Improving the prevention and outcomes of severe complications of pregnancy through international collaborative and comparative studies

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Abstract

Background: International collaborations have been set up to complete combined and comparative studies to improve the evidence to support the prevention and management of severe and rare complications of pregnancy. The utility of such collaborative studies has yet to be tested. This DPhil aims to explore the utility of multinational studies of severe and rare complications of pregnancy.

Methods: Secondary analysis and primary data collection through an international collaboration (INOSS) were used to address four clinical research areas; extreme maternal obesity, massive transfusion in major obstetric haemorrhage, abnormally invasive placenta and anaphylaxis in pregnancy.

Results: A pooled analysis of two national studies of extreme maternal obesity enabled the examination of a rare exposure group (BMI $\geq$60 kg/m^2). Nevertheless, the combination of two national studies did not allow the examination of the most uncommon outcomes, such as perinatal death or stillbirth. A comparison of five population-based studies of massive transfusion in obstetric haemorrhage showed that haemostatic features varied according to aetiology. It also demonstrated the large variation in blood products used between countries. A binational study on abnormally invasive placenta enabled the examination of the association between outcomes and an uncommon management in a rare complication of pregnancy. A prospective international study of a very rare complication of pregnancy, anaphylaxis, overcame the limitations of comparability and provided a more precise estimate of the causal agents and outcomes associated with this complication.

Discussion: Multinational studies are feasible and can be used to address a multitude of clinical questions. They provide the comparison of management across nations, which empowers countries to benchmark their clinical care against that of other countries. The pooling of data creates a unique examination of uncommon modalities of management and a rare exposure group. Prospective studies overcome comparability issues and provide a more robust pooled analysis.

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Abbreviations

ACOG: American College of Obstetricians and Gynecologists

AIP: Abnormally Invasive Placenta

AMOSS: Australasian Maternity Outcomes Surveillance System

aOR: adjusted Odds Ratio

aPTT: activated Prothrombin Times

B.oSS: Belgium Obstetric Surveillance System

BCSH: British Committee for Standards in Haematology

BMI: Body Mass Index

CDC: Centre for Disease Control

CI: Confidence Interval

CNGOF: French college of Gynaecologists and Obstetricians

CROWN: The CoRe Outcomes in Women's and Newborn health initiative

DIC: Disseminated Intravascular Coagulation

EPIMOMS: Épidémiologic de la Morbidité Maternelle Sévère

FFP: Fresh Frozen Plasma

HELLP syndrome: Haemolysis elevated liver enzymes and low platelets

HQIP: Healthcare Quality Improvement Partnership

INOSS: International Network of Obstetric Survey Systems

IPD: individual patient data

ItOSS: Italian Obstetric Surveillance System

ITU: Intensive Therapy Unit

IVF: In Vitro Fertilisation

MBRRACE: Mothers and Babies: Reducing the risk through audits and confidential enquiries across the UK

MHP: Major Haemorrhage protocol

MMR: Maternal Mortality Ratio

MOH: Major Obstetric Haemorrhage

N.I.S: National Inpatient Sample

NethOSS: Netherlands Obstetric Surveillance System

NICU: Neonatal Intensive Care Unit

NPEU: National Perinatal Epidemiology Unit

PPH: Postpartum Haemorrhage

PT: prothrombin

RANZCOG: Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

RBC: Red Blood Cell

RCOG: Royal College of Obstetricians and Gynaecologists

RCT: randomised controlled trial

SCASMM: Scottish Confidential Audit of Severe Maternal Morbidity

SFAR: French Society of Anaesthesiology

TeMpOH-1: Transfusion strategies in women during Major Obstetric Haemorrhage study

UKOSS: United Kingdom Obstetric Surveillance System

uOR: unadjusted Odds Ratio

USA: United States of America

WHO: World Health Organisation

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"Gloria in excelsis Deo" J.S. Bach

Chapter 1. Introduction

1.1 Methodological background

1.1.1 Methodological Rationale

The International Network of Obstetric Survey Systems (INOSS) is a multinational collaboration established to facilitate the study of rare and severe complications of pregnancy (Knight and INOSS, 2014). Knight and INOSS (2014) set out the theoretical benefits of this collaboration in an editorial. INOSS aims to use similar methodologies to prospective or individual patient data (IPD) meta-analyses, which overcome some of the limitations of meta-analyses of data from previously published studies. In theory, this methodology should facilitate more methodologically robust studies through both the creation of a uniform set of cases using a common definition, and shared datasets where variables are harmonised across national datasets; however, it is unclear if this can be achieved to study rare and severe complications of pregnancy.

As outlined by Knight (2014), the INOSS methodology may have the key advantage of increasing the sample size for the study of severe and rare complications of pregnancy. This is beneficial as small countries may not have enough cases to study a very rare complication of pregnancy, for example, in conditions where the incidence is 1 woman per 100,000 maternities there will only be 3 cases in Belgium or the Netherlands in a given year. The combined effort of multiple countries may provide a large enough sample to investigate this very rare complication of pregnancy. The larger sample size would allow more precise estimates of the incidence and outcomes, and would provide a better description of the obstetric management.

A larger sample size is not a unique benefit to multinational studies, but theoretically this collaboration could provide a number of other additional benefits. First, it allows a comparative analysis across countries, which may allow an investigation of the association

between risk factors or management approaches and outcomes. Rose proposed that if a determinant or management is "homogeneous within a population" then analytical studies "will fail to detect it" (Rose, 2001, pg. 427). Similarly, within countries, the management or risk factors of severe conditions may be uniform, however, there may be heterogeneity of management or risk factors across countries. These differences may be mirrored in maternal and infant outcomes of the complication. Multinational studies have the added benefit of allowing the examination of these variations in management. Furthermore, multinational studies may allow countries to benchmark their clinical care against that of other countries, which may provide an incentive for guideline creation and improvement of service delivery and clinical care.

