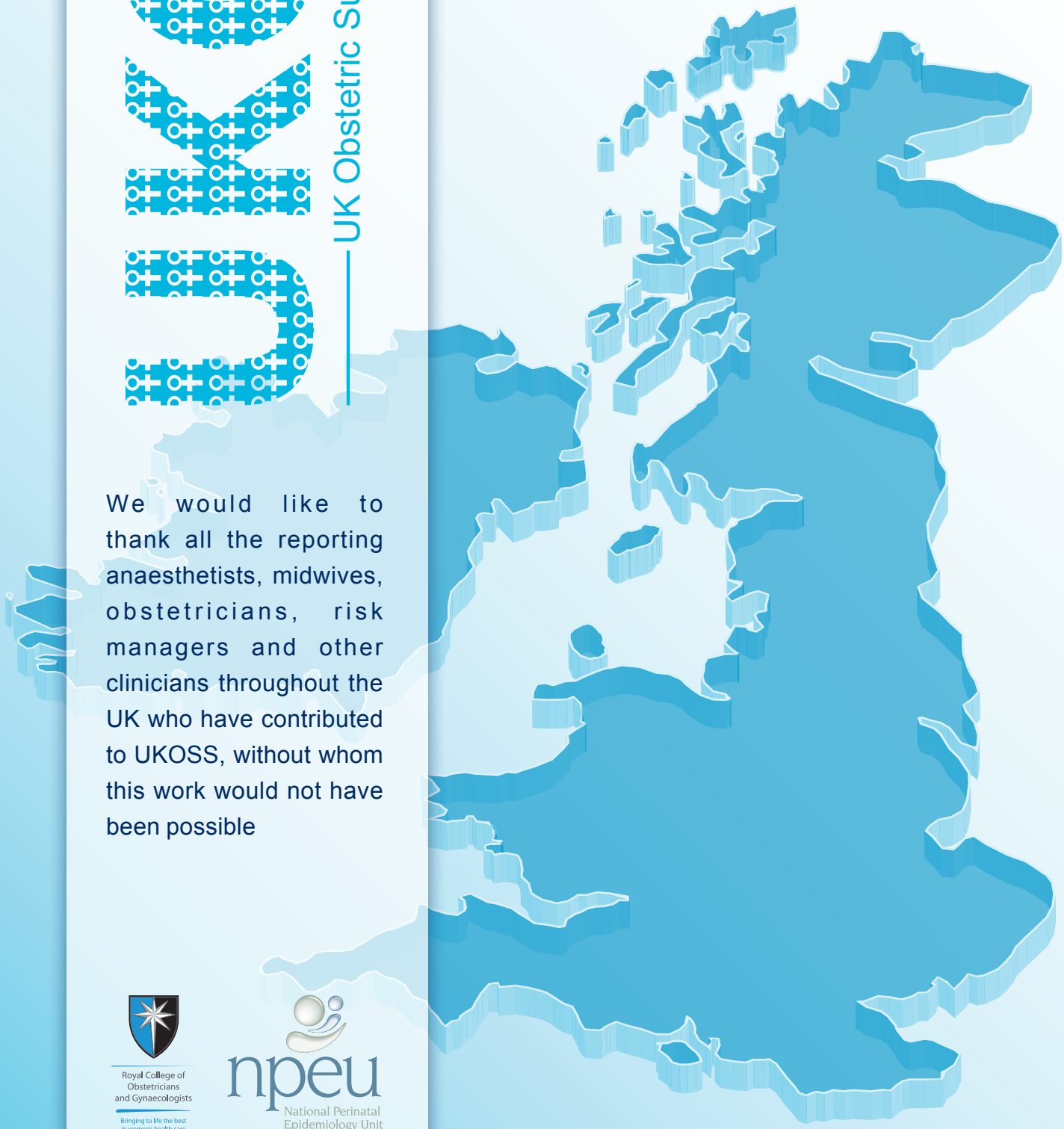
UKOSS

UK Obstetric Surveillance System

Tenth Annual Report 2016



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. UKOSS is also supported by the Royal College of Midwives, the Obstetric Anaesthetists Association, the NCT, the Faculty of Public Health, the Department of Health and Public Health England.

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 the prevention and management of major obstetric complications, inform policy, 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 2000 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. This report outlines the studies undertaken during the eleventh 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 (from anaesthetists, midwives and obstetricians to risk managers and data analysts) 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 2000 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.

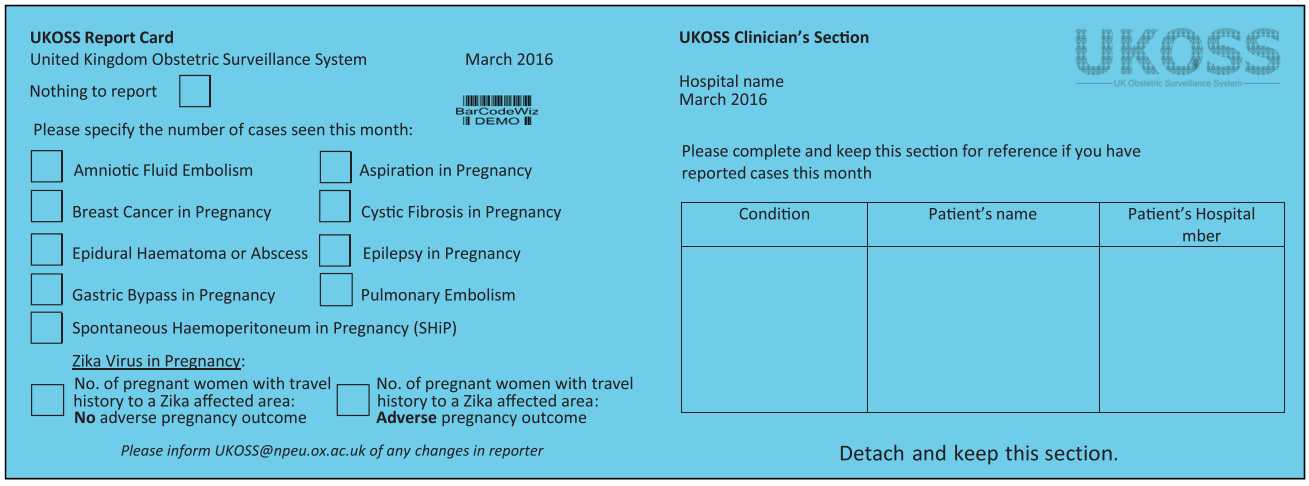
On receiving a case report (return of the monthly card mailing), the UKOSS central team dispatches a data collection form to collect more detailed information about each case. The data collection forms are developed individually for each condition and are designed to be short and easily completed from 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 has Research Ethics Committee approval.

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
   - Analysis of the UKOSS severe sepsis study showed that the incidence of confirmed severe maternal Group B streptococcal sepsis was very low (12).
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) (13).
3. Quantifying risk factors for severe morbidity
   - UKOSS surveillance of uterine rupture showed and quantified 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 (14).
   - UKOSS surveillance of 2009/H1N1 influenza showed a significant association with poor pregnancy outcomes (15).
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 the characteristics of women who died identified through the MBRRACE-UK Confidential Enquiry into Maternal Death with UKOSS data on control women showed that 66% of the increased risk of maternal death from direct and indirect causes at the population level could be attributed to medical comorbidities (16).
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 (17, 18).
7. Responding to emerging public health issues
   - Surveillance of ZIKV associated adverse pregnancy outcomes was rapidly instituted in 2016 in response to the WHO declaration of a global public health emergency.
8. Informing public health policy
   - UKOSS study showing poor perinatal outcomes in pregnant women with 2009/H1N1 influenza (15) was used as evidence to recommend universal immunisation of pregnant women against seasonal influenza (19).

Figure 1: UKOSS Report Card



3. Participation

All 200 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 2015 was 94% (Figure 2), with regional return rates varying between 85% and 100% (Figure 3). These card return rates continue the high rates obtained during the first ten 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 2015

