 16 weeks by units using NO protocol (%)	Anomalies detected prior to 16 weeks by units using a protocol (%)	*p*-value[b]
Fetal anomalies where detection rates < 16 weeks are high AND formal first-trimester protocol had no statistically significant impact (p > 0.01)					
Acrania	5.94	572	94.87	94.35	0.61
Exomphalos	6.97	653	89.36	86.91	0.53
Gastroschisis	3.27	312	75.90	82.97	0.21
Fetal anomalies where detection rates < 16 weeks were significantly impacted by use of formal anatomical protocol (p < 0.01)					
Encephalocele	1.83	108	25.00	67.85	0.0004
Facial clefts[c]	10.76	982	2.92	18.29[c]	< 0.0001
Spina bifida[c]	6.59	607	12.58	30.36[c]	< 0.0001
Limb reduction anomalies	3.60	193	8.77	43.75	0.0026
AVSD[c]	7.66	654	10.19	42.07[c]	< 0.0001
HLHS[c]	3.48	310	4.11	31.82[c]	< 0.0001
TOF[c]	5.28	479	2.21	20.00[c]	< 0.0001
Transposition of great arteries[c]	4.14	381	0.93	7.27[c]	0.0098
Fetal anomalies where detection rates < 16 weeks are low AND the current first-trimester protocols had no statistically significant impact (p > 0.01)					
Lethal skeletal dysplasias	1.67	147	21.95	21.84	0.58
Congenital diaphragmatic hernia	3.94	365	7.78	13.17	0.41
Bilateral renal agenesis	1.54	132	11.63	12.66	0.93

AVSD, Atrioventricular septal defect
a Total number of anomalies includes anomalies diagnosed in study population both antenatally and postnatally.
b *p*-values resulting from pairwise comparison of centres evaluating first-trimester anatomy using a protocol (groups B + C + D) with those who do not use one (Group A) based on chi-squared test or Fisher's exact test (as appropriate).
c For these anomalies, pairwise comparison was made between those centres evaluating the fetal heart, face and spine (Group D) against those units which do not routinely evaluate these structures (Groups A, B and C).

but a significant proportion of anomalies are also being diagnosed at early gestations in units where no first-trimester anatomy assessment is formally declared (27.68%). In keeping with findings from our previous work,[19] a significant association was demonstrated between the sensitivity of early ultrasound at a population level and the use of an anatomical protocol for screening, suggesting that higher detection rates are achieved in those centres with the most detailed protocols for screening ($p < 0.001$).

Previous studies assessing the types of anomalies detectable in the first trimester have suggested that these can be broadly categorised into one of three groups: conditions that are nearly always detectable in the first trimester, anomalies which have the potential to be diagnosed at early gestations, depending on maternal, fetal, sonographer and equipment factors; and those that are rarely identifiable.[16]

TABLE 11 Table showing details of early detection of 14 fetal congenital anomalies by NHS centres based on the type of first-trimester anatomical protocol routinely used for screening

	First-trimester screening protocol group				
	Group A, no protocol	Group B, basic protocol	Group C, advanced protocol	Group D, extended protocol	All
NHS units included (*n*)	27	22	45	16	110
Total number of anomalies (*n*)	1514	1092	2230	1059	5895
Anomalies detected prior to 16 weeks (*n*)	419	341	741	428	1929
Detection rate prior to 16 weeks (%)	27.68	31.23	33.23	40.42	32.72

Note
A chi-squared test for linear trend demonstrated a statistically significant increase in diagnostic sensitivity with increasing detail of protocol ($p < 0.001$).

The findings from this study largely concur with this suggested model: we show that over 80% of fetuses affected by acrania, exomphalos and gastroschisis are currently being identified prior to 16 weeks GA, with little differences in sensitivity seen in those hospitals using a formal screening approach. This suggests that the vast majority of sonographers and doctors are taking it upon themselves to examine, at a minimum, the fetal skull and the fetal cord insertion during the routine first-trimester ultrasound appointment, regardless of the formal practice undertaken in their trust. Our analysis also identified a further group of eight major anomalies where the use of a formal anatomical protocol resulted in a statistically significant improvement in first-trimester detection rates. These results are consistent with findings from our previous work (see *Chapter 5*, Karim *et al.* 2017)[19] and give us a strong indication of which anomalies would be most impacted by the introduction of a protocolised first-trimester anomaly scan.[19] Of note, among this group the four major cardiac anomaly conditions targeted by FASP as part of their current antenatal screening initiatives, which remain among the most prevalent major anomalies in the UK population and which carry significant morbidity.[161] Finally, detection rates for bilateral renal agenesis, congenital diaphragmatic hernia and lethal skeletal dysplasias across all trusts remained low, regardless of the imaging protocol used. These are anomalies where the small size, evolution through pregnancy and impact on amniotic fluid volumes make them significantly easier to detect at later GAs. This suggests that these anomalies will likely remain a focus of the second-trimester anomaly screening programme and would see little impact from a more formalised first-trimester approach.

There are a number of limitations to the analysis which has been performed by this study. Hospital trusts were divided into one of four groups (A, B, C, D) based on the first-trimester screening protocol used in that centre. We acknowledge that time and skill level required to perform early scans are also linked to the use of protocols, and therefore implementation of protocols alone (without the requisite training and infrastructure) may not result in these sensitivities. Secondly, although the level of detail in the protocols within each of the four groups was broadly similar, anatomical structures routinely evaluated were not exactly the same. As an example, in Group D where the most detailed evaluations of first-trimester anatomy were performed, there remained clear differences in the anatomy assessed: 13 of the 16 trusts routinely examined the fetal heart (and not all using CF Doppler routinely), 12 of 16 routinely assessed the fetal spine and 6 of 16 formally evaluated the fetal face. It should also be noted that we assessed these associations at centre and population level: it is likely that there were differences in training background of individual operators performing the scan.

Finally, the data from the Nationwide Survey of Practice were collected in early 2019 and therefore reflects screening practices at that point in time, whereas the data analysed from NCARDRS ranged from April 2017 to 2019, and we have assumed for the purposes of this study that there was consistency in practice over this 2-year time period in all trusts.

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These limitations would be more critical if the aim of this study was to determine with accuracy the sensitivity of the first-trimester scan in England. Rather, the objective for this work was to explore whether the shift in practice towards early anomaly screening reported in the Nationwide Survey of Practice is being reflected in how and when fetal congenital anomalies are being diagnosed in England. The results suggest that this is in fact the case: despite an absence of formal recommendations, a programme of first-trimester anomaly screening practice is already underway in some centres in England. There is an ad hoc approach to the screening, lacking consistency and standardisation between trusts, but which is having a real-time impact on the diagnosis of fetal congenital anomalies in pregnant women.

Chapter 8 Developing a protocol-based approach for anomaly screening in early pregnancy using a Delphi process

Presentations

Data in this chapter were presented at the ISUOG World Congress 2021.

Publications

Karim JN, Gordijn SJ, Papageorghiou AT. OC18.08: developing a first trimester anomaly screening protocol for the UK: a consensus procedure [abstract]. *Ultrasound Obstet Gynecol* 2021;**58**:54–5.

Introduction

Background

The findings from our Nationwide Survey of Practice (see *Chapter 6*) have indicated that there is presently an ad hoc approach to the assessment of fetal anatomy in the first trimester, resulting in variations in screening performance and unequal access to screening for women across the UK. While all units offer patients a first-trimester ultrasound scan, there is significant variation in practice: some centres undertake no formal anatomical screening beyond measurement of CRL, NT and demonstration of a fetal heartbeat; others perform a basic anatomical evaluation and a proportion undertake a detailed anatomical survey with a scope similar to the second-trimester anomaly scan.

Our previous work has shown that use of a standardised, protocol-based approach for the first-trimester anomaly scan is the most important factor impacting screening performance.[19] Hence, the development of a structured and validated framework for first-trimester anomaly screening would be expected to lead to improvements in screening performance in centres that do not undertake anomaly screening; and offer valuable support for unified care in centres that already offer fetal anatomical assessment. A consistent, protocolised approach across the UK would allow sonographers to receive focused and directed training at a national level; enable the development of auditable standards of practice; facilitate reliable and consistent information for patients; and allow proper informed patient consent. Overall, this would support an equitable approach to care across the UK. This would also enable more robust quality control, data comparisons with other screening programmes and allow data synthesis for scientific analyses.

How should such a protocol be developed? There are broadly three approaches. The first is adoption of an existing screening protocol; however, the large number of reported protocols (see *Appendix 4*, *Table 38*) makes the choice complicated, and may in any case not be applicable to the standard of current ultrasound practice in the UK. The second approach is a top-down decision, usually created by an expert committee; the advantage is that this would be relatively easy to create and likely to be evidence based; however it has potential bias from the 'strongest voices' in any committee and the strongly hierarchical structures of the medical framework. The third option is to use a Delphi consensus procedure, a well-established consensus development method. Its key advantage is that it allows group consensus to be reached with the opinion of each participant given anonymously and with equal weighting, thus avoiding potential bias, particularly where the perceived interests of one stakeholder group may otherwise be favoured over another.[162–164]

As our recommendations needed to be pragmatic, fit-for-purpose and feasible to integrate within the routine screening environment in communities across the country, we opted for the third approach. This method also

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offers a degree of involvement or 'buy-in', ensuring the support of key stakeholders for the implementation of the screening recommendations.

The aim of this work package was to develop a protocol for the technical and logistical aspects of the first-trimester anomaly scan using a modified Delphi consensus methodology and involving healthcare providers from across the UK.

Key objectives

The main objective of this work package was to develop recommendations for practice for the first-trimester anomaly scan and specifically to address the following key questions:

1. What role should first-trimester ultrasound play in fetal anomaly screening in the UK?
2. How should first-trimester anomaly screening be performed?
3. What anatomical views should be routinely obtained?
4. Which fetal anomalies should constitute the minimum targets for diagnosis in a routine setting?
5. How should positive or suspicious findings in the first trimester be followed up?

Our aim was to develop UK recommendations for best practice in the form of (1) a basic protocol, which could be used as a standard by NHS units wishing to offer first-trimester anatomy screening to all women and (2) an extended protocol for women deemed to have a higher chance of fetal anomalies.

Methods

The Delphi process is used to address questions which cannot be answered based purely on empirical evidence and/or where the support of key stakeholders is important for the application of the recommendations.[162–164] It involves a process whereby participants are asked to provide their views on a series of statements in a questionnaire format. The results are analysed anonymously at stakeholder group level, summarised and fed back to participants with increasing detail over several rounds. With each iteration, the participants are allowed to revise their opinion in light of the group feedback until relative consensus has been reached.

This study followed a modified Delphi methodology and was conducted entirely using the online platform RedCap (version 12.4.6) (Vanderbilt, Nashville, TN, USA). A decision by the collaborators' group was made to conduct the procedure virtually as the study needed to take place during the COVID-19 pandemic. It was felt that an online approach would be the most inclusive and would allow as many eligible participants as possible a chance to participate from across the UK. Lay experts and patient representatives were not involved, as the study topic comprised development of a protocol of a technical, medical procedure. The consensus procedure in its entirety, including questionnaire development, data collection and analysis, was conducted with the support of an expert in the use of Delphi methodology for consensus in Obstetrics (Dr. Sanne J Gordijn).[165,166]

Participant selection/panel selection

Previous Delphi consensus procedures in obstetrics and fetal medicine have often limited involvement to 'academic experts in the field'.[165–167] The aim of this work was to produce recommendations which were evidence-based. But equally, it was felt that these recommendations needed to be pragmatic, fit-for-purpose and feasible to integrate within the routine screening environment in communities across the country.

We therefore encouraged participation of UK-based healthcare practitioners with relevant knowledge and experience of how routine antenatal screening is performed on a day-to-day basis; as well as clinicians and academics with experience in first-trimester screening.

Invitations were sent out to a list of UK-based sonographers, midwives and doctors known to have an interest in this subject area, and to the membership of the British Medical Ultrasound Society and the British Maternal Fetal Medicine Society. Contacts were encouraged to further disseminate information regarding the Delphi procedure to UK colleagues. Overall, we aimed for an inclusive approach and supported the participation of all healthcare professionals with an interest in this study from across the UK.

Data collection

The Delphi procedure was conducted entirely online using a secure RedCap server as a platform. Healthcare providers who were interested in the consensus procedure were directed to a website where they were provided with background information and objectives of the study. Prior to completion of the first questionnaire, participants were asked to provide informed consent and a contact e-mail address, so that they could be involved in subsequent rounds of the consensus procedure.

Ethical approval for the study was obtained by the ethical board from the University Medical Centre of Groningen (METc 2020/440) prior to commencement. All data collected from participants were kept confidential, analysed anonymously and in aggregate form. Data were held on a secure server in the Netherlands (University of Groningen) and in compliance with General Data Protection Regulation (GDPR) standards. Participants involved in the study were allowed to withdraw at any time.

Delphi questionnaire

Prior to the commencement of the study, a literature search was conducted from 1998 to 2021 to identify (1) all published first-trimester ultrasound protocols evaluating fetal anatomy (see *Appendix 4*, *Table 38*), (2) a list of anomalies detectable at 11–14 weeks and (3) relevant screening factors (see *Appendix 1* for search strategy). The findings from this review were used as a basis for the development of the questionnaire. The questionnaire was validated and piloted over multiple sequential stages with amendments made to study documents as appropriate at each time point:

1. Document review by membership of the NIHR grant collaborators' group for acceptability of content and wording of questions.
2. Document review and piloting of the survey was undertaken by a group of research midwives, clinical fellows, sonographers and fetal medicine specialists with academic knowledge of the topic and from outside the immediate research team (n = 15). This group was asked to ensure that the information being presented was factually accurate, to ensure the instructions for the procedure and phrasing of questions were clear and to assess the questionnaire for face validity and content validity. A selection of this pilot group was asked to complete the questionnaire on multiple occasions to ensure reproducibility of results (test–retest reliability). Data generated from the pilot were analysed to ensure consistency with expected results. This process was repeated on several occasions as substantive changes were made to the questionnaire prior to the development of the final version.

Data analysis

Pre-defined criteria for the inclusion and exclusion of items in the questionnaire were determined prior to the commencement of the study. In cases where the answer to a question received ≥ 80% support from the entire group, we assumed that consensus was reached and that this item should be included in the future protocol. Items receiving between 60% and 80% support were considered to require further discussion between the panel in a subsequent round. In cases where the answer to a question received < 60% support, we assumed that consensus was reached and that this item should be removed from consideration. Partial responses were included on a per section basis, that is if an entire section of responses was complete, then this was included.

A subgroup analysis of round one results was performed to determine whether there were any significant differences between the responses provided by individual healthcare provider groups (sonographers, midwives/midwife sonographers and doctors, respectively).

Round one

Participants were asked to complete the questionnaire (see *Appendix 4*).

First, participants were asked to provide information on their demographic characteristics, including details of their professional work, level of experience with first-trimester ultrasound and the healthcare setting in which they currently provide care. This was done to allow for a subgroup analysis assessing any key differences in the responses from different stakeholder groups.

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Second, they were requested to address screening logistics for the first-trimester anomaly scan, including their opinion on which mode of ultrasound should be used, the GA window during which screening should be provided, standard referral pathways following the finding of a positive or suspicious results, follow-up policies for patients where fetal anatomy was not adequately visualised and the timing of cell-free DNA testing, for parents wishing to include this as part of their antenatal care.

Finally, they were asked to consider the development of a basic protocol, which could be used as a minimum standard by NHS units wishing to offer first-trimester anatomy screening to all women. They were also asked to produce a more detailed and extended protocol which could be offered to women at high risk of fetal anomalies. As part of this process, participants were asked to identify which women (and which a priori risk factors) should lead to the offer of a more detailed examination of fetal anatomy in the first trimester within the context of standard NHS care. Participants were then provided with a list of fetal anomalies and ultrasound views and for each, they were asked to identify which items should be included as part of a 'basic' and/or 'extended' scan protocol. In order to facilitate the process, the items for participant review were categorised by anatomical region such as the fetal face, abdomen, heart and extremities. After each anatomical section, participants were encouraged to suggest any additional anomalies or ultrasound views to be considered. Suggestions raised by the majority were included for consideration in round two of the procedure.

Participants were instructed to use their routine clinical practice and professional experience to guide their answers to the questions, but also to consider the prevalence and severity of the individual anomalies, their detection rates in the first trimester, the anatomical views which may be required to examine first-trimester anatomy (along with the difficulty and skill level required to obtain these views) and the likelihood of associated inconclusive or FP findings. In order to support this process, a briefing guide was provided at the start of the questionnaire summarising anomalies which may be detectable using first-trimester ultrasound, their estimated prevalence in the UK population and estimated first-trimester sensitivity for detection (see *Appendix 4*).

Round two

Participation in round two of the consensus procedure was only permitted to those individuals who had completed the round one process in its entirety, who were e-mailed a unique, personalised and secure link to the second questionnaire. Reminders were sent 7, 5, 2 and 1 days prior to the closing of the consensus procedure.

In round two, participants were provided with the results of all questions from the round one procedure in a graphical format, with data presented in aggregate and anonymous form and based on the entire group's results:

- For items which had received ≥ 80% support, participants were asked to confirm their agreement with the inclusion of these items in the future protocol.
- In cases where the answer to a question received < 60% overall support, they were asked to confirm the withdrawal of the item from consideration. In cases where individuals felt that the withdrawal of an item was unwarranted, they were given an opportunity to have this item re-evaluated by the group in a future round.
- Participants were asked to reconsider items which had received between 60% and 80% support in round one, taking into account the opinions of their peers. In cases where there were significant differences between the responses provided by different types of healthcare providers, participants were provided with a separate overview of responses by sonographers, midwives/midwife sonographers and doctors and asked to reconsider their opinion on the basis of the results provided.

Data collected from round two of the consensus procedure were analysed in the same manner as for round one. The iterative process of the Delphi consensus procedure was planned to continue until consensus was reached on all key questions relating to the logistics and performance of the first-trimester anomaly scan.

Results

The consensus procedure was completed over two rounds. The designated URL with the introduction to the procedure was accessed on 278 occasions. Consent to participate in the study was obtained from 245 individuals, of which 73 provided partially completed responses and therefore could not be included in the study. Round one of the survey was

completed in full by 172 healthcare providers including sonographers (40%), midwives (15%) and doctors (45%). Details regarding the demographic characteristics, healthcare specialisation and self-reported level of experience of all round one participants are reported in *Table 12*. There was participation in the consensus procedure from every region across the UK. The majority of participating sonographers and midwives currently work in secondary care and/or district general hospitals (71% and 73%, respectively), whereas the majority of participating doctors practise in tertiary-care settings (64%). Most of the participants (87%) currently work in a department which offers some form of routine first-trimester anatomy assessment to women presenting for antenatal care.

Round one

Screening logistics

With respect to the GA for screening, there was a clear consensus in round one with over 80% of the panel agreeing that a first-trimester anomaly scan should be offered from 12^{+0} weeks GA with screening completed by 13^{+6} weeks (or earlier). There was also clear agreement on the mode of ultrasound which should be used for screening (TA ultrasound primarily, with TV ultrasound used if required) and on a policy for the direct referral of patients with a positive or suspicious first-trimester anomaly scan to their local fetal medicine department. The panel was presented with these results in the second round, and asked to confirm their agreement with the inclusion of these recommendations in the final protocol.

The panel was asked about recommendations for fetal heart assessment in cases where a non-cardiac anomaly was diagnosed in the first trimester (and where parents have opted to continue with the pregnancy). Some of the group advised that specialist fetal echocardiography should be performed (20% support), while others considered that a sonographer-led fetal heart assessment would be most appropriate (21%). The majority advocated for a cardiac evaluation conducted by a specialist in fetal medicine (52%), although there was a clear difference in opinion based on stakeholder group: the strongest support for this policy was from midwives/midwife sonographers (70%), with only 58% of doctors and 40% of sonographers in agreement with this recommendation.

TABLE 12 Demographic characteristics of 172 healthcare professionals participating in round one of the consensus procedure

Participant characteristic	*n* (% of total)
Occupation	
Sonographer	69 (40.1)
Midwife	26 (15.1)
Midwife (general)	3 (1.7)
Midwife sonographer	23 (13.4)
Doctor	77 (44.8)
General obstetrician/gynaecologist	13 (7.6)
Fetal medicine specialist	61 (35.5)
Clinical geneticist	2 (1.2)
Level of experience	
Fully qualified	110 (64.0)
Consultant/attending doctor	55 (32.0)
Trainee	7 (4.1)
Healthcare setting of practice	
Primary or community care	6 (3.5)

continued

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TABLE 12 Demographic characteristics of 172 healthcare professionals participating in round one of the consensus procedure (*continued*)

Participant characteristic	*n* (% of total)
Secondary care or district general hospital	93 (54.1)
Tertiary care or FM referral centre	58 (33.7)
Private unit	15 (8.7)
Geographical region of healthcare practice	
England – London	48 (27.9)
England – South East	25 (14.5)
England – South West	23 (13.4)
England – North West	15 (8.7)
England – East Midlands	16 (9.3)
England – East of England	13 (7.6)
England – West Midlands	12 (7.0)
England – Yorkshire + Humber	7 (4.1)
England – North East	5 (2.9)
Scotland	4 (2.3)
Wales	2 (1.2)
Northern Ireland	2 (1.2)
Participants currently practising in a unit which routinely offers a first-trimester anatomy assessment to patients[a]	
Yes	150 (87.2)
No	22 (12.8)
Estimated number of first-trimester ultrasounds performed by participants over the past year	
None	13 (7.6)
< 50	26 (15.1)
50–99	30 (17.4)
100–249	42 (24.4)
250–499	30 (17.4)
> 500	31 (18.0)

a Any form of routine first-trimester anatomy assessment was considered acceptable (even a basic check).

Feedback from panel members suggested that the need for fetal cardiac evaluation is influenced by the non-cardiac anomaly detected. Hence, in the following round, the panel was asked how the fetal heart should be assessed after a first-trimester finding of (1) a non-cardiac, non-lethal fetal anomaly which has known associations with cardiac pathology (e.g. exomphalos) and (2) a non-cardiac, non-lethal fetal anomaly which has no clear associations with cardiac pathology (e.g. gastroschisis).

Following round one, there was no clear agreement on how women should be followed up when first-trimester fetal anatomy was inadequately visualised, with some advocating that patients should: (1) wait for their 18- to 20-week scan

(31% support); (2) be re-scanned prior to 18 weeks (28% support); (3) have follow-up determined on a case-by-case basis (25% support); and (4) have a follow-up protocol determined by their healthcare provider based on local resource availability (16%). In addition, there was no agreement on how women requesting cell-free DNA testing [non-invasive prenatal testing (NIPT)] should be advised on the timing of this test in relation to first-trimester anomaly screening with ultrasound. The panel was presented with these results in round two and asked to reconsider their opinion in light of the group feedback.

The basic anomaly screening protocol

A flow chart describing how anomalies and anatomical views were selected for inclusion in the basic protocol over two rounds can be seen in *Figure 13*.

In round one, the panel was able to agree on the inclusion of eight anomalies which should be specifically targeted as part of the first-trimester scan and on the withdrawal of 12 anomalies from the items provided. There were three anomalies, which received between 60% and 80% support and which were put forward for reconsideration by the panel: limb reduction defects (71% support), spina bifida (63%) and abnormalities of situs (61%). On the question of anatomical views which should be included, the panel adopted 6 anatomical views and rejected 42 views. Eleven views were reconsidered in the following round and these included: facial profile (78%), evaluation of situs (75%), evaluation of bilateral feet (69%) and bilateral hands (67%), assessment of placental location (67%) and placental appearance (65%), evaluation of four-chamber cardiac view (66%), nasal bones (66%), evaluation of intact and continuous overlying skin of the spine (65%), determination of fetal heart rate (63%) and measurement of fetal head circumference (HC) (63%). These results were shared with the panel in round two, and they were asked to re-evaluate the inclusion of these items within the final protocol.

The extended anomaly screening protocol

The panel agreed on three indications which should lead to the offer of an extended fetal assessment of fetal anatomy in the first trimester and these included: the finding of an increased fetal NT (≥ 3.5 mm) (85% support), any pregnancy at higher a priori risk for fetal anomaly (82%) and for any woman with a previous maternal history of congenital anomaly (80%).

A flow chart describing how anomalies and anatomical views were selected for inclusion in the extended protocol over two rounds can be seen in *Figure 14*.

In round one, the panel was able to agree on the inclusion of 15 anomalies which should be specifically targeted as part of the first-trimester scan and on the withdrawal of 1 anomaly from the items provided. There were seven anomalies, which received between 60% and 80% support and which were put forward for reconsideration by the panel: congenital diaphragmatic hernia (78%), severe ventriculomegaly (77%), facial clefts (cleft lip and/or palate) (75%), anophthalmia (71%), cerebellar hypoplasia (67%), unilateral renal agenesis (67%) and club foot (60%).

Regarding anatomical views which should be included, the panel adopted 27 views and rejected 10 views in round one. In the second round, 25 views were put forward for reconsideration:

- cerebral peduncles (76% support), thalamus (75%), cisterna magna (75%);
- mandible (78%), upper and lower lip (74%), maxillae (72%), retronasal triangle (70%), anterior palate (66%), brain stem to occipital bone ratio ratio (65%), lenses (62%);
- cardiac outflow tracts with CF Doppler (79%), evaluation of fetal heart rate (78%), TR (77%), DV flow (76%), evaluation of aortic arch (75%), ratio of heart area to chest area (72%), pulmonary venous return (63%), evaluation for aberrant right subclavian artery (63%);
- assessment of umbilical arteries on either side of bladder (79%), measurement of abdominal circumference (AC) (76%) bowel echogenicity (63%);
- assessment of placental appearance (78%) and placental location (76%), cord insertion at the placental interface (67%) and vasa previa (67%).

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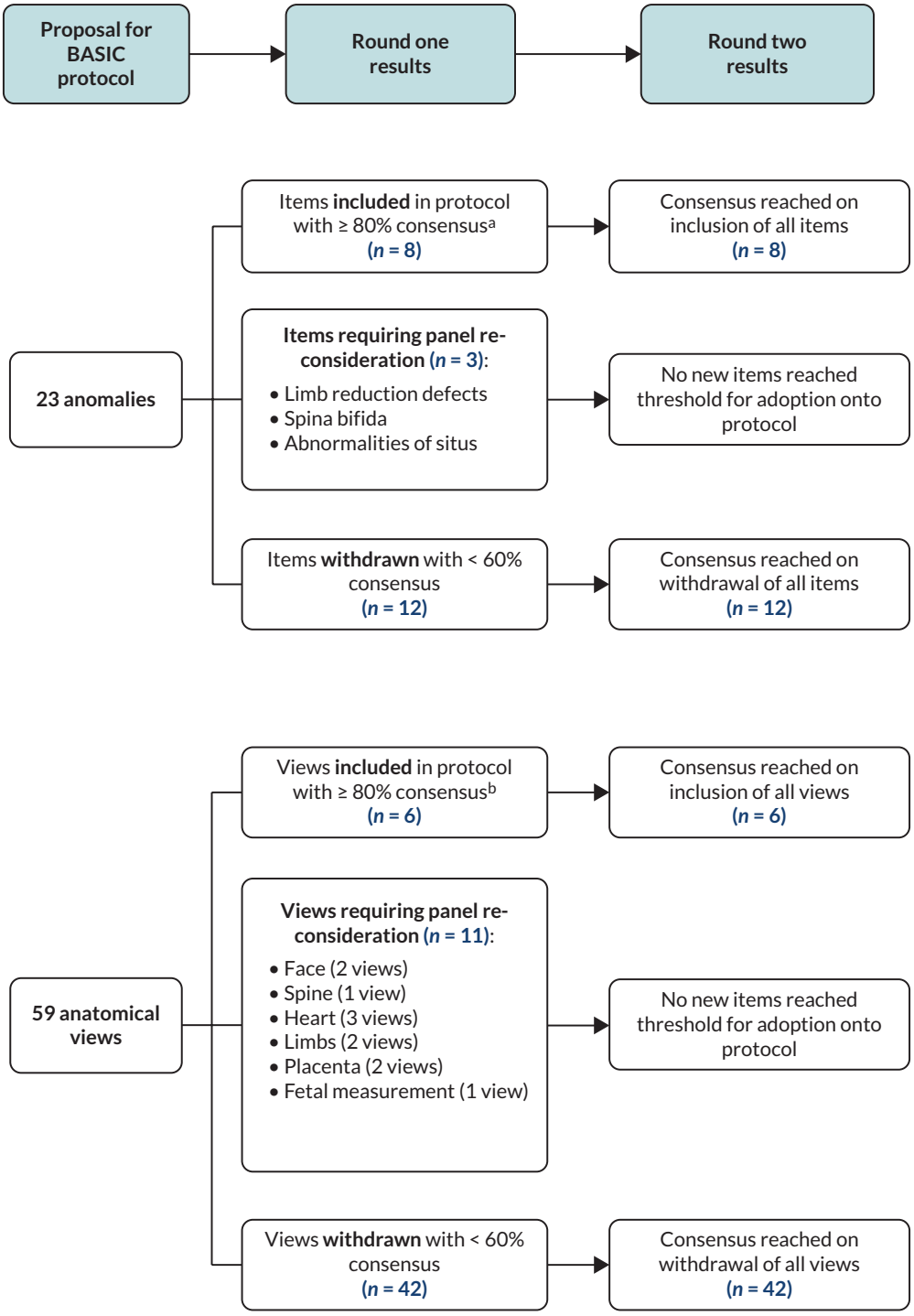

FIGURE 13 Flow chart demonstrating how anomalies and anatomical views were selected for inclusion in the basic protocol over two rounds. a Items included in basic protocol at round one stage: acrania and anencephaly, exomphalos, gastroschisis, megacystis, body stalk anomaly, holoprosencephaly, encephalocele and ectopia cordis. b Anatomical views included in basic protocol at round one stage: demonstration of cranial ossification, evaluation of choroid plexus, demonstration of intact abdominal wall with cord insertion, presence of bladder in fetal pelvis, presence of stomach in the left quadrant, evaluation of all four limbs.

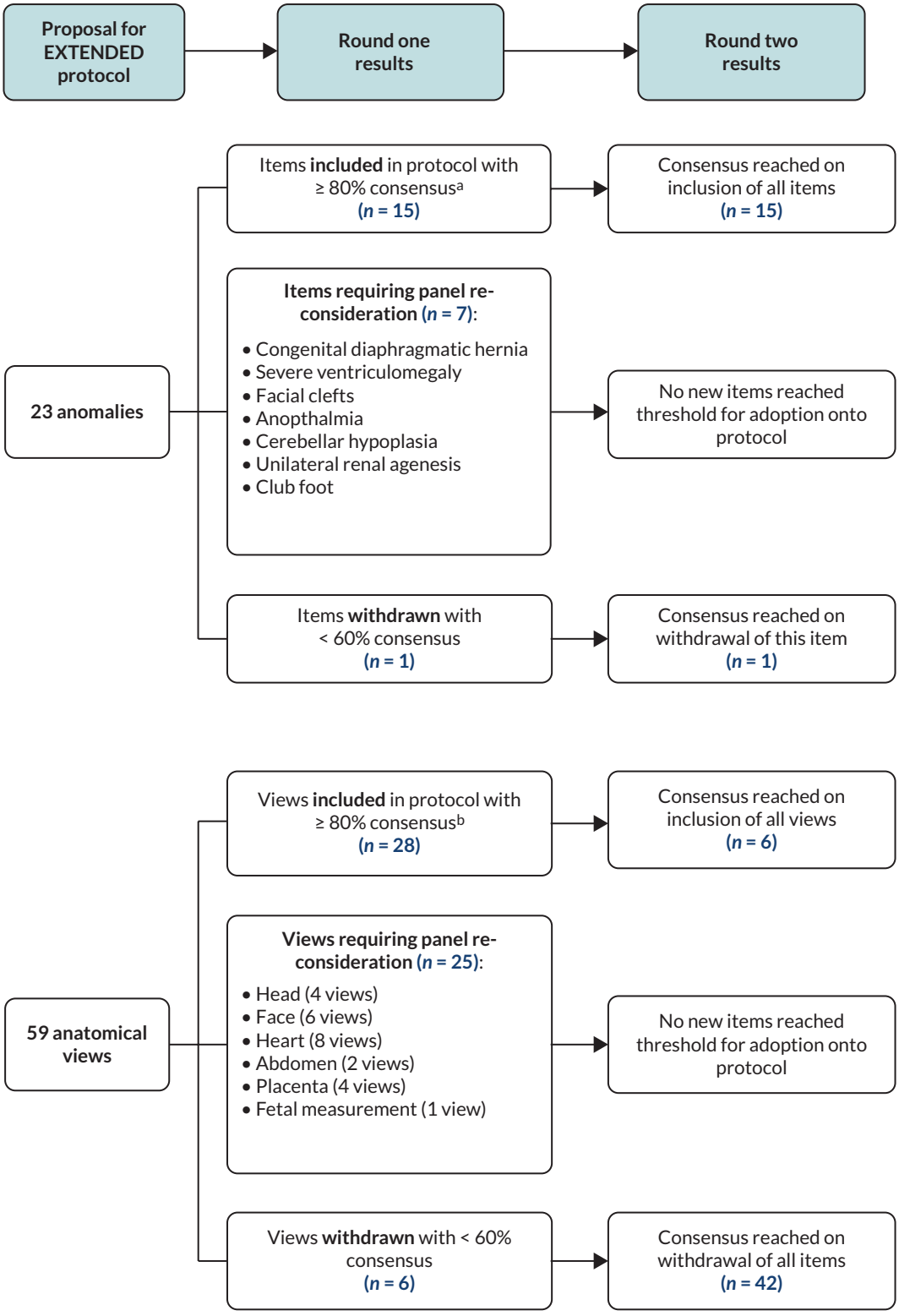

FIGURE 14 Flow chart demonstrating how anomalies and anatomical views were selected for inclusion in the extended protocol over two rounds. a Items included in extended protocol at round one stage: acrania and anencephaly, exomphalos, gastroschisis, megacystis, body stalk anomaly, holoprosencephaly, encephalocele and ectopia cordis, limb reduction defects, open spina bifida, abnormalities of situs, four-chamber view abnormalities, cardiac outflow tract abnormalities, lethal skeletal dysplasias, bilateral renal agenesis. b Anatomical views included in extended protocol at round one stage: demonstration of cranial ossification, evaluation of choroid plexus, demonstration of intact abdominal wall with cord insertion, presence of bladder in fetal pelvis, presence of stomach in the left quadrant, evaluation of all four limbs, view of interhemispheric fissure/falx, view of the posterior fossa, intracranial translucency, facial profile, nasal bone(s), view of orbits, demonstration of the presence and regularity of spinal vertebrae, evaluation of the spine ensuring intact and continuous overlying skin, evaluation of the shape of the thoracic wall, demonstration of diaphragmatic continuity, view of lung fields, situs evaluation, cardiac axis assessment, four-chamber view (with and without CF Doppler), cardiac outflow tract assessment, bilateral presence of kidneys, evaluation of bilateral feet, evaluation of bilateral hands, placental location relative to previous uterine scar, HC measurement, femur length measurement.

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Round two

The round two response rate was 84% (*n* = 144).

Screening logistics

The panel confirmed their support for recommendations which were developed in round one regarding the GA for first-trimester anomaly screening, the mode of ultrasound which should be used for practice and the referral pathway for patients with a screen-positive result. In addition, the panel reached consensus on how the fetal heart should be assessed after a first-trimester finding of a non-cardiac, non-lethal fetal anomaly which has known associations with cardiac pathology. In this case, the panel agreed that a specialist cardiac assessment should be performed either by a fetal medicine specialist or fetal cardiologist, depending on the local availability and skill set of practitioners in the region. The group was unable to agree on a follow-up protocol for non-satisfactory first-trimester examinations, on recommendations for the timing of cell-free DNA testing in relation to the first-trimester anomaly scan, or on the cardiac evaluation of fetuses with non-cardiac anomalies that have no clear association with fetal heart pathology.

The basic and extended anomaly screening protocols

Participants were presented with all items which received ≥ 80% support in round one. Every item was reviewed individually and confirmed for inclusion in the final protocol by the panel. All items which received < 60% approval in round one were presented to participants, and the withdrawal of every item was reviewed and confirmed by the group. The panel was asked to reconsider the inclusion of all items which received between 60% and 80% support in round one; however, none of these items were given sufficient support in round two to allow for their inclusion in the final protocol and were therefore withdrawn.

A summary of all recommendations for first-trimester screening practice which were developed by the panel following the completion of round two, including the recommendations for screening logistics and the final content of both the basic and extended screening protocols, to be used as a minimum standard of care, can be found in *Table 13*.

TABLE 13 Items which have been included as a minimum standard of diagnosis for the basic and extended first-trimester anatomical protocols and level of participant support for each item

Question	Basic protocol	Additional items included in extended protocol
Which anomalies should be targeted?	Acrania/exencephaly/anencephaly Exomphalos/omphalocele Gastroschisis Megacystis Body stalk anomaly Holoprosencephaly Encephalocele Ectopia cordis	Limb reduction defects Open spina bifida Abnormalities of situs Four-chamber view abnormalities Cardiac outflow tract abnormalities Lethal skeletal dysplasias Bilateral renal agenesis
Which anatomical views should be included?	Demonstration of cranial ossification Evaluation of choroid plexus Demonstration of intact abdominal wall with cord insertion Presence of bladder in fetal pelvis Presence of stomach in the left quadrant Evaluation of all four limbs	View of interhemispheric fissure/falx View of the posterior fossa Intracranial translucency Facial profile Nasal bone(s) View of orbits Demonstration of the presence and regularity of spinal vertebrae Evaluation of the spine ensuring intact and continuous overlying skin Evaluation of the shape of the thoracic wall Demonstration of diaphragmatic continuity View of lung fields Situs evaluation

TABLE 13 Items which have been included as a minimum standard of diagnosis for the basic and extended first-trimester anatomical protocols and level of participant support for each item (*continued*)

Question	Basic protocol	Additional items included in extended protocol
		Cardiac axis assessment Four-chamber view (with and without CF Doppler) Cardiac outflow tract assessment Bilateral presence of kidneys Evaluation of bilateral feet Evaluation of bilateral hands Placental location in relation to previous uterine scar HC measurement Femur length measurement
Recommendations regarding Screening Logistics		
What should be the GA for screening?	12^{+0} to 13^{+6} weeks GA	
Which mode of ultrasound should be used for screening?	TA ultrasound primarily, with use of TV ultrasound when required	
What should be the referral pathway after the finding of a positive or suspicious result?	Direct referral to the fetal medicine department	
How should the fetal heart be assessed in the following case? - confirmed non-cardiac, non-lethal fetal anomaly - anomaly has known associations with cardiac pathology - woman intends to continue with pregnancy or is undecided	Specialist cardiac assessment should be undertaken by a either fetal medicine specialist or fetal cardiologist; the decision of who performs the scan should be made on case-by-case basis and will depend on the availability and skill set of local practitioners.	
How should the fetal heart be assessed in the following case? - confirmed non-cardiac, non-lethal fetal anomaly - anomaly has no clear associations with cardiac pathology - woman intends to continue with pregnancy or is undecided	No consensus reached.	
If anatomical structures are inadequately visualised on a basic first-trimester scan, how should these women be followed up?	No consensus reached.	

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Open feedback

In addition to completing the structured section of the questionnaire, approximately one-third of participants (*n* = 57) provided additional feedback at the end of the first round.

A number of participants expressed strong support for fetal anomaly screening in the first trimester and shared relevant aspects of their own first-trimester anomaly screening practice (*n* = 14). There were observations on the wide variation in current practice seen across the NHS with respect to the first-trimester anomaly scan and comments on the need for the development of national screening standards, recommendations for practice and referral pathways (*n* = 17) to ensure 'universal … (and) equitable care for women'. Participants highlighted the need for agreement on an appropriate, minimum time allocation for first-trimester ultrasound anomaly screening (*n* = 10) and on developing a plan for sonographer and doctor training (*n* = 9) to support the undertaking of a routine first-trimester anomaly scan. The importance of informed patient consent, managing patient expectations on what is achievable from first-trimester anomaly screening and counselling support for parents with positive screening results was also emphasised (*n* = 6).

A group of participants called for a pragmatic approach to the scope of any future first-trimester anomaly scan, recognising that this is a GA where the opportunity for anomaly detection should be encouraged, but that it makes most sense to focus national recommendations on anomalies with high detection rates and low FP rates and which can be identified with relative ease in the first trimester, to mitigate the impact on resources (*n* = 11). Some argued that the adoption of an extensive plan for first-trimester anomaly screening would be difficult to implement at present without additional resources and would cause an untenable increase in pressure on sonographers and ultrasound capacity.

Participants felt that any future recommendations would need to recognise the increasing body mass index of the UK maternity population (*n* = 15) and suggested that this may prove to be a significant barrier to effective anomaly screening within the first trimester of pregnancy (recognising that this factor equally is presenting challenges for screening at the second-trimester anomaly scan). It was suggested that clear guidelines will need to be issued regarding the follow-up of patients with inadequate visualisation of fetal anomalies. There were concerns that attempts to complete the first-trimester visualisation of fetal anatomy, particularly in women with increased body habitus, may lead to a significant increase in time needed for first-trimester TV scans and a suggestion that a routine policy of bringing back patients to the unit for early second-trimester 're-scans' would be an inappropriate strain on unit resources.

Discussion

In this national study, which included practising sonographers, midwives, doctors and academics, we have established screening recommendations and a standardised protocol for anatomical assessment in the first trimester using Delphi methodology. Using this, we have produced a basic framework which can be used as a minimum standard for those centres which currently perform and those wishing to initiate a first-trimester anatomy examination as part of their routine antenatal care provision. To our knowledge, this is the first national initiative exploring the opinions of healthcare providers on this issue and which has developed a consensus on how first-trimester anomaly screening should be performed in a routine setting and this could be used as a template for similar screening programmes in other settings.

The results and discussions generated from this procedure have demonstrated that any future national recommendations developed for the first-trimester anomaly scan will require a balance between the clinical benefits to parents; what is theoretically achievable from this practice; and the realities of working in a system with limited resources in particular sonographers. The delicate nature of this balance was articulated by participants within the open feedback section of the study but is also quite evident from the final design of the basic and extended protocols which have been produced by the panel. The anomalies which have been selected for targeted screening as part of the basic scan, together should be detectable in at least 90% of first-trimester assessments (see *Chapter 4*), and would likely require a modest amount of additional training and sonographer scan time for routine early diagnosis. They represent anomalies where the benefit of early detection is very clear because they are associated with significant mortality and morbidity or because they are relevant to first-trimester screening for aneuploidy (e.g. exomphalos, holoprosencephaly and megacystis).

In addition, the six views which have been recommended as part of the basic protocol largely reflect those which have been most commonly adopted by trusts across England already, as evidenced in the national survey (see *Chapter 6*). The close corroboration between the findings of the nationwide survey of current first-trimester ultrasound practice and the attitudes of healthcare practitioners across the country suggest that the basic recommendations produced here could be realistically introduced and adopted into existing practice.

It should be noted that there were several recommendations for the 'basic' protocol which received considerable support from the panel, but which did not reach the 80% consensus threshold required for adoption. These included targeted screening for abnormalities of situs and limb reduction defects as well as ultrasound views confirming normality of situs, hands, feet, facial profile, spine and four-chamber view. In this way, the 'basic' protocol which has been developed for routine screening of women at low a priori risk of anomalies may represent the first step in first-trimester anomaly scan. It is likely that, as sonographers and doctors become increasingly familiar and comfortable with the assessment of first-trimester anatomy, the scope for what is attempted as part of this scan is widened in the future. However, it is clear from this study that at this point the role of the basic first-trimester anomaly scan is seen as a way to identify a group of important fetal anomalies, and not to be a replacement for the existing second-trimester anomaly scan.

As this report focuses on routine screening for all women, the relevant elements of the Delphi process are those on the basic screening pathway. However, we felt it would be useful to take this opportunity to develop an 'extended' protocol for women deemed to have a higher chance of fetal anomalies. Such a protocol may be offered to women with higher a priori chance of a fetal abnormality based on personal and/or family history or raised fetal NT.

Recommendations developed suggest offering the anomaly scan between 12^{+0} and 13^{+6} weeks of GA, using TA ultrasound primarily (with TV ultrasound used when required) and on a policy for the direct referral of patients with a positive or suspicious scan to their local fetal medicine department. The panel's decision regarding the GA window for screening is logical and is supported by evidence from the literature which suggests that the visualisation of fetal anatomy (and therefore the detection of fetal anomalies) significantly improves between 11 and 12 weeks GA. It also allows the GA window of the first-trimester anomaly scan to match with the existing first-trimester ultrasound scan offered by most units across the country (see *Chapter 6*) and the window for measurement of NT, which pragmatically is important if the anomaly scan is to become integrated with existing services. Equally, a primarily TA approach for the first-trimester scan with the offer of TV imaging when required is pragmatic and fits with current first-trimester practice in most centres across England as demonstrated in the Nationwide Survey of Practice (see *Chapter 6*). Of note, the panel was unable to agree on a follow-up protocol for non-satisfactory examinations. The most vocal members of the group suggested in their open feedback that a policy bringing patients back prior to the 18- to 20-week scan to complete an inconclusive first-trimester assessment would be unsustainable. Although from the Nationwide Survey of Practice, we know that 31% of responding trusts who currently undertake a formal first-trimester anomaly scan in England have such a protocol in place and 28% of the panel members concurred with this approach when asked their thoughts on this subject in round one of the consensus procedure. A policy on this issue will have to be established prior to offering patients a first-trimester anomaly scan, but it is a decision perhaps best made at a local level given the resource allocation which is involved. As more trusts across the UK become familiar with implementing a first-trimester anomaly scan, it may become more clear how national policy should be developed.

The strength of this study is that it represents a series of recommendations for practice developed by the equally weighted consensus opinion of 172 healthcare practitioners from centres across the UK. The recommendations have been developed by stakeholders who currently work within the antenatal screening environment, and as such have been put together with the 'real-world' clinical context in mind. As with any study, which involves asking for the time and input of clinical staff, the consensus procedure most likely included an inclusion bias in practitioners with a strong interest in developing a first-trimester anomaly assessment for women in the UK and may have been less likely to include those who are against expanding the scope of the current first-trimester scan. Nonetheless, the study has successfully established a standardised protocol for anatomical assessment in the first trimester using a Delphi consensus procedure. Based on the findings from our previous work which show a clear benefit to the use of standardised protocols for the first-trimester scan, implementation of these UK-based recommendations would be expected to increase the early detection of fetal anomalies and to improve equity of care.

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Chapter 9 The views of pregnant women and their partners on anomaly screening in early pregnancy

Presentations

Data in this chapter were presented at the RCOG World Congress 2021 and the ISUOG World Congress 2020.

Publications

Karim JN, Craik R, Davidson L, Maiz N, Fisher J, Rivero-Arias O, *et al*. Acceptability of the first trimester anomaly scan amongst parents in the UK [abstract]. *BJOG* 2021;**128**(S2):280.

Karim JN, Craik R, Hinton L, Papageorghiou A. Acceptability of the first trimester anomaly scan amongst parents with previous experience of fetal anomalies in pregnancy [abstract]. *Ultrasound Obstet Gynecol* 2020;**56**:12.

Introduction

Our original application to the HTA included a work package aiming to determine the acceptability of the early anomaly scan among women and partners. As this constituted original research it was considered to be beyond the commissioning brief.

Nevertheless, our patient and public voice group strongly felt that this was an important element, and therefore we sought separate funding for this work. This was secured by Research England Strategic Priorities Fund QR allocation. Although not strictly part of the commissioning brief, this work is reported here, because acceptability to women and partners of changes in proposed screening methods must be evaluated prior to implementation. We were unable to identify any previous work on parental attitudes towards first-trimester anomaly screening in the UK.

We undertook a prospective survey of parents across England and Wales. The primary aims of this study were to explore parental attitudes towards first-trimester screening for structural abnormalities of varying severity, to determine whether parents would see this as a positive addition to prenatal care, to quantify the expected uptake of such a scan if implemented and to understand the reasons why parents might accept or decline such a scan. The secondary objectives were to understand which factors influence parental acceptance of first-trimester anatomy screening (including age, parity, previous pregnancy experiences, views towards TOP) and how women who decline or accept screening for chromosomal abnormalities (commonly the current focus of first-trimester ultrasound) would respond to the offer of a first-trimester anatomy assessment.

In order to achieve these aims we recruited parents presenting for routine obstetric ultrasound within the NHS (Cohort A) and parents who have a previous experience of a screen-positive antenatal ultrasound screening result or a child with a fetal anomaly (Cohort B).

Methods

This was a prospective study of patient responses to a self-administered questionnaire (see *Appendix 5*), designed to inform clinical practice. The undertaking of the study and reporting of all results is based on guidelines and reporting checklists for good practice in survey research.[168–170]

Ethics approval

The study underwent full ethics review by the South Central Oxford Research Ethics committee (19/SC/0483) with approvals granted in October 2019. Approvals from the Health Research Authority (England) and the Health and Care Research Wales were granted in November 2019.

Study participants, design and participant recruitment

This was a national, multicentre, prospective study involving the recruitment of two distinct population cohorts.

Cohort A

Cohort A consisted of parents who were currently pregnant and presenting for routine obstetric ultrasound screening within the UK NHS at 1 of 10 participating hospitals across England and Wales: Liverpool Women's NHS Trust; North Tees and Hartlepool NHS Trust; Pennine Acute Hospital NHS Trust; South Tyneside and Sunderland NHS Trust; St Helen's and Knowsley Teaching Hospitals NHS Trust; St Georges University Hospital NHS Trust; Birmingham Women's and Children's NHS Trust; Homerton University Hospital NHS Trust; Oxford University Hospital NHS Trust; Aneurin Bevan University Health Board. Pregnant individuals at any GA and their partners were eligible to participate. Those presenting for emergency ultrasound (e.g. as part of an assessment for reduced fetal movements, bleeding or other indication) and women undergoing ultrasound in a high-risk or FMU were not eligible.

Women and their partners were approached upon arrival for routine obstetric screening at 1 of 10 NHS obstetric ultrasound units. Parents meeting eligibility criteria were given a participant information leaflet describing the objectives and rationale for the study, background information on fetal anomaly screening, and details on how collected data would be stored and reported (see *Appendix 5*). Those parents who decided to take part were given the option to provide consent and complete the survey (see *Appendix 5*) either on paper or online (LimeSurvey), using a quick response code provided.

In selecting participating NHS sites, considerable efforts were made to include ultrasound units from different regions across England and Wales and from different levels of care (district general, secondary care and tertiary care). Each hospital site had a pre-determined target designating the number of patients they were to recruit to the study, ranging from 50 to 200 participants depending on the size of the department and available research staff resources. Once the target had been reached, all recruitment materials were removed from the site and no further participants were actively sought. Several sites were unable to reach their original recruitment target as a result of redeployment of staff and resources during the COVID-19 pandemic. Appropriate modifications were made to adapt to this situation.

Cohort B

Cohort B consisted of parents with experience of a screen-positive result following ultrasound screening for fetal anomalies in a previous pregnancy, or who have a child affected by a congenital anomaly. We felt it was important to specifically consult this group of parents as they might have unique views and additional insights to offer regarding the implementation of first-trimester anomaly screening. Parents with a previous TOP for a fetal anomaly were included, as were those who continued their pregnancies after diagnosis. We also encouraged participation from parents with the experience of a 'false-positive' result after fetal anomaly screening in a previous pregnancy.

Recruitment to this cohort was facilitated with the support of two well-established, national UK-based charities with interests in pregnancy screening and fetal anomalies: Antenatal Results and Choices and the Spina Bifida, Hydrocephalus, Information, Networking, Equality Charity (SHINE). The charities used their websites, online forums and social media platforms to engage their membership. Interested participants were directed to the study website to obtain additional information about our research (equivalent to the participant information leaflet distributed in Cohort A) and if appropriate, to complete a consent form and the questionnaire using a secure, online platform (LimeSurvey). The briefing guide and questionnaire given to participants in this cohort was identical to those used in Cohort A.

Parents in both cohorts were made aware that they could skip any questions they did not feel comfortable answering or found distressing.

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Study questionnaire (see Appendix 5)

The questionnaire comprised of six sections:

1. A 7-point detailed briefing guide for parents explaining the potential benefits and risks of a first-trimester anomaly scan was provided. This included a brief overview of referral pathways and management options that might be offered in the case of a positive or suspicious finding.
2. Questions regarding parental views on the timing of fetal anomaly screening based on the severity of the anomaly being assessed.
3. Ascertainment of whether parents would opt for a first-trimester anomaly scan if this was offered in a future pregnancy (likely future uptake) and reasons motivating this decision.
4. Previous participant experiences of fetal congenital anomalies and ultrasound screening including previous FP results.
5. Questions relating to participant demographics.
6. Questions relating to the participant's current pregnancy (where applicable), including GA, and whether screening for Down, Edwards and Patau syndrome and second-trimester fetal anomaly screening was being undertaken.

Questionnaire design

The questionnaire was adapted from a previously validated instrument used to assess maternal attitudes towards first-trimester anomaly screening in Spain.[171] The wording of several questions was modified and questions were added and tailored to suit the context of British antenatal care and our study objectives. Two optional, free-text questions were included within the survey to give parents an opportunity to share their previous experiences and thoughts about anomaly screening in an unrestricted manner, should they feel comfortable to do so.

The process of questionnaire validation and piloting took place over multiple sequential stages with amendments made to study documents (patient information leaflet, briefing guide and questions) as appropriate at each timepoint:

1. Document review by a qualitative health researcher with expertise in parent experiences of screening LH.
2. Document review by representatives (J.F. and G.Y.) of two large UK-based charities with interests in congenital anomalies (ARC, SHINE). As experts in antenatal screening and communication, their reviews focused on ensuring the content of all documents would be acceptable to parents and that appropriate and sensitive language choices were made throughout.
3. Document review and piloting of survey by a group of research midwives, clinical fellows, sonographers and fetal medicine specialists with academic knowledge of the topic and from outside the immediate research team (n = 12). This group was asked to ensure that the information being presented was factually accurate as well as to assess the questionnaire for face validity and content validity. A selection of this pilot group were asked to complete the questionnaire on multiple occasions to ensure reproducibility of results (test–retest reliability). Answers provided by this group were also assessed to ensure inter-rater reliability and internal consistency of the questionnaire.
4. Full ethics review by a committee composed of both specialists and lay-persons. Study authors (J.N.K. and A.T.P.) undertook a face-to-face discussion with this panel. Suggested amendments were taken on-board and changes were made as appropriate to the questionnaire, briefing guide and study design as recommended.
5. Study documents were piloted with parents at the John Radcliffe Hospital, Oxford University NHS Trust (n = 10). Parents read through documents and completed the questionnaire alongside a research midwife. They were asked to provide constructive feedback and data generated from this pilot was analysed to ensure consistency with expected results. None of the feedback provided at this stage required any further changes to the study documents to be made.

Statistical analysis

Descriptive statistics were performed for all questions (including those involving participant demographic characteristics). Comparisons of parental characteristics on different question answers were performed using the Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables.

Results

Overall, 1373 parents were recruited to the study between November 2019 and January 2021, including 1199 in cohort A and 174 in cohort B.

Demographic characteristics of participants is summarised in *Table 14*.

Overall, the majority of parents would opt for an 11- to 14-week anomaly scan if this was offered to them in a future pregnancy (cohort A: 91%, cohort B: 95%). Reasons for accepting the scan included a desire for early reassurance (A: 86%, B: 74%), desire for early information (A: 83%, B: 87%), additional time to prepare for the birth of an affected child (A: 68%, B: 46%), earlier access to genetic testing (A: 68%, B: 74%), additional time to consider pregnancy termination (TOP, A: 53%, B: 59%) and an opportunity for earlier TOP (A: 48%, B: 65%). In parents who would decline the offer of first-trimester anomaly screening in a future pregnancy [A: n = 35 (3%), B: n = 3 (2%)], the main reason cited was increased anxiety due to inconclusive results. Nearly all parents preferred having a diagnosis at 11–14 weeks for lethal anomalies (A: 89%, B: 95%) and severe anomalies (A: 87%, B: 95%). Most wanted minor conditions assessed as well where possible (A: 77%, B: 79%) and to be informed of a suspected anomaly even if this could not be confirmed until a later GA (A: 75%, B: 82%). Parents felt that receiving a fetal anomaly diagnosis at an earlier gestation of pregnancy might impact their decisions regarding whether or not to proceed with TOP (A: 58%, B: 37%). Of the parents who declined combined screening in this pregnancy (n = 198), 71% would consent to an early anatomy assessment if offered in future. Parents who would consider a TOP for severe/lethal anomalies were more likely to opt for early screening ($p < 0.001$), to request information about minor anomalies ($p < 0.001$) and would prefer to be told about suspicious findings ($p < 0.001$).

TABLE 14 Participant characteristics in Cohorts A and B

Characteristic	Cohort A (n = 1199), N (%)	Cohort B (n = 174), N (%)
Age (years)		
< 24	34 (3)	2 (1)
25–29	305 (25)	19 (11)
30–34	399 (33)	52 (30)
35–39	238 (20)	51 (29)
≥ 40	89 (8)	41 (24)
Undisclosed	34 (3)	9 (5)
Highest level of educational attainment		
No qualifications	21 (2)	0 (0)
GCSE	177 (15)	7 (4)
A-Level	112 (9)	9 (5)
College/vocational training	199 (17)	24 (14)
Undergraduate study	387 (32)	66 (38)
Postgraduate study	219 (18)	53 (30)
Undisclosed	84 (7)	15 (9)
Ethnicity		
Asian or Asian British	92 (8)	4 (2)
Black or Black British	51 (4)	3 (2)
Mixed or mixed British	41 (3)	5 (3)

continued

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TABLE 14 Participant characteristics in Cohorts A and B (*continued*)

Characteristic	Cohort A (*n* = 1199), *N* (%)	Cohort B (*n* = 174), *N* (%)
White	976 (81)	152 (87)
Other ethnic group	10 (1)	1 (1)
Undisclosed	29 (2)	9 (5)
Pregnancy status		
Currently pregnant	1199 (100)	34 (20)
< 14 weeks GA	437 (36)	17 (50)
14^{+0}–23^{+6} weeks GA	376 (31)	12 (35)
> 24 weeks GA	349 (29)	5 (15)
Unavailable GA	47 (4)	-
Plans to undertake screening for Down, Edwards and Patau syndrome this pregnancy?		
Yes	1001 (83)	30 (88)
No	198 (17)	4 (12)
Attitude towards TOP		
May consider for severe and/or lethal anomaly	390 (33)	122 (70)
May consider for lethal anomaly only	147 (12)	19 (11)
Would NOT consider under any circumstances	116 (10)	22 (13)
Don't know	253 (21)	9 (5)
Undisclosed	283 (24)	2 (1)

GCSE, General Certificate of Secondary Education.

