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A clinical and economic evaluation of screening and diagnostic tests to identify and treat women with gestational diabetes: association between maternal risk factors, glucose levels, and adverse outcomes

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Background and Rationale

Diabetes is a metabolic disorder due to defective insulin secretion by pancreatic ß-cells, insulin action, or both. Insulin is a hormone secreted by specialised cells in the pancreas (pancreatic ß-cells) in response to rises in blood glucose levels. Insulin facilitates transfer of glucose from the blood into cells throughout the body for use as fuel, for conversion to other molecules that are involved in metabolic pathways, or for storage. Reduced insulin secretion or resistance to its action will result in hyperglycaemia (high levels of glucose in the blood). Prolonged hyperglycaemia will lead to disturbances in the metabolism of carbohydrate, fat and protein. Diabetes is diagnosed when levels of blood glucose are above a specific threshold.[1]

Normal pregnancy is associated with insulin resistance similar to that associated with type 2 diabetes. The physiological resistance to insulin action during pregnancy becomes apparent in the late second trimester, and insulin sensitivity declines progressively thereafter to term. These changes occur to facilitate the transportation of glucose across the placenta to ensure normal fetal growth and development. The transfer of glucose across the placenta stimulates fetal insulin secretion, and insulin acts as an essential growth hormone.[2] However, if the resistance to maternal insulin action becomes too pronounced, fetal hyperinsulinaemia, accelerated growth and possible organ damage may occur. In normal pregnancy after delivery, maternal pregnancy-associated insulin resistance returns rapidly to normal, and glucose tolerance will usually be normal again within six weeks of delivery.[3]

Gestational diabetes mellitus (GDM) is defined as 'carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy' .[4] GDM therefore includes women with undiagnosed pre-existing diabetes, as well as those for whom the first onset is during pregnancy. Predisposing risk factors for the development of GDM include: advancing maternal age, higher parity, higher body mass index (BMI), Asian, black or middle eastern ethnicity, family history of diabetes, GDM in a previous pregnancy and having had a previous macrosomic (increased birth weight, usually greater than 4kg) infant. Hyperglycaemia is now viewed as a continuum, with continuous associations of maternal glucose levels along the complete distribution being associated with certain adverse effects including increased birth weight and caesarean birth, consequently research is required to determine the appropriate threshold for treatment that is cost effective and strikes an appropriate balance between labelling and treating all or a majority of pregnant women and maximising the potential to reduce adverse perinatal outcomes[5]

GDM is the most common metabolic disorder of pregnancy, affecting up to 7% of pregnancies [6-8] and is associated with increased maternal and perinatal morbidity. Higher maternal pregnancy glucose levels results in greater fetal insulin secretion, which in turn stimulates growth and results in larger and fatter babies and perinatal complications. [9; 10] Specifically, GDM is associated with overgrowth of insulin-sensitive tissue such as adipose tissue, especially around the chest, shoulders and abdomen, which increases the risk of shoulder dystocia, perinatal death, birth trauma [11; 12] and the need for caesarean section.[9; 10] There is also increased risk of hypoxaemia in utero, which can increase the risk of intrauterine death, fetal polycythaemia (too many red blood cells, potentially leading to cerebral infarction), hyperbilirubinaemia (jaundice, potentially leading to Kernicterus) and renal vein thrombosis (blood clot in the kidney vein). At higher levels of maternal glucose and consequent fetal hyperinsulinaemia there is an increased risk of neonatal hypoglycaemia requiring treatment with intravenous fluids. In the longer term the women themselves who experience GDM, and their offspring, are more likely to develop type 2 diabetes [13] and consequent cardiovascular disease,[14 15-18] though the extent to which this reflects genetic or lifestyle predisposition to hyperglycaemia or a direct pregnancy/intrauterine related aetiology is unclear.

The identification of women with gestational diabetes allows treatment which aims to reduce the risk of the adverse outcomes associated with the condition. Two recent randomised trials[19; 20] have demonstrated a beneficial effect in a treated group of women with mild to moderately increased glucose levels compared to an untreated group. Serious perinatal outcomes (composite of death, shoulder dystocia, bone fracture, and nerve palsy) were reduced from 4% to 1% without affecting caesarean birth rate in the Australian Carbohydrate Intolerance trial, [19] however perinatal complications (composite of stillbirth or neonatal death and hypoglycaemia, hyperbilirubinaemia, neonatal hyperinsulinaemia, and birth trauma) were unaffected in a second trial,[20] though infant birth weight and adiposity were reduced as was caesarean birth rate in the treated group.

Screening tools are used to identify risk of disease in a well population, a screening programme for a condition must meet certain criteria, including: that it is an important health problem; that there should be a simple, safe and validated screening test and that a cost-effective treatment is available.[21] The presentation of symptoms normally prompts the use of a diagnostic test; however the aim of a screening test is to identify disease before symptoms are present. Screening may also cause ill effects such as anxiety and this may be compounded by the

risk of false positive results. In the case of GDM, diagnostic tests are also often administered before symptoms are present and this may have contributed to the variation in screening and testing strategies that exist within the UK and internationally. In the UK NICE recommends initial screening by assessment of risk factors at the first pregnancy appointment. Any pregnant woman with one or more risk factor: family history of diabetes; South Asian; black or middle eastern ethnicity; previous history of having a baby with macrosomia; or BMI $\geq$30, should be offered an OGTT between 24 and 28 weeks.[22] In the UK, the two hour 75g OGTT is used to test for GDM and diagnosis made using the World Health Organisation (WHO) criteria.[23]

By contrast, the American Diabetes Association recommend women with risk factors undergo testing (any of: glycated haemoglobin (HbA1c), fasting plasma glucose or OGTT at their first pregnancy appointment to identify undiagnosed type 2 diabetes. In addition all pregnant women (irrespective of risk factors) undergo a diagnostic 75g OGTT at 24-28 weeks. GDM is diagnosed if any one of plasma glucose > 5.0 mmol/l, one hour > 9.9 mmol/l or two hour > 8.4 mmol/l is found.[1]