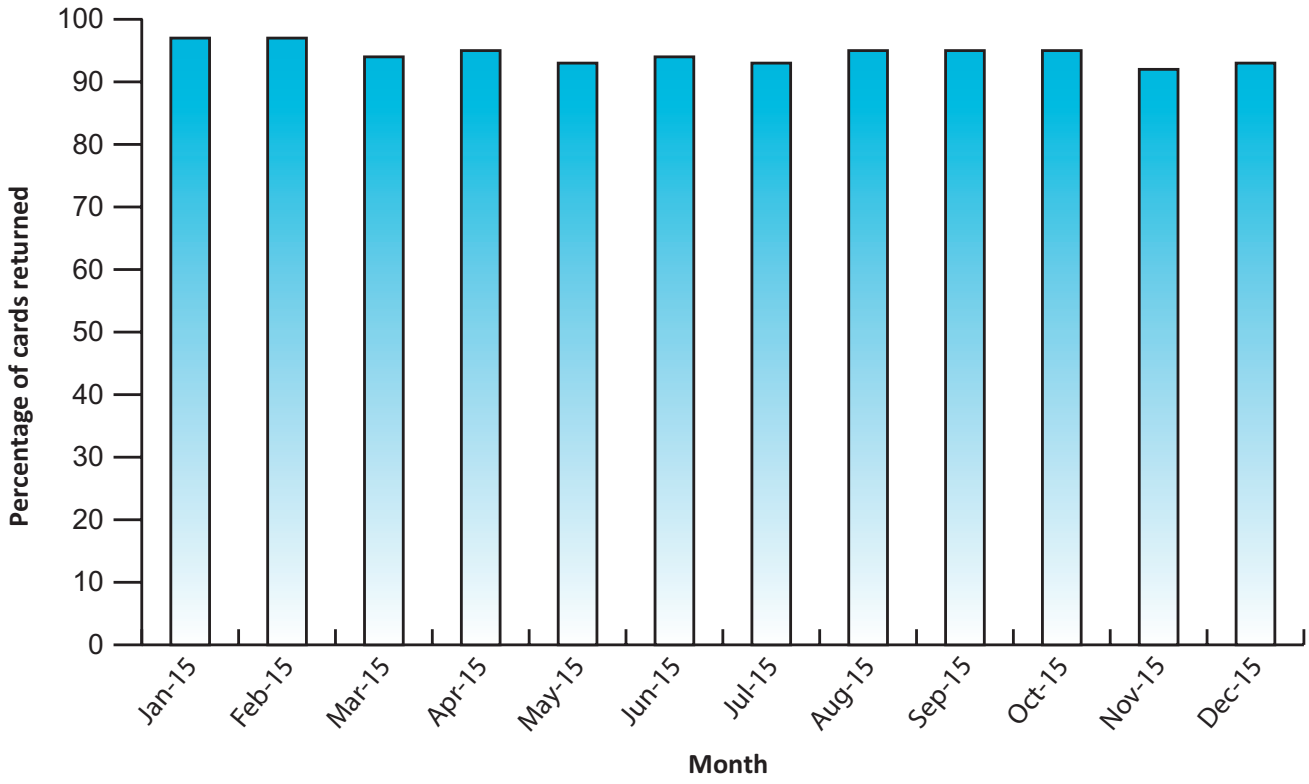
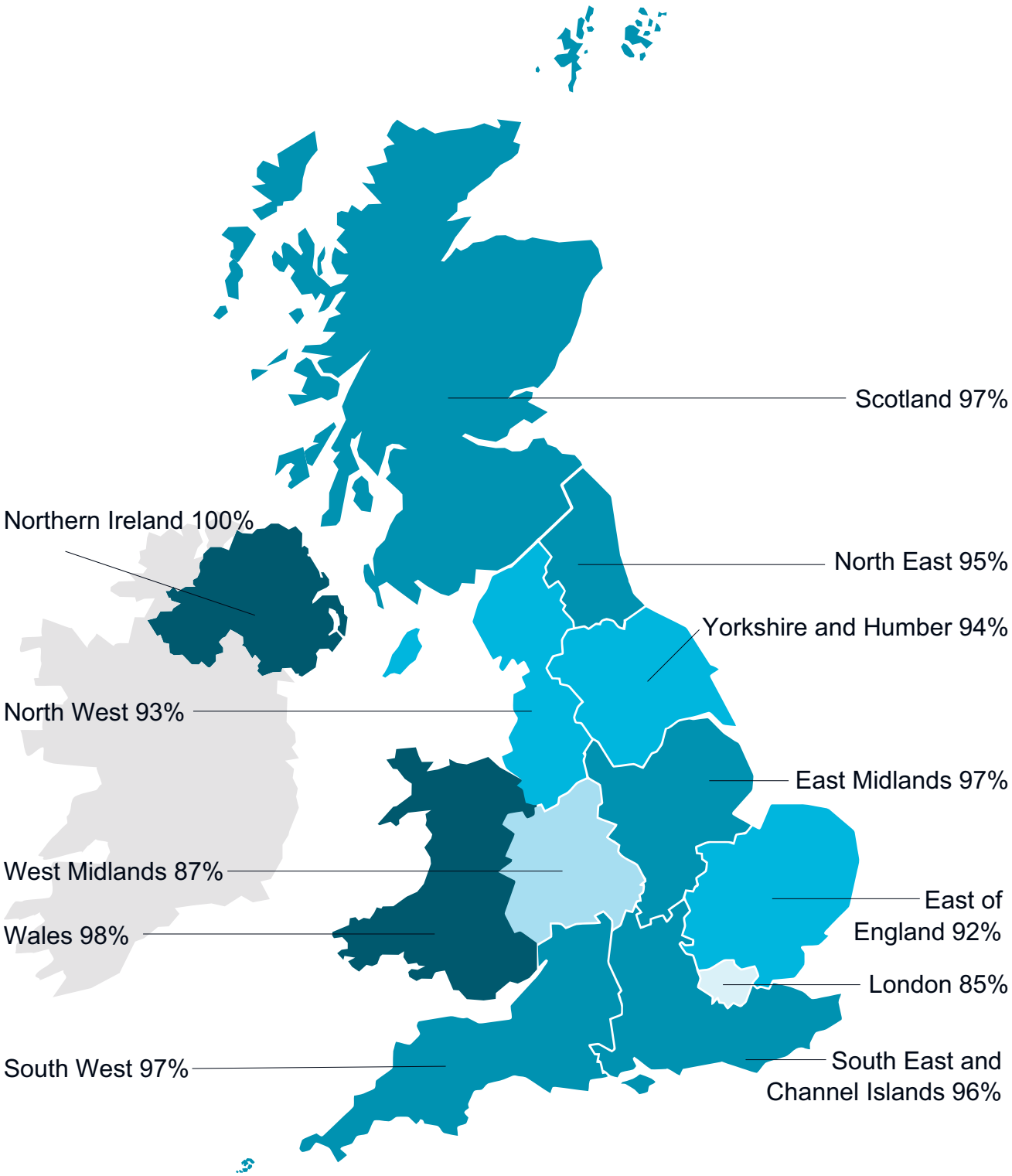


Figure 3: Map showing regional card return rates during 2015

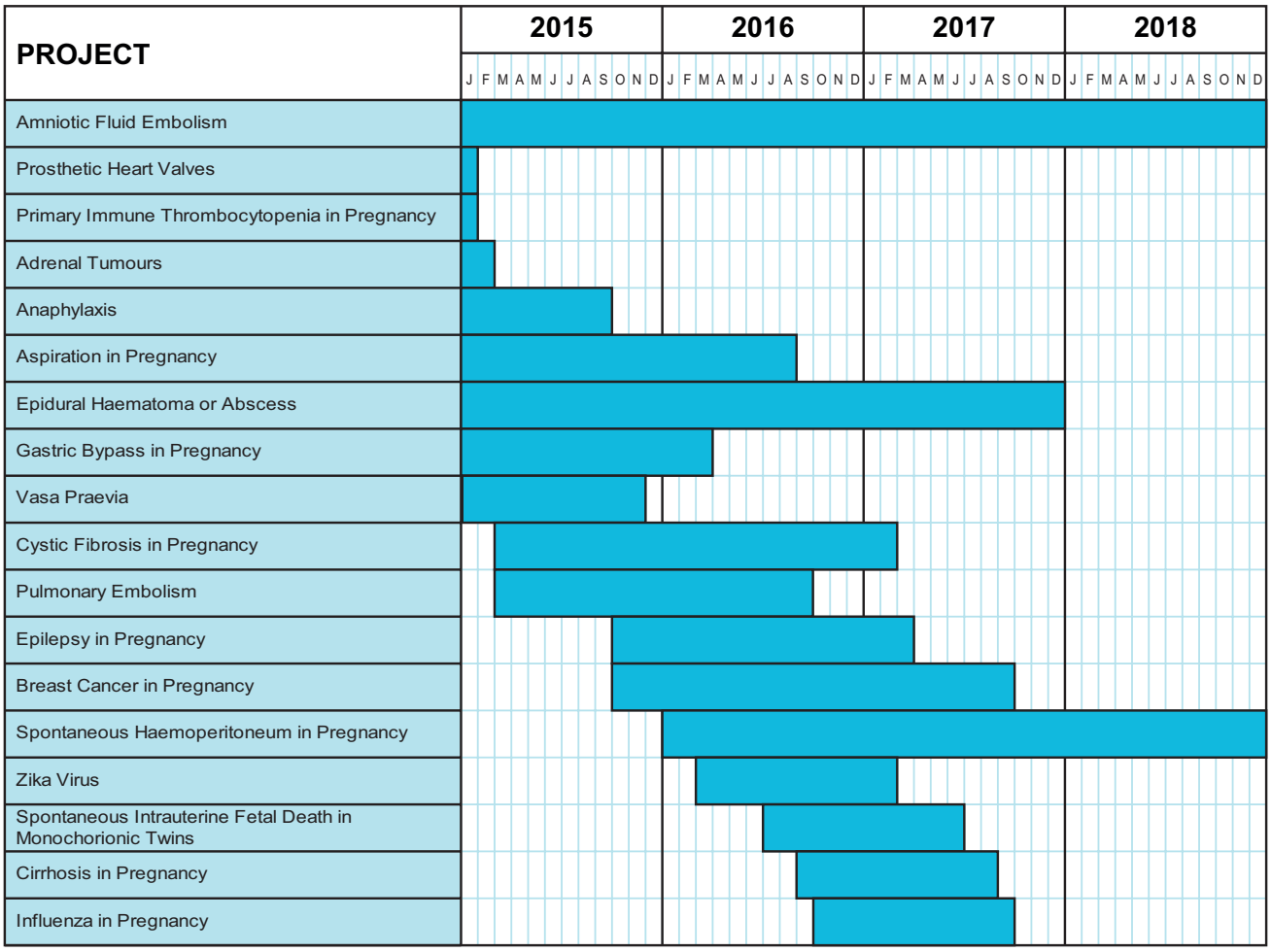


4. Studies

Unless otherwise specified, the results included in this report represent analysis of cases reported and data available up to February 2016. 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 2015-2018



4.2 Studies completed in 2015

4.2.1 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 investigated the current incidence of rare maternal adrenal tumours including phaeochromocytomas, those associated with Conn's Syndrome and Cushing's Syndrome

Background

Tumours of the adrenal glands are very rare (20) 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 (21, 22), including major maternal and fetal morbidity (23) and mortality (24, 25). Adrenal tumours are linked to higher rates of hypertension (20), diabetes (23) and pre-eclampsia among pregnant women. These can also lead to intrauterine growth restriction, fetal hypoxia (26), fetal distress (20, 27), spontaneous abortion, stillbirth, prematurity (23) 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.

Case Definition

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

At the end of the study, 33 cases of adrenal tumours in pregnancy had been reported, and information has been received for 31 (94%). Of these, 16 cases did not meet the inclusion criteria (nine cases were subsequently reported by clinicians as not cases, two were duplicate reports and the notes for one case were reported as lost. The additional cases did not meet the case definition). There were thus 15 confirmed cases in an estimated 3,143,436 maternities. This gives an incidence estimate in the UK of 0.5 cases per 100,000 maternities. The confirmed cases included 10 women with phaeochromocytoma, 3 women with Conn's Syndrome and 2 with Cushing's Syndrome.