Discussion

In this large, nationwide study, we presented parents with information on the benefits, risks and uncertainties associated with first-trimester anomaly screening using ultrasound. Our results show that knowing this information, over 90% of parents would consent to early anomaly screening at the 11- to 14-week scan in a future pregnancy, in addition to the 18–20 weeks anomaly scan. Both parents who are currently pregnant, and those with previous experience of pregnancy affected by a congenital anomaly feel that this additional early screening would be beneficial. Screening was viewed as a desirable addition to care by a wide group of parents, including those who would opt against screening for Down, Edwards and Patau syndromes; and also those who would not consider (or are uncertain about) TOP in the setting of a severe or lethal anomaly.

For parents who would accept a first-trimester anomaly scan, the most cited reason driving this decision was a desire for early reassurance and early information about their pregnancy. The majority of parents would prefer to be made aware of a suspicious finding on an early scan, even if this could not be confirmed until a later GA. This suggests that some parents would be willing to prioritise the advantage of early information offered by a first-trimester anomaly scan over the certainty of a diagnosis that may be offered at a later GA. This study is the first in the UK to explore parental attitudes towards the first-trimester anomaly scan and the findings have important implications for future antenatal screening policy-making.

Our results are consistent with findings of a previous study conducted in Spain,[172] where 97% of women suggested that they would prefer an anomaly scan at 12 weeks and to be informed of all findings regardless of anomaly severity over waiting for an ultrasound assessment at a later GA. A number of studies published in the context of aneuploidy

screening have similarly shown that parents prefer earlier testing, even if this means accessing a first-trimester screening test which is less sensitive than its second-trimester counterpart.[173,174]

The strength of this study is that it includes the views of a large number of parents presenting to different levels of care (tertiary, secondary and district general hospitals) and with varying previous experiences of fetal anomaly in pregnancy. The generalisability of the findings may be limited by the fact that many of the parents who chose to participate in the study were presenting for routine ultrasound in pregnancy at time of recruitment and potentially driven to engage with the survey because of a background interest in antenatal screening. Nonetheless, results showed that over 90% of participants in both cohorts would support the introduction of a first-trimester anomaly scan, which suggests that the future uptake of such screening would be high if implemented within the NHS setting.

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Chapter 10 Cost-effectiveness and health economic modelling

Introduction

This chapter details the health economic model developed to predict the potential costs and consequences associated with implementing the basic first-trimester structural anomaly screening protocol developed by Delphi consensus (see *Chapter 8*) and which includes targeted screening for eight specific anomalies.

As described in *Chapter 1*, the introduction of the protocol will be associated with a number of short- and long-term costs and consequences. In attempting to report cost-effectiveness, we have recognised that the advantages and disadvantages will need to be assessed in terms of (1) potential additional costs and/or savings to the NHS, (2) the impact upon parents (assessed using maternal QALYs) and (3) the impact upon babies (reflected as infant healthcare costs and QALYs). The aim of the health economic model is to provide a transparent and comprehensive account of the implications of a first-trimester anomaly scan for parents presenting for antenatal screening care and therefore the analysis has been designed to incorporate all three aspects.

Methods

Previously published models

A literature search for previously published cost-effectiveness models of antenatal screening for structural fetal anomalies was conducted to help inform the structure of the health economic model. Details of this literature search and findings are presented in *Report Supplementary Material 1*. In summary, only a small number of models (n = 5) were identified and review of these provided limited information on the structuring of pathways and events beyond the screening results. In view of this, a de novo model was developed as described below.

Overview of decision-analytical model

A hybrid-type model was necessary to capture both the short and longer-term implications of screening. As decision trees are suited to modelling short-term care pathways with few repeated events, they were used to model the screening and pregnancy pathways and the potential impact of a first-trimester anomaly screen upon a comprehensive set of pregnancy outcomes. These outcomes comprised live birth with an anomaly, live birth without an anomaly, spontaneous miscarriage, late fetal loss/stillbirth, first- and second-trimester termination and first- and second-trimester fetal loss as a result of genetic diagnostic testing.

As each of these pregnancy outcomes can have longer-term implications for the health and quality of life of the mother, QALYs were used as the model's outcome measure. QALYs permit the impact of an intervention upon both quality and quantity of life to be captured, are generic in nature thus facilitating comparisons of the cost-effectiveness of disparate interventions, and they are the preferred metric of outcome in economic evaluations, by the National Institute for Health and Care Excellence (NICE).[175] Individual Markov models for each pregnancy outcome were constructed to simulate healthcare costs and maternal QALYs to 20 years post pregnancy. Each Markov model was attached to its corresponding pregnancy outcome in the decision tree. Maternal QALYs were used as the primary outcome for the cost-effectiveness analysis.

The implications for the unborn infant were also quantified. For live born infants, additional Markov models simulated expected 20-year healthcare costs and QALYs depending upon the absence or presence of an anomaly, and for the latter, upon the type of anomaly affecting the infant. These expected costs and QALYs were then used as secondary pay-offs within the decision tree, being attached to the appropriate live birth outcomes.

From the outset we were acutely aware of the sensitivities and complexities involved in evaluating an antenatal screening programme that could both increase maternal QALYs, yet through a potential increase in the pregnancy termination rate, decrease infant QALYs. We chose not to perform a simple aggregation of maternal and infant costs and QALYs for the purposes of generating an overall estimate of cost-effectiveness because such an approach would imply that the termination of a fetus and the resulting loss of QALYs is universally considered a devastating harm. While for some in society this will be the case, for others, including some 'screen-positive' women, the feeling may be that a termination is ultimately in the best interests of the child and is not a negative outcome. Indeed Png *et al.* in their recent systematic review of health economic studies of antenatal and newborn screening programmes similarly noted that what constitutes a benefit or a harm will vary by stakeholder.[176] We felt strongly that it was not our place to make such a value judgement and so reported the incremental cost and QALY impact of screening for mothers and infants separately. We based our estimates of cost-effectiveness upon maternal costs and QALYs which are not subject to the same degree of uncertainty with regard to societal preferences.

The analysis time horizon of 20 years was determined by the availability of data pertaining to the long-term implications (for mothers and infants) of some of the anomalies included in the model. Such anomalies are extremely rare, data are limited and a number of assumptions were required to facilitate the modelling out to 20 years. Predictions beyond this time point would have been based largely upon conjecture which would have increased uncertainty further. Infant costs and QALYs are reported alongside those of mothers as a secondary outcome.

The comparator used in the model was current antenatal screening practice, comprising a first-trimester ultrasound scan for fetal viability, CRL and NT, and second-trimester ultrasound screening for structural fetal anomalies. The intervention was first-trimester structural anomaly screening with ultrasound, offered as an adjunct to current practice and taking place at the same time as the current first-trimester scan.

The cohort entering the model was the general population of pregnant women attending for first-trimester antenatal screening in England and Wales and we assumed a mean starting age of 30 years (the average age of mothers across both countries between 2018 and 2020). The model was based on singleton pregnancies and screening was performed using 2D ultrasound. The perspective used was that of the NHS in England and Wales with costs expressed in 2019–20 Great British pounds. Costs and QALYs arising beyond the first 12 months were discounted at a rate of 3.5% in accordance with current guidelines.[177] Although no formal health economic analysis plan was written, we followed good practice guidelines when conducting and reporting the model and its findings.[178] The following sections describe the development and data population of the model.

Developing the decision tree model structure

The decision tree covers the period between the first-trimester screening point (approximately 11–14 weeks' gestation) and the end of a full-term pregnancy at 40 weeks' gestation (an estimated 28-week time horizon). Model pathways were developed through collaborative discussions between the project's clinical and health economic teams. The pathways follow women through the two main antenatal screening points (the 11- to 14-week scan, and the 20-week scan) and on to the end of their pregnancy, acknowledging that for some women, their pregnancies will end prematurely and without the birth of a live baby.

In developing the model, a number of pragmatic assumptions were made. Firstly, we acknowledged that a single fetus may present with multiple structural anomalies. However, the scarcity of published data on multiple malformations makes it challenging to accurately model the combinations of anomalies and also the order in which they will be detected (some anomalies may be easier to detect in the first-trimester than others, or may progressively evolve). Given these foreseeable difficulties, an a priori decision was taken to populate the model using parameters for fetuses presenting with single anomalies. Secondly, we have assumed that all women, regardless of whether offered current or new first-trimester anomaly screening, will be given the option of a Combined Screening Test for Down, Edwards and Patau syndromes concurrently. We recognise that the seemingly independent antenatal screening options offered to parents for genetic syndromes and structural fetal anomalies, are in fact inextricably linked and often overlap. Many fetuses diagnosed with Down, Edwards and Patau syndromes will be subsequently found to have a structural anomaly as well (e.g. a cardiac anomaly) and vice versa. As will be detailed further, the model has been designed so that the finding of an anomaly with strong genetic associations at any GA will lead to the offer of genetic testing to

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parents. However, we have been unable to model the potential impact of a high-risk Combined Screening Test (and the subsequent fetal medicine referral and ultrasound) on the early identification of structural fetal anomalies which may take place in this context. The process of modelling the overlapping impact of Combined Screening in addition to structural anomaly screening in the first trimester (and the lack of reliable, available data in this regard) was deemed too complex for the scope of this project.

We considered alternate model structures, including one using a combined anomaly prevalence estimate (i.e. the probability that any of the structural anomalies in the protocol are present) and combined screening performance statistics. However, early results from the systematic reviews (see *Chapters 4* and *5*) demonstrated that these anomalies are heterogeneous in nature with regard to screening characteristics (i.e. different first-trimester screening sensitivities), fetal outcomes (lethality, spontaneous fetal loss rates and TOP rates), associations with genetic syndromes, permanence (some resolving during the pregnancy), and the approach taken to clinical management. Given these differences, it was deemed necessary to model pregnancy pathways by individual anomaly type. The need for a flexible model with which one could explore the potential of alternative protocols containing different anomalies was also deemed advantageous. With this approach, protocols of varying levels of complexity, targeting different anomalies, could be more readily modelled, not only for the scope of this project but also in the future.

Figure 15 shows the starting structure of the decision tree, which was developed using TreeAge Pro Healthcare 2021 software (TreeAge Software, Inc., Williamstown, MA, USA).[179] The model begins with the policy decision: to introduce protocolised structural anomaly screening as part of the current first-trimester ultrasound scan or to continue with current antenatal screening practice. The model allows women to accept or reject the formal invitation for first-trimester anomaly screening.

The structure continues for both arms of the model with branches for the prevalence of each of the individual structural anomalies targeted as part of the new first-trimester anomaly screening protocol:

- acrania/exencephaly/anencephaly
- exomphalos/omphalocele
- gastroschisis
- body stalk anomaly
- holoprosencephaly
- encephalocele
- LUTO (identified via first-trimester finding of megacystis)
- ectopia cordis.

To the first seven anomalies listed above, we added the broader category of major cardiac anomalies. Major cardiac anomalies have a high prevalence, being the most common structural congenital anomaly in low-risk populations, at 4 per 1000 fetuses.[15,86] They also encompass ectopia cordis, which was selected by the Delphi panel for inclusion in the basic protocol. Associated mortality from major cardiac anomalies remains high, with recent data linking major cardiac anomalies to over 50% of all infant deaths in England.[86] Babies born with the condition may also require costly major surgery and specialist tertiary care. As such, we wanted to explore the implications of a protocol containing early screening for a wider group of major cardiac anomalies.

These eight anomalies are also included in the current practice arm of the model to reflect that even in the absence of a formalised protocol, there is some existing level of case finding at the time of current first-trimester ultrasound screening. *Figure 15* details where the individual anomaly prevalence branches are replicated across the model structure (branching point 1). Beneath the individual prevalence branches is the 1 minus prevalence branch which groups together women without any of the structural anomalies in the model.

The tree is subsequently structured for the first-trimester screening outcomes. Branching point 2 in *Figure 15* is replicated for each anomaly and in both arms of the model; it shows that when present, an anomaly may be visualised in the first trimester by a sonographer and then subsequently confirmed by a fetal medicine specialist (a TP result), or may not be seen by the sonographer at this screening point (a FN result).

For women without any of the specified anomalies, there may be no finding at the first-trimester screen (a TN result) or a sonographer may suspect an anomaly (branching point 3 in *Figure 15*). For some women in this latter group, this 'sonographer FP' will be corrected by a specialist fetal medicine scan and for simplicity these women are classed as having a TN result within the model and incur only the cost of an additional fetal medicine scan. However, for some women, correction of the screening error may not occur and a FP screen (termed a 'fetal medicine FP' within the model) will remain and direct subsequent pregnancy management/decisions.

The effectiveness from adding a basic structural anomaly screening protocol to the current first-trimester scan is implemented within the model via improvements to the first-trimester TP rates with current practice. However, the model also acknowledges that introducing first-trimester anomaly screening may lead to an increase in sonographer FP findings and referrals on to fetal medicine for further investigation.

Four separate subtrees map out the pregnancy pathways following each of the four different first-trimester screening outcomes:

6. First-trimester TP pregnancy pathway (T1 TP subtree)
7. First-trimester FN pregnancy pathway (T1 FN subtree)
8. First-trimester (fetal medicine) FP pregnancy pathway (T1 FP subtree)
9. First-trimester TN pregnancy pathway (T1 TN subtree)

Figure 15 illustrates the placement of each of these subtrees. The structure of each subtree was standardised across the different anomalies (*albeit* populated with anomaly-specific event probabilities), and all are fully described and illustrated in *Appendix 6*, *Figures 26–29*. In addition, one further subtree was developed to model the processes and outcomes of genetic diagnostic testing following a positive screen for a structural anomaly with a strong genetic association. Such testing was assumed to be offered to women screening positive (at the first or second trimester) for any of the five anomalies in the first column of *Table 15*.

The genetic testing subtree is shown in *Figure 16* and is replicated for each of the anomalies with a strong genetic association. Following a positive screen, women are offered a genetic test that they accept or decline. In line with clinical practice, we assumed testing with chorionic villus sampling (CVS) during the first trimester and amniocentesis during the second trimester. For women accepting testing (and depending upon the structural anomaly type), the result may be positive or negative, and following testing women face a risk of suffering an iatrogenic fetal loss as a result of the procedure. As we found no robust UK data regarding the uptake of genetic testing after the finding of a fetal anomaly, we worked on the assumption that an anomaly associated with a chromosomal abnormality is akin to a very high chance Combined Screening Test result. On this basis, we used evidence from the UK literature examining the uptake of genetic testing in the context of a high-risk Combined Screening Test result. This suggests that most women carrying a pregnancy with a high chance of being affect by a genetic condition accept the invitation for diagnostic genetic testing.[180] For the modelling, women who declined genetic testing were assumed to have a euploid fetus.

For women who suffer a fetal loss following genetic testing, the pregnancy pathway ends. For women not suffering an iatrogenic loss, and for women who do not wish to be tested, the pregnancy pathway (subtree) subsequently followed is dependent upon whether their structural anomaly screening result was a TP or a FP finding (see *Figure 15*).

The descriptions of the TP, FN, FP and TN subtrees in *Appendix 6* are accompanied by details of the placement of the genetic diagnostic testing subtree along each pathway.

Developing the maternal Markov model structure

Separate Markov models were developed to simulate the longer-term implications for mothers of each of the various pregnancy outcomes within the decision tree model. Again, these outcomes comprised live birth (with and without an anomaly), spontaneous stillbirth, second-trimester termination, second-trimester iatrogenic fetal loss with genetic testing, spontaneous miscarriage, first-trimester termination and first-trimester iatrogenic fetal loss with genetic testing. For live births with an anomaly, because of the heterogeneous nature of the eight structural anomalies in the protocol, individual maternal Markov models were developed for each anomaly type. For the anomalies with a known

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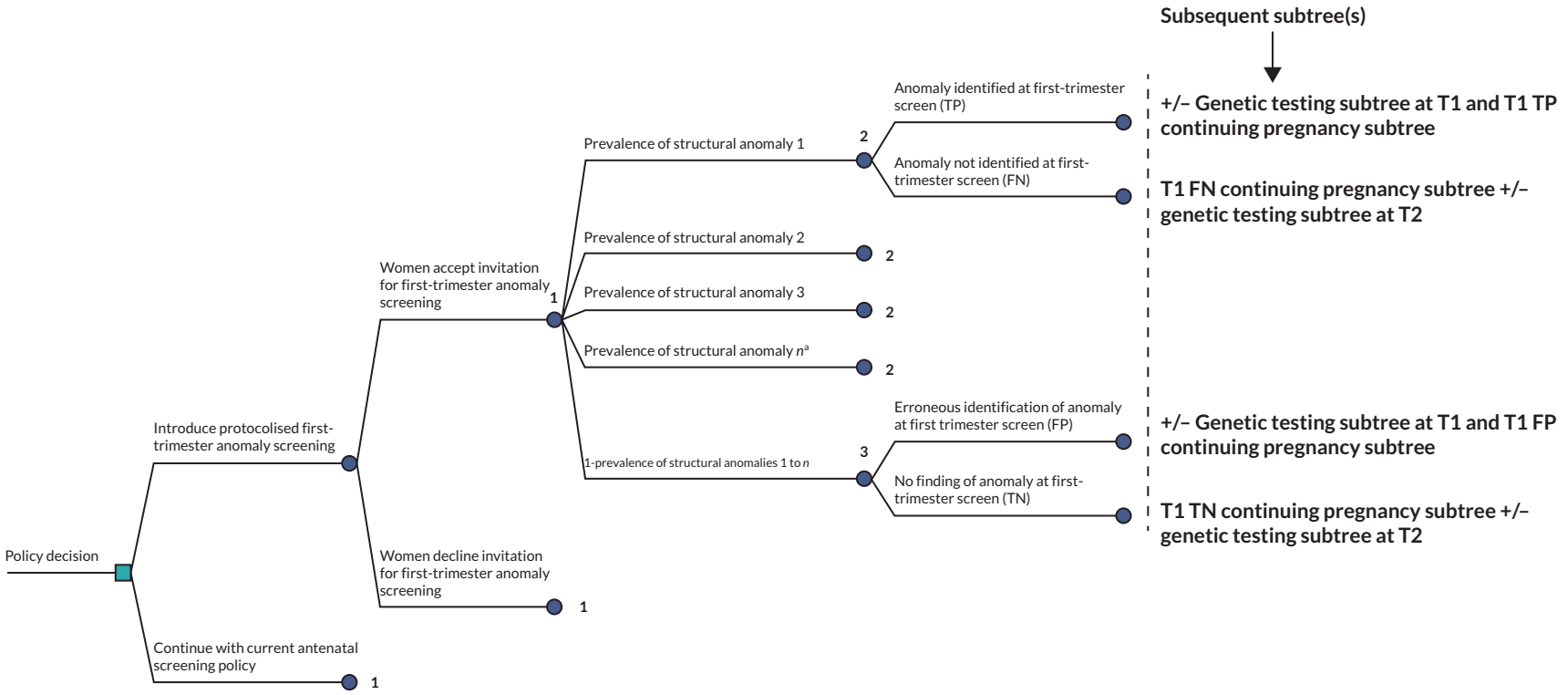

FIGURE 15 Starting structure of the decision tree model showing first-trimester anomaly prevalence and screening outcomes. a For brevity, individual prevalence branches for each anomaly are not shown. 1: Branching point 1 – anomaly prevalence branches repeated, followed by appropriate first-trimester screening outcome branches (branching points 2 and 3). T1, first trimester; T2, second trimester.

TABLE 15 Basic protocol anomalies by genetic association

Strong genetic association[a]	Unlikely/weak genetic association
Holoprosencephaly	Acrania/exencephaly/anencephaly
Encephalocele	Gastroschisis
Exomphalos/omphalocele	Body stalk anomaly
LUTO[b]	
Major cardiac anomaly	

a Offer of genetic testing modelled.
b Lower urinary tract obstruction (identified in first trimester as megacystis).

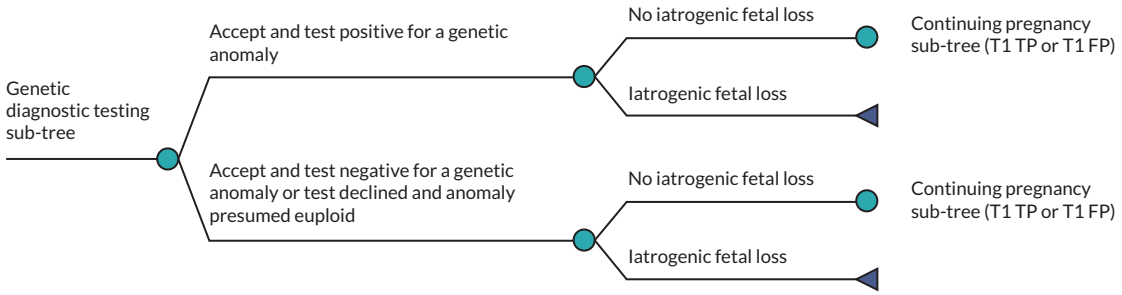

FIGURE 16 Genetic diagnostic testing subtree for women screening positive for a structural anomaly with a strong genetic association.

genetic association (see *Table 15*), separate models were constructed for mothers of infants born with and without an accompanying genetic anomaly. Models were also developed for mothers of infants born without any of the eight structural anomalies and for mothers of those born with a genetic anomaly alone. In total, 14 separate maternal Markov models were constructed.

Each of the Markov models uses a simple alive/dead model structure as shown in *Figure 17*. All women enter the model in the alive health state and each subsequent year, can remain here or suffer death and move to the mother deceased health state. The models are run over a time horizon of 20 years and each year women accrue costs and QALYs specifically related to their pregnancy outcome. QALYs in the model are calculated by adjusting underlying levels of maternal quality of life for the negative psychological symptoms experienced as a consequence of the pregnancy outcomes. For example, women suffering a stillbirth or TOP can experience anxiety and depression for many months and even years following the loss of their baby, and research has shown that mothers raising children with major congenital anomalies can experience significantly greater levels of mortality and morbidity than mothers of unaffected infants.[181–183]

Further, and because a mother's level of well-being is intrinsically linked to that of her baby, for women with a live birth, the corresponding maternal Markov models were constructed so as to link a mother's level of quality of life over time to the prognosis and morbidity likely to be experienced by her child. This was facilitated by identifying anomaly-specific annual infant mortality risks, as well as data on the longer-term morbidity associated with each condition.

Specific costs included in the maternal Markov models are those related to the mental health treatment women may receive for the negative psychological symptoms of their pregnancy outcome.

Developing the infant Markov model structure

A further set of Markov models were developed to simulate the long-term prognosis, and expected healthcare costs and QALYs of live born infants in each arm of the decision tree. In total, 13 separate models were constructed covering

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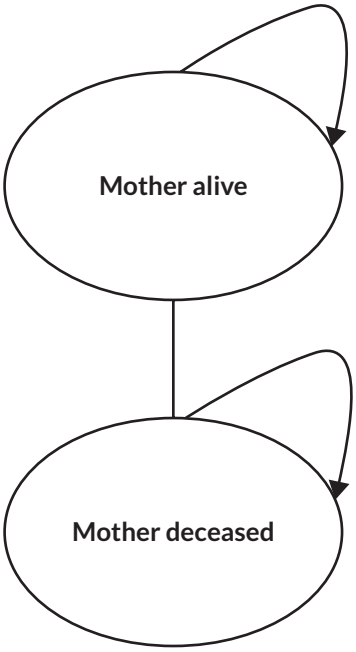

FIGURE 17 Maternal Markov model structure.

live births with each type of anomaly (with and without genetic involvement for anomalies with a known genetic association) (n = 11), the live birth of an unaffected child (n = 1), and the live birth of a child with a genetic anomaly alone (n = 1). These models were structured as per the maternal Markov models, with an infant alive and an infant deceased health state (see *Figure 17*). All infants enter the alive health state of their Markov model and then during subsequent cycles can remain here or move to the infant deceased health state. Daily cycle lengths were used for lethal anomalies resulting in death in the days or weeks following birth, and annual cycles were used for unaffected babies and those born with anomalies that can be managed surgically and have greater life expectancy. For unaffected babies and those with non-lethal anomalies, the model time horizon was set to 20 years.

The models simulated infant QALYs, which were estimated using the same anomaly-specific infant annual mortality risks as used in the maternal Markov models, and by adjusting general population norm infant utility levels for the expected quality-of-life impact of the anomaly affecting the child (see *Appendix 9*, *Table 52*). Expected treatment costs in the first years after birth were included in the models, along with longer-term costs associated with the monitoring and further management of these children (see *Appendix 9*, *Tables 52–55*). The resulting expected costs and QALYs from these models served as the infant pay-offs for the different live birth outcomes simulated by the decision tree. Zero infant healthcare costs and QALYs were assigned to those pregnancies ending prematurely without the live birth of a baby.

Populating the decision tree model

Where data permitted, and so as to facilitate the subsequent VoI analyses, parameter estimates were entered into the model using distributions to reflect their inherent uncertainty. We followed existing guidance and tailored the type of distribution to the type of parameter.[184] Beta distributions were used to propagate the uncertainty around event probabilities and utilities, log-normal distributions for hazard ratios and gamma distributions for cost. For a small number of parameters with weak priors, we used uniform distributions with maximum and minimum values informed by clinical opinion or author assumption.

Event probabilities for the decision tree

The following sections detail the event probabilities used to populate each part of the decision tree, beginning with the starting structure shown in *Figure 15*.

Accept invitation for first-trimester structural anomaly screen

Among 1167 low-risk women surveyed as part of this work (see *Chapter 9*), 1062 said they would accept an invitation for a first-trimester structural anomaly scan. The probability assigned to this branch within the model was thus 0.91 using a beta distribution with moments $\alpha = 1062$ and $\beta = 105$.

First-trimester prevalence for each anomaly

The first-trimester prevalence estimates for each structural anomaly were informed by the project systematic reviews and are reported in *Chapter 4* (see *Table 1* for non-cardiac anomalies) and *Chapter 5* (for major cardiac anomalies – mean and 95% CI of 0.41% and 0.39% to 0.43% respectively). An exception was the prevalence of LUTO, which was challenging to estimate (see *Chapter 4* for details) and was calculated instead using data reported by Malin *et al.*[185] [mean and standard error (SE) of 0.0334% and 0.0019%, respectively]. All prevalence estimates were entered into the model using beta distributions. One minus the sum of the prevalences gave the proportion of women whose babies were unaffected by any of the eight structural anomalies in the basic protocol (estimated to be 0.993).

First-trimester screening performance outcomes

When estimating first-trimester detection (TP) rates for each anomaly with current practice, we prioritised data from the UK; thus, wherever possible, we consulted data submitted by UK congenital anomaly registries to the European Commission's network of population-based registries for the epidemiological surveillance of congenital anomalies – EUROCAT.[186] When such data were not available, we used aggregated data from the project's systematic reviews in the 'no protocol/current practice' arm of studies, on the assumption that the screening performance in the UK would be similar to the international studies included in the review. Within the group of studies in the systematic review performed without a protocol, there was only one study respectively reporting on findings for each of LUTO, encephalocele and body stalk anomaly. For these three anomalies, expert opinion was sought from the project's experienced clinicians, and used to supplement the published estimates in order to establish a more realistic input value for the model parameters. The experts provided mean and 95% CI estimates. *Table 16* shows these 'current practice' first-trimester TP probabilities for each of the anomalies in the basic protocol. Also shown are first-trimester TP probabilities estimated to be achievable with the first-trimester screening protocol. These parameters were again informed by the project's systematic reviews (see *Chapters 4* and *5*). First-trimester FN screening outcomes for each anomaly were estimated as one minus the corresponding first-trimester TP probability.

False-positive rates from screening are difficult to estimate, and when published estimates are available, the methods used to ascertain these statistics are often incomplete. The FP rates used in the model were thus estimated through careful review of cases where post-mortem or postnatal examination was available and supplemented by expert review of relevant papers identified during the project's systematic reviews.

As described previously, we distinguished between two types of FP rates. In the absence of an anomaly, suspicious visualisations by sonographers referred on for fetal medicine evaluation are termed 'sonographer' FPs. We refer to 'fetal medicine' FPs as those sonographer FPs that are referred for specialist fetal medicine screening but remain uncorrected, despite the absence of an anomaly. The available literature does not often report the first-trimester FP rate with this distinction. We were therefore guided by both the literature and by expert opinion, in order to determine these two separate FP rates and the proportion of 'sonographer' FP results which might be 'corrected' at time of fetal medicine referral. SEs for each of the FPs were informed by the 'combined' FPs within the literature. For certain anomalies, the 'sonographer' FP rate was estimated to be higher with protocolised first-trimester early anatomy screening than with current practice, while for others, such as acrania, we assumed no change to sonographer FPs (see *Table 16*). Following a referral, we assumed that the 'fetal medicine' FP rate would be the same regardless of whether the referral came from current practice or as the result of a protocolised first-trimester anomaly screening policy.

When considering the FP rates for exomphalos and for LUTO (identified during the first trimester via megacystis), we needed to address the fact that a significant proportion of these anomalies (in euploid fetuses) are known to spontaneously resolve as the pregnancy progresses. At the time of first-trimester screening, the 'spontaneous resolution' of these anomalies cannot be predicted. As such, a first-trimester finding of exomphalos or megacystis will lead to a fetal medicine referral and the offer of diagnostic testing and appropriate management. In reality, a woman presenting with a euploid fetus and one of these anomalies, would be counselled regarding the high rate of

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TABLE 16 First-trimester screening performance statistics for current practice and with the new anomaly screening protocol

Anomaly type, screening performance parameter	Mean (SE)[a]	Distribution type	Parameters	Source
Major cardiac anomaly				
T1 TP – current practice	0.1351 (0.0373)	Beta	α = 11.21, β = 82.99–α[b]	Karim *et al.* (2022)[84]
T1 TP – anomaly screening protocol[c]	0.3296 (0.0804)	Beta	α = 10.94, β = 33.18–α[b]	Karim *et al.* (2022)[84]
T1 FP – sonographer (current practice)	0.000032 (0.0000178)	Beta	α = 3.23, β = 100,993.12–α[b]	Systematic review/expert opinion
T1 FP – sonographer (anomaly screening protocol)	0.00008 (0.0000178)	Beta	α = 20.20, β = 252,472.17–α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)	0.00004 (0.0000178)	Beta	α = 5.05, β = 126,240.64–α[b]	Systematic review/expert opinion
Acrania				
T1 TP – current practice	0.7037 (0.0213)	Beta	α = 323, β = 459–α	EUROCAT (UK regions, 2015–9)[85]
T1 TP – anomaly screening protocol	0.9796 (0.0080)	Beta	α = 304.90, β = 311.25–α[b]	Systematic review
T1 FP – sonographer (current practice)	0.00001 (0.000005)	Beta	α = 4.0, β = 399,995–α[b]	Systematic review/expert opinion
T1 FP – sonographer (anomaly screening protocol)	0.00001 (0.000005)	Beta	α = 4.0, β = 399,995–α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)	0.00000	–	–	Systematic review/expert opinion
Exomphalos				
T1 TP – current practice	0.5669 (0.0213)	Beta	α = 305, β = 538–α	EUROCAT (UK regions, 2015–9)[85]
T1 TP – anomaly screening protocol	0.9568 (0.0130)	Beta	α = 233.06, β = 243.58–α[b]	Systematic review
T1 FP – sonographer (current practice)[d]	0.0018 (0.0000181)	Beta	α = 9872.00, β = 5,484,446.97–α[b]	Systematic review/expert opinion
T1 FP – sonographer (anomaly screening protocol)[d]	0.0018 (0.0000181)	Beta	α = 9872.00, β = 5,484,446.97–α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)[d]	0.0015 (0.0000181)	Beta	α = 6857.62, β = 4,571,745.89–α[b]	Systematic review/expert opinion
Gastroschisis				
T1 TP – current practice	0.8335 (0.0124)	Beta	α = 751, β = 901–α	EUROCAT (UK regions, 2015–9)[85]
T1 TP – anomaly screening protocol	0.9595 (0.0177)	Beta	α = 118.05, β = 123.04–α[b]	Systematic review
T1 FP – sonographer (current practice)	0.00002 (0.0000072)	Beta	α = 7.72, β = 385,793.75–α[b]	Systematic review/expert opinion

TABLE 16 First-trimester screening performance statistics for current practice and with the new anomaly screening protocol (*continued*)

Anomaly type, screening performance parameter	Mean (SE)[a]	Distribution type	Parameters	Source
T1 FP –sonographer (anomaly screening protocol)	0.00002 (0.0000072)	Beta	α = 7.72, β = 385,793.75–α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)	0.000005 (0.0000072)	Beta	α = 0.482, β = 96,449.14–α[b]	Systematic review/expert opinion
Alobar holoprosencephaly				
T1 TP – current practice	0.4196 (0.2477)	Beta	α = 1.246, β = 2.97–α[b]	Systematic review
T1 TP – anomaly screening protocol	0.9175 (0.0251)	Beta	α = 109.32, β = 119.15–α[b]	Systematic review
T1 FP – sonographer (current practice)	0.00001	Beta	α = 1.56, β = 156,247.44–α[b]	Systematic review/expert opinion
T1 FP – sonographer (anomaly screening protocol)	0.00002	Beta	α = 6.25, β = 312,492.75–α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)	0.000005 (0.000008)	Beta	α = 0.391, β = 78,123.61–α[b]	Systematic review/expert opinion
LUTO				
T1 TP – current practice	0.3307 (0.0500)	Beta	α = 28.95, β = 87.54–α[b]	Systematic review/expert opinion
T1 TP – anomaly screening protocol	0.6613 (0.0500)	Beta	α = 58.59, β = 88.59–α[b]	Systematic review
T1 FP – sonographer (current practice)[d]	0.0009 (0.000056)	Beta	α = 285.06, β = 286,730.51–α[b]	Systematic review/expert opinion
T1 FP –sonographer (anomaly screening protocol)[d]	0.0009 (0.000056)	Beta	α = 285.06, β = 286,730.51–α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)[d]	0.0005 (0.000056)	Beta	α = 79.68, β = 159,358.06–α[b]	Systematic review/expert opinion
Encephalocele				
T1 TP – current practice	0.4495 (0.0373)	Beta	α = 79.50, β = 176.86–α[b]	Systematic review/expert opinion
T1 TP – anomaly screening protocol	0.8990 (0.0373)	Beta	α = 57.77, β = 64.26–α[b]	Systematic review
T1 FP – sonographer (current practice)	0.000005 (0.0000052)	Beta	α = 0.925, β = 184,909.32–α[b]	Systematic review/expert opinion
T1 FP –sonographer (anomaly screening protocol)	0.00001 (0.0000052)	Beta	α = 3.70, β = 369,817.79– α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)	0.000001 (0.0000052)	Beta	α = 0.037, β = 36,981.21–α[b]	Systematic review/expert opinion
Body stalk anomaly				
T1 TP – current practice	0.9851 (0.0109)	Beta	α = 120.72, β = 122.54–α[b]	Systematic review/expert opinion
T1 TP – anomaly screening protocol	0.9859 (0.0106)	Beta	α = 120.99, β = 122.72–α[b]	Systematic review
T1 FP – sonographer (current practice)	0.00001 (0.0000065)	Beta	α = 2.37, β = 236,683.02–α[b]	Systematic review/expert opinion

continued

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TABLE 16 First-trimester screening performance statistics for current practice and with the new anomaly screening protocol (*continued*)

Anomaly type, screening performance parameter	Mean (SE)[a]	Distribution type	Parameters	Source
T1 FP –sonographer (anomaly screening protocol)	0.00001 (0.0000065)	Beta	α = 2.37, β = 236,683.02−α[b]	Systematic review/expert opinion
T1 FP – fetal medicine (both model arms)	0.00000	-	-	Systematic review/expert opinion

T1, first trimester.
a Using systematic review data SEs could only be estimated for the FP rate of screening overall (sonographer plus fetal medicine FPs) for each anomaly. These estimates were thus used to reflect uncertainty around both sonographer and fetal medicine FP rates in the model.
b Estimated from mean and SE using methods of moments approach.
c Based on four-chamber view protocol (without routine use of Colour-Flow Doppler).
d Anomaly is present at the time of screening but spontaneously resolves as the pregnancy progresses and so is considered a T1 FP finding. The difference between T1 sonographer and T1 fetal medicine FPs is accounted for by some anomalies resolving between being identified by a sonographer and being screened by a fetal medicine specialist.

spontaneous resolution. However, within the model, these cases needed to be considered and costed as FP results; as these fetuses have a normal outcome, but would be investigated and managed for the screen-positive finding.

Event probabilities for the genetic testing subtree

The event probabilities used to populate the genetic testing subtree (illustrated in *Figure 16*) are detailed in *Appendix 6*, *Table 39*. The probability of a woman accepting genetic testing was assumed to be the same in both the first and second trimesters. Also, diagnostic testing was assumed to be 100% sensitive and specific. For the structural anomalies with a strong genetic association, we determined the probability that each type would be accompanied by a genetic anomaly in the first and second trimesters. Second-trimester probabilities were generally lower given that more of the anomalies with a genetic component (1) are likely to be identified during the first trimester and leave the routine antenatal screening pathway before reaching the second trimester and (2) result in a spontaneous miscarriage before reaching the second trimester. When a woman without a structural anomaly undergoes genetic testing (e.g. following a FP structural anomaly screen) the probability of a positive test result was set to reflect the general population risk of a genetic anomaly. Probabilities for iatrogenic fetal loss following testing were for CVS and amniocentesis in the first and second trimesters respectively.

The following sections describe the event probabilities required for the model's four different first-trimester screening outcome subtrees (depicted in *Appendix 6*, *Figures 26–29*).

Event probabilities for the T1 true-positive pregnancy subtree

T1 true-positive pregnancy subtree (see *Appendix 6*, *Figure 26*). *Table 40* in *Appendix 6* shows the first-trimester termination probabilities by anomaly type. Data from the systematic reviews showed these probabilities to vary according to the type of anomaly a baby has screened positive for, with rates highest for those structural anomalies known to be lethal or likely to result in severe disability. The confirmed presence of a co-existing genetic abnormality further impacts a woman's decision about termination.

Table 40 in *Appendix 6* also shows the anomaly-specific probabilities of spontaneous miscarriage in women with a T1 TP screening result who choose not to terminate their pregnancy. These probabilities were again predominantly informed by the project's systematic reviews but were adjusted to reflect the conditional nature of the tree structure. For example, an analysis may report that of 100 women with an anomaly identified during T1, 10 opted for a first-trimester termination, 5 suffered a spontaneous miscarriage prior to reaching the second trimester, 2 suffered a stillbirth and the remaining 83 had a live birth. To ensure the model predicts the same proportions of events, the probabilities for each event were conditioned upon the preceding events along the pathway.

This can be illustrated for the live birth outcome in the preceding example. Of the 90 women (90%, n = 100−10) not terminating their pregnancy in the first trimester, n = 5 (or 5.6% of n = 90) suffered a spontaneous miscarriage and the

remaining 85 women (94.4% of *n* = 90) reached the second trimester. Of these women, 2 (or 2.4% of *n* = 85) suffered a stillbirth and the remaining 83 (or 97.6% of *n* = 85) had a live birth. Multiplying the conditioned probabilities along the pathway to a live birth (0.900 × 0.944 × 0.976 = 0.83) ensures the same proportion of the starting cohort is modelled as having a live birth, as the proportion shown in the original data (i.e. 83%).

Table 40 in *Appendix 6* also shows the anomaly-specific conditioned probabilities of a spontaneous late fetal loss/stillbirth among women with a T1 TP screen who chose to continue with their pregnancy and who did not suffer a spontaneous miscarriage.

Event probabilities for the T1 false-negative pregnancy subtree

T1 false-negative pregnancy subtree (see *Appendix 6*, *Figure 27*). Anomaly-specific spontaneous miscarriage probabilities in women receiving routine antenatal care following a T1 FN screening outcome are shown in *Appendix 6*, *Table 41*, along with the probabilities for a subsequent TP screening result in those women reaching the second trimester and attending for routine structural anomaly screening. Also detailed are anomaly-specific probabilities of a spontaneous late fetal loss/stillbirth in women whose structural anomaly was still not identified by the 20-week anomaly scan; it was assumed these undiagnosed anomalies would be unlikely to have genetic involvement.

For women receiving a second-trimester TP screen, *Appendix 6*, *Table 41* shows the proportions with each type of anomaly expected to choose a second-trimester termination; these estimates were informed predominantly by UK registry data submissions to EUROCAT. For women choosing to continue with their pregnancy, the late fetal loss/stillbirth probabilities were as per reported for women with a T1 TP screen.

Event probabilities for the fetal medicine T1 false-positive pregnancy subtree

The fetal medicine T1 false-positive pregnancy subtree (see *Appendix 6*, *Figure 28*). Of the women with a first-trimester FP screen (given in each arm by the sum of the products of the corresponding anomaly-specific T1 sonographer and fetal medicine FP probabilities in *Table 16*), the proportion thought to have a structural anomaly with a strong genetic association, first move through the genetic testing subtree.

Small numbers of women with FP screens for major cardiac anomaly, encephalocele, and holoprosencephaly will receive a positive genetic test result, reflecting the general population risk of a genetic anomaly. As described previously, for exomphalos and LUTO (< 15 mm), the cases attributed as 'FP' were those in which spontaneous resolution of the anomaly (in the setting of a normal fetal karyotype) took place following first-trimester screening. As such, these fetuses were all presumed to be offered a diagnostic genetic test as part of their post-screening investigations (with appropriate costing), with the outcome being a normal karyotype result. As a result of genetic testing some women will suffer an iatrogenic fetal loss (see *Appendix 6*, *Table 39* for parameter values relating to genetic testing).

Table 42 in *Appendix 6* details the event probabilities combined to populate the single T1 FP pregnancy subtree in the model. In each model arm, for women with a FP screen and a genetic anomaly, and for women with a FP screen without a genetic anomaly, we estimated weighted average first-trimester termination probabilities. For each group, such calculations were made by using the proportion of fetal medicine FP screens accounted for by each type of anomaly to weight each corresponding anomaly-specific termination probability (we assumed these to be the same as following a T1 TP screen) and finally summing together these products.

For women whose pregnancies continue, the risk of spontaneous miscarriage varies only according to whether a woman has a genetic anomaly or not (diagnosed along the FP screening pathway). Women without a genetic anomaly face the general population miscarriage risk, while for those with a genetic anomaly, the miscarriage risk used is that for women with Down, Edwards and Patau syndromes (see *Appendix 6*, *Table 42*).

The same table (see *Table 42*) shows the anomaly-specific probabilities that a T1 fetal medicine FP screening result is corrected at the T2 screening point. These input parameters were developed based on expert opinion and on published literature, where available. We used these data (for likelihood of correction at T2) in combination with anomaly-specific data on first-trimester FP rates and termination rates, to create a weighted average probability that a woman with

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a first-trimester fetal medicine FP finding who presented for screening during the second trimester, would have her diagnosis corrected.

The general population spontaneous stillbirth risk was used for women continuing with their pregnancy without a structural or a genetic anomaly.[187] For women without a structural anomaly, but with a genetic anomaly, the probability of a stillbirth was estimated by applying an odds ratio for the increased risk of stillbirth with Down syndrome (estimated using UK data from the EUROCAT database and the MBRRACE-UK report) to the underlying population stillbirth risk (see *Appendix 6*, *Table 42*).

Event probabilities for the T1 true-negative continuing pregnancy subtree

The T1 true-negative continuing pregnancy subtree (see *Appendix 6*, *Figure 29*). Prior to the next scheduled screen at 20 weeks' gestation, a proportion of women with a T1 TN screen will suffer a spontaneous miscarriage, represented in *Table 43* of *Appendix 6* by the general population spontaneous miscarriage rate.

The same table (see *Appendix 6*, *Table 43*) shows the anomaly-specific second-trimester sonographer FP probabilities for women reaching the second trimester and undergoing routine fetal anomaly screening. These probabilities were summed when populating the single T1 TN pathway in the tree.

We assumed that for women with unaffected pregnancies, a sonographer FP result occurring in the second trimester would be corrected by the fetal medicine specialist at time of referral in all cases for the following anomalies: body stalk anomaly, holoprosencephaly, encephalocele, gastroschisis, LUTO (megacystis). For these women, we modelled their pregnancies to continue to term as normal (with the general population risk of stillbirth).

The risk of a FP diagnosis for either major cardiac anomaly or exomphalos following T2 fetal medicine assessment was estimated by available literature and expert opinion. *Table 43* in *Appendix 6* shows a small proportion (0.04%) of major cardiac anomaly sonographer FPs will remain uncorrected following fetal medicine evaluation. For exomphalos, expert opinion suggests that if this anomaly were identified at the time of sonographer screening in a euploid fetus, it is highly likely that this will be corroborated a few day later at time of fetal medicine referral (i.e. remain uncorrected), but that based on natural history, the exomphalos will subsequently resolve spontaneously at a later GA. Using the FP data in *Appendix 6*, *Table 43*, we estimated a weighted average second-trimester fetal medicine FP rate for the model.

Following second-trimester fetal medicine FP results for major cardiac anomaly and exomphalos, women enter the genetic testing subtree and are stratified based upon their test result. As in the first trimester, a FP diagnosis of exomphalos made by a fetal medicine specialist would only occur in a euploid fetus where the documented anomaly subsequently resolves spontaneously.

Second-trimester termination rates were assumed to be the same as those for women with a second-trimester TP screening result (shown in *Appendix 6*, *Table 41*). Women opting to continue with their pregnancy face a risk of spontaneous fetal loss/stillbirth, which is dependent only upon whether they were diagnosed with a genetic anomaly as a result of their FP screen (see *Appendix 6*, *Table 43*).

Utilities for the decision tree

Underlying utility levels

Women's underlying utility levels in the decision tree were assumed to match the UK three-level EuroQol-5 Dimensions (EQ-5D) index population norms for females aged 25–34.[188] This parameter was entered into the model using a beta distribution with a mean EQ-5D index score of 0.93 and a SE of 0.007.

Utility impact of screening and immediate pregnancy outcomes

We then sought to determine the adjustments to underlying levels of quality of life brought about by the various events women experience and the decisions they make as they move along the four different first-trimester screening outcome pathways in the model (i.e. the T1 TP, T1 FN, T1 FP and T1 TN subtrees). As illustrated previously, the pathways are numerous and complex, and many events have the potential to influence and alter a woman's quality

of life. With this in mind, we tabulated each of the different possible screening/genetic testing outcomes along with the pregnancy continuation decisions made at both the first and second-trimester screening points. Each unique sequence of events was given an identifying code combining a sequence number (e.g. S1) and the pregnancy trimester at which the sequence occurred (e.g. T1). *Figure 18* provides an illustration of the approach using first-trimester events and associated sequence numbers for women in the model with a structural anomaly (i.e those receiving TP, FN and no screening results). In S1T1 for example, a woman whose baby has an anomaly receives a positive first-trimester screen followed by a positive genetic test and makes a decision to continue with her pregnancy. Within the model, the underlying utility of this woman is decremented for this S1T1 combination of events. The second-trimester sequences for women with continuing pregnancies, as well as the first and second-trimester sequences for women without an anomaly (FP and TN first-trimester screens) are described fully in *Appendix 7* along with the resulting utility decrements (and increments where appropriate) and descriptions of how these were implemented in the model to adjust underlying levels of maternal utility (see *Appendix 7*, *Table 44*).

A combination of rapid reviews of the literature and free-text web-based searches was conducted to identify studies reporting on the utility impact associated with each sequence, as well as with spontaneous pregnancy losses (miscarriage and stillbirth) which can occur as part of a sequence where the decision is made to continue with a pregnancy. The search strategy for these reviews was developed by combining appropriate utility-related terms from a previous search strategy developed to identify studies reporting health utilities for childhood conditions (see *Report Supplementary Material 1*), with terms pertinent to pregnancy outcomes, for example 'pregnancy' and 'termination or abortion or feticide'.[189] Searches were run during August and September of 2021 in the PubMed database.

The model also incorporated the potential utility impacts of screening results per se (i.e. reassurance from a negative screen and lasting decrements following correction of a FP screen) and additional detrimental utility effects when a pregnancy ends during the second trimester. In addition to rapid literature reviews and free-text web-based searches, any studies identified during the project's clinical systematic reviews as potentially providing a useful source of information on the quality-of-life impact of screening and the screening pathway were also obtained.

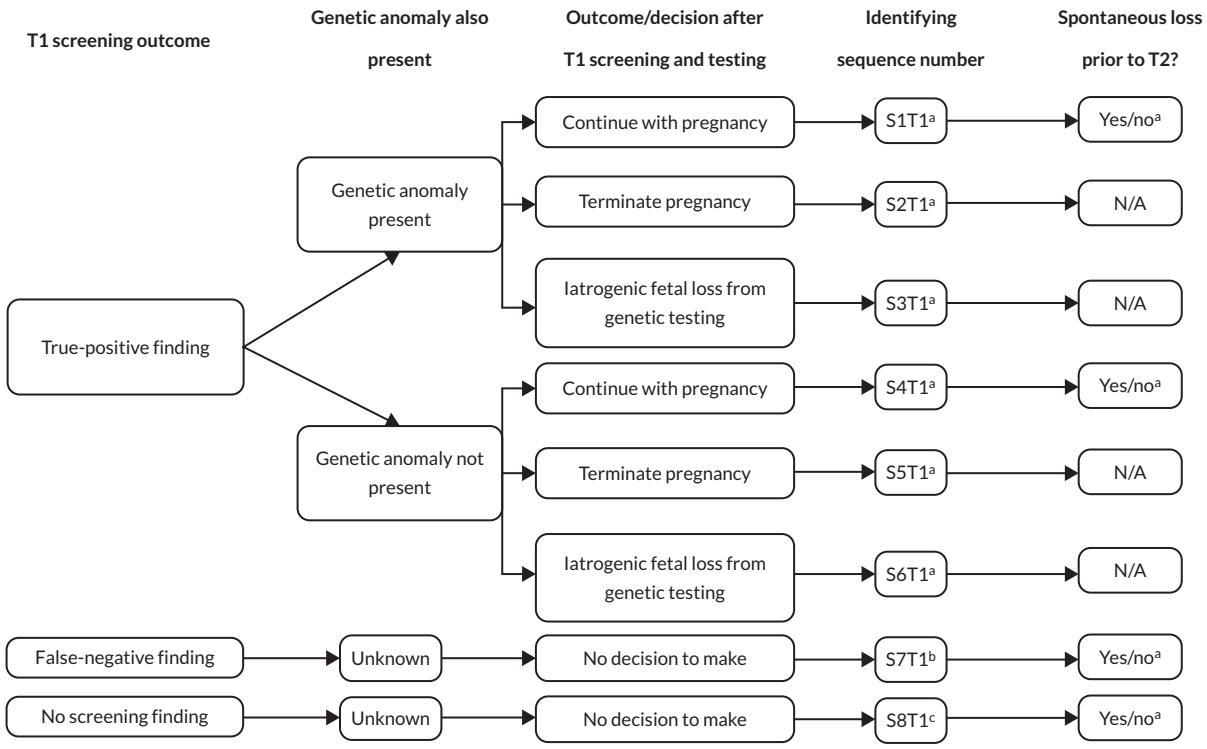

FIGURE 18 First-trimester events and associated sequence numbers (women with a structural anomaly) for which utility adjustment factors (decrements and increments) were estimated. a Associated with a utility decrement. b Reassurance provided by a negative anomaly scan gives a temporary utility increment. c Associated with no change to underlying utility levels (current practice arm and no finding during current T1 scan). N/A, not applicable; T1, first trimester; T2, second trimester.

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Costs for the decision tree

Table 17 shows the unit costs associated with each of the events women experience as they move along the pathways within the decision tree model. These national average unit costs were entered into the model as point estimates without accompanying uncertainty distributions. This is because they were sourced primarily from the 2019–20 National Schedule of NHS Costs, to which NHS trusts in England and Wales submit costs for individual NHS activities estimated using a precise and detailed process for costing patient-level resource use.

Pathway costs

At the first- and second-trimester screening points, the cost of a routine antenatal ultrasound scan was assumed for all pregnant women. Those referred by sonographers for further investigation, additionally incur the cost of a fetal medicine scan. For women screening positive for an anomaly (a TP or a fetal medicine FP screen in the first or second trimesters) we assigned relevant costs according to decisions made about invasive genetic diagnostic testing and pregnancy termination, and for spontaneous pregnancy losses and delivery. Based upon expert opinion, women screening positive during the first trimester and leaving the routine screening pathway, were assumed to receive a further fetal medicine scan prior to any second-trimester screening. In addition, and for major cardiac anomalies, exomphalos, gastroschisis, encephalocele and LUTO, we also costed a first-trimester fetal echocardiogram. For

TABLE 17 Unit costs (2019–20 UK£) used in the decision tree part of the model

Event	Cost estimate (pounds)	Source
Antenatal routine US scan	125	National Schedule of NHS Costs – Year 2019–20.[190] Outpatients. Currency Code NZ21Z, Service Code 501 (obstetrics)
Fetal medicine US scan	136	National Schedule of NHS Costs – Year 2019–20.[190] Outpatients. Currency Code NZ22Z, Service Code 501 (obstetrics)
Invasive genetic diagnostic test	364	National Schedule of NHS Costs – Year 2019–20.[190] Outpatients. Currency Code NZ72Z, Service Code 501 (obstetrics).
Antenatal echocardiogram	144	National Schedule of NHS Costs – Year 2019–20.[190] Outpatients. Currency Code EC21Z, Service Code 501 (obstetrics)
First-trimester termination	1617	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Weighted average of Currency Codes MA51Z (Surgical abortion 14–20 weeks' gestation) and MA54Z (Medical abortion 14–20 weeks' gestation)
Spontaneous miscarriage	622	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Currency Code MB08B
First-trimester iatrogenic fetal loss with genetic testing	1311	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Currency Code MA54Z (medical abortion or miscarriage care 14–20 weeks' gestation)
Second-trimester termination	2553	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Weighted average of Currency Codes MA50Z (surgical abortion over 20 weeks' gestation) and MA53Z (medical abortion over 20 weeks' gestation)
Spontaneous stillbirth	3681	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Weighted average across all delivery Currency Codes
Second-trimester iatrogenic fetal loss with genetic testing	2635	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Currency Code MA53Z (medical abortion or miscarriage care over 20 weeks' gestation)
Delivery	3681	National Schedule of NHS Costs – Year 2019–20.[190] Total activity. Weighted average across all delivery Currency Codes
Post stillbirth[a]	1012	Campbell *et al.* 2018 inflated using Curtis LA and Burns A. Unit Costs of Health and Social Care 2020[191,192]

US, ultrasound.
a Includes cost of post-mortem and suite of investigations routinely performed following a stillbirth.

screen-positive women not suffering a spontaneous miscarriage, during the second trimester, a fetal medicine screen was costed *in lieu* of a routine ultrasound scan. Women who then went on to have a live birth were assumed to have been screened by fetal medicine a further twice before their baby arrived and they were assigned a delivery cost. For screen-positive women who suffered a late fetal loss/stillbirth, only one further fetal medicine scan was costed. For all late fetal losses/stillbirths in the model, the delivery of the baby was included as part of the costing process, as were the investigations/post-mortem performed following a stillbirth.

When a pregnancy ended without a live birth, healthcare costs were included for the management of negative psychological consequences women may suffer immediately following the loss of their baby, up until the end of the decision tree time horizon (longer-term implications were captured in the maternal Markov models). *Table 18* shows the pregnancy loss events within the model, the time point at which these were assumed to occur, and informed by published literature, the proportions of women estimated to have psychological consequences significant enough to require medical intervention.

Following each type of pregnancy loss, it was assumed that not all women with symptoms would present to the health service.[193] Based upon UK Psychiatric Morbidity Survey data, McCrone *et al.* reported that only 64.5% (n = 49/76) of women aged below 45 years and with depression were in contact with healthcare services. This probability (implemented in the model with a beta distribution) was applied to the proportions in *Table 18*, to determine the proportion of women receiving treatment for psychological symptoms following the different pregnancy loss events in the model. The expected annual cost of treatment for depression (including inpatient care, GP consultations, community mental health services, medication and residential care) was also estimated by McCrone *et al.* and was £2440 (after inflation to 2019–20 prices).[193] Dividing this cost by 52 gave a weekly cost estimate which was then assigned to women receiving such treatment from the point their pregnancy ended until the end of the decision tree time horizon (durations shown in the final column of *Table 18*).

TABLE 18 Data used to estimate the proportion of women with clinically significant negative psychological symptoms immediately following a pregnancy loss event

Pregnancy loss event	Assumed weeks' gestation at time of loss	Mean proportion (SE) of women with clinically significant psychological symptoms following loss	Distribution and parameters	Source	Remaining time in decision tree following loss
Spontaneous stillbirth	30 weeks[a]	0.581 (0.0226)[b]	Beta, α = 275, β = 473−α	Inferred using Redshaw *et al.* (2014)[180] and Heazell *et al.* (2016)[181]	10 weeks
Second-trimester termination/iatrogenic fetal loss	20 weeks	First 6 weeks 0.875 (0.0802)[c]	Beta, α = 14, β = 16−α	Davies *et al.* (2005)[40]	20 weeks
		Post 6 weeks 0.571 (0.1278)[c]	Beta, α = 8, β = 14−α	Davies *et al.* (2005)[40]	
Spontaneous miscarriage	16 weeks[d]	0.300 (0.035)[b]	Beta, α = 51.13, β = 170.43−α[e]	Farren *et al.* (2018)[194]/ author assumption	24 weeks
First-trimester termination/iatrogenic fetal loss	12 weeks	First 6 weeks 0.429 (0.1278)[c]	Beta, α = 6, β = 14−α	Davies *et al.* (2005)[40]	28 weeks
		Post 6 weeks 0.417 (0.1367)[c]	Beta, α = 5, β = 12−α	Davies *et al.* (2005)[40]	

IES, impact of event scale.
a Midpoint between 20-week anomaly scan and end of tree time horizon at 40 weeks.
b For a description on how parameters were estimated, see text and *Tables 45* and *46* in *Appendix 7*.
c Proportion of women in Davies *et al.* with a cut off score > 18 (indicating psychiatric morbidity) on the IES following first- and second-trimester terminations.
d Midpoint between first- and second-trimester scans.
e Estimated from mean and SE using methods of moments approach.

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Additional screening costs associated with first-trimester anomaly screening

Two separate cost components associated with the anomaly screening protocol were calculated. Firstly, sonographers would require additional training such that during the first-trimester scan they are proficient in assessing parts of fetal anatomy affected by the anomalies in the protocol. Informed by expert opinion, we assumed sonographers would each receive 5 days of training (a mix of initial training sessions plus later consolidation sessions) provided at an NHS Trust level and delivered by a local clinical lead. There are currently an estimated 3000 sonographers working within the NHS, with the majority employed at Band 7, at a cost of £65 per working hour (inclusive of salary, on-costs, overheads and indirect costs).[192,195,196] The total training time for these individuals is estimated at £7,312,500 (3000 sonographers × 37.5 sonographer hours for training × £65 per hour). Assuming training is provided in each of the 209 NHS trusts by a Consultant in fetal medicine (£123 per working hour inclusive of salary, on-costs, overheads and indirect costs), then the estimated cost of delivering this training is £964,013 (209 NHS trusts × 37.5 consultant hours for training × £123 per hour). Total training costs are estimated at £8,276,513.