While screening tools will usually just identify those at risk of an illness, it is the subsequent management of the illness identified by the screening and diagnostic test that ultimately affects health outcomes. 'Screening' is used interchangeably to refer to an individual screening tool, a screening program, protocol or guideline, which includes the screening tool and subsequent management such as diagnostic testing and treatment. By identifying individuals at high and low risk of a particular illness, as in risk factor screening for GDM, a screening tool identifies those who require diagnostic testing and those who do not[24] (see appendix 3 Flow chart 2)

The relatively high and increasing incidence of GDM, its adverse impact on maternal health and perinatal outcomes, the ability to detect it with relatively non-invasive methods and availability of effective treatments has led to the development and implementation of screening programmes in the UK and internationally. However, there is considerable uncertainty about whether and how best to screen and treat GDM. Different populations have varying baseline risk of GDM development and it may be better to target high risk sub-populations. Evidence suggests a continuous association between maternal glucose levels and adverse outcomes[5] therefore there is no obvious threshold above which treatment is indicated and so there is uncertainty about what risk thresholds to use both for screening, diagnosis and consequently treatment. Various screening and diagnostic tests are available which vary in their accuracy, cost and ease of use and acceptability. There is a trade-off between high yield (lower risk threshold) strategies which will have more false positives and greater costs and other more targeted strategies with higher risk thresholds which may identify and treat fewer women, but also miss some women with GDM thereby increasing the risk of adverse outcomes for this group.

NHS policy makers need reliable intelligence on: the best way to identify women who are at risk of GDM or who have GDM; when in pregnancy should screening and/or testing be employed; what screening/testing strategy should be used and what treatment cut-offs provide the most clinical and cost-effective model. This requires an integrated model where the potential positive and negative effects and costs of different approaches can be examined together, exploring the interdependencies and quantifying the uncertainties.

Aims and objectives

The overall aim of this research is to identify the most cost and clinically-effective strategies for identifying and treating GDM in order to prevent the associated adverse health outcomes for mothers and their infants.

This research involves a thorough and comprehensive assessment of the literature and individual data from cohort studies and trials to estimate the incidence of gestational diabetes and how this varies across populations; the adverse effects and costs associated with GDM; the performance of various screening and diagnostic tests at different times in the pregnancy and using different risk thresholds and the cost-effectiveness of treatments for GDM. All the results of these analyses will be brought together in a comprehensive model to identify optimal screening strategies and how this might vary for different populations (see appendix 2 and Table 1).

The objectives are to:

(1) Determine the risk of adverse outcomes associated with incremental increases in maternal glucose level.

(2) Estimate the prevalence of pregnancy hyperglycaemia and gestational diabetes in the contemporary UK obstetric population.

(3) Compare the characteristics (sensitivity, specificity, acceptability and costs) of screening tests/strategies to identify women at risk of or with hyperglycaemia/GDM.

(4) Compare the characteristics (sensitivity, specificity, acceptability and costs) of diagnostic tests/strategies to identify women with hyperglycaemia/GDM.

(5) Determine the most cost and clinically effective treatments of GDM for lowering glucose level and preventing adverse perinatal outcomes.

Abstract in Plain English

Insulin resistance increases during pregnancy so that glucose (sugar) can cross the placenta to feed the growing fetus. If insulin resistance becomes too great, blood glucose levels increase and gestational diabetes is diagnosed. Women who develop gestational diabetes and their infants are more likely to suffer problems during pregnancy and soon after birth, including Caesarean birth, birth injury and require longer hospital stay and higher levels of care whilst in hospital. Women who develop gestational diabetes are more likely to develop gestational diabetes in a subsequent pregnancy and become permanently diabetic after pregnancy. The infants of women who have had gestational diabetes are more likely to be born large and be fatter in later life; these infants also seem to have more chance of developing diabetes and heart disease as they get older. Identifying and treating women with gestational diabetes is important so that these problems may be reduced or prevented.

Our proposal requests funding to do research that will find the best ways of identifying which women have raised blood glucose levels or gestational diabetes and the best treatments, so that health problems for women and their infants are reduced in the most cost and clinically-effective way. We will do this using information from several sources. Sources of information include those located by searching the published literature. We will complete a detailed search to identify all studies that have compared strategies and tests to identify gestational diabetes or treat women with gestational diabetes or collected information on the associated costs of identifying or treating gestational diabetes. We will use statistical methods to look at the results from all of these studies

We will use individual participant data from a study we already work on, the Born in Bradford (BIB) study. This is the most recent and largest study with relevant information to add to this research, approximately 12,000 women who took part in the Born in Bradford study had an oral glucose tolerance a test that measures blood glucose after an overnight fast and then measures blood glucose again after the woman has drunk a sugary drink) to identify gestational diabetes. We will use statistical methods to investigate the incidence of gestational diabetes in the UK population and the incidence of associated poor health outcomes and associations between increases in maternal glucose level and risk of problems at birth such as birth injury and caesarean birth.

We will use all of the evidence from our research to find out what is the most cost and clinically-effective method of identifying women with gestational diabetes and which is the most accurate, safe and cost and clinically-effective way of treating women so that their health and wellbeing and that of their infant is improved. From this work we may be able to find out when the best time in pregnancy is to screen and administer diagnostic tests and what treatment is most effective

Experienced researchers from the Bradford Institute for Health Research, the University of Bristol and the University of York will work together to ensure the aims and objectives of the project are completed within the specified time frame. Our team includes individuals with obstetric, midwifery, endocrinology (doctors who look after people with diabetes), research (statistics, study design, literature searching) and health economics knowledge and skills. Importantly, members of our team have experience in undertaking systematic reviews of the literature, statistical analysis, epidemiology and economic modelling and we have worked together on the Born in Bradford study and other studies relevant to this proposal. We know therefore that we are able to work and collaborate effectively and can complete good research that is relevant to the NHS, clinical practice and pregnant women. Funding has been carefully calculated and includes funds to employ specialists in library searching skills, three research assistants to collate the data and two research fellows to help undertake the systematic reviews, analyses and cost-effectiveness modelling.