Second, multinational studies may allow the pooling of data. Systematic reviews and meta-analyses of published studies are a method of pooling aggregated data together or providing comparative analyses between countries. These are often limited by heterogeneous definitions, data items and populations (Flather et al., 1997, Lyman and Kuderer, 2005). In addition, these analyses are limited to information provided in the published study and the data are not always comparable across studies (Flather et al., 1997). For example, previous attempts to examine severe complications of pregnancy across countries have been limited by differing definitions and methodologies (Knight et al., 2009). The CoRe Outcomes in Women's and Newborn health (CROWN) initiative has set out to harmonise the definition of outcomes of specific conditions in pregnancy; however, it will require time for their recommendations to be adopted (Duffy et al., 2017). Individual patient data analyses can overcome some of these limitations through the creation of uniform case definitions and datasets (Stewart and Parmar, 1993). The use of common definitions and methodologies allows the comparison of 'like with like'

complications and the use of similar data collection forms enables data items to be comparable, which in turn allows the pooling of data between countries.

The pooling of data is particularly beneficial in the study of rare complications of pregnancy as it enables the examination of rare outcomes and uncommon modalities of management. Furthermore, it may provide a more precise estimate of the causal agents and outcomes of a very rare complication of pregnancy. Unlike meta-analyses of published data where each study has adjusted for different covariates in multivariable analyses, pooled IPD analyses may allow the standardisation of statistical analyses.

Third, a single observational study does not provide sufficient evidence for a relationship or phenomenon to be considered as causal. The replication of findings across multiple nations, alongside other criteria such as biological plausibility and strength of association, which would provide a stronger argument for causality.

At the writing of this thesis there had only been one study completed using the INOSS collaboration, which compared women with eclampsia between the UK and the Netherlands (Schaap et al., 2014). After harmonisation of eclampsia definitions there was still a difference in the incidence and this was thought to be the result of differences in the provision of magnesium sulphate and management of hypertension. It remains unclear if the described benefits are real and the type of studies and clinical questions that can be answered through this collaboration. In addition, the challenges of completing such studies are not fully understood. By uncovering the challenges, it will provide solution opportunities for the collaboration to realise better the benefits of using multinational studies. Therefore, the aim of this DPhil was to investigate whether these potential benefits of this international collaboration can be fully realised.

1.1.2 Rationale for the study of severe maternal morbidity

1.1.2.1 Maternal mortality

Over the past two centuries maternal mortality in Europe has declined from a relatively common event with 300-500 deaths per 100,000 maternities in 1800 (Loudon, 2000) to a very rare event at 12 deaths per 100,000 maternities in 2015 (World Health Organization, 2015). The recent improvement in maternal survival following childbirth has been the result of many factors such as the introduction of aseptic techniques, antibiotics for infection, blood transfusion, oxytocin and advancement of obstetric management (Chamberlain, 2006). Confidential enquiries into maternal mortality have also played their part in the improved survival of mothers and infants at childbirth. In particular, the implementation of recommendations from these reports has facilitated an improvement in service delivery and clinical care over the last 50 years (Knight and Nair, 2017).

1.1.2.2 Severe maternal morbidity

Morbidity during pregnancy can be described as a continuum that extends from a healthy uncomplicated pregnancy at the start of the spectrum to a maternal death at the end of the spectrum (Souza et al., 2010, Say et al., 2016). In the upper end of the spectrum are complicated pregnancies that, without intervention, would have resulted in a maternal death, and these are defined as maternal 'near miss' events (Souza et al., 2010). Despite severe maternal morbidities being individually rare, collectively they contribute a large burden of disease (Say et al., 2016), for example, in the United Kingdom the ratio of severe maternal morbidity to mortality was estimated as 100:1 in 2001 (Waterstone et al., 2001) and each year an estimated 52,000 women in U.S.A. are affected by a severe complication during pregnancy (Callaghan et al., 2012). Furthermore, in 2000 in a low income setting, near miss events were estimated to be 15 times more common than

maternal deaths, therefore ‘near miss’ events represent a significant disease burden to the pregnant population (Filippi et al., 2000).

It is troubling that maternal morbidity in high income settings has increased in recent decades (Callaghan et al., 2012, Marr et al., 2014). This may be explained by an increase in the prevalence of risk factors for severe maternal morbidity in the pregnant population (Nair et al., 2016a, Nair et al., 2014). These risk factors include maternal age (Office for National Statistics, 2017a), BMI at booking (Heslehurst et al., 2007), pre-existing comorbidities (Fridman et al., 2014), and the proportion of women delivered by caesarean section (Betrán et al., 2016).

Previous reports into maternal mortality and morbidity have stated that in high-income settings where maternal mortality is rare there is added value of studying ‘near miss’ events (Lewis and Drife, 2004, Knight et al., 2014, Knight et al., 2016). Maternal deaths and ‘near miss’ events share similar risk factors, which allow the identification of pathways to prevent them. Furthermore, robust studies can be conducted more quickly and results are available sooner due to the larger number of events. As a consequence, the study of ‘near miss’ events can provide recommendations for the improvement of clinical care (Knight et al., 2016). Thus, there is an opportunity to improve and prevent poor outcomes for both mother and child through the epidemiological study of severe and rare complications of pregnancy.

1.1.3 Rare diseases in the general population

In the general population, rare diseases have been defined as conditions having a prevalence of less than 5 per 10,000 people (Rinaldi, 2005). They collectively represent a major burden of disease and impact between 26-36 million people in the European Union (Rinaldi, 2005). As these conditions are rare, they have failed to come to the attention of the scientific community and of research funders. This has resulted in a lack of knowledge as to how these conditions are diagnosed or managed. In particular, they lack "medicine, therapies or protocols for good clinical practice" (Rinaldi, 2005. EMBO Reports. Vol 6: 507–510.). Resultantly, many of these rare conditions have poor outcomes.

1.1.4 Rare and severe complications of pregnancy

1.1.4.1 Requirements of epidemiology

As with any disease or severe morbidity it is essential to know the answers to basic epidemiological questions about the disease of interest, in particular, 'who is susceptible to the disease?', 'where, when and why does this disease occur?' and 'the prevalence of the disease?'. The answers to these questions will provide information on the frequency, distribution and determinants of the disease of interest, which in turn will enable the development of interventions and recommendations to improve and prevent poor outcomes (Hennekens and Buring, 1987). However, the correct methodology is required to provide the robust answers to these fundamental epidemiological questions.

