Detailed project description

Full title of project

Estimating the risk of adverse birth outcome in pregnant women undergoing non-obstetric surgery using routinely collected NHS data.

Aims and objectives

Our hypothesis is that pregnant women who undergo non-obstetric surgery have an increased risk of adverse pregnancy outcomes compared with those not undergoing surgery.

Anonymised English national hospital data are held at the Dr Foster Unit at Imperial College. We will analyse data collected between 2002 and 2013 and identify patients who underwent non-obstetric surgery whilst pregnant. A preliminary analysis suggests that we will be able to identify around 85,000 such patients out of a total of 4 million pregnancies.

We aim to investigate adverse pregnancy outcomes occurring in this group; outcomes we will analyse include miscarriage, stillbirth, preterm labour, low birth weight, prolonged length of neonatal stay and neonatal death prior to discharge from hospital.

Following data extraction and cleaning, we will:

- Carry out a descriptive analysis of the data, describing counts of each adverse outcome by year, maternal age, procedure type, socio-economic status and trimester of pregnancy.
- Calculate the absolute risk and the relative odds of of each adverse outcome in those women who have had surgery compared with those who haven't.
- Independently analyse broad groups such as elective and emergency operations as well as common procedures such as appendicectomy, cholecystectomy, specific cancer surgeries and orthopaedic surgery.

With the data obtained from our study and subsequent statistical analysis, we aim to provide an evidence base with which we can counsel women who face the prospect of undergoing surgery during pregnancy. Following this study, when a pregnant woman is facing the prospect of a non-obstetric operation, it will be possible to give her accurate and up-to-date answers to her inevitable questions regarding the risks to her pregnancy. This accurate information, where there has previously been very little, will improve decision making in a wide range of clinical scenarios.

Background

Pregnant women undergo non-obstetric surgery in approximately 1-2% of pregnancies (Ni Mhuireachtaigh and O'Gorman 2006), common operations being appendicectomy, cancer surgery and orthopaedic procedures. In this situation, women and their doctors are understandably anxious about the risk of harm to the fetus. However there is limited available evidence quantifying the risks

of miscarriage (fetal loss before 24 weeks), still birth (fetal loss after 24 weeks), premature labour, or infant death post-delivery.

Of the evidence that is available, none relates directly to NHS outcomes, and there is no current NHS policy regarding carrying out non-obstetric surgery in pregnant women.

Four registry studies (Duncan et al. 1986; Mazze and Kallen 1989; Mazze and Kallen 1991; Reedy et al. 1997) have aimed to assess the risk of non-obstetric surgery during pregnancy. These, as well as fifty much smaller case series were reviewed by Cohen-Kerem (Cohen-Kerem et al. 2005).

Duncan et al.

This Canadian study investigated data from 2656 women between 1971 and 1978. Patients were matched to controls by age and geographical area. There was no statistically increased risk of fetal loss for the group as a whole. However there was an increased risk of fetal loss in women undergoing a general anaesthetic, which was most marked for women undergoing general anaesthesia for obstetric or gynaecological procedures. However, some of the obstetric procedures were cervical cerclages, a procedure to prevent recurrent fetal loss, and some bias will therefore have resulted.

The study did not differentiate between fetal loss at different stages of pregnancy, did not look at prematurity and did not control for co-existing illness, parity or smoking.

The Swedish health registry studies

The same Swedish dataset was used for each of these three studies. Mazze and Kallen (1989) analysed outcomes of 5405 patients who had had an operation in pregnancy out of the 720,000 Swedish births between 1973 and 1981. There was no increase in rates of congenital malformations or stillbirth; however, there were significant increases in death within 7 days of delivery and in prematurity.

Owing to limitations of the dataset, the Swedish studies were unable to analyse rates of miscarriage. Outcomes were compared with Swedish national data, standardised by year, age, parity and hospital.

The other Swedish studies were subsets of the original data - specifically investigating appendicectomy and laparoscopic surgery (here the data were expanded to include 2,015,000 deliveries from 1973 to 1993). 16% of women having an appendicectomy after 24 weeks delivered on the day of their operation, with 22% delivering within one week. This resulted in a significant increase in prematurity and death within 7 days of delivery, but not of stillbirth.