While training is fundamental, such an investment in nationwide screening can be thought of as an 'upfront' cost, with the knowledge gained being used when screening all subsequent women presenting during the first trimester. To include this cost within the analysis therefore, we assumed that around 6,163,070 women (based upon 616,307 live births and stillbirths in England and Wales in 2020)[197] would present for first-trimester screening over the next 10 years. Dividing the total training cost by this figure produced a training cost per scan of £1.34.

The second cost component is associated with the need for additional screening time for the purposes of assessing the fetal anatomy. Based upon expert opinion and findings from the nationwide site survey reported in *Chapter 6*, the base-case analysis assumed 10 minutes of screening time would need to be added to the current first-trimester scan. The cost of this extra sonographer time at £10.80 per scan (£65/60 × 10) was added to the training cost per scan (£1.34) and entered into the screening protocol arm of the model. To reflect uncertainty around this estimate (some centres may require more time than others), we used a gamma distribution with mean £12.14 and SE of £7. These moments produced a wide sampling distribution with cost estimates of £2.51 and £29.21 for the 2.5th and 97.5th percentiles, respectively (equivalent to additional scanning times of 1 and 26 minutes, respectively).

Populating the maternal Markov models – utility

The following subsection summarises the approaches used for the modelling of maternal health outcomes (QALYs) within each of the 14 maternal Markov models (full details of the estimation methods and parameter values are given in *Appendix 8*).

Underlying maternal mortality and utility

Within each maternal Markov model age- and sex-adjusted life table data for England and Wales provided annual probabilities of maternal death.[198] Maternal utility was modelled using UK-specific age- and sex-adjusted population norm utility values (see *Appendix 8*, *Table 47*).[188] Adjustments were then made to these 'underlying' mortality and utility levels within the maternal Markov models for each of the different pregnancy outcomes in the decision tree.

Adjustments to underlying maternal utility and mortality

Following the live birth of a baby with an anomaly, and in accordance with the literature, levels of underlying maternal utility and mortality were modelled as being negatively affected. As the anomalies contained within the basic protocol vary substantially in terms of their implications for the prognosis for the child (and thus the mother), the magnitude and duration of the decrements to underlying maternal utility levels in the live birth maternal Markov models, were anomaly-specific. Also accounted for were the immediate and sustained quality-of-life impacts for mothers whose infants were live born but then died during infancy/childhood (see *Appendix 8*).

For women whose pregnancy ended prematurely and without the birth of a live baby (e.g. as a result of a stillbirth, or a termination), in the respective Markov models we decremented underlying levels of utility to account for the short- and longer-term quality-of-life impacts associated with the type of pregnancy loss and the gestation at which the loss occurred (full details are provided in *Appendix 8*).

Costs

The longer-term costs included in each of the 14 maternal Markov models were for the medical treatment of negative maternal psychological symptoms associated with each of the pregnancy outcomes from the decision tree. A summary of the methodology is given below, with full estimation details and resulting parameter values provided *Appendix 8*.

For women giving birth to a baby with an anomaly, we estimated the annual proportion for whom negative psychological symptoms would likely reach levels that were clinically significant enough to warrant medical intervention. Such proportions were again estimated by anomaly type, along with the duration for which symptoms would likely persist. For women whose babies died during a cycle of the model, we estimated the proportion for whom symptoms would likely be severe enough to indicate a need for treatment in both the short-term and over the longer term. When costing, and on the basis of published evidence, we assumed not all women with clinically significant symptoms would be known to the health service. To the women presenting for care, we assigned annual treatment costs for anxiety and depression informed by the published literature (see section above on decision tree costs).

As for women with live births, we assumed that a proportion of women whose pregnancies ended without the live birth of a baby would also experience levels of psychological distress reaching levels warranting medical intervention. These proportions and the amount of time for which they persisted and treatment would be provided were again determined by the nature of the pregnancy loss and the gestation at which it ended. Costs were estimated as described above, assuming not all affected women would present to the health service.

Infant Markov models

Infant healthcare costs and QALYs were reported as secondary end points. *Appendix 9* provides details of all parameter estimates and assumptions used when populating each of the 13 infant Markov models developed to simulate 20-year infant costs and QALYs following a live birth with and without each type of anomaly. Briefly, transitions from the alive to the deceased health state within each infant model were informed by appropriate (anomaly-specific or lifetable) age-adjusted mortality risks identified through the project's systematic reviews and supplementary literature searching. Underlying utility for each cycle in the alive health state of a model, was informed by Health Utilities Index 3 (HUI3) reference scores in a population of Canadian children.[199] Within each model, these underlying utility levels were then decremented to account for the impact on quality of life of the specific anomaly being modelled. Such decrements were taken from a UK study estimating utilities (again using the HUI3) for 2236 children with a range of childhood conditions and were applied for varying durations as determined by the prognosis of the anomaly being modelled.[200] Costs included in each model were informed by the published literature and captured the costs of initial and subsequent corrective surgeries (when applicable), ongoing healthcare needs, and end of life care (for lethal anomalies).

Each model was run 10,000 times (each time sampling a set of parameter estimates from the distributions entered) and the resulting expected mean infant healthcare costs and QALYs associated with each type of live birth were extracted and are shown in *Table 19*. These costs and QALYs were then used as model input parameters and were attached as secondary pay-offs (using gamma distributions) to their corresponding live birth end points in the decision tree model. Model pathways culminating in the loss of a baby were assigned zero infant healthcare costs and QALYs.

Running the model

The entire model was run 10,000 times, each time sampling a set of values from the parameter distributions entered. The sampled parameter estimates along with the range of different outcomes were extracted for each run of the model. The following model outputs were available:

- Pregnancy outcomes for women whose babies are affected by the structural anomalies included in the protocol. Outcomes include live births with an anomaly, first-trimester terminations, spontaneous miscarriages, second-trimester terminations, spontaneous late fetal loss/stillbirth, and iatrogenic fetal losses as a result of genetic testing.
- Fetal medicine FP screens for women whose babies are unaffected by any of the anomalies included in the protocol.
- Expected maternal costs and QALYs for the model cohort as a whole (all women attending for first-trimester antenatal screening).
- Expected infant costs and QALYs for babies affected by the anomalies included in the protocol.

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TABLE 19 Simulated 20-year mean discounted infant healthcare costs and QALYs per live birth by anomaly type, and for a healthy infant (used as pay-offs in the decision tree)

Anomaly type	Mean (SE) 20-year cost (£)	Mean (SE) 20-year QALY
Major cardiac anomaly + genetic anomaly	119,874 (5299)	4.173 (0.767)
Major cardiac anomaly – genetic anomaly	77,933 (5270)	9.643 (0.231)
Acrania	3575 (245)	0.000 (0.000)
Omphalocele/exomphalos + genetic anomaly	59,635 (6323)	1.538 (0.581)
Omphalocele/exomphalos – genetic anomaly	57,335 (539)	11.784 (0.345)
Gastroschisis	90,381 (268)	12.285 (0.240)
Alobar holoprosencephaly	15,368 (-)	0.000 (0.000)
LUTO + genetic anomaly	90,404 (7287)	3.249 (0.766)
LUTO – genetic anomaly	57,008 (6876)	9.894 (0.585)
Encephalocele + genetic anomaly	67,346 (3591)	2.778 (0.573)
Encephalocele – genetic anomaly	57,117 (3379)	4.858 (0.623)
Body stalk anomaly	N/A	N/A
Genetic anomaly alone	57,195 (191)	4.168 (0.746)
Infant without anomaly	25,159 (-)	13.241 (0.156)

N/A, not applicable as the model simulated no live births with body stalk anomaly.

Deterministic one-way sensitivity analyses

A small number of deterministic sensitivity analyses focused upon key uncertain model parameters, and the implications for the maternal cost-effectiveness results were assessed.

Costs

Uncertainty exists around the additional scanning time needed by sonographers if they are to systematically screen for structural anomalies during the current first-trimester dating scan. While the base-case analysis allows for an additional 10 minutes per screen, it is possible that in certain scenarios more time may be needed, for example, if in the future, the basic protocol evolves to include additional anomalies affecting other parts of the fetal anatomy.

With this in mind, we conducted a sensitivity analysis, in which the additional scanning time required to screen for structural anomalies during the first trimester was assumed to be 20 minutes. This would amount to an increase in the average screening time currently allotted for an existing first trimester scan of about two-thirds.

Outcomes

As the model predicted changes to the proportions of women undergoing first- and second-trimester terminations and of live births of babies with an anomaly, we sought to explore the uncertainty surrounding some of the key assumptions made about the impact of these pregnancy outcomes upon levels of maternal utility and well-being.

For women giving birth to a baby with an anomaly, the model linked longer-term maternal utility to the survival prognosis of the child. For women suffering the loss of their infant during any given year, utility levels were decremented immediately and substantially before following a gradual 'linear' recovery trajectory. Given the uncertainty around the duration for which maternal psychological symptoms persist following the loss of a child, two alternative analyses were conducted in which women were first assumed to have recovered after 5 years (as per the model's assumption following a stillbirth) and then not until 20 years, some studies having reported women being affected for decades.[201,202]

For the base-case analysis and compared to women undergoing a first-trimester termination, the utility of women undergoing a second-trimester termination was further reduced in the period immediately following the termination, and then by a lesser amount over the longer term. For the sensitivity analysis, we removed both of these additional utility decrements and assumed the impact of a pregnancy termination to be the same for woman, regardless of the GA at which it is performed.

Uncertainty surrounds the magnitude of the temporary utility increment that women in the model receive as a result of being reassured by a negative first-trimester anomaly scan. In the absence of evidence, the base-case analysis was performed assuming a uniform distribution for this parameter, with minimum and maximum values of 0 and 0.02, respectively. Unlike many of the model's other parameters, which relate to the presence of structural anomalies and so affect only a small proportion of the screened population, around 90% of all women in the protocol arm of the model screen negative for a structural anomaly in the first trimester and so receive this transient (8-week) utility increment. As changes to the value of this parameter estimate will affect most women, the potential to impact the cost-effectiveness results is greater. Accordingly, we performed three alternative analyses, in which the utility increment was assigned fixed values of 0 (no reassurance – an extreme and unlikely scenario), 0.01 and 0.02.

Results

Pregnancy outcomes

Table 20 shows the pregnancy outcomes predicted by the model for women whose babies are affected by the anomalies in the protocol. The numbers are scaled up to a population level assuming 616,307 pregnant women present for first-trimester screening during a year (the total number of live births and stillbirths in England and Wales in 2020).[194] Based upon these population numbers and the prevalence estimates for the structural anomalies contained within the basic protocol (see *Table 1*, *Chapters 4* and *5*, women with babies affected by these eight anomalies are estimated to make up around 0.7% of all pregnant women attending for first-trimester screening.

The modelling suggests that the inclusion of a basic protocol to screen for a limited number of fetal structural anomalies at the first-trimester antenatal screening point would lead to a change in pregnancy outcome for some women whose babies are affected by an anomaly (around 680 women or 0.1% of the whole population screened). By providing more women with information about their baby's condition at an earlier stage, the analysis predicts that the number of first-trimester terminations would increase by just over two-thirds from 1003 to 1687. *Table 20* suggests that almost three-fifths of these additional first-trimester terminations would likely occur in women who would still have previously

TABLE 20 Model predicted pregnancy outcomes for women with babies affected by an anomaly[a]

Pregnancy outcomes for women with a fetus affected by a structural anomaly[a]	T1 anomaly screening protocol, *N* (SE)	Current practice, *N* (SE)	Mean difference (95% CI)
Live birth	1878.60 (124.20)	2142.07 (89.54)	−263.47 (−503.77 to −48.06)
T1 termination	1686.82 (168.51)	1003.28 (112.55)	683.54 (374.65 to 1017.91)
Spontaneous miscarriage of fetus	245.32 (42.96)	263.40 (49.25)	−18.08 (−50.48 to 15.45)
T2 termination	392.42 (41.13)	778.85 (58.24)	−386.43 (−501.53 to −279.98)
Spontaneous late fetal loss/stillbirth	90.79 (9.26)	106.48 (9.98)	−15.69 (−25.09 to −7.91)
Iatrogenic fetal loss as a result of genetic testing	5.12 (2.47)	5.00 (1.68)	0.12 (−1.71 to 3.28)

T1, first trimester; T2, second trimester.
a Eight anomalies contained within the proposed basic protocol: acrania, body stalk anomaly, encephalocele, gastroschisis, alobar holoprosencephaly, LUTO, major cardiac anomaly and omphalocele/exomphalos.

Note
Numbers given are based on a general population of 616,307 pregnant women attending for first-trimester screening.

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chosen to terminate their pregnancies but during the second trimester following existing routine anomaly screening. The remaining two-fifths appear to be in women previously continuing with their pregnancy and having a live birth.

For the 99.3% of women whose babies are unaffected by an anomaly, the model suggested the screening protocol would not impact the numbers ultimately being given a fetal medicine FP diagnosis following first-trimester screening [around 1225 women per arm (0.199%), when scaling up results to a population level of 616,307]. Such findings are intuitive for a number of reasons. Firstly, the estimated first-trimester sonographer FP rates for the eight anomalies are already very low with current practice (see *Table 16*). Secondly, for certain anomalies (such as acrania), the protocol is unlikely to increase the number of sonographer FP referrals to fetal medicine, and for others (such as holoprosencephaly and encephalocele) even a doubling of current practice FP rates means only small numbers of additional women being referred to fetal medicine. Thirdly, the first-trimester fetal medicine FP rates (assumed to be the same in both model arms) are also very low (see *Table 16*), meaning the vast majority of sonographer FP referrals received are corrected by fetal medicine consultants.

Maternal costs and quality-adjusted life-years

Table 21 shows, for a cohort of all pregnant women presenting at the first-trimester screening point, the estimated mean 20-year per woman costs and QALYs both with and without a protocol for first-trimester anomaly screening. A small mean cost increase per woman of £11 (95% CI £1 to £29) is associated with the addition of a protocolised first-trimester anomaly scan. This incremental cost is attributable primarily to the additional sonographer training and screening time that would be required to facilitate implementation of the protocol across all women.

The increased cost is accompanied by a small yet significant maternal QALY gain of 0.002065 QALYs (95% CI 0.00056 to 0.00358). This gain comes from the temporary reassurance provided to all screened women with a negative first-trimester anomaly scan and through a reduction in negative maternal psychological symptoms attributable to changes in the pregnancy outcomes of women with affected fetuses (see *Table 20*). Dividing the additional costs by the additional QALYs allows calculation of the incremental cost-effectiveness ratio (ICER), at £5270 per QALY gained. *Table 22* shows these same data, but once more scaled up for a general population of 616,307 pregnant women attending for first-trimester antenatal screening.

TABLE 21 Estimated 20-year mean costs and maternal QALYs per pregnant woman, and incremental cost per QALY

	T1 anomaly screening protocol	Current practice	Mean difference (95% CI)
Mean (SE) cost per woman	£4210 (£27)	£4199 (£26)	£11 (£1 to £29)
Mean (SE) QALYs per woman	13.656 (0.083)	13.654 (0.083)	0.002065 (0.00056 to 0.00358)
Incremental cost-effectiveness ratio			£5270

T1, first trimester.

TABLE 22 Estimated 20-year total costs and maternal QALYs for a population of 616,307 pregnant women attending for first-trimester screening

	T1 anomaly screening protocol	Current practice	Mean difference (95% CI)
Total (SE) costs	£2,594,541,358 (£16,632,351)	£2,587,832,615 (£16,059,304)	£6,708,742 (£688,280 to £17,598,285)
Total (SE) QALYs	8,416,545 (50,935)	8,415,272 (50,937)	1273 (348 to 2208)

T1, first trimester.

Probabilistic sensitivity analysis

Figure 19 plots the 10,000 simulated estimates of mean cost and maternal QALY differences on the cost-effectiveness plane. The cloud of points lies predominantly within the upper right-hand quadrant of the plane. The solid diagonal line denotes a maximum willingness to pay (WTP) value for a QALY of £20,000, a value that in the UK, is thought to be representative of society's maximum WTP for a QALY. Just over 95% of the plotted cost and QALY differences lie below and to the right of this line, and thus generate ICERs lower than £20,000 per QALY.

The implications of joint parameter uncertainty for the cost-effectiveness results are also depicted using the cost-effectiveness acceptability curve (CEAC), which illustrates for a range of maximum WTP values for a QALY, the likelihood that the addition of an anomaly screening protocol to first-trimester routine antenatal screening will represent a cost-effective use of scarce healthcare resources. *Figure 20* shows the CEAC for the model's base-case results.

Figure 20 shows the CEAC climbs steeply. At a maximum WTP for a QALY of just £10,000, the probability that screening for structural anomalies during the first-trimester scan will be cost-effective, is 81.1%. At a WTP value of £15,000 per QALY, it is 91.3%, and at £20,000 per QALY, it is 95.5%.

Infant costs and quality-adjusted life-years

Table 23 shows the expected 20-year costs and QALYs for those infants affected by the eight anomalies contained within the proposed protocol. The results are again scaled to a general population level assuming 616,307 pregnant women presenting for first-trimester antenatal screening. The model results suggest first-trimester structural anomaly screening would be associated with significant changes to infant healthcare costs and QALYs.

Deterministic sensitivity analysis for maternal costs and quality-adjusted life-years

Figure 21 plots the CEACs for the base-case analysis and the alternative scenario assuming an additional 20 minutes would be required to facilitate first-trimester anomaly screening. The mean cost difference per woman increases from £11 (95% CI £1 to £29) in the base-case analysis to £22 (95% CI £10 to £38), and the ICER increases from £5270 to

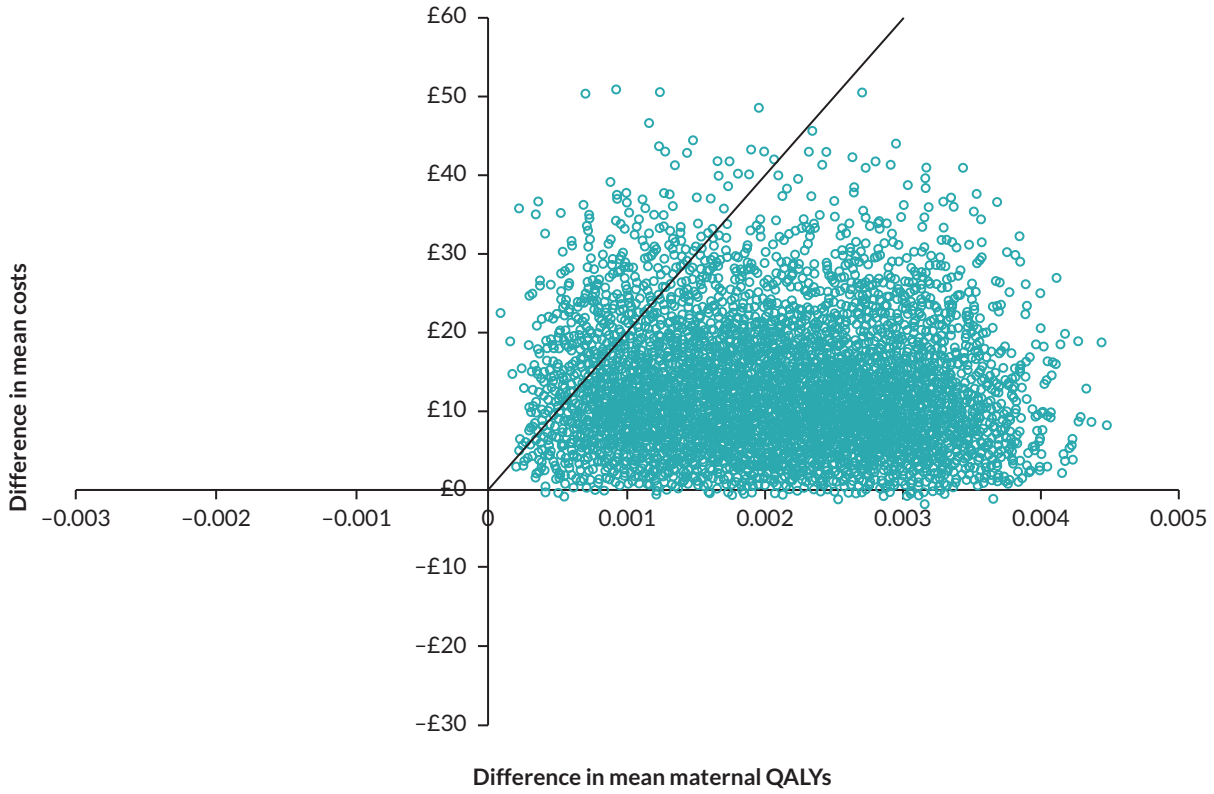

FIGURE 19 Cost-effectiveness plane showing 10,000 pairs of mean cost and maternal QALY differences between current antenatal screening practice plus a basic first-trimester anomaly screening protocol, and current antenatal screening practice alone.

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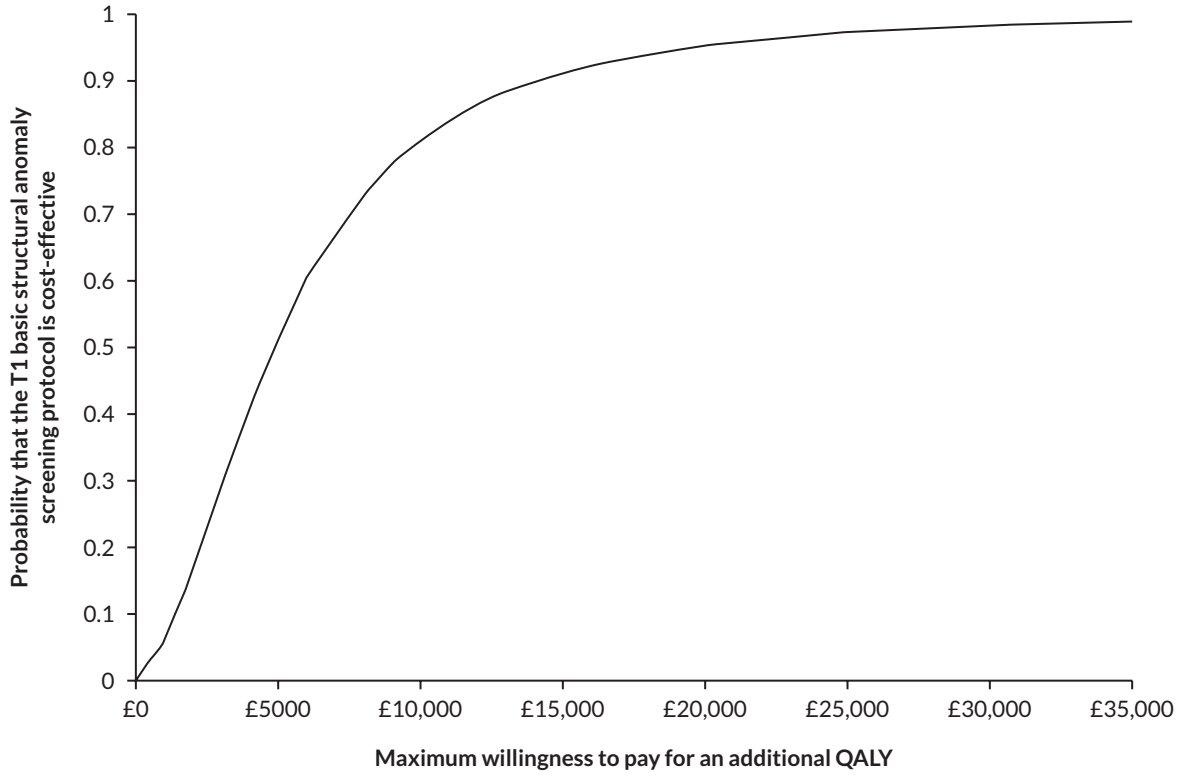

FIGURE 20 Cost-effectiveness acceptability curve.

TABLE 23 Estimated 20-year total costs and QALYs for infants affected by the eight structural anomalies in a population of 616,307 pregnant women attending for first-trimester screening

	T1 anomaly screening protocol	Current practice	Mean difference (95% CI)
Total (SE) costs	£143,077,691 (£12,180,642)	£162,307,600 (£11,164,783)	−£19,229,909 (−£38,376,249 to −£2,440,806)
Total (SE) QALYs	18,442 (1259)	20,671 (960)	−2229 (−4522 to −198)

T1, first trimester.

£10,514. The probability that the addition of a protocol for first-trimester anomaly screening would be cost-effective at £20,000 per QALY under this scenario is 83.7%. *Table 24* presents the results of the other deterministic sensitivity analyses conducted.

Discussion

This chapter has described the development and population of a substantial health economic model developed to provide an insight into the short- and long-term costs and consequences of a decision to implement a protocol for first-trimester structural anomaly screening within the current NHS antenatal screening pathway.

Results from the model predict that second-trimester terminations would fall by around one-half (see *Table 20*). For these women, first-trimester structural anomaly screening would not alter their decision to terminate the pregnancy, rather the detection of their baby's anomaly during the first trimester, would allow women to make the same decision but at an earlier GA. For a smaller proportion of women, the model suggests first-trimester fetal structural anomaly

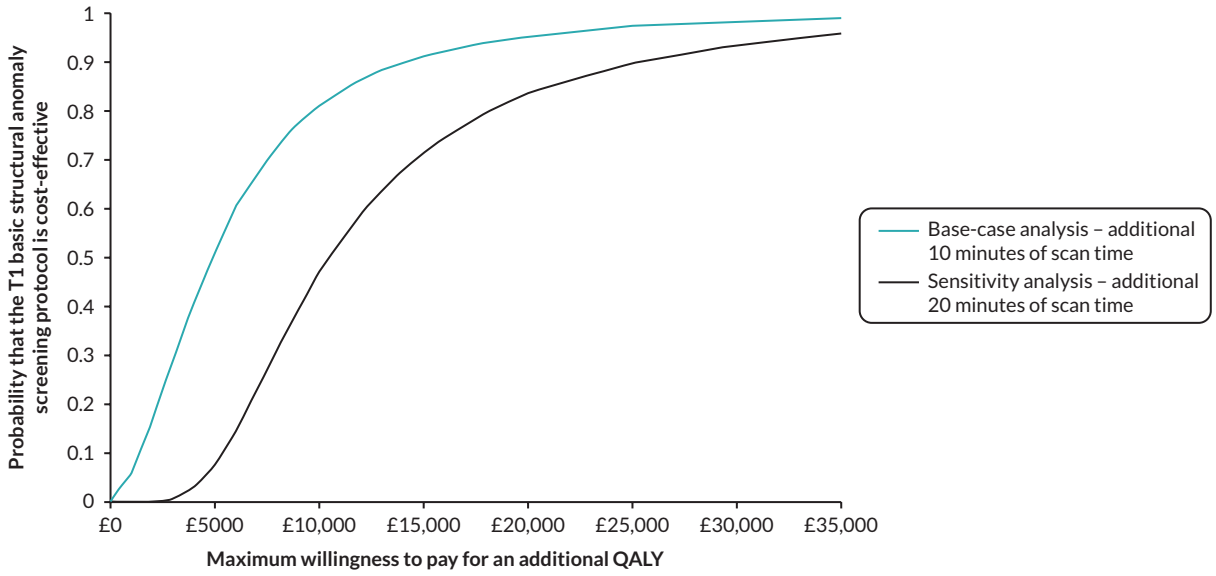

FIGURE 21 Cost-effectiveness acceptability curves for the base-case analysis (maternal healthcare costs and QALYs) and alternative scenarios assuming implementation of a protocol for first-trimester anomaly screening would require an additional 20 minutes of scanning time.

TABLE 24 Results of the deterministic sensitivity analysis for mean maternal healthcare cost and QALY differences and cost-effectiveness

Analysis description	Mean cost difference (£)	Mean QALY difference	Incremental cost per QALY gained	Probability T1 anomaly screening is cost-effective at £20,000 per QALY (%)
1. Base-case results	11 (1 to 29)	0.002065 (0.00056 to 0.00358)	£5270	95.45
2. The duration over which a woman's utility recovers to underlying norm levels following the live birth and then loss of her infant is set to 20 years.	11 (1 to 28)	0.002337 (0.00082 to 0.00389)	£4580	97.88
3. The duration over which a woman's utility recovers to underlying norm levels following the live birth and then loss of her infant is set to 5 years.	11 (1 to 29)	0.001754 (0.00039 to 0.00312)	£6326	91.04
4. The additional utility decrements assigned to women undergoing a second-trimester termination are removed.	11 (1 to 29)	0.001961 (0.00048 to 0.00347)	£5552	93.86
5. The temporary reassurance utility increment assigned to women following a negative anomaly scan is fixed at 0 (i.e. no reassurance received).	11 (1 to 29)	0.000674 (0.00020 to 0.00134)	£16,147	62.92
6. The temporary reassurance utility increment assigned to women following a negative anomaly scan is fixed at 0.01.	11 (1 to 29)	0.002061 (0.00159 to 0.00273)	£5281	99.59
7. The temporary reassurance utility increment assigned to women following a negative anomaly scan is fixed at 0.02.	11 (1 to 29)	0.003448 (0.00298 to 0.00413)	£3157	100.00

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screening will alter their decision about pregnancy continuation. *Table 20* shows around 260 fewer births of infants affected by an anomaly, as women who may have previously received a diagnosis during the second trimester and decided to continue with their pregnancy, now choose a first-trimester termination.

Cost reductions and maternal QALY gains predicted by the model arise from fewer second-trimester terminations, which evidence suggests are associated with greater procedural risks (and costs) as well as increased and persisting levels of maternal psychological distress, when compared with first-trimester terminations.[38,40,203] The financial and the physical and emotional implications for women of raising a child with a major congenital anomaly are also substantial and with a first-trimester screening protocol the model simulates further cost reductions and maternal QALY gains.

Such changes to costs and maternal QALYs might be expected to affect < 0.2% of all women screened, and so when averaged across the whole screening cohort they amount to small incremental changes at the level of the individual woman. QALY gains with the new protocol are attributable in the main to the 'reassurance' utility increment women receive from being given a negative first-trimester anomaly screening result. Although the magnitude of this increment is small and temporary (0.01 lasting only for the 8-week period between first- and second-trimester scans), it is received by around 90% of women in the protocol arm of the model. As such, it accounts for just over two-thirds of the mean difference in maternal QALYs observed in the base-case analysis (see corresponding sensitivity analyses in *Table 24*).

The additional per woman costs associated with first-trimester structural anomaly screening are likely to be low. This is because the infrastructure needed to conduct such screening is already in place via the NHS antenatal screening programme. Also, and as shown by the site survey in *Chapter 6*, a high proportion of centres are already performing some assessment of fetal anatomy within the context and time constraints of the current first-trimester scan. The analysis thus assumes additional costs relating only to sonographer training and additional scanning time. For the purposes of the modelling, the training costs were apportioned across all screened women over a period of 10 years, but it is pertinent to acknowledge that in practice the investment in staff training would be an upfront cost that would need to be borne by the NHS. Further, staff turnover will result in the need for some ongoing training, however such costs would add little to those reported here. One must consider that if the basic protocol were extended to encompass additional anomalies and the need for more screening time than modelled here, then additional assessments around NHS capacity (e.g. staff and machine availability) would likely be required.

The cost savings described above relating to the changes in pregnancy outcomes for small numbers of women, offset only around 10% (£1.25) of the average additional screening cost (£12.14 in the base-case analysis). Thus, overall, first-trimester structural anomaly screening is associated with a small cost increase (£11) and a small maternal QALY gain (0.002065) when compared with current practice (see *Table 21*).

Incremental analysis suggests implementation of the proposed protocol is likely to be cost-effective. One-way deterministic sensitivity analysis showed cost-effectiveness results to be most sensitive to changes in a small number of parameters, including the cost of additional scanning time required for first-trimester structural anomaly screening. A requirement for an additional 20 minutes of scanning time for example reduced the probability of cost-effectiveness from 95% to 84%, but extensions to screening times of this duration are in reality unlikely. Results also varied according to the size of the utility increment added to the model to reflect the reassurance the majority of screened women receive following a negative anomaly screening result. Although it was not possible to identify any studies reporting a 'reassurance' utility increment for use in the model, evidence from a number of published sources suggested a normal screen result does provide reassuring qualities for women.[204–206] Furthermore, in the survey of women's views of anomaly screening reported in *Chapter 9*, 86% of pregnant women in favour of a first-trimester anomaly scan cited early reassurance as one of the main reasons that they would accept a screening invitation. Guided further by expert opinion we adopted a conservative approach to this parameter by including in the model only a small utility increment (0.01) over a short period of time (8 weeks).

Although cost-effectiveness was estimated on the basis of maternal costs and QALYs, in an attempt to be transparent and comprehensive, we also simulated and reported the potential impact of the proposed protocol upon infant healthcare costs and QALYs. Analysts reporting economic evaluations of antenatal screening programmes that may result in the termination of affected fetuses have previously been criticised for either ignoring the implications for

the infant or quantifying the benefits of such programmes solely in terms of the future healthcare cost savings that follow as a result of the termination of a fetus with a disability.[207,208] Petrou noted that in taking the latter approach, the analyst is ascribing the fetus or unborn child a future human status, which should, by convention, mean that some valuation of the health forgone as a result of the termination, is also required.[207] While we have attempted in part to follow this approach and have modelled and reported costs and QALYs for mothers and infants separately, we cannot, within the scope of this project, address the unresolved methodological challenges facing economists around how to reconcile such opposing effects of antenatal screening. We are, however, well aware of the ethical dilemmas that such analyses present.

Such challenges are evidenced elsewhere in the literature. Little *et al.*, for example, in their model of prenatal screening for spinal muscular atrophy, acknowledged the implications of pregnancy termination, but noted that considering neonatal QALYs alongside maternal QALYs would have biased against any screening regimen.[209] For the same reasons, Karnon *et al.* suggested QALYs to be inappropriate for use in assessing antenatal evaluations.[210] A recent piece of work involving one of the authors of this report (ORA), has suggested analysts reporting economic evaluations of antenatal and newborn screening programmes continue to grapple with challenges around how to measure health impact and that there is an immediate need to provide guidance that can be followed when evaluating and interpreting the overall implications such programmes.[175] In this instance, and for the reasons outlined in the *Methods* section above, we have used maternal QALYs as the basis of our cost-effectiveness results and report infant costs and QALYs alongside. A reduction in infant costs and QALYs is predicted with first-trimester anomaly screening as a consequence of fewer live births of infants with an anomaly. Until further research is able to determine society's preferences for such a screening programme however, we cannot say with certainty that this would widely be considered a harm. Aggregating maternal and infant costs and QALYs would be akin to assuming this is the case and could lead to erroneous conclusions being drawn about the net health impact of first-trimester anomaly screening.

As with any modelling study, there are limitations to our analysis. It was necessary to make a number of simplifying assumptions for example relating to the structure of the model and the estimation of some parameters, and we have attempted to be as transparent as possible in documenting and justifying these. The rarity of the conditions modelled made it particularly challenging when estimating maternal and infant costs and QALYs, as few studies report data of the management, surveillance and outcomes for sizeable cohorts of children born with these anomalies. As a result, infant healthcare costs (and their associated uncertainty) in particular are likely to be under-estimated. Also, the perspective of the analysis, was restricted to that of the NHS, but we acknowledge that the implications of first-trimester screening for structural anomalies is likely to be much more far reaching, and will touch partners, wider family members, and employers. Additionally, and as with any model synthesising data from multiple sources, one must ensure the data inputs are representative of the study jurisdiction. For this project, steps were taken to prioritise UK-based data in the first instance, followed by data from countries comparable to the UK in terms of their gross domestic product and healthcare provision. When data were not available from any source, we sought expert opinion from obstetricians working within the NHS. Finally, the time horizon for the analysis was restricted to 20 years. Had it been possible to simulate costs and maternal QALYs over a longer duration, it is unlikely that cost-effectiveness would have increased substantially; first-trimester anomaly screening alters pregnancy outcomes and thus has longer-term implications for a very small proportion of all pregnant women attending for screening.

The model presented in this chapter is novel in its comprehensiveness. It was devised to capture the short-term implications for women of the first-trimester anomaly screening results they receive, and both the short and longer-term effects of the ensuing decisions they make following positive screening findings. For women giving birth to infants with anomalies, the model connects a mother's outcomes with those of her child, as the two are inextricably linked. Healthcare costs and QALYs for infants are also modelled and reported separately. We are unaware of any similarly comprehensive models previously published in the area of antenatal screening.

The following chapter uses outputs from this model within a VoI framework to ascertain whether current levels of evidence are sufficient to inform a decision on the adoption of first-trimester structural anomaly screening now, or whether additional evidence is needed to support this decision in the future.

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Chapter 11 Value-of-information analysis

Introduction

In the previous chapter, we provided a complete description of the decision-analytic cost-effectiveness model. Results suggested that first-trimester detailed anomaly screening was likely to be cost-effective with a probability of 95% in our base-case analysis of maternal healthcare costs and QALYs.

Based on these findings, can we safely modify the current FASP? To answer this question, we have to recognise that the adoption of a screening programme modification is subject to decision uncertainty. However, in this case, the amount of decision uncertainty around the potential impact upon maternal healthcare costs and QALYs appears low. One approach would be to present these cost-effectiveness results with associated uncertainty to the UK NSC and ask them to consider the associated decision uncertainty before they make a recommendation about whether or not to adopt the screening programme modification. The decision to adopt or not would then be based on their attitudes towards risk of making the wrong decision. Another alternative is to formally evaluate this decision uncertainty using a framework that provides relevant information to the UK NSC about two key aspects. Firstly, whether given the current level of evidence used to inform the mean estimates and associated uncertainty of the parameters in the decision-analytic model, we should adopt first-trimester detailed anomaly ultrasound screening as a programme modification in the NHS, and secondly, whether additional evidence is needed to support this decision in the future. VoI provides such a framework and is the focus of the analysis presented in this chapter. The VoI analysis was conducted on the model's base-case results for maternal costs and QALYs.

Methods

We followed the processes recommended by the recent International Society for Pharmacoeconomics and Outcomes Research Value of Information Analysis Emerging Good Practices Task Force to undertake and report the results of our VoI analysis.[211] These procedures are presented in detail in *Figure 22*. At the centre of this process, there is a decision-analytic model representing the decision problem. The first four steps were covered in the previous chapter and included the conceptualisation and construct of the model, its parametrisation with evidence and the characterisation of uncertainty. Steps 5 and 6, respectively, describe approaches to determine whether more research is potentially worthwhile, and the value of specific research. The final step 7 indicates that the whole process may start again in light of new evidence.

VoI metrics are derived from net-benefit statistics, which we make use of in this chapter to present cost-effectiveness and VoI results. Net-monetary benefits are calculated at a WTP of £20,000 per QALY.[183] To establish whether more research was potentially worthwhile, the EVPI and the EVPPI were first estimated (*Figure 22*, Step 5). EVPI is the expected cost of the uncertainty given current evidence and is interpreted as the ideal research efforts that would remove all the uncertainties in a model. A non-parametric approach to EVPI using the PSA output directly was used, and we estimated EVPI per person and for the entire population that will benefit from screening over a time horizon for which the decision question around first-trimester screening was assumed to remain relevant.[183] In our analysis, we assumed the annual number of women undergoing first-trimester screening in England and Wales to be 616,307 (total number of live and stillbirths recorded in both countries in 2020).[197] We selected a time horizon of 20 years because screening programmes once implemented, are likely to remain in place unless technology breakthroughs render the screening programme obsolete or accumulated evidence suggests it generates more harms than benefits. To assess the impact of time horizon on the EVPI results, we replicated the analysis using 5, 10 and 15 years. Population EVPI values were compared with the expected costs of research to establish whether further research was potentially worthwhile.

If further research appeared valuable based on the population EVPI, we estimated EVPPI to identify whether research efforts concentrated on one or several studies to remove uncertainty on a group of parameters was worthwhile.

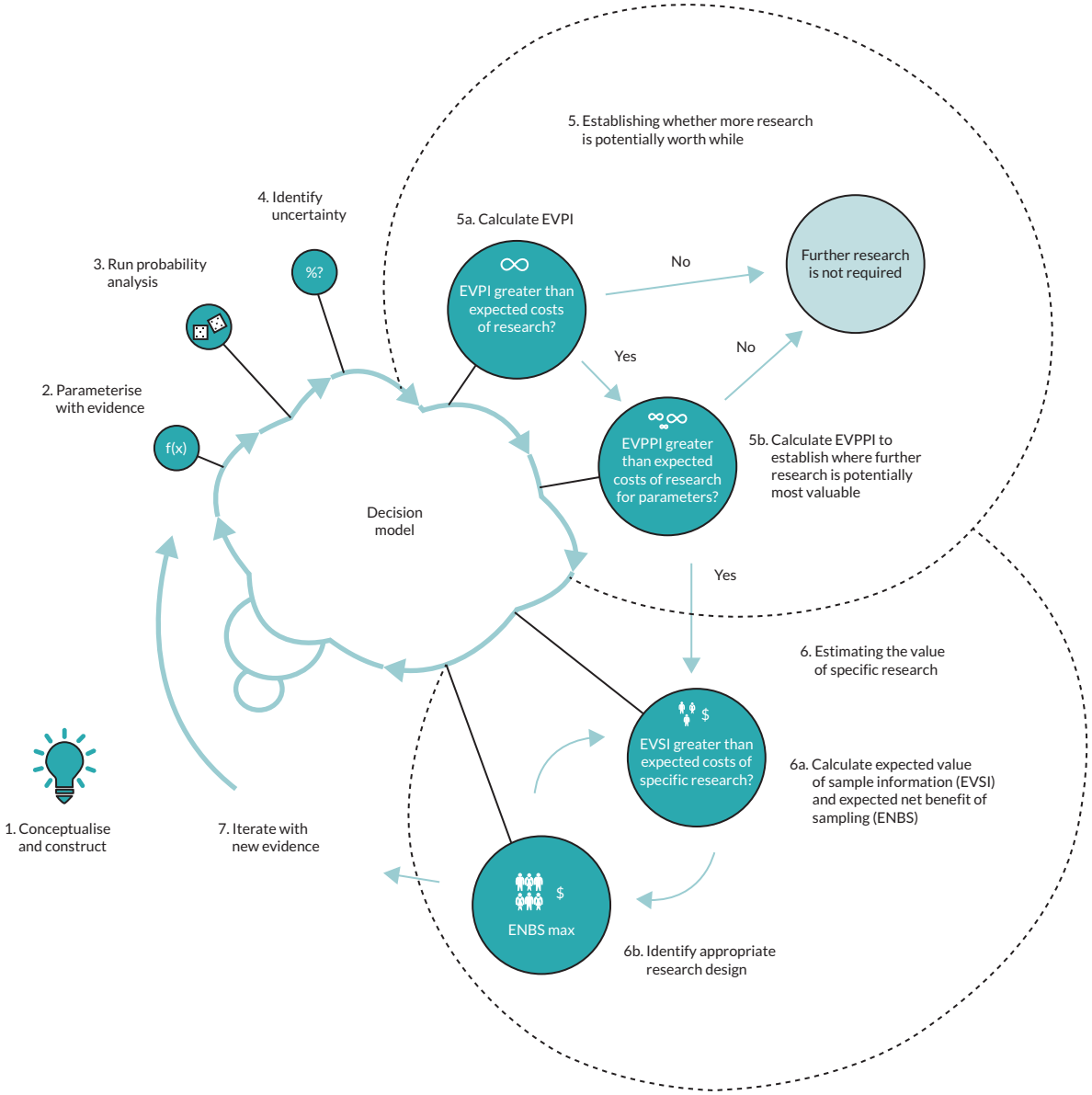

FIGURE 22 The process of VoI analysis. Reproduced with permission from Elsevier from Fenwick *et al.*[211]

We categorised the parameters as in *Table 25* representing areas of potential future research. EVPPI was estimated using the Sheffield Accelerated Value of Information tool that implements a non-parametric regression method using a generalised additive model for groups of up to five parameters and Gaussian process regression for groups with five or more parameters.[212] Population EVPPIs were compared with the expected costs of research for each group of parameters to determine whether research was potentially valuable.

If further research for groups of parameters was considered worthwhile based on the EVPPI analysis, the next step would be to estimate the value of specific research using expected value of sample information (EVSI) and expected net benefit of sampling (ENBS) (*Figure 22*, Step 6). EVSI indicates the upper limit on the value of specific research based on different sample sizes. The unit normal loss integral function and linear regression metamodeling as described by Jalal and colleagues can be used to estimate EVSI for different sample sizes.[213] This approach allows the estimation of VoI metrics directly from the PSA output and relies on the assumption that the incremental net benefit is normally distributed. The difference between the population EVSI for a specific study and the expected costs of the study is

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TABLE 25 Groups of parameters used in the EVPPI analysis

Group of parameters	Brief description	Number of parameters included
Anomaly characteristics	Individual anomaly prevalences, and co-existence of genetic anomalies at both first- and second-trimester screening points	17
Additional screening cost	Additional cost per anomaly scan, inclusive of staff training and extra scanning time	1
Maternal psychological symptoms	Probability of maternal psychological symptoms associated with each of the modelled pregnancy outcomes	19
Pregnancy outcomes	Anomaly-specific probabilities for each pregnancy outcome for example first and second-trimester terminations, spontaneous miscarriages, stillbirths etc.	57
Screening performance	First- and second-trimester anomaly-specific screening performance probabilities for example TPs, and sonographer and fetal medicine FPs.	58
Screening and testing acceptance	Probabilities of accepting first-trimester anomaly screening, and in women screening positive for a structural anomaly, of accepting genetic diagnostic testing.	2
Maternal utility (screening)	Utility increment associated with reassurance received from a negative anomaly scan and utility decrement persisting after a FP scan result is corrected.	2
Maternal utility (all other)	Underlying maternal utility levels and utility decrements associated with all other screening and pregnancy outcomes	19

the ENBS. A positive ENBS indicates that the benefits associated with the potential new study, outweigh the costs of undertaking such study suggesting that further research is worthwhile. It is possible to identify an optimal sample size that maximises ENBS, and a range of study sample sizes associated with a positive expected return on investment.

Results

Figure 19 in the previous chapter plotted the base-case PSA results on the cost-effectiveness plane. The plot illustrated how the cloud of points was predominantly in the North East quadrant of the plane. Ninety-five per cent of plotted points fell to the left of the solid line representing a maximum WTP of £20,000 per QALY.

Figure 23 plots the distribution of the incremental net-monetary benefit statistic. The figure again shows how the proportion of model simulations producing a net benefit less than zero (identified by the vertical dashed line) and thus suggesting first-trimester structural anomaly screening would not be cost-effective is low.

The per patient EVPI was estimated to be £0.28 in the base-case and with a size of the beneficiary population estimated to be 616,307 per year, the population EVPI for England was £3,461,151 over a 20-year horizon (see *Table 26*). This value is the upper limit for the value of all research efforts that eliminate all uncertainty across the 175 parameters included in the PSA. Although it is unlikely that the expected costs of research to reduce the uncertainty across all 175 parameters will be less than £3,461,151, we still considered the per person and population EVPPI for the groups of parameters in *Table 25* representing different research areas.

Table 27 presents the per-person and population EVPPI for different groups of parameters (left column) representing defined research areas. The parameter for the additional cost of screening and the group of parameters representing screening performance (58 parameters) had the largest contributions to the per person EVPPI, at 48% and 43%, respectively. However, the expected cost of research associated with the screening performance parameters is likely to be higher than the population EVPPI of £87,836 over 20 years, given that this group includes the true and FP statistics

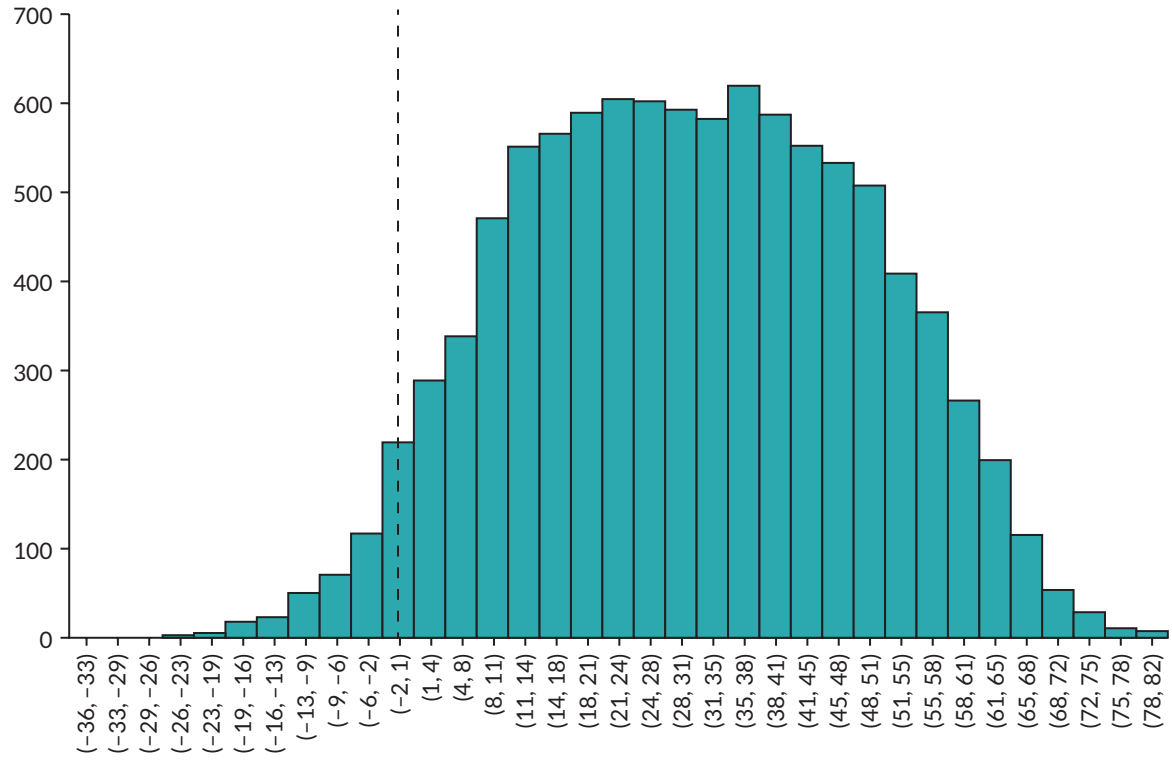

FIGURE 23 Incremental monetary net-benefit statistic (at WTP of £20,000 per QALY) comparing first-trimester detailed ultrasound scan vs. usual practice. Positive values indicate first-trimester anomaly scan is cost-effective.

TABLE 26 Individual and overall EVPI (expected value of removing all current decision uncertainty)

	Overall EVPI (£)
Per person affected by the decision	0.28
Per year in England assuming 616,307 persons affected per year	173,100
Over 5 years	865,300
Over 10 years	1,731,000
Over 15 years	2,596,000
Over 20 years	3,461,151

for 8 different structural anomalies at the 2 screening time points for both current practice and first-trimester structural anomaly screening, 58 parameters in total. In the case of the parameter for the additional cost of first-trimester anomaly screening it is unlikely that research could be conducted for less than the population EVPPI value. To more accurately estimate the additional screening costs associated with the first-trimester anomaly screening protocol would require a prospective study collecting per-woman screening durations across a number of sites working with and without the anomaly screening protocol, as well as further detailed exploration of the additional sonographer training required. Given these results we did not conduct further analysis in the form of EVSI and ENBS.

Discussion

This chapter has presented a detailed VoI analysis to determine (1) whether given the current level of evidence used to inform the mean estimates and associated uncertainty of the parameters in the decision-analytic model, first-trimester

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TABLE 27 Individual and overall EVPPI (expected value of removing decision uncertainty when uncertainty is removed on a group of parameters)

	Per-person EVPPI (£)	% EVPPI per person	EVPPI (£) for England per year	EVPPI (£) for England over 20 years
Anomaly characteristics	0.000	0	0	0
Additional screening cost	0.008	48	4939	98,787
Maternal psychological symptoms	0.000	0	0	0
Pregnancy outcomes	0.001	5	529	10,579
Screening performance	0.007	43	4392	87,836
Screening and testing acceptance	0.000	0	0	0
Utility (screening reassurance and FPs)	0.000	0	0	0
Utility (all other)	0.001	3	354	7081

structural anomaly screening as a programme modification in the NHS should be adopted and (2) whether additional evidence was needed to support this decision in the future. Our results suggest that early anomaly screening is likely to be cost-effective (see *Chapter 10*), that decision uncertainty is low, and that it would not be a cost-effective use of resources to invest in new research to try to reduce this uncertainty further.

Alongside these findings, it is pertinent to acknowledge that results from a VoI analysis are based on an implicit assumption that that the structure of the decision model developed is 'perfect' and includes parameters representing everything of value. Decision models invariably represent a simplified view of the world, and in the process of developing the model presented in *Chapter 10*, it was necessary to make a number of pragmatic assumptions. Among these was the assumption that fetuses present with only a single structural anomaly, whereas in reality for some fetuses, multiple structural anomalies may be present. Had it been possible to model multiple malformations, for which terminations following routine structural anomaly screening in the second trimester would presumably be higher, then it is possible that with first-trimester screening affording earlier detection and management, that further cost savings, maternal benefits and thus greater cost-effectiveness could be realised. Of course, one must also consider that multiple structural anomalies may be more identifiable in the first trimester even in the absence of a protocol and thus formal screening may effect little change in the pregnancy outcomes of these women.

A further simplifying assumption was that the model was not built to account for structural anomalies already detected during the first trimester as a result of investigations following a positive finding on the concurrent Combined Screening Test for Down, Edwards and Patau syndrome. The model was structured such that an ultrasound finding of an anomaly with a strong genetic association in the first trimester would lead to the offer of genetic testing; however, it is possible that a proportion of these cases would have already been identified in current practice as a result of combined screening.

One can hypothesise that the implications of these assumptions for the results presented here are unlikely to be substantial. This is because women with fetuses affected by the structural anomalies in the protocol account for fewer than 0.7% of all pregnant women attending for screening, and within the analysis, account for less than one-third of the overall maternal QALY gains. Were the model to have overestimated the maternal QALY gains from first-trimester anomaly screening for these women by as much as 10%, 20% or even 50%, the probability of cost-effectiveness would still exceed 90% and decision uncertainty would remain low.

Consideration must also be given to the finding that effectiveness (maternal QALYs) was driven largely by the reassurance that the majority of women in the protocol arm of the model receive following a negative first-trimester anomaly screening result. While uncertainty does surround the magnitude and duration of this 'benefit', its existence

does not seem to be in doubt, having previously been noted in both the literature (see *Appendix 7*) and cited by the majority of pregnant women surveyed about first-trimester anomaly screening as part of this project (see *Chapter 9*). Following discussions with clinical members of the project team, a conservative approach was taken to the inclusion of this parameter within the model, with only a small utility increment (0.01) modelled over an 8-week duration. In reality, the utility increment following a negative screen may be larger, and especially so in the weeks immediately following the scan. Were this to be the case, the cost-effectiveness results presented here would be improved and the decision uncertainty reduced even further.

Finally, the uncertainty surrounding the data used to estimate infant costs and QALYs must be acknowledged. Although the impact upon infants did not form part of the model's primary cost-effectiveness results or feature in the VoI analysis (for the reasons given in *Chapter 10*), the scarcity of data encountered when modelling the short- and long-term healthcare costs and outcomes of such rare anomalies should be noted. Future research in this area would likely be beneficial, and ongoing initiatives such as the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System will contribute to the limited evidence base. The implications of early screening for infants is important, whether they be presented alongside the primary cost-effectiveness results as is the case here or whether, if future research can resolve issues around societal preferences for such a programme and how to evaluate overall impact, they can be more formally integrated within a measure of cost-effectiveness.

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Chapter 12 Future studies

In this chapter, we draw together the findings and recommendations from the project. The aim here was to develop the relevant parameters. However, health economic and VoI analyses have demonstrated that screening appears to be cost-effective, that decision uncertainty is low, and that investment in additional research to reduce uncertainty further would not be a cost-effective use of resources. Overall, our report suggests that first-trimester ultrasound screening for fetal anomalies is clinically effective and cost-effective, and that further prospective studies would not constitute an efficient investment.

A possible obstacle to implementing such a policy is that there is no direct evidence from a RCT on earlier anatomical screening. Therefore, as part of this study we convened a large group of methodologists, trialists, clinicians and patient representatives to discuss potential further studies that could provide additional evidence on the clinical effectiveness of first-trimester anatomical assessment. These are listed below:

Prospective studies of diagnostic effectiveness

A prospective cohort screening study where ultrasound findings are revealed and acted upon was deemed of low utility. This is because of the abundance of data of this type found in the systematic reviews (see *Chapters 4* and *5*), including 416,877 fetuses screened in 40 studies for non-cardiac anomalies and 306,872 fetuses screened in 45 studies for cardiac anomalies. Meta-analysis showed that, for the group of major anomalies prioritised, detection rates were 93.29% (95% CI 90.37% to 95.71%) with a specificity of 99.99% (99.98% to 99.99%) and a PPV of 96.54% (93.27% to 98.76%). For major cardiac anomalies, detection rates were 55.80% (95% CI 45.87% to 65.50%) with a specificity of 99.98% (99.97% to 99.99%) and a PPV of 94.85% (91.63% to 97.32%). There was acknowledgement that most of the reported studies were from centres of excellence, and that detection rates during routine screening within the NHS would be lower. Nevertheless, data from NCARDRS (see *Tables 10* and *11*) confirm that nationally a sizeable proportion of anomalies can be detected in the first trimester when a protocol-based approach is taken. In conjunction with the findings from the VoI analysis, and the fact that the majority of NHS trusts already perform this type of screening (see *Chapter 6*), this study design was not deemed useful.

One of the criteria for a Level 1 study of diagnostic effectiveness is blinding results from the screening test being evaluated, in this case the finding of an abnormality on ultrasound. The potential for undertaking such a blinded study was discussed, but was dismissed as not being acceptable to women, their partners or caregivers. This was because it was considered unethical not to reveal anomalies, as the findings are associated with a very high PPV and a low FP rate. For abnormalities that may resolve spontaneously, such as exomphalos or megacystis, it was felt that the focus should be on provision of clear information for the parents as well as management pathways for caregivers; but non-disclosure was again not felt appropriate as both of these easily identifiable anomalies are strongly associated with trisomy 13 and 18.[7,214]

Randomised trials

It would also be possible to undertake a parallel-group individually randomised trial with women randomised to either undergoing or not undergoing a first-trimester anomaly screening scan, although whether women would agree to participate is debatable. A cluster-randomised approach could also be taken as could an adaptive trial design. In all three cases women in the intervention arm would be screened and compared to standard of care. In the intervention arm, women with a positive first-level screening result would then have further detailed assessment. The most achievable primary outcome would be the proportion of women receiving a diagnosis before 16 weeks of gestation. This study design was felt not to be advantageous for three reasons:

First, ultrasound is already used for the measurement of fetal CRL and NT, and there is an unmeasurable overlap between this and anomaly detection. Thus, it can be seen (see *Table 11*) that even in the absence of a protocol, many

major anomalies are detected even in those hospitals that do not perform formal anatomical assessment. The detection rates are highest for the most major anomalies, and for those that are evident in a sagittal view of the fetus, necessary for the performance of even the most basic first-trimester ultrasound assessment. Thus, the difference in detection between the two arms would be expected to be small for major anomalies (see *Chapter 4*). Such a comparison would also require a very large target sample size. Between-group differences in detection rates would be larger for less severe anomalies, making a trial for such anomalies more feasible; however, data from the systematic review suggested that detection rates do not approach those required for population screening.

