Ninth Annual Report 2015

UKOSS

UK Obstetric Surveillance System

We would like to thank all the reporting anaesthetists, midwives, obstetricians, risk managers and other clinicians throughout the UK who have contributed to UKOSS, without whom this work would not have been possible

Royal College of Obstetricians and Gynaecologists

Bringing to life the best in women's health care

npeu National Perinatal Epidemiology Unit

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1. Introduction

The UK Obstetric Surveillance System (UKOSS), a joint initiative between the National Perinatal Epidemiology Unit (NPEU) and the Royal College of Obstetricians and Gynaecologists, was launched in February 2005. This national system has been used to study a range of rare disorders of pregnancy through a system of ongoing data collection, made possible through multi-centre collaborations across the UK[1]. UKOSS is also supported by the Royal College of Midwives, the Obstetric Anaesthetists Association, the NCT, the Faculty of Public Health and the Department of Health.

In the UK, where maternal death is rare, UKOSS provides a platform to generate robust evidence about the risk factors for severe life-threatening complications related to pregnancy and childbirth. Clinicians from all hospitals with consultant-led maternity units in the UK report cases for conditions that are under surveillance, within a designated period, through this routine reporting system. This minimises the possibility of selection bias and inclusion of false positive cases. Furthermore, UKOSS enables collection of detailed information to answer specific clinical questions which cannot be otherwise answered by studies that use routinely collected data[1]. Since its inception, UKOSS has successfully generated evidence to guide prevention and management of major obstetric complications, inform policies, service planning and address patient safety issues and emerging public health issues[1-7]. This has encouraged Australia, New Zealand and several countries in Europe to establish similar systems[8].

Studies using UKOSS may be undertaken by any investigator who identifies a suitable topic and secures funding[9]. Suitable disorders to study are those which are uncommon (usually no more than one case per 2,000 births annually in the UK); are an important cause of maternal or perinatal morbidity or mortality; and which have research questions that can be addressed using the UKOSS methodology (prospective descriptive, cohort or case-control studies). Examples of questions that have been addressed using UKOSS studies are provided in Box-1 overleaf. This report outlines the studies undertaken during the tenth year of surveillance using UKOSS.

2. Methods

This rolling programme is maintained through case notification cards sent to all consultant-led obstetric units in the UK every month with an approach of 'nil-reporting'. We anticipate that all women who experience a condition investigated through UKOSS will be admitted to a consultant-led unit even if their initial care is provided in a different maternity setting. Up to four nominated clinicians (anaesthetists, midwives, obstetricians and risk managers) in each hospital with a consultant-led maternity unit in the UK report to UKOSS. Every month, the nominated individuals are sent a report card with a list of conditions currently under surveillance (Figure 1). They are asked to complete a box indicating the number of cases which have occurred in the previous month, or if none, to return the card indicating a nil return. As a guide, only conditions with an estimated incidence of less than one in 2,000 births are surveyed, and thus the most common response is a nil return. Nil returns are, however, extremely important as they allow us to confirm the number of women in the denominator birth cohort for each study and to ensure that cases are not missed.

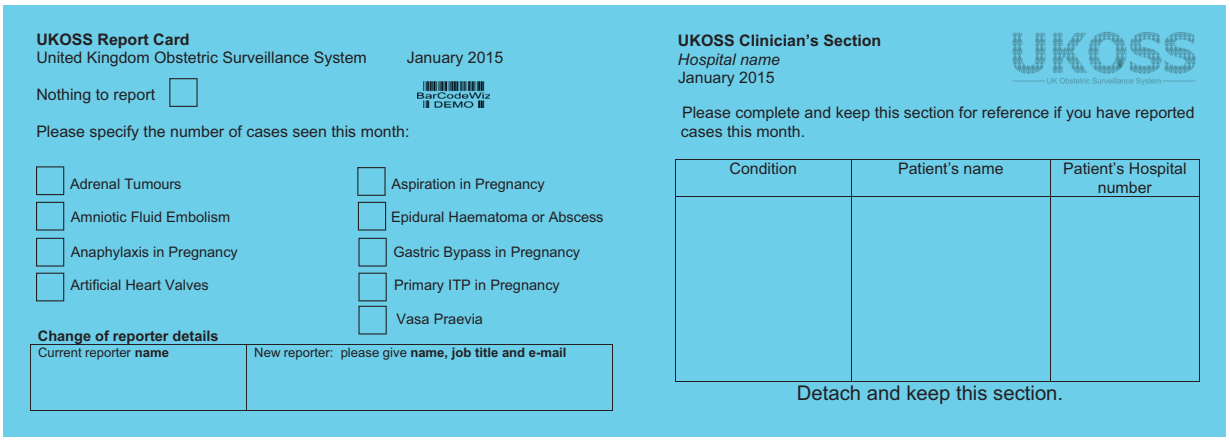
On receiving a case report (return of the monthly card mailing), the UKOSS central team dispatches a data collection form to collect more detailed information about each case. The data collection forms are developed individually for each condition and are designed to be short and easily completed from a woman's case notes without requiring reference to any other sources of information. The data collection forms seek confirmation of the appropriate case definition and additional information on risk factors, management and outcomes according to the protocol relating to each condition. UKOSS does not collect any personally identifiable information, such as women's names, addresses, dates of birth or hospital numbers. Reporting clinicians are asked to keep their own record of the names of women they have reported, in order that they can retrieve the woman's case notes to complete the data collection form. The collection of information only, for the purpose of studying incidence and identifying means to improve patient care, which is not individually identifiable and does not lead to any change in management for the individual patient, is acceptable without requiring individual patient consent[10, 11]. The UKOSS methodology and that of each individual study are approved by a Research Ethics Committee.

In order to perform case-control or cohort studies, information is also collected on control or comparison women for some studies. For these studies only, clinicians who report a case are asked to follow specific instructions to identify appropriate comparison women and complete a similar data collection form from their case notes. The process of selecting comparison women is individual to each study.

Box 1: Examples of questions which can be addressed using UKOSS studies

1. Estimating disease incidence
   - UKOSS surveillance of eclampsia demonstrated a 45% reduction in incidence between 1992 and 2005[3].
2. Describing the prevalence of factors associated with near-miss maternal morbidity
   - A UKOSS study estimated that in 2007-8 more than 1 in every 1200 women delivering in the UK was extremely obese (BMI 50kg/m^2 or greater)[12].
3. Quantifying risk factors for severe morbidity
   - UKOSS surveillance of uterine rupture showed a significant association with induction or augmentation of labour in women with a previous caesarean delivery[6].
   - UKOSS surveillance also showed that women with prior caesarean delivery and placenta praevia diagnosed antenatally had an increased odds of having placenta accreta/increta/percreta[13].
   - UKOSS surveillance of 2009/H1N1 influenza showed a significant association with poor pregnancy outcomes[14].
4. Investigating different management techniques
   - Use of total versus subtotal hysterectomy was examined in the UKOSS study of peripartum hysterectomy for severe haemorrhage but no significant differences in complication rates between the two techniques were found[1, 2].
5. Investigating disease progression
   - A comparison of UKOSS data on severe morbidity with information on women who died identified through the MBRRACE-UK Confidential Enquiry into Maternal Death showed that women who had co-existing medical conditions were more likely to die[15].
6. Auditing of national guidelines
   - UKOSS surveillance of antenatal pulmonary embolism (PE) showed that very few women who had a PE were not receiving thromboprophylaxis according to Royal College of Obstetricians and Gynaecologists guidelines[16, 17].
7. Responding to emerging public health issues
   - In response to the 2009/H1N1 influenza ('swine flu') pandemic, surveillance of women admitted to hospital with confirmed infection was initiated and informed ongoing changes to clinical guidance concerning pregnancy during the course of the pandemic[18].
8. Informing public health policy
   - UKOSS study showing poor perinatal outcomes in pregnant women with 2009/H1N1 influenza[14] was used as evidence to recommend universal immunisation of pregnant women against seasonal influenza[19].

Figure 1: UKOSS Report Card



UKOSS Report Card
United Kingdom Obstetric Surveillance System January 2015

Nothing to report ☐

BarCodeWiz DEMO

Please specify the number of cases seen this month:

☐ Adrenal Tumours
☐ Amniotic Fluid Embolism
☐ Anaphylaxis in Pregnancy
☐ Artificial Heart Valves
☐ Aspiration in Pregnancy
☐ Epidural Haematoma or Abscess
☐ Gastric Bypass in Pregnancy
☐ Primary ITP in Pregnancy
☐ Vasa Praevia

Change of reporter details

Current reporter **name**	New reporter: please give **name, job title and e-mail**

UKOSS Clinician's Section
Hospital name
January 2015

UKOSS
UK Obstetric Surveillance System

Please complete and keep this section for reference if you have reported cases this month.

Condition	Patient's name	Patient's Hospital number

Detach and keep this section.

3. Participation

All 202 units with consultant-led maternity units in the UK contribute to UKOSS. This represents 100% participation of eligible units and effectively means that the denominator for all UKOSS studies is the entire birth cohort in the UK. The mean monthly card return rate during 2014 was 94% (Figure 2), with regional return rates varying between 85% and 99% (Figure 3). These card return rates continue the high rates obtained during the first nine years of reporting, and are a testament to the dedication of reporting clinicians throughout the UK.