Why this research is needed now

Gestational diabetes (GDM) is increasing globally and poses a substantial threat to health and a substantial burden to the NHS because of the increased risk of adverse health outcomes. Developing GDM in pregnancy predisposes to development of the condition in a subsequent pregnancy and up to 30% of women who have had GDM will develop type 2 diabetes. The infants of mothers with GDM have a higher risk of developing metabolic syndrome and subsequent diabetes and cardio-vascular disease. Therefore the health burden from the repeated adverse effects associated with GDM is increasing.

Certain populations seem particularly vulnerable to developing GDM, because of genetic and lifestyle predisposition. There is no consensus regarding the best method to identify[24; 25] or treat women with GDM[26] (see appendix 3 Flow chart 2). For women treated for hyperglycaemia/ GDM it is unclear what the target glucose level should be, though limited evidence from observational studies and two randomised trials suggests that glucose levels during pregnancy should be kept lower than those outside pregnancy. NICE however recommend a fasting blood glucose of between 3.5 and 5.9 mmol/litre and 1-hour and postprandial blood glucose below 7.8 mmol/litre.[22] It is also unclear how these glycaemic levels are best achieved, in terms of diet regimen or if pharmacological intervention is required, what is the best hypoglycaemic agent or which method of insulin administration, type of insulin or regimen is most effective.[26]

It is ten years since the last Health Technology Assessment funded review of current knowledge regarding screening, diagnosis and treatment for GDM.[27] Since that time new information has become available from randomised trials and observational studies and further work is now needed to synthesize these data, to produce knowledge that will assist policy makers and guide practice. New methods of economic analysis have been developed also that will help estimate the cost and clinical effectiveness of alternative identification and treatment strategies.

The increasing incidence of GDM and uncertainty as to the best ways to identify and treat it along with the availability of more data from relevant studies and better analytic techniques makes this area a research priority for the NHS which has a responsibility to provide consistent care that is both cost and clinically-effective.

Research Plan

Objectives 1 and 2 will be accomplished by undertaking systematic reviews of the published literature and by carrying out appropriate analyses. A new analysis of individual participant data will be undertaken to determine the associations between incremental increases in maternal glucose levels and adverse outcomes (for example macrosomia, operative delivery, birth injury and perinatal death).

Objectives 3 and 4 will be accomplished by undertaking systematic reviews of published literature and by carrying out appropriate analyses. Characterisation of the screening and diagnostic strategies for GDM within a decision analytic model, will allow differences to be translated into differences in total costs and health outcomes from the perspective of the UK NHS

Objective 5 will be achieved by undertaking systematic reviews of published literature and by carrying out appropriate analyses and through the characterisation of treatments for GDM within a decision analytic model, as for objectives 3 and 4 this will allow differences to be translated into differences in total costs and health outcomes from the perspective of the UK NHS.

Search strategy

Searches will be performed by an experienced information specialist, Julie Glanville based at York Health Economics Consortium with assistance from her team and the research fellows and the wider research team who are applicants on this proposal (see appendix 1 Flow chart 1). Searches will be undertaken to identify studies in English language and include randomised trials, pilot, feasibility and observational studies, which will inform a range of reviews on the following areas: (1) investigating associations between glycaemic level/GDM and rates of adverse outcomes (2) incidence of hyperglycaemia/gestational diabetes (3) compared screening tests and strategies including costs (4) compared diagnostic tests and strategies including costs (5) compared treatments including costs. These correspond to the objectives of the research and are summarised in Table1and Appendix 2.

We will only search for the concepts of the antenatal period and diabetes/glucose. This broad approach will maximise the potential that papers relevant to tests, epidemiology, treatments, and costs will be identified by one search. Searches will be conducted on key databases including MEDLINE, EMBASE, The Cochrane Library, CINAHL, Maternity and Infant Care, and specific trials registers. Appropriate search filters will be used to remove animal studies (which is less prone to excluding relevant study than specifying 'human' in the search terms). In order to ensure a comprehensive approach, a focused Grey literature search will also be conducted.

The search will be updated before the final report is written (six months before the end of the grant) to ensure it is as recent as possible, any new relevant studies identified that meet the inclusion criteria will be included as appropriate in the analyses. Initial scoping searches reveal 249 records for gestation* near/4 diabet* and screen* 485 records and 361 records for diabetes-gestational/gdm OR glucose near/4 pregnan* OR glucose near/4 gestational OR glucose near/4 prenatal OR glucose near/4 antenatal OR glucose near/4 maternal.

The searches have to inform a range of reviews therefore we will search for concepts of antenatal period and diabetes/glucose. This will ensure that tests, epidemiology, treatments, and costs will be identified by one sensitive search. The strategy removes animal studies (safer than focusing onhuman studies) and case reports and editorials. If required we will also remove letters, but with the knowledge that letters can sometimes lead to reports of relevant research. We will not exclude comments as these may highlight early retractions.