Second, the number of participating hospitals would be limited, as about 77% of all units already perform anatomical assessment (screening approximately 350,000 pregnancies per year), and this would limit the ability to undertake a trial.

Finally, the VoI analysis shows that, even though there is no direct RCT evidence in favour of first-trimester anatomical screening, the model estimates a very high chance that it is the most cost-effective approach and does not highlight parameters with levels of uncertainty that would make future trials a cost-effective use of resources.

The option of implementation

Given the findings above, the deliberations of the study group centred around implementation. There was a recognition that the work already represents several steps of an implementation framework: it has established stakeholder engagement; defined the issues and likely effects and developed a process of screening. In the UK, such implementation could be undertaken and overseen via the FASP and the Fetal Maternal and Child Health group of the UK NSC. This would not represent a new screening programme, but a modification of the current programme, with the some of the aims (e.g. anomaly detection at 20 weeks) brought forward to 11–14 weeks. The FASP has a successful track record of such implementation in second-trimester anatomical screening and successful modifications of the programme, such as additional views to improve screening for fetal heart abnormalities.[215]

The challenges outlined for conducting randomised trials in this scenario, that is, an overlap between current first-trimester ultrasound and anomaly detection, the fact that the majority of hospitals already undertake such screening and the results of our VoI analysis, led the co-applicant group to recommend implementation as the best model forward. This would aim to ensure a national standard of care, equity and access to care for all women, provision of appropriate pre-screening information and appropriate management pathways, all with PPI endorsement.

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Chapter 13 Overall conclusions and assessment of evidence required for a national screening programme

Overall conclusions

Current standard antenatal care includes an ultrasound scan at 11–14 weeks' gestation to date the pregnancy and screen for Down syndrome, and a further scan at 18–20 weeks' gestation to detect fetal abnormalities. Evidence from systematic reviews suggests that due to improvements in ultrasound quality, many fetal anomalies are detectable during the late first and early second trimester. This may allow women to make an earlier decision regarding continuation of the pregnancy when fetal malformations are detected. However, there may also be unintended consequences in terms of additional clinical uncertainty resulting from some findings, leading to costs of further investigations and increased anxiety for the parents.

In *Chapter 3*, we outlined 10 key research questions relating to first-trimester detailed ultrasound scan for the earlier detection of fetal anomalies:

1. Based on systematic reviews and meta-analysis, the diagnostic accuracy of ultrasound in the early detection of fetal abnormalities is known:

    - For the group of major anomalies prioritised by the FASP and consensus procedure, this scan will detect 93.29% (95% CI 90.37% to 95.71%) of anomalies with a specificity of 99.99% (99.98% to 99.99%) and a PPV of 96.54% (93.27% to 98.76%). These estimates are based on 416,877 fetuses screened in 40 studies.
    - For major cardiac anomalies, this scan will detect 55.80% (95% CI 45.87% to 65.50%) of anomalies with a specificity of 99.98% (99.97% to 99.99%) and a PPV of 94.85% (91.63% to 97.32%). These estimates are based on 306,872 fetuses screened in 45 studies.
    - In addition, previous studies have shown that the use of a standardised anatomical protocol improves the detection rate of first-trimester ultrasound screening for major anomalies.

2. Despite an absence of national recommendations, about three-quarters of all units in the UK already perform some first-trimester anomaly screening, and the majority of trusts do this within the current time allocation of 25–30 minutes. However:

    - This screening is ad hoc without consistency or standardisation.
    - There is regional and between-hospital discordance, resulting in inequity in provision of care.
    - Most units do not report the provision of pre-scan information or consent.
    - Training of sonographers regarding first-trimester anatomical screening varies widely.

3. Data from the NCARDRS suggest that NHS hospitals undertaking first-trimester anomaly screening provide significantly more patients with an early diagnosis (before 16 weeks of gestation).
4. Our work has defined the anatomical protocols to be used for routine first-trimester screening based on the information from systematic reviews; and consensus from UK-based sonographers, midwives and doctors.
5. The existing screening literature does not provide strong evidence on the best GA to screen. However, studies in visualisation and consensus procedure suggest the screening should be ideally carried out from 12^{+0} to 13^{+6} weeks of gestation.
6. The existing screening literature does not demonstrate a difference in screening performance by method of scanning (TA vs. TV). This, together with the consensus procedure and common practice established by our survey, means TA scanning should be the primary method.
7. The vast majority of parents feel that first-trimester anomaly screening would be beneficial.

- Over 90% of parents currently pregnant and over 95% of those with a previous experience of a pregnancy with a congenital anomaly would opt for such screening if available.
- Importantly, this includes couples who would opt against screening for chromosomal abnormalities and would not consider TOP.
- Most parents would prefer to be made aware of a suspicious finding on an early scan even if this cannot be conformed until a later GA.
- As these results were based on a quantitative survey, we suggest further qualitative work to understand parental perceptions of screening, recommendations for implementation, barriers to acceptance and their information and support needs. This should be underpinned with co-design methods to ensure it is inclusive of parent perspectives.

8. A substantial health economic model providing insight into the short and long-term costs and consequences of a decision to implement a protocol for first-trimester anomaly screening within the current NHS antenatal screening pathway shows that.

    - Additional costs per woman are likely to be low because the infrastructure needed to conduct such screening is already in place via the NHS antenatal screening programme.
    - First-trimester anomaly screening is associated with a small cost increase (£11) and a small maternal QALY gain (0.002065) when compared with current practice.
    - Incremental analysis based upon maternal costs and QALYs suggests implementation of the proposed protocol is likely to be cost-effective.
    - Earlier screening will likely lead to a reduction in the number of live births of babies with an anomaly.

9. Based on VoI analysis, the results suggest that decision uncertainty is low, and that it would not be cost-effective to invest in additional research to reduce this uncertainty further.

If there is value in undertaking additional future research, what should the study design be? Although there is no direct evidence from RCTs of first-trimester anomaly screening, our analysis suggests such screening is likely to be cost-effective. Although uncertain parameters were identified through the VoI analysis, the magnitude of the uncertainty was small, and the cost of additional future research required to reduce it would likely be greater than the gain in net benefit that would be subsequently realised. Overall, our report suggests that first-trimester ultrasound screening for fetal anomalies is clinically effective and cost-effective, and that further prospective studies would not constitute an efficient investment.

To the best of our ability, we attempted to increase external validity by including data reflective of the whole of the UK. The systematic reviews and meta-analyses (see *Chapters 4* and *5*) included international data; the Nationwide Survey of Practice (see *Chapter 6*) was undertaken in collaboration with PHE and therefore includes data from England; this also meant that the linkage analysis (see *Chapter 7*) was restricted to England (and in any case, NCARDRS only covers outcomes from England); the Delphi consensus procedure (see *Chapter 8*) included UK-wide practitioners; views of parents (see *Chapter 9*) included women from across the UK; finally, the health economics analysis and VOI (see *Chapter 10* and *11*) were based on the studies above and NHS-wide costs and statistics.

Equality, diversity and inclusion

Committed to ensuring equality, diversity and inclusion, we adhered to best practice and the NIHR-INCLUDE guidance in this report that deals in its entirety with pregnant people – an underserved group. The group of individuals leading the research represents a range of experience, expertise, gender and background. We ensured that there was provision of development opportunities for more junior members of the team in areas of science, dissemination and policy.

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Patient and public involvement

In addition to the above, we formed a large Patient and Participant Voice group that had a central role, in turn informed by large patient groups (through relevant stakeholder charities). We strongly believe that the practice of having one (or a small number of 'lay experts') cannot properly represent patient and participant views, and for this reason, we undertook a large-scale survey of the views of prospective parents (see *Chapter 9*). Both parents were included in this survey (based on the principle of 'no decision about me, without me'), and this was regardless of gender; and we purposely sampled all geographic areas; including parents from all educational backgrounds and age ranges in keeping with population estimates. In particular, we also ensured representation of couples who had a child born with congenital conditions and disabilities to ensure inclusivity. Finally, we included views from couples of all views on fetal screening, including those that would opt against prenatal testing for chromosomal conditions, to ensure representation. Thus, we ensure that the views on how such screening should be undertaken went beyond the core research group but was informed by a Nationwide Survey of Practice, as well as a formal consensus procedure involving sonographers, midwives and doctors involved in screening on a day-to-day basis.

Consultation with the National Screening Committee

Given that the findings of this work may lead to a recommendation for implementation of a unified model of first-trimester screening for major fetal abnormalities, we presented the scientific summary of the project to the FASP and the Fetal Maternal and Child Health group of the UK NSC. We discussed the lack of a clear case for further research. Implementation of such a programme was discussed in depth; this would not be a new screening programme, but a modification of the current programme, with the same aims (anomaly detection) brought forward from 18–20 to 11–14 weeks. We are now working with the UK NSC on a proposal for such a programme modification.

An approach similar to that used in the NIPT evaluative roll-out could be one option: here, an in-service evaluation over a pre-defined period of 2 years is taking place. This involves all NHS hospitals; during this roll-out, all patients are provided with the new standard of care, namely the offer of NIPT for a high chance combined screening result for trisomies. The intention is that after this time the screening performance of the roll-out is assessed and then continued (or not), depending on the results. Such a model works well as an evaluation as it involves the commissioning and use of a lab-based test, which is fairly easy to start and to stop based on centralised screening policy. However, given that implementation of first-trimester anomaly screening would involve training, support, infrastructure and referral pathways, this may not be the best model for significant changes to every day clinical practice. Instead, a pilot approach starting in a group of hospitals not currently offering such screening may be a better approach and also allow lessons learnt and best practice to be disseminated. Whatever the precise methods of implementation be, we are optimistic that, based on the wealth of information in this report, such a programme modification will be recommended.

Additional information

Contributions of authors

Jehan N Karim (https://orcid.org/0000-0002-1199-6283) (Clinical Research Fellow, University of Oxford, UK) was responsible for all day-to day grant research activities and was involved with conception and design of all study chapters, data collection and data analysis/interpretation for all clinical chapters, critical input into design of health economics models, drafting of all clinical chapters, drafting of report introduction and conclusions and gave final approval of the report submitted to the NIHR.

Helen Campbell (https://orcid.org/0000-0003-2070-7794) (Researcher in Health Economics, University of Oxford, UK) was responsible for all day-to-day research activities relating to the health economics (see *Chapters 10* and *11*). She was involved with conception and design, data collection, data analysis/interpretation and drafting of health economics *Chapters 10* and *11* and provided additional input to the drafting of the entire report and gave final approval of the report submitted to the NIHR.

Pranav Pandya (Professor, University College London Hospitals NHS Foundation Trust, UK) was involved in grant protocol development, actively involved in study design and undertaking of Nationwide Survey of Practice (see *Chapter 6*) and study design, data analysis/interpretation of NCARDRS data (see *Chapter 7*), participated in group discussions managing ongoing challenges which came up while undertaking the grant, was a member of panel group discussing possible future trials which could be designed as an outcome of this report, provided critical input on the draft of the final report and gave final approval of the report submitted to the NIHR.

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Christos Ioannou (https://orcid.org/0000-0002-3147-6613) (Consultant Obstetrics and Fetal Medicine, Oxford University Hospitals NHS Trust, UK) provided critical input on the draft of the final report and gave final approval of the report submitted to the NIHR.

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Basky Thilaganathan (https://orcid.org/0000-0002-5531-4301) (Professor, St George's University Hospitals NHS Foundation Trust, UK) was involved in grant protocol development, was local Principal Investigator responsible for recruitment for the ACAS Study at St George's NHS University Hospital Trust, participated in group discussions managing ongoing challenges which came up while undertaking the grant, was a member of panel group discussing possible future trials which could be designed as an outcome of this report, provided critical input on the draft of the final report and gave final approval of the report submitted to the NIHR.

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Gillian Yaz (SHINE UK) was involved in grant protocol development, was involved participant recruitment for the ACAS Study (see *Chapter 9*), participated in group discussions managing ongoing challenges which came up while undertaking the grant, was a member of panel group discussing possible future trials which could be designed as an outcome of this report, provided critical input on the draft of the final report and gave final approval of the report submitted to the NIHR.

Oliver Rivero-Arias (https://orcid.org/0000-0003-2233-6544) (Lead Health Economist, University of Oxford, UK) was responsible for overseeing all activities related to health economics and for its contributions to the overall conclusions of this report, provided critical input on the draft of the final report and gave final approval of the report submitted to the NIHR.

Aris T Papageorghiou (https://orcid.org/0000-0001-8143-2232) (Professor, Principal Investigator, University of Oxford, UK) was responsible for overseeing and actively engaged with all activities related to this grant.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/NLTP7102.

Primary conflicts of interest: Pranav Pandya declares Chairmanship of the Fetal Anomaly Screening Programme Advisory Group. Zarko Alfirevic declares roles in Data Safety Monitoring for the University of Sydney; Trial Steering Committee member for the 'C-Stitch-2' study; leadership roles for the Cochrane Library and Cochrane Pregnancy and Childbirth; HTA Funding Teleconference Membership (May–October 2016); and HTA Commissioning Committee membership (May 2012–March 2017). Elizabeth Duff declares a salaried role as policy adviser for the National Childbirth Trust. Lisa Hinton works at THIS Institute, which is supported by the Health Foundation, an independent charity; she was co-investigator for a NIHR Applied Research Programme grant (April 2016–December 2021); principal investigator for a MRC/ESRC/Wellcome Trust/DFID Health Systems Research Initiative (March 2020–March 2022); and co-investigator for a NIHR Health Technology Assessment (January 2020–January 2022; co-investigator for NIHR Health Services Research and Delivery (March 2020–January 2025); co-investigator for a project funded by the Stroke Association and British Heart Foundation (January 2018–September 2020); full committee membership of NIHR HS&DR (January 2023–6) and Associate Membership (2016–8). Christos Ioannou is a visiting consultant at the United Arab Emirates for educational visits, hospital lectures and training in the fields of ultrasound and fetal medicine. Edmund Juszczak was a Member of the HTA General Committee (August 2016–May 2018), and HTA Commissioning Committee (July 2013–July 2016). Professor Gordon Smith declares contracts with Wellcome Leap and Roche Diagnostics Ltd; grants from the MRC, Wellcome Trust, NIHR Cambridge Biomedical Research Centre; consultancy, membership of the expert panel and data monitoring committee for RSV vaccination in pregnancy for GSK; ambassadorship for UK stillbirth charity, Sands; and receipt of services and consumables from Illumina. Basky Thilaganathan declares he is Emeritus Editor of Ultrasound in Obstetrics and Gynecology and Clinical Director, Tommy's National Centre for Maternity Improvement, RCOG/RCM. Oliver Rivero-Arias declares membership of the Fetal Maternal and Child Health Reference Group, of the National Screening Committee; and director of Maths in Health (MiH) a health economics consultancy. Aris T Papageorghiou declares grant support from the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC), NIHR/HTA, EPSRC, GCRF, ERC, NIH, Wellcome LEAP and Bill and Melinda Gates Foundation. He receives royalties for published books; is a co-founder and senior advisor for Intelligent Ultrasound, undertaken via Oxford University Innovations which manages consulting activities of the University staff. He declares honoraria and travel expenses for lectures and meetings; and a patent entitled 'A system and method are provided to automatically categorise biological and medical images'. He works part of his time in private medical practice, and is Editor in Chief for BJOG for which he receives remuneration.

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Acknowledgements

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Qualitative researcher with expertise in parent experiences of screening: Lisa Hinton (University of Cambridge, UK).

Patient and public voice group: Jane Fisher (Lead, Antenatal Results and Choices, UK), Elizabeth Duff (National Childbirth Trust, UK), Anne Rhodes (Tiny Tickers, UK), Gil Yaz (SHINE UK).

Acknowledgement of involvement of non-study authors

Ms Annette McHugh, Programme Manager for the Fetal Anomaly Screening Programme (PHE) for her support with design and undertaking of the Nationwide Survey of Ultrasound Practice (see *Chapter 6*).

Ms Jennifer Broughan (Principal Analyst – NCARDRS, NHS Digital) and Mr Nick Aldridge (Analyst – NCARDRS, NHS Digital) for their support with study design, data extraction, data analysis and revision of written draft of *Chapter 7*.

Dr Sanne Gordijn, Obstetrician and Fetal Medicine Consultant, University of Groningen, Netherlands, for her support with design of the Delphi consensus for the development of a first-trimester screening protocol (see *Chapter 8*).

Dr Elizabeth Bradburn, Clinical Research Fellow, University of Oxford, for her contributions as second reviewer of systematic review (see *Chapter 5*).

Dr Daniele DiMascio, Resident Doctor, Sapienza Universita di Roma, Italy, for his contributions as second reviewer of systematic review (see *Chapter 4*).

Dr Lien Davidson, Medical Student, University of Oxford, for her contribution with data synthesis from paper surveys collected during the ACAS Study (see *Chapter 9*).

To the teams from NHS trusts participating in the ACAS Study (see *Chapter 9*):

- Liverpool Women's NHS Trust
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- St Helen's and Knowsley Teaching Hospitals NHS Trust
- Birmingham Women's and Children's NHS Trust
- Aneurin Bevan University Health Board Wales
- South Tyneside and Sunderland NHS Trust
- North Tees and Hartlepool NHS Trust
- Oxford University Hospital NHS Trust
- Homerton University Hospital NHS Trust
- St Georges University Hospital NHS Trust

Data-sharing statement

Requests for access to data should be addressed to the corresponding author.

Ethics statement

The appropriate ethics approvals were obtained and are outlined in the relevant chapters. For *Chapter 7*, formal ethics approval was obtained after full review by the North West – Preston Research Ethics committee (21/NW/0173) in March 2021. In addition, approval for the conduct of this research was obtained formally from the NDR Project Review Panel on behalf of PHE. For *Chapter 8*, ethical approval for the study was obtained by the ethical board from the University Medical Centre of Groningen (METc 2020/440) prior to commencement of the study. For *Chapter 9*, the study underwent full ethics review by the South Central Oxford Research Ethics committee (19/SC/0483) with approvals granted in October 2019. Approvals from the Health Research Authority (England) and the Health and Care Research Wales were granted in November 2019.

Information governance statement

The University of Oxford is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Oxford is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here https://compliance.admin.ox.ac.uk/about.

Publications

Karim JN. *Detection of Structural Anomalies at 11–14 Weeks: What Factors Determine Detection Rates?* Invited guest lecturer on the 'ISUOG First Trimester Certificate Course' held at the World Congress on Ultrasound in Obstetrics and Gynecology, Singapore, October 2018.

Karim JN, Yaqub M, Cook K, Volpe G, Drukker L, Cavallaro A, *et al.* Image review for quality of the first trimester anomaly scan [abstract]. *Ultrasound Obstet Gynecol* 2018;**52**(S1):48–9. (Oral Presentation given at World Congress – Singapore, October 2018). https://doi.org/10.1002/uog.19343

Karim JN. *National First Trimester Ultrasound Practice in England – What is the Current State of Affairs?* Invitation to speak at the Public Health England's National Screening Committee bi-annual meeting to present findings from a National Survey of First Trimester Ultrasound Practice in England (September 2019).

Karim JN, Pandya P, McHugh A, Papageorghiou AT. Significant variation in practice for first trimester anatomy assessment: results from a Nationwide Survey [abstract]. *Ultrasound Obstet Gynecol* 2019;**54**(S1):60. (Oral Presentation given at World Congress – Berlin, October 2019). https://doi.org/10.1002/uog.20586

Karim JN, Papageorghiou AT. Cardiac anomaly screening in the first trimester – a systematic review and meta-analysis of ultrasound sensitivity and factors impacting detection [abstract]. *Ultrasound Obstet Gynecol* 2019;**54**(S1):289–9. (Poster Presentation given at World Congress – Berlin, October 2019). https://doi.org/10.1002/uog.21324

Karim JN, Craik R, Hinton L, Papageorghiou A. Acceptability of the first trimester anomaly scan amongst parents with previous experience of fetal anomalies in pregnancy [abstract]. *Ultrasound Obstet Gynecol* 2020;**56**:12. (Oral Presentation given at ISUOG Virtual World Congress 2020.) https://doi.org/10.1002/uog.22225

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Karim JN, Papageorghiou AT. How can we improve first trimester screening for fetal anomalies? Invitation to speak and debate as a panelist on an internationally broadcast webinar by GE Healthcare in collaboration with The Scan Academy (5 July 2020 and re-aired 5 September 2020 – over 10,000 viewers worldwide).

Karim JN, Bradburn L, Roberts N, Papageorghiou AT; ACCEPTS study. First trimester ultrasound for the detection of fetal heart anomalies: a systematic review and meta-analysis. *Ultrasound Obstet Gynaecol* 2021. https://doi.org/10.1002/uog.23740

Karim JN, Craik R, Davidson L, Maiz N, Fisher J, Rivero-Arias O, *et al.* Acceptability of the first trimester anomaly scan amongst parents in the UK [abstract]. *BJOG* 2021;**128**(S2). (Oral Presentation given at RCOG Virtual World Congress 2021. https://doi.org/10.1002/uog.23913

Karim JN, Gordijn SJ, Papageorghiou AT. OC18.08: Developing a first trimester anomaly screening protocol for the UK: a consensus procedure [abstract]. *Ultrasound Obstet Gynecol* 2021;**58**:54–5. (Oral Presentation given at ISUOG Virtual World Congress 2021.) https://doi.org/10.1111/1471-0528.2316715

Bilardo CM, Chaoui R, Hyett JA, Kagan KO, Karim JN, Papageorghiou AT, *et al.* ISUOG practice guidelines: performance of a 11–14 weeks ultrasound scan. *Ultrasound Obstet Gynaecol*. Accepted for publication October 2022. https://doi.org/10.1002/uog.26106

Presentations

Karim JN. *Patient Acceptability of the First Trimester Scan*. Invited guest lecturer at the 42nd Annual Pregnancy Meeting of the Society for Maternal Fetal Medicine (SMFM), online, February 2022.

Karim JN. *The First Trimester Anomaly Scan – Is It Time for National Screening Recommendations?* Keynote Speaker at the Ulster Obstetrical and Gynaecological Society Annual Summer Meeting, Belfast, Northern Ireland, June 2022.

Karim JN. *The First Trimester Anomaly Scan – What are the Systems Factors Impacting Detection Rates?* Invited guest speaker at the Fetal Medicine Foundation (FMF) World Congress, Crete, Greece, June 2022.

Karim JN, Campbell H, Rivero-Arias O, Papageorghiou AT; ACCEPTS study. *First Trimester Screening Scan Workshop*. Full day set of lectures and discussion presenting work from the ACCEPTS study to the UK Fetal Anomaly Screening Committee (UKHSA), January 2022.

Karim JN, Papageorghiou AT. *The First Trimester Anomaly Scan – Is It Time for National Screening Recommendations and What Would be Required for Implementation in England?* Joint presentation to the UK National Screening Committee, online, May 2022.

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Appendix 1 Systematic review and meta-analysis of major non-cardiac anomalies using first-trimester ultrasound: methods and description of included studies

Search strategy

The global search strategy involved two independent searches (A and B) combined with an 'all' function. The search was conducted using MEDLINE, EMBASE, Web of Science and the Cochrane Library from 1 January 1998 until 17 July 2020.

MEDLINE

Search #	Searches conducted
1	Ultrasonography, Prenatal/
2	Prenatal diagnosis/ and exp ultrasonography/
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*).ti,ab.
4	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*) adj3 (screen* or scan* or structural assessment* or structural survey*)).ti,ab.
5	1 or 2 or 3 or 4
6	Pregnancy Trimester, First/
7	(1st trimester or first trimester).ti,ab.
8	(early pregnan* or early gestation*).ti,ab.
9	((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
10	((10week? or 11week? or 12week? or 13week? or 14week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
11	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
12	6 or 7 or 8 or 9 or 10 or 11
13	exp *Congenital Abnormalities/
14	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
15	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
16	(structural adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
17	((non-chromosomal or nonchromosomal or chromosomal) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
18	neural tube defects/ or anencephaly/ or encephalocele/ or exp Spinal Dysraphism/
19	craniofacial abnormalities/ or holoprosencephaly/ or cleft palate/
20	Hernia, Umbilical/
21	Gastroschisis/
22	Bone Diseases, Developmental/ or Leg Length Inequality/ or limb deformities, congenital/ or exp polydactyly/

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Search #	Searches conducted
23	exp 'Transposition of Great Vessels'/ or Hypoplastic Left Heart Syndrome/
24	exp heart septal defects/ or 'tetralogy of fallot'/
25	hernia, diaphragmatic/ or hernias, diaphragmatic, congenital/
26	(acrania? or anencephaly or exencephaly or holoproscencephaly).ti,ab.
27	(encephalocele or ((brain or cereb*) adj bifid*)).ti,ab.
28	(omphalocele or exomphalos or (umbilical adj2 hernia?)).ti,ab.
29	gastroschisis.ti,ab.
30	megacystis.ti,ab.
31	(skelet* adj2 dysplasia?).ti,ab.
32	((limb? or leg? or arm?) adj2 (short* or reduc* or inequality or unequal*)).ti,ab.
33	polydactyly.ti,ab.
34	(transpos* adj3 (great arteries or great vessel?)).ti,ab.
35	((ventric* or heart) adj2 hypoplas*).ti,ab.
36	'tetralogy of fallot'.ti,ab.
37	((atrioventric* or atrio-ventric* or septal) adj2 defect?).ti,ab.
38	double outlet right ventric*.ti,ab.
39	spina bifida.ti,ab.
40	((face or facial or lip* or palate*) adj2 cleft?).ti,ab.
41	(diaphragm* adj2 hernia*).ti,ab.
42	(((kidney or renal) adj2 agenesis) or potter* syndrome).ti,ab.
43	body stalk anomal*.ti,ab.
44	(club foot or club feet or talipes).ti,ab.
45	ventriculomegaly.ti,ab.
46	cystic hygroma?.ti,ab.
47	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	5 and 12 and 47
49	((fetal or foetal or fetus or foetus) adj (anatomy or defect? or malformation? or abnormalit* or anomal*) adj5 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
50	12 and 49
51	((early pregnan* or early gestation* or 1st trimester or first trimester) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
52	(((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
53	(((10week? or 11week? or 12week? or 13week? or 14week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.

Search #	Searches conducted
54	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week? adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
55	51 or 52 or 53 or 54
56	47 and 55
57	48 or 50 or 56
58	exp animals/ not humans.sh.
59	57 not 58

EMBASE

# ▲	Searches
1	fetus echography/
2	prenatal diagnosis/ and (echography/ or transvaginal echography/)
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*).ti,ab.
4	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*) adj3 (screen* or scan* or structural assessment* or structural survey*)).ti,ab.
5	1 or 2 or 3 or 4
6	first trimester pregnancy/
7	(1st trimester or first trimester).ti,ab.
8	(early pregnan* or early gestation*).ti,ab.
9	((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
10	((10week? or 11week? or 12week? or 13week? or 14week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
11	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
12	6 or 7 or 8 or 9 or 10 or 11
13	exp *congenital malformation/
14	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
15	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
16	(structural adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
17	((non-chromosomal or nonchromosomal or chromosomal) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
18	neural tube defect/ or anencephalus/ or encephalocele/ or exp spinal dysraphism/ or holoprosencephaly/
19	cleft palate/ or cleft face/ or cleft lip/ or cleft lip palate/
20	umbilical hernia/
21	Gastroschisis/
22	bone dysplasia/ or leg length inequality/ or polydactyly/
23	great vessels transposition/ or hypoplastic left heart syndrome/ or exp heart septum defect/
24	diaphragm hernia/

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# ▲	Searches
25	kidney agenesis/
26	(acrania? or anencephaly or exencephaly or holoproscencephaly).ti,ab.
27	(encephalocele or ((brain or cereb*) adj bifid*)).ti,ab.
28	(omphalocele or exomphalos or (umbilical adj2 hernia?)).ti,ab.
29	gastroschisis.ti,ab.
30	megacystis.ti,ab.
31	(skelet* adj2 dysplasia?).ti,ab.
32	((limb? or leg? or arm?) adj2 (short* or reduc* or inequality or unequal*)).ti,ab.
33	polydactyly.ti,ab.
34	(transpos* adj3 (great arteries or great vessel?)).ti,ab.
35	((ventric* or heart) adj2 hypoplas*).ti,ab.
36	'tetralogy of fallot'.ti,ab.
37	((atrioventric* or atrio-ventric* or septal) adj2 defect?).ti,ab.
38	double outlet right ventric*.ti,ab.
39	spina bifida.ti,ab.
40	((face or facial or lip* or palate*) adj2 cleft?).ti,ab.
41	(diaphragm* adj2 hernia*).ti,ab.
42	(((kidney or renal) adj2 agenesis) or potter* syndrome).ti,ab.
43	body stalk anomal*.ti,ab.
44	(club foot or club feet or talipes).ti,ab.
45	ventriculomegaly.ti,ab.
46	cystic hygroma?.ti,ab.
47	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	5 and 12 and 47
49	((fetal or foetal or fetus or foetus) adj (anatomy or defect? or malformation? or abnormalit* or anomal*) adj5 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
50	12 and 49
51	((early pregnan* or early gestation* or 1st trimester or first trimester) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
52	(((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
53	(((10week? or 11week? or 12week? or 13week? or 14week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
54	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week? adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.

# ▲	Searches
55	51 or 52 or 53 or 54
56	47 and 55
57	48 or 50 or 56

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ID	Search
#1	MeSH descriptor: [Ultrasonography, Prenatal] this term only
#2	ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*:ti,ab,kw (Word variations have been searched)
#3	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*) near/3 (screen* or scan* or structural assessment* or structural survey*)):ti,ab,kw (Word variations have been searched)
#4	#1 or #2 or #3
#5	MeSH descriptor: [Pregnancy Trimester, First] explode all trees
#6	1st trimester or 'first trimester':ti,ab,kw (Word variations have been searched)
#7	early pregnan* or 'early gestation*':ti,ab,kw (Word variations have been searched)
#8	((('10 week*' or '11 week*' or '12 week*' or '13 week*' or '14 week*') and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#9	(((10week* or 11week* or 12week* or 13week* or 14week*) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#10	ten week? or 'eleven week?' or 'twelve week?' or 'thirteen week?' or 'fourteen week?':ti,ab,kw (Word variations have been searched)
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	MeSH descriptor: [Congenital Abnormalities] explode all trees
#13	((congenital* near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#14	(((fetal or foetal or fetus or foetus) near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#15	((structural near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#16	(((non-chromosomal or nonchromosomal) near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#17	(Acrania* or anencephaly or exencephaly or holoproscencephaly OR encephalocele or ((brain or cereb*) NEXT bifid*) OR omphalocele or exomphalos or (umbilical NEAR/2 hernia*) OR gastroschisis OR megacystitis OR (skelet* NEAR/2 dysplasia*) OR ((limb* or leg* or arm*) NEAR/2 (short* or reduc* or inequality or unequal*)) OR polydactyly OR (transpos* NEAR/3 ('great arteries' or 'great vessel*')) OR ((ventric* or heart) NEAR/2 hypoplas*) OR 'spina bifida' OR ((face or facial or lip* or palate*) NEAR/2 cleft*) OR (diaphragm* NEAR/2 hernia*) OR ((kidney or renal) NEAR/2 agenesis) or 'potter* syndrome' OR "tetralogy of fallot "OR ((atrioventric* or atrio-ventric* or septal) near/2 defect*) OR 'double outlet right ventric*' OR 'Body Stalk Anomal*' OR 'Club Foot' OR 'Club Feet' OR Talipes OR Ventriculomegaly OR Cystic Hygroma*):ti,ab,kw
#18	#12 or #13 or #14 or #15 or #17
#19	#4 and #11 and #18
#20	(((fetal or foetal or fetus or foetus) next (anatomy or defect* or malformation* or abnormalit* or anomal*) near (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*))):ti,ab,kw (Word variations have been searched)

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ID	Search
#21	#11 and #20
#22	((('early pregnan*' or 'early gestation*' or 1st trimester or first trimester) near/3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*))):ti,ab,kw (Word variations have been searched)
#23	((((('10 week*' or '11 week*' or '12 week*' or '13 week*' or '14 week*') near/3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#24	((((('ten week*' or 'eleven week*' or 'twelve week*' or 'thirteen week*' or 'fourteen week*') near/3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#25	#22 or #23
#26	#18 AND #25
#27	#19 OR #21 OR #26

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# 13	#12 OR #8
# 12	#11 AND #4
# 11	#10 OR #9
# 10	TS=('fetal anatomy' OR 'fetal defect*' OR 'fetal malformation*' OR 'fetal abnormalit*' OR 'fetal anomal*' OR 'foetal anatomy' OR 'foetal defect*' OR 'foetal malformation*' OR 'foetal abnormalit*' OR 'foetal anomal*') AND TS = (scan* OR survey* OR assessment? OR screen*)
# 9	TS=('fetal anatomy' OR 'fetal defect*' OR 'fetal malformation*' OR 'fetal abnormalit*' OR 'fetal anomal*' OR 'foetal anatomy' OR 'foetal defect*' OR 'foetal malformation*' OR 'foetal abnormalit*' OR 'foetal anomal*') AND TS = (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*)
# 8	#7 AND #4 AND #1
# 7	#6 OR #5
# 6	TS = (acrania* or anencephaly or exencephaly or holoproscencephaly) OR TS = (encephalocele or ((brain or cereb*) NEXT bifid*)) OR TS = (omphalocele or exomphalos or (umbilical NEAR/2 hernia*)) OR TS = gastroschisis OR TS = megacystitis OR TS = (skelet* NEAR/2 dysplasia*) OR TS=((limb* or leg* or arm*) NEAR/2 (short* or reduc* or inequality or unequal*)) OR TS = polydactyly OR TS = (transpos* NEAR/3 ('great arteries' or 'great vessel*')) OR TS=((ventric* or heart) NEAR/2 hypoplas*) OR TS="spina bifida" OR TS=((face or facial or lip* or palate*) NEAR/2 cleft*) OR TS = (diaphragm* NEAR/2 hernia*) OR TS=(((kidney or renal) NEAR/2 agenesis) or 'potter* syndrome') OR TS=("tetralogy of fallot "OR ((atrioventric* or atrio-ventric* or septal) near/2 defect*) OR 'double outlet right ventric*') OR TS= ('Body Stalk Anomal*' OR 'Club Foot' OR 'Club Feet' OR Talipes OR Ventriculomegaly OR Cystic Hygroma*)
# 5	TS = (congenital* NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (fetal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (foetal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (fetus NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (foetus NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (structural NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (non-chromosomal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (nonchromosomal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS = (chromosomal NEAR/2 (defect* or malformation* or abnormalit* or anomal*))
# 4	#3 OR #2
# 3	TS=('1st trimester' or 'first trimester') OR TS=('early pregnan*' or 'early gestation*') OR TS=('10 week*' or '11 week*' or '12 week*' or '13 week*' or '14 week*') OR TS = (10week* or 11week* or 12week* or 13week* or 14week*) OR TS=('ten week*' OR 'eleven week*' OR 'twelve week*' OR 'thirteen week*' OR 'fourteen week*')

# 2	TS=('1st trimester' or 'first trimester') OR TS=('early pregnan*' or 'early gestation*')
# 1	TS=((pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)) AND TS = (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*)

Quality assessment of diagnostic accuracy studies-2 assessment tool

Defining the review question:

1. What is the sensitivity of first-trimester ultrasound for the detection of non-cardiac malformations?
2. What factors might impact detection rates?

- Patient selection: pregnant women with GA prior to 14^{+6} weeks, mothers with either singleton or multiple pregnancies were included.
- Index test: TV and/or TA 2D ultrasound prior to 14^{+6} weeks GA.
- Reference standard: postnatal examination of fetus or post-mortem of fetus for evidence/confirmation of structural abnormalities.
- Target condition: major congenital abnormalities.

Domain 1: Patient selection

A. **Risk of bias:** Could the selection of patients have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
i. Was a consecutive (vs. random sample) of patients enrolled?	YES/NO/UNCLEAR
ii. Did the study avoid inappropriate exclusions?	YES/NO/UNCLEAR
B. **Applicability:** Are there concerns that the included patients and setting do not match the review question (i.e. severity of the target condition, demographic features, presence of comorbidity, setting)?	LOW/HIGH/UNCLEAR

Domain 2: Index test

A. **Risk of bias:** Could the conduct or interpretation of the index test have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
ii. Were sonographers blinded to the history (risk profile) of the patients?	YES/NO/UNCLEAR
ii. Were all of the included first-trimester scans performed prior to 14^{+6} weeks GA?	YES/NO/UNCLEAR
B. **Applicability:** Are there concerns that the index test, its conduct, or interpretation differ from the review question?	LOW/HIGH/UNCLEAR

Domain 3: Reference standard

A. **Risk of bias:** Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
i. Was an appropriate reference standard used to correctly classify the target condition?	YES/NO/UNCLEAR
ii. Were the reference standard results interpreted without knowledge of the results of the index test?	YES/NO/UNCLEAR
B. **Applicability:** Are there concerns that the target condition as defined by the reference standard does not match the question?	LOW/HIGH/UNCLEAR

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Domain 4: Flow and timing

A. Risk of bias: Could the patient flow have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
i. Did all patients included in the study undergo examination with the reference standard? (either postnatal examination for live births or post-mortem for stillbirths/TOPs in those with diagnosed malformations).	YES/NO/UNCLEAR
ii. Were all patients enrolled in the study included in the analysis?	YES/NO/UNCLEAR
iii. Were all measures of 1st-trimester ultrasound detection accuracy (e.g. TP, FP, TN, FN) reported?	YES/NO/UNCLEAR

See *Appendix 2* for protocol details of the following studies: Hartge 2011 and Tudorache 2016.

TABLE 28 Characteristics of studies reporting on detection of major anomalies by first-trimester ultrasound in non-high-risk populations

Study (year)	Fetuses (*n*)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience	Anomalies included in study
Whitlow (1999)[47]	6634	11–14^{+6}	Unselected, consecutive recruitment	University Hospital	Yes (0.7)	TA/TV (20.1%)[c]	6 clinicians and 4 sonographers. All trained in first-trimester US.	All
Carvalho (2002)	2853	11–14	Unselected, singleton	University Hospital, Tertiary Care	Yes (0.9)	TA/TV	8 operators: 2 fetal medicine specialists, 5 research fellows in fetal medicine, 1 fetal echocardiography specialist	All
Drysdale (2002)	984	12–14	Unselected	District General Hospital	Yes	TA/TV	2 sonographers with FMF certification	All
Cheng (2003)	3600	10–13	Retrospective	Single Centre	Yes (presumed)	N/A	N/A	Acrania only
Taipale (2003)	20,751	11–15^{+6}	Unselected, consecutive recruitment	Local Hospital	Yes (0.3)	TV/TA (3%)	2 doctors, 5 midwives trained in obstetric sonography	All
Cedergren (2006)[52]	2708	11–14	Unselected, consecutive recruitment	University Hospital	Yes (0.3)	TA	Midwife sonographers with at least 10 years' experience	All
Saltvedt (2006)	18,053	12–14	Unselected, RCT	Multicentre (8)	No	TA (TV)	46 midwives with median of 11 years US experience, 11- to 14-week scan certification from FMF	All
Souka (2006)[54]	1148	11–14	Unselected	Unclear	Yes	TA/TV[c]	N/A	All
Srisupundit (2006)[55]	597	11–14	Unselected women attending NT scan, singleton pregnancies only, prospective study	University Hospital	Yes	TA	N/A	All
Dane (2007)[56]	1290	11–14	Unselected	Research Hospital	Yes	TA/TV[c]	2 operators with 6 and 2 years' experience respectively	All
Weiner (2007)	1723	11–13^{+6}	Patients presenting for NT examination	2 Maternal Fetal Medicine Centres	Yes	TA/TV (15%)	Sonographers experienced in first-trimester ultrasound examination	All
Chen (2008)[58] (control group)	3693	10–14^{+6}	Unselected, singleton pregnancies only, consecutively randomised (RCT)	One university and one regional hospital	Yes	TA/TV[c]	8 experienced operators	All

continued

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TABLE 28 Characteristics of studies reporting on detection of major anomalies by first-trimester ultrasound in non-high-risk populations (*continued*)

Study (year)	Fetuses (*n*)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience	Anomalies included in study
Chen (2008)[58] (study group)	3949	12–14^{+6}	Unselected, singleton pregnancies only, consecutively randomised (RCT)	One university and one regional hospital	Yes	TA/TV[c]	8 experienced operators	All
Li (2008)[59]	2232	11–14	Unselected, consecutive recruitment	Unclear	Yes	TA/TV[c] (2.0%)	N/A	All
Oztekin (2009)[110]	1085	11–14	Unselected	Research Hospital	Yes	TA/TV[c]	Single sonographer	All
Abu-Rustum (2010)[61]	1370	11–13^{+6}	Unselected, retrospective study	Unclear	Yes	TA/TV[c]	Single sonographer with FMF certification	All
Hildebrand (2010)	6692	11–14	Unselected, consecutive recruitment	University Hospital	Yes (0.2)	TA	Majority of exams performed by specialist trained midwives	All
Hartge (2011)[63]	3521	11–13^{+6}	Mixed high-risk and low-risk population, singleton pregnancies only, retrospective study	Tertiary referral centre	Yes	TA/TV[c] (35.8%)	N/A	All
Jakobsen (2011)[64]	9324	11–14	Unselected, retrospective study	University Hospital	Yes	TA/TV[c]	N/A	All
Syngelaki (2011)[16]	44,859	11–13	Unselected, singleton pregnancies only (presumed euploid), retrospective study,	Multicentre (3) including tertiary-care referral centre	No	TA/TV[c] (1%)	N/A	All
Becker (2012)[65]	6544	11–13^{+6}	Women with normal NT only (≤ 95th centile), prospective, consecutive recruitment	University Hospital	Yes (0.6)[d]	TA/TV[c] (23.4%)	Single examiner with 10 years' experience	All
Grande (2012)[66]	13,723	11–14	Mixed (majority low-risk scans, 13% for raised NT), singleton pregnancies only, retrospective study	Tertiary-Care Centre	No	TA/TV	19 obstetricians	All

Study (year)	Fetuses (*n*)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience	Anomalies included in study
Novotna (2012)[67]	9150	11–14	Unselected, prospective study	Single centre	Yes	TA/TV	23 operators with minimum 2 years' experience.	All
Pilalis (2012)[68]	3902	11–14	Unselected, retrospective study	Private maternity hospital	Yes	TA/TV[c]	FMF certified; 2 years special training in ultrasound.	All
Iliescu (2013)[69]	5472	12–13^{+6}	Unselected, prospective study	University Hospital	Yes (0.4)	TA/TV[c] (7.8%)	Obstetricians specialising in prenatal diagnosis with at least 5 years accreditations and specific training for early fetal cardiac assessment.	All
Sepulveda (2013)	11,068	11–13^{+6}	Retrospective	Tertiary referral centre	Y	TA/TV		All
Wang (2013)[71]	2822	11–14	Not stated	University Hospital	Yes	TA	5 experienced obstetric sonographers	All
Natu (2014)	551	11–14	Low a priori risk as defined by study authors (age < 30 years, singleton, no relevant personal or family history, no maternal comorbidities)	Unclear	Yes	Unclear	N/A	All
Andrew (2015)[73]	4421	11–14	Unselected, consecutive recruitment, retrospective study	Tertiary referral centre;	Yes	TA/TV[c]	4 operators with NT certification	All
Colosi (2015)[74]	5924	11–13^{+6}	Unselected, singleton pregnancies only, prospective study	FMU	Yes (4.7)	TA/TV (1.9%)[c]	4 operators with FMF certification	All
Roman (2015)	23,790	11–13^{+6}	Retrospective, singleton only	Single centre	Yes (presumed)	TA/TV	18 diagnostic medical sonographers with accreditation from NT Quality Review program, all working under supervision of MFM specialists	All
Takita (2016)[76]	2028	11–13^{+6}	Unselected, singleton pregnancies only, prospective study	University Hospital	Yes (0.6)	TA	N/A	All

continued

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Study (year)	Fetuses (*n*)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience	Anomalies included in study
Tudorache (2016)[77]	3240	11^{+2}–13^{+4}	Unselected, prospective, consecutive recruitment	University Hospital, Tertiary referral centre	Yes	TA	N/A	All
Vellamkondu (2017)[78]	440	11–14	Unselected, singleton pregnancies only, prospective study	University Hospital, Tertiary care	Yes (0.5)	TA/TV	N/A	All
Kenkhuis (2018)[79]	5534	11–13^{+6}	Unselected women offered Combined Test for Aneuploidy screening (*n* = 5237) and women at a priori high risk of fetal anomalies (297)	2 referral centres; 6 community ultrasound practices	Yes	TA/TV[c]	Sonographers given specific first-trimester US training	All
Vayna (2018)[81]	6114	11–14	Unselected, retrospective study	University Hospital	Yes	TA/TV[c]	N/A	All
Chen (2019)[82]	10,294	11–13^{+6}	Low-risk cohort, prospective study,	Single centre	Yes	N/A	Sonographers with DEGUM II Certificate	All
Petousis (2019)	3378	11–13^{+6}	Prospective observational study, singleton pregnancies, mix low-risk (*n* = 433)/high-risk population (*n* = 71)	University Hospital	No	TA/TV (4%)	Doctors with FMF certification	All
Syngelaki (2019)[11]	101,793	11–13^{+6}	Unselected, singleton pregnancies only (presumed euploid), retrospective study of prospectively collected data	2 University hospitals (one Tertiary care, one regional)	No	TA/TV[c] (3%)	476 sonographers with FMF certification	All
Sainz (2018)[80]	504	11–14^{+6}	Mixed low-risk (*n* = 433) and high-risk population (*n* = 71), singleton pregnancies only, prospective study	University Hospital	Yes	TA	2 sonographers: one with > 5 years obstetric US experience, one with SESEGO Level 3 training but < 1 year experience.	All

Study (year)	Fetuses (*n*)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience	Anomalies included in study
Liao (2021)	59,063	11–13^{+6} weeks	Retrospective, unselected, singleton	Single centre	Yes	TA/TV (< 1%)	All sonographers underwent rigorous 6-month training prior to study commencement	All

DEGUM, German Society of Ultrasound in Medicine and Biology; NB, nasal bone examination; SESEGO, Spanish Society of Gynecology and Obstetrics (SEGO) ultrasonography certification; US, ultrasound.
a In studies where aneuploid fetuses were included, percentage of the study population confirmed as aneuploid by karyotyping has been indicated in parentheses.
b In studies where both TA and TV ultrasound were used, the number in parentheses refers to the percentage of the study population who received screening with both screening tests.
c Studies where TV ultrasound was performed only in situations when visualisation with TA was suboptimal.
d Only known euploid fetuses included in this meta-analysis as insufficient data provided on entire study cohort.

Note
Only first author given for each study. Total number of fetuses included in this subgroup *n* = 410,441.

TABLE 29 Details of anatomical protocols used by studies evaluating non-high-risk populations

Study	No protocol used	Head	Face	Stomach	Bladder	Kidneys	Abdo wall (CI)	Diaphragm	Thorax	Spine	Limbs (long bones)	Hands	Feet
Whitlow (1999)[47]	x	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓
Carvalho (2002)	x	✓		✓	✓	x	✓	x	x	✓	✓	x	x
Drysdale (2002)	✓	x	x	x	x	x	x	x	x	x	x	x	x
Cheng (2003)	Protocol used for screening, but no details provided.												
Taipale (2003)	x	✓	x	✓	✓	✓	✓	x	x	✓	✓	x	x
McAuliffe (2005)	x	✓	✓	✓	✓	x	✓	x	x	✓	✓	x	x
Cedergren (2006)[52]	✓	x	x	x	x	x	x	x	x	x	x	x	x
Saltvedt (2006)	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x
Souka (2006)[54]	x	✓	✓	✓	✓	✓	✓	x	x	✓	✓	✓	✓
Srisupundit (2006)[55]	✓	✓	x	✓	✓	✓	✓	x	✓	x	✓	x	x
Dane (2007)[56]	x	✓	x	✓	✓	x	✓	x	x	✓	✓	x	x

continued

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TABLE 29 Details of anatomical protocols used by studies evaluating non-high-risk populations (*continued*)

Study	No protocol used	Head	Face	Stomach	Bladder	Kidneys	Abdo wall (CI)	Diaphragm	Thorax	Spine	Limbs (long bones)	Hands	Feet
Weiner (2007)	Sagittal view of fetus examined while undertaking NT examination. No other views examined routinely. Anatomical structures visualised as part of protocol were not defined.												
Chen (2008)[58] (control group)	✓	x	x	x	x	x	x	x	x	x	x	x	x
Chen (2008)[58] (study group)	x	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓
Li (2008)[59]	✓	x	x	x	x	x	x	x	x	x	x	x	x
Oztekin (2009)[109]	x	✓	✓	✓	✓	✓	✓	x	x	✓	✓	x	x
Abu-Rustum (2010)[61]	x	✓	x	✓	✓	✓	✓	✓	x	✓	✓	x	x
Hildebrand (2010)	✓	x	x	x	x	x	x	x	x	x	x	x	x
Jakobsen (2011)[64]	✓	x	x	x	x	x	x	x	x	x	x	x	x
Syngelaki (2011)[16]	x	✓	✓	✓	✓	x	✓	x	✓	✓	✓	✓	✓
Becker (2012)[65]	x	✓	x	✓	✓	✓	✓	x	x	x	✓	x	x
Grande (2012)[66]	x	✓	x	✓	x	✓	✓	✓	✓	x	✓	✓	✓
Novotna (2012)[67]	x	✓	x	✓	✓	x	✓	x	x	✓	✓	x	x
Pilalis (2012)[68]	x	✓	✓	✓	✓	x	✓	x	✓	x	✓	✓	✓
Iliescu (2013)[69]	x	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓
Sepulveda (2013)	x	✓	x	x	x	x	x	x	x	x	x	x	x
Wang (2013)[71]	x	✓	✓	x	✓	x	x	x	✓	x	✓	x	x
Natu (2014)	x	✓	x	x	x	x	x	x	x	✓	✓	x	x
Andrew (2015)[73]	x	✓	✓	✓	✓	x	✓	✓	✓	x	✓	✓	✓
Colosi (2015)[74]	x	✓	✓	✓	✓	x	✓	x	✓	x	✓	x	x
Roman (2015)	x	✓	x	x	x	x	✓	x	x	✓	x	x	x
Takita (2016)	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Study	No protocol used	Head	Face	Stomach	Bladder	Kidneys	Abdo wall (CI)	Diaphragm	Thorax	Spine	Limbs (long bones)	Hands	Feet
Vellamkondu (2017)[78]	Complete fetal anatomical survey, but no details provided.												
Kenkhuis (2018)[79]	x	✓	✓	✓	✓	x	✓	✓	x	✓	✓	✓	✓
Vayna (2018)[81]	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zheng (2018)	x	✓	✓	x	x	x	x	x	x	x	x	x	x
Chen FC (2019)[82]	x	✓	x	x	x	x	x	x	x	✓	x	x	x
Petousis (2019)	x	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓
Syngelaki (2019)[11]	x	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓
Sainz (2020)[80]	x	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓
Liao (2021)	x	✓	✓	✓	✓	x	✓	x	✓	x	✓	✓	✓

Notes
(✓) Identifies anatomical views and/or examinations included in the study protocol.
(x) Identifies anatomical views and/or examinations which were not routinely reported as being included in the study protocol.

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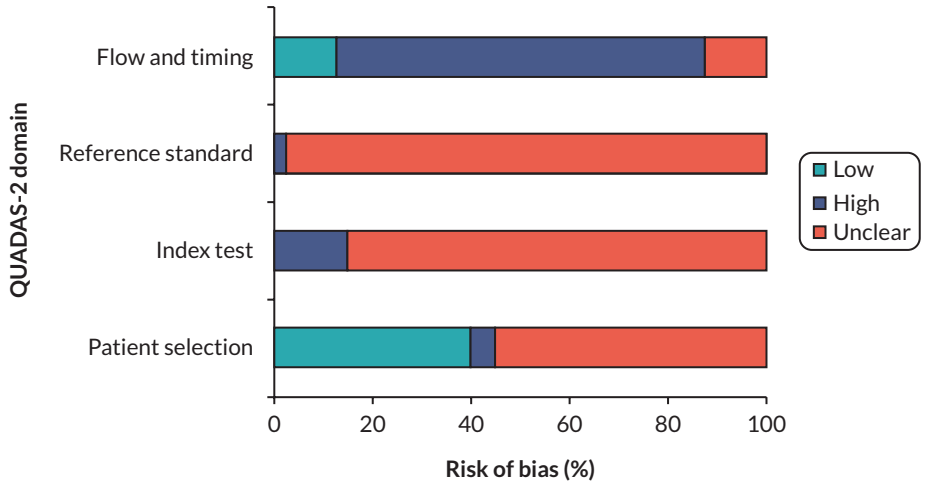

FIGURE 24 Quality assessment of studies included in systematic review for risk of bias (22) and concerns regarding applicability (23), according to QUADAS-2.

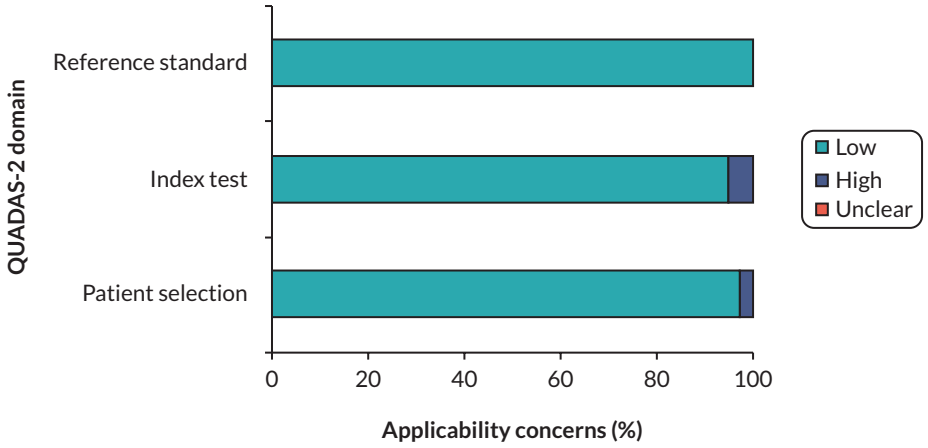

FIGURE 25 Quality assessment of studies included in systematic review for risk of bias (22) and concerns regarding applicability (23), according to QUADAS-2.

Appendix 2 Systematic review and meta-analysis of major cardiac anomalies using first-trimester ultrasound: methods and description of included studies.

Quality assessment of diagnostic accuracy studies-2 assessment tool

Defining the review question:

1. What is the sensitivity of first-trimester ultrasound for the detection of cardiac malformations?
2. What factors might impact detection rates?

- Patient selection: pregnant women with GA prior to 14^{+6} weeks, mothers with either singleton or multiple pregnancies were included.
- Index Test: TV and/or TA 2D Ultrasound prior to 14^{+6} weeks GA.
- Reference Standard: Postnatal examination of fetus or post-mortem of fetus for evidence/confirmation of structural abnormalities.
- Target condition: congenital cardiac abnormalities.