1.1.4.2 Evidence for clinical practice in pregnancy

Research ethics committees have often considered the pregnant population as vulnerable due to duties of care for both the mother and fetus, and these obligations of care produce a population that is difficult to study (Blehar et al., 2013, Van der Zande et al., 2017). In addition, the pregnant population differs physiologically to non-pregnancy populations

(Impey and Child, 2017), which does not allow research, evidence and recommendations from other specialities to be immediately generalised to pregnancy. Medical practice should be guided by evidence (Sackett, 1997), and conventionally the top of the hierarchy of the evidence pyramid is the randomised controlled trial (RCT). It has been argued, that if RCTs are completed correctly, they provide the most robust evidence. However, practice changing research has also been driven through cohort studies and guideline evidence (Coombs et al., 2017).

It can be difficult to complete RCTs in the pregnant population due to ethical and practical considerations. Ethical issues arise due to concerns over fetal harms and gaining consent during emergency situations (American College of Obstetricians Gynecologists, 1999). Nevertheless, recent trials have overcome issues of gaining consent in emergency situations, for example, the WOMAN trial (Houghton et al., 2018). Despite this step forward in research for maternal health, it is nearly impossible to complete RCTs in emergency situations if the obstetric condition is rare. Self-evidently, the available sample size will remain small due to the low incidence of the condition. In addition, study power may be limited even further due to differential skills between surgeons and high inter-individual variability in the treatments received (Augustine et al., 2013). Under these limitations, observational studies are then relied upon to provide evidence for clinical practice.

1.1.4.3 Challenges of small numbers in research

A major limitation of a large majority of research on rare conditions is that the studies often have small sample sizes. Small numbers are a challenge in medical research as they can lead to wide confidence intervals around a point estimate, false negative and false positives results. First, they will provide a wide confidence interval around a point estimate as the width of the confidence interval has an inverse square relationship to the sample size. The equations below show the confidence interval for a proportion, where X is the number of cases with the disease, n is the total sample size and Z is the confidence level or margin of error.

$$\hat{P} = \frac{X}{n}$$

$$CI = \hat{P} \pm Z \cdot \sqrt{\frac{\hat{P}\,(1 - \hat{P})}{n}}$$

Using this equation, a fourfold increase in the sample size will diminish the confidence interval by a half. A wide confidence interval illustrates a large imprecision around the point estimate. This imprecision limits what can be concluded about the study, and hence, the result is unlikely to impact clinical practice.

Second, a common error associated with a small sample size is a type II error (β), which is the probability of rejecting the null hypothesis when it is false. This is to conclude, in studies with small samples sizes, that there was no clinical significance where statistically significance was not met. This becomes problematic because a study with an inadequate sample size may have lacked the power to detect an important clinical difference as being statistically significant (Altman and Bland, 1995). Resultantly, it is difficult to distinguish between a truly null finding and a finding that was not statistically significant due to

inadequate study power (Hennekens and Buring, 1987). This arises in studies where the true effect size of an exposure on an outcome is small, therefore, a large study sample size is required to show a modest effect as being statistically significant.

Third, small sample sizes may increase the likelihood of a false positive. This is where the statistically significant result does not reflect a true difference (Button et al., 2013). Often studies with low statistical power overestimate the effect size and the result is not reproducible (Button et al., 2013). Simulation studies have shown that underpowered genetic studies have a 97% likelihood of obtaining a false positive result (Sullivan, 2007). The positive predictive value (PPV) is related to the sample size, and this is the probability that the positive study finding reflects the true value. The PPV is dependent on four components, the power of the study (1- β), the pre-study odds of a real relationship existing (R), bias and the type I error rate (α) (see equation below) (Ioannidis, 2005). Thus, an underpowered study will provide a smaller PPV or a smaller likelihood that the positive study finding reflects the true value.

$$PPV = \frac{(1-\beta)R}{(R-\beta R+\ \alpha)}$$

Therefore, large unbiased studies are required for the robust examination of rare complications of pregnancy. These can be provided through multinational studies. Subsequently, the findings from multinational studies on rare conditions are likely to be more precise than national studies and will provide more assurance that the study findings actually reflect that of the true value.

1.1.5 Robust evidence?

Robust observational studies are difficult to conduct when studying rare and severe complications of pregnancy. Subsequently, there is a paucity of high quality evidence to guide the prevention and management of severe but rare maternal morbidities (Royal College of Obstetricians and Gynaecologists, 2015a, Mavrides et al., 2016, Shaylor et al., 2017). This is problematic as ill-informed surgical and medical decisions may result in suboptimal outcomes for both mother and baby. Therefore, it is imperative that high quality observational studies are undertaken to examine rare and severe complications of pregnancy.

1.1.5.1 Which methodology: routine data sources?

One of the easiest and cheapest methods to study rare and severe complications is by using data collected through routine data sources, such as Hospital Episode Statistics in England, medical birth registry data from the Nordic countries and the National Inpatient Sample (N.I.S.) in the U.S.A. However, this methodology is not without its limitations, for example, Nair et al. (2016b) showed routine resources in England lacked the quality and reliability to study rare and severe complications of pregnancy. Similarly, a Canadian study, which used routine data sources, found that variations in the incidence of morbidity between regions could be explained by differences in coding practices (Joseph et al., 2010). Due to an inability to check medical records, there is concern over the validity of included cases. This is a major limitation of routine data sources for the study of rare conditions, as even a small number of false positives included in the study population would result in an increase in the incidence of the condition and vice versa for false negatives (Knight et al., 2012). It would also introduce bias if there were differential classification between exposure groups.

1.1.5.2 A better alternative: obstetric surveillance systems

The limitations of routine data systems have been overcome through the use of prospective case notification and data collection systems to study rare and severe complications of pregnancy (Knight et al., 2005). These systems adhere to a strict case definition and use the women's medical records to ensure all cases meet the strict case definition; thus preventing the inclusion of false positives and safeguards a higher validity of cases within the study (Kayem et al., 2013, Knight et al., 2005, Knight and INOSS, 2014). Furthermore, the use of a bespoke data collection system guarantees that data items collected are relevant to the research question.