Cochrane library

(gestation* near/4 diabet*) and screen* (485 records)
diabetes-gestational/ (249 records)
gdm OR glucose near/4 pregnan* OR glucose near/4 gestational OR glucose near/4 prenatal OR glucose near/4 antenatal OR glucose near/4 maternal (361 records)

MEDLINE (OVIDSP)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 (gestation$ adj4 diabet$).ti,ab. (6436)
2 exp diabetes, gestational/ (5842)
3 gdm.ti,ab. (2221)
4 (glucose adj4 (pregnan$ or gestation$ or prenatal or antenatal or maternal)).ti,ab. (3022)
5 or/1-4 (10298)
6 animals/ not humans/ (3659358)
7 english.la. (17267779)
8 5 not 6 (9389)
9 8 and 7 (8172)
10 editorial.pt. (312579)
11 9 not 10 (8056)
12 case reports.pt. (1581358)
13 11 not 12 (7702)
14 news.pt. (152687)
15 13 not 14 (7676)

Databases
MEDLINE and MEDLINE IN PROCESS (OVID)
EMBASE (OVID)
COCHRANE LIBRARY
MEDION
SCIENCE CITATION INDEX
MATERNITY AND INFANT CARE
HEED
CEA REGISTRY
PEDE

GREY LITERATURE SEARCH TO INCLUDE:
- NHS EVIDENCE
- OAISTER
- OPENGREY
- REPEC
- WEBSITES OF KEY DIABETES AND PREGNANCY CONFERENCES
  - American Diabetes Association Meetings
  - European Association for the Study of Diabetes meetings
  - ISPOR
  -
- Websites of key organisations
  - FDA
  - MHRA

Review strategy

We will use standard methods of the Cochrane Collaboration (http://www.cochrane-handbook.org/) and Centre for Reviews and Dissemination (CRD) (www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) to undertake the reviews. The project is registered with CRD at http://www.crd.york.ac.uk/PROSPERO the registration number is: CRD42013004608

For each objective, results will be combined and stored in a separate Endnote library. Numbers of references found from each database will be recorded. Duplicates will be identified and deleted. Results of the abstracts and full text screenings will be recorded in the Endnote Library, including the reason for exclusions (See Appendix 2). Data extraction will be undertaken, using a piloted pro-forma designed by the team of applicants and appropriate staff and collaborators. It will be undertaken independently by two individuals a research fellow and the PI, for all reviews, except the review of costs for which abstractions will be undertaken by the research fellow and Dr Susan Griffin. Levels of consensus between the two abstractors will be checked, if the rate of differences due to data entry errors is greater or equal to 10% across all fields in any review a third independent reviewer (one of the team of applicants) will independently abstract the data. Where neither abstractor can agree what a field should be, these will be resolved through discussion, including with the wider applicant team. All abstractors will be able to discuss any queries related to complex statistics within a paper with the study statistical leads Lesley Fairley (Bradford) and Martin Bland (York). Once all data have been abstracted and agreed, the applicant team will discuss how appropriate it is to pool results across studies and if so whether this should be done by fixed or random effect meta-analysis. An analysis protocol will be written and applied following an initial review of the abstracted data. If support is required related to pooling of data from studies using different study designs Professor Tony Ades (Bristol) expert in multi-parameter evidence synthesis will support the research team and provide advice on a consulting basis. A fee for support from Professor Ades has been written into the grant.

Analyses
The Born in Bradford (BIB) cohort study includes ~12,000 women who had a glucose tolerance test (OGTT) at 26-28 weeks (approximately 6 months) pregnant. For BIB participants we have detailed information on demographic and lifestyle factors such as smoking during pregnancy, maternal age, alcohol use in pregnancy, ethnicity, maternal height, socioeconomic status and birth data including infant sex, parity, maternal booking weight and height, from which BMI has been derived, birthweight, gestational age, adverse birth outcomes including macrosomia, caesarean delivery, birth injury and admission to special care. Gestational age at OGGT is available for participants, and in addition to the assessment of fasting and postload glucose, fasting insulin and lipids were assayed on all participants and plasma and serum stored at -80^{O}C for future research use.

Objective 1: Determine the risk of adverse outcomes associated with incremental increases in maternal glucose level. To investigate the associations between maternal glucose levels and adverse outcomes we will use individual participant data from BIB and from other studies identified by our systematic review. Glucose levels will be considered as both categorical and continuous variables in multiple logistic regression models to investigate the association between glucose levels and adverse birth outcome. The adverse birth outcomes we will look at are: macrosomia, caesarean and instrumental delivery, birth injury and admission to special care.

For categorical analysis we will categorise each measure of glucose according to thresholds used in clinical practice for screening or diagnosis. We will compare associations using different thresholds reflecting differences between different guidelines. The frequency of each outcome across the categories will be calculated. We will calculate the odds ratios and 95% confidence intervals for each category, as compared with the lowest category (i.e. the one considered healthy according to the guidelines being used) using logistic regression models.

The above analyses will allow us to examine associations using what are currently considered clinically relevant cut-points. However, there is evidence that the association of maternal glucose in pregnancy with offspring outcomes is continuous across the whole distribution; i.e. it does not exhibit a threshold effect.[5] We will therefore undertake additional analyses to determine whether this is the case for the UK population, including within subgroups (e.g. based on ethnicity) within that population. We will do this by first splitting the measures of maternal glucose into 10th of their distributions and plotting the frequency and 95% confidence intervals of each outcome by 10th of the glucose distribution. This will allow us to see if there is visual evidence of a non-linear association. We will statistically test for deviation from linearity using a likelihood ratio test to compare a logistic regression model in which the 10th of the distribution are entered as 9 indicator variables (non-linear model) to one in which they are entered as a score from 1 to 10 (linear model). If this confirms a linear association we will the explore the association of each glucose measure as a continuous variable, by estimating odds ratios of outcomes for a 1 standard deviation (SD) increase in glucose levels.

All models will be adjusted for potential maternal confounding variables: maternal pregnancy smoking, age, parity, BMI, gestational age at OGTT. We will also explore whether any associations are mediated by the relationship between gestational diabetes and preterm, instrumental or Caesarean delivery. We will examine whether any associations vary by infant sex by examining these stratified by sex and testing for statistical interaction between sex and glucose in their association with outcomes. We will examine whether any associations differ by ethnicity in the same way. If there is evidence of differences by infant sex or ethnicity results will be presented by relevant strata. If there is no evidence of any differences all participants will be analysed together and adjustment for ethnicity and infant sex undertaken. We will also use multivariable linear regression (as above) to examine the associations between glucose levels and birthweight, where the birthweight outcome will be measured on a continuous scale.