Domain 1: Patient selection

C. **Risk of bias:** Could the selection of patients have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
i. Was a consecutive (vs. random sample) of patients enrolled?	YES/NO/UNCLEAR
ii. Did the study avoid inappropriate exclusions?	YES/NO/UNCLEAR
D. **Applicability:** Are there concerns that the included patients and setting do not match the review question (i.e. severity of the target condition, demographic features, presence of comorbidity, setting)?	LOW/HIGH/UNCLEAR

Domain 2: Index test

A. **Risk of bias:** Could the conduct or interpretation of the index test have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
i. Were sonographers blinded to the history (risk profile) of the patients?	YES/NO/UNCLEAR
ii. Were all of the included first-trimester scans performed prior to 14^{+6} weeks GA?	YES/NO/UNCLEAR
B. Applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question?	LOW/HIGH/UNCLEAR

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Domain 3: Reference standard

A. Risk of bias: Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
i. Was an appropriate reference standard used to correctly classify the target condition?	YES/NO/UNCLEAR
ii. Were the reference standard results interpreted without knowledge of the results of the index test?	YES/NO/UNCLEAR
B. **Applicability:** Are there concerns that the target condition as defined by the reference standard does not match the question?	LOW/HIGH/UNCLEAR

Domain 4: Flow and timing

B. Risk of bias: Could the patient flow have introduced bias?	LOW/HIGH/UNCLEAR
Signalling questions:	
ii. Did all patients included in the study undergo examination with the reference standard? (either postnatal examination for live births or post-mortem for stillbirths/TOPs in those with diagnosed malformations).	YES/NO/UNCLEAR
ii. Were all patients enrolled in the study included in the analysis?	YES/NO/UNCLEAR
iii. Were all measures of 1st trimester ultrasound detection accuracy (e.g. TP, FP, TN, FN) reported?	YES/NO/UNCLEAR

TABLE 30 Characteristics of studies reporting on detection of major cardiac anomalies by first-trimester ultrasound in non-high-risk populations

Study (year)	Fetuses (*n*)	Prevalence of major cardiac anomalies (*n* per 100 fetuses)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience
Whitlow (1999)[47]	6634	0.18 (0.09–0.32)	11–14^{+6}	Unselected, consecutive recruitment	University Hospital	Yes (0.7)	TA/TV (20.1)[c]	6 clinicians and 4 sonographers. All trained in first-trimester US
Michailidis (2001)[105]	6650	0.15 (0.07–0.28)	38–84	Unselected, consecutive recruitment, prospective study	University Hospital	No	TA/TV (14%)[c]	N/A
McAuliffe (2005)[106]	325	0.62 (0.07–2.21)	11–13^{+6}	Unselected, singleton pregnancies only, prospective study	University Hospital, Tertiary Care	No	TA/TV (24.6%)[c]	N/A
Cedergren (2006)[52]	2708	0.11 (0.02 0.32)	11–14	Unselected, consecutive recruitment	University Hospital	Yes (0.3)	TA	Midwife sonographers with at least 10 years experience
Souka (2006)[54]	1148	2.54 (1.92–3.29)	11–14	Unselected	Unclear	Yes	TA/TV[c]	N/A
Srisupundit (2006)[55]	597	0.34 (0.04–1.20)	11–14	Unselected women attending NT scan, singleton pregnancies only, prospective study	University Hospital	Yes	TA	N/A
Vimpelli (2006)[107]	584	1.03 (0.38–2.22)	11–13^{+6}	Unselected	Unclear	Yes	TV	N/A
Dane (2007)[56]	1290	0.31 (0.08–0.79)	11–14	Unselected	Research Hospital	Yes	TA/TV[c]	2 operators with 6 and 2 years experience respectively
Lombardi (2007)[108]	623	0.48 (0.10 1.40)	12^{+3}–13^{+6}	Unselected women attending routine NT scan; singleton pregnancies only	Unclear	Yes	TA	N/A
Chen (2008)[58] (control group)	3693	0.48 (0.10–0.77)	10–14^{+6}	Unselected, singleton pregnancies only, consecutively randomised (RCT)	One university and one regional hospital	Yes	TA/TV[c]	8 experienced operators

continued

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TABLE 30 Characteristics of studies reporting on detection of major cardiac anomalies by first-trimester ultrasound in non-high-risk populations (*continued*)

Study (year)	Fetuses (*n*)	Prevalence of major cardiac anomalies (*n* per 100 fetuses)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience
Chen (2008)[58] (study group)	3949	0.43 (0.25–0.69)	12–14^{+6}	Unselected, singleton pregnancies only, consecutively randomised (RCT)	One university and one regional hospital	Yes	TA/TV[c]	8 experienced operators
Li (2008)[59]	2232	0.22 (0.07–0.52)	11–14	Unselected, consecutive recruitment	Unclear	Yes	TA/TV[c] (2.0%)	N/A
Bennasar (2009)[109]	64	17.19 (8.90–28.68)	11–14^{+6}	Mixed cohort (majority unselected combined with high-risk women), singleton pregnancies only, prospective study	University Hospital	Yes	TV	'Non-expert' operators trained in first-trimester US and fetal echocardiography
Oztekin (2009)[110]	1085	0.28 (0.06–0.81)	11–14	Unselected	Research Hospital	Yes	TA/TV[c]	Single sonographer
Abu-Rustum (2010)[61]	1370	0.80 (0.40–1.43)	11–13^{+6}	Unselected, retrospective study	Unclear	Yes	TA/TV[c]	Single sonographer with FMF certification
Sinkovskaya (2010)[112]	100	8.00 (3.52–15.16)	11–14^{+6}	Consecutive recruitment; singleton pregnancies only; prospective study	Unclear	Yes	TA/TV[c] (19%)	N/A
Hartge (2011)[63]	3521	2.87 (2.34–3.47)	11–13^{+6}	Mixed high-risk and low-risk population, singleton pregnancies only, retrospective study	Tertiary referral centre;	Yes	TA/TV[c] (35.8%)	N/A
Jakobsen (2011)[64]	9324	0.46 (0.33–0.62)	11–14	Unselected, retrospective study	University Hospital	Yes	TA/TV[c]	N/A
Krapp (2011)[113]	690	2.75 (1.67–4.27)	45–84	Mixed high- and low-risk population, retrospective study	Unclear	Yes	TA/TV[c] (5.2%)	N/A
Syngelaki (2011)[16]	44,859	0.26 (0.21–0.31)	11–13	Unselected, singleton pregnancies only (presumed euploid), retrospective study,	Multicentre (3) including tertiary-care referral centre	No	TA/TV[c] (1%)	N/A
Volpe (2011)[114]	4445	0.58 (0.38–0.86)	45–84	Unselected, prospective cohort	Single centre, University Hospital	Yes	TA/TV[c] (7.3%)	Sonographers with extensive experience, FMF certified.

Study (year)	Fetuses (*n*)	Prevalence of major cardiac anomalies (*n* per 100 fetuses)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience
Becker (2012)[65]	6544	0.23 (0.13–0.38)	11–13^{+6}	Women with normal NT only (≤ 95th centile), prospective, consecutive recruitment	University Hospital	Yes (0.6)[d]	TA/TV[c] (23.4%)	Single examiner with 10 years' experience
Eleftheriades (2012)[115]	3774	0.90 (0.62–1.26)	11–13^{+6}	Unselected fetuses undergoing routine prospective ultrasound	Private FMU	Yes	TA	Obstetrician with extensive experience and FMF certificate. In case of abnormality, further examination by fetal cardiologist.
Grande (2012)[66]	13,723	0.27 (0.19–0.37)	11–14	Mixed (majority low-risk scans, 13% for raised NT), singleton pregnancies only, retrospective study	Tertiary-Care Centre	No	TA/TV	19 Obstetricians
Novotna (2012)[67]	9150	0.20 (0.12–0.31)	11–14	Unselected, prospective study	Single centre	Yes	TA/TV	23 operators with minimum 2 years' experience.
Pilalis (2012)[68]	3902	0.28 (0.14–0.50)	11–14	Unselected, retrospective study	Private maternity hospital	Yes	TA/TV[c]	FMF certified; 2 years special training in ultrasound.
Iliescu (2013)[69]	5472	0.62 (0.43–0.87)	12–13^{+6}	Unselected, prospective study	University Hospital	Yes (0.4)	TA/TV[c] (7.8%)	Obstetricians specialising in prenatal diagnosis with at least 5 years accreditations and specific training for early fetal cardiac assessment.
Wang (2013)[71]	2822	0.35 (0.17–0.65)	11–14	Not stated	University Hospital	Yes	TA	5 Experienced obstetric sonographers
Orlandi (2014)[116]	4820	0.44 (0.27–0.67)	11–14	Unselected, singleton pregnancies only, prospective study	Centre for prenatal diagnosis	Yes	TA/TV[c] (5%)	3 Experienced sonographers with FMF certificates for NT, NB, TR, DV.
Andrew (2015)[73]	4421	0.07 (0.01–0.20)	11–14	Unselected, consecutive recruitment, retrospective study	Tertiary referral centre	Yes	TA/TV[c]	4 operators with NT certification
Colosi (2015)[74]	5924	0.05 (0.01–0.15)	11–13^{+6}	Unselected, singleton pregnancies only, prospective study	FMU	Yes (4.7)	TA/TV (1.9%)[c]	4 operators with FMF certification

continued

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TABLE 30 Characteristics of studies reporting on detection of major cardiac anomalies by first-trimester ultrasound in non-high-risk populations (*continued*)

Study (year)	Fetuses (*n*)	Prevalence of major cardiac anomalies (*n* per 100 fetuses)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience
Wiechec (2015)[117]	1084	3.41 (2.41–4.67)	11–13^{+6}	Unselected, prospective study	University Hospital Clinic	Yes (6.6)	TA/TV (5.25%)[c]	N/A
Takita (2016)[76]	2028	0.74 (0.41–1.22)	11–13^{+6}	Unselected, singleton pregnancies only, prospective study	University Hospital	Yes (0.6)	TA	N/A
Tudorache (2016)[77]	3240	0.99 (0.68–1.39)	11^{+2}–13^{+4}	Unselected, prospective, consecutive recruitment	University Hospital, Tertiary referral centre	Yes	TA	N/A
De Robertis (2017)[118]	5343	0.62 (0.43–0.87)	45–84	Unselected, singleton pregnancies only, consecutive recruitment, prospective study. Excluded all pregnancies which underwent TOP for cardiac anomaly in the first-trimester.	Tertiary Care	Yes	TA/TV (7%)	Expert sonographers, FMF certified
Vellamkondu (2017)[78]	440	0.91 (0.25–2.31)	11–14	Unselected, singleton pregnancies only, prospective study	University Hospital, Tertiary care	Yes (0.5)	TA/TV	N/A
Fernandez (2018)[119]	663	0.75 (0.25–1.75)	11–13^{+6}	Low-risk singleton pregnancies only, prospective study	FMU	Yes	TV/TA	2 sonographers with > 10 years' experience
Kenkhuis (2018)[79]	5534	0.23 (0.13–0.40)	11–13^{+6}	Unselected women offered Combined Test for Aneuploidy screening (*n* = 5237) and women at a priori high risk of fetal anomalies (297)	2 Referral centres; 6 community ultrasound practices	Yes	TA/TV[c]	Sonographers given specific first-trimester US training
Sainz (2018)[80]	504	2.98 (1.68–4.87)	11–14^{+6}	Mixed low-risk (*n* = 433) and high-risk population (*n* = 71), singleton pregnancies only, prospective study	University Hospital	Yes	TA	2 sonographers: one with > 5 years obstetric US experience, one with SESEGO Level 3 training but < 1 year experience.
Vayna (2018)[81]	6114	0.51 (0.34–0.72)	11–14	Unselected, retrospective study	University Hospital	Yes	TA/TV[c]	N/A

Study (year)	Fetuses (*n*)	Prevalence of major cardiac anomalies (*n* per 100 fetuses)	GA (weeks) or CRL (mm)	Population and recruitment characteristics	Healthcare setting	Aneuploid fetuses included? (%)[a]	Index test[b]	Sonographer experience
Zheng (2018)[120]	1592	1.88 (1.27–2.68)	45–84	Unselected women presenting for NT scan, consecutive recruitment	University Hospital	Yes	TA/TV[c]	2 Sonographers with FMF certification
Chen (2019)[82]	10,294	1.18 (0.98–1.40)	11–13^{+6}	Low-risk cohort, prospective study,	Single centre	Yes	N/A	Sonographers with DEGUM II Certificate
Duta (2019)[121]	7693	0.44 (0.31–0.62)	11–14	Unselected, retrospective study of prospectively, consecutively collected data	FMU, Single centre	No	TA/TV[c]	8 sonographers certified for 11- to 14-week scan
Ebrashy (2019)[122]	3400	2.94 (2.40–3.57)	11–13^{+6}	Unselected, prospective study	FMU, University Hospital	Yes	TA/TV[c] (31.3%)	Fetal medicine specialists with FMF certification
Erenel (2019)[123]	707	1.70 (0.88–2.95)	11–14	Prospective, Unselected	Perinatology clinic affiliated with University and Research Hospital	Yes	TA/TV[c] (4.6%)	5 clinicians with experience in first-trimester ultrasound
Syngelaki (2019)[11]	101,793	0.35 (0.31–0.39)	11–13^{+6}	Unselected, singleton pregnancies only (presumed euploid), retrospective study of prospectively collected data,	2 University Hospitals (one Tertiary care, one regional)	No	TA/TV[c] (3%)	476 Sonographers with FMF certification

DEGUM, German Society of Ultrasound in Medicine and Biology; DV, ductus venosus examination; NB, nasal bone examination; NT, nuchal translucency examination; SESEGO, Spanish Society of Gynecology and Obstetrics (SEGO) ultrasonography certification; TR, tricuspid regurgitation examination; US, ultrasound.

a In studies where aneuploid fetuses were included, percentage of the study population confirmed as aneuploid by karyotyping has been indicated in parentheses.

b In studies where both TA and TV ultrasound were used, the number in parentheses refers to the percentage of the study population who received screening with both screening tests.

c Studies where TV ultrasound was performed only in situations when visualisation with TA was suboptimal.

d Only known euploid fetuses included in this meta-analysis as insufficient data provided on entire study cohort.

Note

Only first author given for each study. Total number of fetuses included in this subgroup *n* = 306,872. Pooled prevalence of major cardiac anomalies (*n* per 100 fetuses) in this subgroup was 0.41% (fixed-effects model, 95% CI 0.39% to 0.43%).

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TABLE 31 Details of anatomical protocols used by studies evaluating non-high-risk populations

Study	No protocol used	Situs	Cardiac axis	Four-chamber view	Outflow/inflow tract assessment[a]	Colour flow Doppler	Pulsed Doppler	Ductus venosus assessment	Tricuspid valve assessment	Fetal ECHO[b]	Protocol analysis group[c]
Whitlow (1999)[47]	X	x	x	✓	x	x	x	x	x	x	2
Michailidis (2001)[105]	X	x	x	✓	x	x	x	x	x	x	2
McAuliffe (2005)[106]	X	✓	x	✓	x	x	x	x	x	x	2
Cedergren (2006)[52]	✓	x	x	x	x	x	x	x	x	x	1
Souka (2006)[54]	X	x	x	✓	3VV (pulmonary artery, aorta and superior vena cava)	x	x	x	x	x	4
Srisupundit (2006)[55]	No details regarding protocol used in study provided by authors.										
Vimpelli (2006)[107]	X	✓	x	✓	Longitudinal views of the aorta and pulmonary trunk, crossing of aorta and pulmonary trunk (and/or 3VV), aortic arch, ductal arch	x	x	x	x	✓	4
Dane (2007)[56]	✓	x	x	x	x	x	x	x	x	x	1
Lombardi (2007)[108]	x	✓	✓	✓	Crossing of the main pulmonary artery with the aorta; straight line of the pulmonary artery surrounded by aortic arch; connection of the aorta and ductus arteriosus	✓	x	x	✓	✓	5
Chen (2008)[58] (control group)	✓	x	x	x	x	x	x	x	x	x	1
Chen (2008)[58] (study group)	X	x	x	✓	Aortic and pulmonary outflow tracts	x	x	x	x	x	4
Li (2008)[59]	✓	x	x	x	x	x	x	x	x	x	1
Bennasar (2009)[109]	X	✓	x	✓	Continuity between the aortic root and the interventricular septum; pulmonary trunk in a short-axis view, pulmonary branching; Crossover of the aorta and pulmonary trunk. 3VVT.	✓	x	x	x	✓	5
Oztekin (2009)[110]	X	x	✓	✓	Examination of great vessels	x	x	x	x	x	4
Abu-Rustum (2010)[61]	X	✓	x	✓	x	x	✓	x	✓	x	2
Sinkovskaya (2010)[112]	X	x	✓	✓	Imaging of the outflow tracts	x	x	x	x	x	4

Study	No protocol used	Situs	Cardiac axis	Four-chamber view	Outflow/inflow tract assessment[a]	Colour flow Doppler	Pulsed Doppler	Ductus venosus assessment	Tricuspid valve assessment	Fetal ECHO[b]	Protocol analysis group[c]
Hartge (2011)[63]	X	✓	x	✓	Fetal echocardiography carried out using standardised anatomical transverse and longitudinal planes	✓	✓	✓	x	✓	5
Jakobsen (2011)[64]	✓	x	x	x	x	x	x	x	x	x	1
Krapp (2011)[113]	x	✓	x	✓	Pulmonary vein inflow into left atrium; outflow of the aorta from the left ventricle; 3VV (outflow of the main pulmonary artery from right ventricle); transverse aortic arch; branching of the brachiocephalic trunk, left common carotid and left subclavian artery.	✓	x	x	x	✓	5
Syngelaki (2011)[16]	X	x	x	✓	x	x	✓	x	✓	x	2
Volpe (2011)[114]	X	✓	x	✓	Left ventricular outflow tract; Right ventricular outflow tract; Crossover of the great arteries; 3VVT.	✓	x	x	x	x	5
Becker (2012)[65]	X	✓	x	✓	Visualisation of inflow and outflow tracts	✓	x	x	x	✓	5
Eleftheriades (2012)[115]	X	✓	x	✓	x	x	x	x	x	x	2
Grande (2012)[66]	X	x	x	✓	x	x	✓	✓	x	x	2
Novotna (2012)[67]	✓	x	x	x	x	x	x	x	x	x	1
Pilalis (2012)[68]	✓	x	x	x	x	x	x	x	x	x	1
Iliescu (2013)[69]	X	✓	x	✓	Aorta arising from left ventricle and pulmonary trunk arising from right ventricle and crossing to fetal left side over ascending aorta; 3VVT;	✓	x	✓	x	x	5
Wang (2013)[71]	✓	x	x	x	x	x	x	x	x	x	1
Orlandi (2014)[116]	X	✓	x	✓	Origin of aorta from left ventricle; Origin of pulmonary artery from right ventricle, and vessels crossing	✓	x	x	x	x	5
Andrew (2015)[73]	X	✓	x	✓	Examination of great vessels	✓	✓	✓	✓	x	5
Colosi (2015)[74]	X	x	x	✓	x	x	✓	✓	x	x	2
Wiechec (2015)[117]	X	x	x	✓	3VVT: number of arterial arms, subjective assessment of their size ration and flow direction	✓	x	x	x	x	5

continued

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TABLE 31 Details of anatomical protocols used by studies evaluating non-high-risk populations (*continued*)

Study	No protocol used	Situs	Cardiac axis	Four-chamber view	Outflow/inflow tract assessment[a]	Colour flow Doppler	Pulsed Doppler	Ductus venosus assessment	Tricuspid valve assessment	Fetal ECHO[b]	Protocol analysis group[c]
Takita (2016)[76]	X	✓	x	✓	x	x	x	x	x	x	2
Tudorache (2016)[77]	X	✓	x	✓	3VVT; Outflow tract crossing	✓	x	✓	✓	x	5
De Robertis (2017)[118]	X	✓	x	✓	3VVT	✓	x	x	x	x	5
Vellamkondu (2017)[78]	No details regarding protocol used in study provided by authors.										
Fernandez (2018)[119]	X	✓	x	✓	Axial section at level of great vessels showing pulmonary artery, aorta and vena cava	x	x	x	x	x	4
Kenkhuis (2018)[79]	X	✓	x	✓	x	✓	✓	x	x	x	3
Sainz (2018)[80]	X	x	x	✓	Aortic and pulmonary outflow tracts	x	x	x	x	x	4
Vayna (2018)[81]	X	✓	x	✓	Origin of the aorta and pulmonary artery; 3VV; aortic arch; right subclavian artery	✓	x	✓	✓	x	5
Zheng (2018)[120]	X	x	✓	✓	3VVT	✓	x	x	x	x	5
Chen (2019)[82]	X	x	x	✓	Evaluation of major vessels	x	x	x	x	x	5
Duta (2019)[120]	X	✓	✓	✓	Aorta, pulmonary artery, 3VVT, and subclavian artery	✓	x	x	x	x	5
Ebrashy (2019)[122]	x	x	✓	✓	Examination of great arteries, (vessel diameter, crossing); aortic arch; ductal arch	✓	x	x	x	✓	5
Erenel (2019)[123]	X	✓	x	✓	3VV	✓	x	x	x	x	5
Syngelaki (2019)[11]	X	x	x	✓	Examination of outflow tracts	✓	✓	x	✓	x	5

3VV, three-vessel view; 3VVT, three-vessel and trachea view.

a Evaluation of the cardiac outflow and inflow tracts varied significantly and assessment is listed in the table as described by each study respectively.

b Identifies studies which have described their first-trimester cardiac assessment as fetal echocardiography.

c For the purposes of analysis, studies were divided into five groups based on the protocol they used for cardiac assessment: (1) no protocol used, (2) assessment of four-chamber view without use of colour flow Doppler, (3) assessment of four-chamber view with use of colour flow Doppler, (4) assessment of four-chamber view and any type of outflow tract evaluation without colour flow Doppler, (5) assessment of four-chamber view and any type of outflow tract evaluation with use of colour flow Doppler.

Notes

(✓) Identifies anatomical views and/or examinations included in the study protocol.

(x) Identifies anatomical views and/or examinations which were not routinely reported as being included in the study protocol.

TABLE 32 Number of major cardiac anomalies diagnosed or suspected in the first trimester with independent secondary confirmation in non-high-risk populations

Study	Major cardiac anomalies detected or suspected In first trimester (TP – *n*)	FP diagnoses following diagnosed or suspected major cardiac anomaly in first trimester (FP – *n*)	Secondary confirmation of T1 detected anomalies: Major cardiac anomalies (TP) with post-mortem or postnatal confirmation, *n* (%)
Whitlow (1999)[47]	2	0	NR
Michailidis (2001)[105]	1	0	NR
McAuliffe (2005)[106]	0	0	NrA
Cedergren (2006)[52]	0	0	N/A
Souka (2006)[54]	3	0	2 (66.67)
Srisupundit (2006)[55]	2	0	NR
Vimpelli (2006)[107]	1	0	NR
Dane (2007)[56]	1	0	NR
Lombardi (2007)[108]	3	0	2 (66.67)
Chen (2008)[58] (control group)	1	0	1 (100.00)
Chen (2008)[58] (study group)	6	0	6 (100.00)
Li (2008)[59]	1	0	NR
Bennasar (2009)[109]	10	0	10 (100.00)
Oztekin (2009)[110]	0	0	N/A
Sinkovskaya (2010)[112]	6	0	6 (100.00)
Hartge (2011)[63]	85	0	50 (58.82)
Jakobsen (2011)[64]	3	0	NR
Krapp (2011)[113]	17	0	6 (35.29)
Syngelaki (2011)[16]	29	0	NR
Volpe (2011)[114]	21	0	15 (71.43)
Becker (2012)[65]	7	0	NR
Eleftheriades (2012)[115]	16	0	1 (6.25)
Grande (2012)[66]	24	0	NR
Novotna (2012)[67]	1	0	NR
Pilalis (2012)[68]	2	0	NR
Iliescu (2013)[69]	32	0	NR

continued

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TABLE 32 Number of major cardiac anomalies diagnosed or suspected in the first trimester with independent secondary confirmation in non-high-risk populations (*continued*)

Study	Major cardiac anomalies detected or suspected In first trimester (TP – *n*)	FP diagnoses following diagnosed or suspected major cardiac anomaly in first trimester (FP – *n*)	Secondary confirmation of T1 detected anomalies
			Major cardiac anomalies (TP) with post-mortem or postnatal confirmation, *n* (%)
Wang (2013)[71]	4	0	NR
Orlandi (2014)[116]	19	0	3 (15.79)
Andrew (2015)[73]	3	0	NR
Colosi (2015)[74]	0	0	N/A
Takita (2016)[76]	2	0	NR
Tudorache (2016)[77]	25	14	6 (24.00)
Vellamkondu (2017)[78]	1	0	1 (100.00)
Fernandez (2018)[118]	5	0	5 (100.00)
Kenkhuis (2018)[79]	5	0	2 (40.00)
Sainz (2018)[80]	13	0	NR
Vayna (2018)[81]	22	0	6 (27.27)
Zheng (2018)[120]	28	0	28 (100.00)
Chen (2019)[82]	63	3	NR
Duta (2019)[121]	26	0	NR
Ebrashy (2019)[122]	85	16	NR
Erenel (2019)[123]	12	2	5 (41.67)
Syngelaki (2019)[11]	112	0	NR
Pooled Result	699	35	155 (22.17)

N/A, not applicable; NR, not reported by study.

TABLE 33 Characteristics of major cardiac anomalies diagnosed following first-trimester ultrasound assessment in non-high-risk populations

Study	Total major cardiac anomalies present (TP + FN)	Major cardiac anomalies detected In first trimester (TP) (*n*)	FP (*n*)	T1 cardiac anomalies with change of diagnosis at later gestation (*n*)	Sensitivity for detection of major cardiac anomalies (% – 95% CI)	% of Antenatal major cardiac anomaly diagnoses made in the first trimester (% – 95% CI)	Specificity	PPV
Whitlow (1999)[47]	12	2	0	0	16.67 (2.09 to 48.41)	22.22 (2.81 to 60.01)	100.00 (99.94 to 100.00)	100.00 (15.81 to 100.00)
Michailidis (2001)[105]	10	1	0	0	10.00 (0.25 to 44.50)	20.00 (0.51 to 71.64)	100.00 (99.94 to 100.00)	100.00 (2.50 to 100.00)
McAuliffe (2005)[106]	2	0	0	0	0.00 (0.00 to 84.19)	0.00 (0.00 to 97.50)	99.85 (98.56 to 100.00)	50.00 (0.04 to 99.96)
Cedergren (2006)[52]	3	0	0	0	0.00 (0.00 to 70.76)	0.00 (0.00 to 99.94)	99.98 (99.82 to 100.00)	50.00 (0.04 to 99.96)
Souka (2006)[54]	4	0	0	0	0.00 (0.00 to 60.24)	0.00 (0.00 to 60.24)	100.00 (99.83 to 100.00)	100.00 (90.00 to 100.00)
Srisupundit (2006)[55]	2	2	0	0	100.00 (15.81 to 100.00)	100.00 (15.81 to 100.00)	100.00 (99.38 to 100.00)	100.00 (15.81 to 100.00)
Vimpelli (2006)[107]	6	1	0	0	16.67 (0.42 to 64.12)	50.00 (1.26 to 98.74)	100.00 (99.36 to 100.00)	100.00 (2.50 to 100.00)
Dane (2007)[56]	4	1	0	0	25.00 (0.63 to 80.59)	33.33 (0.84 to 90.57)	100.00 (99.71 to 100.00)	100.00 (2.50 to 100.00)
Lombardi (2007)[108]	3	0	0	0	0.00 (0.00 to 70.76)	16.67 (0.00 to 82.33)	99.92 (99.25 to 100.00)	50.00 (0.04 to 99.96)
Chen (2008)[58] (control group)	18	1	0	0	5.56 (0.14 to 27.29)	10.00 (0.25 to 44.50)	100.00 (99.90 to 100.00)	100.00 (2.50 to 100.00)
Chen (2008)[58] (study group)	17	5	0	1	35.29 (14.21 to 61.67)	42.86 (17.66 to 71.14)	100.00 (99.91 to 100.00)	100.00 (54.07 to 100.00)
Li (2008)[59]	5	1	0	0	20.00 (0.51 to 71.64)	33.33 (0.84 to 90.57)	100.00 (99.83 to 100.00)	100.00 (2.50 to 100.00)
Bennasar (2009)[109]	11	10	0	0	90.91 (58.72 to 99.77)	100.00 (69.15 to 100.00)	100.00 (93.28 to 100.00)	100.00 (69.15 to 100.00)

continued

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TABLE 33 Characteristics of major cardiac anomalies diagnosed following first-trimester ultrasound assessment in non-high-risk populations (*continued*)

Study	Total major cardiac anomalies present (TP + FN)	Major cardiac anomalies detected In first trimester (TP) (*n*)	FP (*n*)	T1 cardiac anomalies with change of diagnosis at later gestation (*n*)	Sensitivity for detection of major cardiac anomalies (% – 95% CI)	% of Antenatal major cardiac anomaly diagnoses made in the first trimester (% – 95% CI)	Specificity	PPV
Oztekin (2009)[110]	3	0	0	0	0.00 (0.00 to 70.76)	0.00 (0.00 to 97.50)	99.95 (99.57 to 100.00)	50.00 (0.04 to 99.96)
Sinkovskaya (2010)[112]	8	6	0	0	75.00 (34.91 to 96.81)	75.00 (34.91 to 96.81)	100.00 (96.07 to 100.00)	100.00 (54.07 to 100.00)
Hartge (2011)[63]	101	85	0	0	84.16 (75.55 to 90.67)	85.86 (77.41 to 92.05)	100.00 (99.89 to 100.00)	100.00 (95.75 to 100.00)
Jakobsen (2011)[64]	43	3	0	0	6.98 (1.46 to 19.06)	25.00 (5.49 to 57.19)	100.00 (99.96 to 100.00)	100.00 (29.24 to 100.00)
Krapp (2011)[113]	19	17	0	0	89.47 (66.86 to 98.70)	89.47 (66.86 to 98.70)	100.00 (99.45 to 100.00)	100.00 (80.49 to 100.00)
Syngelaki (2011)[16]	115	29	0	0	25.22 (17.58 to 34.17)	26.61 (18.60 to 35.92)	100.00 (99.99 to 100.00)	100.00 (88.06 to 100.00)
Volpe (2011)[114]	26	17	0	4	80.77 (60.65 to 93.45)	80.77 (60.65 to 93.45)	100.00 (99.92 to 100.00)	100.00 (83.89 to 100.00)
Becker (2012)[65]	15	7	0	0	46.67 (21.27 to 73.41)	58.33 (27.67 to 84.83)	100.00 (99.94 to 100.00)	100.00 (59.04 to 100.00)
Eleftheriades (2012)[114]	34	16	0	0	47.06 (29.78 to 64.87)	48.48 (30.80 to 66.46)	100.00 (99.90 to 100.00)	100.00 (79.41 to 100.00)
Grande (2012)[66]	37	24	0	0	64.86 (47.46 to 79.79)	68.57 (50.71 to 83.15)	100.00 (99.97 to 100.00)	100.00 (85.75 to 100.00)
Novotna (2012)[67]	18	1	0	0	5.56 (0.14 to 27.29)	14.29 (0.36 to 57.87)	100.00 (99.96 to 100.00)	100.00 (2.50 to 100.00)
Pilalis (2012)[68]	11	2	0	0	18.18 (2.28 to 51.76)	18.18 (2.28 to 51.78)	100.00 (99.91 to 100.00)	100.00 (15.81 to 100.00)
Iliescu (2013)[69]	34	29	0	Unable to report[a]	85.29 (68.94 to 95.05)	85.29 (68.94 to 95.05)	100.00 (99.93 to 100.00)	100.00 (88.06 to 100.00)

Study	Total major cardiac anomalies present (TP + FN)	Major cardiac anomalies detected In first trimester (TP) (*n*)	FP (*n*)	T1 cardiac anomalies with change of diagnosis at later gestation (*n*)	Sensitivity for detection of major cardiac anomalies (% – 95% CI)	% of Antenatal major cardiac anomaly diagnoses made in the first trimester (% – 95% CI)	Specificity	PPV
Wang (2013)[71]	10	4	0	0	40.00 (12.16 to 73.76)	44.44 (13.70 to 78.80)	100.00 (99.87 to 100.00)	100.00 (39.76 to 100.00)
Orlandi (2014)[116]	21	16	0	1	89.47 (66.86 to 98.70)	85.00 (62.11 to 96.79)	100.00 (99.92 to 100.00)	100.00 (80.49 to 100.00)
Andrew (2015)[73]	3	1	0	0	33.33 (0.84 to 90.57)	33.33 (0.84 to 90.57)	100.00 (99.92 to 100.00)	100.00 (80.49 to 100.00)
Colosi (2015)[74]	3	0	0	0	0.00 (0.00 to 70.76)	0.00 (0.00 to 70.76)	100.00 (99.92 to 100.00)	100.00 (2.50 to 100.00)
Takita (2016)[76]	15	2	0	0	13.33 (1.66 to 40.46)	33.33 (4.33 to 77.72)	99.99 (99.92 to 100.00)	50.00 (0.04 to 99.96)
Tudorache (2016)[77]	32	22	13	1	75.00 (56.60 to 88.54)	71.88 (53.25 to 86.25)	100.00 (99.82 to 100.00)	100.00 (15.81 to 100.00)
Vellamkondu (2017)[78]	4	1	0	0	25.00 (0.63 to 80.59)	50.00 (1.26 to 98.74)	99.60 (99.31 to 99.78)	63.89 (46.22 to 79.18)
Fernandez (2018)[118]	5	5	0	0	100.00 (47.82 to 100.00)	100.00 (47.81 to 100.00)	100.00 (99.16 to 100.00)	100.00 (2.50 to 100.00)
Kenkhuis (2018)[79]	13	5	0	0	38.46 (13.86 to 68.42)	50.00 (18.71 to 81.29)	100.00 (99.44 to 100.00)	100.00 (47.82 to 100.00)
Sainz (2018)[80]	15	13	0	0	86.67 (59.54 to 98.34)	86.67 (59.54 to 98.34)	100.00 (99.93 to 100.00)	100.00 (47.82 to 100.00)
Vayna (2018)[81]	31	22	0	0	70.97 (51.96 to 85.78)	75.86 (56.46 to 89.70)	100.00 (99.25 to 100.00)	100.00 (75.29 to 100.00)
Zheng (2018)[119]	30	27	0	(1)[b]	93.33 (77.93 to 99.18)	93.33 (77.93 to 99.18)	100.00 (99.94 to 100.00)	100.00 (84.56 to 100.00)
Chen (2019)[82]	121	63	0	0	52.07 (42.80 to 61.23)	52.07 (42.80 to 61.23)	100.00 (99.76 to 100.00)	100.00 (87.66 to 100.00)

continued

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TABLE 33 Characteristics of major cardiac anomalies diagnosed following first-trimester ultrasound assessment in non-high-risk populations (*continued*)

Study	Total major cardiac anomalies present (TP + FN)	Major cardiac anomalies detected In first trimester (TP) (*n*)	FP (*n*)	T1 cardiac anomalies with change of diagnosis at later gestation (*n*)	Sensitivity for detection of major cardiac anomalies (% – 95% CI)	% of Antenatal major cardiac anomaly diagnoses made in the first trimester (% – 95% CI)	Specificity	PPV
Duta (2019)[121]	34	26	0	0	76.47 (58.82 to 89.25)	81.25 (63.56 to 92.79)	100.00 (99.96 to 100.00)	100.00 (94.31 to 100.00)
Ebrashy (2019)[122]	100	85	0	0	85.00 (76.47 to 91.35)	85.00 (76.47 to 91.35)	100.00 (99.95 to 100.00)	100.00 (86.77 to 100.00)
Erenel (2019)[123]	12	10	2	1	91.67 (61.52 to 99.79)	91.67 (61.52 to 99.79)	99.71 (98.97 to 99.97)	84.62 (54.55 to 98.08)
Syngelaki (2019)[11]	354	112	0	0	31.64 (26.82 to 36.76)	32.94 (27.97 to 38.22)	100.00 (99.89 to 100.00)	100.00 (95.75 to 100.00)
Pooled Result	1364	674	15	9	51.20 (40.92 to 61.43)	57.81 (47.48 to 66.30)	99.99 (96.99 to 100.00)	96.58 (93.95 to 98.48)

N/A, not applicable; NR, not reported.

a Iliescu *et al.* (2013) report 108 FP results relating to the cardiovascular system, but no breakdown which would allow understanding of what proportion of these anomalies constitute FP of major cardiac anomalies and therefore this could not be reported.

b 1× case described by study authors as resolution of ventricular aneurysm.

TABLE 34 Characteristics of major cardiac anomalies suspected following first-trimester ultrasound assessment in non-high-risk populations

Study	Sample size (*n*)	Total major cardiac anomalies present in study population (*n*)	Number of suspected diagnoses made in T1	Suspected diagnosis confirmed[a] (TP – *n*)	FP (*n*)	Major cardiac anomaly confirmed, but change in specific diagnosis (*n*)	Sensitivity of suspected diagnosis for the detection of major cardiac anomalies (% – 95% CI)[b]	Specificity of suspected diagnosis for the detection of major cardiac anomalies (% – 95% CI)	Positive predictive value of suspected diagnosis in the detection of major cardiac anomalies (95% CI)
Souka (2006)[54]	1148	4	3	3	0	0	75.00 (19.41 to 99.37)	100.00 (99.68 to 100.00)	100.00 (29.24 to 100.00)
Lombardi (2007)[108]	623	3	3	3	0	0	100.00 (29.24 to 100.00)	100.00 (99.41 to 100.00)	100.00 (29.24 to 100.00)
Iliescu (2013)[69]	5472	34	3	3	0	0	60.00 (14.66 to 94.73)	100.00 (99.93 to 100.00)	100.00 (29.24 to 100.00)
Orlandi (2014)[115]	4820	21	2	2	0	0	50.00 (6.76 to 93.24)	100.00 (99.92 to 100.00)	100.00 (15.81 to 100.00)
Andrew (2015)[73]	4421	3	2	2	0	0	100.00 (15.81 to 100.00)	100.00 (99.92 to 100.00)	100.00 (15.81 to 100.00)
Tudorache (2016)[77]	3240	32	3	2	1	0	22.22 (2.81 to 60.00)	99.97 (99.83 to 99.99)	66.67 (9.43 to 99.16)
Chen (2019)[82]	10,294	121	3	0	3	0	0.00 (0.00 to 6.16)	99.97 (99.91 to 99.99)	0.00 (0.00 to 70.76)
Ebrashy (2019)[122]	3400	100	16	0	16	0	0.00 (0.00 to 21.80)	99.52 (99.22 to 99.72)	0.00 (0.00 to 20.59)
Erenel (2019)[123]	707	12	1	1	0	1	100.00 (2.50 to 100.00)	100.00 (99.47 to 100.00)	100.00 (2.50 to 100.00)
Pooled	34,125	330	36	16	20	1	44.60 (15.08 to 76.41)	99.96 (99.88 to 100.00)	67.81 (27.84 to 96.37)

a Refers to a diagnosis which was confirmed either on ultrasound at later gestation, on post-mortem and/or postnatally and therefore considered a TP. FN in this situation was considered number of anomalies not diagnosed, suspected or labelled as AUS at time of the first-trimester scan.
b For the purposes of this sensitivity calculation, an anomaly which was suspected in the first trimester but underwent a subsequent change in diagnosis, was a considered a TP for a major cardiac anomaly.

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TABLE 35 Characteristics of major cardiac anomalies reported as cardiac abnormalities of unknown significance following first-trimester ultrasound assessment non-high-risk populations

Study	Sample size (*n*)	Total major cardiac anomalies present in study population (*n*)	Number of AUS diagnoses given in T1	TP (*n*)	FP (*n*)	Sensitivity of AUS for the detection of major cardiac anomalies (% – 95% CI)	Specificity of AUS for the detection of major cardiac anomalies (% – 95% CI)	Positive predictive value of AUS in the detection of major cardiac anomalies (95% CI)
Abu-Rustum (2010)[61,a]	1370	11	10	9	1	81.89 (48.22 to 97.72)	99.93 (99.59 to 100.00)	90.00 (55.50 to 99.75)
Wiechec (2015)[117,a]	1084	37	33	33	0	89.19 (74.58 to 96.97)	100.00 (99.65 to 100.00)	100.00 (89.42 to 100.00)
De Robertis (2017)[118,a]	5343	33	32	26	6	78.79 (61.09 to 91.02)	99.89 (99.75 to 99.96)	81.25 (63.56 to 92.79)
Kenkhuis (2018)[79]	5534	13	1	0	1	0.00 (0.00 to 36.94)	99.98 (99.89 to 99.99)	0.00 (0.00 to 97.50)
Pooled	13,331	94	76	68	8	63.00 (28.53 to 91.24)	99.94 (99.87 to 99.98)	85.95 (61.48 to 99.03)

a Studies screened exclusively for abnormalities of the four-chamber or OTVs in the first trimester (e.g. ventricular and/or outflow tract disproportions, abnormalities in spatial relationship of vessels, etc.) with the objective of providing a formal and specific diagnosis at a later gestation in pregnancy.

TABLE 36 Details of cases where diagnosis or suspicion of a specific major cardiac anomaly made in the first trimester of pregnancy was changed in low-risk, mixed-risk and unselected populations

Study (year)	First-trimester diagnosis	Second-trimester diagnosis	Postnatal/post-mortem confirmation
Chen (2008)[58]	VSD	Complex heart disease	Confirmed
Volpe (2011)[114]	VSD	Partial AVSD	Confirmed
Volpe (2011)[114]	DORV	TGA	Confirmed
Volpe (2011)[114]	Critical aortic stenosis	HLHS	Unclear
Volpe (2011)[114]	Misaligned VSD	TOF	Confirmed
Orlandi (2014)[116]	Single ventricle + Truncus arteriosus	Single ventricle + DORV	TOP – Unconfirmed by autopsy
Tudorache (2016)[77]	HRHS	Tricuspid atresia with intact septum	TOP – Unconfirmed by autopsy
Erenel (2019)[123]	Suspected HLHS	Coarctation of the aorta with right to left ventricular disproportion	Confirmed
Erenel (2019)[123]	TOF and pulmonary valve regurgitation	Absent pulmonary valve syndrome, agenesis of ductus arteriosus, VSD, over-riding aorta	Confirmed

AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; TGA, transposition of the great arteries.

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TABLE 37 Screening characteristics of ultrasound in the first trimester for the detection of individual cardiac anomalies by diagnosis in non-high-risk populations

	Low-risk/mixed-risk/unselected population							Characteristics of T1 detected anomalies		Secondary confirmation of T1 anomalies
Anomaly	Studies (*n*)	Total anomalies (*n*)	Anomalies detected[a] (TP – *n*)	FP[b] (*n*)	Diagnosis change at a later GA (*n*)	Detection rate[c] % (95% CI)	Specificity for anomaly detection (%) with 95% CI	Additional cardiac anomalies[c]	Additional non-cardiac anomalies[c]	Anomalies with post-mortem or postnatal confirmation[c] *n* (%)
HLHS	30	145	118	1	1	73.28 (59.86 to 84.82)	100.00 (100.00 to 100.00)	9	5	23 (19.49)
HRHS	7	20	19	2	1	91.65 (77.23 to 99.21)	99.99 (99.97 to 99.99)	3	0	0 (0)
Univentricle	15	17	13	0	0	71.21 (52.11 to 87.03)	99.99 (99.98 to 99.99)	2	0	2 (15.38)
TOF	31	120	50	1	0	40.95 (30.16 to 52.20)	100.00 (100.00 to 100.00)	7	3	10 (20.00)
TGA	26	84	35	3	0	45.05 (29.29 to 61.35)	100.00 (100.00 to 100.00)	8	1	15 (42.86)
CoA	24	67	26	0	0	37.23 (23.96 to 51.56)	100.00 (99.99 to 100.00)	12	2	10 (38.46)
VSD	36	360	53	23	1	23.92 (14.41 to 34.97)	99.99 (99.98 to 99.99)	24	10	20 (37.74)
AVSD	32	209	171	1	0	77.24 (63.62 to 88.42)	100.00 (100.00 to 100.00)	11	21	48 (28.07)
ASD	8	16	3	0	0	21.53 (6.78 to 41.66)	100.00 (99.99 to 100.00)	0	1	2 (66.67)
Truncus arteriosus	13	19	16	0	1	76.73 (58.94 to 90.62)	100.00 (100.00 to 100.00)	5	4	3 (18.75)
DORV	15	34	22	0	0	63.11 (44.90 to 79.59)	100.00 (99.99 to 100.00)	7	0	6 (27.27)
Heterotaxy syndromes	17	33	25	0	0	72.59 (55.75 to 86.63)	100.00 (100.00 to 100.00)	9	0	1 (3.03)
Ectopia cordis	5	13	13	0	0	93.26 (76.03 to 99.98)	100.00 (100.00 to 100.00)	0	9	5 (38.46)

	Low-risk/mixed-risk/unselected population							Characteristics of T1 detected anomalies		Secondary confirmation of T1 anomalies
Anomaly	Studies (*n*)	Total anomalies (*n*)	Anomalies detected[a] (TP – *n*)	FP[b] (*n*)	Diagnosis change at a later GA (*n*)	Detection rate[c] % (95% CI)	Specificity for anomaly detection (%) with 95% CI	Additional cardiac anomalies[c]	Additional non-cardiac anomalies[c]	Anomalies with post-mortem or postnatal confirmation[c] *n* (%)
Ebstein's anomaly	7	11	2	0	0	25.03 (4.83 to 54.08)	100.00 (99.99 to 100.00)	0	0	1 (50.00)
Rhabdo-myoma	3	12	0	0	0	4.87 (0.19 to 22.09)	100.00 (100.00 to 100.00)	-	-	-
Aortic stenosis	10	24	9	3	1	38.81 (15.77 to 64.90)	99.99 (99.98 to 99.99)	6	1	2 (22.22)
Pulmonary valve/ Pulmonary artery stenosis	15	42	7	0	0	19.45 (8.99 to 32.74)	100.00 (100.00 to 100.00)	3	0	3 (42.86)
Pulmonary atresia	10	26	17	0	0	59.68 (23.63 to 90.53)	100.00 (100.00 to 100.00)	5	1	3 (17.65)
Tricuspid atresia/ dysplasia	12	28	26	2	0	88.63 (76.00 to 96.94)	100.00 (99.99 to 100.00)	3	1	3 (11.54)
Complex cardiac defects	10	57	43	0	0	76.31 (57.46 to 90.92)	100.00 (100.00 to 100.00)	-	0	9 (20.93)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; TGA, transposition of the great arteries.

a Refers to anomalies which were either diagnosed, suspected or labelled as AUS at time of first-trimester ultrasound screening.

b The FP rate used in the specificity calculation in this table includes those listed as FP plus those where the diagnosis was changed to another cardiac anomaly at a later gestation.

c Rates for individual anomalies were only calculated for those conditions where more than 10 cases were reported (see methods). This excluded the following abnormalities: cardiomegaly (*n* = 7), double-inlet left ventricle (*n* = 6), cardiomyopathy (*n* = 5), ventricular aneurysm (*n* = 4), endocardial fibroelastosis (*n* = 4), aortic arch hypoplasia (*n* = 3), total anomalous pulmonary venous drainage (*n* = 3), interrupted aortic arch (*n* = 2), pulmonary valve regurgitation (*n* = 2), aortic valve atresia (*n* = 3), mitral valve atresia (*n* = 3), polyvalvular dysplasia (*n* = 1), cord triatriatum (*n* = 1). Detailed data available on request.

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Appendix 3 Distributed nationwide survey to all National Health Service units in England

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NHS National Institute for Health Research

Dear Colleagues,

We need your help!

We are currently working on an NIHR HTA grant exploring whether first trimester fetal anomaly screening would be clinically and cost-effective for women in England.

As part of our remit, we are planning a nationwide survey of all providers of NHS maternity care. The aim is to establish an understanding of how the current first trimester scan is undertaken and determine to what extent this differs from one trust to another.

We are working with the NHS fetal anomaly screening programme (NHS FASP) in developing and distributing this questionnaire. The findings will also be shared with FASP.

We need your input at this stage of the process.

Please answer all questions:

- The questionnaire should be completed by one person for each maternity care provider.
- If you have multiple sites offering first trimester ultrasound please answer and submit one questionnaire covering both the main and satellite units if the policies are the same at each site.
- Where policies differ on separate sites, please complete separate questionnaires for each site but indicate to which main provider the satellite unit is accountable.
- The questionnaire should be completed by the unit screening support sonographer or another nominated sonographer and submitted electronically to the following email: **jehan.karim@wrh.ox.ac.uk**.
- If preferable, you may print out the form and send via post to: Dr. Jehan Karim, Level 3 Women's Centre, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU. Please send us an email to inform us that you will be sending a hard copy.

If you have any queries regarding completion of the questionnaire please contact: jehan.karim@wrh.ox.ac.uk

Thank you in advance for your support.

Jehan Karim & Aris Papageorghiou
Department of Women's and Reproductive Health, University of Oxford.

Annette McHugh & Pranav Pandya
NHS Fetal Anomaly Screening Programme

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A. GENERAL INFORMATION

1. Please identify the ultrasound unit (and trust if applicable) where you currently work and your role:

2. Which identifier best describes your healthcare setting? (Please check all that apply):

- ☐ Community Care
- ☐ District General Hospital
- ☐ Tertiary Care
- ☐ University Hospital/Academic Centre
- ☐ Private Unit

B. QUESTIONS ABOUT THE FIRST TRIMESTER SCAN IN YOUR UNIT

3. In total, how many first trimester obstetric ultrasound examinations were performed in your unit over the past one year (between 10^{+0} and 14^{+1})?

4. When does your centre offer first trimester ultrasound screening? (NB: This is a 2 part question)

Beginning from: (check one box only)	**Offered until:** (check one box only)
☐ 10^{+0} weeks GA	☐ 10^{+0} weeks GA
☐ 11^{+0} weeks GA	☐ 11^{+0} weeks GA
☐ 11^{+2} weeks GA	☐ 11^{+2} weeks GA
☐ 12^{+0} weeks GA	☐ 12^{+0} weeks GA
☐ 13^{+0} weeks GA	☐ 13^{+0} weeks GA
☐ 13^{+6} weeks GA	☐ 13^{+6} weeks GA
☐ 14^{+0} weeks GA	☐ 14^{+0} weeks GA
☐ 14^{+1} weeks GA	☐ 14^{+1} weeks GA
☐ Other:	☐ Other:

5. What mode of ultrasound is used routinely for first trimester scans in your unit? (Please check one box only)

- ☐ Transabdominal ultrasound only
- ☐ Transvaginal ultrasound only
- ☐ Transabdominal ultrasound primarily, with use of transvaginal probe when required
- ☐ Transvaginal ultrasound primarily, with use of transabdominal probe when required

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6. How much time is routinely allocated to a first trimester scan for a singleton pregnancy? (Please check one box only)

☐ < 10mins ☐ 10 mins ☐ 15 mins ☐ 20 mins ☐ 25 mins
☐ 30 mins ☐ 35 mins ☐ 40 mins ☐ 45 mins ☐ >45 mins

7. How much time is routinely allocated to a first trimester scan for a multiple pregnancy? (Please check one box only)

☐ < 10mins ☐ 10 mins ☐ 15 mins ☐ 20 mins ☐ 25 mins
☐ 30 mins ☐ 35 mins ☐ 40 mins ☐ 45 mins ☐ >45 mins

8. Apart from ultrasound scanning, does the time allocated to each first trimester scan (as indicated above) include time for any of the following: (Please check all that apply)

☐ Pre-test counselling? ☐ Informed verbal consent?
☐ Post-test counselling/disclosure of findings? ☐ Other:

9. Which of the following assessments are routinely performed as part of your current first trimester fetal ultrasound scanning protocol? (Please check all that apply)

N.B.: Assessments marked with * indicate examinations which are not currently required by NHS FASP first trimester guidance.

☐ Confirmation of fetal viability ☐ CRL measurement for pregnancy dating
☐ Nuchal Translucency ☐ Nasal Bone*
☐ Ductus Venosus Flow* ☐ Tricuspid regurgitation*
☐ Placenta (location)* ☐ Placenta (appearance)*

☐ Head Circumference (HC) measurement (in addition to CRL) *
☐ Bi-parietal Diameter (BPD) measurement (in addition to CRL) *
☐ Evaluation of amnionicity/chorionicity in cases of multiple pregnancy
☐ Visualization of fetal anatomy*

Note: If the 'Visualization of fetal anatomy' box has been checked – please proceed to question 10; If your unit does not assess any fetal anatomy routinely in any women in the first trimester then please omit questions 10 to 21 and proceed directly to question 22.

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10. Assessment of first trimester fetal anatomy in your centre is offered in which of the following cases: (Please check all that apply)

- ☐ Routinely offered to all women
- ☐ For women with previous obstetric history
- ☐ For women with previous family/personal history
- ☐ For women with advanced maternal age
- ☐ For women with maternal risk factors (medication history, T1DM, etc)
- ☐ For pregnancies with raised nuchal translucency? (Eg. NT ≥ 3.5mm)
- ☐ Any woman deemed to be at higher chance of carrying a fetus with an anomaly
- ☐ Parental request
- ☐ Other:

11. Are women routinely provided with written pre-scan information regarding first trimester screening for fetal anomalies specifically?

- ☐ Yes – women receive a locally developed leaflet about first trimester anomaly screening only
- ☐ Yes – women receive the PHE handout 'Screening tests for you and your baby' only
- ☐ Yes – women receive both the PHE handout 'Screening tests for you and your baby' AND a locally developed leaflet about first trimester anomaly screening.
- ☐ No – women do not receive written pre-scan information prior to first trimester anomaly screening

12. Does your unit provide a formal anatomical protocol for sonographers to use requiring visualization of specific anatomical structures in the first trimester? (Please check one box only)

☐ Yes ☐ No ☐ No pre-set protocol by department – sonographer dependent

13. What anatomical fetal structures are routinely assessed as part of first trimester anomaly screening in your centre? (Please check all that apply)

☐ Head	☐ Face	☐ Neck (additional to NT)
☐ Thorax	☐ Heart	☐ Spine
☐ Stomach	☐ Bladder	☐ Kidneys
☐ Cord Insertion	Limbs	☐ Placenta
☐ Other:	☐	

14. Does your unit advocate routine use of colour flow Doppler for the performance of first trimester anomaly screening?

☐ Yes ☐ No

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15. In approximately what % of cases are the objectives of the first trimester anomaly scan unable to be completed (after the first attempt)? (Please check one box only)

☐ <2% ☐ 5% ☐ 10% ☐ 25% ☐ 50% ☐ >50% ☐ Unable to answer

16. Is it policy in your unit to offer a follow-up/repeat ultrasound appointment prior to 18 weeks in cases where all the objectives specific to anomaly screening in the first trimester ultrasound have not been met? (Please check one box only)

☐ Yes ☐ No ☐ Only in specific cases:

17. Are sonographers routinely required to archive/store images relating to visualization of first trimester anatomy (not including NT or CRL)? (Please check one box only)

☐ All images are routinely stored
☐ None of the images are routinely stored
☐ Only images of abnormal or suspicious anatomy are stored
☐ Selected views are stored:
☐ Sonographer dependent
☐ Other:

18. What methods are used for first trimester anomaly image storage? (Please check all that apply)

☐ Thermal image system
☐ Other:
☒ Electronic Digital Archiving System (Eg. picture archiving and communication system) No images stored

19. Does your unit require sonographers performing first trimester anomaly screening to undergo any form of mandatory training specific to the detection of anomalies prior to 14 weeks GA?

☐ Yes - Formal training provided for sonographers in-house.
☐ Yes - Sonographers required to complete external course. Please indicate which course (eg. FMF, ISUOG, etc.):
☐ No – Formal training specific to first trimester anomaly detection not required for sonographers.
☐ No – Formal training specific to first trimester anomaly detection not required for sonographers BUT they are encouraged to attend external courses to supplement knowledge and existing skills specific to this area.

20. Is it hospital policy to notify the National Congenital Anomaly and Rare Diseases Registration Service (NCARDRS) regarding anomalies detected in the first trimester?

☐ Yes ☐ No ☐ Only in specific cases:

21. Is there a specific local protocol in place in your unit for management of patients with either a suspected or positively identified fetal anomaly in the first trimester? (Please check all that apply)

☐ Yes – policy advocating immediate disclosure of results after first scan suggesting anomaly.
☐ Yes – policy advocating deferral of disclosure of results to patient until confirmation scan.
☐ Yes – policy of patient referral to second sonographer within unit for confirmation of finding.
☐ Yes – policy of patient referral to GP for further management/investigations.
☐ Yes – policy of patient referral to Obstetrics team for further management/investigations
☐ Yes – policy of patient referral to local FMU for further management/investigations.
☐ No formal policies in place specific to management of first trimester anomalies.

C. ABOUT YOUR SONOGRAPHER TEAM & AVAILABLE RESOURCES:

22. Who performs first trimester ultrasound screening in your unit? (Please check all that apply)

☐ Qualified midwife sonographers
☐ Fetal medicine consultants
☐ Consultant radiologists
☐ Other associate specialists
☐ Qualified radiology sonographers
☐ Fetal medicine fellows
☐ Radiology fellows

23. How many sonographers (radiographer or midwife sonographers) conduct obstetric ultrasound in your unit?

Number: Full time equivalent:

24. Of the sonographers included above in Question 23, how many perform first trimester ultrasound?

Number: Full time equivalent:

25. How many sonographers in your unit are registered with the Down's Syndrome Quality Assurance Support Service (DQASS)?

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26. Do any of your sonographers have Fetal Medicine Foundation (FMF) certification for the first trimester anomaly ultrasound scan?

- ☐ Yes – All sonographers working in the unit
- ☐ Yes – Some sonographers in the unit - The number of sonographers with FMF certification is (if available):
- ☐ None of the sonographers working in the unit

27. Do sonographers in your unit routinely have access to the following equipment for the purposes of first trimester scanning?

A. High frequency (5-9MHz) trans-abdominal probe (curved transducer)	☐ Yes	☐ No
B. High frequency (5-9MHz) trans-abdominal probe (linear transducer)	☐ Yes	☐ No
C. High frequency (5-12MHz) trans-vaginal probe	☐ Yes	☐ No

28. Regarding the ultrasound machines used in your department for first trimester screening:

A. How many machines are used for first trimester screening?
B. How many of these machines are less than 5 years old?
C. How many of these machines are less than 10 years old?
D. How many of these machines are greater than 10 years old?

29. Does your unit have the capacity and resources to meet current demands for first trimester screening from your catchment area?

- ☐ Yes – we are generally able to meet demand
- ☐ No – we are frequently unable to provide first trimester ultrasound screening during the appropriate gestational age window

30. How often are sonographers in your unit able to undertake DQASS feedback and image review?

- ☐ Always
- ☐ Often
- ☐ Sometimes
- ☐ Rarely
- ☐ Never

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D. ABOUT LOCAL POLICIES IN YOUR UNIT:

31. Does your unit routinely offer women an ultrasound scan prior to 10^{+0} weeks gestational age (GA)? (Please check all that apply)

- ☐ Yes – offered to all women who have booked prior to 10^{+0} weeks
- ☐ Yes – offered to women on clinical indication (eg.previous ectopic, chance of multiples, etc.)
- ☐ Yes – offered to women upon request
- ☐ No – this is not routine practice in our unit

32. In women who decline screening for Down's syndrome, Edwards' syndrome and Patau's syndrome, is it policy to offer a first trimester ultrasound scan between 10^{+0}-14^{+1} weeks in your unit? (Please select only one answer)

- ☐ Yes – first trimester ultrasound scan offered between 10^{+0}-14^{+1} weeks
- ☐ Yes – first trimester ultrasound scan offered – but not necessarily between 10^{+0}-14^{+1} weeks
- ☐ No first trimester ultrasound scan offered

33. In women who decline screening for Down's syndrome, Edwards' syndrome and Patau's syndrome, is it policy for nuchal translucency to be routinely measured in your unit? (Please select only one answer)

☐ Yes ☐ No

34. In women who decline screening for Down's syndrome, Edwards' syndrome and Patau's syndrome, is there a local policy in place regarding the disclosure of unexpected/incidental ultrasound findings (including enlarged nuchal translucency and/or fetal anomaly findings)? (Please select only one answer)

☐ Yes ☐ No

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35. Regarding termination of pregnancy (TOP) taking place as a result of findings from first trimester screening undertaken in your unit:

A. Who is the responsible provider? ☐ NHS ☐ Independent Unit (eg. British pregnancy advisory service) ☐ Unable to answer

B. What method of TOP is offered? ☐ Predominantly Medical ☐ Predominantly Surgical ☐ Both medical and surgical options given ☐ Unable to answer

C. What is the setting for TOP? ☐ Predominantly Inpatient ☐ Predominantly Outpatient ☐ Predominantly Day Case ☐ Unable to answer

D. Are patients offered option of post-mortem or autopsy after first trimester termination? ☐ Yes ☐ No ☐ Unable to answer

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36. Is there anything further you would like us to know about first trimester ultrasound screening in your centre? Any clarifications you'd like to make regarding the answers given above?

Has your unit faced any challenges in implementing first trimester ultrasound screening? Is there anything you feel should be addressed by the UK NSC regarding the evidence for first trimester anomaly ultrasound screening, the NHS FASP regarding the current screening pathway or NHS England as to how first trimester screening is delivered?

Thank you!