1.1.5.3 The International Network of Obstetric Survey Systems

The International Network of Obstetric Survey Systems (INOSS) is a collaboration that aims to examine the incidence, management and outcomes of rare complications of pregnancy by bringing together data from multiple countries (Knight and INOSS, 2014). The majority of its members have recently established obstetric surveillance systems, which collect data about severe and rare complications of pregnancy (Colmorn et al., 2015, Netherlands Obstetric Surveillance System, 2013, Knight and INOSS, 2014). Table 1 presents the international studies and systems that were used in this thesis. The possible utility of comparative and collaborative studies has yet to be tested (Knight and INOSS, 2014). It should be noted that the context of this thesis is in high-income settings, thus outcomes and conditions considered rare may be more common in other settings.

Table 1. The included studies and systems included in this thesis.

Country	Name of system or dataset	Type of system
Australia	Australasian Maternity Outcomes Surveillance System	National obstetric surveillance system. Collected data from hospitals with more than 50 births. During the extreme obesity study it had coverage of 66% of all women giving birth in Australia.
Belgium	Belgium Obstetric Surveillance System (B.OSS)	National obstetric surveillance system.
Nordic countries: Finland, Denmark, Sweden, Norway and Iceland. **Finland only participated.**	Part of the Nordic Obstetric Surveillance Study (NOSS) collaborative system: Finnish Medical Birth Registry and linked medical records	National routine data from Finland and linked to medical records of cases for validation.
France (Abnormally invasive placenta)	PACCRETA study	Population-based study from 182 centres across eight regions of France over a two-year period.
France (Anaphylaxis)	INOSS anaphylaxis study	Network of anaesthetists and centralised laboratories. Relied on the identification of anaphylaxis from anaesthetists in the whole of France.
France (Massive transfusion)	Épidémiologic de la Morbidité Maternelle Sévère study (EPIMOMS)	Population-based study from all maternity units in 6 regions in France: Alsace Champagne-Ardenne, Lorraine, Auvergne, Rhone-Alpes, Ile-de-France and Normandy over a year.
Italy	Italian Obstetric Surveillance System (ItOSS)	Women identified from six regions in Italy, namely Piedmont and Emilia-Romagna, Tuscany, Lazio, Campania and Sicily, which represent 49% of births in Italy over a two-year period.
The Netherlands (Anaphylaxis)	Netherlands Obstetric Surveillance System (NethOSS)	National obstetric surveillance system.
The Netherlands (Massive transfusion)	Transfusion strategies in women during Major Obstetric Haemorrhage study (TeMpOH-1)	National retrospective cohort study between January 2011 and January 2013 in the Netherlands, which included all hospitals.
United Kingdom	United Kingdom Obstetric Surveillance System (UKOSS)	Obstetric surveillance system that collected data nationally from all consultant-led hospitals.
United States of America (U.S.A.)	National Inpatient Sample (N.I.S.)	Retrospective routine data collected from a sample of 20% of hospitalisations in U.S.A. which aims to be representative of the population. No access to medical records.

1.1.6 Topic and scope

This thesis investigates the methodological and clinical utility of using multinational studies to study rare and severe complications of pregnancy. Examining rare and severe complications in pregnancy is challenging and it is unclear in what ways multinational studies can add to the limited evidence base which is concerned with the prevention and management of these conditions. This thesis will investigate the utility of multinational collaborative studies to examine severe and rare complications of pregnancy. The utility will be examined through a number of different studies, and each chapter will consider a different rare and severe complication, which in turn will investigate a different methodological aspect of the collaborative studies. It is anticipated that the output of this thesis will provide high quality evidence in an under researched area with the aim of identifying the value of different methodological approaches to enable the study of rare disorders in pregnancy, in order to generate evidence, in an attempt to improve clinical practice, service delivery and guideline development.

This investigation of the utility of multinational studies of rare and severe complications is conducted using secondary analysis and primary data collection through an international consortium and will address four important clinical research areas: extreme maternal obesity, massive transfusion in major obstetric haemorrhage, abnormally invasive placenta and anaphylaxis in pregnancy.

1.1.7 Methodology for literature searches

1.1.7.1 Extreme maternal obesity

A scoping review was completed to identify studies that examined extreme maternal obesity and its association with maternal and infant outcomes. Studies were included if they met both of these criteria: (i) examined pregnant or postpartum women BMI>50kg/m^2 with any BMI comparison group (ii) included an association with an outcome. The search was completed in Medline (1996-2nd week July 2016) and Embase using search terms (See Box 5, Appendix 1).

After removing duplicates, 3657 titles were identified, 481 abstracts were identified for studies that examined an association between maternal obesity and outcomes. Full text review was restricted to texts that examined extreme maternal obesity. Thirteen full texts were identified for full text review and seven were included in the literature review. A further full text was included after the review was completed as it had been published after the search (Kim et al. 2018). In addition, the review was also used to examine the confounders and mediators between extreme obesity and outcomes. If there were no extreme maternal obesity studies available to provide information about confounders or mediators between certain outcomes and obesity, review articles on maternal obesity (>30kg/m^2) were identified to provide information.

1.1.7.2 Massive transfusion

A narrative review was completed to identify the haemostatic features and blood products administered for major blood loss at delivery. Articles were included if they had examined major obstetric haemorrhage defined as a blood loss more than 1500mls and/or administration of five units of blood. In addition, review articles and guidelines were also included. The search was completed in Medline (1996-3rd week September 2017) and

Embase. The Medline search terms can be found in Box 6. The search identified 1193 titles, after screening of titles and abstracts there were 143 articles included for review. These articles were examined on a narrative basis to provide general clinical information on major obstetric haemorrhage. The purpose of the chapter was to describe the variation in haematological management between countries. Therefore, national clinical guidelines were compared in Table 3. This table was adapted from Shaylor et al. (2017), where the ACOG guideline was excluded and the Collis and Collin's (2015) clinical guideline was included.

A formal review was not undertaken for the abnormally invasive placenta chapter because the management and outcomes were already known prior to start of the study. However, studies that examined a conservative management were identified using the output of a FIGO guideline (Sentilhes et al., 2018) and reference lists of cited studies. A conservative management was defined as placenta left in situ and these studies were compared in table 4. In addition, both the RCOG and ACOG guidelines and reference lists were reviewed to provide an overview of the recommended management (Royal College of Obstetricians and Gynaecologists, 2011, American College of Obstetricians Gynecologists, 2012).