We will use multiple imputation techniques applicable to cohort study data to improve the integrity of the data and reduce the risk of biased results that may arise from complete case analysis results only. We will use multivariate multiple imputation to impute missing values of confounders and covariables for participants. In the prediction (imputation) equations we will include all risk factors, covariables, outcomes and any other potential predictors of missing. We will compare results using the multiple imputation datasets (including distributions of all characteristics and association results) with those from the complete case observed data.

Objective 2: Estimate the prevalence of pregnancy hyperglycaemia and gestational diabetes in the contemporary UK obstetric population. Using OGTT data from BIB and other identified studies we will determine the prevalence of GDM in different risk groups (e.g. by age, overweight/obesity, ethnicity) for which national data are likely to be available. Poisson regression models, or other models as appropriate, will be used to estimate prevalence rate ratios to examine the association between risk factors and gestational diabetes adjusting for maternal confounders. When examining rates by BMI categories in South Asian groups we will use both WHO and South Asian specific criteria for defining overweight and obesity based on maternal BMI.

Objectives 3 and 4: Compare the characteristics (sensitivity, specificity, acceptability and costs) of screening and diagnostic tests/strategies to identify women at risk of or with hyperglycaemia/GDM. The accuracy of different methods to identify women at increased risk of gestational diabetes (screening test) and women with gestational diabetes (diagnostic test) will be determined by sensitivity, specificity, positive predictive value and negative predictive value. Analyses using BIB (and other relevant data) will be done separately comparing South Asian and white European women.

For the BIB sample, data are available on gestational age and when the OGTT was administered, therefore we will look at prevalence of gestational diabetes over different gestational ages in pregnancy.

Cost-effectiveness analysis
The cost-effectiveness analysis is structured using backwards induction to solve first the question of what diagnostic threshold to use, then what diagnostic test, then which screening threshold, then which screening test (if any) for a population with a given expected prevalence of GDM. This allows the optimal strategies to be identified in stages, without having to compare an unlimited number of predefined complete strategies. The final complete model will describe the complete strategies, but will be informed by optimal threshold and test combinations identified through the process of backward induction.

Objective 5: Determine the most cost and clinically effective treatments of GDM for lowering glucose level and preventing adverse perinatal outcomes

Stage 1. Cost-effectiveness of treatment for GDM
Women diagnosed with GDM are offered treatment with the aim of preventing adverse perinatal outcomes. Review 5 will be used to identify (i) what are the current recommended treatments for women diagnosed with GDM; and (ii) what are the costs and health outcomes for women who receive those treatments in comparison to the cost and health outcomes that would have occurred in the absence of treatment (see appendix 4).
The relevant costs will include:

- the costs of providing treatment for those with GDM [A (true positives) and B (false positives)]
- the costs of treating adverse effects associated with treatment for GDM (A and B)
- the costs associated with the health consequences of untreated GDM (relative to women without GDM), including for example increased rates of large birth-weight babies requiring caesarean delivery and treatments for birth injuries [C (false negatives)]

The relevant health outcomes will include:

- the health impacts for women undergoing treatment for GDM (A and B)
- the health consequences of untreated GDM relative to women who do not have GDM
- the effect of treatment on reducing health consequences of untreated GDM (A)

The current treatment for GDM that is recommended by guidelines in the UK and that is cost-effective will be characterised within the decision analytic model in order to predict, for a woman diagnosed with GDM, what would be the expected costs and quality adjusted life years. Individual participant data from the BIB cohort can be used to estimate the pregnancy outcomes for participants treated for GDM. The efficacy of treatment for GDM in terms of reduced adverse pregnancy outcomes will be estimated from RCTs and systematic reviews identified from Review 5 and can be used to predict what health outcomes would have been in the absence of treatment for GDM. Those same studies can be used to estimate the rate of any adverse effects and the health related quality of life impact associated with treatment for GDM. The costs of treatment for GDM will be estimated from previous economic evaluations identified from Review 5 and from routine UK data sources (e.g. British National Formulary). The health consequences for the population of untreated/treated GDM will be identified in the Review for objective 1. The costs associated with the health consequences of GDM will be estimated from previous economic evaluations identified from the Review for objective 5 and routine UK data sources (e.g. NHS reference costs).

Stage 2. Cost-effectiveness of diagnostic strategies for GDM
All pregnant women or women considered at risk of GDM (depending on the screening strategy being considered e.g. women who screen positive for GDM, those with known risk factors, or all pregnant women) may be offered a diagnostic test to determine whether they should be offered treatment. The positive predictive value of the diagnostic test and so the test yield will depend on both the sensitivity and specificity of the test (which should be independent of level of risk) and the prevalence of GDM among women offered the test (which will vary depending on risk factors, the stage of the pregnancy when tested and screening test results). Individual participant data from BIB and other studies will be combined with evidence from systematic reviews and summary data from other cohort studies in order to estimate the expected prevalence of GDM according to the presence of risk factors and according to stage of pregnancy.

The data from the review from objective 4 will be used to determine (i) what are relevant diagnostic tests for GDM; and for each alternative diagnostic test (i.e. tests will differ on the basis of stage of pregnancy that they are administered, the amount of glucose and how it is delivered in the test and the thresholds used for maternal fasting and postload blood glucose levels) (ii) what are the sensitivity and specificity; and (iii) what are the costs (costs to the woman, cost to the NHS and costs to society) of providing those tests. The alternative diagnostic strategies will be characterised within the decision analytic model, which can then be used to determine, for each diagnostic strategy, for a given expected level of prevalence of GDM in the tested population (determined by knowledge of screening test results, presence of risk factors and stage of pregnancy), what is the most clinically and cost-effective diagnostic threshold at which to start treatment. The cost-effective diagnostic threshold will be determined by the point at which the health gains to women correctly identified and treated for GDM outweigh any health costs from those undergoing the test and those left untreated in addition to health losses that result from any diversion of existing NHS resources required to deliver the diagnostic tests. Using this diagnostic threshold, the decision model can then be used to determine which is the most cost-effective diagnostic strategy conditional on prevalence of GDM in the tested population. Among the alternative strategies the decision analytic model (see appendix 4) will also include a strategy of universal testing in which all women identified are assumed to receive treatment for GDM (this will represent a strategy of treating following a positive screening test).