The study showed that women with adrenal tumours have an increased risk of adverse outcomes for mother and baby.

For pregnancy outcome, the frequency of specific adverse outcomes was quantified in UKOSS cases and in all cases with each specific tumour reported on PubMed from 1985-2015. The rates of preterm labour and stillbirth were compared to those reported in UKOSS controls. There were significantly increased rates of these adverse outcomes in women with each adrenal tumour type.

Table 1: Comparison of rates of preterm delivery and stillbirth in pregnant women with hormone-secreting adrenal tumours and controls with uncomplicated pregnancy.

Diagnosis	No. cases studied (i.e. UKOSS cases and all reported in the literature)	UKOSS controls (n= 2250)	RR/MD*
Phaeochromocytoma			
Preterm delivery	59/106 (55.6%) (45.6- 65.3)	144 (6.4%) (5.4- 7.5)	8.7 (6.9- 10.9)
Stillbirth	15/119 (12.6%) (7.2- 19.9)	11 (0.5%) (0.2- 0.8)	25.8 (12.1- 54.9)
Primary aldosteronism			
Preterm delivery	18/35 (51.4%) (33.9- 68.6)	144 (6.4%) (5.4- 7.5)	8.03 (5.6- 11.5)
Stillbirth	2/35 (5.7%) (0.7- 19.2)	11 (0.5%) (0.2- 0.8)	11.69 (2.69-50.8)
Cushing's syndrome			
Preterm delivery <37 weeks	74/158 (46.8%) (38.8-54.9)	144 (6.5%) (5.4-7.4)	1.01 (0.79-1.30)
Stillbirth	9/158 (5.6%) (2.6- 10.5)	11 (0.5%) (0.2- 0.8)	11.65 (4.9- 27.7)
Preterm delivery <37 weeks	74/158 (46.8%) (38.8-54.9)	144 (6.5%) (5.4-7.4)	1.01 (0.79-1.30)
Stillbirth	9/158 (5.6%) (2.6- 10.5)	11 (0.5%) (0.2- 0.8)	11.65 (4.9- 27.7)

*RR = relative risk, MD = mean difference

All three types of adrenal tumour that were studied (phaeochromocytoma, primary aldosteronism and Cushing's Syndrome) were associated with severe maternal hypertension and there were significantly increased rates of preterm labour and stillbirth. Affected women also had increased rates of caesarean section. The study provided useful insights into specific management challenges for each tumour type.

- Phaeochromocytoma: phenyoxybenzamine was the treatment of choice for adrenal tumours in pregnancy as well as outside pregnancy. While women had very severe (and potentially life threatening) hypertension before phenyoxybenzamine was commenced, all treated women had good blood pressure control when on treatment. The study also showed that women with undiagnosed phaeochromocytoma may have misleadingly normal blood pressure readings at times, consistent with the paroxysmal character of hormone release for these tumours.
- Primary aldosteronism: all affected women had severe hypertension in conjunction with hypokalaemia which was improved by amiloride.

Interim Conclusions

- Adrenal tumours in pregnancy are associated with severe, and potentially life-threatening maternal hypertension.
- Pregnant women with paeochromocytoma, primary aldosteronism and Cushing's Syndrome have a significantly increased risk of preterm labour and stillbirth, and are more likely to be delivered by caesarean section.
- Affected women and their babies are at high risk of adverse pregnancy outcomes and detailed management guidelines should be generated to improve outcomes for women with these rare, but high-risk diseases.

Investigators

Catherine Williamson, Kimberly Lambert, Imperial College London; David McCance, Royal Victoria Hospital; Mandish Dhanjal, Queen Charlotte's Hospital; Marian Knight, NPEU.

Funding

This study is funded by SPARKS.

4.2.2 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 collected information about the incidence, management and outcomes of anaphylaxis in pregnancy in the UK.

Background

Anaphylaxis is a 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 (28). Current estimates of incidence suggest that maternal anaphylaxis occurs in approximately 1 in 37,000 pregnancies, although this is based on limited evidence (29). 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 (30-33).

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 (34, 35). 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 (33, 34) 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, thus are **included all women in whom the final clinical diagnosis was anaphylaxis, irrespective of the presence or absence of skin/mucosal changes**.

Surveillance Period

October 2012 – September 2015

Interim Results

There were 37 confirmed cases of anaphylaxis in pregnancy, giving an estimated incidence of 1.6 (95%CI 1.1-2.2) per 100,000 maternities. The majority of women had a single identified causal agent; in five women multiple candidate causal agents were reported. The main reported causal agents were: penicillin based antibiotics (n=11), cephalosporins (n=3), metronidazole (n=4), oxytocics (n=4), blood products (n=3), and intravenous iron (n=2). For one woman reported to have had a reaction to oxytocics there was no other reported possible cause of the anaphylactic reaction. Only three women were reported to have a reaction to an anaesthetic agent, either suxamethonium, thiopentone or 'unspecified agents' used for spinal anaesthesia. Nineteen (51%) of the cases occurred in obstetric theatre, 10 (27%) in the delivery suite. Twenty-nine women (78%) were managed with adrenaline, 28 (76%) received chlorphenamine and 34 (92%) received hydrocortisone. Tryptase levels were measured in 31 (84%) women after resuscitation and were raised in 9 (24%) cases. Two women died (5%), 14 (38%) women were admitted to level 3 critical care. No infants died; however, 10 (30%) of 33 infants were admitted to NICU and there was one case of neonatal encephalopathy.

Interim Conclusions

Anaphylaxis is an extremely rare severe complication of pregnancy that may result from administration of antibiotics and other drugs. Reactions to anaesthetic agents are an infrequent cause, and less frequent than reported reactions to oxytocic agents. Reactions to antibiotics appear no more frequent than in the general population. Anaphylaxis may have severe outcomes for both mother and fetus but these were uncommon.

Investigators

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

Funding

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

4.2.3 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 investigated 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% (36) with a 2.9% case fatality (37)). 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 (37) but is associated with a higher fetal loss (estimates as high as 59%) (36), and can have damaging effects on the fetus (37). In contrast, unfractionated heparin or LMWH are safe for the fetus, but doubts have been expressed about their efficacy in preventing maternal thrombotic complications (38). 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 (39). 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

There was a high maternal mortality with 5 deaths occurring in the cohort of 60 women (8.3%). In addition to the women who died, 17 other women (28.3%) had serious maternal morbidity. Postpartum bleeding complications were experienced by 13 women (secondary PPH 5 women, intraperitoneal bleeding or wound haematoma requiring return to theatre 8 women); 4 had valve thrombosis and 3 had a cerebrovascular accident (3 women had two complications). Of the 26 women delivered by LSCS, 8 (31%) needed to return to theatre due to bleeding complications.

Interim Conclusions

The maternal morbidity and mortality described in this study are higher than previously reported. Previous publications may have been overly reassuring, as they frequently report results from selected specialist centres, whereas this study reports cases from all maternity units in the UK. The study highlights the need for close multidisciplinary working between obstetricians, cardiologists and haematologists to optimise outcomes for women.

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

4.2.4 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 investigated 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 (40). 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 (41, 42). ITP accounts for 3% of cases of thrombocytopenia in pregnancy (42).

Current treatment recommendations for ITP in pregnancy are largely based on clinical experience and expert consensus (40). 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 (40). Without clear guidance or a 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 sought to estimate the current incidence and describe management and outcomes of severe ITP in pregnancy in the UK.

Case Definition

Any pregnant woman who had 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 had been excluded (i.e. 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 had been made.

Excluded

Women with secondary immune thrombocytopenia

Surveillance Period

June 2013 – January 2015

Interim Results

Of 109 women with confirmed ITP in pregnancy, 62 women were previously diagnosed with primary ITP. Median lowest platelet count in pregnancy was 34 x 10^9/L (range:4-81). Eighty-five women required antenatal treatment for thrombocytopenia, 39 were treated with steroids, 17 had IVIG, 29 required a combination of treatments including other therapies such as eltrombopag or platelet transfusion for non-responders. The caesarean section rate was 39%. There were no maternal deaths and no complications of epidural/spinal anaesthesia; one mother suffered a postpartum haemorrhage resulting in hysterectomy. There were no cases of neonatal death or intracranial haemorrhage irrespective of mode of delivery.

Interim Conclusions

This is the largest reported population cohort of severe ITP in pregnancy. Current incidence of severe ITP in the UK is approximately 0.1 per 1,000 pregnancies. With current treatment strategies the incidence of serious maternal and neonatal outcomes is extremely low.

Investigators

Angharad Care, Liverpool Women's Hospital;

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

Marian Knight, NPEU.

Funding

This study was funded by the ITP Support Association

itp
Idiopathic Thrombocytopenic Purpura

4.2.5 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 for women with confirmed vasa praevia and for women with some risk factors in the absence of vasa praevia.
- This study estimated the incidence of vasa praevia in the UK over one year and examined 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% (43). 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 (44). This is because “there is insufficient information on the case definition, natural history and epidemiology of the condition”(45). 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 estimated the incidence of vasa praevia in the UK over one year and examined 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:

1. 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).
2. Palpation or visualisation of the fetal vessels during labour.
3. Rupture of membranes with bleeding associated with fetal death/exsanguination or severe neonatal anaemia.
4. Antenatal or intrapartum bleeding of fetal origin with pathological CTG and/or positive Apt test.
5. VP documented in medical records as the reason for admission and caesarean section.

AND at least one of:

6. 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.
7. Pathological confirmation of vasa praevia.
8. Torn umbilical cord or placenta (hence unable to provide placental examination).

Surveillance Period

December 2014 – November 2015

Interim Results

Up to the end of February 2016, a total of 101 cases of vasa praevia were reported with data received for 87. Of these, 17 were reported by clinicians as not cases (and therefore reported in error) and the reporters were unable to locate the hospital notes for two cases.

Conclusions

Data collection is being finalised and analysis will commence shortly.

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.