1.1.7.3 Anaphylaxis in pregnancy

The purpose of this scoping review was to identify the incidence, causal agents and outcomes of anaphylaxis in pregnancy. A scoping search was completed to identify all case series, case-control, cohort studies and guidelines on anaphylaxis in pregnancy. Any study that had examined anaphylaxis in pregnancy was included. This was completed in Medline (1996- April 2016) (See Box 7, Appendix 1). There were 35 studies identified for full text review. There were 22 case reports, two articles (one population-based study on anaphylaxis and one case-control study on sensitisation during pregnancy), two guidelines,

five review articles, one letter and three texts in foreign languages. The three review articles (Hepner et al., 2013, Simons and Schatz, 2010, Chaudhuri et al., 2008) and the population-based study (Mulla et al., 2010) provided the scientific basis for the introduction section and justification for variables in the model. In addition, the UK study on anaphylaxis in pregnancy was published after the search was completed; this was also included in the introduction (McCall et al., 2018).

1.2 Clinical studies: background and rationale

This DPhil research has been designed to explore the utility of multinational collaborations through four epidemiological population-based studies. These studies address important clinical questions that may be answered through collaboration, and thus, have the capacity to illustrate the benefit of using multinational studies. The DPhil can be separated into four clinical studies that highlight different aspects of the utility of the INOSS collaboration. The following sections will outline the background for each chapter and provide the rationale for the clinical questions that will be addressed.

1.2.1 Clinical background and rationale: extreme maternal obesity

1.2.1.1 Obesity in pregnancy: a public health problem

Obesity is defined as a body mass index (BMI) of ≥30 kg/m^2. Obesity is a major risk factor for non-communicable disease and morbidity. Obesity has reached epidemic levels in many high-income settings across all age-ranges. In the United Kingdom in 2013, 19% of women of child bearing age were obese; while the prevalence was even higher at 27.4% in Australia in 2014 (NatCen Social Research, 2017, OECD, 2013). Associated with rising rates in the general population, there is an increasing trend (Heslehurst et al., 2010) towards obesity in pregnancy and it represents a significant public health problem in high-income settings (Bhattacharya et al., 2007).

1.2.1.2 Obesity: how severe is it?

Maternal obesity is a risk factor for a number of pregnancy related complications including thromboembolism, hypertensive disorders of pregnancy and gestational diabetes (Bhattacharya et al., 2007, Catalano and Ehrenberg, 2006). Obese women are also more likely to be induced, delivered by caesarean section, have a general anaesthetic for delivery

and experience anaesthetic complications (Catalano and Ehrenberg, 2006). In addition, maternal obesity may impact on the infant as it increases the risk of macrosomia, meconium aspiration, stillbirth and neonatal mortality (Cedergren, 2004, Lu et al., 2001).

1.2.1.3 Obesity and maternal mortality

The most recent Confidential Enquiry into Maternal Deaths in the United Kingdom showed that 33% of the maternal deaths during 2013-2015 were of obese women (Knight et al., 2017). The proportion of women who died who were obese was higher than the prevalence of obesity in the pregnant population (Heslehurst et al., 2010). However, maternal obesity was not found to be associated with maternal mortality after adjusting for a comprehensive list of risk factors (Nair et al., 2014, Nair et al., 2016a). Previous research has suggested that the association between obesity in general and maternal mortality could be partially explained by the presence of comorbidities, some of which are associated with obesity (McCall et al., 2017). In women with the highest BMIs, it is not clear is whether the relationship between obesity and poor pregnancy outcomes is also explained by the comorbidities associated with obesity.

1.2.1.4 What BMI cut off should be used for extreme maternal obesity?

Although a BMI >30kg/m^2 is associated with poor maternal and infant outcomes it is too common to study using obstetric surveillance systems (Knight et al., 2005). As a result, extreme maternal obesity was considered a more suitable rare event to be studied using these systems.

In the general population, there has been an increasing trend to obesity with the largest increases in the highest BMI groups (Sturm, 2007). For example, in the United States of America (U.S.A.) the number of people with a BMI ≥50 kg/m^2 was 75% higher in 2005 compared to 2000 (Sturm, 2007). In addition, there have been several studies investigating

the prevalence, outcomes and management of extreme obesity in pregnancy, and these studies have defined extreme maternal obesity as a BMI ≥50 kg/m^2 (Crane et al., 2013, Martin et al., 2014, Knight et al., 2010, Marshall et al., 2012). Existing studies of extreme obesity in pregnancy (BMI >50 kg/m^2) have shown it to have a low prevalence: 6.0 per 1000 women giving birth in Newfoundland, Canada (Crane et al., 2013); 2.1 per 1000 women giving birth in Australia (Sullivan et al., 2015); and 0.9 per 1000 women giving birth in the United Kingdom (Knight et al., 2010). Extremely obese women represent a relatively small population in pregnancy and as a result, national studies or longitudinal studies are required to investigate the impact of extreme obesity robustly.

1.2.1.5 Rationale for study of extreme maternal obesity

Extreme maternal obesity is a challenge for the clinicians responsible for the care of the mother and baby as there is an increased amount of resources required for the safe management of the women (Knight et al., 2010). In particular, these maternities require specialist equipment, such as tailored beds and hosts. These women also require specialist care, such as a multidisciplinary team including an obstetrician and anaesthetist, as a consequence there are a limited number of locations in which delivery of these women can occur (Saravanakumar et al., 2006, Centre for Maternal and Child Enquiries and Royal College of Obstetricians and Gynaecologists, 2010). Furthermore, extremely obese women are at an increased risk of delivery by caesarean section and independently there is an increased likelihood of difficulties in intubation and anaesthesia placement compared to women with a normal BMI (Saravanakumar et al., 2006, Centre for Maternal and Child Enquiries and Royal College of Obstetricians and Gynaecologists, 2010, Knight et al., 2010). As a result, this special population requires different care and from the outset these women have an increased risk of adverse maternal and infant outcomes.