Figure 2: UKOSS national card return rates January-December 2014

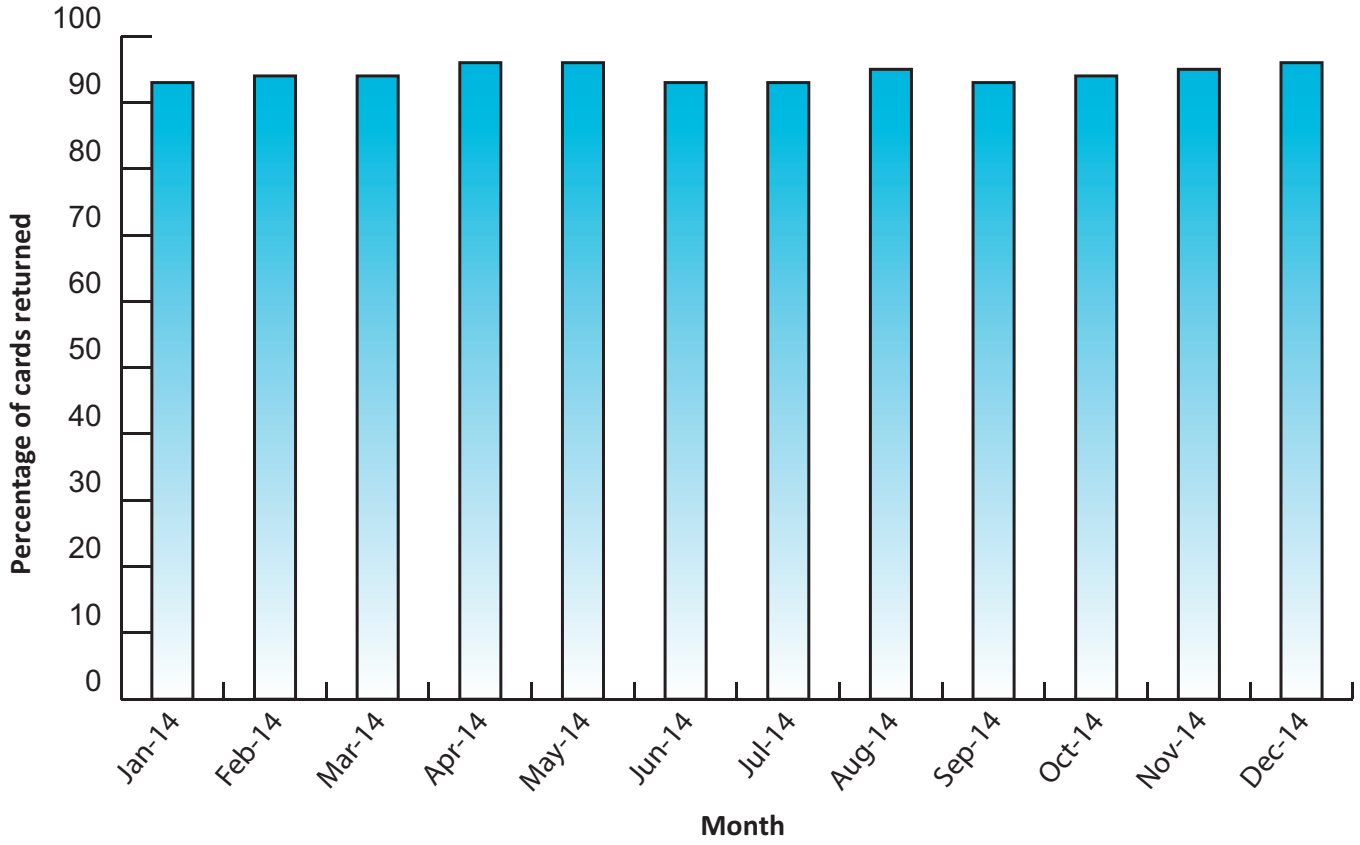
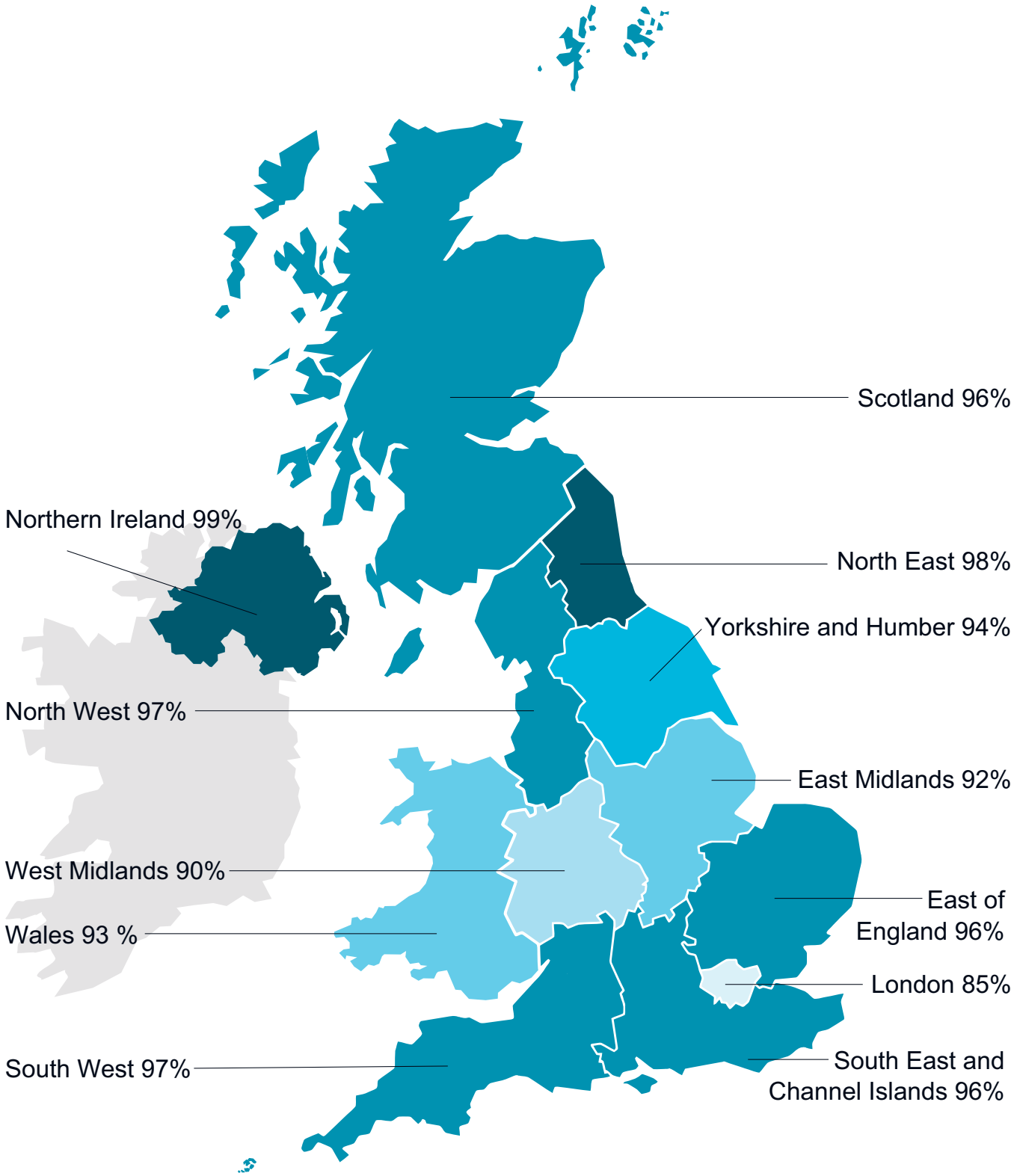


Figure 3: Map showing regional card return rates during 2014

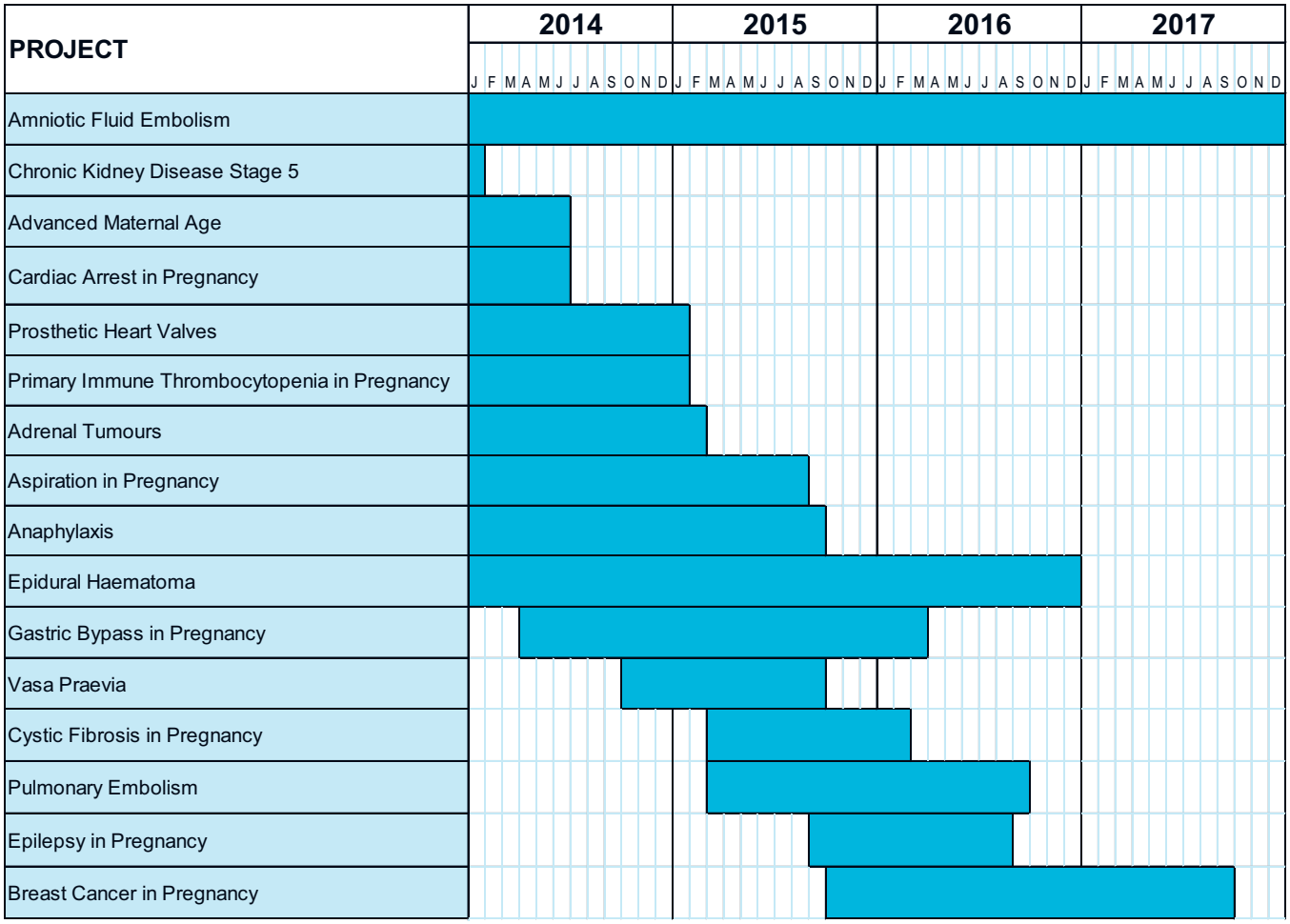


4. Studies

Unless otherwise specified, the results included in this report represent analysis of cases reported and data available up to January 2015. Please note the data presented are provisional, not peer reviewed and definitive conclusions should not be drawn from them.

4.1. Study Timetable

Figure 4: Provisional UKOSS Study Data Collection Timetable 2014-2017



4.2. Studies completed in 2014

4.2.1 Advanced Maternal Age

Key points

- Pregnancies at advanced maternal age are becoming increasingly common in high income countries. In addition, developments in assisted reproductive technologies may contribute to an increasing incidence of pregnancies in women outside of the normal reproductive age.
- Many studies have reported an association between advanced maternal age and adverse maternal and infant outcomes. However, few studies have quantified the risks in women of advanced maternal age.
- This study collected data to describe the characteristics, management and outcomes of women giving birth at advanced maternal age (>48 years) in the UK and estimated the risk of adverse outcomes attributable to very advanced maternal age.