Cohen-Kerem et al.

This systematic review of the literature from 1966 to 2002 identified 54 papers, totalling 12,452 patients. There was overlap of the Swedish registry patients; the total number of patients excluding the Swedish registry was 4473, over half of these from the Canadian paper.

Miscarriage rates in patients undergoing surgery during pregnancy were 5.8% (10.5% if surgery took place in the first trimester). Still birth occurred in around 2% and premature delivery in 8.2%. There were however no controls for comparison.

The clearest data (though still poorly controlled) exist for appendicitis, with surgery-induced delivery in 4.6% and still birth at 2.6%, versus 1.2% for other surgical procedures ($P < 0.001$). Fetal loss in the presence of peritonitis was 10.9% which suggests that the condition itself rather than the operation may lead to fetal harm.

Limitations and implications

There are a number of problems with the current level of evidence. It is all between 20 and 40 years old and is therefore unlikely to be representative of current outcomes given the improvements in anaesthetic drugs, surgical techniques, and neonatal care. The Swedish data are also designed to study births, and therefore miscarriage is unrecorded in this, the largest group of patients. The studies are also, in general, poorly controlled and have conflicting results regarding the risk of surgery. Duncan suggests that there is an increased risk of fetal loss (including miscarriage), and the Swedish studies suggest that there is no increase in still-birth, but that there is an increase in prematurity and early neonatal death, particularly in the case of appendicitis.

Furthermore, whilst it is clear from the data on appendicitis, that the risk to the fetus when a pregnant woman undergoes surgery is not uniform, there have been few attempts to quantify the risk by other types of surgery.

Cohen-Kerem concludes that *'This review and analysis underscores our lack of knowledge in this area and points out a critical need for better data, with details not only on surgical condition, the anesthetic and surgical techniques, but also careful attention to confounders'.*

Proposed study

We carried out a preliminary analysis of our data for a single year and identified 437,254 pregnancies of which 8673 women had a non-obstetric procedure (2%). We found the unadjusted relative risk of preterm delivery in patients who had undergone surgery to be 1.54. By extending our analysis to cover 10 years, we will be able to identify around 85,000 patients, over ten times the total in the published literature to date. This large number will allow us to drill down into the effects of specific procedures in different trimesters, and to adjust for many confounders. Our results will reflect current outcomes within the NHS.

With the data obtained from our study and subsequent statistical analysis, we therefore intend to provide an evidence base with which we can counsel women who face the prospect of undergoing surgery during pregnancy.

Need

Lack of published guidance

The NHS currently publishes no guidance regarding the management of women who are being considered for an operation during pregnancy. Although our preliminary data analysis is crude, its relevance has been recognised by professional bodies including the Obstetric Anaesthetist's Association (OAA). The OAA provides education and training for anaesthetists who specialise in the care of mother and baby and has an international membership of over 2450. An abstract presenting this analysis was submitted to the OAA and selected for poster presentation and discussion at their

Annual Scientific Meeting in May 2013. The abstract was also selected for publication in the supplement to the International Journal of Obstetric Anesthesia, May 2013.

The American College of Obstetricians and Gynecologists Committee Opinion (February 2011), one of the few published opinions on this issue, advises that *'if possible, non-urgent surgery should be performed in the second trimester when preterm contractions and spontaneous abortion are least likely'*, however admits that *'because of the difficulty of conducting large-scale randomized clinical trials in this population, there are no data to allow for specific recommendations'.*

The responsibility deciding whether or not to operate and the timing of the operation are therefore left to individual clinicians, most of whom will have limited experience in this area because of its uncommon nature. These clinicians and their patients are understandably anxious about the risk of harm to the fetus.

Patient concerns

Our study arose as a direct result of questions posed in the high risk obstetric anaesthetic clinic by patients who were scheduled to have cancer surgery whilst pregnant. Patients wanted to know the statistical risks of an adverse outcome to the pregnancy, including miscarriage, stillbirth, premature delivery or problems following birth such as admission to neonatal intensive care. Unfortunately the current evidence base is not sufficient to answer these questions and therefore this constitutes a "knowledge gap". There is no reliable figure for risk of an adverse pregnancy outcome in those who undergo surgery whilst pregnant, and except in the case of appendicectomy, there has been no investigation of specific risks posed by particular operations.