4.3 Studies in progress

4.3.1 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 ten years of UKOSS surveillance.
- Further investigation is needed to establish whether earlier treatments can reverse the cascade of deterioration leading to severe outcomes.
- This study forms part of a wider multi-country study using the International Network of Obstetric Surveillance Systems (INOSS).

Background

AFE remains one of the leading causes of direct maternal mortality in high-income countries. Estimates of incidence vary from 1.9 to 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 February 2016, 220 cases were reported. Information has been received for 212 of these (96%). Of these, 22 do not meet the case definition, 30 were subsequently reported by clinicians as not cases, 14 were found to be duplicates and the hospital notes for one were reported as lost.

Interim Conclusions

Following analysis of cases reported up to January 2014, the results of which were published in 2015, further investigation is needed to establish whether earlier treatments can reverse the cascade of deterioration leading to severe outcomes. A multi-country analysis is planned for 2018.

Investigators

Kate Fitzpatrick, Marian Knight, NPEU;

Derek Tuffnell, Bradford Teaching Hospitals NHS Foundation Trust.

Funding

Wellbeing of Women have funded this multi-country study.

4.3.2 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 (46, 47). 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 (48). 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 (49). 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 (50, 51). 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" (52). 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 (48).

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 unprotected airway while unconscious, semi-conscious or paralysed.

AND

- A clinical history consistent with regurgitation of stomach contents and pulmonary aspiration (e.g. 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 2016

Interim Results

There were 9 confirmed cases of aspiration in an estimated 1,496,720 maternities, representing an incidence of 6.0 per 1,000,000 maternities (95% CI 2.8-11.4). Seven cases (78%) occurred in association with general anasthesia; an estimated 2.2 per 10,000 GAs (95% CI 0.9-4.5), based on an estimated 16,000 obstetric GAs in the UK annually (53). Two cases occurred when the woman was semi-conscious for other reasons. Five of the 7 women who were undergoing general anaesthesia received prior antacid prophylaxis (71%); 3 of 7 (43%) were known to have had fluid intake within the preceding 6 hours. At the time of the aspiration event, two women were reported to have an LMA Supreme™ airway in place, two had an oropharyngeal airway and one had an endotracheal tube. One further aspiration event occurred in the context of a difficult intubation and one following extubation. Six women (67%) showed X-ray signs consistent with aspiration. One woman died (case fatality 11%).

Interim Conclusions

Gastric aspiration in pregnancy or immediately postpartum in the UK is extremely rare. Reassuringly, there does not appear to be a substantial number of cases associated with oral intake in labour following the change in policy.

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).

4.3.3 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 becoming pregnant as survival rates increase, but surveillance of this would form 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 (54) 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 (55) and UK specific advice from the RCOG about the timing of interventions and delivery (56). A group in Australia and New Zealand are conducting a similar study, which will make comparisons hugely informative (57).

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

Surveillance Period

October 2015 – September 2017

Interim Results and Conclusions

Up to February 2016, 17 cases of newly diagnosed breast cancer in pregnancy were reported. So far information has been received for nine cases. It is thus not possible to draw any definitive conclusions at this stage.

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)

4.3.4 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 5 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 sixteen. Fertility in menstruating females with CF is near normal (58), 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 (59, 60). Based on the limited published evidence, a guideline was published in 2008 for the management of pregnant women with CF (61) 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 (59), 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 2017

Interim Results

Up to February 2016, 52 cases of cystic fibrosis in pregnancy were reported. Information has been received for 32 cases (94%). Of these, 3 were reported in error and there are three duplicate cases.

Interim Conclusions

Data collection is still incomplete and it is not possible to draw any definitive 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

4.3.5 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 occur in any obstetric unit that offers regional analgesia/anaesthesia and are 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 (62). 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 (63). 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 2016, 15 cases of epidural haematoma or abscess have been reported. Information has been received for 11 cases (73%) of which 8 are confirmed cases (73%), 2 were reported in error and one was a duplicate. Of the 8 confirmed cases, 4 are cases of epidural abscess and 4 epidural haematoma.

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.

4.3.6 Epilepsy in Pregnancy

Key points

- Epilepsy is the most common neurological disorder encountered in pregnancy and affects one percent of the UK population (64, 65).
- 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 the management of women with epilepsy who die can be improved (66).
- There have been repeated calls amongst the research community for high-quality, prospective data enabling the value of current policy recommendations to be assessed (67-69).

Background

Amongst women presenting for maternity care, approximately 1 in 200 are receiving treatment for epilepsy, with a mortality risk that is amongst 10 times greater than that of the general maternity population (100 versus 11 per 100,000 maternities respectively) (70, 71).

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(66). Of these 14 deaths, 12 were classified as cases of 'Sudden Unexplained Death in Epilepsy' (SUDEP)(66). 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 (67, 72). 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 (68, 71, 73). Whilst this is certainly feasible for the majority of women, it is clear that seizures persist for a minority of women in whom it is considered that treatment plans are adequate (74). 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 compromise 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 through restricting follow-up to include only live newborns (75). 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 women in the UK who fulfil at least one of the following criteria:

1. 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
2. A woman with epilepsy who is admitted to hospital for management of generalised tonic-clonic seizures during pregnancy or postpartum period
3. All women being treated with >3 anti-epileptic drugs at any point during their pregnancy

Surveillance Period

October 2015 – March 2017

Interim Results

Up to February 2016, 76 cases of epilepsy in pregnancy were reported with information received for 31 cases (41%). Of these 31, 5 were reported in error and there was one duplicate.

Interim Conclusions

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

Investigators

Bryn Kemp and Marian Knight, NPEU; David Williams, University College London Hospitals; Andrew Kelso, Barts Health NHS Trust.

Funding

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

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)(76). The adverse consequences of obesity on maternal and perinatal health are well established (77).

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 (78). 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 (77-79) 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 (78-81). Complications such as intestinal hernias, nutritional deficiencies (79, 80) and birth defects (81) 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 1 year after bypass surgery (77, 82). However, studies have shown similar maternal and neonatal outcomes between patients who conceived during the first post-operative year, and those who conceived later (77, 83).

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).

Exclude: Any woman who had a gastric band.

Surveillance Period

April 2014 – March 2016

Interim Results

Up to February 2016, 298 cases of gastric bypass in pregnancy were reported. Information has been received for 263 cases (88%). Of these, 197 (75%) are confirmed cases, 54 (21%) did not meet the case criteria and there were 12 duplicate repports (5%).

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 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 and 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 (66), 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 (84) 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 (85).

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 (86).

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 (84) . 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 (87).

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

Up to February 2016, 179 cases were reported with information received for 116 (65%). Of these 116, 14 were reported in error and the reporters were unable to locate the hospital notes for one case.

Conclusions

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

Investigators

Steve Goodacre, Matt Stevenson, Michael Campbell, Judith Cohen, Fiona Elizabeth Lecky, University of Sheffield; Beverley J Hunt, Catherin 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.

4.3.9 Spontaneous Haemoperitoneum in Pregnancy

Key points

- SHiP is the occurrence of sudden haemorrhage intra-abdominally in pregnancy – unrelated to trauma or rupture of the uterus.
- SHiP has been associated with endometriosis, rupture of uterine artery or varicose veins and aneurysms of the splenic artery.
- SHiP is rare but potentially fatal for the mother and the fetus.
- The data from this study will form part of an international collaborative study using the International Network of Obstetric Survey Systems (INOSS).

Background

Spontaneous Haemoperitoneum in Pregnancy (SHiP) is the occurrence of sudden haemorrhage intra-abdominally in pregnancy (unrelated to trauma or rupture of the uterus) and has been associated with endometriosis, rupture of uterine artery or varicose veins and aneurysms of the splenic artery (88).

SHiP is rare but potentially fatal for both mother and baby but it is currently extremely difficult to estimate the incidence of SHiP. Six maternal deaths occurred between 2009 and 2012 in the UK that were attributed to rupture of non-aortic aneurysms. However, little is known about morbidity during that time (66). Anecdotally, some cases have been noted to occur in women undergoing thrombolysis, but the prognostic factors are currently unclear on a population basis. The data from this study will form part of an international collaborative study using the International Network of Obstetric Survey Systems (INOSS).

Case Definition

Any woman 20 weeks or more gestation with sudden intra-abdominal haemorrhage requiring surgery (CS, laparotomy, laparoscopy), without preceding trauma.

EXCLUDE: women with uterine rupture or trauma.

Surveillance Period

January 2016 – December 2017

Interim Results and Conclusions

This study is at a very early stage and data collection has only recently commenced; it is thus not possible to draw any conclusions.

Investigators

Marian Knight, NPEU, UK; Janne Foss Berlac, and Jens Langhoff-Roos, University of Copenhagen, Denmark

Funding

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

4.3.10 Zika Virus in Pregnancy

Key points

- Zika virus (ZIKV) is an emerging viral infection with increasing transmission in South and Central America over the past few months.
- Even though not yet scientifically proven, a causal relationship between ZIKV infection in pregnancy and fetal microcephaly is strongly suspected.
- This study will describe the risk of an adverse pregnancy outcome related to infection with ZIKV during pregnancy.

Background

Since early 2015 when Zika virus (ZIKV) infection was first reported in Brazil, ZIKV has rapidly spread over most countries in South and Central America, the Caribbean and countries outside this region. An unusually high number of babies born with microcephaly were reported in Brazil, six months after the rapid increase of cases of ZIKV infection, concentrated particularly in those areas with high rates of the disease. The high numbers of cases are likely to be an overestimate due to case ascertainment; however they are considerable and thus ZIKV was declared as a Public Health Emergency of International Concern by the WHO in February 2016. Even though not yet scientifically proven, a causal relationship between ZIKV infection in pregnancy and microcephaly is strongly suspected. Two babies with microcephaly and confirmed ZIKV infection of mothers resident in countries without active ZIKV but who had travelled to Brazil during their pregnancy have been reported to date (89).

Almost 1.4 million UK residents travelled to South and Central America and the Caribbean on average each year between 2010 and 2014, 25% of those were women of child bearing age.

This study will carry out national surveillance in the UK, to assess the risk of having an adverse pregnancy outcome after travel to a country with active Zika transmission.