Background

Childbearing at advanced maternal age is becoming increasingly common in high income countries[20, 21]. Furthermore, developments in artificial reproductive technologies, such as ovum donation, may contribute to an increasing incidence of pregnancies in women outside of the normal reproductive age. In England and Wales the average age at childbearing has increased steadily since the mid-1970s from 26.4 years in 1975 to 30.0 years in 2013, with a corresponding rise in the proportion of women delivering in their 30s and 40s[22].

Many studies have reported an association between advanced maternal age and a higher risk of adverse maternal and infant outcomes[23-25]. However, the majority of studies have reported outcomes in women aged ≥35 years or women aged ≥40 years. These studies therefore include only a small number of the oldest mothers and have not specifically assessed the risks in women of advanced maternal age, in whom adverse outcomes could be more common. The small numbers of studies that have specifically investigated outcomes in relation to advanced maternal age[26] have largely not made any attempt to control for potential confounding factors and have predominantly been conducted using retrospective review of medical records over a number of years in a single or small number of institutions. Such studies suffer from a number of limitations such as limited generalisability and lack of statistical power.

Case Definition

All pregnant women in the UK of 20 weeks gestation or more, who are aged 48 years or older at their estimated date of delivery.

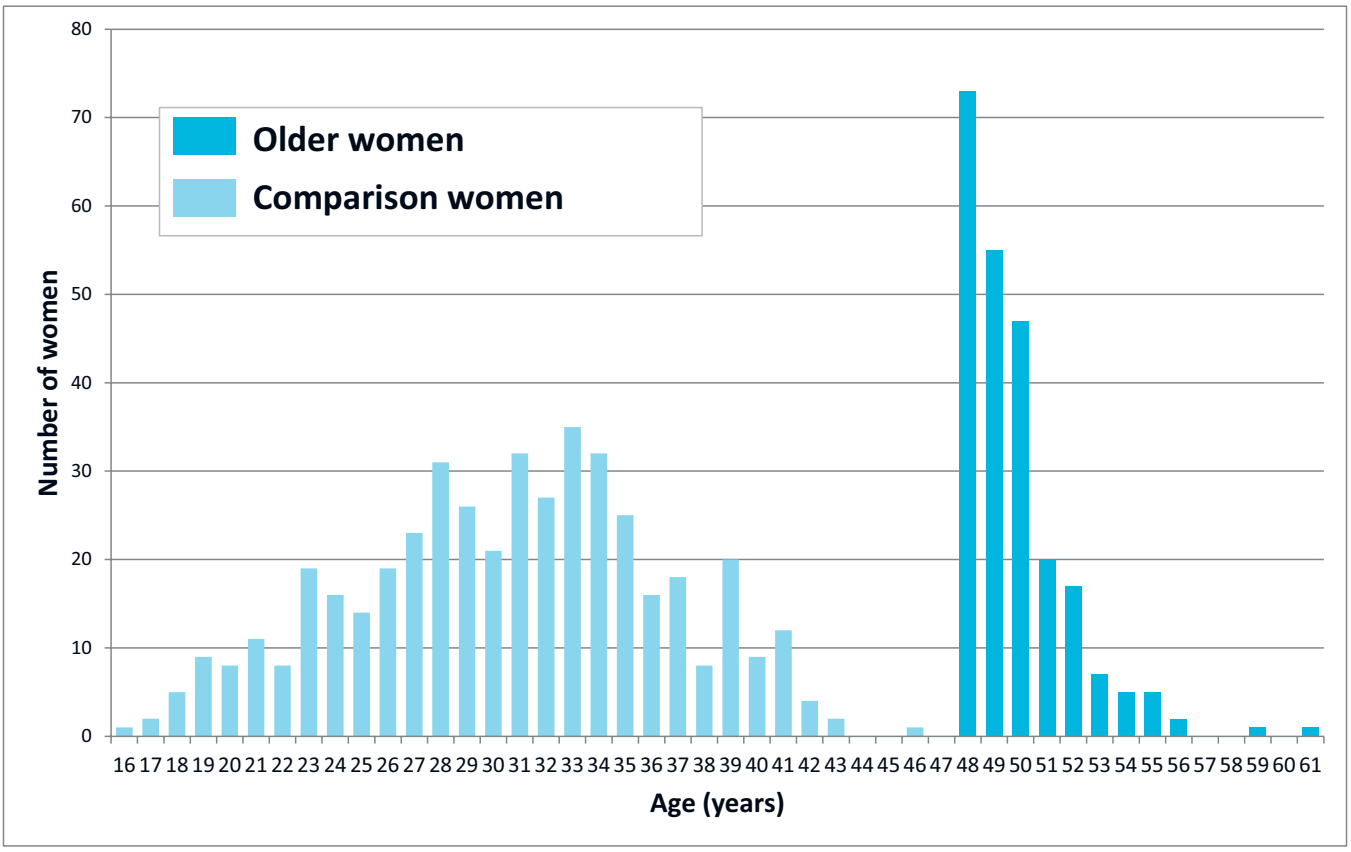
Surveillance Period

July 2013 – June 2014

Interim Results

A total of 233 women of advanced maternal age were notified to UKOSS along with 454 comparison women. The median age of the older women was 49 years (range 48-61 years) while the median age of the comparison women was 31 years (range 16-46 years) (Figure 5). Older women were significantly more likely than comparison women to be overweight (33% v 23%, p=0.0011) or obese (23% v 19%, p=0.0318), to be non-smokers (99% v 90%, p=0.004), have had previous uterine surgery not including previous caesarean section (26% v 7%, p<0.0001), have previous or pre-existing medical condition(s) (44% v 28%, p<0.0001), be nulliparous (53% v 44%, p=0.0299), have a multiple pregnancy (18% v 2%, p<0.0001), and have conceived following assisted conception (78% v 4%, p<0.0001). Unadjusted analysis suggests that older women were more likely than comparison women to have a range of complications including gestational hypertensive disorders (uOR 3.11, 95% CI 1.79-5.38), gestational diabetes (u0R 5.41, 95% CI 3.04-9.65), postpartum haemorrhage (uOR 1.95, 95% CI 1.32-2.88), caesarean delivery (uOR 7.29, 95% CI 5.03-10.55), iatrogenic (uOR 4.49, 95% CI 2.43-8.30) and spontaneous (uOR 2.53, 95% CI 1.27-5.02) preterm delivery and ITU admission (uOR 12.13, 95% CI 1.45-1401.40).

Figure 5: Age distribution of older and comparison women



Interim Conclusions

This interim analysis suggests that women giving birth who are aged 48 or over are at very high risk of both maternal and infant complications and adverse outcomes. These findings should be considered when counselling and managing women of very advanced maternal age.

Investigators

Kate Fitzpatrick, Marian Knight, Jenny Kurinczuk, NPEU;

Derek Tuffnell, Bradford Teaching Hospitals NHS Foundation Trust.

Funding

This study was funded by the National Institute for Health Research as part of the UK National Maternal Near-miss Surveillance Programme (UKNes)*.

UKNeS
The National Maternal Near-miss Surveillance Programme

4.2.2 Cardiac Arrest in Pregnancy

Key points

- The risk of death following a cardiac arrest in pregnancy is extremely high for both mother and child, but both can be resuscitated if fast action is taken.
- Cardiac arrest is managed by resuscitation and periarrest/perimortem caesarean section (PMCS).
- There is little information about survivors of cardiac arrest or PMCS.
- This study investigated the incidence of cardiac arrest and PMCS in pregnancy. It described the current management by resuscitation and PMCS, the associated outcomes for women and their infants, and will help to develop guidelines for optimal management.

Background

Cardiac arrest in pregnancy affects around 1 in 30,000 women[27]; the incidence is thought to be rising due to the increasing age and morbidity of the antenatal population in the UK. The risk of death for mother and child is extremely high but some causes of cardiac arrest are reversible. Aggressive resuscitation is required, including caesarean section in most cases over 20 weeks gestation. The importance of rapid delivery after cardiac arrest for maternal benefit is becoming a widely accepted practice and there is evidence to suggest that MOET (Managing Obstetric Emergencies & Trauma) training in obstetric resuscitation is leading to an increase in the use of PMCS in maternal cardiac arrest in the UK[28] and in Europe[29]. In the UK 52 cases of PMCS were recorded between 2003-2005 amongst women who subsequently died[30]. There is, however, minimal information on survivors of cardiac arrest or PMCS.

Case Definition

Any woman who has received immediate basic life support (BLS) (i.e. chest compressions and usually ventilation breaths) at any point in pregnancy, up to the point of delivery of the baby. **Note** that women requiring ventilatory support only, are **not** included.

Surveillance Period

July 2011 – June 2014

Interim Results

This study was completed at the end of June 2014 and the dataset confirmed by the end of December 2014. A total of 127 cases of cardiac arrest in pregnancy were reported. There were 57 cases which were subsequently reported by clinicians as not cases, duplicate reports or cases which did not meet the case definition. There were thus 70 confirmed cases, an estimated incidence of 2.9 cases per 100,000 maternities. In 47 women (67%) perimortem caesarean section was carried out. Overall 42 women (60%) survived cardiac arrest.

Interim Conclusions

Data analysis and manuscript preparation for this study is still incomplete and it is not possible to draw any definitive conclusions at this stage. However, it appears that these prospective data on cardiac arrest amongst the UK obstetric population are in keeping with previous retrospective estimates; around 1 in 34,000 women developed cardiac arrest during pregnancy.

Investigators

Virginia A. Beckett, Laura McCarthy, Bradford Teaching Hospitals NHS Trust;

Paul Sharpe, University Hospitals of Leicester NHS Trust;

Marian Knight, NPEU.

Funding

This study was funded by Wellbeing of Women.

WELLBEING OF WOMEN

4.2.3 Chronic Kidney Disease Stage 5

Key points

- Pregnancy in women with Chronic Kidney Disease (CKD) Stage 5 is associated with poor fetal outcomes and an increased incidence of maternal complications.
- Dialysis strategies for the management of this group of women are continually developing; however the effects of changes in dialysis dose on mother and fetus are not well defined.
- This study collected information about the incidence, management and outcomes of pregnancy in women with CKD Stage 5 in the UK. This information is important to inform future management and counselling of these women.