A postal survey of women who had undergone non-obstetric surgery during pregnancy in our maternity unit over a five year period was then conducted. All respondents (response rate 75%) expressed concern regarding the lack of statistical data available which could guide their decision. Although they felt they were adequately counselled, they all agreed that if there had been more information available, they would have been more confident in their decision-making and less anxious regarding the pregnancy outcome.

The case for independent analysis of specific conditions

The case of appendicectomy is interesting, because the fetal loss rate following appendicectomy has been found to be 2.6% versus 1.2% for patients who had other operations. There was also a statistically significant increase in preterm delivery. When peritonitis was present, rates of fetal loss were over 10% (Cohen-Kerem et al., 2005; Mazze and Kallen, 1991). This indicates that risk of adverse fetal outcome is non-homogenous, and may in fact be caused by the disease rather than the operation and underscores the need for further research looking at specific diseases.

Our large dataset will permit us to describe the risk of an adverse pregnancy outcome for women having specific types of operations. Surgeons and patients will therefore have accurate information, specific to them, on which to base decisions. Risk may also vary with gestation. Our findings will therefore permit optimal timing of surgery to minimize risk of an adverse outcome.

Potential to change management

Pregnant women and their healthcare advisors are familiar with using epidemiological data from populations to assist decision making. The best example is the risk of miscarriage after

amniocentesis and chorionic villous biopsy for the determination of potential fetal abnormality. Women, particularly in older age groups, have to balance the risks of acquiring information against the benefits for them and their families, aided by population risk estimates. Such estimates have acquired greater precision over the years as the quantity of data in established databases has increased.

In the case of surgery during pregnancy, the lack of available data, combined with a desire to avoid causing harm, has led to a reluctance among many surgeons to operate on pregnant women. Information produced by this study will therefore enable more evidence-based decision making. An example would be a woman requiring surgery for thyroid cancer. This does not involve the abdomen and may not carry a significantly increased risk of an adverse fetal outcome. If that were the case, the operation should take place according to normal procedures. If on the other hand, it was shown that there was an increased chance of premature labour postoperatively, it may be possible to delay surgery to beyond certain pregnancy milestones to improve the chances of a good neonatal outcome, thus balancing the risk to the fetus against the risk of maternal cancer progression.

Another example would be a pregnant woman with a broken arm. Surgical fixation may, in some circumstances, improve the chances of good bone alignment and functional outcome when compared with non-surgical management in a plaster cast. This would therefore be the option chosen in the non-pregnant patient. If, however, surgery significantly increases the chances of losing the pregnancy, a mother and her surgeon may choose to manage conservatively. If on the other hand, there is no increased risk to the pregnancy and fetus of a short surgical procedure remote from the abdomen, the operation should probably take place.

Abdominal operations are likely to carry the greatest risk to the fetus. However there is some evidence that they may be carried out safely (Reedy et al. 1997, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines). In the case of intra-abdominal pathology, there may be significant risks to both the mother *and* the fetus of not operating. For instance non-operative management of symptomatic gallstones in gravid patients results in acute cholecystitis or gallstone pancreatitis in 23% of patients, with gallstone pancreatitis resulting in fetal loss in 10% to 60% (SAGES guidelines, Graham et al. 1998). The Graham study highlights once again the lack of published evidence - a review of the literature found only 69 published cases which noted the pregnancy outcome following laparascopic cholecystectomy. Despite reports of good outcomes in all trimesters, Graham recommends that surgery be carried out in the second trimester because of the perceived risks of miscarriage in the first trimester and premature labour in the third trimester. The SAGES guidelines however state that *'the significant morbidity and mortality associated with untreated gallbladder disease in the gravid patient favor surgical treatment*'. This is one of many examples of conflicting opinion, based on a lack of evidence, which cause confusion and concern for women and those involved in their care.