Stage 3. Cost-effectiveness of screening strategies for GDM
Pregnant women may be screened for risk factors for GDM and/or offered a screening test to identify groups with glucose levels indicating raised risk of GDM who may then go on to be offered further diagnostic tests and/or treatment. The proportion of women who screen positive for GDM will depend partly on the stage of pregnancy at which the screening test is administered and the nature of this screening. For example, screening strategies include: (a) assessment of non-blood based risk factors in early pregnancy, such as BMI, family history, ethnicity, previous experience of GDM or large birth weight baby; (b) a blood based screening test, such as glycaeted haemoglobin, random glucose, fasting glucose or an oral glucose tolerance test in early pregnancy or (c) some combination of (a) and (b).

The data from the review from objective 3 will be used to determine (i) what are the relevant screening tests for GDM in the UK; (ii) what are the sensitivity and specificity (fixed) of those tests; and (iii) what are the costs of

providing those tests. Information from the review from objective 3 in combination with individual participant data from the BIB cohort and other studies will be used to predict the prevalence of GDM according to different risk factors.

The alternative screening strategies will be characterised within the decision analytic model, which can then be used to determine, for each screening strategy and at a given stage of pregnancy, what is the most cost-effective threshold at which to proceed to diagnosis and/or treatment. The screening strategies will include assessing women for a set of easily measured risk factors and risk markers (e.g., age, ethnicity, BMI, past history) associated with GDM, administering a screening test, or combinations of the two. The threshold of the screening test will determine those at risk of GDM. The threshold of the diagnostic test will determine the expected prevalence of GDM among those who screen positive and negative. The appropriate subsequent diagnostic and/or treatment strategies conditional on prevalence of GDM and stage of pregnancy will have been identified in stages 1 and 2 of the cost-effectiveness analysis. This allows the threshold for a given screening strategy to be determined in terms of the most cost-effective threshold. Using this screening threshold, the decision model can then be used to determine which is the most cost-effective screening strategy conditional on expected prevalence of GDM in the screened population.

Stage 4. Cost-effectiveness of screening for GDM for different participant populations
Stages 1 to 3 of the cost-effectiveness analysis will have identified, conditional on prevalence of GDM, what is the most cost-effective screening, diagnosis and treatment strategy. In stage 4 the results will be combined in an overall cost-effectiveness analysis that will identify, for populations of participants defined by a set of risk factors, what is the most cost-effective strategy for identifying women to be treated for GDM in terms of screening test and threshold and/or diagnostic test and threshold (see appendix 4). The populations that will be described will include the current UK population of pregnant women and subgroups who may be considered of particular interest, for example women of South Asian ethnic origin.

Stage 5. Value of information analysis
The uncertainty in the values used in the decision analytic model will be characterised using probabilistic sensitivity analysis. This will be used to estimate the probability that any particular strategy of screening and/or diagnosis and treatment could be considered to be a cost-effective use of NHS resources. Value of information analysis will be used to estimate the potential opportunity cost to the NHS of initiating an apparently cost-effective strategy for the screening, diagnosis and treatment of GDM on the basis of uncertain evidence. The value of information analysis will be used to indicate key uncertainties and whether there may be value in further research, and if so what type of information that research should collect.

Dissemination of findings
As well as producing a full report for the HTA we will publish this work in high impact journals and at conferences. We will work closely with colleagues responsible for developing and updating NICE guidance for use in antenatal care in the UK and the National Screening Committee. We will disseminate our findings through relevant professional bodies, nationally and internationally to ensure that clinicians are aware of and have access to the findings. We will also work with participant and pregnancy support groups to ensure findings are disseminated to the public in an understandable and appropriate way.

Research project plan
Funding is requested to undertake the project over two years to complete the objectives set out in Table 1 (appendix 2).

1. Three research assistants will be employed to carry out risk factor data extraction of the Born in Bradford (BIB) Cohort. Data will be inputted into a secure web interface, this will take approximately six months. The data will be added to the existing BIB data warehouse. The data interface will be comprehensively tested.

2. If appropriate the data from BIB will be merged with other individual participant data obtained from other studies. Analysis of this data will be undertaken to assess for example incidence of GDM and incidence of adverse health outcomes (including macrosomia, birth injury and caesarean birth).

3. Two research fellows will be employed: one in Bradford, to undertake the systematic reviews for objectives one to four and to work with the principal applicant Dr Farrar and one in York to undertake a review of costs and to work with Dr Griffin and Professor Sculpher on the cost and clinical-effectiveness model and economic evaluation.

4. A Protocol and standard operating procedure for the data extraction from source data (maternity notes) of women in the Born in Bradford cohort will be written to ensure quality and consistency.

5. Protocols for the literature reviews will be written and include detailed and coded data extraction sheets. Data extraction sheets will be tested appropriately.

6. Searches of the available literature will be undertaken by an information specialist and full text copies of those not excluded because they are duplicates or the title makes it clear they are not appropriate (for example it is an animal study), will be obtained. The selected papers will be reviewed for inclusion by two members of the research team, any disagreements will be discussed with a third member and agreement reached via consensus.

7. Data obtained from the searches for each of the reviews will be combined as appropriate, this will include narrative review, meta-analysis of diagnostic accuracy studies, meta-analysis of RCTs or multi-parameter evidence synthesis.

6. Individual participant data extracted from the Born in Bradford cohort will be analysed as outlined in the pre-specified protocol and according to the analysis plan.