1.2.1.6 Terminology and definitions

BMI is an easily calculated index to classify adults into underweight, normal weight, overweight and obese categories. The World Health Organisation (WHO) has defined obesity as a body mass index of ≥30 kg/m^2 (World Health Organization, 2016). Obesity is divided into three further categories: Class I, 30 to 34.9 kg /m^2; Class II, 35 to 39.9 kg/m^2 and Class III is ≥40 kg/m^2. This has left the highest categories of obesity separately undefined other than as class III; however recent studies examining women with a BMI ≥50 kg/m^2 have used two terms to describe this group, namely, super obesity (Alanis et al., 2010, Hartge et al., 2013, Marshall et al., 2012, Martin et al., 2014, Salihu et al., 2009, Slavin et al., 2013, Sullivan et al., 2015) and extreme obesity (Crane et al., 2013, Gunatilake et al., 2013, Homer et al., 2011, Salihu et al., 2007, Knight et al., 2010). For the purposes of the work reported here this study will use the extreme obesity terminology to define these women.

1.2.1.6.1 Obesity as part of a continuum

Obstetric surveillance systems have the ability to study both severe and rare outcomes and exposures. In the context of BMI as a whole, a review of systematic reviews has shown that obese women (>30 kg/m^2) are more likely to have gestational diabetes, preeclampsia and obstetric interventions, compared to those with normal BMI (Marchi et al., 2015). There is an even higher likelihood of these outcomes for women with a BMI >35 kg/m^2. Obstetric surveillance systems can aid the study of this continuum of BMI by examining women with extreme BMIs. It is likely that these women are at an even greater risk of gestational diabetes, preeclampsia and obstetric interventions compared to those with lower but nevertheless abnormal BMIs.

There have been several studies investigating the prevalence, outcomes and managements of extreme obesity in pregnancy (BMI ≥50 kg/m^2) (Crane et al., 2013, Martin et al., 2014, Knight et al., 2010, Marshall et al., 2012). These have aimed to test whether there was a dose response relationship between increased BMI and complications of pregnancy. Within the extremely obese group (BMI ≥50 kg/m^2) BMIs of included women have ranged from ≥50 to <80 kg/m^2. It is possible that above a certain BMI, the risk of maternal and perinatal complications as a result of BMI, do not increase due to the competing risks of other comorbidities. This remains to be robustly investigated, as only one study has examined extremely obese women any higher than BMI ≥60 kg/m^2 (Kim et al., 2017). This study was not population based and used data collected over a ten year period (Kim et al., 2017); thus, it is likely that the management and risk profile of this population changed over this period. As a result, there remains opportunity to examine robustly extreme maternal obesity at a higher cut-off than a BMI ≥50 kg/m^2.

1.2.1.6.2 Lack of power to examine rare outcomes

Outcomes such as perinatal death and stillbirth are considered rare in high-income settings, while they are more common in low resource settings (Smith et al., 2018, Ahmed et al., 2018). Existing literature shows that maternal obesity (defined in this study as BMI >30kg/m^2) increases the risk of relatively rare outcomes such as stillbirth, perinatal death and shoulder dystocia (Aune et al., 2014, Mazouni et al., 2006). It is a reasonable assumption that this association would be even stronger in extremely obese women (BMI ≥50 kg/m^2). Studies examining the outcomes and comorbidities of extremely obese women are presented in Table 1. Only two studies identified from this literature search examined stillbirth; these studies found no statistically significant association between extreme obesity and stillbirth (Alanis et al., 2010, Crane et al., 2013). Only three studies examined

birth trauma or shoulder dystocia and they did not find a statistically significant association with extreme obesity (Knight et al., 2010, Marshall et al., 2012, Crane et al., 2013).

1.2.1.7 Clinical questions

There are a number of clinical questions that remain unanswered. First, does extreme maternal obesity increase the risk of relatively rare outcomes such as stillbirth, perinatal death and shoulder dystocia? Secondly in a cohort of extremely obese women, does a higher BMI cut-off result in an increased risk of poor outcomes compared to those who are extremely obese i.e. is there an increased likelihood of poor outcomes in those with a BMI >60 kg/m^2 compared to those who have a BMI >50-59 kg/m^2 ?

Table 2. Characteristics and results of the literature search examining extreme maternal obesity.

Author, year and type of study	**Study description**	**Comparator**	**Definition of exposure**	**Study size**	**Sociodemographic characteristics or comorbidities** (BMI ≥50 kg/m^2 vs. comparators)	**Maternal outcomes**	**Perinatal outcomes**
Alanis et al. 2010, Medical University of South Carolina, cross-sectional study	To determine the increased risk of complications to super obese women	Obese (Class I, II and III); comparator group was BMI 30.0–49.9 kg/m^2	Super obese women BMI ≥50 kg/m^2	BMI ≥50 kg/m^2: n= 425 BMI 30-49 kg/m^2: n = 19,275	Increased likelihood of pre-existing diabetes and hypertension (no adjusted odds ratio provided)	Increased odds of preeclampsia(aOR:2.14 (95%CI: 1.64–2.80)); gestational diabetes (aOR: 1.90 (95%CI: 1.40–5.57)) and caesarean delivery (aOR:2.86 (95%CI: 2.35–3.49)	Stillbirth (N.S); preterm birth (N.S); congenital abnormality (N.S); Apgar @ 5 minutes < 7 (aOR: 1.74 (95%CI: 1.19–2.55)) and Apgar 1minute <7 (aOR:1.74 (95%CI: 1.19–2.55)). Unadjusted linear association: large for gestational age. Small for gestational age did not have a clear association.
Crane et al. 2013, Labrador, Newfoundland, population-based	To evaluate the impact of extreme obesity of maternal and perinatal outcomes	Women who had a BMI 18.5 -24.9 kg/m^2	Extreme maternal obesity BMI ≥50 kg/m^2	BMI ≥50 kg/m^2: n= 71 BMI 18.5-24.9 kg/m^2: n = 5717	Statistically significant increased proportion of nulliparous, pre-existing diabetes and essential hypertension. No difference in age, marital status or smoking	Gestational diabetes (aOR: 2.04 (95% CI: 1.74-2.38)); gestational hypertension (aOR: 1.56 (95%CI: 1.33-1.82)); caesarean delivery (aOR: 1.46 (95%CI: 1.29-1.65)); postpartum haemorrhage (N.S); venous thromboembolism (N.S); ICU admission (N.S) and induction of labour (N.S)	Stillbirth (N.S); neonatal death (N.S); shoulder dystocia (N.S at univariable level*); NICU admission (aOR: 1.28 (95%CI: 1.07 -1.52)) and birthweight ≥ 4500grams (aOR: 1.87 (95%CI: 1.57- 2.23)). *Shoulder dystocia was statistically significant in an adjusted analysis although there were only two cases.
Kim et al. 2018 Minnesota, U.S.A. retrospective study	To investigate neonatal morbidity and maternal complication rates with delivery body mass index (BMI) 60 or greater.	Women who had a BMI 30-59 kg/m^2	BMI ≥60 kg/m^2	BMI ≥60 kg/m^2 n=39 BMI 30-59 kg/m^2 n=299	None examined	Caesarean delivery (aOR: 3.88 (1.6–9.3)); wound complication (aOR:7.46 (1.9–29.9)); Postpartum haemorrhage (aOR: 3.1 (95% CI: 1.2–8.0)); ITU stay >5 days (aOR:7.81 (95% CI: 3.1–19.9); blood transfusion (N.S) and 3rd or 4th degree tear (N.S)	Composite score of neonatal morbidity, which included 5-minute Apgar score less than 7, hypoglycemia, respiratory distress syndrome, neonatal intensive care unit admission, neonatal hospital stay greater than 5 days, proven diagnosis of sepsis, or neonatal death during the birth admission. (aOR: 6.32 (95% 2.8-14.3); preterm labour (N.S) and birthweight ≥ 4500grams (N.S)