Case Definition

Two case definitions are included on the reporting card

1. Any pregnant woman with a history of travel to a country with active ZIKV transmission during pregnancy or 4 weeks before conception and no adverse pregnancy outcome.
2. Any pregnant woman with a history of travel to a country with active ZIKV transmission during pregnancy or 4 weeks before conception where a fetal abnormality has been detected or miscarriage, stillbirth, neonatal death or termination of pregnancy occurred.

Reporters are requested to report the numbers of women in their unit who fall into either category. Detailed data will only be requested on women with an adverse pregnancy outcome at this stage i.e. UKOSS will only collect numbers of women falling into group 1; reporting clinicians will not be requested to complete a data collection form. Data collection forms will be sent for completion of further details about women in group 2.

Surveillance Period

March 2016 – February 2017

Interim Results and Conclusions

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

Investigators

Richard Pebody, Clarissa Oeser, Public Health England; Asma Khalil, St. George's Hospital, University of London; Patrick O'Brien, University College London Hospitals; Marian Knight, NPEU

Funding

This study is being funded by Public Health England.

4.4 Future Studies

These studies have been approved by the UKOSS Steering Committee to commence in 2016.

4.4.1 Cirrhosis in Pregnancy

Key points

- Cirrhosis is defined as permanent scarring of the liver as a result of continuous long term damage.
- There are few reports of pregnancy in women with cirrhosis although some small studies have suggested that there is an increased incidence of adverse maternal and perinatal outcomes in women with cirrhosis.
- This study will establish the incidence of cirrhosis in pregnancy in the UK and describe the management and perinatal outcomes of pregnancies affected by cirrhosis.

Background

Cirrhosis is defined as permanent scarring of the liver as a result of continuous long term damage and it is estimated to affect 45/100,000 women of child-bearing age (90). There are few reports of pregnancy in women with cirrhosis, and therefore data regarding pregnancy outcomes and optimal management are sparse. Several studies have suggested that there are higher rates of both maternal and neonatal mortality in women with cirrhosis (90-95), and women with portal hypertension and oesophageal varices appear to be at higher risk; however none have been large enough to accurately quantify the risks. Other maternal complications include higher rates of anaemia, post-partum haemorrhage, pre-eclampsia, placental abruption and maternal death (93, 95). Fetal complications are reported to include miscarriage, pre-term delivery and intrauterine growth restriction (91-93, 95).

Management of cirrhosis largely relates to treatment of the underlying pathology. There is no consensus on the optimal treatment for variceal bleeding and there are concerns over the use of injection sclerotherapy and octreotide (90). Endoscopy and ligation banding appears to be safe but there are no randomised controlled trials. Furthermore, there are limited data regarding the best way to deliver women with cirrhosis. There are concerns over women labouring as the process involves repeated Valsalva manoeuvres which raise intra-abdominal pressure and therefore increase the risk of variceal rupture (90).

This study will also aim to establish the maternal outcomes associated with cirrhosis, and to determine the effect of a pregnancy on disease progression.

Case Definition

All pregnant women with an established history of cirrhosis defined by either confirmation by liver biopsy OR on the basis of radiological findings (nodular liver with enlarged spleen) with either a history of complications of liver disease (ascites, variceal bleeding, encephalopathy, pervious bacterial peritonitis) or supportive laboratory findings (low platelets, low albumin, prolonged prothrombin time or INR).

Main research questions

- What is the incidence of cirrhosis in pregnant women in the UK?
- What are the current management strategies used to treat cirrhosis in pregnancy?
- What is the incidence of co-existent pre-eclampsia, gestational diabetes and pregnancy specific liver disease (Acute Fatty Liver of Pregnancy and Intrahepatic Cholestasis of Pregnancy) in pregnant women with cirrhosis?
- What are the perinatal outcomes of pregnancies affected by cirrhosis?

Investigators

Catherine Williamson, Victoria Geenes, Michael Heneghan, Leonie Penna, King's College London; Marian Knight, NPEU

Funding

The Lauren Page Trust

4.4.2 Influenza in Pregnancy

Key points

- Women continue to die in the UK from influenza in pregnancy from subtypes of influenza other than A/H1N1.
- It is unclear whether there is also an ongoing burden of severe morbidity from seasonal influenza.
- The aim of this study is to identify women hospitalised with seasonal influenza in pregnancy, and a group of control women, in order to investigate risk factors, management and outcomes.

Background

Pregnancy is known to be a risk factor for severe influenza, as evidenced by the influenza A/H1N1 pandemic in 2009-10. However, women continue to die in the UK from influenza in pregnancy from subtypes of influenza other than A/H1N1, and while it is clear that these deaths are usually in unvaccinated women, it is unclear whether there is also an ongoing burden of severe morbidity from seasonal influenza. This project, therefore, aims to collect data nationally using the UK Obstetric Surveillance System, on all women hospitalised with seasonal influenza in pregnancy, and a group of control women, in order to investigate risk factors, management and outcomes.

Case Definition

Any pregnant women hospitalised with confirmed or suspected influenza in pregnancy. Include women admitted with secondary pneumonia in whom preceding influenza infection is confirmed on testing.

Main research questions

- What is the incidence of hospitalisation with seasonal influenza in pregnancy?
- What are the risk factors for admission with seasonal influenza in pregnancy? What proportion of cases occur in unvaccinated women?
- How are women with seasonal influenza in pregnancy managed?
- What are the outcomes of hospitalisation with seasonal influenza in pregnancy for mother and infant and are any factors associated with poor outcomes?

Investigators

Marian Knight, NPEU

Funding

This study is funded by the Department of Health as part of the programme of work of the Policy Research Unit in Maternal Health and Care.

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4.4.3 Single Intrauterine Fetal Death (sIUD) in Monochorionic Twins

Key points

- Monochorionic (MC) twins constitute 20-30% of all twin pregnancies and 2.6-6.2% will have a single intrauterine fetal death.
- This event is associated with increased risk of premature delivery and perinatal mortality and morbidity for the other twin.
- There is a lack of robust data regarding the incidence of single twin demise; interventions offered; maternal, fetal and neonatal outcomes and any prognostic indicators.
- The knowledge gained from this study will enable recommendations for the management of monochorionic twin pregnancies following single twin demise and improve the counselling and management.

Background

Perinatal mortality is increased in multiple compared to singleton pregnancies, with single twin demise presenting a rare but unique perinatal problem with reported incidence of single twin demise after 14 weeks between 2.6 to 6.2 percent of all twin pregnancies (96). Fetal morbid sequelae may include prematurity, death of the surviving fetus or survival with perinatal morbidity (97). In addition, maternal morbidity has been reported as increased with higher (than background) rates of pre-eclampsia, coagulopathy and sepsis (98, 99). Management of pregnancies complicated by intrauterine death in a twin may be challenging as controversy exists regarding the optimal timing of delivery, the frequency of antenatal surveillance, the appropriate investigations to determine cerebral impairment and the effects on maternal wellbeing (both physical and psychological) of retaining one dead fetus. Current evidence is limited by small numbers and significant heterogeneity in terms of diagnosis, investigation, management and postnatal follow-up.

Case Definition

Any women in the UK with a monochorionic twin pregnancy with single twin demise after 14 weeks gestation, defined as:

a) Monochorionic twin pregnancy – chorionicity confirmed at first trimester scan (<14 weeks) due to ultrasonic absence of the lambda sign (an echogenic V-shaped chorionic projection of tissue in dichorionic placentation).

b) Single intrauterine fetal death – intrauterine death of one twin (including spontaneous single twin demise or selective feticide).

EXLUDE: Multiple pregnancies where multifetal pregnancy reduction has taken place.

Main research questions

- What is the incidence of single twin demise in this study?
- What are the characteristics of pregnancies affected by single twin demise (maternal demographics, gestation, suspected aetiology)?
- What is the nature and incidence of antenatal intervention following single twin demise?
- What are the maternal, fetal and neonatal outcomes following single twin demise?
- Are there prognostic indicators associated with single twin demise (e.g. maternal age)?

Investigators

Mark Kilby, Katie Morris, University of Birmingham; Marian Knight, NPEU.

Funding

This study is being funded by a BMFMS (British Maternal Fetal Medicine Society) and TAMBA (Twins and Multiple Births Association) bursary.

5. Publications

5.1 Progression from severe sepsis in pregnancy to death: a UK population-based case-control analysis

Published Article

Mohamed-Ahmed O, Nair M, Acosta C, Kurinczuk JJ, Knight M. Progression from severe sepsis in pregnancy to death: a UK population-based case-control analysis. BJOG 2015; DOI: 10.1111/1471-0528.13551.

Key points

- Maternal sepsis, including respiratory, urinary and other infections as well as genital tract sepsis, remains of concern internationally. However, few studies have investigated the factors association with progression from severe sepsis to death.
- The aim of this study was to use data from UKOSS and the MBRRACE-UK Confidential Enquiry into Maternal Death to identify factors associated with progression from pregnancy-associated severe sepsis to death in the UK.
- Forty-three women who died from non-influenza related maternal sepsis between January 2009 and December 2012 were compared with 358 women who survived severe non-influenza sepsis in pregnancy between June 2011 and May 2012.
- Only 14 (33%) of the women who died received antibiotics within the 'golden hour'.
- Women who died were more likely to have never received antibiotics (aOR = 22.7, 95% CI 3.64–141.6), to have medical comorbidities (aOR = 2.53, 95% CI 1.23–5.23) and to be multiparous (aOR = 3.57, 95% CI 1.62–7.89).
- Anaemia (aOR = 13.5, 95% CI 3.17–57.6) and immunosuppression (aOR = 15.0, 95% CI 1.93–116.9) were the two most important factors driving the association between medical comorbidities and progression to death.
- This study emphasises further the importance of continued vigilance for the risks of infection in pregnant women with medical comorbidities. Improved adherence to national guidelines, alongside prompt recognition and treatment with antibiotics, may reduce the burden from sepsis-related maternal deaths.

5.2 The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-section study

Published Articles

Green L, Knight M, Seeney FM, Hopkinson C, Collins PW, Collis RE, Simpson NAB, Weeks A, Stanworth SS. The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study. BJOG 2015; DOI: 10.1111/1471-0528.13831.