Appendix 4 Appendices to *Chapter 8* (Delphi consensus) including summary of relevant research and first round questionnaire

TABLE 38 Summary table of currently available screening protocols published in the literature

Anatomical structure	Structure required to be visualised	Plane of visualisation	Supporting protocols
Skull/brain	Cranial ossification (contour/shape)	Transverse	16,69,81,101,216–218
		Transverse + Coronal	3,219
		Longitudinal	220
		No plane specified	51,54,61,66,71,76,82,110,126,138,221–228
	Choroid plexus filling lateral ventricles (butterfly sign)	Transverse	3,16,69,81,101,216,217,219,220,223
		No plane specified	51,54,61,66,71,76,110,222,224,226–228
	Cerebral peduncles	Transverse	69,218
	Thalamus	Transverse	219,220
		Mid-Sagittal	223
		No plane specified	225
	Interhemispheric fissure/falx	Transverse	3,16,76,81,101,138,216–218,220
		No plane specified	51,54,66,71,221,223–225,227,228
	Posterior fossa	Mid-Sagittal	81
		No plane specified	226
	Posterior fossa + demonstration of intracranial translucency	Mid-Sagittal	69,101
		Transverse + Mid-Sagittal	223
	Intracranial Translucency	Longitudinal	220
	Cisterna magna	Transverse	216,218
		Transverse + Mid-Sagittal	223
	Cerebellum	Transverse	216,218
		No plane specified	51,71,76,110,219,225,226,228
Face	Orbits	Transverse	3,69,81,216,220
		Coronal	219
		Transverse or Coronal	100
		No plane specified	54,76,110,126,217,218,222–227
	Lenses	Transverse	3,216
		No plane specified	54,226

continued

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TABLE 38 Summary table of currently available screening protocols published in the literature (*continued*)

Anatomical structure	Structure required to be visualised	Plane of visualisation	Supporting protocols
	Anterior palate	Transverse	69,81
		Mid-Sagittal	223
		No plane specified	228
	Nasal bones	Mid-Sagittal	3,16,81,219,223
		Sagittal	69,216
		Coronal	218
		Longitudinal	27
		No plane specified	71,110,222,224,226
	Correct position of mandible	Mid-Sagittal	3
		Transverse + Sagittal	216
		Transverse or Coronal	101
		No plane specified	125,218,223,225
	Correct position of maxillae	Transverse + Sagittal	216
		Transverse or Coronal	101
		Mid-Sagittal	81
		No plane specified	125,225
	Facial profile	Mid-Sagittal	3,81,101,218,219
		Sagittal	69,216
		Longitudinal	220
		No plane specified	54,76,110,126,217,220–224,228
	Ears	No plane specified	226
	Retronasal triangle	Coronal	69,81,220,223
	Upper and/or lower lip	Coronal	3,216,218
		No plane specified	101,126,217,220,226
Spine	Presence/regularity of vertebrae from cervical to sacral regions	Longitudinal	16,61,69,81,217,220
		Longitudinal + Transverse	3,51,101,110,125,218,219,225
		Sagittal + Coronal + Transverse	216
		No plane specified	54,76,223
	Intact, continuous overlying skin	Longitudinal	69,217
		Longitudinal + Transverse	51,110,218,225
		Sagittal	3,224
		No plane specified	54,71,216,219,223

TABLE 38 Summary table of currently available screening protocols published in the literature (*continued*)

Anatomical structure	Structure required to be visualised	Plane of visualisation	Supporting protocols
Thorax/chest	Shape of the thorax	Transverse	216
		No plane specified	82,217,218
	Lung fields	Transverse	3,101,216
		No plane specified	66,76,217–219,222,223,226,228
	Diaphragmatic continuity	Longitudinal	220
		Para-Sagittal	81
		No plane specified	3,62,66,71,76,101,125,216–219,222,223,225
Heart	Situs evaluation	Transverse	69,101,226
		Longitudinal	220
		No plane specified	3,51,61,71,81,110,126,138,219,223,228
	Heart area in relation to chest	Transverse	69,81
	Cardiac axis	Transverse	3,51,71,81,110,226
		No plane specified	221
	Four-Chamber view (with AV valve offsetting)	Transverse	3,16,69,81,101,216,218,226
		Longitudinal	220
		No plane specified	51,54,61,62,66,71,76,110,126,217,219,223–226,227,228
	Outflow tracts (pulmonary artery, aorta, SVC – three-vessel view)	Transverse	69,81,216,218,226
		Longitudinal	220
		No plane specified	54,82,101,110,126,219,223,224,228
	Aortic arch	No plane specified	51,81,226
	Fetal heart rate		3,51,71,76,110,218,219
Abdomen	Presence of stomach in left quadrant	Transverse + Sagittal	16,101
		Transverse + Coronal	3
		Transverse	81,216,218
		Longitudinal	220
		No plane specified	51,54,61,66,69,71,76,82,110,126,138,217,219,221,223–228
	Presence of bladder in fetal pelvis	Transverse	81,218
		Transverse + Sagittal	16,101,226
		No plane specified	3,51,54,61,62,69,71,76,82,110,126,138,217,219,221–228
	Bilateral presence of kidneys	Coronal + Transverse	216
		Coronal	3,81,219
		Transverse	218
		No plane specified	51,54,61,62,66,69,76,82,101,110,126,222–226

continued

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TABLE 38 Summary table of currently available screening protocols published in the literature (*continued*)

Anatomical structure	Structure required to be visualised	Plane of visualisation	Supporting protocols
	Intact abdominal wall with demonstrated umbilical cord insertion	Transverse + Sagittal	16,101
		Transverse	219,220
		No plane specified	3,51,54,61,66,69,71,76,81,82,110,126,138,216,217,219,222–228
	Bowel echogenicity	No plane specified	62,69,216,226
	Gallbladder	No plane specified	226
	External genitalia	No plane specified	76,82,218
	Bifurcation of portal vein	Transverse	216
Limbs	Symmetry and adequate views of long bones of all 4 limbs	No plane specified	3,51,54,61,62,66,69,71,76,82,101,110,126,138,216–219,221–228
		Longitudinal	220
		Longitudinal + Transverse + Coronal	81
		Transverse + sagittal	16
	Bilateral feet visible with correct orientation	Transverse + sagittal	16
		Longitudinal + Transverse + Coronal	81
		Longitudinal	220
		No plane specified	3,54,62,66,69,71,101,126,216–219,222–227
	Bilateral toes visible	Longitudinal + Transverse + Coronal	81
		No plane specified	54,69,76,216,224
	Bilateral hands visible with correct orientation	Transverse + sagittal	16
		Longitudinal + Transverse + Coronal	81
		Longitudinal	220
		No plane specified	3,54,62,66,69,71,101,126,216–219,222–227
	Bilateral fingers visible	Longitudinal + Transverse + Coronal	81
		No plane specified	54,69,76,216,221,224,228

AV, atrioventricular valve; SVC, superior vena cava.

Note
Excluded assessment of soft markers (e.g. NT), Doppler investigations and fetal biometry.

Participant briefing guide for first round of Delphi procedure

First-trimester anomaly screening – a summary

1. **Key results** from a recent systematic review and meta-analysis on the detection of fetal congenital anomalies in the first trimester:[19]

   - In **low-risk/unselected** populations, major anomalies can be detected in **46.10%** (95% CI 36.88 to 55.46%) at 11–14 weeks.
   - In **high-risk** populations, **61.18%** (95% CI 37.71 to 82.19%) of all fetal anomalies can be detected at 11–14 weeks.
   - Use of a standardised protocol for screening significantly improves anomaly detection rates ($p < 0.0001$).

2. **Summary table of anomalies potentially amenable to first-trimester ultrasound detection:**

Anomaly	UK prevalence (per 10,000 births)[15a]	First-trimester screening sensitivity[11] (%)	Included in current FASP criteria[228]
Acrania/anencephaly	5.59 (5.26–5.94)	100	X
Alobar holoprosencephaly	1.81 (1.62–2.01)	100	
Encephalocele	1.40 (1.24–1.58)	100	
Cerebellar hypoplasia	-	13	
Severe ventriculomegaly	-	78	
Severe microcephaly	1.38 (1.22–1.56)	0	
Facial clefts	16.51 (15.94–17.10)	35	X
Anophthalmia	0.18 (0.13–0.26)	-	
Open spina bifida	6.21 (5.86–6.57)	59	X
Exomphalos/omphalocele	4.77 (4.47–5.09)	100	X
Gastroschisis	3.96 (3.68–4.25)	100	X
Megacystis (> 7 mm)	-	100[16]	
Bilateral renal agenesis	1.47 (1.30–1.66)	15	X
Body stalk anomaly	-	100	
Ectopia cordis	-	100	
Congenital diaphragmatic hernia	3.65 (3.39–3.93)	29	X
Hypoplastic left heart syndrome	3.23 (2.98–3.50)	93	X
Atrioventricular septal defect	5.71 (5.38–6.06)	91	X
TOF	4.38 (4.08–4.68)	39	X
Transposition of great arteries	4.07 (3.79–4.37)	13	X
Lethal skeletal dysplasias	2.06 (1.86–2.27)	71	X
Limb reduction defects	4.97 (4.66–5.30)	75	
Polydactyly	7.23 (6.85–7.62)	60[16]	
Club toot (talipes)	11.45 (10.97–11.94)	2	

a Prevalence (including fetuses with genetic conditions) reported, where available. Data provided includes prevalence for all types of spina bifida, all types of holoprosencephaly (including alobar) and all types of skeletal dysplasias (including lethal ones).

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Delphi Consensus Questionnaire – First Trimester Anomaly Scan

Round One (Please note this study was conducted using RedCap)

Dear Colleague,

Thank you for participating in our UK Based - Consensus Procedure on First Trimester Anomaly Screening.

Data from our recent survey show that there is very unequal access to anatomical screening at the 11-13 week scan around the UK. Some centres undertake no anatomical screening (only measuring CRL and NT), others perform very basic anatomy screening, and some do quite advanced screening.

This results in significant inequity of care. It also raises issues around the consistency of patient information provided and whether referral pathways are effective. Our research has shown that a protocol-based approach to the first trimester anomaly scan significantly improves detection rates. Therefore, a standardized approach will help all centres that wish to perform early anatomy screening.

What is the Objective?

We would like to develop consensus amongst sonographers, midwives and doctors regarding the following questions:

1) What role should first trimester ultrasound play in fetal anomaly screening in the UK?

2) How should first trimester anomaly screening be performed?

3) What anatomical views should be obtained?

4) Which fetal anomalies should be targeted?

5) How should positive or suspicious findings in the first trimester be followed-up?

Our aim is to develop UK recommendations for best practice in the form of (i) a basic protocol, which could be used as a standard by NHS units wishing to offer first trimester anatomy screening to all women, and (ii) an extended protocol for women deemed to have a higher chance of fetal anomalies.

For the purposes of the questionnaire please assume that training, equipment and time are available.

What is a Delphi Consensus Procedure?

The Delphi procedure is a well-established consensus development method. It involves an anonymous process whereby participants are initially asked to provide their views on a series of statements. The results are summarized and fed back to participants with increasing detail over subsequent rounds. With each iteration, the participants are allowed to revise their opinion in light of the group feedback until relative consensus has been reached.

What considerations should we take into account?

Please use your routine clinical practice and professional experience to guide your answers to the questions asked. The following considerations are worth keeping in mind:

- Prevalence of fetal anomalies
- Their severity/lethality
- Detection rates for anomalies using first trimester ultrasound
- Anatomical views required to examine first trimester anatomy
- Likelihood of inconclusive or false positive findings
- Difficulty, skill level and time required to obtain the anatomical views in question

However, any future screening program would address resources required to meet the objectives.

How much time commitment will be required from participants?

The first questionnaire should take approximately fifteen minutes to complete. We anticipate that we will need you to complete a further one to two surveys (each taking ten mins to complete).

What about my data? All information collected from participants will be kept strictly confidential. All analysis will be anonymous and in aggregate form. We will ask for your email address for the sole purpose of contacting you for participation in future rounds of the consensus procedure. We will not share or disclose your email with anyone else. All data collected, including your email, will be held on a secure server in the Netherlands, in keeping with GDPR Standards.

INFORMED CONSENT

- I have read and understood the information provided.
- I have had sufficient time to decide about my participation in the study.
- I understand that my participation is voluntary.
- I understand that if I withdraw my participation, my data and details up to the time of withdrawal can be used.
- I agree to data collection, data storage, and the use of my (personal) data for answering the research questions addressed in this project. Data will be stored for

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15 years.
- Data will be coded and analysed anonymously.
- Personal data will be stored separately from the data used for analysis.
- No personal data will be provided in any publication UNLESS you wish to be mentioned in the acknowledgements. Consent for this will be asked in a separate form.

I agree to participate in this study:

☐ Yes ☐ No

What is your email address? _____

We will only contact you for participation in future rounds of the consensus procedure.

Your email address will be held on a secure server, in keeping with GDPR Standards. We will not share of disclose your email with anyone else.

Section I – Please tell us about yourself

A. What is your occupation?

☐ Sonographer
☐ Midwife Sonographer
☐ Midwife
☐ Other:_____
☐ General Obstetrician/Gynaecologist
☐ Fetal Medicine Specialist
☐ Obstetrician/Gynaecology trainee
☐ Radiologist

B. What is your level of training?

☐ Fully qualified
☐ Consultant
☐ Trainee
☐ Other:_____

C. Which identifier best describes your current healthcare practice setting?

(Please check all that apply):

☐ Primary/Community Care
☐ Secondary Care/General Hospital
☐ Tertiary Care/Regional Fetal Medicine Unit
☐ Private Unit

D. In which region of the UK do you primarily practice?

- ☐ England – North East
- ☐ England – North West
- ☐ England – Yorkshire and the Humber
- ☐ England – East of England
- ☐ England – West Midlands
- ☐ England - London
- ☐ England – South East
- ☐ England – South West
- ☐ Wales
- ☐ Scotland
- ☐ Northern Ireland

E. Do you currently practice in a unit which routinely offers a first trimester anatomy assessment to patients (any form of anatomy assessment is acceptable, even a basic check):

☐ Yes ☐ No

F. Approximately how many first trimester ultrasounds did you personally perform as part of your practice over the past year?

- ☐ None
- ☐ 50-99
- ☐ 249-499
- ☐ < 50
- ☐ 100-249
- ☐ >500

Section II – First Trimester Screening Logistics

A. At what gestational age should first trimester anomaly screening be performed?

Beginning from: (check one box only)	**Offered until:** (check one box only)
☐ From 10^{+0} weeks GA	☐ From 10^{+0} weeks GA
☐ From 11^{+0} weeks GA	☐ From 11^{+0} weeks GA
☐ From 11^{+2} weeks GA	☐ From 11^{+2} weeks GA
☐ From 12^{+0} weeks GA	☐ From 12^{+0} weeks GA
☐ From 13^{+0} weeks GA	☐ From 13^{+0} weeks GA
☐ From 13^{+6} weeks GA	☐ From 13^{+6} weeks GA

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☐ From 14^{+0} weeks GA

☐ From 14^{+1} weeks GA

☐ Other (Please specify gestational weeks and days in your response):

☐ From 14^{+0} weeks GA

☐ From 14^{+1} weeks GA

☐ Other (Please specify gestational weeks and days in your response):

B. What mode of ultrasound should be used for a first trimester anatomy assessment?

☐ Trans-abdominal ultrasound only
☐ Trans-vaginal ultrasound only
☐ Trans-abdominal ultrasound primarily, with use of trans-vaginal probe when required
☐ Trans-vaginal ultrasound primarily, with use of trans-abdominal probe when required
☐ Both Trans-abdominal and Trans-vaginal ultrasound should be performed

C. For low risk/unselected women presenting for routine first trimester basic fetal anatomy ultrasound assessment, which of the following is the most appropriate:

☐ If all anatomical structures are not adequately visualized, women should be asked to return for a follow-up ultrasound PRIOR to 18-21 week anatomy scan in order to complete the assessment.

☐ If all anatomical structures are not adequately visualized, women should be asked to WAIT until their routine 18-21 week anatomy scan.

☐ Decisions regarding follow-up of inadequately visualized structures should be made on a case by case basis

☐ Decisions regarding follow-up of inadequately visualized structures should be made by each ultrasound unit independently based on available resources.

☐ Other:

D. What should be included in the standard management pathway for women who have a suspicious/positive finding on a first trimester anomaly scan?

Please check all that apply.

☐ Same day independent secondary confirmation of anomaly by another sonographer in the same unit
☐ Independent secondary confirmation by another sonographer in the same unit within 3 working days
☐ Fetal medicine referral

☐ Other or any further comments on referral after suspicious/positive findings:_____

E. For women with a confirmed diagnosis of a non-cardiac anomaly in the first trimester and who have opted to continue with their pregnancy:

☐ Cardiac normality should be confirmed by a qualified sonographer
☐ Cardiac normality should be confirmed by a fetal medicine specialist
☐ Cardiac normality should be confirmed by formal fetal echocardiography examination
☐ I am not sure
☐ Other:

F. For women requesting Cell-Free DNA/ Non-Invasive Prenatal Testing (NIPT), what advice should be given?

☐ NIPT should be undertaken BEFORE first trimester anomaly scan
☐ NIPT should be undertaken AFTER first trimester anomaly scan
☐ NIPT can be performed at ANY TIME in relation to the first anomaly scan
☐ I am not sure
☐ Other:

G. What should be the indications for performing an extended/advanced first trimester anatomy scan?

Please check all that apply.

☐ Any woman deemed to be at higher chance of carrying a fetus with an anomaly
☐ Previous maternal obstetric history of fetal anomaly
☐ Family history or parental history of fetal anomaly
☐ Advanced maternal age (≥ 40 years)
☐ Maternal medication history
☐ Maternal history of uncontrolled diabetes
☐ IVF Pregnancy
☐ Multiple pregnancy
☐ Presence of raised nuchal translucency? (Eg. NT ⩾ 3.5mm)
☐ Parental request

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☐ Other:

Section III – Anomalies to be Targeted in the First Trimester

Which anomalies should we target as part of first trimester anomaly screening?

For each anomaly, please tell us if it should be (**select ONE option**):

(1) Included in a **basic** protocol: to be used **routinely** as a standard by NHS units for **all** women.

(2) Included in an **extended** protocol: to be used for women who are at **higher risk** for fetal anomalies.

(3) Included in **BOTH** a **basic** and **extended** protocol.

(4) If **formal assessment** of this anatomical view is **NOT required** in the first trimester.

EXAMPLE:

	Protocol Options:				
Anomaly:	**BASIC protocol ONLY**	**EXTENDED protocol ONLY**	**BOTH BASIC and EXTENDED Protocol**	**Formal assessment NOT Required**	**I don't know**
Spina Bifida	**✓ Check this box if:** Spina bifida screening should **ONLY** be included in a BASIC protocol.	**✓ Check this box if:** Spina bifida screening should **ONLY** be included in an EXTENDED protocol.	**✓ Check this box if:** Spina bifida screening should be included in **BOTH** a BASIC and an EXTENDED protocol.	**✓ Check this box if:** Spina bifida should **NOT** be routinely assessed in the first trimester.	**✓ Check this box if:** You do not have sufficient knowledge or experience to comment.

For your reference, we provide a short summary table of first trimester anomaly detection rates. If you would like to download this, please click the following link:

→ Summary of First Trimester Anomaly Detection Rates.pdf

Which anomalies should we target as part of first trimester anomaly screening?

Anomaly	BASIC protocol only	EXTENDED protocol only	Both BASIC and EXTENDED protocol	Formal Assessment NOT Required	I don't know
Acrania/Exencephaly/Anencephaly	☐	☐	☐	☐	☐
Holoprosencephaly	☐	☐	☐	☐	☐
Encephalocele	☐	☐	☐	☐	☐
Cerebellar Hypoplasia	☐	☐	☐	☐	☐
Ventriculomegaly	☐	☐	☐	☐	☐
Facial Clefts	☐	☐	☐	☐	☐
Anopthalmia	☐	☐	☐	☐	☐
Open Spina Bifida	☐	☐	☐	☐	☐
Exomphalos/Omphalocele	☐	☐	☐	☐	☐
Gastroschisis	☐	☐	☐	☐	☐
Megacystis	☐	☐	☐	☐	☐
Unilateral Renal Agenesis	☐	☐	☐	☐	☐
Bilateral Renal Agenesis	☐	☐	☐	☐	☐
Body Stalk Anomaly	☐	☐	☐	☐	☐
Ectopia Cordis	☐	☐	☐	☐	☐
Diaphragmatic Hernia	☐	☐	☐	☐	☐
Major 4 chamber abnormalities (e.g. Hypoplastic Left Heart Syndrome, Atrio-ventricular septal defect)	☐	☐	☐	☐	☐
Major outflow tract anomalies (e.g. Transposition of the Great Arteries, Tetralogy of Fallot)	☐	☐	☐	☐	☐
Abnormalities of situs	☐	☐	☐	☐	☐
Lethal Skeletal Dysplasias	☐	☐	☐	☐	☐
Arthrogryposis	☐	☐	☐	☐	☐
Limb reduction	☐	☐	☐	☐	☐
Club Foot (Talipes)	☐	☐	☐	☐	☐
Polydactyly	☐	☐	☐	☐	☐

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Section IV – Which anatomical views should we obtain as part of first trimester anomaly screening?

For each anatomical view, please tell us if it should be (select ONE option):

1. Included in a basic protocol: to be used routinely as a standard by NHS units for all women.
2. Included in an extended protocol: to be used for women who are at higher risk for fetal anomalies.
3. Included in BOTH a basic and extended protocol.
4. If formal assessment of this anatomical view is NOT required in the first trimester.

Please assume that existing practice includes assessing fetal viability, multiple pregnancy and chorionicity, measurement of the fetal CRL and NT.

Your answers will guide future recommendations for best practice. Assume that training, equipment, staff and time will be made available to achieve these objectives.

The following questions should be answered in the same way as for Section III. Please refer to the example table on page 4.

Region A – Fetal Skull/Brain

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Cranial ossification (contour/shape)	☐	☐	☐	☐	☐
Choroid plexus (butterfly sign)	☐	☐	☐	☐	☐
Cerebral peduncles	☐	☐	☐	☐	☐
Thalamus	☐	☐	☐	☐	☐
Interhemispheric fissure/falx	☐	☐	☐	☐	☐
Posterior fossa	☐	☐	☐	☐	☐

Intracranial translucency	☐	☐	☐	☐	☐
Brain stem diameter (BS) to Brain stem-to occipital bone distance (BSOB) ratio	☐	☐	☐	☐	☐
Cavum Septum Pellucidum	☐	☐	☐	☐	☐
Cisterna magna	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal head/brain which you feel should have been included in the list above if applicable:_____

Region B – Fetal Face

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Orbits	☐	☐	☐	☐	☐
Lenses	☐	☐	☐	☐	☐
Anterior palate	☐	☐	☐	☐	☐
Nasal bone(s)	☐	☐	☐	☐	☐
Correct position of mandible	☐	☐	☐	☐	☐
Correct position of maxillae	☐	☐	☐	☐	☐
Facial Profile	☐	☐	☐	☐	☐
Retronasal triangle/Maxillary gap	☐	☐	☐	☐	☐

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Upper and Lower lip	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal face which you feel should have been included in the list above if applicable:_____

Region C – Fetal Spine

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Presence/regularity of vertebrae from cervical to sacral regions	☐	☐	☐	☐	☐
Intact, continuous overlying skin	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal spine which you feel should have been included in the list above if applicable:_____

Region D – Fetal thorax

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Shape of the thorax/thoracic wall	☐	☐	☐	☐	☐
Lung Fields	☐	☐	☐	☐	☐
Diaphragmatic Continuity	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal thorax which you feel should have been included in the list above if applicable:_____

Region E – Fetal heart

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Situs evaluation	☐	☐	☐	☐	☐
Measurement of heart area in relation to chest	☐	☐	☐	☐	☐
Cardiac axis	☐	☐	☐	☐	☐
Four-chamber view	☐	☐	☐	☐	☐
Outflow tract view	☐	☐	☐	☐	☐
Pulmonary venous return	☐	☐	☐	☐	☐
Fetal heart rate	☐	☐	☐	☐	☐
Routine use of Colour-Flow Doppler for examination of the 4 chamber-view (based on ALARA principles)	☐	☐	☐	☐	☐
Routine use of Colour-Flow Doppler for cardiac outflow tracts (based on ALARA principles)	☐	☐	☐	☐	☐

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For which of the following examinations, should Doppler be routinely used?					
Ductus venosus flow	☐	☐	☐	☐	☐
Tricuspid regurgitation	☐	☐	☐	☐	☐
Aberrant right subclavian artery	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal heart which you feel should have been included in the list above if applicable:_____

Region F – Fetal Abdomen

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Presence of stomach in left quadrant	☐	☐	☐	☐	☐
Presence of bladder in fetal pelvis	☐	☐	☐	☐	☐
Bilateral presence of kidneys	☐	☐	☐	☐	☐
Intact abdominal wall with demonstrated umbilical cord insertion	☐	☐	☐	☐	☐
Umbilical arteries using Colour-Flow Doppler near the bladder	☐	☐	☐	☐	☐
Bowel echogenicity	☐	☐	☐	☐	☐

External genitalia	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal abdomen which you feel should have been included in the list above if applicable:_____

Region G – Fetal limbs

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Evaluation of all 4 limbs (symmetry and adequate views of long bones)	☐	☐	☐	☐	☐
Bilateral feet visible (+ verification of correct orientation)	☐	☐	☐	☐	☐
Bilateral hands visible (+ verification of correct orientation)	☐	☐	☐	☐	☐
Bilateral fingers visible	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the fetal limbs which you feel should have been included in the list above if applicable:_____

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Region H – Placenta

Which of the following anatomical views should be obtained as part of a routine basic and extended first trimester anatomy screening protocol?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Placental appearance	☐	☐	☐	☐	☐
Placental location	☐	☐	☐	☐	☐
Location in relation to any previous uterine scar	☐	☐	☐	☐	☐
Cord insertion (placental interface)	☐	☐	☐	☐	☐
Vasa previa with bi-lobed placenta	☐	☐	☐	☐	☐

Please list any other anatomical structures or views of the placenta which you feel should have been included in the list above if applicable:_____

Section V - Measurements

Which of the following should be measured routinely?

Suggested Anatomical Structure for T1 Visualization	Check at least one box for each plane of visualization:				
	BASIC protocol only	EXTENDED protocol only	BOTH basic and extended protocol	Formal assessment not required	I don't know
Bi-Parietal Diameter (BPD)	☐	☐	☐	☐	☐
Head Circumference (HC)	☐	☐	☐	☐	☐

Abdominal Circumference (AC)	☐	☐	☐	☐	☐
Femur Length (FL)	☐	☐	☐	☐	☐
Humerus Length (HL)	☐	☐	☐	☐	☐
Bladder (longitudinal length)	☐	☐	☐	☐	☐

Are there any additional fetal measurements which you feel should have been included in the list above?:_____

Section VI – Additional Comments

Please provide any additional comments you have regarding the first trimester anomaly scan below:_____

Thank you!

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Appendix 5 Patient information form and patient questionnaire developed for the acceptability of the early anomaly ultrasound scan study

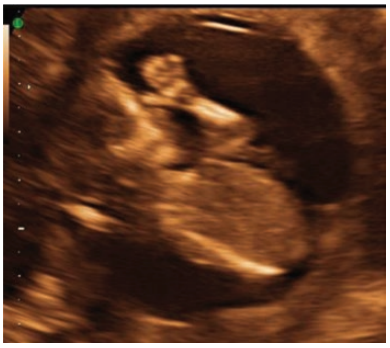
Acceptability of the early anomaly ultrasound scan study

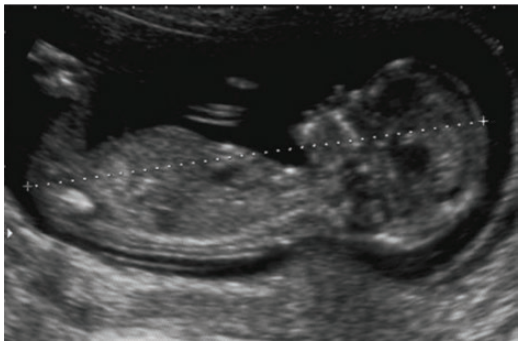
Looking for physical conditions in unborn babies in the first trimester of pregnancy from 11 to 14 weeks:

What do parents think?

We'd like to invite you to take part in our research study. Before deciding to participate, please read the information below to find out about the research and what it would involve for you. Alternatively, you can visit our website to read about the study and complete the survey online: https://acasstudy.limequery.com/1?lang=en

If there is anything that is unclear or you would like additional information, please contact Dr. Jehan Karim via e-mail at jehan.karim@wrh.ox.ac.uk.





In England, women are offered two ultrasound scans during pregnancy. The first scan is between 11 and 14 weeks. It checks the baby is alive, measures the baby to give an estimated due date, and looks for twins. At this scan, women are also given the option to have screening for Down, Edwards and Patau syndrome.

The second scan is at 18–20 weeks. It checks how the baby is developing. Unfortunately, in about 2–5% of pregnancies, a serious physical condition is found (e.g. a major heart defect). Sometimes, the scan identifies conditions which mean the baby may not survive after birth. Other conditions may require a baby to have surgery or may have an important long-term effect on a child's life. Some conditions detected may be minor.

With improvements in ultrasound equipment, we can now identify about half of all serious physical conditions earlier – between 11 and 14 weeks.

What is the purpose of the study? To understand what parents think of introducing an early scan looking at the development of the baby in the first trimester (11–14 weeks). This would be performed as an addition to the first-trimester scan currently offered for parents who would like this to be done.

Finding serious physical conditions earlier may have advantages: it gives parents more time for extra testing, to speak to specialists, to make preparations for the baby's birth and if they wish, to think about terminating the pregnancy. For parents deciding to have a termination, having this done earlier can be safer.

But there may be disadvantages too: early scanning could suggest that the baby has a condition which further testing shows is not the case. This could cause worry and further unnecessary tests. For example, a positive or suspicious finding at 11–14 weeks will mean you are given the option to be referred to a fetal medicine specialist, who will evaluate the baby in more detail. At that point you may be offered additional genetic tests and follow-up with additional ultrasounds, but whether to have these will always be your choice. As some conditions may only be suspected and need to be confirmed later in pregnancy, this can mean up to 2–8 weeks of uncertainty.

We want to see what parents think of an early scan looking at the baby's development by asking them to complete a survey. The survey results may impact decisions that are made about pregnancy care in the future. This work is funded by the NIHR HTA Assessment group and forms part of a University of Oxford doctoral thesis.

Why have I been invited? We are interested in the opinions of parents (both mothers and their partners) on how such a scan should be developed and what information parents would like to be given in this setting. The survey can be completed by either parent (the mother carrying the pregnancy or their partner) or by both individuals together.

Do I have to take part? No. Taking part in this research study is completely voluntary. If you decide not to participate, this will not affect your pregnancy care in any way.

What will happen if I decide to take part? You will be asked to sign a consent form and complete a questionnaire. This should take about 15 minutes. Once completed, you will be able to return your questionnaire to the receptionist at the ultrasound registration desk. If you would like additional time to provide your responses, please use the pre-paid envelope provided at the desk and send us your responses by post. Alternatively, you can complete a consent form with the questionnaire online at https://acasstudy.limequery.com/1?lang=en. Your answers will be analysed anonymously. Once your answers are submitted, you will only be contacted again if you indicate an interest in participating in future research.

Are there any possible disadvantages or risks from taking part?

No. Your answers to the survey will not affect your healthcare in any way.

As some of the questions in the survey are about receiving unexpected or difficult news from scans, answering them could make you anxious or upset. This might be especially true if you have had experience of difficult news in pregnancy or someone close to you has. Please do not feel you have to complete the survey if you find it upsetting and you can skip any questions you find particularly distressing.

Please be assured that all the information you are able to provide will be kept anonymous and any information you can give will help us better understand the point of view of women and partners.

What are the possible benefits of taking part? There is no direct benefit to you. However, your ideas and opinions will be used to help develop future NHS care for pregnant women.

Will my taking part in the study be kept confidential? Yes. All information collected from participants will be kept strictly confidential. Consent forms and participant contact information will be separated and stored independently from the questionnaire responses once submitted. This will ensure that data from the questionnaires remain anonymous including any quotes or comments written in the text boxes. Responsible members of the University of Oxford [and the relevant NHS Trust(s)] may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data? Data protection regulation requires that we state the legal basis for processing information about you. The University of Oxford is the data controller for this study and will be responsible for looking after your information and using it properly. Only authorised study staff will have access to the information data. We will keep identifiable information about you for 3 years after the study has finished. If you agree to your details being held to be contacted regarding future research, we will retain a copy of your consent form until such time as your details

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are removed from our database but will keep the consent form and your details separate. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights You can find out more about how we use your information by contacting jehan.karim@wrh.ox.ac.uk.

What will happen if I don't want to carry on with the study? Participation is entirely voluntary. If you decide you don't want to finish the survey after starting, you can just withdraw and discard the paper survey or exit the website. If you change your mind after you submit the survey it will not be possible to withdraw your data, because all forms are stored anonymously.

What will happen to the results of this study? They will be published in a peer-reviewed scientific medical journal and on the OSPREA website (www.osprea.ox.ac.uk.) The results will also be used to inform future healthcare policy.

What if there is a problem? If you have questions and would like to discuss the content of the survey in more detail or if you feel anxious and require additional support after completing the survey, please contact Dr. Jehan Karim at jehan.karim@wrh.ox.ac.uk or on 01865 572260. If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Dr. Jehan Karim at jehan.karim@wrh.ox.ac.uk or Prof. Aris Papageorghiou aris.papageorghiou@wrh.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, e-mail ctrg@admin.ox.ac.uk. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

Who has reviewed the study? All research in the NHS is looked at by an independent committee, to protect participants' interests. This study has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee (Reference number: 19/SC/0483).

Participation in Future Research: If you wish to participate in future research relating to early anomaly ultrasound, then we will ask you to provide your contact details. Please be aware that agreeing to be contacted does not oblige you to participate. Your contact details, if provided, will be held separately from your answers to the survey (ensuring answers are anonymous). Your details will be held in a locked secure cabinet in the department (if you complete a paper survey) or on a database saved to a high security University of Oxford server (if you complete an online survey). In the first instance, any future contact will come from our research team. Your details can be removed from the register at any time.

For further information: Please contact Dr. Jehan Karim via e-mail at jehan.karim@wrh.ox.ac.uk.

Thank you for considering taking part in our study

Please indicate your consent to participate in the ACAS Survey

If you agree with the statements below, please initial:	
I confirm that I have read the information sheet for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	Check box
I understand that my participation is voluntary and will not have any impact on my future medical care or legal rights.	Check box
I agree to take part in this study.	Check box

Please only complete the survey once in your pregnancy. Print and sign below to indicate your consent.

Print Name	Sign	dd/mm/yyyy
Name of Participant	Signature	Date

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ACAS Study Questionnaire: Acceptability of the Early Anomaly Ultrasound Scan

Thank you for agreeing to participate in the ACAS Study. This questionnaire will ask you about your preferences regarding the use of ultrasound in the first trimester of pregnancy to check for how your baby is developing.

As some of the questions in the survey are about receiving unexpected or difficult news from scans, answering them may make you anxious. This might be especially true if you have had experience of difficult news in pregnancy or someone close to you has. Please do not feel you have to complete the survey if you find it upsetting and you can skip any questions you find particularly distressing.

Please be assured that all the information you are able to provide will be kept anonymous and any information you can give will help us better understand the point of view of women and partners.

Region

At which NHS Hospital Trust did you hear about this survey?

☐ Oxford University Hospitals NHS Foundation Trust

☐ St. George's University Hospitals NHS Foundation Trust

☐ Birmingham Women's and Children's NHS Foundation Trust

☐ Homerton University Hospital NHS Foundation Trust

☐ Liverpool Women's NHS Foundation Trust

☐ Basildon and Thurrock NHS Foundation Trust

☐ Pennine Acute Hospital NHS Trust

☐ St. Helens and Knowsley Teaching Hospitals NHS Trust

☐ Other:_____

Your views regarding prenatal ultrasound screening

Women are currently offered two scans in pregnancy: a first trimester scan at 11-14 weeks and a second-trimester scan at 18-20 weeks.

These are some important facts about checking the development of your baby in the first trimester (at 11-14 weeks):

About half of all serious physical conditions can be identified at this stage of pregnancy.

An anomaly scan at 11-14 weeks may exclude some serious conditions, but some conditions can only be detected later.

Some of the conditions identified at 11-14 weeks may be minor and may have little impact on the child.

Some conditions may be easily diagnosed at this time, but others may only be suspected and need to be confirmed later in pregnancy (possibly 2-8 weeks later).

After a positive or suspicious finding at 11-14 weeks you will be offered the option to be referred to a fetal medicine specialist, who will evaluate your baby in more detail. At that point you may be offered additional genetic tests and follow-up with additional ultrasounds, but whether to have these will always be your choice.

The option of termination of pregnancy may be discussed in cases where the condition means your baby may not survive after birth or may have serious disabilities.

Ultrasound scanning at any time in pregnancy will never be able to identify all physical conditions affecting babies. There are some conditions which can only be found after birth.

Knowing this information, which option would you prefer?

☐ Having the anomaly scan in the first trimester (11-14 weeks) and being informed of all the findings, followed by the usual scan offered in the second trimester (18-20 weeks)

☐ Having the anomaly scan in the first trimester (11-14 weeks) and being informed only about conditions that mean your baby may not survive after birth or may have serious disabilities, followed by the usual scan offered in the second trimester (18-20 weeks)

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☐ Waiting until the second trimester of pregnancy (18-20 weeks) to have my first scan looking at the development of my baby

☐ No preference

In a future pregnancy, if your baby were to have a condition which meant they were unlikely to survive after birth, when would you prefer to be informed?

☐ In the first trimester (11-14 weeks) ☐ In the second trimester (18-20 weeks)

☐ No preference ☐ I don't know

☐ I would not wish to be informed

In a future pregnancy, if your baby were to have a condition which would cause your baby to have a severe disability after birth, when would you prefer to be informed?

☐ In the first trimester (11-14 weeks) ☐ In the second trimester (18-20 weeks)

☐ No preference ☐ I don't know

☐ I would not wish to be informed

In a future pregnancy, if your baby were to have a minor condition, when would you prefer to be informed?

☐ In the first trimester (11-14 weeks) ☐ In the second trimester (18-20 weeks)

☐ No preference ☐ I don't know

☐ I would not wish to be informed

In a future pregnancy, if your baby were to have a condition which was suspected at 11-14 weeks but could not be confirmed until later in the pregnancy, would you like to be informed of this at 11-14 weeks?

☐ Yes ☐ No ☐ I don't know

In a future pregnancy, if your baby was diagnosed with a condition which meant that they were unlikely to survive after birth or may have a severe disability after birth, would termination of pregnancy be an option for you?

☐ Yes, in both cases

☐ Yes, but only if the condition means my baby would not survive after birth

☐ Yes, but only if the condition means my baby would have a severe disability after birth

☐ No

☐ I don't know

☐ I prefer not to answer this question

In the case where a serious condition is identified, do you think that knowing it earlier (at 11-14 weeks) as opposed to later (at 18-20 weeks) would influence your decision about ending or carrying on with the pregnancy?

☐ Yes ☐ No ☐ I don't know ☐ I prefer not to answer

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If you were offered an anomaly ultrasound scan during the first trimester of your pregnancy (11-14 weeks) in addition to the 18- to 20- week scan, would you take up this option?

☐ Yes ☐ I don't know ☐ No

If you selected 'Yes' – What are the reasons that have influenced this decision?

Please check all that apply.

- ☐ Early reassurance
- ☐ I would like to know as much information about my baby as early as possible
- ☐ The test will not cause harm to my baby
- ☐ I want to make sure my baby is healthy
- ☐ My previous experiences of prenatal screening
- ☐ My friends' and/or family's previous experiences of prenatal screening
- ☐ If my baby has a physical condition, I would have more time to prepare myself mentally for the birth
- ☐ If my baby has a physical condition, I would have more time to prepare my life and my family for the birth

If you selected 'No' – What are the reasons that have influenced this decision?

Please check all that apply.

- ☐ I don't think the test is necessary
- ☐ There may be anxiety and uncertainty if there is a suspicious or uncertain result from the test
- ☐ I don't think the test is reliable enough
- ☐ My (or my partner's) religious beliefs
- ☐ My previous experiences of prenatal screening
- ☐ My friends' and/or family's previous experiences of prenatal screening
- ☐ I wouldn't do anything with the information obtained from this ultrasound screening test
- ☐ I would rather have only one ultrasound looking for physical conditions between 18-20 weeks
- ☐ I don't want to know if my baby has any physical conditions before they are born

☐ If my baby has a physical condition, I would have access to earlier genetic tests and be able to speak to relevant health experts at an earlier stage	☐ I think this test is an inefficient use of NHS funding
☐ If my baby has a physical condition, I would have more time to make a decision about termination	☐ I would never consider having a termination of pregnancy
☐ If my baby has a physical condition, I would have access to an earlier and medically safer termination	☐ My baby is not at high risk for having a problem in the pregnancy
☐ Other: _____	☐ Other: _____

Your personal experiences

Do you know of anyone who has experienced a pregnancy where the baby was diagnosed with either a genetic or a physical condition?

☐ Yes ☐ No ☐ Prefer not to answer

Have you or anyone you know experienced a 'false alarm' situation where the baby was suspected of having a condition but after further investigations, this was found not to be the case?

☐ Yes ☐ No ☐ Prefer not to answer

Do you have any personal experience of carrying a pregnancy where the baby was diagnosed with either a genetic or a physical condition?

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☐ Yes ☐ No ☐ Prefer not to answer

If you have answered yes, can you please tell us any information you feel comfortable to share with us about the condition affecting your baby and the outcome of this pregnancy:

All information provided below will be anonymized.

Please tell us some general information about yourself

Who is completing this survey?

☐ I am the person who is currently pregnant ☐ My partner is currently pregnant

☐ We have completed this survey together

If you have completed the survey together with your partner, please fill in the remainder of the questions in this section with the mother of the baby's details.

What is your gender?

☐ Female ☐ Male ☐ Other: _____

How old are you?

☐ <20 years old ☐ 20-24 years old ☐ 25-29 years old ☐ 30-34 years old

☐ 35-39 years old ☐ 40-44 years old ☐ ≥ 45 years old ☐ Prefer not to answer

How many times have you been pregnant (or if you are a partner, how often has your partner been pregnant)? Please include your current pregnancy.

☐ Once ☐ Twice ☐ Three Times

☐ Four Times ☐ Five Times ☐ Six Times

☐ Seven Times ☐ Eight or more times ☐ Prefer not to answer

How many children do you currently have? Please exclude your current pregnancy.

☐ None ☐ One ☐ Two ☐ Three

☐ Four ☐ Five ☐ Six or more ☐ Prefer not to answer

What is your highest level of educational attainment?

☐ No qualifications

☐ GCSE level or O level

☐ A-Level / International Baccalaureate / Completion of High School/ Equivalent

☐ College certificate or vocational qualification

☐ Bachelor's or Undergraduate University Degree

☐ Postgraduate level – masters or doctoral level studies

☐ Other: _____

☐ Prefer not to answer

Which of the following groups best identifies your ethnicity? Please check one box.

Asian or Asian British

☐ Asian British

☐ Indian

☐ Pakistani

☐ Bangladeshi

☐ Chinese

☐ Any other Asian Background

Black or Black British

☐ Black British

☐ Black African

☐ Black Caribbean

☐ Any other Black background

Mixed or Mixed British

☐ White & Black Caribbean

☐ White & Black African

☐ White and Asian

☐ Any other mixed/multiple ethnic background

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White	Other Ethnic Group
☐ White British	☐ Arab
☐ White Irish	☐ Any other ethnic group
☐ Gypsy or Traveller	
☐ Any other White Background	

If you or your partner is currently pregnant – please proceed to the next question

If you or your partner is not currently pregnant – please proceed to Question 24 (page 10)

Information about your current pregnancy:

Did you require any medical help from a fertility specialist in order to become pregnant?

☐ Yes – This is an in-vitro fertilization pregnancy

☐ Yes – Fertility medications were required but did not include in-vitro fertilization in this pregnancy

☐ No – No fertility medication was necessary

Approximately how many weeks pregnant are you?

☐ Less than 8 weeks	☐ 8 or more weeks but less than 14 weeks
☐ 14 or more weeks but less than 24 weeks	☐ 24 or more weeks but then less than 36 weeks
☐ 36 or more weeks but less than 40 weeks	☐ 40 weeks or more

☐ I am uncertain of my pregnancy dates at this time

Do you have plans to have (or have you already undertaken) screening for Down's, Edwards' and Patau's syndrome in this pregnancy?

☐ Yes ☐ No

Do you have plans to have (or have you already had) an ultrasound at 18-20 weeks to look for possible structural conditions in the baby?

☐ Yes ☐ No

Do you have any reason to believe that you are at higher risk of carrying a pregnancy with a baby affected by a physical condition?

☐ Yes ☐ No

If you answered yes to the previous question, why is this the case?

☐ I have previously had a baby with either genetic or structural abnormalities

☐ My family has a history of pregnancies where babies have been diagnosed with genetic or structural conditions

☐ Either myself or my partner were born with a genetic syndrome or a structural condition

☐ I have a history of taking medication in early pregnancy which may increase the risk of having a baby with structural conditions

☐ I am expecting more than one baby (e.g.. twins)

☐ I have a history of uncontrolled diabetes which was diagnosed prior to my pregnancy

☐ Other: _____

Are there any further thoughts or comments you'd like to share with us regarding first trimester anomaly scanning? Or is there any additional information you think is important for us to consider? All information provided below will be anonymized.

_____

_____

_____

_____

_____

_____

_____

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Future Involvement in Research

Would you be interested in participating in future ethically approved research relating to the early anomaly scan?

☐ Yes ☐ No

If you answered yes, please email jehan.karim@wrh.ox.ac.uk with your name, contact number, email address and postal address. Please put 'ACAS Future Involvement' in the email heading.

THANK YOU FOR YOUR HELP!

Appendix 6 Structure and event probabilities for the first-trimester anomaly screening outcome subtrees (true positive, false negative, false positive, true negative)

Subtree structures

The structures of the subtrees developed to model the occurrence of events following each first-trimester screening outcome; a TP finding of an anomaly, a FN finding, a FP finding and a TN finding, are detailed in the following four subsections.

First-trimester true-positive subtree

Figure 26 shows the pregnancy pathway for women who receive a TP screening result during the first trimester (the T1 TP subtree). This pathway is replicated within the model for each anomaly. Women screening TP for an anomaly without a strong genetic association (see *Table 15* in *Chapter 10*), enter the T1 TP subtree immediately following their first-trimester screening results (branching point 2 in *Figure 15* in *Chapter 10*). Women who screen TP for a structural anomaly with a genetic association will first enter the genetic testing subtree (*Figure 16* in *Chapter 10*). These women are stratified based upon whether the diagnostic genetic test was positive or negative (or unknown), and they then subsequently enter the T1 TP subtree.

Following a first-trimester TP screen (+/– genetic testing), a proportion of women will choose to terminate their pregnancy. Women who continue with their pregnancies are now monitored with additional scans by fetal medicine specialists but may have a spontaneous miscarriage prior to reaching the second-trimester screening point. Following further additional monitoring during the second trimester, a woman's pregnancy continues and may end with a late fetal loss/stillbirth or she may give birth to a live baby with an anomaly. The pathway in *Figure 26* assumes that if a woman chose not to terminate her pregnancy during the first trimester, she would not then choose a termination during the second trimester, even if she was given additional information about her baby's condition.

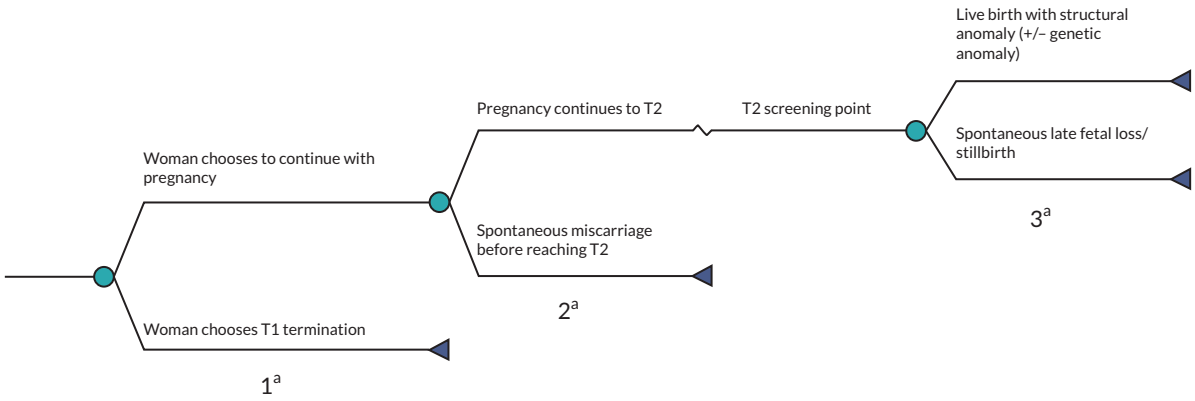

FIGURE 26 Pregnancy T1 TP subtree structures for women with a structural anomaly present. T1: first trimester, T2: second trimester. a, Probabilities for numbered events are shown in *Tables 40* and *41* in the section below on event probabilities.

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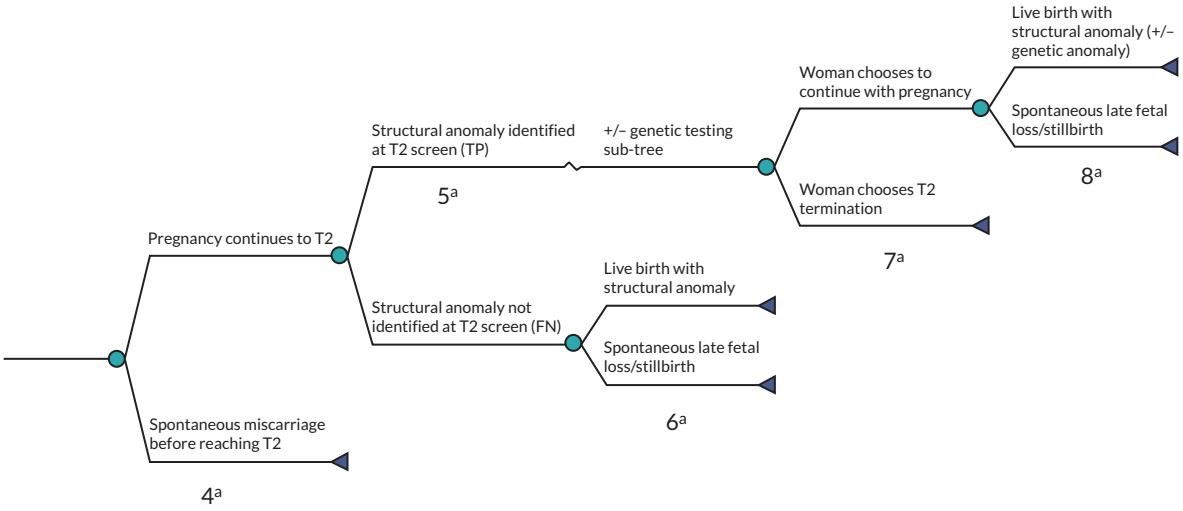

FIGURE 27 Pregnancy T1 FN subtree structure for women with a structural anomaly present. T1: first trimester, T2: second trimester. a, Probabilities for numbered events are shown in *Tables 40* and *41* in the section below on event probabilities.

First-trimester false-negative subtree

The T1 FN pregnancy pathway is also replicated within the model for each of the eight anomalies. *Figure 27* shows that following a FN first-trimester screening outcome, women continue along the pregnancy pathway and may suffer a spontaneous miscarriage. Of the women who undergo routine second-trimester anomaly screening, their baby's anomaly may now be detected (a TP finding) or it may remain undetected (a further FN finding). A proportion of women with FN screens will give birth to a baby with an anomaly that remained undetected throughout pregnancy.

Women screening TP in the second trimester for an anomaly without a strong genetic association choose a termination or to continue with their pregnancy. Women who screen TP for a structural anomaly with a genetic association, enter the genetic testing subtree (*Figure 16* in *Chapter 10*). They are then stratified based upon whether the test result was positive or negative (or unknown) and make a decision about whether to proceed with a termination. Women continuing with their pregnancy, regardless of whether genetic test positive or negative, can experience a spontaneous late fetal loss/stillbirth or give birth to a live baby with an anomaly.

First-trimester (fetal medicine) false-positive subtree

Figure 28 shows the pregnancy pathway for women who receive a FP screening result during the first trimester (T1 FP subtree). This pathway features in the model only once (*Figure 15* in *Chapter 10*) and combines the T1 fetal medicine FPs for all eight anomalies in the basic protocol. Women with fetal medicine FP screens for structural anomalies without a genetic association enter this subtree immediately following their screening result (branching point 3 in *Figure 15*). Women with fetal medicine FP screens for anomalies with a genetic association, enter the subtree after first passing through the genetic testing subtree.

The pregnancy pathway for women with a T1 FP screen is the same as for women with a T1 TP screen until the point of second-trimester anomaly screening, when women may or may not have their T1 FP finding corrected by further fetal medicine screening. Following T2 screening women may suffer a spontaneous late fetal loss/stillbirth or may give birth to a live baby without a structural anomaly. Again, it is assumed that women choosing not to terminate their pregnancies during the first trimester following the (false) positive screening result (and any genetic diagnostic testing), would not then choose a termination during the second trimester if the error remained uncorrected.

First-trimester true-negative subtree

Figure 29 shows the pregnancy subtree constructed for women with a first-trimester TN screening outcome (T1 TN subtree). As for the T1 FP subtree, this pathway features in the model only once, modelling subsequent pathways for all women whose babies are unaffected by any of the eight anomalies in the protocol and who are without a T1 fetal medicine FP screening outcome.

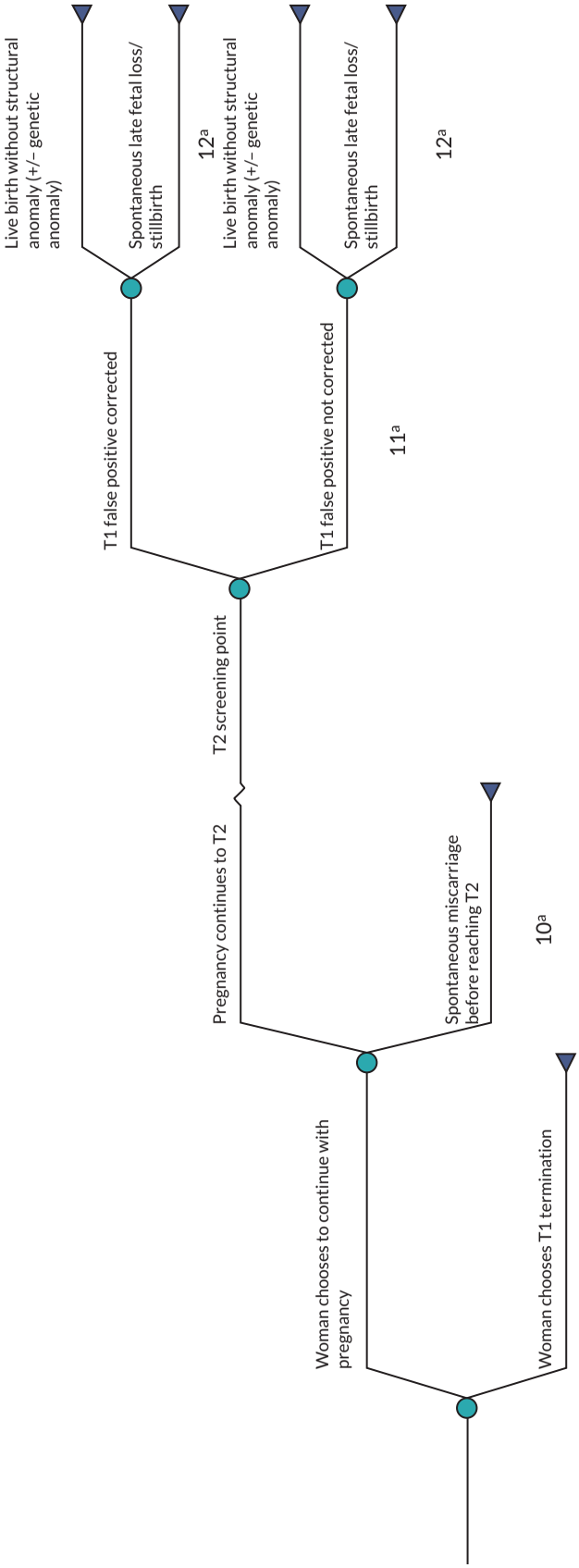

FIGURE 28 T1 fetal medicine FP pregnancy subtree structure for women without a structural anomaly present. T1, first trimester; T2, second trimester. a, Probabilities for numbered events are shown in *Tables 42* and *43* in the section below on event probabilities.

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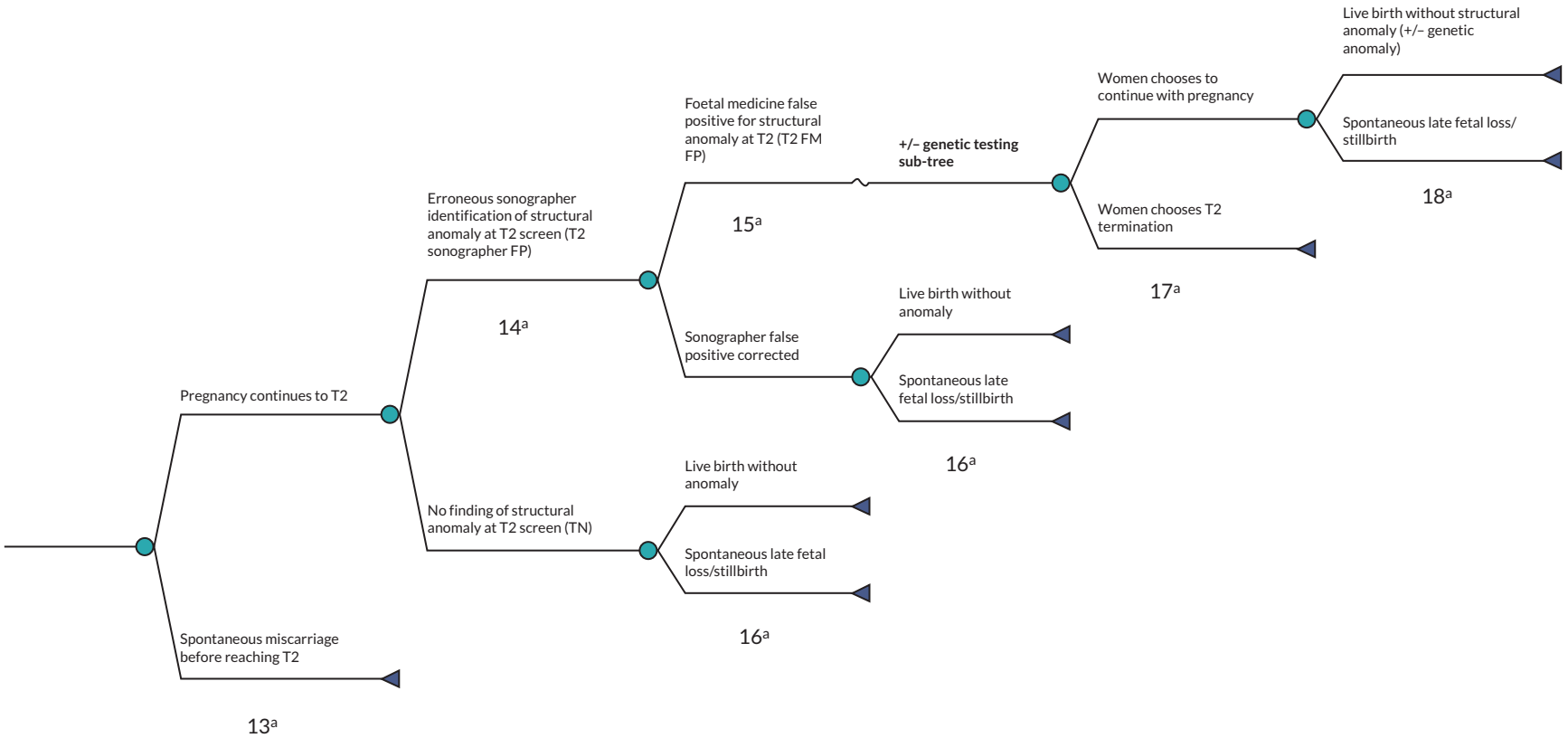

FIGURE 29 T1 TN Pregnancy subtree structure for women without a structural anomaly present. T1, first trimester; T2, second trimester. a, Probabilities for numbered events are shown in *Tables 42* and *43* in the section below on event probabilities.