Background

Current pre-pregnancy advice given to women with CKD Stage 5 is to delay conception until they receive a renal transplant to restore fertility and improve pregnancy outcomes. Women ineligible for prospective transplantation are counselled regarding high rates of fetal loss, severe preterm delivery, fetal growth restriction and small for gestational age infants, and maternal complications including pre-eclampsia. Dialysis strategies are continually developing; however more intensive dialysis regimes are likely to be associated with treatment related complications (e.g. infection, fluid volume shifts) which may have adverse consequences for the mother and fetus. Furthermore, the dialysis dose (urea clearance) has not yet been shown to be predictive of fetal outcome[31, 32]. More information is needed about the intrauterine effects and neonatal consequences of changes in dialysis dose. This project collected contemporary information about pregnancy outcomes amongst women who currently have CKD Stage 5 during pregnancy in the UK and assessed the role of dialysis regimens and other factors in the outcomes of women and their infants. Outcomes were compared with women with renal transplants matched for age, parity and ethnicity to compare pregnancy outcomes between different forms of renal replacement therapy i.e. dialysis and transplantation.

Case Definition

Any pregnant woman identified as having CKD Stage 5 prior to, or during their pregnancy.

This would usually include any pregnant woman in one of the following groups:

- A woman with an estimated glomerular filtration rate (eGFR) <15mls/min/1.73m^2 pre-pregnancy
- A woman receiving peritoneal or haemodialysis at conception
- A woman with a serum creatinine >300umol/l pre-pregnancy
- A woman with a serum creatinine >250umol/l on two or more occasions during pregnancy
- A woman commenced on peritoneal or haemodialysis to treat CKD during pregnancy

Surveillance Period

February 2012 – January 2014

Interim Results

Forty-one CKD cases were reported and 37 forms received, of which 19 were confirmed cases (11 did not meet the case criteria, 6 were reported in error and there was 1 duplicate).

Thirteen pregnancies in women receiving haemodialysis were identified in the study period, including four women starting haemodialysis during pregnancy. No pregnancies in women receiving peritoneal dialysis were reported. The median number of hours dialysis received per week was 22.5. Adverse dialysis related events included one line infection, one episode of intradialysis hypotension and one fistula thrombosis. One woman had nocturnal haemodialysis. The live birth rate was 100%.

Pregnancy outcomes in women receiving haemodialysis (HD) were compared with those of women with renal transplants (Tx) collected in a previous UKOSS study. There were no differences in maternal age or BMI between HD and Tx pregnancies, but gestation at delivery was earlier in HD pregnancies compared with Tx pregnancies (Median 34.0 weeks (29.6, 37.1) v 36.6 (34.0, 38.0); p=0.049), birth weight was lower (Median 1840g (1385, 2470) v 2522g (2188, 3062); p=0.001) and the proportion of neonatal intensive care admissions was higher (75.0% HD v 33.3% Tx; p=0.01) in women with HD compared with Tx pregnancies.

Rates of pre-eclampsia (25.0% HD v 21.9% Tx) and caesarean section (66.7% HD v 66.7% Tx) were comparable. There was no relationship between number of dialysis hours and neonatal outcomes, or in outcomes between women starting HD or previously established on HD.

Additional analysis will be performed on women with CKD Stage 5 who did not require dialysis during pregnancy.

Interim Conclusions

All women receiving haemodialysis during pregnancy have worse neonatal outcomes than those with renal transplants. The number of dialysis hours per week appears to be increased during pregnancy, but the effects of further augmentation of dialysis dose needs to be explored.

Investigators

Catherine Nelson-Piercy, St Thomas' Hospital, London;

Kate Bramham, Maternal and Fetal Research Unit, King's College London.

Funding

The Lauren Page Trust.

4.3. Studies in progress

4.3.1 Adrenal Tumours in Pregnancy

Key points

- Adrenal tumours secrete excessive hormones which adversely affect maternal and fetal health.
- Maternal adrenal tumours are managed with specific drugs or surgery, but it is not known how these affect the mother, the fetus or the neonate.
- This study is investigating the current incidence of rare maternal adrenal tumours including phaeochromocytomas, those associated with Conn's Syndrome and Cushing's Syndrome. It will describe their current management and the resultant outcomes for women and their infants, and help develop guidelines for their optimal management.

Background

Tumours of the adrenal glands are very rare[33] and information in the medical literature about their incidence and management during pregnancy, and associated maternal, fetal and neonatal outcomes is limited. Phaeochromocytomas, tumours associated with Conn's Syndrome, and adrenal or pituitary tumours linked to Cushing's Syndrome produce excess steroid hormones which are associated with major pregnancy complications[34, 35], including major maternal and fetal morbidity[36] and mortality[37, 38]. Adrenal tumours are linked to higher rates of hypertension[33], diabetes[36] and pre-eclampsia among pregnant women. These can also lead to intrauterine growth restriction, fetal hypoxia[39], fetal distress[33, 40], spontaneous abortion, stillbirth, prematurity[36] and fetal death. Currently, there are no data on the incidence of adrenal tumours in pregnancy in the UK and the associated maternal, fetal and neonatal morbidity and mortality. In addition, there are few guidelines on the appropriate pharmacological or surgical management of these tumours during pregnancy. This study is examining the effects of the drugs used to treat these tumours in relation to maternal, fetal and neonatal complications and timing of the surgery to remove the tumours. This will help the development of guidelines on the management of adrenal tumours in pregnancy with the ultimate aim of improving maternal and infant outcomes.

Case Definition

All pregnant women in the UK with a functioning adrenal neuroendocrine tumour, including women diagnosed pre-pregnancy who have not undergone surgery to remove the tumour.

Included:

Phaeochromocytoma	Neuroendocrine adrenal tumour secreting catecholamines (dopamine, nor-adrenaline, adrenaline, metadrenaline and normetadrenaline)
Cushing's Syndrome	Adrenal cortex tumour secreting excessive amounts of cortisol
Conn's Syndrome	Adrenal cortex adenoma secreting excessive amounts of aldosterone
Excluded:	Women with non-functioning adrenal tumours

Surveillance Period

March 2011 – February 2015

Interim Results

Up to January 2015, 33 cases of adrenal tumours in pregnancy were reported. Information has been received for 31 of these cases (94%). Of these, there were nine cases which were subsequently reported by clinicians as not cases, two duplicate reports and the notes for one case were reported as lost. Seven further cases did not meet the case definition. There were thus 12 confirmed case in an estimated 3,143,436 maternities. This gives an incidence estimate in the UK of 0.4 cases per 100,000 maternities (95% CI = 0.2 to 0.7 per 100,000). The confirmed cases included 7 women with phaeochromocytoma, 4 women with Conn's Syndrome and 1 with Cushing's Syndrome.

Interim Conclusions

Data collection for this study remains incomplete and it is not possible to draw any definitive conclusions at this stage. However, these preliminary results suggest that adrenal tumours in pregnancy are extremely rare.

Investigators

Catherine Williamson, Kimberly Lambert, Imperial College London;

David McCance, Royal Victoria Hospital.

Funding

This study is funded by SPARKS.

4.3.2 Amniotic Fluid Embolism

Key points

- Amniotic fluid embolism (AFE) is a leading cause of direct maternal mortality in the UK; however estimates of incidence and mortality vary widely.
- AFE is associated with older maternal age, multiple pregnancy, placenta praevia, induction of labour, instrumental vaginal and caesarean delivery in the UK population.
- There is no evidence of an increase in incidence over the nine years of UKOSS surveillance.
- Further investigation is needed to establish whether earlier treatments can reverse the cascade of deterioration leading to severe outcomes.

Background

AFE remains one of the leading causes of direct maternal mortality in high-income countries. Estimates of incidence vary from 1.9 and 7.7 per 100,000 maternities. Estimates of the case fatality of this condition also vary widely from 11% to 43%. There is also little consistency in the factors reported to be associated with the occurrence of AFE and very limited data regarding factors associated with severe outcomes.

Case Definition

Either	A clinical diagnosis of AFE (acute hypotension or cardiac arrest, acute hypoxia or coagulopathy in the absence of any other potential explanation for the symptoms and signs observed)
Or	A pathological diagnosis (presence of fetal squames or hair in the lungs)

Surveillance Period

February 2005 – ongoing

Interim Results

Up to January 2015, 203 cases were reported. Information has been received for 195 of these cases (96%). Of these, 21 do not meet the case definition, 26 were subsequently reported by clinicians as not cases, 11 were found to be duplicates and the notes for one case were reported as lost.

The data have been analysed in detail up to January 2014. Up to that date there were 186 notified cases, 23 of which were subsequently reported by clinicians as not cases. Data collection forms were received for 155 (95%) of the remaining notified cases and one additional case identified through the UK Confidential Enquires into Maternal Deaths: 36 were subsequently excluded (11 because they were duplicates, 21 because they did not meet the case definition and four because they were identified by MBRRACE-UK as not cases following confidential enquiry), leaving a total of 120 confirmed cases, 23 of which were fatal (case fatality 19%, 95% CI 12–29%), in an estimated 7,001,438 maternities. This represents a total incidence of

1.7 per 100,000 maternities (95% CI 1.4–2.1) and a fatal incidence of 0.3 per 100,000 maternities (95% CI 0.2–0.5). There was no significant temporal trend in either the total or fatal incidence of AFE during the study period.

Older maternal age, multiple pregnancy, placenta praevia and induction of labour were associated with the occurrence of AFE. Instrumental vaginal and caesarean deliveries were associated with the occurrence of AFE postnatally. No notable change was evident in the risk factors for AFE during the study period.

During the study period, 23 women with AFE died (case fatality 19%) and seven of the surviving women (7%) had permanent neurological injury. Women who died or had permanent neurological injury were more likely to present with cardiac arrest (83% versus 33%; p<0.001), be from ethnic minority groups (adjusted odds ratio (aOR) 2.85, 95% CI 1.02-8.00), have had a hysterectomy (unadjusted odds ratio (uOR) 2.49, 95% CI 1.02-6.06), had a shorter time interval between the AFE event and when the hysterectomy was performed (median interval 77 minutes versus 248 minutes, p=0.03) and were less likely to receive cryoprecipitate (uOR 0.30, 95% CI 0.11-0.80).

Interim Conclusions

Further investigation is needed to establish whether earlier treatments can reverse the cascade of deterioration leading to severe outcomes.

Investigators

Kate Fitzpatrick, Marian Knight, NPEU;

Derek Tuffnell, Bradford Teaching Hospitals NHS Foundation Trust.

Funding

This study was funded by the National Institute for Health Research as part of the UK National Maternal Near-miss Surveillance Programme (UKNes)*.

4.3.3 Anaphylaxis in Pregnancy

Key Points

- Although rare, anaphylaxis during pregnancy can be associated with significant adverse outcomes for both mother and infant, and can be fatal for both.
- There are published guidelines for the management of anaphylaxis in adults; however there is little information about how anaphylactic shock in pregnancy should be managed in order to optimise the outcome for both mother and baby.
- This study is collecting information about the incidence, management and outcomes of anaphylaxis in pregnancy in the UK.