Author, year and type of study	Study description	Comparator	Definition of exposure	Study size	Sociodemographic characteristics or comorbidities (BMI ≥50 kg/m^2 vs. comparators)	Maternal outcomes	Perinatal outcomes
Knight et al. 2010, United Kingdom, population-based cohort study	To estimate the prevalence and describe the managements and outcomes of extreme maternal obesity	Comparator cohort of women who had a BMI <50 kg/m^2 collected nationally.	Extreme maternal obesity BMI ≥50 kg/m^2	BMI ≥50 kg/m^2: 665 from 764,387 deliveries; BMIs <50 kg/m^2: 634	Manual occupations (uOR: 1.70 (95% CI:1.27–2.27)); pre-existing hypertension (uOR: 10.1 (95%CI: 3.59–28.3)); pre-exiting diabetes (N.S); previous caesarean delivery (uOR: 2.20 (95%CI: 1.55–3.12) and parity ≥3 (uOR: 2.85 (95%CI: 1.98–4.11))	Any hypertensive disorder (aOR: 5.49 (3.65–8.25)); preeclampsia (aOR: 4.46 (2.43–8.16)); gestational diabetes (aOR: 7.89 (95%CI: 3.94–15.80)); induced (aOR: 1.97 (95%CI:1.53–2.54); thrombotic events (N.S) and caesarean delivery (aOR:3.50 (95%CI:2.72–4.51)	Preterm birth (aOR: 1.58 (95%CI: 1.04–2.40)); very preterm birth (aOR:2.82 (95%CI: 0.89–8.95)); post term birth (N.S) and shoulder dystocia (N.S)
Marshall et al. 2012, Missouri, USA, retrospective cohort study	Determine the effect of maternal super obesity compared to morbid obesity (Class III) or obesity (Class I and II) on perinatal outcomes.	Morbid obesity (Class III BMI >40 – 49.9 kg/m^2) or obesity (Class I and II BMI>30-39.9 kg/m^2)	Super obesity BMI ≥50 kg/m^2	BMI ≥50 kg/m^2 n=1185 BMI >30 - 39.9 kg/m^2 (Obese) n=53,032 BMI >40 – 49.9 kg/m^2 (Morbid obese) n=10,055	Super obese women had higher proportions of multiparity, smoking during pregnancy, African American and lower educational levels, which were statistically significant at the 5% level.	Preeclampsia: aOR: 1.7 (95%CI: 1.4- 2.1) vs. obese comparison. Preeclampsia vs. morbid obese (N.S).	Obese comparator Low Apgar: aOR:1.9 (95%CI:1.1, 3.2); Macrosomia: aOR: 1.8 (95%CI: 1.3-2.5); Low birthweight (N.S); Neonatal hypoglycaemia: aOR:2.0 (95%CI:1.5-2.7); aOR:1.4 (95%CI:1.0, 1.9); birth trauma (N.S). Morbid obese comparator Low Apgar (N.S); macrosomia N.S); low birthweight (N.S); birth trauma (N.S).
Marshall et al. 2014, Missouri, USA, retrospective cohort study	To determine the effect of maternal obesity on perinatal outcomes in women with diabetes	Reference group in adjusted analysis (BMI: 18.5-24.9 kg/m^2). Adjusted associations.	Super obesity BMI ≥50 kg/m^2	BMI 18.5-24.9 kg/m^2: 3959 BMI ≥ 50 kg/m^2: 330	Extremely obese women were more likely to smoke during pregnancy and use Medicaid.	Caesarean delivery in nulliparous: aOR: 5.5 (95%CI: 3.4-8.7); caesarean delivery in multiparous: aOR: 4.7 (95% CI: 2.8-7.7).	Macrosomia: aOR 3.0 (95% CI: 1.8-5.0); hypoglycaemia 1.9 (95%: 1.4- 2.6); length of stay >5 days 2.0 (95% CI: 1.3- 3.0); low Apgar 4.1 (95% CI: 1.9-8.6); composite morbidity 2.0 (95% CI: 1.6-2.6)