Green, L., Knight, M., Seeney, F., Hopkinson, C., Collins, P. W., Collis, R. E., Simpson, N. A. B., Weeks, A. and Stanworth, S. J. (2016), The haematological features and transfusion management of women who required massive transfusion for major obstetric haemorrhage in the UK: a population based study. British Journal of Haematology, 172: 616–624. doi: 10.1111/bjh.13864

Key points

- Postpartum haemorrhage (PPH) remains a common cause of maternal morbidity and mortality worldwide, however, little is known about the incidence, management and outcomes of women with severe PPH undergoing massive transfusion.
- The aims of this study were to ascertain the incidence of massive transfusion in obstetrics in the UK, and describe the current management practices and clinical outcome for these women.
- The study identified 181 women who had undergone massive transfusion, giving an estimated incidence of 23 per 100 000 maternities (95% CI 19–26).
- The median estimated blood loss was 6 l (interquartile range 4.5–8.0 l) and the principal causes of haemorrhage were uterine atony (40%), placental abnormalities (33%) and trauma including uterine rupture (19%).
- At presentation, the median platelet count was lowest for placenta accreta, compared with other causes, while the median prothrombin time and fibrinogen were <1·5 × mean normal and <3 g/l, respectively for all aetiologies.
- The median platelet count and fibrinogen fell to <75 × 109 /l and <2 g/l, respectively for all causes during bleeding, except for trauma.
- In total, 45% of women underwent hysterectomy; women with placenta accreta had the highest hysterectomy rate. Two women died, 82% were admitted to intensive care/high-dependency units, and 28% developed major morbidities.
- This study showed that massive transfusion due to PPH is associated with high rates of morbidity and hysterectomy. The coagulopathy in women with PPH undergoing massive transfusion differs significantly depending on its cause, suggesting that more targeted transfusion strategies are required.

5.3 Selected maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System

Published Article

Nair M, Soffer K, Noor N, Knight M, Griffiths M. Selected maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System. BMJ Open 2015;5: e007434. Doi:10.1136/bmjopen-2014-007434

Key points

- A previous UKOSS study showed that uterine rupture is a rare and serious complication of vaginal birth after caesarean section (VBAC), but when comparing elective repeat caesarean section (ERCS) and VBAC it is important to consider other maternal complications.
- The aim of this study was therefore to estimate the rates of other specific maternal risks associated with VBAC and ERCS using available national data from other UKOSS studies:
- The analysis showed that the risks of all complications examined in both groups were low. The rates of peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation were not significantly different between the two groups in absolute or relative terms.
- Large epidemiological studies could further help to assess whether the incidence of these rare outcomes would significantly differ between the VBAC and ERCS groups if a larger number of cases were to be examined. In the interim, this study provides important information to help pregnant women in their decision-making process.

5.4 Severe sepsis in women with group B Streptococcus in pregnancy: an exploratory UK national case-control study

Published Article

Kalin A, Acosta C, Kurinczuk JJ, Brocklehurst P, Knight M. Severe sepsis in women with group B Streptococcus in pregnancy: an exploratory UK national case-control study. BMJ Open 2015;5:e007976. Doi:10.1136/bmjopen-2015-007976

Key points

- While much research has focused on the risks and outcomes of neonatal group B Streptococcus (GBS) sepsis, there have been no comprehensive studies investigating maternal GBS sepsis in the UK.
- The aim of this study was to use data from the UKOSS maternal sepsis study to estimate the incidence of severe maternal sepsis due to presumed or confirmed GBS in the UK, and to investigate the associated outcomes for mother and infant.
- A total of 30 women with GBS-positive cultures in the context of severe maternal sepsis were identified between June 2011 and May 2012; 7 were confirmed cases and 23 were presumed cases of severe maternal GBS sepsis.
- The incidences of confirmed and presumed severe maternal GBS sepsis were thus 1.0 and 2.8 per 100 000 maternities, respectively, giving an overall incidence of 3.8 per 100 000 maternities.
- Compared with controls, severe GBS sepsis was associated with higher odds of additional maternal morbidity (OR 12.35, 95% CI 3.96 to 35.0), requiring level 2 (OR 39.3, 95% CI 16.0 to 99.3) or level 3 (OR 182, 95% CI 21.0 to 8701) care and longer hospital stay ($p<0.001$). None of the women died.
- Severe maternal GBS sepsis was associated with higher odds of infant sepsis (OR 32.7, 95% CI 8.99 to 119.0); 79% of infants, however, did not develop sepsis. There were no associated stillbirths or neonatal deaths.
- This study shows that, although associated with adverse maternal and neonatal outcomes, severe maternal GBS sepsis is very rare in the UK.

5.5 Abstracts

The following abstracts were presented at meetings in 2015/2016:

- Anaphylaxis in Pregnancy and Severe ITP in Pregnancy, preliminary findings. British Maternal and Fetal Medicine 8th Annual Conference, April 2016.
- Aspiration and Anaphylaxis in Pregnancy, preliminary findings. Obstetric Anaesthetists Association Annual Meeting, May 2016.
- Gastric Banding in Pregnancy, FIGO (International Federation of Gynecology and Obstetrics), October 2015.

5.6 UKOSS Publications to date

2005

Knight M, Kurinczuk JJ, Tuffnell D, Brocklehurst P. (2005). "The UK Obstetric Surveillance System for rare disorders of pregnancy." BJOG 112(3): 263-265.

Knight M, Kurinczuk JJ, Brocklehurst P. (2005). "UK Obstetric Surveillance System uncovered." RCM Midwives 8(1): 38-39.

2007

Knight M on behalf of UKOSS (2007). "Eclampsia in the United Kingdom 2005." BJOG 114(9): 1072-1078.

Knight M on behalf of UKOSS (2007). "Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage." BJOG 114(11): 1380-1387.

2008

Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. (2008). "Cesarean delivery and peripartum hysterectomy." Obstet Gynecol 111(1): 97-105.

Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P. (2008). "A prospective national study of acute fatty liver of pregnancy in the UK." Gut 57(7): 951-956.

Knight M on behalf of UKOSS (2008). "Antenatal pulmonary embolism: risk factors, management and outcomes." BJOG 115(4): 453-461.

2009

Knight M, Kurinczuk JJ, Nelson-Piercy C, Spark P, Brocklehurst P. (2009). "Tuberculosis in pregnancy in the UK." BJOG 116(4): 584-588.

Knight, M., Kurinczuk J. J., Spark P., Brocklehurst P. (2009). "Inequalities in maternal health: national cohort study of ethnic variation in severe maternal morbidities." BMJ 338: b542.

Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle M-H, Ford J, Joseph KS, Lewis G, Liston RM, Roberts CL, Oats J, Walker J. (2009). "Trends in post-partum haemorrhage in high resource countries." BMC Pregnancy and Childbirth 9: 55.

2010

Knight M, Tuffnell D, Brocklehurst P, Spark P, Kurinczuk JJ. (2010). "Incidence and risk factors for amniotic-fluid embolism." Obstet Gynecol 115(5): 910-917.

Knight M, Kurinczuk JJ, Spark S, Brocklehurst P. (2010). "Extreme obesity in pregnancy in the United Kingdom." Obstet Gynecol 115(5): 989-997.

Homer CS, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. (2010). "A novel use of a classification system to audit severe maternal morbidity." Midwifery 26(5): 532-536.

Yates LM, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, Valappil M, Brocklehurst P, Thomas SH, Knight M. (2010). "Influenza A/H1N1v in pregnancy: An investigation of the characteristics of affected women and the relationship to pregnancy outcomes for mother and infant." Health Technol Assess 14(34): 109-182.

2011

Kayem G, Kurinczuk JJ, Alfirevic Z, Spark P, Brocklehurst P, Knight M. (2011). "Uterine compression sutures for the management of severe postpartum hemorrhage." Obstet Gynecol 117(1): 14-20.

Knight M, Pierce M, Seppelt I, Kurinczuk JJ, Spark P, Brocklehurst P, McLintock C, Sullivan E. (2011). "Critical illness with AH1N1v influenza in pregnancy: a comparison of two population-based cohorts." BJOG 118(2): 232-239.

Homer CSE, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. (2011). "Planned vaginal delivery or planned caesarean delivery in women with extreme obesity." BJOG 118(4): 480-487.

Knight M, Pierce M, Allen D, Kurinczuk JJ, Spark P, Roberts DJ, Knight M. (2011). "The incidence and outcomes of fetomaternal alloimmune thrombocytopenia: a UK national study using three data sources." Brit J Haematol 152(4): 460-468.

Lewis GE Ed. (2011). “Saving Mothers’ Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom.” BJOG 118 Suppl 1: 1-203.

Kayem G, Kurinczuk JJ, Alfirevic Z, Spark P, Brocklehurst P, Knight M. (2011) “Specific second-line therapies for postpartum haemorrhage: a national cohort study.” BJOG.118 (7):856-64.

Kayem G, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. (2011), “Maternal and obstetric factors associated with delayed postpartum eclampsia: a national study population.” Acta Obstet Gynecol Scand. 2011 Sep;90(9):1017-23.

Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. (2011) “Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study.” BMJ 2011;342:d3214

Kayem G, Kurinczuk JJ, Lewis G, Golightly S, Brocklehurst P, Knight M. (2011) “Risk factors for progression from severe maternal morbidity to death: a national cohort study.” PLoS One. 2011;6(12):e29077.

2012

Fitzpatrick KE, Kurinczuk JJ, Alfirevic Z, Spark P, Brocklehurst P, Knight M. (2012) “Uterine Rupture by Intended Mode of Delivery in the UK: A National Case-Control Study.” PLoS Med 9(3): e1001184.

Knight, M, Berg C, Brocklehurst P, Kramer M, Lewis G, Oats J, Roberts CL, Spong C, Sullivan E, van Roosmalen J, Zwart J. (2012) “Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations.” BMC Pregnancy and Childbirth, 2012. 12(1): 7.

Scott CA, Bewley S, Rudd A, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. (2012) “Incidence, risk factors, management, and outcomes of stroke in pregnancy.” Obstet Gynecol. 2012; 120(2 Pt 1):318-24.

Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. (2012) “Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study.” PLoS One. 2012;7(12):e52893.

Overton TG, Pierce MR, Gao H, Kurinczuk JJ, Spark P, Draper ES, Marven S, Brocklehurst P, Knight M. (2012) “Antenatal management and outcomes of gastroschisis in the U.K.” Prenat Diagn. 2012;32(13):1256-62.

2013

Cook J, Jarvis S, Knight M, Dhanjal M. (2013) “Multiple repeat caesarean section in the UK: incidence and consequences to mother and child. A national, prospective, cohort study.” BJOG. 2013; 120(1):85-91.

Quinn AC, Milne D, Columb M, Gorton H, Knight M. (2013) “Failed tracheal intubation in obstetric anaesthesia: 2 yr national case–control study in the UK.” Br J Anaesth. 2013;110(1):74-80.

Bush N, Nelson-Piercy C, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. (2013) “Myocardial infarction in pregnancy and postpartum in the UK.” Eur J Prev Cardiol. 2013 Feb; 20(1):12-20.

Bramham K, Nelson-Piercy C, Gao H, Pierce M, Bush N, Spark P, Brocklehurst P, Kurinczuk JJ, Knight M. (2013) “Pregnancy in Renal Transplant Recipients: A UK National Cohort Study.” Clin J Am Soc Nephrol. 2013 Feb;8(2):290-8.

Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. (2014) “The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study.” BJOG. 2013 Jan;121(1):62-70.

Knight M, Lindquist A. (2013) “The UK Obstetric Surveillance System: Impact on Patient Safety.” Best Practice & Research Clinical Obstetrics & Gynaecology. 27 (2013) 621-630.

Lindquist A, Knight M, Kurinczuk JJ. (2013) “Variation in severe maternal morbidity according to socioeconomic position: a UK national case-control study.” BMJ Open 2013;3:e002742 doi:10.1136/bmjopen-2013-002742.

2014

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.

Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. (2014) “Association of severe intrahepatic cholestasis of pregnancy with adverse outcomes: a prospective population-based case-control study.” Hepatology. 2014 Apr;59(4):1482-91.

Fitzpatrick KE, Hinshaw K, Kurinczuk JJ, Knight M. (2014) “Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome.” Obstet Gynecol. 2014 Mar;123(3):618-27.

Mohamed-Ahmed O, Nelson-Piercy C, Bramham K, Gao H, Kurinczuk JJ, Brocklehurst P, Knight M. (2014) “Pregnancy Outcomes in Liver and Cardiothoracic Transplant Recipients: A UK National Cohort Study.” PLoS One. 2014; doi: 10.1371/journal.pone.0089151.

Nair M, Kurinczuk JJ, Knight M. (2014) “Ethnic Variations in Severe Maternal Morbidity in the UK – A Case Control Study.” PLoS One, 2014. 9(4):p e95086.

2015

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]

Green L, Knight M, Seeney FM, Hopkinson C, Collins PW, Collis RE, Simpson NAB, Weeks A, Stanworth SS. “The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study.” BJOG 2015; DOI: 10.1111/1471-0528.13831.

Kalin A, Acosta C, Kurinczuk JJ, et al. “Severe sepsis in women with group B Streptococcus in pregnancy: an exploratoryUK national case-control study.” BMJ Open 2015;5:e007976. Doi:10.1136/bmjopen-2015-007976

Mohamed-Ahmed O, Nair M, Acosta C, Kurinczuk JJ, Knight M. “Progression from severe sepsis in pregnancy to death: a UK population-based case-control analysis.” BJOG 2015; DOI: 10.1111/1471-0528.13551.

Nair M, Kurinczuk J, 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.

Nair M, Soffer K, Noor N, Knight M, Griffiths M. “Selected maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System.” BNJ Open 2015;5: e007434. Doi:10.1136/bmjopen-2014-007434

Oteng-Ntim E, Ayensah B, Knight M, 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.” BJH. 2015; Apr;169(1):129-37

2016

Green L, Knight M, Seeney F, Hopkinson C, Collins PW, Collis RE, Simpson NAB, Weeks A, Stanworth SJ. “The haematological features and transfusion management of women who required massive transfusion for major obstetric haemorrhage in the UK: a population based study.” BJH, 2016; 172: 616–624. doi: 10.1111/bjh.13864

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7. References

1. Knight M, Lindquist A. The UK Obstetric Surveillance System: Impact on Patient Safety. Best Practice and Research Clinical Obstetrics & Gynaecology. 2013;27(4):621-30.
2. Knight M. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. BJOG. 2007;114(11):1380-7.
3. Knight M. Eclampsia in the United Kingdom 2005. BJOG. 2007;114(9):1072-8.
4. Knight M. Antenatal pulmonary embolism: risk factors, management and outcomes. BJOG. 2008;115(4):453-61.
5. Knight M, Kurinczuk J, Nelson-Piercy C, Spark P, Brocklehurst P. Tuberculosis in pregnancy in the UK. BJOG. 2009;116(4):584-8.
6. Eds. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Cesarean delivery and peripartum hysterectomy. Obstet Gynecol. 2008;111(1):97-105.
7. Knight M, Nelson-Piercy C, Kurinczuk J, Spark P, Brocklehurst P. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;Online Early:doi:10.1136/gut.2008.148676.
8. Knight M, INOSS. The International Network of Obstetric Survey Systems (INOSS): benefits of multi-country studies of severe and uncommon maternal morbidities. Acta Obstetricia et Gynecologica Scandinavica. 2014;93(2):127-31.
9. UKOSS. The UK Obstetric Surveillance System [April 2016]. Available from: *http://www.npeu.ox.ac.uk/ukoss/*.
10. Confidentiality and Security Advisory Group for Scotland. Edinburgh: The Scottish Executive; 2001.
11. Department of Health. Guidance Notes: Section 60 of the Health and Social Care Act 2001 [Accessed April 2004]. Available from: *http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108953*.
12. Kalin A, Acosta C, Kurinczuk JJ, Brocklehurst P, Knight M. Severe sepsis in women with group B Streptococcus in pregnancy: an exploratory UK national case-control study. BMJ open. 2015;5(10):e007976.
13. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Extreme obesity in pregnancy in the United Kingdom. Obstet Gynecol. 2010;115(5).
14. Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. Incidence and Risk Factors for Placenta Accreta/Increta/Percreta in the UK: A National Case-Control Study. PLoS ONE. 2012;7(12):e52893.
15. Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M, UKOSS. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ. 2011;342:d3214.
16. Nair M, Kurinczuk JJ, Brocklehurst P, Sellers S, Lewis G, Knight M. Factors associated with maternal death from direct pregnancy complications: a UK national case-control study. BJOG. 2015;122(5):653-62.
17. Knight M, UKOSS. Antenatal pulmonary embolism: risk factors, management and outcomes. BJOG: An International Journal of Obstetrics & Gynaecology. 2008;115(4):453-61.
18. Nelson-Piercy C, MacCallum P, Mackillop L. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium (RCOG Green-top Guideline no. 37a) 2015. Available from: *https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a/*.
19. Nicoll A. Poor pregnancy outcomes associated with maternal infection with the A(H1N1) 2009 virus during the pandemic - findings from a European cohort study. European Center for Disease Prevention and Control (ECDC) [Review] 18 Jul 2011. Available from: *http://www.ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f-77d4-4ad8-b6d6-bf0f23083f30&ID=1157&MasterPage=1*.
20. Robar C, Poremba J, Pelton J, Hudson L, Higby K. Current diagnosis and management of aldosterone-producing adenomas during pregnancy. The Endocrinologist. 1998;8:403-8.

21. Grodski S, Jung C, Kertes P, Davies M, Banting S. Phaeochromocytoma in pregnancy. Intern Med J. 2006;36(9):604-6.

22. Lindsay JR, Nieman LK. Adrenal disorders in pregnancy. Endocrinol Metab Clin North Am. 2006;35(1):1-20, v.

23. Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK. Cushing's syndrome during pregnancy: personal experience and review of the literature. J Clin Endocrinol Metab. 2005;90(5):3077-83.

24. Ahlawat SK, Jain S, Kumari S, Varma S, Sharma BK. Pheochromocytoma associated with pregnancy: case report and review of the literature. Obstet Gynecol Surv. 1999;54(11):728-37.

25. Schenker JG, Chowers I. Pheochromocytoma and pregnancy. Review of 89 cases. Obstet Gynecol Surv. 1971;26(11):739-47.

26. Bakri YN, Ingemansson SE, Ali A, Parikh S. Pheochromocytoma and pregnancy: report of three cases. Acta Obstet Gynecol Scand. 1992;71(4):301-4.

27. Matsumoto J, Miyake H, Isozaki T, Koshino T, Araki T. Primary aldosteronism in pregnancy. J Nippon Med Sch. 2000;67(4):275-9.

28. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P, et al. Emergency treatment of anaphylactic reactions-guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69.

29. Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. Annals of Allergy, Asthma & Immunology. 2010;104(1):55-9.

30. Stannard L, Bellis A. Maternal anaphylactic reaction to a general anaesthetic at emergency caesarean section for fetal bradycardia. BJOG: An International Journal of Obstetrics & Gynaecology. 2001;108(5):539-40.

31. Gallagher JS. Anaphylaxis in pregnancy. Obstetrics & Gynecology. 1988;71(3, Part 2):491.

32. Entman SS, Moise KJ. Anaphylaxis in pregnancy. Southern Medical Journal. 1984;77(3):402.

33. Sengupta A, Kohli JK. Antibiotic prophylaxis in cesarean section causing anaphylaxis and intrauterine fetal death. Journal of Obstetrics and Gynaecology Research. 2008;34(2):252-4.

34. Khan R, Anastasakis E, Kadir R. Anaphylactic reaction to ceftriaxone in labour. An emerging complication. Journal of obstetrics and gynaecology. 2008;28(7):751-3.

35. Harboe T, Benson M, Oi H, Softeland E, Bjorge L, Guttormsen A. Cardiopulmonary distress during obstetrical anaesthesia: attempts to diagnose amniotic fluid embolism in a case series of suspected allergic anaphylaxis. Acta anaesthesiologica scandinavica. 2006;50(3):324-30.

36. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. BJOG. 2000;107:245-53.

37. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: A systematic review of the literature. Arch Intern Med. 2000;160:191.

38. Roberts N, Ross D, Flint SK, Arya R, Blott M. Thromboembolism in pregnant women with mechanical prosthetic heart valves anticoagulated with low molecular weight heparin. BJOG. 2001;108:327-9.

39. Eds. Steer PJ, Gatzoulis MA, Baker P. Consensus views arising from the 51st Study Group: Heart Disease in Pregnancy Heart Disease and Pregnancy. RCOG Press. 2006.

40. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopaenia. Blood. 2010;115(2):168-86.

41. Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. J Thromb Haemost. 2006;4:2377-83.

42. Sainio S, Kekomaki R, Riikonen S, Teramo K. Maternal thrombocytopenia at term: a population based study. Acta Obstet Gynecol Scand. 2000;79:744-9.

43. Oyelese Y, Catanzarite V, Prefumo F, Lashley S, Schachter M, Tovbin Y, et al. Vasa previa: the impact of prenatal diagnosis on outcomes. Obstet Gynecol. 2004;103(5 Pt 1):937-42.

44. Committee UNS. The UK NSC policy on Vasa praevia screening in pregnancy. 2013 [16/05/2014]. Available from: *http://www.screening.nhs.uk/vasapraevia*.

45. Johnston TA, Paterson-Brown S. Placenta Praevia, Placenta Praevia Accreta and Vasa Praevia: Diagnosis and Managment (RCOG Green-top Guideline No.27) 2011. Available from: *https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg27/*.

46. Clayton T, Prout R. Critical incidents: pulmonary aspiration. Anaesthesia and Intensive Care Medicine. 2004;5(9):297-8.

47. Lykens MG, Bowton DL. Aspiration and acute lung injury. International Journal of Obstetric Anesthesia. 1993;2:236-40.

48. Cook T, Woodall N, Frerk C, (ed). 4th National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society: Major complications of airway management in the United Kingdom. The Royal College of Anaesthetists and The Difficult Airway Society. 2011.

49. Pinder A. Complications of obstetric anaesthesia. Current Anaesthesia and Critical Care. 2006;17:151-62.

50. National Collaborating Centre for Women's and Children's Health: Caesarean section. NICE Clinical Guideline London: RCOG Press. 2011;2nd edition:116.

51. Singata M, Tranmer J, Gyte GML. Restricting oral fluid and food intake during labour. Cochrane Database of Systematic Reviews. 2010(1).

52. National Collaborating Centre for Women's and Children's Health: Intrapartum care: care of healthy women and their babies during childbirth. NICE Clinical Guideline London: RCOG Press. 2007:83-36.

53. Kinsella SM, Winton AL, Mushambi MC, Ramaswamy K, Swales H, Quinn AC, et al. Failed tracheal intubation during obstetric general anaesthesia: a literature review. Int J Obstet Anesth. 2015;24(4):356-74.

54. Ayyappan AP, Kulkarni S, Crystal P. Pregnancy-associated breast cancer: spectrum of imaging appearances. The British journal of radiology. 2010;83(990):529-34.

55. Amant F, Deckers S, Van Calsteren K, Loibl S, Halaska M, Brepoels L, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. European journal of cancer. 2010;46(18):3158-68.

56. RCOG. Green-top Guideline no. 12. Pregnancy and Breast Cancer 2011. Available from: *https://www.rcog.org.uk/globalassets/documents/guidelines/gtg12pregbreastcancer.pdf*.

57. AMOSS. Available from: *http://www.bcig.net.au/files/Gestational%20Breast%20Cancer%20(GBC)%20June2013_1371468215.pdf*.

58. Edenborough FP. Women with cystic fibrosis and their potential for reproduction. Thorax. 2001;56(8):649-55.

59. Thorpe-Beeston JG, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancies in women with cystic fibrosis-single centre experience 1998-2011. Bjog. 2013;120(3):354-61.

60. Edenborough FP, Mackenzie WE, Stableforth DE. The outcome of 72 pregnancies in 55 women with cystic fibrosis in the United Kingdom 1977-1996. BJOG. 2000;107(2):254-61.

61. Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2008;7 Suppl 1:S2-32.

62. Moen V, Irestedt L. Neurological complications following central neuraxial blockades in obstetrics. Current Opinion in Anesthesiology. 2008;21(3):275-80.

63. Ruppen W, Derry S, McQuay H, Moore R. Incidence of epidural hematoma, infection and neurological injury in obstetric patients with epidural analgesia/anesthesia. Anesthesiology. 2006;105(2):394-9.

64. Kurtzke JF. Epilepsy: Frequency, causes and consequences. Archives of Neurology. 1992;49(4):342-.

65. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain : a journal of neurology. 2000;123 (Pt 4):665-76.

66. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ, et al. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2014.

67. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia. 2014;55(7):e72-4.

68. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Management issues for women with epilepsy--focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009;50(5):1247-55.

69. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. BMJ. 2014;348:g254.

70. Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. Journal of neurology, neurosurgery, and psychiatry. 2004;75(11):1575-83.

71. Sveberg L, Svalheim S, Tauboll E. The impact of seizures on pregnancy and delivery. Seizure. 2015;28:29-32.

72. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology. 2005;64(7):1131-3.

73. Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. Seizure control in antiepileptic drug-treated pregnancy. Epilepsia. 2008;49(1):172-6.

74. Battino D, Tomson T, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia. 2013;54(9):1621-7.

75. Tomson T, Battino D, Craig J, Hernandez-Diaz S, Holmes LB, Lindhout D, et al. Pregnancy registries: differences, similarities, and possible harmonization. Epilepsia. 2010;51(5):909-15.

76. Usha-Kiran TS, Hemmadi S, Bethel J, Evans J. Outcome of pregnancy in a woman with an increased body mass index. BJOG. 2005;112(6):768-72.

77. National Obesity Observatory. Bariatric Surgery for Obesity: Department of Health; 2010: Department of Health. Available from: *http://www.noo.org.uk*.

78. Josefsson A, Blomberg M, Bladh M, Frederiksen SG, Sydsjo G. Bariatric surgery in a national cohort of women: sociodemographics and obstetric outcomes. Am J Obstet Gynecol. 2011;205(3):206 e1-8.

79. Guelinckx I, Devlieger R, Vansant G. Reproductive outcome after bariatric surgery: a critical review. Human reproduction update. 2009;15:189-201.

80. Kjaer MM, Lauenborg J, Breum BM, Nilas L. The risk of adverse pregnancy outcome after bariatric surgery: a nationwide register-based matched cohort study. Am J Obstet Gynecol. 2013;208(6):464 e1-5.

81. Kjaer MM, Nilas L. Pregnancy after bariatric surgery-a review of benefits and risks. Acta Obstet Gynecol Scand. 2013;92(3):264-71.

82. Dalfra M, Busetto L, Chilelli MC, Lapolla A. Pregnancy and Foetal outcome after bariatric surgery: a review of recent studies. Journal of Maternal-Fetal & Neonatal Medicine. 2012;25(9):1537-43.

83. Sheiner E, Edri A, Balaban E, Levi I, Aricha-Tamir B. Pregnancy outcome of patients who conceive during or after the first year following bariatric surgery. Am J Obstet Gynecol. 2011;204(1):50 e1-6.

84. Thomson A, Greer I. Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management (RCOG Green-top Guideline no 37b) 2015. Available from: *https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37b.pdf*.

85. National Institute for Health and Care Excellence. NICE clinical guideline 144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. 2012. Available from: *http://guidance.nice.org.uk/CG144*

86. Chan WS, Lee A, Spencer FA, Chunilal S, Crowther M, Wu W, et al. D-dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis. Journal of thrombosis and haemostasis : JTH. 2010;8(5):1004-11.

87. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. European heart journal. 2014;35(43):3033-69, 69a-69k.

88. Brosens IA, Fusi L, Brosens JJ. Endometriosis is a risk factor for spontaneous hemoperitoneum during pregnancy. Fertility and sterility. 2009;92(4):1243-5.

89. WHO Zika situation report 12th February 2016 [Accessed February 2016]. Available from: *http://www.who.int/emergencies/zika-virus/situation-report/who-zika-situation-report-12-02-2016.pdf?ua=1*.

90. Tan J, Surti B, Saab S. Pregnancy and cirrhosis. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2008;14(8):1081-91.

91. Murthy SK, Heathcote EJ, Nguyen GC. Impact of cirrhosis and liver transplant on maternal health during labor and delivery. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2009;7(12):1367-72, 72.e1.

92. Pajor A, Lehoczky D. Pregnancy in liver cirrhosis. Assessment of maternal and fetal risks in eleven patients and review of the management. Gynecol Obstet Invest. 1994;38(1):45-50.

93. Rasheed SM, Abdel Monem AM, Abd Ellah AH, Abdel Fattah MS. Prognosis and determinants of pregnancy outcome among patients with post-hepatitis liver cirrhosis. Int J Gynaecol Obstet. 2013;121(3):247-51.

94. Russell MA, Craigo SD. Cirrhosis and portal hypertension in pregnancy. Seminars in perinatology. 1998;22(2):156-65.

95. Shaheen AA, Myers RP. The outcomes of pregnancy in patients with cirrhosis: a population-based study. Liver international : official journal of the International Association for the Study of the Liver. 2010;30(2):275-83.

96. Pharoah PO, Adi Y. Consequences of in-utero death in a twin pregnancy. Lancet. 2000;355(9215):1597-602.

97. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. Obstet Gynecol. 2011;118(4):928-40.

98. Santema JG, Swaak AM, Wallenburg HC. Expectant management of twin pregnancy with single fetal death. Br J Obstet Gynaecol. 1995;102(1):26-30.

99. Kilby MD, Govind A, O'Brien PM. Outcome of twin pregnancies complicated by a single intrauterine death: a comparison with viable twin pregnancies. Obstet Gynecol. 1994;84(1):107-9.

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