Background

Anaphylaxis is severe and potentially fatal systemic hypersensitivity reaction. It is characterised by a combination of life-threatening airway, breathing and/or circulatory problems with skin or mucosal changes[41]. Current estimates of incidence suggest that maternal anaphylaxis occurs in approximately 1 in 37,000 pregnancies, although this is based on limited evidence[42]. There is currently no published information relating to the incidence of anaphylaxis during pregnancy available for the UK and although this condition is rare, the importance of studying it is highlighted by a number of case studies showing that anaphylaxis during pregnancy can be associated with significant adverse outcomes for both mother and infant[43-46].

Anaphylaxis can be caused by a wide variety of agents and it is unclear as to whether the risk factors for anaphylaxis in the general population such as age, concomitant co-morbidities and previously documented hypersensitivity can accurately predict risk of anaphylaxis in pregnancy[47, 48]. The recent proposed and actual policy changes with regard to antibiotic administration in pregnancy, including the use of prophylactic antibiotics up to one hour prior to delivery by caesarean section and for maternal group B streptococcal carriage in labour[46, 47] have the potential to impact on the incidence and/or outcomes of anaphylaxis during pregnancy, making this study very timely.

Case Definition

Anaphylaxis is defined as a severe, life-threatening generalised or systemic hypersensitivity reaction. The following three criteria must be met for a diagnosis of anaphylaxis to be made:

1. A life-threatening airway problem and/or breathing problem and/or circulatory problem
2. Skin and/or mucosal changes
3. Sudden onset and rapid progression of symptoms

However, skin and/or mucosal features in particular may not be evident if treatment is rapidly implemented, so **include all women in whom the final clinical diagnosis is anaphylaxis, irrespective of the presence or absence of skin/mucosal changes**.

Surveillance Period

October 2012 – September 2015

Interim Results

Up to March 2015, 48 cases of anaphylaxis in pregnancy had been reported. Information has been received for 43 of these cases (90%). There were seven cases which were subsequently reported by clinicians as not cases and one set of notes reported as lost. Six further cases did not meet the case definition criteria. Thus, there were 29 confirmed cases in an estimated 1,959,322 maternities, giving an estimated incidence of 1.5 per 100,000 maternities (95% CI 1.0 to 2.1 per 100,000).

Interim Conclusions

Data collection for this study is still incomplete and it is not possible to draw any definitive conclusions at this stage.

Investigators

Marian Knight, NPEU; Peter Brocklehurst, Institute for Women's Health UCL; Kim Hinshaw, Sunderland Royal Hospital; Nuala Lucus, Northwick Park Hospital; Derek Tuffnell, Bradford Hospitals; Benjamin Stenson, Edinburgh Royal Infirmary; Rhiannon D'Arcy, Oxford University Hospitals.

Funding

This study is part funded by the National Institute for Health Research as part of the UK National Maternal Near-miss Surveillance Programme (UKNeS)* and as part of the programme of work of the Policy Research Unit in Maternal Health and Care (reference number: 108/0001).

4.3.4 Aspiration in Pregnancy

Key points

- Pulmonary aspiration is the most common cause of death in association with complications of airway management.
- Pregnant women are at increased risk of aspiration due to a number of factors including delayed gastric emptying.
- Current policies recommend a light diet in established labour; however it is not clear whether this recent change to policy on oral intake will impact on the incidence of maternal aspiration.
- This study is collecting data to estimate the incidence of maternal aspiration in the UK. It will identify other associated factors and investigate the outcomes for mothers and infants in order to further inform current guidance.

Background

Pulmonary aspiration is defined as the inhalation of foreign material below the level of the vocal cords and into the lower respiratory tract[49, 50]. A recent national audit conducted by the Royal College of Anaesthetists (NAP4) identified aspiration as the most common cause of death in association with complications of airway management[51]. The factors increasing the risk of aspiration associated with pregnancy include the gravid uterus, progesterone-mediated lower oesophageal sphincter relaxation, lower gastric pH and delayed gastric emptying during labour[52]. It has therefore been common practice for maternity units to restrict fluid and oral intake during active labour to reduce the risk of aspiration should the need for an unplanned general anaesthetic occur[53, 54]. However, recent National Institute for Health and Care Excellence (NICE) guidelines have changed and now recommend that "women may eat a light diet in established labour unless they have received opioids or they develop risk factors that make general anaesthetic more likely"[55]. It is not clear whether the change to policy on oral intake will impact on the frequency of maternal aspiration. In addition to a potential increased risk in association with changes in oral intake policy, other known risk factors for aspiration, for example obesity, are becoming more common in the pregnant population. There are thus concerns that maternal aspiration and the consequent risks of severe maternal morbidity and mortality may become an increasing problem in the UK obstetric population. Balanced against this is the increasing use of airway devices, for example second generation supraglottic airway devices, which may protect more effectively against aspiration in the emergency situation than classic devices[51].

Case Definition

All women in the UK at 20 weeks gestation or greater with a final diagnosis of pulmonary aspiration during pregnancy or delivery or up to postpartum discharge from hospital.

Maternal pulmonary aspiration includes women with the following features:

- Women who have had an uprotected airway while unconscious, semi-conscious or paralysed.

AND

- A clinical history consistent with regurgitation of stomach contents and pulmonary aspiration (eg. vomiting after induction of anaesthesia or gastric contents seen in the oropharynx).

AND

- Symptoms/signs of respiratory compromise requiring supplementary oxygen and antibiotics or level 2 or level 3 (HDU or ITU) respiratory support, in the absence of any other clear cause.

Classical radiological findings may or may not be present.

Surveillance Period

September 2013 – August 2015

Interim Results

Up to January 2015, five cases of aspiration in pregnancy were reported. Information has been received for all of these cases (100%).

Interim Conclusions

Data collection for this study is still incomplete and therefore it is not possible to draw any definitive conclusions at this stage. However, the condition appears reassuringly rare.

Investigators

Marian Knight, Vikash Mistry, Jenny Kurinczuk, NPEU; David Bogod, Nottingham City Hospital; Audrey Quinn, Leeds General Infirmary.

Funding

This study has been funded as part of the programme of work of the Policy Research Unit in Maternal Health and Care (reference number: 108/0001).

PRUMHC
POLICY RESEARCH UNIT - MATERNAL HEALTH & CARE

4.3.5 Cystic Fibrosis in Pregnancy

Key points

- The number of recorded pregnancies in the UK of women with cystic fibrosis (CF) has increased over the past five years.
- Pre-pregnancy lung function is often cited as the most important factor in predicting the outcomes of pregnancy for both mother and baby; however it is necessary to clarify the current outcomes in women with CF across the spectrum of lung function.
- This study aims to provide reliable incidence and risk estimates and describe different management strategies across the UK, giving an accurate representation of current practice and outcomes.

Background

Advances in the care of people with CF have led to increasing survival, such that the median predicted survival age of patients in the UK with CF is now 41.4 years, and 53% of all females with the disease are over the age of 16. Fertility in menstruating females with CF is near normal[56] , and increasingly medical professionals are confronted with issues regarding fertility, family planning and pregnancy in this patient group.

Pre-pregnancy lung function is often cited as the most important factor in predicting the outcome of pregnancy for both mother and baby. Maternal forced expiratory volume in one minute (FEV_1) of less than 60% correlates with increased risk of premature delivery, delivery by caesarean section and adverse fetal outcomes such as low birth weight and perinatal death[57, 58]. Based on the limited published evidence, a guideline was published in 2008 for the management of pregnant women with CF[59] which states that along with pre-existing pulmonary hypertension and cor pulmonale, an FEV_1 of less than 50% predicted should be suggested as an absolute contraindication to pregnancy. However, successful pregnancies have been documented in women with much greater impairment in lung function and pre-pregnancy FEV_1 between 20% and 30% predicted are reported[57], leading to the suggestion that advising such women to avoid pregnancy may be unwarranted. Further study is clearly necessary to clarify the current outcomes for pregnancy in women with CF across the spectrum of lung function.

It is anticipated that the results obtained from this study will guide medical professionals in supporting the care of women both planning and during pregnancy and ultimately enabling them to make informed choices regarding pregnancy and planning a family.

Case Definition

All pregnant women with a diagnosis of CF confirmed by CF mutation genotyping either prior to or during the current pregnancy who are booked for antenatal care in a UK obstetric unit.

Surveillance Period

March 2015 – February 2016

Interim Results and Conclusions

This study is at a very early stage, it is thus not possible to draw any conclusions at this stage.

Investigators

Lucy Mackillop, Anna Ashcroft, Stephen Chapman, Oxford University Hospitals NHS Trust.

Funding

This study has been funded by Wellbeing of Women.

WELLBEING OF WOMEN

4.3.6 Epidural Haematoma or Abscess

Key points

- Epidural haematoma and epidural abscess are clinically severe and can cause permanent neurological damage unless diagnosed and treated rapidly.
- The current incidence of both conditions is not fully known yet women are counselled regularly.
- In the case of epidural haematoma, the potential for iatrogenic coagulopathy with Low Molecular Weight Heparin (LMWH) is increasing. Without information about when regional analgesia is safe, women might be denied effective pain relief unnecessarily and equally, regional techniques may well be used at an inappropriate time.
- Both conditions can affect any obstetric unit that offers regional analgesia/anaesthesia and is not limited to high-risk tertiary referral centres.

Background

Approximately 140,000 epidurals are placed annually for labour analgesia in the UK. There are two major but rare complications which merit study as they both occur in an occult manner leading to problems with diagnosis and further management[60]. Vertebral canal haematoma is a very rare but potentially devastating complication occurring either during placement or more typically after removal of an epidural catheter. Epidural abscess formation tends to follow a slower course, with symptoms developing over several days. Diagnosis in both cases can be difficult but delay in recognition and treatment leads rapidly to permanent neurological deficit. These complications are commonly mentioned in the pre-procedure counselling given to women.

Existing estimates of the incidence of epidural haematoma are based on retrospective studies or meta-analysis of the same and are obviously subject to ascertainment bias in that it is unlikely that all obstetric cases are reported in the available literature[61]. The data themselves come from studies from up to and over 20 years old and practice has changed not least in the increasing use of LMWH.

Case Definition

All pregnant women identified as having an epidural haematoma or abscess after a regional anaesthetic technique or attempt at technique.

Surveillance Period

January 2014 – December 2017

Interim Results

Up to January 2015, 12 cases of epidural haematoma or abscess have been reported. Information has been received for six cases (50%) in an estimated 834,408 maternities, all of which are confirmed cases (100%).

Interim Conclusions

Data collection for this study is still incomplete and it is not possible to draw any definitive conclusions at this stage.

Investigators

Felicity Plaat, Imperial College Healthcare;

Marian Knight, NPEU.

Funding

This study is funded by the National Institute for Academic Anaesthesia – The Obstetric Anaesthetists Association Grant.