Following this study, when a pregnant woman is facing the prospect of a non-obstetric operation, it will be possible to give her accurate and up-to-date answers to her inevitable questions regarding the risks to her pregnancy. This accurate information, where there has previously been very little, will improve decision making in a wide range of clinical scenarios. Although we recognise the limitations of our analysis in being able to provide only an absolute risk, and not a true relative risk of outcomes compared to choosing not to have a procedure, we feel that some comparison of

outcomes with mothers not facing a procedure will be useful. If we were to find no excess risk in certain procedures, that may help to reassure mothers, and help remove barriers to potentially unnecessary delays to treatments.

Pregnant women are currently routinely counselled regarding the absolute risk of adverse outcome to the pregnancy if they undergo invasive procedures for diagnostic or therapeutic purposes related to the pregnancy. For example, the risk of miscarriage after amniocentesis performed between 15-20 weeks gestation is quoted as 0.5-1 %; the risk of preterm labour if amniocentesis is performed after 20 weeks is 2-3%. Another example would be external cephalic version (ECV) - external manipulation with ultrasound guidance to turn a breech baby into the cephalic position, in order to facilitate vaginal delivery. Women offered this procedure are for example quoted a 0.5% risk of placental abruption. Women can decide whether or not to proceed with these interventions based on these statistics.

Methods

Proposed stages of research:

1) Define, extract and clean the data.
2) Derive variables within the data set.
3) Analyse the data.
4) Write up.

Stage 1: Define, extract and clean the data

We already hold English hospital episode data. We propose to examine 10 years of data from 2002/3 to 2012/13 and extract data on over 4 million pregnancies.

Gestational age and birth weight are under-recorded on the data in the “baby tails”, but we have recently developed a method for defining such birth cohorts (Murray et al, 2012). We will link delivery records back to form a retrospective cohort of the mothers’ previous admissions and outpatient appointments using patient identifiers. We will use a previously defined classification of significant operating theatre surgical operations (Bottle et al. 2009) to determine what percentage of women undergo operations and when operations are carried out (by trimester).

Stage 2: Derive variables within the data set

For analysis of subsets of data, and for case mix adjustment, we propose to define a number of variables. We will be able to classify both the procedures undertaken during pregnancy with our established OPCS 4 (Classification of Surgical Operations and Procedures, 4th revision) procedure groupings (Bottle et al. 2008), and diagnosis groups using the AHRQ ICD10 Clinical Classification Software.

Flags will be derived for records linked to previous procedures within the data. Other categories will be defined for adjustment for confounders such as maternal age, co-morbidities (using a published score such as Charlson or Elixhauser), socio-economic deprivation (using Carstairs), year of procedure, planned induction or caesarean.

We will derive outcomes based on both the infants' records (low birth weight, prematurity, long length of stay) and the mothers' records (delivery method, long length of stay, complications).

Stage 3: Analysis of data

We will carry out a descriptive analysis of the data describing counts of events (pre-term delivery, low birth weight, long length of stay, delivery methods, complications) by year, maternal age, procedure type, socioeconomic status, trimester of procedure.

We will identify which operations and conditions take place sufficiently frequently to analyse independently. We will also produce a single model incorporating all procedures, adjusting for procedure type as day case v inpatient and, for inpatients, as broad mortality risk group if numbers permit.

We will examine subsets of data with well-coded fields for multiple gestations, parity, gestational age and birth weight, and examine the extent to which the results in those patients missing these data items differ in both outcomes and in other respects. We will carry out sensitivity analysis to examine the possible effects of missing data.

We will calculate the absolute risk and the relative odds of an adverse birth outcome (for miscarriage, still-birth (acknowledging the variable coding of this outcome), preterm delivery, fetal death in hospital, birth weight, NICU admission, long length of stay) occurring in the women who have had a non-obstetric procedure compared with women who haven't during their pregnancy, adjusted for confounders using logistic regression, adjusting for the clustering of patients within hospitals if necessary.

Factors for which we will attempt to adjust include:

- Maternal age
- Multiple gestation
- Parity
- Co-morbidities (in particular diabetes, preeclampsia, pregnancy induced hypertension, obstetric cholestasis and cardiac disease)
- Previous emergency admissions
- Area-level socio-economic status
- Type of procedure
- Year of procedure (i.e. more recent outcomes may be better)

Adjustment for potential confounders is important for attribution of any higher risk that is found to the surgery. We believe that the above list is substantial, though some residual confounding is always possible.