Women may suffer a spontaneous miscarriage before reaching the second trimester. For those undergoing routine second-trimester anomaly screening, most women will receive a TN screening result and their pregnancy will result in the live birth of an unaffected baby. However, a small proportion of women may have a structural anomaly erroneously identified by a sonographer (second-trimester sonographer FP result). This error may be corrected by a fetal medicine specialist, but if left uncorrected, a woman may make subsequent decisions about her pregnancy on the assumption that her baby has an anomaly. Depending upon the anomaly diagnosed, this may include a decision to undergo invasive genetic diagnostic testing with its associated risk of iatrogenic loss. Some women may choose to have a second-trimester termination while others may make a decision to continue with their pregnancy believing their baby to have a structural anomaly. Of these women, some will suffer a late fetal loss/stillbirth with those remaining giving birth to an unaffected baby.

Subtree event probabilities

Tables 39–43 contain the parameter estimates used to populate the genetic diagnostic testing subtree and the different first-trimester screening outcome subtrees.

Diagnostic genetic testing subtree (shown in Figure 16 in Chapter 10)

TABLE 39 Probabilities relating to diagnostic genetic testing

Description	Mean (SE)	Distribution type	Parameters	Source
Woman will accept the invitation for genetic testing[a]	0.8479 (0.019)	Beta	α = 301, β = 355−α	Spencer *et al.* 2003[180]
Structural anomaly is accompanied by a genetic anomaly at T1 screening point				
Major cardiac anomaly	0.2132 (0.010)[b]	Beta	α = 363, β = 1703−α	NCARDRS 2019 Report[161]
Exomphalos/omphalocele	0.4965 (0.060)	Beta	α = 34.3, β = 69.1−α[c]	Systematic reviews
Alobar holoprosencephaly	0.7838 (0.067)	Beta	α = 29, β = 37−α	Syngelaki *et al.* 2017[7]
LUTO (and megacystis)	0.2069 (0.034)	Beta	α = 30, β = 145−α	Liao *et al.* 2003[230]
Encephalocele	0.1407 (0.021)[b]	Beta	α = 37, β = 263−α	EUROCAT 2015-2019[84]
Structural anomaly is accompanied by a genetic anomaly at T2 screening point				
Major cardiac anomaly	0.2132 (0.010)[b]	Beta	α = 363, β = 1703−α	NCARDRS 2019 Report[161]
Exomphalos/omphalocele	0.3832 (0.016)	Beta	α = 338, β = 882−α	EUROCAT UK 2011–18[15,231]
Alobar holoprosencephaly	0.4421 (0.027)	Beta	α = 149, β = 337−α	Bullen et al, 2001[232]
LUTO	0.1600 (0.036)	Beta	α = 16, β = 100−α	Malin *et al.* 2012[185]
Encephalocele	0.1407 (0.021)[b]	Beta	α = 37, β = 263−α	EUROCAT 2015-2019[85]
A genetic anomaly is present in the absence of a structural anomaly	0.0040 (0.00005)	Beta	α = 7977, β = 1,982,731−α	NCARDRS 2018 Report[233]

continued

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TABLE 39 Probabilities relating to diagnostic genetic testing (*continued*)

Description	Mean (SE)	Distribution type	Parameters	Source
Genetic testing will result in an iatrogenic fetal loss in T1	0.0020 (0.001)[d]	Beta	α = 2.3, β = 1127.4−α[c]	Salomon *et al.* 2019[234]
Genetic testing will result in an iatrogenic fetal loss in T2	0.0030 (0.001)	Beta	α = 9.5, β = 3177.9−α[c]	Salomon *et al.* 2019[234]

T1, first trimester; T2, second trimester.
a Based on screening risk of > 1 : 150.
b Probability that structural anomaly is accompanied by a genetic anomaly assumed to be same in first and second trimesters given lack of informative data.
c Estimated from mean and SE using method of moments approach.
d SE estimated from reported CI after setting lower bound to zero.

Event probabilities for the T1 true-positive pregnancy subtree

TABLE 40 Event probabilities used in the T1 TP pregnancy subtree

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
[1] First-trimester termination following a TP screening result				
Major cardiac anomaly				
With genetic anomaly	0.8732 (0.0392)	Beta	α = 62, β = 71−α	Hartge *et al.* 2012,[235] Efthearides *et al.* 2012,[115] Orlandi *et al.* 2014,[116] Sainz *et al.* 2018[80]
Without genetic anomaly[b]	0.7080 (0.0426)	Beta	α = 80, β = 113−α	Minnella *et al.* 2020[236]
Acrania	1.0000	–	*n*/*N* = 82/82	Syngelaki *et al.* 2011[16] Grande 2012[66] Liao 2021[12]
Exomphalos/omphalocele				
With genetic anomaly	0.7929 (0.0220)	Beta	α = 268, β = 338−α	EUROCAT 2011–8[186]
Without genetic anomaly[b]	0.1582 (0.0591)	Beta	α = 5.87, β = 37.1−α[c]	Systematic review
Gastroschisis	0.0526 (0.0499)	Beta	α = 1, β = 19−α	Syngelaki *et al.* 2011[16]
Alobar holoprosencephaly				
With genetic anomaly	1.0000	–	*n*/*N* = 15/15	Kagan *et al.* 2010[237]
Without genetic anomaly[b]	1.0000	–	*n*/*N* = 29/29	Kagan *et al.* 2010[237]
LUTO				
With genetic anomaly	0.8667 (0.0611)	Beta	α = 26, β = 30− α	Liao *et al.* 2003[230]
Without genetic anomaly[b]	0.3684 (0.0450)	Beta	α = 42, β = 114- α	Liao *et al.* 2003[230]
Encephalocele				
With genetic anomaly	0.7838 (0.0668)	Beta	α = 29, β = 37−α	EUROCAT 2011–8[186]
Without genetic anomaly[b]	0.7434 (0.0290)	Beta	α = 168, β = 226−α	EUROCAT 2011–8[186]
Body Stalk Anomaly	0.9747 (0.0176)	Beta	α = 77, β = 79−α	Syngelaki 2011[16] Liao 2021[12] Murphy 2011[238] Daskalakis 1997[239]

TABLE 40 Event probabilities used in the T1 TP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
[2] Spontaneous miscarriage before the second trimester, in women with a TP screening result who chose to continue with their pregnancy[d]				
Major cardiac anomaly				
With genetic anomaly	0.8571 (0.1237)	Beta	α = 6, β = 7–α	Hartge *et al.* 2012[235]
Without genetic anomaly[b]	0.2727 (0.0764)	Beta	α = 9, β = 33–α	Minnella *et al.* 2020[236]
Acrania	NA[e]	–	–	–
Exomphalos/omphalocele				
With genetic anomaly	0.1000 (0.0060)	Beta	α = 249.9, β = 2499–α[c]	Morris 2008[240]/expert opinion
Without genetic anomaly[b]	0.0500 (0.0279)	Beta	α = 3, β = 60–α	Kagan *et al.* 2010[237]
Gastroschisis	0.0058 (0.00059)[f]	Beta	α = 96.07, β = 16,564.24–α[c]	Expert opinion/Salomon *et al.* 2019[234]
Alobar holoprosencephaly				
With genetic anomaly	NA[e]	–	–	–
Without genetic anomaly[b]	NA[e]	–	–	–
LUTO				
With genetic anomaly	0.1158 (0.0064)[g]	Beta	α = 290, β = 2505–α	Expert opinion/EUROCAT 2011–8[186]
Without genetic anomaly[b]	0.1111 (0.0368)	Beta	α = 8, β = 72–α	Liao *et al.* 2003[230]
Encephalocele				
With genetic anomaly	0.1158 (0.0064)[g]	Beta	α = 290, β = 2505–α	Expert opinion/EUROCAT 2011-2018[186]
Without genetic anomaly[b]	0.0058 (0.00059)[g]	Beta	α = 96.07, β = 16564.24–α[c]	Expert opinion/Salomon *et al.* 2019[234]
Body Stalk Anomaly	0.5000 (0.0500)	Beta	α = 49.5, β = 99–α[c]	Expert opinion
[3] Spontaneous late fetal loss/stillbirth in women with a TP screening result who chose to continue with their pregnancy and did not suffer a spontaneous miscarriage[d]				
Major cardiac anomaly				
With genetic anomaly	0.1048 (0.0211)	Beta	α = 22, β = 210–α	Garne *et al.* 2001[155]
Without genetic anomaly[b]	0.0149 (0.0030)	Beta	α = 24, β = 1614–α	Garne *et al.* 2001[155]
Acrania	NA[e]	–	–	
Exomphalos/omphalocele				
With genetic anomaly	0.3000 (0.0544)	Beta	α = 21, β = 70–α	EUROCAT 2011–8[186]
Without genetic anomaly[b]	0.1107 (0.0194)	Beta	α = 29, β = 262–α	EUROCAT 2011–8[186]
Gastroschisis	0.0293 (0.0065)	Beta	α = 20, β = 683–α	EUROCAT 2011–8[186]
Alobar holoprosencephaly				
With genetic anomaly	NA[e]	–	–	–
Without genetic anomaly[b]	NA[e]	–	–	–

continued

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TABLE 40 Event probabilities used in the T1 TP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
LUTO				
With genetic anomaly	1.0000	–	*n*/*N* = 4/4	Liao *et al.* 2003[230]
Without genetic anomaly[b]	0.1864 (0.0357)	Beta	α = 22, β = 118–α	Malin *et al.* 2012[185]
Encephalocele				
With genetic anomaly	0.1250 (0.1102)	Beta	α = 1, β = 8–α	EUROCAT 2011–8[186]
Without genetic anomaly[b]	0.1207 (0.0424)	Beta	α = 7, β = 58–α	EUROCAT 2011–8[186]
Body Stalk Anomaly	1.0000	–	*n*/*N* = 2/2	Syngelaki 2011[16] Liao 2020[12] Murphy 2011[238] Daskalakis 1997[239]

N/A, not applicable.
a Event probability numbers correspond to those shown beneath the tree branches in *Figure 26*.
b The model assumes women not genetically tested have a euploid fetus and a termination rate analogous to that of women who receive a negative genetic test result.
c Estimated from mean and SE using method of moments approach.
d These probabilities are conditioned upon the events preceding them within the model (see text in corresponding section in *Chapter 10* for explanation).
e All pregnancies affected by this structural anomaly were terminated during the first trimester.
f In the absence of data to inform this parameter and as suggested by expert opinion, the miscarriage rate was assumed to be as for the general population of pregnant women.
g In the absence of data to inform this parameter, the miscarriage rate was assumed to be driven by the co-existing genetic anomaly.

Event probabilities for the T1 false-negative pregnancy subtree

TABLE 41 Event probabilities used in the T1 FN pregnancy subtree

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
[4] Spontaneous miscarriage before reaching the second trimester, in women whose anomaly went undiagnosed during the first trimester				
Major cardiac anomaly				
With genetic anomaly	0.0845 (0.0328)	Beta	α = 6, β = 71–α	Hartge *et al.* 2012,[235] Eleftheriades *et al.* 2012,[115] Orlandi *et al.* 2014,[116] Sainz *et al.* 2018[80]
Without genetic anomaly	0.0796 (0.0254)	Beta	α = 9, β = 113–α	Minnella *et al.* 2020[236]
Acrania	0.0058 (0.00059)[b]	Beta	α = 96.07, β = 16,564.24–α[c]	Salomon *et al.* 2019[234]
Exomphalos/omphalocele				
With genetic anomaly	0.1000 (0.0060)	Beta	α = 249.9, β = 2499–α[c]	Morris 2008[240]/expert opinion
Without genetic anomaly	0.0500 (0.0279)	Beta	α = 3, β = 60–α	Kagan *et al.* 2010[237]
Gastroschisis	0.0058 (0.00059)[b]	Beta	α = 96.07, β = 16,564.24–α[c]	Salomon *et al.* 2019[234]

TABLE 41 Event probabilities used in the T1 TP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
Alobar holoprosencephaly				
With genetic anomaly	0.1158 (0.0064)[d]	Beta	α = 290, β = 2505–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.0058 (0.00059)[b]	Beta	α = 96.07, β = 16,564.24–α[c]	Salomon *et al.* 2019[234]
LUTO				
With genetic anomaly	0.1158 (0.0064)[d]	Beta	α = 290, β = 2505–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.1111 (0.0368)	Beta	α = 8, β = 72–α	Liao *et al.* 2003[230]
Encephalocele				
With genetic anomaly	0.1158 (0.0064)[d]	Beta	α = 290, β = 2505–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.0058 (0.00059)[b]	Beta	α = 96.07, β = 16,564.24–α[c]	Salomon *et al.* 2019[234]
Body stalk anomaly	0.5000 (0.0500)	Beta	α = 49.5, β = 99–α[c]	Expert opinion
[5] TP second-trimester screening result in women whose anomaly went undiagnosed during the first trimester				
Major cardiac anomaly	0.5000 (0.0069)	Beta	α = 2593, β = 5186–α	EUROCAT 2015–9[85]
Acrania	0.9541 (0.0070)	Beta	α = 853, β = 894–α	EUROCAT 2015–9[85]
Exomphalos/omphalocele	0.9853 (0.0051)	Beta	α = 538, β = 546–α	EUROCAT 2015–9[85]
Gastroschisis	0.9772 (0.0049)	Beta	α = 901, β = 922–α	EUROCAT 2015–9[85]
Alobar holoprosencephaly	0.9175 (0.0251)	Beta	α = 109.32, β = 119.15–α[c]	Systematic review
LUTO	0.5070 (0.0296)	Beta	α = 144, β = 284–α	Malin *et al.* 2012[185]
Encephalocele	0.8994 (0.0365)	Beta	α = 60.18, β = 66.91–α[c]	Systematic review
Body Stalk Anomaly	0.9851 (0.0109)	Beta	α = 120.72, β = 122.54–α[c]	Systematic review
[6] Spontaneous late fetal loss/stillbirth in women whose anomaly went undiagnosed during the first trimester and who then received a FN screening result during the second trimester[e]				
Major cardiac anomaly	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]
Acrania	0.4937 (0.0559)	Beta	α = 39, β = 79–α	EUROCAT 2011–8[15]
Exomphalos/omphalocele	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]
Gastroschisis	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Alobar holoprosencephaly (without genetic anomaly)	0.1818 (0.0575)	Beta	α = 8, β = 44–α	EUROCAT 2011–8[15]
LUTO	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]
Encephalocele	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]	As in *Table 40*[f]
Body stalk anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*

continued

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TABLE 41 Event probabilities used in the T1 TP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
[7] Second-trimester termination in women whose anomaly remained undetected during the first trimester but then who received a TP screening result during the second trimester				
Major cardiac anomaly				
With genetic anomaly	0.8049 (0.0276)	Beta	α = 165, β = 205–α	Garne *et al.* 2005[231]
Without genetic anomaly	0.2952 (0.0277)	Beta	α = 80, β = 271–α	Garne *et al.* 2005[231]
Acrania	0.9241 (0.0082)	Beta	α = 962, β = 1041–α	EUROCAT 2011–8[15]
Exomphalos/omphalocele				
With genetic anomaly	0.7929 (0.0220)	Beta	α = 268, β = 338–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.5184 (0.0214)	Beta	α = 282, β = 544–α	EUROCAT 2011–8[15]
Gastroschisis	0.0869 (0.0103)	Beta	α = 65, β = 748–α	EUROCAT 2011–8[15]
Alobar holoprosencephaly				
With genetic anomaly	0.9060 (0.0238)	Beta	α = 135, β = 149–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.7660 (0.0308)	Beta	α = 144, β = 188–α	EUROCAT 2011–8[15]
LUTO				
With genetic anomaly	0.8667 (0.0611)	Beta	α = 26, β = 30–α	Liao 2003[230]
Without genetic anomaly	0.3723 (0.0352)	Beta	α = 70, β = 188–α	Malin *et al.* 2012[185]
Encephalocele				
With genetic anomaly	0.7838 (0.0668)	Beta	α = 29, β = 37–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.7434 (0.0290)	Beta	α = 168, β = 226–α	EUROCAT 2011–8[15]
Body stalk anomaly	0.9747 (0.0176)	Beta	α = 77, β = 79–α	Syngelaki 2011[16] Liao 2021[12] Murphy 2011[238] Daskalakis 1997[239]
[8] Spontaneous late fetal loss/stillbirth in women whose anomaly remained undetected during the first trimester but who then received a TP screening result during the second trimester and chose to continue with their pregnancy				
Major cardiac anomaly				
With genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Without genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Acrania	0.4937 (0.0559)	Beta	α = 39, β = 79–α	EUROCAT 2011–8[15]
Exomphalos/omphalocele				
With genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Without genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Gastroschisis	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Alobar holoprosencephaly				
With genetic anomaly	0.4286 (0.1278)	Beta	α = 6, β = 14–α	EUROCAT 2011–8[15]
Without genetic anomaly	0.1818 (0.0575)	Beta	α = 8, β = 44–α	EUROCAT 2011–8[15]

TABLE 41 Event probabilities used in the T1 TP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
LUTO				
With genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Without genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Encephalocele				
With genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Without genetic anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*
Body stalk anomaly	As in *Table 40*	As in *Table 40*	As in *Table 40*	As in *Table 40*

a Event probability numbers correspond to those shown beneath the tree branches in *Figure 27*.
b In the absence of data to inform this parameter and as suggested by expert opinion, the miscarriage rate was assumed to be as for the general population of pregnant women.
c Estimated from mean and SE using method of moments approach.
d In the absence of data to inform this parameter, the miscarriage rate was assumed to be driven by the co-existing genetic anomaly.
e For simplicity, all anomalies not detected during the first or second trimester were assumed not to have any accompanying genetic anomaly.
f Relevant value from *Table 40* is that for anomaly without genetic association.

Event probabilities for the fetal medicine T1 false-positive pregnancy subtree

TABLE 42 Event probabilities used in the T1 FP pregnancy subtree

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
[9] First-trimester termination following a FP screening result				
For each structural anomaly (+/− a genetic anomaly), see *Table 40*[b]	See *Table 40*	See *Table 40*	See *Table 40*	See *Table 40*
[10] Spontaneous miscarriage before the second trimester, in women with a FP structural anomaly screening result who chose to continue with their pregnancy				
With genetic anomaly	0.1158 (0.0064)	Beta	α = 290, β = 2505−α	EUROCAT 2011–8[186]
Without genetic anomaly	0.0058 (0.00059)	Beta	α = 96.07, β = 16,564.24−α[c]	Salomon *et al.* 2019[234]
[11] First-trimester FP screen for a structural anomaly is corrected at the second-trimester screening point, in women who chose to continue with their pregnancy and did not suffer a spontaneous miscarriage[d]				
Major cardiac anomaly	0.9500 (0.005)	Beta	α = 1804.05, β = 1899−α[c]	Expert opinion
Acrania	N/A[e]	–	–	–
Exomphalos/omphalocele	0.9250 (0.005)	Beta	α = 2565.95, β = 2774−α[c]	Kagan 2010[237]/ expert opinion
Gastroschisis	1.0000	–	–	Expert opinion
Alobar holoprosencephaly	N/A[f]	–	–	–
LUTO	0.9000 (0.005)	Beta	α = 3239.1, β = 3599−α[c]	Kagan 2010[237]/ expert opinion

continued

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TABLE 42 Event probabilities used in the T1 FP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
Encephalocele	1.0000	–	–	Expert opinion
Body stalk anomaly	N/A[e]	–	–	Expert opinion
[12] Spontaneous late fetal loss/stillbirth in women with a FP screening result who chose to continue with their pregnancy and did not suffer a spontaneous miscarriage				
With genetic anomaly	0.0711[g]	Log normal	Mean = 2.8160, SE = 0.0856	EUROCAT 2011–8[186]
Without genetic anomaly	0.0046 (0.00008)	Beta	α = 3368, β = 738,332–α	Draper *et al.* 2019[187]

N/A, not applicable.
a Event probability numbers correspond to those shown beneath the tree branches in *Figure 28*.
b For each model arm (and +/− a genetic anomaly) weighted average first-trimester termination probabilities were estimated by combining data on the proportion of fetal medicine FPs accounted for by each anomaly (calculated using the data in *Table 16* in *Chapter 10*) and corresponding anomaly-specific first-trimester termination probabilities (see *Table 40*).
c Estimated from mean and SE using method of moments approach.
d For each model arm (and +/− a genetic anomaly), weighted average second-trimester FP correction probabilities were estimated by combining data on the proportion of FP screens for each anomaly type reaching this point in the model with their corresponding second-trimester correction probabilities.
e All sonographer FPs for these anomalies are corrected by fetal medicine in the first trimester (see *Table 16* in *Chapter 10*).
f All pregnancies thought to be affected by this structural anomaly were assumed to be terminated during the first trimester.
g Estimated by applying an odds ratio for the increased risk of stillbirth with Down syndrome (shown in adjacent columns) to the underlying odds of a stillbirth in the general population (calculated using data from the row immediately below).

Event probabilities for the T1 true-negative continuing pregnancy subtree

TABLE 43 Event probabilities used in the T1 TN pregnancy subtree

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
[13] Spontaneous miscarriage before the second trimester, in women without a structural anomaly and a TN finding (with screening) or no finding (with current practice)				
Spontaneous miscarriage	0.0058 (0.00059)	Beta	α = 96.07, β = 16,564.24–α[b]	Salomon *et al.* 2019[234]
[14] Second-trimester sonographer FP screen for a structural anomaly in women who did not suffer a spontaneous miscarriage[c]				
Major cardiac anomaly	0.0211 (0.0014)	Beta	α = 210, β = 9959–α	Expert opinion
Acrania	0.0000	–	–	Systematic review/expert opinion
Exomphalos/omphalocele	0.0010 (0.0010)	Beta	α = 1, β = 1000–α	Kagan 2010[236]/expert opinion
Gastroschisis	0.00002 (0.00004)	Beta	α = 0.2, β = 10,000–α	Systematic review/expert opinion
Alobar holoprosencephaly	0.00002 (0.00004)	Beta	α = 0.2, β = 10,000–α	Systematic review/expert opinion
LUTO	0.00002 (0.00004)	Beta	α = 0.2, β = 10,000–α	Systematic review/expert opinion

TABLE 43 Event probabilities used in the T1 TP pregnancy subtree (*continued*)

Event probability number[a] and description	Mean (SE)	Distribution type	Parameters	Source
Encephalocele	0.00001 (0.00003)	Beta	α = 0.1, β = 10,000−α	Systematic review/expert opinion
Body stalk anomaly	0.00001 (0.00003)	Beta	α = 0.1, β = 9998−α	Systematic review/expert opinion
[15] Second-trimester fetal medicine FP screen in women who did not suffer a spontaneous miscarriage and who received a second-trimester sonographer FP screen and presented to the fetal medicine clinic[d]				
Major cardiac anomaly	0.0004 (0.0002)	Beta	α = 4, β = 10,000−α	Systematic review/expert opinion
Acrania	N/A	–	–	–
Exomphalos/omphalocele	1.0000	–	–	Kagan 2010[236]/expert opinion
Gastroschisis	0.0000	–	–	Expert opinion
Alobar holoprosencephaly	0.0000	–	–	Expert opinion
LUTO	0.0000	–	–	Expert opinion
Encephalocele	0.0000	–	–	Expert opinion
Body stalk anomaly	0.0000	–	–	Expert opinion
[16] Spontaneous late fetal loss/stillbirth in women with a second-trimester TN anomaly screening result and those for whom a FP sonographer screen is correct by fetal medicine				
General population risk	0.0046 (0.00008)	Beta	α = 3368, β = 738,332−α	Draper *et al.* 2019[187]
[17] Second-trimester termination in women without an anomaly but who received a fetal medicine FP screening result following routine second-trimester anomaly screening[e]				
Second-trimester termination probabilities relevant only for major cardiac anomaly and exomphalos – see *Table 41*	See *Table 41*	See *Table 41*	See *Table 41*	See *Table 41*
[18] Spontaneous late fetal loss/stillbirth in women with a second-trimester FP structural anomaly screening result and who chose to continue with their pregnancy				
With genetic anomaly	0.0711[f]	Log normal	Mean = 2.8160, SE = 0.0856	EUROCAT 2011–8[15]
Without genetic anomaly	0.0046 (0.00008)	Beta	α = 3368, β = 738,332−α	Draper *et al.* 2019[187]

N/A, not applicable.
a Event probability numbers correspond to those shown beneath the tree branches in *Figure 29*.
b Estimated from mean and SE using method of moments approach.
c Entered in the model as the sum of the second-trimester sonographer FPs for each anomaly.
d Combined with the second-trimester sonographer FPs in the table to estimate a weighted average second-trimester fetal medicine FP probability.
e Weighted average second-trimester termination probability estimated.
f Estimated by applying an odds ratio for the increased risk of stillbirth with Down syndrome (shown in adjacent columns) to the underlying odds of a stillbirth in the general population (calculated using data from the row immediately below).

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Appendix 7 Utility impact for women of events and decisions arising following different first-trimester screening outcomes in the decision tree component of the model

The approach used to identify utility estimates for use in the decision tree is outlined in *Chapter 10* of the report. While it was not always possible to identify UK-specific studies assessing the quality-of-life impact of events along the screening and pregnancy pathways, our estimates were informed by studies conducted either in the UK or in developed countries similar to the UK (e.g. the USA and Sweden) and where the utility implications for women of pregnancy outcomes, are likely to be similar.

Assumptions around adjustments to women's underlying utility levels in the decision tree

When considering adjustments to underlying levels of maternal utility following the various screening outcomes in the decision tree, we made a number of assumptions. Firstly, following a positive screen (a true or a FP result) we assumed the impact upon maternal quality of life to be the same, regardless of the type of anomaly identified. This assumption was deemed appropriate from a clinical perspective, as all of the candidate structural anomalies for first-trimester screening are considered major or significant in terms of their implications for the prognosis of the fetus. Secondly, for structural anomalies accompanied by a genetic anomaly, we assumed the latter would become of primary concern to a woman and so modelled the quality-of-life impact of a diagnosis of a genetic anomaly.

In subsequently detailing the underlying utility modifiers used within the decision tree, women are classified according to their first-trimester ultrasound findings for a fetal structural anomaly: TP, FN, FP, TN. We also distinguish women in the current practice arm (and those declining first-trimester anomaly screening) for whom there was no 'negative' anomaly screening finding as such. These classifications govern the subsequent sequences of events in each of the model's four screening outcome subtrees as described in *Appendix 6*.

Utility impact of a true-positive screen and subsequent events in the T1 true-positive pregnancy subtree (see *Appendix 6*, *Figure 26*)

The first six rows of *Table 44* (labelled S1T1–S6T1) each represent a sequence of first-trimester events for women with a TP finding of a structural anomaly (see also *Figure 16* in *Chapter 10*). In S1T1 (Scenario 1 at Trimester 1), the anomaly has a known genetic association and the woman accepts the invitation for genetic testing and receives a positive result; she then makes a decision to continue with her pregnancy. S2T1 and S3T1 differ only in that the woman chooses to terminate her pregnancy in the first-trimester (S2T1) or genetic testing leads to a first-trimester iatrogenic fetal loss (S3T1). In S4T1, the anomaly presents without any genetic involvement and a decision to continue with the pregnancy is made. In S5T1, the woman opts for termination, and in S6T1 genetic testing is performed and leads to an iatrogenic loss.

Utility adjustments for sequences S1T1–S3T1

A series of papers by Kuppermann and colleagues used time trade-off and standard gamble methodologies to examine the preferences (utility) of different cohorts of pregnant women in San Francisco, USA, for short- and longer-term outcomes of genetic testing during pregnancy.[241,243–246] Short-term or initial impact utility scores reported in these papers were obtained from interviews with 281 women ≥ 18 years of age, < 20 weeks' gestation and carrying a singleton fetus, and were elicited using the time trade-off methodology. Different sequences of genetic screening, testing and subsequent maternal decisions around continuing or terminating a pregnancy were valued.

TABLE 44 Utility adjustments (multipliers, decrements and increments) applied to underlying utility levels following the various first-trimester screening outcomes and subsequent screening and pregnancy outcomes

True status	US screening outcome at T1	Screening/testing outcomes and reproductive decisions at T1	T1 Mean (SE) utility adjustment[a]	US screening outcome at T2[b]	Screening/testing outcomes and reproductive decisions at T2	T2 Mean (SE) utility adjustment[a]
Structural anomaly present	TP finding	S1T1. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, continue with pregnancy	0.655[c] (0.021)[d]	Unchanged from T1	Outcomes/decisions unchanged from T1	Unchanged from T1
		S2T1. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, terminate pregnancy	0.772[c] (0.021)[d]	–	–	–
		S3T1. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, iatrogenic loss due to testing	0.744[c] (0.021)[d]	–	–	–
		S4T1. Screen +ve for structural anomaly (TP), test −ve for a genetic anomaly (or fetus presumed euploid), continue with pregnancy	0.272[e] (0.033)[f]	Unchanged from T1	Outcomes/decisions unchanged from T1	Unchanged from T1
		S5T1. Screen +ve for structural anomaly (TP), test −ve for a genetic anomaly (or fetus presumed euploid), terminate pregnancy	0.156[e] (0.019)[f]	–	–	–
		S6T1. Screen +ve for structural anomaly (TP), test −ve for a genetic anomaly (or fetus presumed euploid), iatrogenic loss due to testing	0.183[e] (0.022)[f]	–	–	–
	FN (FN) finding	S7T1. Screen −ve for structural anomaly (FN), continue with pregnancy	Uniform distribution with min = 0 and max = 0.02[g]	TP finding	S1T2. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, continue with pregnancy	As for S1T1
					S2T2. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, terminate pregnancy	As for S2T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[eh]

continued

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TABLE 44 Utility adjustments (multipliers, decrements and increments) applied to underlying utility levels following the various first-trimester screening outcomes and subsequent screening and pregnancy outcomes (*continued*)

True status	US screening outcome at T1	Screening/testing outcomes and reproductive decisions at T1	T1 Mean (SE) utility adjustment[a]	US screening outcome at T2[b]	Screening/testing outcomes and reproductive decisions at T2	T2 Mean (SE) utility adjustment[a]
					S3T2. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, iatrogenic loss due to testing	As for S3T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[ef]
					S4T2. Screen +ve for structural anomaly (TP), test –ve for a genetic anomaly (or fetus presumed euploid), continue with pregnancy	As for S4T1
					S5T2. Screen +ve for structural anomaly (TP), test –ve for a genetic anomaly (or fetus presumed euploid), terminate pregnancy	As for S5T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[e,h]
					S6T2. Screen +ve for structural anomaly (TP), test –ve for a genetic anomaly (or fetus presumed euploid), iatrogenic loss due to testing	As for S6T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[e,h]
				FN finding	S7T2. Screen –ve for structural anomaly (FN), continue with pregnancy	Uniform distribution with min = 0 and max = 0.02[g]
	No finding	S8T1. No anomaly screening protocol is implemented, structural anomaly is not identified	0.000	TP finding	S1T2. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, continue with pregnancy	As for S1T1
					S2T2. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, terminate pregnancy	As for S2T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[e,h]
					S3T2. Screen +ve for structural anomaly (TP), test +ve for a genetic anomaly, iatrogenic loss due to testing	As for S3T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[e,h]

True status	US screening outcome at T1	Screening/testing outcomes and reproductive decisions at T1	T1 Mean (SE) utility adjustment[a]	US screening outcome at T2[b]	Screening/testing outcomes and reproductive decisions at T2	T2 Mean (SE) utility adjustment[a]
					S4T2. Screen +ve for structural anomaly (TP), test −ve for a genetic anomaly (or fetus presumed euploid), continue with pregnancy	As for S4T1
					S5T2. Screen +ve for structural anomaly (TP), test −ve for a genetic anomaly (or fetus presumed euploid), terminate pregnancy	As for S5T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[e,h]
					S6T2. Screen +ve for structural anomaly (TP), test −ve for a genetic anomaly (or fetus presumed euploid), iatrogenic loss due to testing	As for S6T1 less decrement based on uniform distribution with min = 0.01 and max = 0.044[e,h]
				FN finding	S7T2. Screen −ve for structural anomaly (FN), continue with pregnancy	Uniform distribution with min = 0 and max = 0.02[g]
Structural anomaly not present	FP finding	S9T1. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, continue with pregnancy	0.655[c] (0.021)[d]	TN finding	S8T2. Screen −ve for structural anomaly (TN), known genetic anomaly, continue with pregnancy	Unchanged from T1
				FP finding	S9T2. Screen +ve for structural anomaly (FP), known genetic anomaly, continue with pregnancy	Unchanged from T1
		S10T1. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, terminate pregnancy	0.772[c] (0.021)[d]	–	–	–
		S11T1. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, iatrogenic loss due to testing	0.744[c] (0.021)[d]	–	–	–

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TABLE 44 Utility adjustments (multipliers, decrements and increments) applied to underlying utility levels following the various first-trimester screening outcomes and subsequent screening and pregnancy outcomes (*continued*)

True status	US screening outcome at T1	Screening/testing outcomes and reproductive decisions at T1	T1 Mean (SE) utility adjustment[a]	US screening outcome at T2[b]	Screening/testing outcomes and reproductive decisions at T2	T2 Mean (SE) utility adjustment[a]
		S12T1. Screen +ve for structural anomaly (FP), test –ve for a genetic anomaly (or fetus presumed euploid), continue with pregnancy	0.272[e] (0.033)[f]	TN finding	S10T2. Screen –ve for structural anomaly (TN), previously tested negative for genetic anomaly (or fetus presumed euploid), continue with pregnancy	Population norm less decrement based on a uniform distribution with min = 0 and max = 0.012[e,i]
				FP finding	S11T2. Screen +ve for structural anomaly (FP) previously tested negative for genetic anomaly (or fetus presumed euploid), continue with pregnancy	Unchanged from T1
		S13T1. Screen +ve for structural anomaly (FP), test –ve for a genetic anomaly (or fetus presumed euploid), terminate pregnancy	0.156[e] (0.019)[f]		–	–
		S14T1. Screen +ve for structural anomaly (FP), test –ve for a genetic anomaly (or fetus presumed euploid), iatrogenic loss due to testing	0.183[e] (0.022)[f]		–	–
	TN finding	S15T1. Screen –ve for structural anomaly (TN), continue with pregnancy	Uniform distribution with min = 0 and max = 0.02[g]	FP finding	S9T2. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, continue with pregnancy	As for S1T2
					S12T2. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, terminate pregnancy	As for S2T2
					S13T2. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, iatrogenic loss due to testing	As for S3T2
					S11T2. Screen +ve for structural anomaly (FP), test –ve for a genetic anomaly (or fetus presumed euploid), continue with pregnancy	As for S4T2

True status	US screening outcome at T1	Screening/testing outcomes and reproductive decisions at T1	T1 Mean (SE) utility adjustment[a]	US screening outcome at T2[b]	Screening/testing outcomes and reproductive decisions at T2	T2 Mean (SE) utility adjustment[a]
					S14T2. Screen +ve for structural anomaly (FP), test −ve for a genetic anomaly (or fetus presumed euploid), terminate pregnancy	As for S5T2
					S15T2. Screen +ve for structural anomaly (FP), test −ve for a genetic anomaly (or fetus presumed euploid), iatrogenic loss due to testing	As for S6T2
				TN finding	S16T2. Screen −ve for structural anomaly (TN), continue with pregnancy	Uniform distribution with min = 0 and max = 0.02[g]
		S16T1. No anomaly screening protocol is implemented, so no TN finding as such	0.000	FP finding	S9T2. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, continue with pregnancy	As for S1T2
					S12T2. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, terminate pregnancy	As for S2T2
					S13T2. Screen +ve for structural anomaly (FP), test +ve for a genetic anomaly, iatrogenic loss due to testing	As for S3T2
					S11T2. Screen +ve for structural anomaly (FP), test −ve for a genetic anomaly (or fetus presumed euploid), continue with pregnancy	As for S4T2
					S14T2. Screen +ve for structural anomaly (FP), test −ve for a genetic anomaly (or fetus presumed euploid), terminate pregnancy	As for S5T2

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TABLE 44 Utility adjustments (multipliers, decrements and increments) applied to underlying utility levels following the various first-trimester screening outcomes and subsequent screening and pregnancy outcomes (*continued*)

True status	US screening outcome at T1	Screening/testing outcomes and reproductive decisions at T1	T1 Mean (SE) utility adjustment[a]	US screening outcome at T2[b]	Screening/testing outcomes and reproductive decisions at T2	T2 Mean (SE) utility adjustment[a]
					S15T2. Screen +ve for structural anomaly (FP), test −ve for a genetic anomaly (or fetus presumed euploid), iatrogenic loss due to testing	As for S6T2
				TN finding	S16T2. Screen −ve for structural anomaly (TN), continue with pregnancy	Uniform distribution with min = 0 and max = 0.02[g]

T1, first trimester; T2, second trimester; US, ultrasound.
a All utility adjustments are applied to underlying general population utility levels and were entered within the model using beta distributions with mean and SEs shown, unless otherwise stated.
b For women continuing with their pregnancies and who reach the second-trimester screening point. For women who suffer a spontaneous miscarriage, the implications for their underlying utility levels are discussed in the text and in *Table 45*.
c Multiplier.
d Source is Kuppermann *et al.* (2016).[240]
e Decrement.
f Estimated as described in the text, using data from Kaasen *et al.* (2017)[242] and Kuppermann *et al.* (2016).[241]
g Utility increment associated with reassurance from a negative anomaly scan (applied for 8 weeks).
h Additional utility decrement associated with second-trimester termination/second-trimester iatrogenic fetal loss from genetic testing.
i Additional utility decrement associated with a first-trimester FP screening finding of a structural anomaly.

Three of the sequences evaluated were considered relevant to women in our model following sequences S1T1 to S1T3 in *Table 44*.[241] In all three, an initial unspecified screening test for genetic risk returned a high-risk finding and women subsequently consented to a diagnostic genetic test and received a positive result. In sequence 1, women chose to continue with the pregnancy; in sequence 2, they chose to terminate the pregnancy and in sequence 3, the diagnostic testing resulted in an iatrogenic fetal loss. The mean (SE) utility scores elicited for these health states were 0.655 (0.021), 0.771 (0.021) and 0.744 (0.021), respectively. We assumed these utility estimates would be reflective of the initial quality-of-life impacts for women in our model with the S1T1, S2T1 and S3T1 sequences. In adapting the utility scores to our setting however, we assumed the first-trimester ultrasound finding of a structural anomaly with a known genetic association (rather than a genetic screening test as in Kuppermann *et al.*) would convey the 'increased risk' of genetic involvement, thus leading to genetic testing.

Within the model, the utility score for each sequence was entered as a beta distribution, and then used as a multiplier, to reduce the underlying sex- and age-specific population norm utility values detailed above. We assumed the resulting decremented level of utility would remain unchanged through the second trimester (further screening would not alter the TP first-trimester findings) and up until a live birth at 40 weeks' gestation. For women choosing to continue with their pregnancies but then suffering a spontaneous miscarriage or late fetal loss/stillbirth, we used the utility multiplier of 0.655 up until the fetal loss, and then switched to using a utility modifier reflecting the maternal impact of the pregnancy loss. We assumed miscarriage occurred at 16 weeks' gestation (the midpoint between first and second-trimester screening) and late fetal death/stillbirth, at 30 weeks' gestation (the midpoint between second-trimester screening and a term delivery).

We could identify no suitable studies assessing the initial impact of a miscarriage upon maternal utility levels. A recent systematic review of cohort studies assessing the psychological impact of miscarriage reported that in the 2 weeks following a miscarriage, between 22% and 36% of women reached clinically defined thresholds for depression.[194] At 1–2 months following miscarriage, figures were between 8% and 20%, and between 3 and 6 months were around 5–13%. Anxiety was reported to be the more frequent morbidity and the effects to be more sustained. Like depression, cases of anxiety were highest immediately after the miscarriage (affecting 30–41% of women) and declined over time, but more slowly; at 3–6 months figures were still around 15–32%.

With this in mind and given the scarcity of utility data, we assumed 30% of women in our model suffering the spontaneous miscarriage of an affected baby would experience moderate levels of anxiety/depression in the short term. This proportion was calculated by taking the midpoint of a range constructed from the mid-points of each of the ranges above for anxiety immediately following the miscarriage (35.5%) and 3–6 months later (23.5%). In the absence of further data to quantify the uncertainty around this estimate, we assumed a SE of 0.035 such that when propagated using a beta distribution, a wide uncertainty interval was achieved, with proportion estimates ranging from 17% up to 44% (see *Table 45*).

Using a utility score reflecting average EQ-5D utility levels reported by a cohort of Swedish individuals with moderate depression during a 6-month course of treatment in a primary care setting (three-level EQ-5D with responses converted to a single index using the UK value set estimated by Dolan *et al.*), we estimated a utility decrement from underlying population norm utility levels of 0.355 (SE = 0.033) – (see *Table 45*).[247,248] We subtracted this decrement from underlying

TABLE 45 Estimation of impact of spontaneous miscarriage upon maternal utility

Description	Mean (SE)	Distribution type	Parameters	Source
Proportion of women experiencing moderate anxiety/depression in the 6 months following a miscarriage	0.3000 (0.035)	Beta	α = 51.13, β = 170.43–α[a]	Farren *et al.* 2018[194]/ Author assumption
Utility decrement associated with moderate anxiety/ depression	0.355 (0.033)	Beta	α = 74.29, β = 209.26–α[a]	Kind P *et al.* 1999[188]/Sobocki P *et al.* 2007[247]

a Estimated from the mean and SE using the methods of moments approach.

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levels of utility for the proportion of women predicted to be suffering with moderate anxiety/depression following a miscarriage. The decrement was maintained for the remaining 24 weeks of the decision tree model.

Similarly, we identified few studies assessing the immediate impact of a spontaneous late fetal death/stillbirth upon maternal utility levels. The WOMAN trial evaluated the use of tranexamic acid for post-partum haemorrhage and collected EQ-5D data (using the three-level version) for over 1800 women at hospital discharge or 42 days following a stillbirth.[249] Findings showed 31% of women reporting problems with anxiety and depression; however, the majority of stillbirths occurred in women recruited from low- and middle-income countries. In contrast, in the UK Listening to Parents Study (*n* = 473), 68% of women suffering a stillbirth reported experiencing at least four negative psychological symptoms 10 days following the loss of their baby, declining to 35% at 9 months.[181,182] For the 2016 Lancet Stillbirth Series, a systematic review conducted by Heazell and colleagues noted almost all parents report negative psychological symptoms after a stillbirth, with high rates of depression, anxiety, and post-traumatic stress (PTS) among the most frequently reported negative maternal psychological symptoms.[182]

Considering these data, we assumed that around 58% of the women experiencing a stillbirth at 30 weeks' gestation would suffer with moderate levels of depression over the remaining 10 weeks in the decision tree model. This estimate was inferred by assuming a downward linear trend in symptom reporting between 10 days (68%) and 9 months (35%) in the Listening to Parents Study– see *Table 46*.

Table 46 shows that for these 58% of women, we assumed a utility decrement of 0.355 (SE = 0.033) calculated as described above, to persist for the remaining 10 weeks in the decision tree.[247] For the remaining 42% of women suffering a stillbirth, we assumed mild depression and a utility decrement of 0.25 (SE = 0.027) calculated using EQ-5D utility levels from individuals with mild depression in the same Swedish study (three-level EQ-5D responses again converted to a single index using the UK value set estimated by Dolan *et al.*) (see *Table 46*).[247,248]

For the two sequences resulting in pregnancy termination and iatrogenic fetal loss following positive first-trimester findings of structural and genetic anomalies (S2T1 and S3T1, respectively), the health state descriptions used by Kuppermann *et al.* to elicit utilities were not specific about the timing of these sequences.[241] In the model therefore, we used the elicited utility scores as multipliers to reflect the relative utility impact of these sequences when occurring during the first trimester. For the sequence ending with pregnancy termination (S2T1) the resulting utility score was 0.717 (0.930 × 0.771) and for the sequence ending with iatrogenic fetal loss (S3T1) was 0.692 (0.930 × 0.744). These scores were held constant for the remaining 28 weeks of the decision tree model.

Utility adjustments for sequences S4T1–S6T1

We could not identify any study reporting preferences or utility scores for women who screen positive for a structural anomaly only. A 2017 study by Kaasen *et al.* measured psychological distress in 48 Norwegian women screening positive for a structural anomaly, using the General Health Questionnaire-28 (GHQ-28), Impact of Event Scale-22 (IES), and Edinburgh Postnatal Depression Scale (EPDS).[242] All women had chosen to continue with their pregnancies and completed the questionnaires: (1) a few days following their positive screening result, (2) 3 weeks later, (3) at 30 weeks'

TABLE 46 Estimation of impact of spontaneous late fetal loss/stillbirth upon maternal utility

Description	Mean (SE)	Distribution type	Parameters	Source
Proportion of women experiencing moderate anxiety/depression in the 10 weeks following a late fetal loss/stillbirth	0.581 (0.0227)	Beta	$\alpha = 275$, $\beta = 473-\alpha$	Inferred using Redshaw *et al.* 2014[181] and Heazell *et al.* 2016[182]
Utility decrement associated with moderate anxiety/depression	0.355 (0.033)	Beta	$\alpha = 74.29$, $\beta = 209.26-\alpha$[a]	Kind P *et al.*[188]/Sobocki P *et al.* 2007[247]
Utility decrement associated with mild anxiety/depression	0.250 (0.027)	Beta	$\alpha = 64.05$, $\beta = 256.20-\alpha$[a]	Kind P *et al.*[188]/Sobocki P *et al.* 2007[247]

a Estimated from the mean and SE using the methods of moments approach.

gestation and (4) at 36 weeks' gestation. Analysis of questionnaire data showed that compared to women with a normal ultrasound screen, women with a structural anomaly had significantly increased levels of anxiety and depression on the GHQ-28 and heightened emotional and behavioural responses on the IES, at the first three assessment points. Scores on the EPDS were significantly higher at all four assessments. Women with both a GHQ-28 case score ≥ 6 and an IES intrusion score ≥ 20 were categorised as having clinically significant psychological distress and intrusion and avoidance responses. At each of the four assessment points, the number of women falling into this category were 23 (48%), 13 (27%), 8 (17%) and 4 (8%), respectively.

As no mapping algorithms currently exist to convert the GHQ-28, the IES, or the EPDS scores into utility scores, the following assumptions were made to estimate a utility decrement based upon the data reported by Kaasen *et al.* For women reporting clinically significant psychological distress at each time point, we assumed a utility decrement reflecting moderate levels of depression (0.355 as described above). For the remaining women at each time point, we assumed a decrement of 0.250, commensurate with mild depression, and reflecting the generally raised levels of psychological symptoms observed by Kaasen *et al.* over the remaining course of the pregnancy.

We took a weighted average of these mild and moderate decrements at each time point, and used the duration between assessment points to calculate an average decrement between diagnosis and delivery. The resulting estimated decrement was 0.272 as shown for sequence S4T1 in *Table 44*. In the absence of suitable data, a SE of 0.033 was assumed when fitting a beta distribution for this parameter such that a wide uncertainty interval, ranging from 0.15 to 0.40 was achieved when sampling.

For women with a TP finding of a fetal structural anomaly at T1, no genetic involvement, and a decision to continue with the pregnancy, this decrement was subtracted from underlying utility levels. For women with a live birth (S4T1) the decrement was applied until a live birth at 40 weeks' gestation. For women continuing with their pregnancy but then suffering a miscarriage or a late fetal loss/stillbirth, we applied the same utility decrements and assumptions as described above for women experiencing these events following the S1T1 sequence.

It was not possible to determine utility decrements in the first trimester for women who chose to terminate their pregnancy as a result of a structural anomaly alone (S5T1), or who suffered an iatrogenic loss following a negative genetic test (S6T1). Thus, we considered the relative differences in the utility scores generated by applying the utility multipliers informed by Kuppermann *et al.* to the underlying population norm utilities for women with positive screening and genetic test results but who differed in their pregnancy decisions (S1T1–S3T1 above). For example, the utility score for a woman choosing to terminate her pregnancy following a diagnosis, was, at 0.717 (0.930 × 0.771), 17.7% greater than the score for a woman choosing to continue with her pregnancy [0.609 (0.93 × 0.655)]. The utility score for a woman suffering an iatrogenic loss following genetic testing was 13.6% greater than the score for a women with a continuing pregnancy (0.692 vs. 0.609). These percentages were used to estimate utility scores and subsequently the utility decrements, for women in the model who chose to terminate their pregnancy as a result of a structural anomaly alone (S5T1), and those who suffered an iatrogenic loss following a negative genetic test (S6T1). The resulting utility decrements were 0.1559 (SE = 0.019) for S5T1 and 0.1830 (SE = 0.022) for S6T1 (see *Table 44*) and were entered into the model using beta distributions. They were applied for the same durations as described previously for the S2T1 and S3T1 sequences.

Utility impact of a false-negative screen and subsequent events in the T1 false-negative pregnancy subtree (see *Appendix 6*, *Figure 27*)

Utility adjustment for sequence S7T1

There is debate around whether a negative anomaly screen (a true or a FN finding) can reduce anxiety and provide reassurance to women about the health and well-being of their baby. Structured reviews of the literature have reported that significant declines in maternal anxiety observed following a normal screening result, likely reflect a reduction of heightened anxiety levels observed pre-screening.[250,251]

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Although psychological benefits in terms of reduced anxiety seem questionable, there is a general acknowledgement that a normal screening result has reassuring qualities for women.[204] A structured review by Garcia *et al.* identified 25 studies providing insight into what women value about ultrasound screening.[205] Most reported screening to be a positive experience for women and several studies asking women to describe their feelings following a normal scan reported a majority use of positive adjectives. Seeing their baby for the first time is a joyous experience for most women; however, adjectives such as 'optimistic', 'secure', 'confident', 'attached' and 'reassured' imply some additional sense of positive well-being that arises when no adverse outcomes are detected. Indeed, to gain reassurance about the well-being of the fetus is one of the three main elements of ultrasound screening for pregnant women identified by Clement *et al.* (along with meeting the baby, and having a visual confirmation of the reality of pregnancy).[206] When coupled with data from the ACAS survey (see *Chapter 9*) showing reassurance to be one of the main reasons that most women (over 90%) would consent to a first-trimester anomaly scan, these findings suggest some degree of reassurance is gained from receiving the news that fetal anatomy looks normal during an anomaly scan.

Thus, within the model, we wished to include some positive impact upon maternal utility that comes from receiving a negative anomaly scan. However, we could identify no studies to inform such a value. Indeed, Gross and colleagues note that few economic evaluations in health care in general attempt to measure or value wider utility outcomes, such as reassurance from a test result or 'spillover' effects on family members.[252] For the base-case analysis therefore, and assisted by expert opinion, we implemented a small reassurance utility increment using a uniform distribution with minimum and maximum values of 0 and 0.02, respectively. As data suggest the reassuring qualities of a screen are likely to be transient, we assumed the effect to last only until the point of second-trimester anomaly screening (approximately 8 weeks later) or until the point of miscarriage if this occurred prior to a woman reaching the second trimester.[204]

A FN first-trimester anomaly screen may be altered by second-trimester anomaly screening. As shown in *Table 44*, the S7T1 sequence of events may be followed in the second trimester by any one of the range of TP sequences detailed above (but now denoted S1T2 to S6T2 to reflect the second-trimester screening point). A second FN screening finding (S7T2) is also possible.

When a second-trimester TP screen followed a first-trimester FN finding, and the woman chose to continue with her pregnancy (S1T2 if a genetic anomaly was also diagnosed and S4T2 for a structural anomaly only), we used the same utility multipliers and decrements as described above for the analogous health states occurring in the first trimester (S1T1 and S4T1). These were assigned to women from the point of second-trimester screening until birth at 40 weeks and were amended as described above for the proportion of women expected to suffer a late fetal death/stillbirth.

Uncertainty exists as to whether the termination of a pregnancy for a fetal anomaly has a greater negative impact upon a woman in the second trimester as compared with the first trimester. At a later GA, women are visibly pregnant, are likely to have felt their baby move and may have developed a greater sense of attachment. Also, terminations at a later stage may be more emotionally and physically traumatic, painful and risky. A number of papers have reported additionally increased levels of distress among women undergoing pregnancy termination during the second trimester.[38,40]

A series of studies from the early 1990s conducted utility-based decision analyses comparing CVS with amniocentesis in women referred for genetic testing in the US because of advanced age.[253–255] In one of these studies pregnant women referred for genetic testing were asked to give their preferences for different screening/testing/and reproductive decision sequences, which included first- and second-trimester terminations following positive screening and genetic testing results. Respondents placed a cross reflecting their preferences on a 0–100 scale where a value of 0 represented the worst possible outcome (birth of a child with a chromosomal abnormality) and 100 the best possible outcome (birth of a child without a chromosomal anomaly). Women rated a second-trimester termination at 4.4 units lower than a first-trimester termination (0.044 on a 0–1 scale).[254] In another paper by the same authors reporting a cost-effectiveness analysis, an additional decrement of 0.02 was applied to a second-trimester termination compared to a first-trimester termination.[255] The source of this estimate however was unclear.

A more recent UK study assessed women's preferences for various aspects of Down syndrome screening using the standard gamble approach.[256] A group of 100 women who had given birth to a healthy baby, valued a first-trimester

termination following positive screening and genetic testing with CVS only marginally higher [mean = 0.81, standard deviation (SD) = 0.22] than a second-trimester termination following a positive screen and amniocentesis (mean = 0.80, SD = 0.25). The authors acknowledged that women may have focused primarily upon the identical outcomes of the scenarios (i.e. a positive screen followed by a positive genetic test, followed by a pregnancy termination) rather than on the different time points of the diagnoses and resulting pregnancy outcomes.

The US studies provided women with vignettes that incorporated additional information on the stage of pregnancy and the method of termination. For example, in the first (second) trimester women were asked to imagine they would not yet be (would be) visibly pregnant, would not (would) have experienced fetal movement and their termination would not (would) involve an induced labour. Such additional detail may explain the larger decrements reported for second-trimester terminations in these studies, although other differences in methodology also existed between the studies.

To women in the model choosing to terminate their pregnancies following a TP second-trimester diagnosis of a structural with a genetic anomaly (S2T2) or a structural anomaly alone (S5T2), we first applied the same utility multipliers and decrements as described above for the analogous health states occurring in the first trimester (S2T1 and S5T1). A woman's utility was then reduced further by entering into the model an additional decrement for a second-trimester termination. This parameter was entered using a uniform distribution with maximum and minimum values of 0.01 and 0.044, respectively, reflecting the upper and lower estimates of women's preferences reported in the papers detailed above – see *Table 44*. Decrements were assigned to women from the point of second-trimester screening until the end of the decision tree time horizon (a duration of 20 weeks).

For women suffering an iatrogenic fetal loss with genetic testing following a second-trimester positive screen for a structural anomaly (S3T2 and S6T2), we again used the same utility multipliers and decrements for the analogous health states in the first trimester (S3T1 and S6T1). To reflect the likelihood that such a loss during the second trimester would likely lead to further distress given a woman's advanced GA, we further reduced utility using the same utility decrement parameter described above for a second-trimester termination – see *Table 44*. Again, decrements were assigned for a duration of 20 weeks.

Finally, a second-trimester FN screening finding, following a first-trimester FN screening finding (S7T2) was assigned the same utility reassurance increment as in the first trimester, with this increment again maintained for 8 weeks.

Utility adjustment for sequence S8T1

For women in the current practice arm of the model (and those declining first-trimester anomaly screening) whose babies are affected by an anomaly but which is not incidentally detected in the first trimester (sequence S8T1 in *Table 44*), we assumed no utility increment for reassurance was associated with the scan as formal anomaly screening is not being conducted. For these women being screened during the second trimester however, the same event sequences as described above for women with a FN first-trimester screening result, are possible and so the same utility adjustments were made – see *Table 44*.

Utility impact of a fetal medicine false-positive screen and subsequent events in the T1 false-positive pregnancy subtree (see *Appendix 6*, *Figure 28*)

Women receiving a first-trimester fetal medicine FP screen in the model, were assumed to follow the same first-trimester sequences and thus experience the same levels of quality of life as women receiving a TP first-trimester screening finding. *Table 44* shows the sequences (coded S9T1–S14T1) have the same utility adjustments used for the TP first-trimester screen sequences (S1T1–S6T1).

For women whose pregnancies continue to the second trimester, further screening at this point may or may not correct the erroneous first-trimester diagnosis. For women who had a genetic anomaly diagnosed as a consequence of a first-trimester FP ultrasound screen (S9T1), regardless of whether their FP screening result was subsequently corrected (S8T2 or S9T2), we assumed no change to their utility levels from the first trimester, on account of the genetic anomaly

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that was previously diagnosed. These levels were maintained until birth and were amended as described above for the proportion of women expected to suffer a late fetal death/stillbirth.

For women without a concomitant diagnosis of a genetic anomaly (S12T1), and whose FP screening result from the first trimester, is corrected by second-trimester screening (S10T2), we removed the utility decrement applied in the first trimester but assumed women's quality of life would not return fully to underlying norm levels. This is because studies have shown that even after correction of a FP screening result, women can continue to experience slightly elevated levels of anxiety through the remainder of their pregnancy.[257,258] Marteau *et al.* suggested that this may be as a result of a woman's belief that an initial positive result must be indicative of another underlying problem with her baby. In a study by Baillie *et al.* two-thirds of women with an initial FP screening finding reported residual feelings of anxiety driven by a fear that something else unexpected may occur during their pregnancy.[257,258]

Data reported by Kuppermann *et al.* showed the difference between women's utility valuations of health states where an initial accurate negative screening finding was returned (0.931) and where a FP screening finding was returned and then subsequently corrected with further testing (0.925) to be 0.006.[241] We assumed this value to be the midpoint of a uniform distribution with minimum and maximum values of 0 and 0.012, respectively. The resulting utility decrement was used to reduce a woman's utility for the remainder of her pregnancy, unless she suffered a stillbirth.