4.3.7 Gastric Bypass in Pregnancy

Key points

- Obesity is associated with significant maternal and fetal complications during pregnancy and birth.
- Gastric bypass surgery is increasingly being used to treat women of reproductive age, resulting in an increased number of pregnancies following gastric bypass surgery.
- Guidelines for optimal management of pregnancy following gastric bypass surgery have not yet been established.

Background

The prevalence of maternal obesity is rising dramatically in the UK, with approximately 5% of women having a BMI of 35 or over at some point in pregnancy. Indeed, 2% of women giving birth are morbidly obese (BMI>40)[62]. The adverse consequences of obesity on maternal and perinatal health are well established[63]. Gastric bypass surgery is an effective procedure used to achieve weight loss in people with morbid obesity. The most commonly performed surgery is a Roux-en-Y gastric bypass, which can be carried out as an open or laparoscopic procedure. It involves creating a small pouch from the stomach and reconnecting this to a section of the small intestine, bypassing the larger, remaining stomach. These anatomical changes reduce food intake and absorption, thereby inducing weight loss[64]. The increase in gastric bypass surgery amongst women of reproductive age has resulted in an increasing number of pregnancies following bypass surgery.

Several studies and reviews[63-65] have analysed pregnancy outcomes following bariatric surgery. Reports show that pregnancy following gastric bypass surgery is largely safe for both mother and child. Studies demonstrate a reduction in obesity-related gestational complications such as gestational diabetes and maternal hypertension. However, there appears to be conflicting results regarding the incidence of intrauterine growth restriction and mode of delivery following bariatric surgery[64-67]. Complications such as intestinal hernias, nutritional deficiencies[65, 67] and birth defects[67] in pregnancies following gastric bypass surgery have also been cited. Studies conducted thus far emphasise the importance of appropriate monitoring and effective nutritional control, although this is not currently defined.

There is a need for robust evidence regarding how long to delay pregnancy following bariatric surgery. Due to the potential nutritional deficiencies and concomitant complications associated with rapid weight loss, current advice is to delay pregnancy for one year after bypass surgery[63, 68]. However, studies have shown similar maternal and neonatal outcomes between patients who conceived during the first post-operative year, and those who conceived later[63, 69].

Case Definition

Any woman with a confirmed ongoing pregnancy following gastric bypass surgery. Include all types of surgery (Roux-en-Y, duodenal switch, gastric sleeve or other). Excluded: Any woman who had a gastric band.

Surveillance Period

April 2014 – March 2016

Interim Results

Up to January 2015, 124 cases of gastric bypass in pregnancy have been reported. Information has been received for 81 cases (65%) in an estimated 641,853 maternities. Of these, 58 (72%) are confirmed cases, 11 did not meet the case criteria, nine were reported in error and there were three duplicate cases.

Interim Conclusions

Data collection for this study is still incomplete and it is not possible to draw any definitive conclusions at this stage.

Investigators

Katie Cornthwaite, Dimitrios Siassakos, Judith Hyde, Tim Draycott, Andrew Johnson, Southmead Hospital, Bristol.

Funding

This study is funded by North Bristol NHS Trust.

North Bristol NHS Trust

4.3.8 Prosthetic Heart Valves

Key points

- Lifelong anticoagulation is required to prevent thrombosis in women with artificial heart valves.
- Warfarin, the usual anticoagulant, can cause fetal abnormalities. Low molecular weight heparin (LMWH) injections can be used instead and these are safe for the baby, but concerns have been expressed about their efficacy in protecting the mother against heart valve thrombosis.
- This study is investigating the risks associated with an artificial heart valve in pregnancy and the effects of different anticoagulation regimes in order to inform future management guidance.

Background

Women with mechanical prosthetic heart valves require lifelong anticoagulation, usually with warfarin, to prevent valve thrombosis. During pregnancy their thrombotic risk increases (estimated to be as high as 29%[70] with a 2.9% case fatality[71]. Thus, the need for effective anticoagulation is greater than in the non-pregnant state. Warfarin treatment throughout pregnancy appears to be associated with the lowest risk of maternal thrombotic complications[71] but is associated with a higher fetal loss (estimates as high as 59%)[70], and can have damaging effects on the fetus[71]. In contrast, unfractionated heparin or LMWH are safe for the fetus, but doubts have been expressed about their efficacy in preventing maternal thrombotic complications[72]. Factors, such as the type and position of the mechanical valve, choice of anticoagulant regime and patient compliance may all affect the rate of thrombosis.

Counselling of women with artificial heart valves about the risks during pregnancy is difficult due to the paucity of good data relating to maternal or fetal outcomes. Recommendations from various expert groups have suggested that since there is no ideal anticoagulant regime, women should be given the information and encouraged to choose their therapy[73]. Whilst the concept of 'informed choice' is appealing, there is a need for accurate information on which to base this choice. The aim of this study is to provide population based estimates of the incidence of maternal and fetal complications with the different anticoagulant regimes. This would help optimise the future management of pregnant women with artificial valves, to obtain the best outcomes for mother and baby.

Case Definition

All women with artificial mechanical prosthetic heart valves in the UK, who become pregnant during the study period, irrespective of the outcome of the pregnancy. This includes any woman in whom one or more heart valves have been replaced with an artificial mechanical prosthetic heart valve e.g Starr-Edwards ball in cage, Bjork-Shiley tilting disc or St Jude's bi-leaflet valve.

Excluded: Women with a bioprosthetic valve e.g Carpentier-Edwards, Medtronic Intact or Hancock, women with a homograft or women who have had a valvotomy or valvoplasty (unless they also have an artificial mechanical prosthetic heart valve).

Surveillance Period

February 2013 – January 2015

Interim Results

Up to January 2015, 77 cases of pregnancy in women with mechanical prosthetic heart valves have been reported. Information has been received for 63 cases (82%) in an estimated 1,540,446 maternities. Of these, 49 (78%) are confirmed cases, five were reported in error, three did not meet the case definition and there were six duplicate cases. The incidence of mechanical prosthetic heart valves in pregnant women is thus estimated to be 3.2 per 100,000 maternities in the UK (95% CI = 2.4 to 4.2 per 100,000).

Interim Conclusions

Data collection for this study is still incomplete and it is not possible to draw any definitive conclusions at this stage.

Investigators

Sarah Vause, Bernard Clarke, Clare Tower, Charles Hay, Central Manchester University Hospitals NHS Trust; Marian Knight, NPEU.

Funding

This study is funded by Wellbeing of Women.

WELLBEING OF WOMEN

4.3.9 Pulmonary Embolism

Key points

- Thromboembolic disease, including pulmonary embolism (PE) is the current leading cause of direct maternal mortality in the UK.
- The investigations used to diagnose PE carry risks of radiation exposure, reaction to contrast media and false positive diagnosis, are inconvenient for patients and incur costs for the health services.
- This study forms a part of a larger study (DiPEP) aiming to estimate the diagnostic accuracy, effectiveness and cost-effectiveness of strategies for selecting pregnant or postpartum women with suspected PE for imaging.

Background

Thromboembolic disease, including pulmonary embolism (PE) has been identified as the leading cause of direct maternal mortality in the UK[74], but can be difficult to diagnose. Pregnant and postpartum women with appropriately diagnosed and treated PE have a low risk of adverse outcomes, so accurate diagnosis can result in substantial benefits. However, the investigations used to diagnose PE (diagnostic imaging with VQ scanning or CT pulmonary angiography) carry risks of radiation exposure, reaction to contrast media and false positive diagnosis, are inconvenient for patients and incur costs for the health services. Clinicians therefore face a difficult choice when deciding how to investigate suspected PE in pregnant and postpartum women, between risking the potentially catastrophic consequences of missed diagnosis if imaging is withheld and risking iatrogenic harm to women without PE if imaging is over-used.

Current practice

Guidelines from the RCOG[75] recommend that pregnant or postpartum women with suspected PE should all receive diagnostic imaging. Current data suggest that use of this unselective approach is resulting in a low prevalence of PE among those investigated. The most recent studies of suspected PE in pregnancy report prevalence of between 1.4 and 4.2%, while audit data from Sheffield Teaching Hospitals NHS Foundation Trust show a prevalence of 2% among those undergoing imaging. We therefore appear to be exposing 50 women (and fetuses in pregnant women) to the risks of diagnostic imaging for everyone who actually has PE.

These recommendations for pregnant and postpartum women contrast with National Institute for Health and Care Excellence (NICE) guidelines for the general (non-pregnant) population with suspected PE, for whom diagnostic imaging is selectively used based upon structured clinical assessment and D-dimer measurement[76].

D-dimer: current guidance

Studies of D-dimer in pregnant and postpartum women suggest that high levels of positivity at conventional test thresholds limit the diagnostic value of this test. However, indirect evidence from studies of D-dimer for suspected DVT in pregnancy suggests it may have potential diagnostic value with use of a higher threshold[77].

The current RCOG guidance states that D-dimer testing should not be performed to diagnose acute venous thromboembolism (VTE) in pregnancy, but does note that a low level of D-dimer in pregnancy is likely, as in the non-pregnant woman, to suggest that there is no VTE[75]. Guidelines from the European Society for Cardiology state that in pregnancy D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients, i.e. indicates that PE is very unlikely[78].

This study is therefore specifically seeking information about D-dimer levels in women in whom PE is diagnosed, in order that we can further evaluate its diagnostic value and reporters are asked to ensure that this information is obtained where available.

Case Definition

EITHER	PE is confirmed using suitable imaging (angiography, computed tomography, echocardiography, magnetic resonance imaging or ventilation-perfusion scan)
OR	PE is confirmed at surgery or post-mortem
OR	a clinician has made a diagnosis of PE with signs and symptoms consistent with PE present, and the patient has received a course of anticoagulation therapy (>1 week)

Surveillance Period

March 2015 – September 2016

Interim Results and Conclusions

This study is at a very early stage, it is thus not possible to draw any conclusions.

Investigators

Steve Goodacre, Matt Stevenson, Michael Campbell, Judith Cohen, Fiona Elizabeth Lecky, University of Sheffield; Beverley J Hunt, Catherine Nelson-Piercy, Guy's and St. Thomas' NHS Foundation Trust; Wee-Shian Chan, BC Women's Hospital and Health Care, Canada; Steven Thomas, Sheffield Teaching Hospitals NHS Foundation Trust; Marian Knight, NPEU.

Funding

This study has been funded by NIHR HTA.

4.3.10 Severe Primary Immune Thrombocytopenia (ITP) in Pregnancy

Key points

- Primary Immune Thrombocytopenia (ITP) is an acquired immunological disorder characterised by an isolated low platelet count.
- This condition can be acquired during women's reproductive years and is known to develop in pregnancy, but there are no accurate estimates of UK incidence.
- Additionally, there are no high quality prospective studies or randomised clinical trials to inform management of the mother or the delivery.
- This study is investigating the current incidence rate and aims to describe the management and outcomes of severe ITP in pregnancy in the UK.