7. The information and results from completing objectives one to five will be assimilated into the cost and clinical-effectiveness model

8. A comprehensive report will be written of the work undertaken; the findings will be presented at scientific conferences and to the wider community. Manuscripts will be prepared for publication in peer reviewed journals.

9. The full research team will meet six monthly or more often if necessary, Dr Farrar, Dr Griffin and all others as appropriate will meet every three months to discuss progress and any research management or data issues.

Project management
Good project management will be established at the start of the project. The PI (Farrar) will work with the co-applicants to establish efficient and effective systems of support to ensure that the reviews, the analysis of individual participant data and the integration of the information into the cost and clinical effectiveness model is undertaken in a timely and effective way and to ensure high quality research governance.

The research team will include all the co-applicants and the research fellows. The research team will meet every 6 months for the duration of the project. The research groups at Bradford and York wlll include all researchers involved in the project at each of these sites, they will meet monthly and if appropriate joint meetings between Bradford and York willl be held via teleconferencing facilities. Costs for these meetings have been included in the requested budget for this research project.

The PI (Farrar) will draft protocols and standard operating procedures (SOP) for the reviews and BIB data extraction and data inputting. The co-applicants will comment on the drafts, this will ensure they are appropriate and comprehensive. Dr Griffin will ensure development of the design analytic model is accomplished. Adherence to prespecifed protocols and SOPs will ensure consistency and clarity in the work undertaken. The work will be carried out within the time frame set out in the project plan, if unforseen problems occur for example due to illness in the research team, the team will meet to devise a strategy to resolve the problem.

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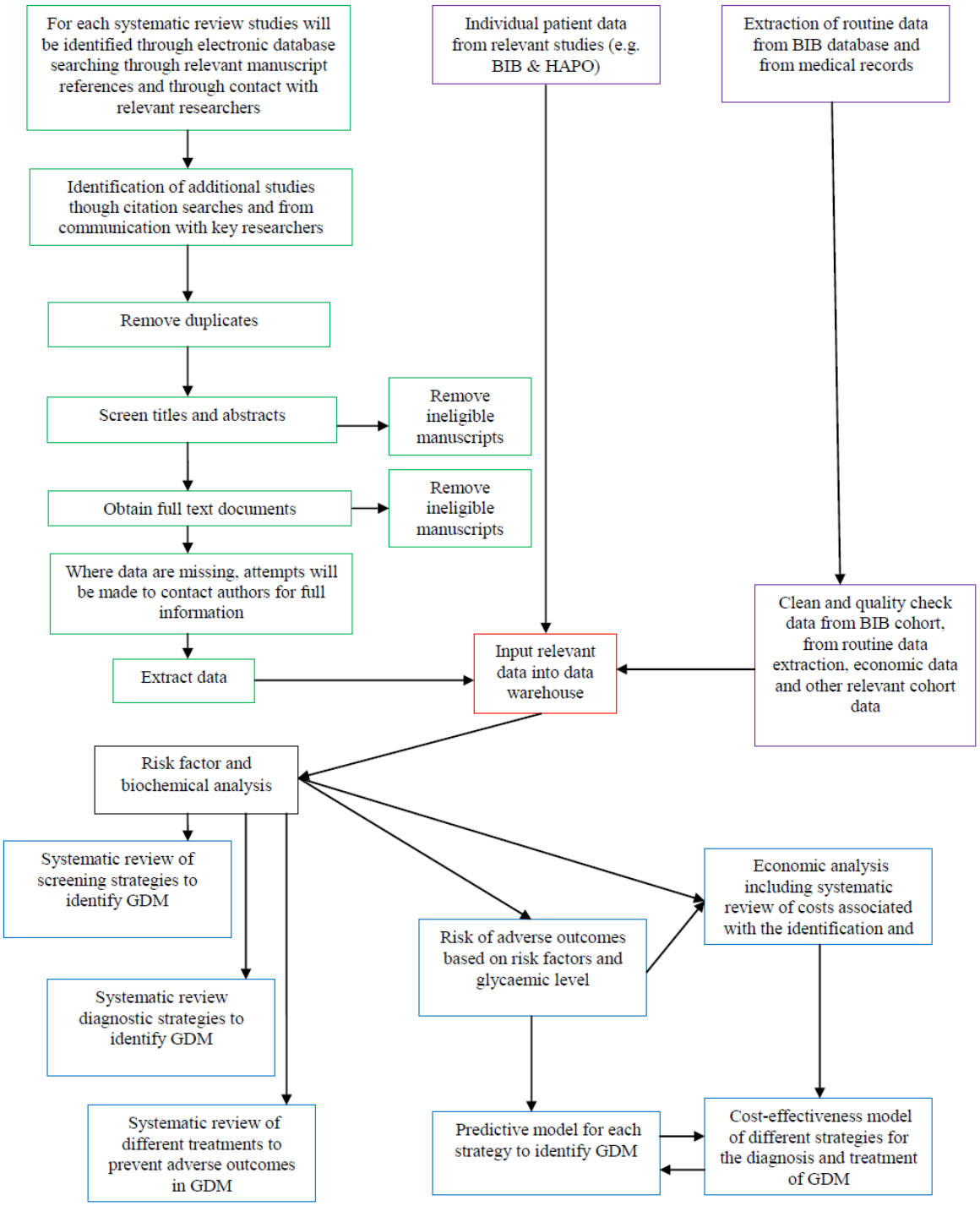
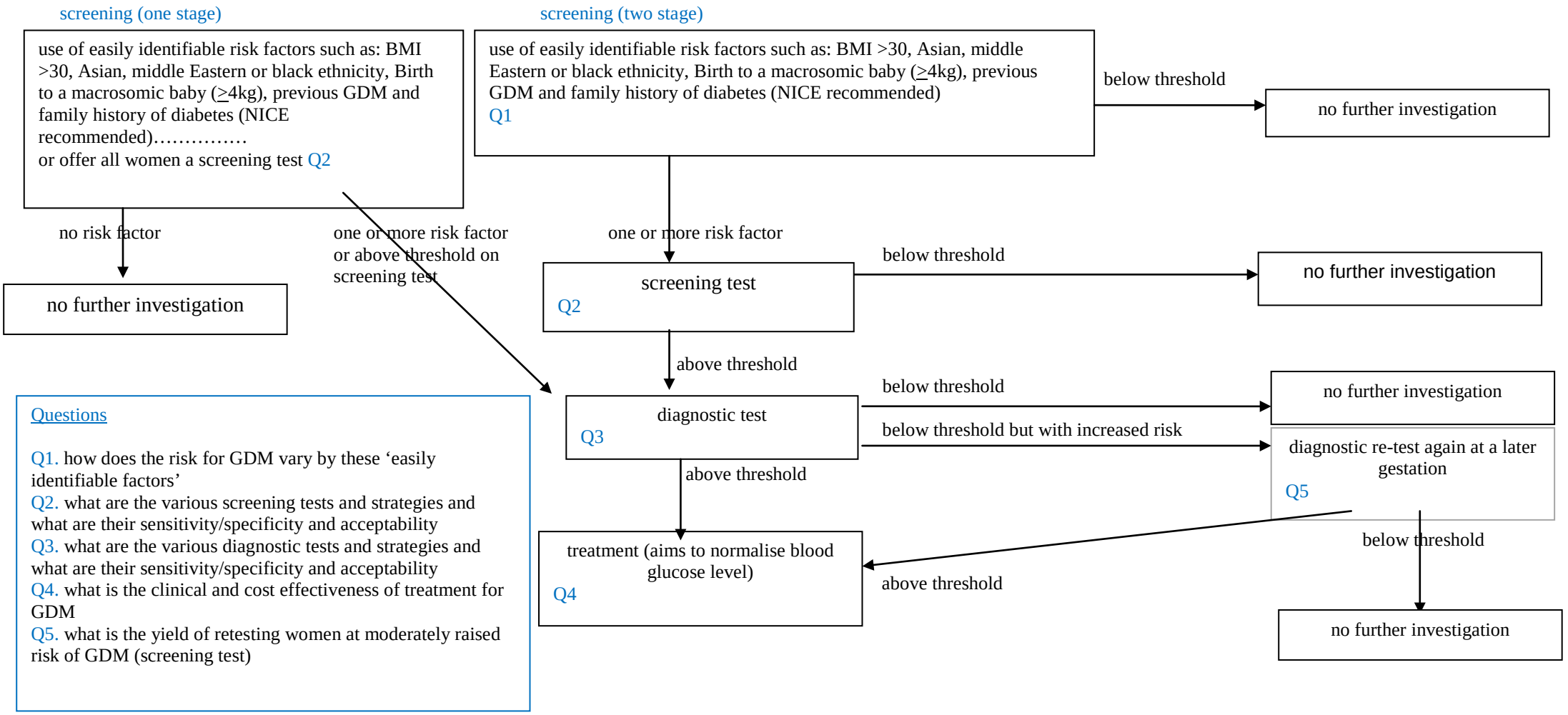
Appendix 1. Flow Chart 1- Screening for hyperglycaemia/GDM