For women without a concomitant diagnosis of a genetic anomaly (S12T1), and whose FP screening result from the first trimester, is not corrected by the second-trimester anomaly screen (S11T2), we assumed no change to utility levels from the first trimester until a live birth or stillbirth of the baby.

Utility impact of a true-negative screen and subsequent events in the T1 true-negative pregnancy subtree (see *Appendix 6*, *Figure 29*)

We applied the 'reassurance' utility increment to women receiving a TN result on their first-trimester anomaly screen (S15T1 in *Table 44*). This increment was again maintained for 8 weeks unless a woman suffered a miscarriage and her utility was adjusted as described above. For women in the model with no structural anomaly, no formal first-trimester anomaly screening, and no false incidental findings (scenario S16T1 in *Table 44*), we made no 'reassurance' adjustment to underlying utility levels on account that they were not formally screened for structural anomalies at this time point.

With second-trimester routine anomaly screening, and as shown in *Table 44*, some women in the S15T1 and S16T1 groups may receive a fetal medicine FP finding, (S9T2 and S11T2–S15T2). Utility levels for these women were adjusted for the various scenario outcomes with the same utility decrements and multipliers used for women with a TP finding during the second trimester (scenarios S1T2–S6T2).

Most women without an anomaly however would receive a TN diagnosis and were thus assigned the reassurance increment for the next 8 weeks (S16T2 in *Table 44*).

Appendix 8 Methods and parameters used to populate the maternal Markov models for each of the pregnancy outcomes modelled by the decision tree

Estimation of quality-adjusted life-years within the maternal Markov models for each pregnancy outcome

Underlying maternal mortality and utility

Table 47 details the sources of data used to model underlying levels of maternal mortality and utility in each of the maternal Markov models. The following sections describe the adjustments made to these underlying levels for each pregnancy outcome modelled.

Adjustments to underlying levels of maternal mortality and utility within the live birth Markov models

Maternal mortality adjustment

As mothers of children born with major congenital anomalies are known to face increased mortality risks, the underlying annual probabilities of maternal death in each anomaly-specific live birth Markov model were adjusted using published hazard ratios (see *Table 47*).[182] No mortality adjustments were made in the maternal Markov model following the birth of an unaffected baby.

Maternal utility adjustment

We assumed that each year, the utility of a woman with a live birth would depend upon whether her baby had been born with an anomaly, and if so, the implications of that anomaly for the child's prognosis. Taking each anomaly in turn, for the proportion of women expected to suffer the loss of their baby each year, we modelled the maternal utility impact of an infant death during that year and for a woman's remaining time in the model (see *Table 47*).

For women whose live born infants died, we modelled the impact upon their utility levels as follows:

1. We used published data to estimate anomaly-specific annual infant mortality risks from birth to 20 years. These data are described and tabulated in *Tables 49* and *50* of *Appendix 9*. Mortality risks were also obtained for the models developed for the live birth of child with a genetic anomaly only and for an unaffected child (see *Table 51* of *Appendix 9*).
2. The underlying utility levels for those mothers predicted to experience the loss of their child during a year, were then adjusted. A utility value of 0.07 was assumed for women immediately following the loss of a child.[259–261] We utilised the value of 0.07 to estimate a decrement from underlying utility levels of 0.8649 [0.930–(0.930 × 0.070)] for the first year following the infant loss. A SE for the decrement of 0.03 was assumed in the absence of variability/precision data (see *Table 47*) and produced a sampling distribution with 2.5th and 97.5th percentiles of 0.80 and 0.91, respectively.

With time, there is a lessening of the psychological symptoms women experience immediately following the loss of a child.[263] Systematic reviews however have reported variability in published estimates of the proportions of women who continue to experience negative psychological consequences over time.[262,263] To incorporate this uncertainty, we created a parameter to represent the duration (in years) required for a mother's levels of quality of life to recover to close to underlying norm values. This parameter was entered into the model using a uniform distribution with minimum and maximum values of 5 and 20 years respectively (see *Table 47*). For each duration sampled from the distribution, we assumed a constant annual rate of maternal utility improvement from the decrement observed immediately following the loss of the infant.

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TABLE 47 Parameters used to populate maternal Markov models for live births with each type of anomaly and for a live birth without an anomaly

Parameter	Mean (SE)	Distribution type	Parameters	Source
Underlying maternal mortality and utility levels				
Underlying annual mortality risk	Age- and sex-adjusted life table data	–	–	ONS[198]
Underlying utility level for female aged 25–34	0.930 (0.007)	Beta	α = 1234.64, β = 1327.57−α	Kind *et al.*[188]
Underlying utility level for female aged 35–44	0.910 (0.009)	Beta	α = 919.20, β = 1010.11−α	Kind *et al.*[188]
Underlying utility level for female aged 45–54	0.850 (0.014)	Beta	α = 552.08, β = 649.51−α	Kind *et al.*[188]
Adjustments following a live birth				
Increased risk (hazard ratio) of mortality in mothers of children with major congenital anomalies. Years 0–10	1.27 (0.13)	Log normal	Mean = 0.239, SE = 0.103	Fuller *et al.* 2021[183]
Increased risk (hazard ratio) of mortality in mothers of children with major congenital anomalies. Years 11–20	1.25 (0.10)	Log normal	Mean = 0.223 SE = 0.078	Fuller *et al.* 2021[183]
Annual mortality risks for infant born with each type of structural anomaly				
With genetic anomaly	Various – see *Tables 49* and *50* of *Appendix 9*	–	–	Various – see *Tables 49* and *50* of *Appendix 9*
Without genetic anomaly	Various – see *Tables 49* and *50* of *Appendix 9*	–	–	Various – see *Tables 49* and *50* of *Appendix 9*
Annual mortality risk for infant in general population. Years 1–20	Age- and sex-adjusted life table data	–	–	ONS[198]
Annual mortality risk for infant born with a genetic anomaly only. Years 1–20	See *Table 51* of *Appendix 9*	–	–	Tennant *et al.* 2010[265]
Decrement in maternal utility in the first year following the death of a child	0.8649 (0.030)	Beta	α = 111.43, β = 128.83−α	Chung *et al.* 2021[259] Odibo *et al.* 2006[260] Song *et al.* 2010[201]
Years taken for a mother's utility to recover to underlying levels following the death of a child	12.500 (4.317)	Uniform	Min = 5 years Max = 20 years	Author assumption
For mothers with surviving infants: multiplier used to decrement maternal utility each year following the birth of an infant with a genetic anomaly (± a structural anomaly) or with a neurodevelopmental disability	0.621 (0.021)	Beta	α = 330.80, β = 532.69−α	Kuppermann *et al.* 2016[241]
For mothers with surviving infants: multiplier used to decrement maternal utility during the first year of life of an infant with a structural anomaly only[a]	0.670 (0.084)	Beta	α = 20.32, β = 30.34−α[b]	D'Souza *et al.* 2019[266]

TABLE 47 Parameters used to populate maternal Markov models for live births with each type of anomaly and for a live birth without an anomaly (*continued*)

Parameter	Mean (SE)	Distribution type	Parameters	Source
Proportion of infants with encephalocele affected by neurodevelopmental disability	0.600 (0.0581)	Beta	α = 42, β = 70−α	Da Silva *et al.* 2015[267]
Annual proportion of infants with LUTO developing end-stage renal failure requiring dialysis and kidney transplantation during first 6 years of life	0.056	–	–	Biard *et al.* 2005[268] Berte *et al.* 2018[269]
Additional utility decrement for mothers whose infants are born with LUTO and develop renal failure requiring dialysis and kidney transplant	0.060 (0.016)	Beta	α = 13.16, β = 219.31−α	Wu *et al.* 2020[270]
Proportion of mothers suffering with postnatal depression during the first year following the birth of a baby without an anomaly[c]	0.078 (0.0029)	Beta	α = 650, β = 8323−α	Heron *et al.* 2004[271]
Utility decrement applied to women suffering postnatal depression in the years following the birth of an infant without an anomaly	0.355 (0.033)	Beta	α = 74.29, β = 209.26−α	Kind P *et al.* 1999[188]/ Sobocki P *et al.* 2007[247]

ONS, Office for National Statistics; SE, standard error.
a The multiplier is increased by a constant amount in years 2 and 3, and by year 4 takes on a value of 1 (i.e. there is no further detrimental impact to underlying maternal utility levels).
b Parameters estimated from median and interquartile range.
c Proportion is reduced each year at a constant rate such that after 3 years, no women are suffering with depression.

As acrania and alobar holoprosencephaly are lethal anomalies, all women giving birth to babies with these conditions were modelled as losing their infants in the first year of the corresponding Markov models.[232,264] Body stalk anomaly is also lethal but as the decision tree suggested all women with this anomaly either select termination or suffer a spontaneous fetal loss, a maternal Markov model for this condition was not required.

For women whose babies survived each year, underlying utility was adjusted according to published evidence on the maternal quality-of-life impact of raising a child with each type of congenital anomaly. For women whose babies were born with a non-lethal structural anomaly (a major cardiac anomaly, an omphalocele, gastroschisis, LUTO or encephalocele) and who did not suffer the loss of their infant during a given year, underlying utility levels were adjusted to account for the impact of being a parent to a child born with a major congenital anomaly. Such implications are varied and wide-reaching, and can include feelings of grief, anger, anxiety and depression, increased levels of fear, stress and uncertainty about the future, worry around economic insecurity, the physical and emotional burden of meeting a child's additional care needs, and detrimental impacts upon partners and wider familial relationships.[272–274] As the anomalies modelled can vary substantially in terms of their prognoses, the availability of corrective treatment, and the implications for the child's physical and neurodevelopmental functioning, we considered the impact of each type of anomaly upon maternal utility as described in the following paragraphs.

Maternal utility: non-lethal structural anomalies with a genetic anomaly

Four of the non-lethal anomalies have strong genetic associations (major cardiac anomaly, omphalocele, encephalocele, and LUTO) and some women whose babies are affected by these anomalies will test positive for a genetic syndrome. For these mothers, we assumed the genetic anomaly would exert the greater and more prolonged impact upon quality of life. We modelled the potential impact upon underlying utility levels by applying a utility multiplier of 0.621 (SE = 0.0209) in each of the four corresponding Markov models (see *Table 47*). This value was taken from a study using the time trade-off technique to assess the preferences of 191 pregnant women for a live birth of a child with Down

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syndrome or another intellectual disability.[241] Given the permanence of such syndromes, we applied the multiplier for each year an infant survived over the model's 20-year time horizon.

Maternal utility: non-lethal structural anomalies without a genetic anomaly

The four non-lethal anomalies discussed above can also occur without a genetic syndrome. Additionally, gastroschisis is an anomaly without a strong genetic association. For mothers of babies born with each of these five isolated structural anomalies, when adjusting utility levels, we considered the potential implications of both routine clinical management following birth and of the anomaly per se, for longer-term infant prognosis.

All five anomalies are likely to require surgical intervention soon after the baby is born.[275,276] A recent systematic review found that parents of children with complex congenital cardiac anomalies are at a significantly increased risk of psychological problems following their infant's surgery.[273] A similar impact has been hypothesised for parents of babies born with other anomalies requiring at least one major surgery during the first year of life.[275]

For mothers of these infants, we used a utility multiplier of 0.670 (SE = 0.084) to adjust underlying utility levels for the first year following birth (see *Table 47*). This score was elicited by D'Souza using the time trade-off technique in 40 pregnant women who were asked to value a health state in which a baby develops a major physical defect while in the womb.[266] Although a specific anomaly was not identified in the health state description, women were told that the defect may require multiple surgeries or life-long medications and doctors' visits.

Long-term follow-up studies of infants with an isolated major cardiac anomaly, an omphalocele, and gastroschisis suggest near-normal levels of health-related quality of life can eventually be attained by many children.[265,277,278] For parents, this will mean a decline in the psychological symptoms experienced after the birth and initial surgical management of their child. A systematic review by Woolf-King *et al.* supports this hypothesis, but noted uncertainty as to the duration for which the psychological impact persists for parents, with recovery times ranging from 12–18 to 36 months.[273,279,280]

Within the model, we assumed that utility levels of mothers of surviving infants with an isolated major cardiac anomaly, omphalocele and gastroschisis would return to underlying levels after 3 years. This was implemented by assuming a constant annual increase in the Year 1 utility multiplier [0.670 (SE = 0.084)], such that by Year 4 the multiplier value was 1.

The longer-term prognosis of infants born with an isolated encephalocele is less certain. The involvement of the brain means that even after surgery, a proportion of children will suffer with neurological disability. Studies have suggested around a quarter of children will have severe neurological disability and up to 60% will suffer either mild/moderate or severe developmental delay.[267,280–283]

Using data reported by the most recent of these studies, the model assumed 60% (n = 42/70) of mothers whose babies were born with an encephalocele and survived each year, would be raising a child with a neurodevelopmental disability (see *Table 47*).[267] The underlying utility of these mothers was decremented by applying the same utility multiplier described above for mothers of babies with a genetic anomaly [0.621 (SE = 0.0209)].[241] The decrement was applied for a woman's remaining time in the model. For the 40% of women whose infants did not have developmental delay, utility was modelled as for mothers of infants with an isolated major cardiac anomaly, an omphalocele, or gastroschisis.

The long-term prognosis of infants born with an isolated LUTO is also uncertain. Studies suggest that during the first 6–10 years following birth, around one-third may develop chronic renal failure leading to end-stage renal disease, renal dialysis and ultimately, kidney transplantation.[268,269] To account for the maternal impact of this, we assumed that renal failure leading to end-stage renal disease occurred at a constant annual rate over the first 6 years of the model – approximately 5.6% per year (see *Table 47*). Utility levels for the proportion of mothers affected were reduced further using a utility decrement of 0.06 (SE = 0.016) estimated using SF-12 responses from 54 parents of infants with rare genetic kidney diseases[270] (see *Table 47*). As some children will suffer with ongoing morbidity following transplant, for example, if the kidney is rejected, there are complications of immunosuppressant therapy, an increased number of infections or continuing poor bladder function,[284] we maintained this decrement for the remainder of a woman's time

in the Markov model. For women whose infants did not develop renal failure, utility was modelled as for mothers of infants with an isolated major cardiac anomaly, an omphalocele, or gastroschisis (see above).

Maternal utility: genetic anomaly alone

For women whose children are born and survive each year with a genetic syndrome but no structural anomaly, underlying maternal utility levels were adjusted by applying the multiplier of 0.621 (SE = 0.021) described previously (see *Table 47*).

Maternal utility: no congenital anomaly

A proportion of mothers with babies unaffected by an anomaly will still suffer with postnatal depression. Survey data from 8323 women in the UK Avon Longitudinal Study of Parents and Children (ALSPAC) showed just under 8% (*n* = 650/8323) suffered symptoms of clinical depression following the birth of their baby.[271] In the live birth no anomaly maternal Markov model, underlying utility levels for these women were reduced using the previously described utility decrement estimated for moderate depression (mean = 0.355, SE = 0.033). We reduced the proportion of women affected year on year, such that after 3 years, no women had symptoms. No utility adjustments were made for women in this Markov model who were unaffected by depression.

Adjustments to underlying levels of maternal utility within the stillbirth Markov model Based upon data from the UK Listening to Parents Study, around 35% of women (inferred *n*/*N* 166/473) still experience clinically significant psychological symptoms 9 months after the stillbirth of their baby.[181,182] During the first year of the 'stillbirth' maternal Markov model, we assumed a moderate depression utility decrement of 0.355 (SE = 0.033) for these women and, for the remaining 65% of women, a mild depression utility decrement of 0.250 (SE = 0.027).

After 12 months, underlying utility levels were decremented by applying a utility multiplier of 0.880 (SE = 0.011). This value was elicited by a study using the time trade-off technique in 279 pregnant women and reflected long-term preferences for a health state where the loss of a baby with a genetic anomaly was followed by a repeat pregnancy and the birth of a healthy baby 2 years later.[246] While some women recover in the years immediately following their stillbirth, others endure symptoms for longer; a recent systematic review suggested at least 4 years. The utility multiplier was thus applied within the model for 5 years.[182] All utility decrements/multipliers were implemented within the model using beta distributions.

Adjustments to underlying levels of maternal utility within the second-trimester termination Markov model

We maintained the utility decrements assigned to women having a second-trimester termination in the decision tree model (for a duration of 20 weeks), for the first 32 weeks in the second-trimester maternal Markov model. Beyond this, the health related quality of life impact was estimated using studies exploring women's responses to pregnancy termination for fetal anomaly.[38,40] Davies *et al.* reported that at 12 months, 41% (*n* = 9/22) of women were suffering with PTS/psychiatric disorders.[40] Korenromp *et al.* found that at a mean time since termination of 4.1 years (range 2–7 years), PTS remained the most prevalent condition, with 17.3% of 254 women reporting pathological PTS scores (> 39 on the revised IES).[38] We used the data from Davies *et al.* (propagated using a beta distribution) for the proportion of women experiencing psychological symptoms at 12 months following a termination. Informed by Korenromp *et al.* we assumed that after 5 years utility levels would have recovered. This was implemented assuming a downward linear trend in the proportion of women with psychological problems between years 2 and 5 of the model.

A published EQ-5D score reported for a cohort of individuals with PTS disorder was used as a multiplier to decrement underlying utility levels for the proportion of women suffering symptoms each year.[285] This published score, (mean 0.63, SE = 0.013) was estimated by applying the US tariff to responses on the three-level version of the questionnaire, and was implemented in the model using a beta distribution.[286]

Whether, over the longer term, a second-trimester termination exerts a sustained additional detrimental impact upon a woman's utility as compared to a first-trimester termination is unclear. In a comparison by Davies *et al.* women having a second-trimester termination had significantly higher levels of PTS at 6 weeks; levels also remained higher at 6 and 12 months *albeit* not significantly so.[40] Grief also appeared higher in women having a second-trimester termination, but

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not significantly so. In contrast, levels of maternal grief in the years following termination, were significantly associated with increasing GA at termination in the study by Korenromp *et al.*, as were women's feelings of doubt about the decision to terminate.[38] A trend toward increased PTS was also observed.

Given these data, we included an additional 'longer-term' utility decrement for women who had undergone a second-trimester termination. In the absence of data to inform this parameter, we implemented a small decrement, using a uniform distribution with minimum and maximum values of 0 and 0.01 respectively. This was maintained over the Markov model's 20-year time horizon.

Adjustments to underlying levels of maternal utility within the second-trimester iatrogenic fetal loss Markov model

We could identify no studies assessing the longer-term psychological impact for mothers suffering an iatrogenic fetal loss following genetic testing. One small Canadian study included 14 women who had lost their babies following CVS or amniocentesis.[287] The women completed the Centre for Epidemiological Studies-Depression Scale (revised) (CED-D) recalling how they felt 1 week after the loss of their baby, but the authors also noted from additional comments provided that 'time had not softened the pain' suggesting a possible sustained psychological impact. Like women who have undergone a termination, women suffering an iatrogenic loss reported feelings of guilt, anger, and blamed themselves for taking a risk.

We maintained the utility decrements assigned to women in the decision tree model suffering an iatrogenic loss in the second trimester (a duration of 20 weeks), for the first 32 weeks in the Markov model. Beyond this, we applied the same utility decrement assumptions made for women undergoing a second-trimester termination (see above).

Adjustments to underlying levels of maternal utility within spontaneous miscarriage Markov model

A systematic review assessing the impact of miscarriage, identified several studies showing women's levels of anxiety and depression generally return to population norm levels between 6 months and 1 year.[194] We assumed that of the 30% of women estimated to suffer moderate anxiety and depression in the 24 weeks following a miscarriage, half would still have moderate anxiety and depression for the first 28 weeks in the Markov model. For these women we again assumed a utility decrement for moderate depression of 0.355 (SE = 0.033). Beyond 28 weeks and for the remaining 20-year time horizon of the model, we assumed no further utility decrement.

Adjustments to underlying levels of maternal utility within the first-trimester termination Markov model

For women who had undergone a first-trimester termination, utility was adjusted in the same way as for women undergoing a second-trimester termination, less the additional utility decrement assigned following termination at a more advanced GA.

Adjustments to underlying levels of maternal utility within the first-trimester iatrogenic fetal loss Markov model

For women suffering a first-trimester iatrogenic fetal loss with genetic testing, utility was adjusted in the same way as for women suffering the same event in the second trimester, less the additional utility decrement assigned following the loss of a baby at a more advanced GA.

Estimation of longer-term costs within the maternal Markov models for each pregnancy outcome

Maternal healthcare costs: live birth Markov models

As with the modelling of utility, we assumed the impact upon a woman's mental health and thus her need for treatment would depend upon whether her baby had been born with an anomaly, and if so, the implications of that anomaly for the child's prognosis and survival. For a woman suffering the loss of her child during a model cycle (determined using the infant annual mortality rates shown in *Appendix 9*), we used data from the published literature to estimate the likelihood of psychological symptoms reaching levels that were clinically significant enough to warrant medical intervention.

Meert *et al.* studied 138 parents who had suffered the loss of a child in a paediatric intensive care unit (ICU).[288] At 6 months, 59% (*n* = 82/138) were classified as suffering from complicated grief using the Inventory of Complicated Grief (ICG score > 30).[289] At 18 months, the percentage was 38% (*n* = 53/138). These data were used within each of the live birth maternal Markov models, for the proportion of women experiencing significant psychological symptoms in the first and second years following the death of a child (see *Table 48*, *Appendix 8*). Given the uncertainty around the duration for which such symptoms persist, we used the same parameter developed to represent uncertainty around the duration (in years) required for a mother's quality of life to recover to underlying norm values following the death of her infant (see *Table 47*). For each value sampled from this distribution, we assumed a constant annual rate of reduction in the proportion of women affected by complicated grief at 2 years.

As for costs in the decision tree, we assumed not all women with significant psychological symptoms would have engaged with the healthcare system and would be receiving treatment (see *Table 48*).[193] The expected annual cost of such care when given was again assumed to be £2440, as described in the section on decision tree costs in *Chapter 10* of the main report.

Given the lethality of acrania and alobar holoprosencephaly, costs modelled for all women giving birth to babies with these conditions were as described above for mothers suffering the loss of their child. A maternal Markov model for a live birth with body stalk anomaly was not required for the analysis (see section on Markov model utilities above).

Mothers not suffering the loss of their infant during a model cycle, may still suffer distress as a result of the psychological, practical and economic challenges associated with raising a child born with a major congenital anomaly.[272–274] As for utilities, such determinations were made by anomaly type, and are described in the following subsections. In all maternal Markov models, for mothers predicted to have clinically significant negative psychological symptoms each year, we again assumed that a proportion (64.5%) would seek help and receive treatment at an expected cost of £2440 per annum (see *Table 48*).

Maternal healthcare costs: non-lethal structural anomalies with a genetic anomaly

For mothers of babies with a non-lethal structural anomaly co-existing with a genetic anomaly (a major cardiac anomaly, an omphalocele, an encephalocele or a LUTO), we again assumed that the genetic anomaly would exert the greater impact. Published studies have shown the quality of life and mental health of mothers of young children with Down syndrome to be significantly impaired when compared to matched controls.[274,290] Swanepeol *et al.* reported that among 30 mothers of children with Down syndrome with a mean age of 6 months, 8 (26.7%) met the criteria for major clinical depression on the EPDS. We used this estimate for the proportion of mothers of children with a genetic anomaly experiencing significant psychological symptoms each year (see *Table 48*). Given the permanence of the condition, this proportion remained fixed during each Markov model cycle.

Maternal healthcare costs: non-lethal structural anomalies without a genetic anomaly

As discussed previously, the five non-lethal anomalies within the protocol (a major cardiac anomaly, an omphalocele, an encephalocele, a LUTO and gastroschisis) are usually managed surgically following birth and this places a considerable burden upon mothers.[273,275] Solberg *et al.* in studying mothers of infants born with a severe cardiac anomaly found that at 6 months following delivery, 30% (*n* = 22/73) had reached thresholds defined for moderate depression on the EPDS.[279] In the absence of comparable data for the other 'surgical' anomalies, this estimate was used for the proportion of mothers suffering with significant depression in the first year following birth of a baby with an isolated major cardiac anomaly, an omphalocele, LUTO or gastroschisis (see *Table 48*).

As for utilities, we assumed such symptoms in mothers of infants with a major cardiac anomaly, an omphalocele or gastroschisis, would diminish at a constant rate over 3 years. For isolated LUTO, we used the same assumptions but beyond 4 years we assumed that all mothers whose infants develop renal failure leading to dialysis and kidney transplant (5.6% per year out to 6 years) would be affected by clinically significant levels of depression.[268,269]

For mothers of the 40% of infants with an isolated encephalocele and no neurodevelopmental disability, costs were estimated as described for isolated major cardiac anomalies, omphalocele and gastroschisis.[267] For mothers of infants with encephalocele and neurodevelopmental disability, we assumed the proportion with clinically significant

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TABLE 48 Parameters used to estimate annual costs in the live birth Markov models for each anomaly and for a live birth without an anomaly

Parameter	Mean (SE)	Distribution type	Parameters	Source
Proportion of women who suffer the loss of their infant and who develop levels of psychological symptoms significant enough to warrant healthcare intervention				
Probability of significant maternal psychological symptoms in the first year following the death of an infant	0.594 (0.042)	Beta	α = 82, β = 138−α	Meert *et al.* 2011[288]
Probability of significant maternal psychological symptoms in the second year following the death of an infant	0.384 (0.041)	Beta	α = 53, β = 138−α	Meert *et al.* 2011[288]
Years taken for a mother's clinically significant negative psychological symptoms following the death of a child to diminish	12.500 (4.317)	Uniform	Min = 5 years Max = 20 years	Author assumption
Probability of symptom diagnosis and annual cost of treatment				
Probability of psychological symptoms being diagnosed and treated by a medical professional	0.645 (0.055)	–	α = 49, β = 76−α	McCrone *et al.*[193]
Annual cost of treatment given for significant psychological symptoms	2440.17	–	–	McCrone *et al.*[193] Jones and Burns 2021[192]
Proportion of women raising an infant with an anomaly and who develop levels of psychological symptoms significant enough to warrant healthcare intervention				
Annual probability of significant psychological symptoms in mother of a child with a genetic anomaly or a neurodevelopmental disability. Years 1–20.	0.267 (0.079)	Beta	α = 8, β = 30−α	Swanepoel *et al.* 2018[274]
Probability of significant psychological symptoms in mother of a child with a structural anomaly only. Year 1[a]	0.301 (0.053)	Beta	α = 22, β = 73−α	Solberg *et al.* 2011[279]
Proportion of mothers of a child with LUTO suffering significant psychological symptoms from Year 4 onwards	0.056[a] model cycle number	–	–	Biard *et al.* 2005[268,269] Berte *et al.* 2018[71]

a The probability is reduced by a constant amount in years 2 and 3 and, by year 4, takes on a value of 0 (i.e. there are no women suffering with clinically significant levels of psychological symptoms).

psychological symptoms each year to be the same as for women raising an infant with a genetic anomaly (26.7%, *Table 48*).[274]

Maternal healthcare costs: genetic anomaly alone

In the Markov model for a live birth with a genetic anomaly alone, we again assumed the proportion of women reaching clinically significant levels of depression each year to be 26.7%.[274]

Maternal healthcare costs: no congenital anomaly

For women giving birth to babies unaffected by a congenital anomaly, costs were estimated based upon the proportion of women estimated to suffer with postnatal depression each year (see the corresponding Markov model utility section above and *Table 48*).

Maternal healthcare costs: stillbirth Markov model

As for utilities, 35% of women (inferred n/N = 166/473) were assumed to experience significant psychological symptoms in the year following a stillbirth.[181,182] Symptoms were modelled as diminishing year on year at a constant rate such that by 5 years no women would be in need of treatment.[191]

Maternal healthcare costs: second-trimester termination Markov model

To estimate longer-term costs following a second-trimester termination we assumed the same annual proportions of women with significant psychological symptoms each year as used when estimating longer-term utilities following this outcome.

Maternal healthcare costs: second-trimester iatrogenic fetal loss with genetic testing Markov model

The psychological impact for mothers of a second-trimester iatrogenic fetal loss with genetic testing and the associated costs were estimated, as for a second-trimester termination.

Maternal healthcare costs: spontaneous miscarriage Markov model

Following a miscarriage, costs were estimated based on the assumption that 15% of women would still be suffering with moderate anxiety and depression for the first 28 weeks in the Markov model (see Markov model utility section above). Thereafter we assumed no further costs.

Maternal healthcare costs: first-trimester termination and iatrogenic fetal loss Markov models

Within the Markov model, costs following first-trimester terminations and iatrogenic fetal losses with genetic testing were estimated in the same way as for second-trimester terminations and iatrogenic fetal losses.

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Appendix 9 Methods and parameters used to populate the infant Markov models for live births with each anomaly type and without any anomaly

Annual infant mortality risks

This section details the estimation of annual infant mortality risks used within the anomaly-specific infant Markov models to model transitions between the infant alive and deceased health states. The same infant mortality risks were also used to link infant outcomes to those of mothers when modelling maternal QALYs for the analysis (see *Appendix 8* for details). Estimates were informed by studies included in the project's systematic reviews as well as other published studies identified by running free-text searches for papers reporting on survival, prognosis or mortality for each anomaly type. Shown in *Tables 49* and *50*, these data were used deterministically within the model.

Live birth with a major cardiac anomaly

Few data were identified on the long-term survival profiles of cohorts of individuals born specifically with a major cardiac anomaly (with no accompanying genetic anomaly). Annual mortality risks out to 20 years were thus estimated by combining the survival data reported in a large population-based study of congenital anomalies reported by Tennant *et al.* for the main major cardiac anomaly categories identified by NCARDRS.[86,265]

For infants born with a major cardiac anomaly and a genetic anomaly, it was not possible to determine the incremental impact of the presence of the genetic anomaly upon infant survival. Analyses of data published by Tennant *et al.* suggested prognosis was poorer for infants born with a major cardiac anomaly, than for those born with a chromosomal anomaly.[265] Within the Markov model for infants born with a major cardiac and a genetic anomaly, we used the same annual mortality risks as used for infants with a major cardiac anomaly without genetic involvement.

Live birth with acrania/exencephaly/anencephaly

Acrania is a lethal anomaly with all infants born with the condition dying soon after birth as shown in column 4 of *Tables 49* and *50*.[264]

Live birth with omphalocele/exomphalos

Based upon data reported by Springett *et al.* it was assumed that 8% of women giving birth to a baby with omphalocele/exomphalos without a genetic anomaly would suffer the loss of their child during the first year following birth.[292] With data from a number of studies showing no further deaths from the condition beyond the first year, infants with the condition surviving the first year were assumed to face general population mortality risks.[265,291,293]

For infants born with an omphalocele/exomphalos and a genetic anomaly, prognosis during the first year is poor, as the prominent associated genetic anomalies are trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome).[294] Infant mortality during the first year was modelled at 73.3% as reported by Springett *et al.*[292] Thereafter we used the mortality risk reported by Tennant *et al.* for chromosomal anomalies from year 2 onwards.[265]

Live birth with gastroschisis

Around 4% of infants born with gastroschisis were assumed to die during the first year of life.[295] With a number of studies showing no further deaths in infants with the condition after the first year, from year 2 onwards, infants born with gastroschisis were assumed to face general population mortality risks.[265,277]

Live birth with alobar holoprosencephaly

Like acrania, alobar holoprosencephaly is a lethal anomaly, with no infants born with the condition surviving beyond the neonatal period.[232]

TABLE 49 Annual mortality risks for infants born with various structural anomalies

Year (Infant age)	Annual probability of infant death with major cardiac anomaly[a,b]	Source	Annual probability of infant death with acrania	Source	Annual probability of infant death with omphalocele (no genetic anomaly)	Source	Annual probability of infant death with omphalocele (with genetic anomaly)	Source	Annual probability of infant death with gastroschisis	Source	Annual probability of infant death with alobar holoprosencephaly	Source	Annual probability of infant death with LUTO (no genetic anomaly)	Source	Annual probability of infant death with LUTO (with genetic anomaly)	Source
1	0.1578		1.000		0.0809	Springett *et al.* 2014[298]	0.7333	Springett *et al.* 2014[298]	0.0399	Bradnock *et al.* 2011[299]	1.000		0.2292	Malin *et al.* 2012[301]{Malin, 2012 #43}	0.2292	Malin *et al.* 2012
2	0.0072		NA		0.0002		0.008		0.0002		NA		0.0002		0.008	
3	0.0072		NA		0.0001		0.008		0.0001		NA		0.0001		0.008	
4	0.0073		NA		0.0001		0.008		0.0001		NA		0.0001		0.008	
5	0.0073	Estimated from data in Tennant *et al.* 2010[265]	NA		0.0001		0.008		0.0001		NA		0.0001		0.008	
6	0.0008		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
7	0.0008		NA	Baird and Sadovnick 1984[271]	0.0001	Office for National Statistics 2017–9[291]	0.002		0.0001	Office for National Statistics 2017–9[291]	NA		0.0001	Office for National Statistics 2017–9[291]	0.002	
8	0.0008		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
9	0.0008		NA		0.0001		0.002	Tennant *et al.* 2010[265]	0.0001		NA		0.0001		0.002	
10	0.0008		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
11	0.0020		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
12	0.0020		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
13	0.0020		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
14	0.0020		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
15	0.0020		NA		0.0001		0.002		0.0001		NA		0.0001		0.002	
16	0.0025		NA		0.0001		0.001		0.0001		NA		0.0001		0.001	
17	0.0025		NA		0.0002		0.001		0.0002		NA		0.0002		0.001	
18	0.0025		NA		0.0002		0.001		0.0002		NA		0.0002		0.001	
19	0.0025		NA		0.0003		0.001		0.0003		NA		0.0003		0.001	
20	0.0025		NA		0.0003		0.001		0.0003		NA		0.0003		0.001	

NA, not applicable.
a Estimated by synthesising survival data reported by Tennant *et al.* for the main types of cardiac anomaly identified by NCARDS as 'major'.
b Also used to model mortality risk for infants born with this structural anomaly and a genetic anomaly.

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TABLE 50 Annual mortality risk for infants born with various structural anomalies

Year (Infant age)	Annual probability of infant death with encephalocele (no genetic anomaly)	Source	Annual probability of infant death with encephalocele (with genetic anomaly)	Source	Annual probability of infant death with body stalk anomaly	Source
1	0.3570	Estimated from data in Tennant *et al.* 2010 and Office for National Statistics 2017–9[265,291]	0.3570	Estimated from data in Tennant *et al.* 2010[265]	N/A	NA
2	0.0556		0.0556		N/A	
3	0.0589		0.0589		N/A	
4	0.0626		0.0626		N/A	
5	0.0667		0.0667		N/A	
6	0.0001		0.0022		N/A	
7	0.0001		0.0022		N/A	
8	0.0001		0.0022		N/A	
9	0.0001		0.0022		N/A	
10	0.0001		0.0022		N/A	
11	0.0001		0.0020		N/A	
12	0.0001		0.0020		N/A	
13	0.0001		0.0020		N/A	
14	0.0001		0.0020		N/A	
15	0.0001		0.0020		N/A	
16	0.0001		0.0008		N/A	
17	0.0002		0.0008		N/A	
18	0.0002		0.0008		N/A	
19	0.0003		0.0008		N/A	
20	0.0003		0.0008		N/A	

N/A, not applicable.
a Estimated by synthesising survival data reported by Tennant *et al.* for the main types of cardiac anomaly identified by NCARDS as 'major'.
b Also used to model mortality risk for infants born with this structural anomaly and a genetic anomaly.

Live birth with lower urinary tract obstruction

For infants born with LUTO, mortality during the first year was informed by Malin *et al.* 2012 who observed 22 deaths (all during the 28-day neonatal period) among 96 live births (23%).[185] A small number of studies conducting longer-term follow-up of infants (between 12 and 20 years) reported few or no further deaths beyond the neonatal period and so within the model, between years 2 and 20, we assumed general population age-adjusted annual mortality risks.[86,265,296]

For infants born with LUTO and a genetic anomaly, mortality during the first year was again informed by Malin *et al.* 2012 (n = 22/96, 23%).[185] Thereafter, annual mortality risks were estimated from data reported by Tennant *et al.* for infants born with chromosomal anomalies.[265]

Live birth with encephalocele

Annual mortality risks for infants born with encephalocele were estimated using survival data reported by Tennant *et al.*[265] A number of studies with long-term follow-up showed no further deaths to occur in infants with encephalocele who survived surgery and the earlier years of life and so within the model, between years 6 and 20, we assumed general population age-adjusted annual mortality risks.[86,265,282]

For infants born with encephalocele and a genetic anomaly, it was not possible to determine the incremental impact of the presence of the genetic anomaly upon infant survival. Analyses of data published by Tennant *et al.* suggested prognosis was poorer for infants born with an encephalocele, than for those born with all types of chromosomal anomaly. We therefore used the same annual infant mortality risk as used for infants with an encephalocele without genetic involvement up to year 6 within the model (see *Tables 49* and *50*). Between years 6 and 20 we assumed mortality risks estimated using data from Tennant *et al.* for infants born with a chromosomal anomaly.[265]

Live birth with body stalk anomaly

No live births were predicted by the model for babies affected by body stalk anomaly.

Live birth with genetic anomaly only

In addition to the structural anomalies described above, the decision tree model also allows for a live birth outcome where the infant is affected by a genetic anomaly without any structural involvement. Within the Markov model for this live birth outcome, the annual infant mortality risks used were based upon data reported by Tennant *et al.* for survival of infants born with chromosomal anomalies – see *Table 51*.[265]

Live birth of infant without an anomaly

For the majority of women in the model, the pregnancy will end with the live birth of a baby without a congenital anomaly. Following this birth outcome, we assumed general population annual infant mortality risks drawn from National Life Tables for England and Wales and averaged across males and females (see *Table 51*).[86]

Parameters for estimating infant quality-adjusted life-years and healthcare costs

Underlying utility levels for infants between birth and 20 years were informed by HUI3 reference scores reported for a population of Canadian children.[199] In the absence of utility data for very young children, we assumed the mean score reported for infants between 5 and 12 years would also reflect underlying utility in children below the age of 5 years. These scores were entered into the models using beta distributions with parameters as shown in *Table 52*.

The following sections describe how these underlying levels were adjusted to take account of the impact of each type of anomaly upon a child's quality of life, as well as how the resulting utilities were used to weight predicted life expectancy to facilitate the calculation of QALYs. Also detailed is the estimation of infant costs with each anomaly.

Major cardiac anomaly – without genetic anomaly

Utility was decremented most heavily during the first 2 years of life when infants born with a major cardiac anomaly will undergo major corrective surgeries, investigations and close monitoring. The utility decrement used (mean 0.445, SE = 0.074, beta distribution) was estimated using the HUI3 instrument for 44 children with cardiovascular disease, by Petrou and Kupek.[200] The full decrement was applied during year 1 and half of the decrement was applied in year 2 as surviving infants recover from surgery and their quality of life improves. Thereafter, we switched to using an absolute utility score of 0.8284 (SE = 0.0168) reported by Hunter *et al.* to reflect average quality-of-life levels in infants surviving repair of TOF, which is one of the main anomalies under the umbrella heading of major cardiac anomalies.[298] This parameter was entered as a beta distribution, and was applied to infants surviving each year over the model's remaining 20-year time horizon.

Costs in the first year of life were also informed by Hunter *et al.* who reported detailed resource use relating to a first repair of TOF in 30 babies treated at Great Ormond Street Hospital in the UK.[298] Resource use covered the period between birth and surgery and included investigations, inpatient days on ICU, high dependency unit (HDU), and general wards, pre-operative assessment and outpatient clinic attendances. The mean (SE) counts for each of these variables were entered into the model using gamma distributions and were costed using national unit costs before being summed to give a pre-surgery cost[299,300] – see *Table 53*. The cost for the index surgery per se reported by Hunter *et al.* was inflated to 2019–20 prices, giving a cost estimate of £27,128 (SE = £3381), also entered into the model using a gamma distribution (see *Table 53*).

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TABLE 51 Annual mortality risks for infants born with a genetic anomaly only and with no congenital anomaly

Year (infant age)	Annual probability of infant death with genetic anomaly only[a]	Source	Annual probability of infant death without a congenital anomaly[b]	Source
1	0.1715	Estimated from data in Tennant *et al.* 2010	0.0039	Office for National Statistics 2017–9
2	0.008		0.0002	
3	0.008		0.0001	
4	0.008		0.0001	
5	0.008		0.0001	
6	0.002		0.0001	
7	0.002		0.0001	
8	0.002		0.0001	
9	0.002		0.0001	
10	0.002		0.0001	
11	0.002		0.0001	
12	0.002		0.0001	
13	0.002		0.0001	
14	0.002		0.0001	
15	0.002		0.0001	
16	0.001		0.0001	
17	0.001		0.0002	
18	0.001		0.0002	
19	0.001		0.0003	
20	0.001		0.0003	

a Based on survival data reported by Tennant *et al.* for infants born with a chromosomal anomaly.[265]
b Based upon national life table data reported by the Office for National Statistics.[297]

TABLE 52 Mean population norm utility scores used within the infant Markov models[199]

Age (years)	*n*	Mean	SD	Distribution type and parameters used in model
5–12	538	0.92	0.11	Beta, mean = 0.92, SE = 0.0047
13–15	391	0.90	0.15	Beta, mean = 0.90, SE = 0.0076
16–19	469	0.85	0.18	Beta, mean = 0.85, SE = 0.0083
20–24	422	0.85	0.18	Beta, mean = 0.85, SE = 0.0088

The same authors reported on ongoing healthcare contacts for surveillance of children during the first and second decades following their index surgery. We entered into the model, data on mean (SE) numbers of surveillance contacts including echos, magnetic resonance imagings (MRIs), electrocardiograms (ECGs), 24 hours ECGs, and cardiac catheterisations using gamma distributions. Contacts were costed using national unit costs before being divided through by 10 to give an annual cost per year – see *Table 53*.[299]

TABLE 53 Treatment and surveillance costs (2019/20 UK£) used in the infant Markov model for major cardiac anomaly

Cost type	Parameter estimate (£)	Distribution and parameters
Cost between birth and index surgery for major cardiac anomaly	19,274	Gamma, various[a]
Cost of index surgery for major cardiac anomaly	27,128	Gamma, mean = £27,128, SE = £3381
Annual surveillance costs for infants with major cardiac anomaly during the first decade after birth	45.63	Gamma, various[a]
Annual surveillance costs for infants with major cardiac anomaly during the second decade after birth	241.44	Gamma, various[a]

a Cost estimate is an aggregate of individual resource use components from Hunter *et al.* each entered into the model using gamma distributions.

In their retrospective study of 1220 infants who had undergone an index surgery for a congenital heart defect in Southampton, UK, Monro *et al.* reported for each type of major cardiac anomaly, the proportion of infants requiring further surgery.[301] These proportions were applied to the number of cases of each type of major cardiac anomaly reported by Tennant *et al.* so as to estimate a weighted average probability of re-operation for the group of major cardiac anomalies as a whole.[265] The resulting proportion (0.216) was entered into the model using a beta distribution with $\alpha = 262$, $\beta = 1214 - \alpha$. Within the model, this estimate was converted into an annual probability and multiplied by the same surgery cost as used to cost an index procedure (£27,128, SE = £3381).[298]

In addition to these costs, also included in the model were deterministic average age-specific NHS spending costs per annum obtained from the Office for Budget Responsibility and shown in *Table 54*.[301]

Major cardiac anomaly – with genetic anomaly

Underlying utility was adjusted using a decrement estimated by Petrou and Kupek for children with Down syndrome in the UK.[200] The decrement of 0.566 (SE = 0.062) was entered into the model using a beta distribution, and given the permanence of a genetic condition, was applied for each year a child spent in the live health state of the model.

Costs included were as for the infant Markov model developed for a major cardiac anomaly without a genetic anomaly, but with the addition of extra healthcare provision for an infant with a genetic anomaly. The costs of such care were informed by an Australian study in which 361 families of a child/young adult with Down syndrome completed a questionnaire asking about healthcare resource use including hospital, medical, pharmaceutical, community and respite care, over the previous year.[303] Mean annual costs reported by age group in 2009 $AUD were converted into UK£ using Purchasing Power Parities (PPPs) before being inflated to 2019–20 prices.[300,304] *Table 55* shows these costs, which were entered into the model as point estimates as measures of variability/uncertainty were not reported.

Acrania/exencephaly/anencephaly

Registry data on the survival of a cohort of 181 infants born with acrania in Canada showed 58% of infants died within the first 24 hours, 85% had died within 3 days, and there were no survivors beyond 14 days.[264] The infant Markov model for acrania thus cycled on a daily basis, with the daily probability of death informed by these data shown in *Table 56*. We assumed zero utility for these infants and set daily costs for the live health state equal to the per diem cost for neonatal intensive care (£1708) in the 2019/2020 National Schedule of NHS Costs.[299]

Omphalocele/exomphalos – without genetic anomaly

Omphalocele is largely managed surgically following birth, and evidence suggests that after a period of short-term morbidity, the longer-term outlook is positive with levels of quality of life similar to that of peer controls.[276,305] On this basis, we reduced underlying utility during the first 2 years of life only using a decrement estimated by Petrou and Kupek using HUI3 responses from 24 children with liver and digestive disorders.[200] The decrement of 0.350 (SE = 0.085)

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TABLE 54 Annual NHS expenditure by age

Infant age (years)	Annual NHS expenditure
0	3000
1	2833
2	2667
3	2500
4	2333
5	2167
6	2000
7	1800
8	1600
9	1400
10	1200
11	1000
12	960
13	920
14	880
15	840
16	800
17	825
18	850
19	875

TABLE 55 Annual healthcare costs for infants born with a genetic anomaly[303]

Infant age (years)	Mean annual cost (£UK, 2019/2020)
0–4	5037
5–9	2496
10–14	1808
15–19	1594

was entered into the model using a beta distribution and applied fully during year 1 and at 50% in year 2 as surviving infants recover from surgery and their quality of life improves. Beyond 2 years, no further decrements to utility were made.

We could not identify any studies providing detailed resource use estimates for surgical treatment of omphalocele during the early years of life. One study of neonates undergoing surgery at a tertiary neonatal unit in England did report length of hospital stay data (by level of care) for 12 infants with omphalocele/exomphalos but the costs of the surgery per se were not included.[306] Median length of stay rather than mean was reported and so a statistical formula was used to approximate the mean total length of stay from the median, range values and the sample size.[307] Using these data, the proportion of the total mean length of stay in ICU, HDU, and special care was inferred and costed using assuming

TABLE 56 Daily mortality risks for infants born with acrania[264]

Day	Daily probability of death, (*n*/*N*)
0	0.575 (104/181)
1	0.455 (35/77)
2	0.357 (15/42)
3	0.333 (9/27)
4	0.278 (5/18)
5	0.308 (4/13)
6	0.556 (5/9)
7	0.500 (2/4)
8	0.500 (1/2)
9–13	0.000
14	1 (1/1)

£1708 per day for neonatal ICU, £1059 per day for neonatal HDU, and £536 per day for special care.[299] Summing expected costs for each level of care produced an estimate of £33,518, which was assigned deterministically to infants during the first year of the model.

Studies suggested that beyond the first year, some infants born with omphalocele required further surgery, the types of which were similar to additional surgical procedures seen in infants born with gastroschisis; for example inguinal hernia procedures.[276,277] On this basis, we used data reported in a study of 93 gastroschisis infants to estimate the proportion of additional surgeries required during the first 5 years of life.[308] In that study, 21 of 93 (22.6%) infants had subsequent surgery and this proportion was entered into the model using a beta distribution and then converted into an annual probability. Costs for the various types of procedures recorded were obtained from the National Schedule of NHS Costs and were used to estimate a weighted average cost for an additional surgery (£1917) which was entered into the model as a point estimate and was assigned to the proportion of infants predicted to undergo additional surgery each year. In addition to these costs, also included in the model were average age-specific NHS spending costs per annum shown in *Table 54*.[302]

Omphalocele/exomphalos – with genetic anomaly

Underlying utility was adjusted using the utility decrement estimated by Petrou and Kupek for infants with Down syndrome in the UK.[200] The decrement of 0.566 (SE = 0.062) was entered into the model using a beta distribution, and was used to reduce underlying utility for each year a child spent in the alive health state.

As noted above, for infants born with an omphalocele/exomphalos and a genetic anomaly, prognosis during the first year is poor (see *Tables 49* and *50*). When estimating costs for the first year in the model therefore, we calculated a weighted average cost across the 73% of infants expected to die, and the 27% who will survive.[292] For the former, we assumed that the deaths all occurred in infants with trisomy 18, and used survival data from a UK registry study by Wu *et al.* of all births with trisomy 18 in England between 2004 and 2011 to determine the proportion of infants that died within 1 week, 1 month, 3 months and by 12 months.[294] Taking the midpoint of each time period in days as an estimate of expected survival time, we assumed that infants would have remained in neonatal intensive care up until the point of death and costed this time accordingly (using a cost per NICU bed day of £1708).[299] The resulting expected cost estimate of £44,573 was entered into the model as a point estimate. For infants surviving the first year we assumed the same first year costs as estimated for infants born with an omphalocele/exomphalos without any genetic involvement (£33,518) and added in the cost of a year of extra healthcare provision for an infant with a genetic anomaly (see *Table 55*). These first-year costs for survivors and non-survivors were then weighted by their appropriate probabilities to generate a weighted average cost for the first year of the model.

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For infants surviving beyond the first year, we used the same annual costs as described above for infants born with omphalocele/exomphalos without a genetic anomaly and again added the annual costs of healthcare provision for an infant with a genetic anomaly (see *Table 55*).

Gastroschisis

As with isolated omphalocele, data from the literature suggest that from year 2 onwards (and following surgical repair), levels of health-related quality of life in infants born with gastroschisis are unlikely to differ significantly from levels in infants born without the condition.[277,278] On this basis, utility for infants with gastroschisis was modelled as described above for omphalocele/exomphalos without a genetic anomaly.

Costs in the first year of life were estimated using data from a retrospective cost analysis of inpatient hospital stay data reported for 93 infants treated for gastroschisis at the Centre for Paediatric Surgery in Southampton, UK, between 1996 and 2005.[308] For each infant in that study, data were extracted on the level of neonatal unit care (ICU, HDU, and special care) received and associated length of stay, as well as on days spent on a paediatric ward. Bed days were costed using appropriate national tariffs in 2005 UK £. Surgery costs were not included as the authors noted that they form only a small proportion of total costs. For the modelling presented here, the reported mean cost estimate across all patients was inflated to 2019–20 UK £ and assigned to the first year of the Markov model.[300] This value (£65,634) was entered as a point estimate.

Costs for subsequent years were estimated as for costs for subsequent years in the infant Markov model developed for omphalocele without a genetic anomaly (see above).

Alobar holoprosencephaly

Like acrania, alobar holoprosencephaly is a lethal anomaly with the majority of women choosing termination. Bullen *et al.* reported just one live birth of a baby with alobar holoprosencephaly out of 18 with the condition in a population-based congenital anomaly register in the North of England between 1985 and 1998.[232] The infant died 9 days following birth. The model for alobar holoprosencephaly was thus developed to cycle on a daily basis. Infants born with the condition were assumed to remain alive until day 9. We again assumed zero utility for these infants and set daily costs for the live health state equal to the per diem cost for neonatal intensive care (£1708) in the 2019–20 National Schedule of NHS Costs.[299]

Lower urinary tract obstruction – without genetic anomaly

During the first 6–10 years following birth, around one-third of infants born with LUTO may develop chronic renal failure leading to end-stage renal disease and need for renal dialysis and ultimately, kidney transplantation.[268,269] We assumed renal failure leading to end-stage renal disease occurred at a constant annual rate over the first 6 years of the model (approximately 5.6% per year), and reduced the underlying utility of these infants by 0.332 (SE = 0.104) (beta distribution) – the utility decrement estimated for children with renal disease by Petrou and Kupek.[200] We assumed dialysis for a year prior to kidney transplantation (see below section on costs). Following transplant, we reduced the quality-of-life decrement by a half to reflect the likelihood of some ongoing morbidity for example if the kidney is rejected, there are complications of long-term immunosuppressant therapy, an increased number of infections (such as urinary tract infections) or continuing poor bladder function.[284] For infants with LUTO and good renal functioning, we assumed age-adjusted general population utility levels in line with evidence from the published literature.[268]

To determine costs during the first year of the model and informed by Malin *et al.* we estimated the number of infants undergoing valve resection to remove the obstruction during the first year of life (n = 39/42, 93%) and the number receiving vesicotomy followed later by valve resection (n = 3/42, 7%).[184] These procedures were respectively costed using the national cost estimates for major endoscopic bladder procedures (weighted average of codes LB13C–LB13F, £2627) and intermediate endoscopic bladder procedures (code LB14Z, £995) and a weighted average cost calculated and assigned to all infants in the model.[299] For the proportion of infants who died during the neonatal period (see section on mortality above), we assumed an average survival time of 14 days and costed these days using a neonatal intensive care bed day cost of £1708 taken from the National Schedule of NHS Costs (currency code XA01Z, service code CCU13).[184,299] For infants who survived the first year, we assumed 4 days in neonatal intensive care, and 8.47 days on general wards as reported over 12 months for infants with LUTO in the control arm of the PLUTO trial of

percutaneous vesicoamniotic shunting for LUTO.[309] Neonatal intensive care bed days were costed as described above and ward days at £404 per night (National Schedule of NHS Costs, currency code XA05Z, service code CCU15).

For infants developing end-stage renal failure each year, we assumed 12 months receiving dialysis prior to transplantation.[310] Dialysis was costed assuming three sessions per week at a cost of £237 per session (National Schedule of NHS Costs, weighted average of renal dialysis codes LD01B, LD02B, LD05B, LD06B, LD09B, LD10B, LD11B, LD12B, LD13B), thus giving a total cost of £36,923.[299] Infants were then assigned the cost of a kidney transplantation, estimated to be £20,580 (National Schedule of NHS Costs, weighted average of codes LA01B–LA03B).[299] In the years following transplantation, infants were assumed to start life-long immunosuppression therapy. Based upon NICE guidance, this therapy was assumed to comprise of: induction therapy with basiliximab [20 mg given intravenously in two 10 mg doses and costing £1644 (2015 cost of £1517 inflated to 2020 prices)], and maintenance therapy with tacrolimus [given at a dose of 0.3 mg/kg/day and costing £37 per week (2015 cost of £34 inflated to 2020 prices)] and with mycophenolate mofetil (given at a dose of 1200 mg/m^2) and costing £3.77 per week (2015 cost of £3.48 inflated to 2020 prices).[311]

In the background, and for all surviving infants, we again included NHS annual spending by age.[302]

Lower urinary tract obstruction – with genetic anomaly

For infants with LUTO and a genetic anomaly, underlying utility was reduced by 0.566 (SE = 0.061), a decrement previously estimated for children with Down syndrome.[200] For those developing end-stage renal failure, utility was further reduced using the same approach and decrement used for infants with LUTO without a genetic anomaly.

Costs were estimated as for infants with LUTO and no genetic anomaly, but with the addition of annual healthcare costs for infants with Down syndrome.[303]

Encephalocele – without a genetic anomaly

The risk of neurological disability in surviving infants with encephalocele is high.[267,281,282] Within the model and based upon data reported by Da Silva and colleagues, we assumed 20% of infants (n = 14/70, beta distribution) would be living with permanent severe neurological disability.[267] Underlying utility for these infants was reduced over the model's 20-year time horizon using a decrement for severe learning disabilities/global developmental delay (mean = 0.549, SE = 0.063, beta distribution).[200]

For infants without severe neurological impairment, around 40% (n = 28/70, beta distribution) may still have mild to moderate levels of disability.[267] Underlying utility levels for these infants were reduced using a decrement of 0.510 (SE = 0.060, beta distribution) previously reported for children with learning disabilities.[200] The proportion of infants without any neurological impairment was determined as the residual of those with severe and mild/moderate disabilities. No adjustment was made to underlying utility levels for these children.

For the purposes of costing, we could identify few studies reporting detailed data on the surgical management of cohorts of infants born with an encephalocele. A number of studies described surgical outcomes for small cohorts of infants born with encephalocele but not sufficient detail to estimate the surgical costs associated with the anomaly.[312,313] Based upon studies by Lo *et al.* and Da Silva *et al.*, we made the following assumptions:

- Following birth, and prior to surgery, all infants would undergo magnetic resonance imaging at a cost of £139.62 (National Schedule of NHS Costs, weighted average of MRI imaging codes aged 5 and under RD01C and RD02C).[299]
- Twenty-six per cent (n = 40/155) of affected infants would also suffer with hydrocephalus and in addition to corrective surgery, would require a ventriculo-peritoneal (VP) shunt at a cost of £8825 (National Schedule of NHS Costs, weighted average of Very Major Intracranial Procedures codes for 18 years and under – AA52E, AA52F, AA52G).[299,314]
- Corrective surgery for all infants would be carried out soon after birth (or insertion of a VP shunt) at a cost of £20,419 (National Schedule of NHS Costs, weighted average of Very Complex Intracranial Procedures codes for 18 years and under – AA50D, AA50E, AA50F).[299]
- Additional MRI imaging would be conducted following surgery.

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For infants with encephalocele who do not survive, data suggest most deaths occur within the first week following birth.[265] We assumed these patients would have undergone the above package of care prior to death and included no additional costs.

For surviving infants, and in addition to the above care, it is reported within the NHS Children's NeuroScience Networks Specification Standards, that approximately 30% of VP shunts will require revision within the first year, followed by an annual revision rate of 5% thereafter.[315] Based upon these data, we costed these revision proportions for infants having VP shunts for hydrocephalus and surviving each year using the same cost as used for a primary VP shunt.

In the background, we again included NHS annual spending by age. In addition and for the 60% expected to have some neurological disability, we assumed additional healthcare needs to be similar to those of a child with Down syndrome and costed as describe above.[303]

Encephalocele – with a genetic anomaly

For infants born with an encephalocele and a genetic anomaly, underlying utility was reduced by 0.566 (SE = 0.061), the decrement estimated for children with Down syndrome by Petrou and Kupek.[200] Costs were estimated as for infants with encephalocele without a genetic anomaly, but with the addition of incremental annual costs for infants with Down syndrome.[303]

Body stalk anomaly

The model simulated no live births with the condition.

Genetic anomaly alone

Underlying infant utility levels (see *Table 52*) were adjusted using a utility decrement for Down syndrome [0.566 (SE = 0.061), beta distribution].[200] The decrement was applied over the 20-year time horizon of the Markov model. Costs each year comprised of the average NHS spending costs by age (see *Table 54*) plus the costs for additional healthcare provision for infants with a genetic anomaly (see *Table 55*).

Infant without anomaly

When estimating QALYs we used the underlying utility levels for infants shown in *Table 52*. Costs each year were based only upon the average NHS expenditure costs by age (see *Table 54*).

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