Background

Primary Immune Thrombocytopenia (ITP) is an acquired immunological disorder characterised by an isolated low platelet count (thrombocytopenia) necessary for normal clotting function. It is defined as a blood peripheral platelet count of <100 x 10^9/l and the absence of any initiating or underlying cause such as antiphospholipid antibody syndrome, SLE or viral infections[79]. This condition can be acquired during women's reproductive years and is known to develop in pregnancy. The current incidence of ITP in pregnancy is not yet estimated accurately. Discrepancies in definition and clinical criteria have led to a wide range of estimates reported to be between 0.1 and 1 case per 1,000 pregnancies[80, 81]. ITP accounts for 3% of cases of thrombocytopenia in pregnancy[81].

Current treatment recommendations for ITP in pregnancy are largely based on clinical experience and expert consensus[79]. There are no high quality prospective studies or randomised clinical trials to inform management of the mother or the delivery. First line treatments include corticosteroids and/or immunoglobulin. Second line treatments include combination therapy of high dose methylprednisolone and IVIg, and rarely splenectomy (advised in the second trimester)[79]. Without clear guidance or strong evidence base for treatment of this rare condition, it is not known how this patient cohort is currently managed in the UK. This study seeks to estimate the current incidence and describe management and outcomes of severe ITP in pregnancy in the UK.

Case Definition

Any pregnant woman who has been diagnosed with thrombocytopenia with a platelet count of <50 x 10^9/l at any point in her pregnancy prior to delivery where obstetric and hereditary causes for thrombocytopenia have been excluded (ie. pre-eclampsia, HELLP syndrome, acute fatty liver of pregnancy, known antiphospholipid antibody syndrome or other hereditary thrombocytopenias)

OR

Any pregnant woman diagnosed with an isolated thrombocytopenia where a clinical decision to treat the thrombocytopenia prior to delivery of the infant has been made.

Excluded

Women with secondary immune thrombocytopenia.

Surveillance Period

June 2013 – January 2015

Interim Results

Up to January 2015, 195 cases of ITP in pregnancy have been reported. Information has been received for 149 cases (76%). Of these, 24 were reported in error, one set of case notes was reported as lost, 14 did not meet the case definition and there were three duplicate cases. Thus, there are currently 107 known confirmed cases in an estimated 1,283,705 maternities. This gives an estimated incidence in the UK of 8.3 per 100,000 maternities (95% CI = 6.8 to 10.1 per 100,000).

Interim Conclusions

Data collection is still incomplete and it is not possible to draw any definitive conclusions at this stage.

Investigators

Angharad Care, Liverpool Women's Hospital;

Zarko Alfirevic, University of Liverpool/Liverpool Women's Hospital;

Marian Knight, NPEU.

Funding

This study has been funded by the ITP Support Association.

4.3.11 Vasa Praevia

Key points

- Vasa praevia carries no major risk to the mother but is associated with significant risk to the fetus.
- Currently routine screening for vasa praevia is not advised by the RCOG and is not supported by the National Screening Committee, on the basis of insufficient information on the case definition, natural history and epidemiology of the condition.
- There is also uncertainty about the accuracy and practical application of the best test to diagnose vasa praevia, and there is no agreed management pathway from women with confirmed vasa praevia and for women with some risk factors in the absence of vasa praevia.
- This study will estimate the incidence of vasa praevia in the UK over one year and examine the clinical management of the condition as well as maternal and neonatal outcomes.

Background

Vasa praevia (VP) describes fetal vessels coursing through the fetal membranes (amnion and chorion) over the internal cervical os and below the fetal presenting part, unprotected by placental tissue or the umbilical cord. Risk factors include bilobed placenta, accessory placental lobes, velamentous cord insertion, multiple pregnancy and in vitro fertilisation (IVF). Data are limited but the reported incidence varies between 1 in 2,000 and 1 in 6,000 pregnancies.

Vasa praevia carries no major risk to the mother but is associated with significant risk to the fetus. When the fetal membranes rupture, the unprotected fetal vessels are at risk of disruption with consequent fetal haemorrhage. Loss of relatively small amounts of blood can have major fetal implications because the fetus has a relatively small blood volume. Planned caesarean section before labour onset and before rupture of the fetal membranes has occurred, is believed to prevent damage to the fragile fetal vessels, and antenatal diagnosis of vasa praevia with planned caesarean section near to term is reported to lead to survival of up to 97%[82]. The incidence of undiagnosed and asymptomatic vasa praevia is not known and has not been previously investigated in the UK.

Currently routine screening for vasa praevia is not advised by the RCOG guideline on management of placenta praevia, and is not supported by the National Screening Committee[83]. This is because "there is insufficient information on the case definition, natural history and epidemiology of the condition". There is also uncertainty on the accuracy and practical application of the best test to diagnose vasa praevia, and there is no agreed management pathway for women with confirmed vasa praevia and for women with some risk factors in the absence of vasa praevia. This study will estimate the incidence of vasa praevia in the UK over one year and examine the clinical management of the condition as well as maternal and neonatal outcomes.

Case Definition

Any woman in the UK with at least one of the following:

- Suspected VP on antenatal U/S >18 weeks gestation, and confirmed VP on antenatal U/S >31 weeks gestation (if not delivered prior to 31 weeks).
- Palpation or visualisation of the fetal vessels during labour.
- Rupture of membranes with bleeding associated with fetal death/exsanguination or severe neonatal anaemia.
- Antenatal or intrapartum bleeding of fetal origin with pathological CTG and/or positive Apt test.
- VP documented in medical records as reason for admission and caesarean section.

AND at least one of:

- Clinical examination of the placenta confirming intact or ruptured velamentous vessels. These may be a velamentous insertion of the umbilical cord or exposed fetal vessels between placental lobes.
- Pathological confirmation of vasa praevia.
- Torn umbilical cord or placenta (hence unable to provide placental examination).

Surveillance Period

December 2014 – November 2015

Interim Results and Conclusions

Up to March 2015, 15 cases of vasa praevia were reported. So far information has been received for four cases. It is thus not possible to draw any definitive conclusions at this stage.

Investigators

George Attilakos, UCLH; Anna David, Institute for Women's Health UCL; Peter Brocklehurst, Institute for Women's Health UCL.

Funding

This study has been funded by the UCLH NIHR Research Capability Fund.

4.4. Future Studies

These studies have been approved by the UKOSS Steering Committee to commence in 2015.

4.4.1 Breast Cancer in Pregnancy

Key points

- The diagnosis of breast cancer in pregnancy can have devastating consequences for women and their families.
- Treatment regimens vary and we do not know either the incidence of newly diagnosed breast cancer or the short-term outcomes for women and their babies.
- Little is known about what choices women make when continuing with pregnancy.
- The knowledge gained from this study will enable further study of all breast cancer in pregnancy and longer term outcomes in the UK.

Background

The actual incidence of breast cancer in pregnancy in the UK is not known. Estimates from other countries range from 2.4 to 7.8 cases per 100,000 births. This gives an estimated 18 to 61 cases per year in the UK. We are seeing women with a history of breast cancer now getting pregnant as survival rates increase, but surveillance of this would inform a further study in the future.

Although the incidence of breast cancer rises with age, the observation that many women are delaying their families until later in life means that the incidence of breast cancer arising for the first time in pregnancy may be rising. At the other end of the scale, for women under 30, a significant proportion (more than 10%) of breast cancers may be associated with pregnancy, or within a year afterwards.

The diagnosis of breast cancer in pregnant women may be difficult[84] and there is a potential for under-treatment of the mother and iatrogenic prematurity for the fetus. Due to its relative rarity, we lack a standardised approach to managing these women. There is also an apparent contradiction between advice in Europe in general[85] and UK specific advice from the RCOG about the timing of interventions and delivery[86]. A group in Australia and New Zealand are conducting a similar study, which will make comparisons hugely informative[87].

It is clear that such cases should be managed within a multidisciplinary team within established cancer networks, in close liaison with obstetric and paediatric teams. Treatment is influenced by a number of factors, including histological grade, receptor and HER2 (Human epidermal growth factor receptor 2) status and suspicion of metastases. There is variation in approach to surgery and chemotherapy regimens that have yet to be described. A 2 – 3 week gap is recommended after last chemotherapy prior to delivery in order to reduce the problems of neonatal neutropenia, for example, but this may not always be possible or planned.

Case Definition

Any women meeting one of the following criteria:

- Newly diagnosed cases of breast cancer during pregnancy.
- Pathological diagnosis of breast cancer during pregnancy.
- Confirmed diagnosis of breast cancer during pregnancy determined from the medical record.

Excluded:

- Breast cancer diagnosed before pregnancy.
- Recurrence of breast cancer in current pregnancy.

Main research questions

- What is the current incidence of primary breast cancer in pregnancy in the UK?
- How does breast cancer present and at what gestation?
- How is breast cancer managed in pregnancy in the UK?
- Is there variation in the timing of surgical intervention?
- What are the short-term outcomes for mother and infant?

Investigators

Philip Banfield, Claudia Hardy, BCUHB North Wales; Julie Jones, North Wales Cancer Centre; Sarah Davies, Lynda Sackett, BCU Health Board North Wales; Marian Knight, NPEU.

Funding

This study is being funded by the Betsi Cadwaladr University Health Board (BCUHB)

4.4.2 Epilepsy in Pregnancy

Key points

- Epilepsy is the most common neurological disorder encountered in pregnancy and affects one percent of the UK population[88, 89].
- The majority of women with epilepsy can expect a normal pregnancy, however epilepsy continues to be an important indirect cause of death for a minority of women.
- It is clear from successive confidential enquiries that the management of women with epilepsy who die can be improved[90].
- There have been repeated calls amongst the research community for high-quality, prospective data enabling the value of current policy recommendations to be assessed[91-93].

Background

Amongst women presenting for maternity care, approximately 1 in 200 are receiving treatment for epilepsy, with a mortality risk that is almost 10 times greater than that of the general maternity population (100 versus 11 per 100,000 maternities respectively)[94, 95].

Between 2010 and 2012, 14 maternal deaths were attributed to epilepsy (maternal mortality risk =0.04/100,000), more than any direct cause of death with the exception of thrombosis, and unchanged from 2006-2008[90]. Of these 14 deaths, 12 were classified as cases of 'Sudden Unexplained Death in Epilepsy' (SUDEP)[90]. Whilst the definition of SUDEP implies a diagnosis of exclusion, expert-consensus maintains that generalised tonic-clonic seizure activity is likely to be a significant component of the phenomenon and should be considered as a sentinel event leading up to death[91, 96]. As such, it follows logically that women in whom generalised tonic-clonic seizure activity persists during pregnancy represent a severe disease phenotype amongst women with epilepsy, with an increased risk of mortality.