Appendix 2. Table 1- objectives 1 – 5, incidence rates, screening, diagnosis and treatment of hyperglycaemia /gestational diabetes in pregnancy

	objective 1	**objective 2**	**objective 3**	**objective 4**	**objective 5**
title	adverse outcome incidence rates at different levels of glycaemia	incidence of hyperglycaemia/GDM in the whole obstetric population and in sub-populations (e.g. by ethnicity, by BMI category) over the duration of pregnancy	sensitivity, specificity, acceptability and costs of screening tests/strategies to identify hyperglycaemia /gestational diabetes	characteristics and costs of diagnostic tests/strategies to identify hyperglycaemia /gestational diabetes	effectiveness and cost-effectiveness of treatments for GDM (aim is to normalise blood glucose level)
includes	short term perinatal: stillbirth, macrosomia, birth injury, instrumental birth (c-section or forceps) admission to neonatal unit and long term: metabolic dysfunction leading to obesity, CVD and diabetes	risk factors (NICE-UK) 1. BMI $\geq$30 2. previous macrosomic baby $\geq$ 4kg 3. family history of diabetes 4. South Asian, black and middle eastern ethnicity 5. previous GDM	1. glucose loads including: 50g glucose challenge, jelly beans/chocolate bars 2. risk factors (see review 2) 3. fasting plasma glucose 4. urine testing 5. random plasma glucose 6.glycated haemoglobin	1. selective 75g oral glucose tolerance test (UK with WHO criteria, US with ADA criteria) 2. 100g oral glucose tolerance test (formally used in US)	1. diet and exercise modification 2. oral hypoglycaemics (e.g. metformin) 3. insulin (either multiple daily injections or continuous insulin infusion^)
who to include	whole obstetric population	whole obstetric population and in selected groups including: BMI $\geq$30, ethnic group	offer all pregnant women screening test (universal offer)l or selective (offer screening test to sub-populations at increased risk)	pregnant women of varying risk	across different glucose thresholds
when is it best to administer	-	-	yield over the duration of pregnancy	yield over the duration of pregnancy	-
economic evaluation	average cost per affected pregnancy by level of maternal glucose and associated adverse outcomes	-	costs associated with different screening tests/strategies	costs associated with different testing strategies	costs associated with treatment strategies (diet, oral hypoglycaemics, insulin)
source of Information/ data	individual participant data, reviews of cohort and randomised trial data	individual participant data, reviews of cohort and randomised trial data	reviews of cohort and randomised trial data	individual participant data, reviews of cohort and randomised trial data	reviews of cohort and randomised trial data

Appendix 3. Flow chart 2 - one and two stage screening process to identify GDM



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Appendix 4. schematic 1- cost and clinical effectiveness decision analytic model