If antenatal operative intervention is associated with higher risk, then numbers needed to harm (NNH) will be estimated.

Stage 4: Write up of results and publication

We will write up our findings and publish them in peer reviewed journals. We will brief the profession through conference presentations, and publicise our results to the general public.

Contribution to collective research effort and research utilisation

The results of this research are relevant to a variety of medical practitioners, including obstetricians, surgeons, anaesthetists and general practitioners, as well as to patients. We will therefore seek to publish our findings in broadly-read general medical journals, as well as presenting them at specialty-specific conferences and producing patient information leaflets. Although we recognise the limitations of our analysis in being able to provide an absolute risk, and not a true relative risk of outcomes compared to choosing not to have a procedure, we feel that some comparison of outcomes with mothers not facing a procedure will be useful. We will make clear these limitations in the dissemination of our work.

Thyroid and breast disease, including cancer, are clinical areas in which the uncertainty of anaesthetic and surgical risk to a pregnancy causes particular anxiety. We have engaged with the British Society of Endocrine and Thyroid Surgeons and the Association of Breast Surgery, both of which have guideline areas (respectively http://www.baets.org.uk/guidelines/; http://www.associationofbreastsurgery.org.uk/publications-guidelines/guidelines/). Both organisations have agreed to consider hosting guidance we produce on their websites.

The data will also be used by institutions such as the Royal College of Obstetricians and Gynaecologists (RCOG) and American College Obstetricians and Gynecologists (ACOG). We are in contact with the RCOG and they are supportive of our study and would assist in the dissemination of findings to both healthcare professionals and the public. In addition, the RCOG currently have several answers to questions on non-obstetric operations in pregnancy in their online query bank, which cite level IV evidence. This evidence level could therefore be improved for future queries.

ACOG publish a committee opinion on non-obstetric surgery during pregnancy, updated to reflect current evidence (last updated 2011). We will contact them directly following publication to ensure they are aware of our study. We will also discuss the possibility of publishing a British guideline taking into account all available evidence, with the RCOG and the Anaesthetists Association of Great Britain and Northern Ireland (AAGBI) and the Royal College of Midwives (RCM).

We will contact the Royal College of Midwives directly to ensure they are aware of our study, and make sure they are included in any joint guidelines produced.

Increasingly, patients are using the internet to search for information - this is particularly true of our patient population. We will ensure that a lay summary of our peer-reviewed findings is available online, initially on the Imperial College website. The Royal College of Anaesthetists publish a series of patient information leaflets which we also aim to use to provide an overview of all the available evidence.

Plan of investigation and timetable

We plan a number of overlapping phases of work within the study, and these are detailed in the attached Gantt chart. We plan to carry out recruitment for our research assistant in the four months prior to the study starting. Any further ethics committee approval that we may require, we hope to resolve in this period too.

- Recruitment and ethics approval – 4 months prior to project starting
- Define extract and clean the data – months 1 and 2
- Derive variables within the data set – months 1 to 4
- Analysis of data – months 4 to 11
- Writing up of results and publication – months 10 to 12.

Approval by ethics committees

Under the UK Health Departments' Governance Arrangements for Research Ethics Committees (GAfREC), there are legal and policy requirements for ethical approval from the National Research Ethics Service (NRES) to be obtained for this project. Under the Health Service (Control of Patient Information) Regulations 2002, Section 251 of the NHS Act 2006, ethical approval is legally required as the project involves access to, and processing of, the confidential information of patients/service users by researchers outside the normal care team without consent (NRES, 2011).

The Dr Foster Unit has permission from the National Information Governance Board under Section 251 of the NHS Act 2006 (formerly Section 60 approval from the Patient Information Advisory Group) to hold confidential data and analyse them for research purposes (ref PIAG 2-05 (d)2007). We have approval to use them for research and measuring quality of delivery of healthcare, from the South East Ethics Research Committee (ref 10/H1102/25). Further permissions will be applied for, as appropriate prior to the study starting, and we have allowed for this in our research timetable. The PI will notify both the ethics committee and the newly formed HRA Confidentiality Advisory Group about the details of this project, but we do not foresee any major issues in obtaining any further ethical permission to carry out this project if required.