Treatment goals for women with epilepsy in pregnancy target a seizure free 'steady-state' before conception on the basis that 1) the risk of seizures during pregnancy reduces as a function of the length of the seizure-free period before conception, and 2) those women who are able to remain seizure free for >12 months prior to conceiving are highly unlikely to have a recurrence of seizure activity when pregnant [93, 95, 97]. Whilst this is certainly feasible for the majority of women, it is clear that seizures persists for a minority of women in whom it is considered that treatment plans are adequate[98]. What is unclear amongst this group of women with poorly controlled epilepsy, is the relative contribution of women with severe, drug-resistant epilepsy versus the proportion of women whose disease management is suboptimal, or in whom fears about the potential for teratogenic side effects when using anti-epileptic drugs compromises their treatment adherence.

To date, the majority of published data describing maternal outcomes are derived from secondary analyses of studies assessing the safety and efficacy of anti-epileptic drug use in terms of fetal outcomes and are thus subject to a range of biases; primarily as the consequence of selecting only those women requiring anti-epileptic drugs for management of epilepsy but also by excluding cases that result in maternal death and restricting follow-up to include only live newborns[99]. As a consequence, the extent to which findings can be generalised to the wider pregnant population as the basis for policy and guideline development must be questioned.

Case Definition

Any pregnant woman in the UK who fulfils at least one of the following criteria:

- A woman with epilepsy who dies during pregnancy or up to day 42 postpartum, where the cause of death is directly attributed to the consequences of epilepsy, including SUDEP
- A woman with epilepsy who is admitted to hospital for management of generalised tonic-clonic seizures during pregnancy or the postpartum period
- All women being treated with >3 anti-epileptic drugs at any point during their pregnancy

Main research questions

- What is the prevalence of poorly controlled epilepsy amongst pregnant women in the UK?
- How are women clinically managed with poorly controlled epilepsy?
- What is the uptake of specialist obstetric and epilepsy services amongst women with poorly controlled epilepsy?
- What are the seizure characteristics of pregnancy women with poorly controlled epilepsy?
- What are the maternal and newborn pregnancy outcomes amongst women with poorly controlled epilepsy compared to those with well controlled epilepsy?

Investigators

Bryn Kemp and Marian Knight, NPEU; David Williams, University College London Hospitals.

Funding

This study is funded by the National Institute for Health Research (NIHR) as part of a Professorship award to Professor Marian Knight.

5. Publications

5.1. Factors associated with maternal death from direct pregnancy complications: a UK national case-control study

Published Article

Nair M, Kurinczuk JJ, Brocklehurst P, Sellers S, Lewis G, Knight M. (2015) Factors associated with maternal death from direct pregnancy complications: a UK national case-control study. BJOG. 2015; DOI: 10.1111/1471-0528.13279.

Key points

- The most recent report from the MBRRACE-UK Confidential Enquiry into Maternal Deaths showed that almost three quarters of women who died during or shortly after pregnancy had co-existing medical disorders. This included women who died from direct causes as well as indirect causes.
- The objectives of this analysis were to further investigate the potential role of medical co-morbidities in the progression from severe morbidity to direct maternal death among pregnant women in the UK, by undertaking a case–control study comparing data from UKOSS on women who survived, with data from MBRRACE-UK on women who died from specific direct pregnancy complications.
- Data on 135 women who died from eclampsia, pulmonary embolism, severe sepsis, amniotic fluid embolism, and peripartum haemorrhage between 2009 and 2012 were compared with data on 1661 women who survived these complications identified from UKOSS studies conducted between 2005 and 2013.
- Six factors were independently associated with maternal death: inadequate use of antenatal care (adjusted odds ratio, aOR 15.87, 95% CI 6.73-37.41); substance misuse (aOR 10.16, 95% CI 1.81-57.04); medical comorbidities (aOR 4.82, 95% CI 3.14-7.40); previous pregnancy problems (aOR 2.21, 95% CI 1.34-3.62); hypertensive disorders of pregnancy (aOR 2.44, 95% CI 1.31-4.52); and Indian ethnicity (aOR 2.70, 95% CI 1.14-6.43).
- Seventy percent of the increased risk associated with maternal death could be attributed to these factors (95% CI 66-73%). Almost 50% of the increased risk was associated with medical co-morbidities.
- This study shows that medical comorbidities are importantly associated with direct (obstetric) deaths and not solely indirect deaths. This highlights the importance of optimal care for women with pre-existing medical problems in pregnancy.

5.2. Pregnancy outcome in patients with sickle cell disease in the UK – a national cohort study comparing sickle cell anaemia (HbSS) with HbSC disease

Published Article

Oteng-Ntim E, Ayensah B, Knight M and Howard J. (2015) Pregnancy outcome in patients with sickle cell disease in the UK – a national cohort study comparing sickle cell anaemia (HbSS) with HbSC disease. British Journal of Haematology. 2015; Apr;169(1):129-37

Key points

- Historical data suggest that sickle cell disease (SCD) in pregnancy is associated with a high incidence of maternal and fetal complications; however, there are few recent studies.

- The objectives of this study were to describe on a national basis the maternal and fetal outcomes of SCD in pregnancy and to compare outcomes in the two most common genotypes, HbSS and HbSC.
- One hundred and nine pregnancies in women with SCD were reported over one year; the majority (88%) were Black Caribbean or Black African women. 51 women (47%) had HbSS and 44 (40%) had HbSC.
- Women with HbSS were significantly more likely than women with HbSC to receive a transfusion during pregnancy (43% vs. 7%), have a painful crisis during pregnancy (77% vs 27%) or postnatally (22% vs 2%), and to be admitted to an intensive care unit (29% vs 11%).
- Severe or extremely severe crises (requiring hospital attendance or admission) occurred in 18% of women with HbSS and 9% of women with HbSC (P = 0·23). Acute Chest Syndrome was seen in both HbSS and HbSC (10% vs. 5%, P = 0·3).
- Women with HbSS were more likely to deliver at <37 weeks gestation (P = 0·01) and their babies were more likely to have reduced birth weight. Delivery at <34 weeks was increased in both HbSS and HbSC women (6% vs. 5%) compared to national data.
- This study confirms a high rate of maternal and fetal complications in mothers with SCD, even in women with HbSC, which has previously been considered to have a more benign phenotype in pregnancy.

5.3. Severe maternal sepsis in the UK, 2011-2012: a national case-control study

Published Article

Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M on behalf of the United Kingdom Obstetric Surveillance System. (2014) Severe maternal sepsis in the UK, 2011-2012: a national case-control study. PLoS Med. 2014 Jul 8;11(7):e1001672.

Key points

- Maternal death from sepsis is increasing in countries with advanced healthcare systems. Sepsis is now the leading cause of direct maternal death in the UK.
- The objectives of this national prospective case-control study were to estimate the incidence, describe the causative organisms and sources of infection, and identify the risk factors for severe maternal sepsis in the UK.
- There were 365 confirmed cases of severe maternal sepsis between June 2011 and May 2012, an incidence of 4.7 (95% CI 4.2–5.2) per 10,000 maternities; 71 (19.5%) women developed septic shock; and five (1.4%) women died.
- Genital tract infection (31.0%) and the organism *E coli* (21.1%) were most common.
- Women had significantly increased adjusted odds of severe sepsis if they were black or other ethnic minority (aOR = 1.82; 95% CI 1.82–2.51), were primiparous (aOR = 1.60; 95% CI 1.17–2.20), had a pre-existing medical problem (aOR = 1.40; 95% CI 1.005–1.94), had febrile illness or were taking antibiotics in the two weeks prior to presentation (aOR = 12.07; 95% CI 8.11–17.97).
- All forms of operative delivery were associated with increased risk of sepsis.
- Multiple pregnancy (aOR = 5.75; 95% CI 1.54–21.45) and infection with group A streptococcus (aOR = 4.84; 2.17–10.78) were associated with progression to septic shock.
- This study suggests that for each maternal sepsis death, approximately 50 women have life-threatening morbidity from sepsis. Follow-up to ensure infection is eradicated is important.
- The rapid progression to severe sepsis highlights the importance of following the international Surviving Sepsis Campaign guideline of early administration of high-dose intravenous antibiotics within one hour of admission to hospital for any woman with suspected sepsis.
- Signs of severe sepsis in peripartum women, particularly with confirmed or suspected group A streptococcal infection, should be regarded as an obstetric emergency.

5.4. Incidence, Risk Factors, Management and Outcomes of Amniotic Fluid Embolism: a population-based cohort and nested case-control study

Published Article

Fitzpatrick K, Tuffnell D, Kurinczuk J, Knight M. (2015) Incidence, Risk Factors, Management and Outcomes of Amniotic Fluid Embolism: a population-based cohort and nested case-control study. BJOG. 2015 Feb 12; doi: 10.1111/1471-0528.13300 [Epub ahead of print]

Key points

- Amniotic fluid embolism (AFE) remains an important cause of maternal death, which is difficult to study due to its rarity. Surveillance of AFE through UKOSS has been ongoing since 2005.
- The objectives of this analysis were to describe the incidence, risk factors, management and outcomes of AFE over time, using data collected through UKOSS between 2005 and 2014.
- One hundred and twenty women with AFE were identified over nine years, representing an incidence of 1.7 cases per 100,000 maternities (95% CI 1.4-2.1), with a case fatality rate of 19% (95% CI 12-29%).
- The results showed that there was no significant change in the incidence or fatal incidence of AFE over the time period of the study.
- In common with previous analyses, women aged 35 years and over had significantly raised odds of having AFE. The odds of having AFE were also significantly increased in women who had a multiple pregnancy, placenta praevia and induction of labour using any method.
- Women who died or who had permanent neurological injury were more likely to present with cardiac arrest (83% versus 33%, $P < 0.001$), be from ethnic-minority groups (aOR 2.85, 95% CI 1.02–8.00), to have had a hysterectomy (OR 2.49, 95% CI 1.02–6.06), and were less likely to receive cryoprecipitate (OR 0.30, 95% CI 0.11–0.80).
- These findings may reflect that the women who die or have permanent neurological injury are sickest at presentation; however, further investigation is warranted to establish whether better and more rapid correction of coagulopathy, through the use of cryoprecipitate, fresh frozen plasma, platelets and fibrinogen is associated with improved outcomes.

5.5. Abstracts

The following abstracts were presented at meetings in 2014/2015:

- Cardiac Arrest in Pregnancy, preliminary findings. British Maternal and Fetal Medicine 17th Annual Conference, April 2015.
- Haemostatic changes, transfusion management and clinical outcomes of obstetric massive transfusion cases in the UK. BSH Annual Scientific Meeting, April 2015.
- Pregnancy at very advanced maternal age in the UK. British Maternal and Fetal Medicine 17th Annual Conference, April 2015.

5.6. UKOSS Publications to date

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