Author, year and type of study	Study description	Comparator	Definition of exposure	Study size	Sociodemographic characteristics or comorbidities (BMI ≥50 kg/m^2 vs. comparators)	Maternal outcomes	Perinatal outcomes
Niewoudt et al. 2014, Tygerberg Hospital – Western Cape, South Africa, prospective cohort study	Examine the difference between adverse pregnancy outcomes between morbidly obese and super obese women	Morbidly obese women. BMI: 40-49.9 kg/m^2	Super obesity BMI≥50	BMI 40-49.9 kg/m^2: n=66 BMI ≥50 kg/m^2: n=46	Morbidly obese women are more likely to smoke than extremely obese women. Pre-existing conditions such as hypertension, diabetes mellitus, asthma and HIV were not statistically different between the groups.	Higher proportion of preeclampsia (23.9% vs. 9.1, P<0.005); complications during caesarean delivery (36 vs. 7) and statistically higher median blood pressure (P<0.05).	Gestational hypertension (N.S); higher proportion of hospital stay (65.2 vs. 42.4, P<0.01); N.S HDU admission; complications (N.S); body weight (N.S).
Sullivan et al. 2015, Australia, population-based cohort study	Determine the prevalence, risk factors, management and perinatal outcomes of super-obese women giving birth in Australia.	Not extremely obese women with BMI <50 kg/m^2	Super-obesity BMI >50 kg/m^2 or >140 kgs	BMI >50 kg/m^2: n=370 BMI <50 kg/m^2: n=621	Super obese women have a lower proportion of smoking during pregnancy, private health care insurance, multiparous, higher proportion of social disadvantage and a higher proportion of caesarean section.	Caesarean delivery aOR: 2.73 (95% CI: 2.02-3.96); preeclampsia aOR:3.43 (1.72-6.84); gestational hypertension aOR:10.24 (4.67-22.44); obstetric problems during pregnancy aOR: 2.42 (95% CI: 1.77-3.29); medical problems during pregnancy 2.89 (95% CI: 2.64-2.11); admission to ICU and HDU aOR: 5.67 (95% CI: 2.31-13.93)	Birthweight ≥4500g aOR: 19.94 (95% CI: 6.81-58.36); NICU aOR: 1.83 (95% CI: 1.27-2.65); preterm birth (N.S).

N.S: statistically non-significant association; uOR unadjusted odd ratio; aOR: adjusted odds ratio; CI: confidence interval. BMI Units: kg/m^2

1.2.2 Clinical background and rationale: massive transfusion in major obstetric haemorrhage

1.2.2.1 Postpartum haemorrhage, incidence and morbidity

Internationally, there is no standard definition of postpartum haemorrhage (PPH) or severe postpartum haemorrhage (Rath, 2011). However, PPH is commonly defined as blood loss ≥500 millilitres (mls) within 24 hours of vaginal delivery and it is sometimes defined as ≥1000 mls blood loss after a caesarean section (Rath, 2011, Pahlavan et al., 2001). The incidence of PPH is increasing and is estimated to occur in ~3-7% of deliveries in high-income countries (Knight et al., 2009, Bateman et al., 2010, Skupski et al., 2017). The reasons behind this trend remain unknown but it may be partially explained by an increase in obesity during pregnancy, a greater number of caesarean sections, repeat caesarean delivery and an increased use of uterotonics during delivery (Knight et al., 2009, Belghiti et al., 2011, Cook et al., 2013, Betrán et al., 2016).

Severe postpartum haemorrhage or major obstetric haemorrhage (MOH) remains a major cause of maternal morbidity and is the leading cause of admission to intensive care in postpartum women in several countries (Sullivan et al., 2007, Chantry et al., 2015, Zwart et al., 2010b, SCASMM, 2013, Waterstone et al., 2001). Uncontrolled haemorrhage can result in coagulopathy, haemorrhagic shock, tissue necrosis, cardiac arrest, acute respiratory failure, multiple organ failure and death. Furthermore, it can result in the loss of fertility with 99% of peripartum hysterectomies performed as a consequence of haemorrhage (Knight and UKOSS, 2007). Thus, prevention and timely management of the haemorrhage before it leads to severe morbidity and hysterectomy is of primary concern for the woman and her clinician.

1.2.2.2 Maternal death and haemorrhage

Maternal death as the result of haemorrhage is an uncommon, but clearly a devastating event (Knight and Nair, 2017, Berg et al., 2010). The United Kingdom confidential enquiry into maternal deaths has highlighted that haemorrhage accounts for around 10% of all direct deaths (Knight and Nair, 2017). In France, haemorrhage was the leading cause of maternal mortality and accounted for 18% of all maternal deaths over the 10 year period 1998-2007 (Saucedo et al., 2013). Similarly a report from nine states in the U.S.A., presented haemorrhage as the leading cause of maternal mortality, which was responsible for 14% of maternal deaths (Brantley et al., 2018). Although, the absolute rate of haemorrhage-related maternal mortality remains very low in high-income nations [2.2 per 100,000 live births in France, 1.9 per 100,000 in Italy, 0.7 per 100,000 in the Netherlands and 0.49 per 100,000 in the United Kingdom], concerns remain about the identification and timely management of severe maternal haemorrhage (Schutte et al., 2010, Saucedo et al., 2013, Donati et al., 2018). Differences in identification and timely management may account for some of the differences in maternal mortality rates reported between countries (Kassebaum et al., 2014).

The United Kingdom confidential enquiry into maternal deaths during the period 2009-2012 and 2013-2015, noted women who died from haemorrhage had delays in blood product administration or inadequate resuscitation. The severity of the situation was not recognised in two thirds of women (Knight et al., 2014, Knight and Paterson-Brown, 2017). In France and New Zealand approximately half of haemorrhage related deaths over a similar period were considered avoidable (Saucedo et al., 2013, Farquhar et al., 2011).

1.2.2.3 Aetiology of obstetric haemorrhage

McKinnon-Edwards (2017) outlines that the aetiology of obstetric haemorrhage traditionally has been subdivided into four main categories: tone, trauma, tissue and thrombin (the '4Ts').

Atony (or tone) describes an atonic uterus and accounts for 80% of postpartum bleeds (Bateman et al., 2010). This is where the uterus is unable to contract during the third stage of labour. This may be the result of an exhausted uterus due to prolonged labour or overstimulation due to excessive uterotonics, lack of perfusion or mechanical obstacles such as fibroids or retained placenta that prevent the contraction of the uterus (McKinnon-Edwards, 2017).

Trauma refers to traumatic injury such as tears to the lower genital tract, vaginal haematoma, extensions of lacerations in the lower uterine segment, uterine artery and uterine rupture (Baird, 2017).

Tissue is a collective term to denote abnormal placentation such as abnormally invasive placenta (AIP) or retained placenta which prevents the uterus from contracting after delivery.

'Thrombin' as a cause of haemorrhage is used as a shorthand for coagulation abnormalities. Although rare, women with inherited bleeding disorders such as haemophilia or von Willebrand disease are at increased risk of bleeding during pregnancy. Coagulation abnormalities more commonly occur in the absence of inherited bleeding disorders in other causes such as amniotic fluid embolism and placental abruption.

1.2.2.4 Haemostasis

1.2.2.4.1 The coagulation cascade

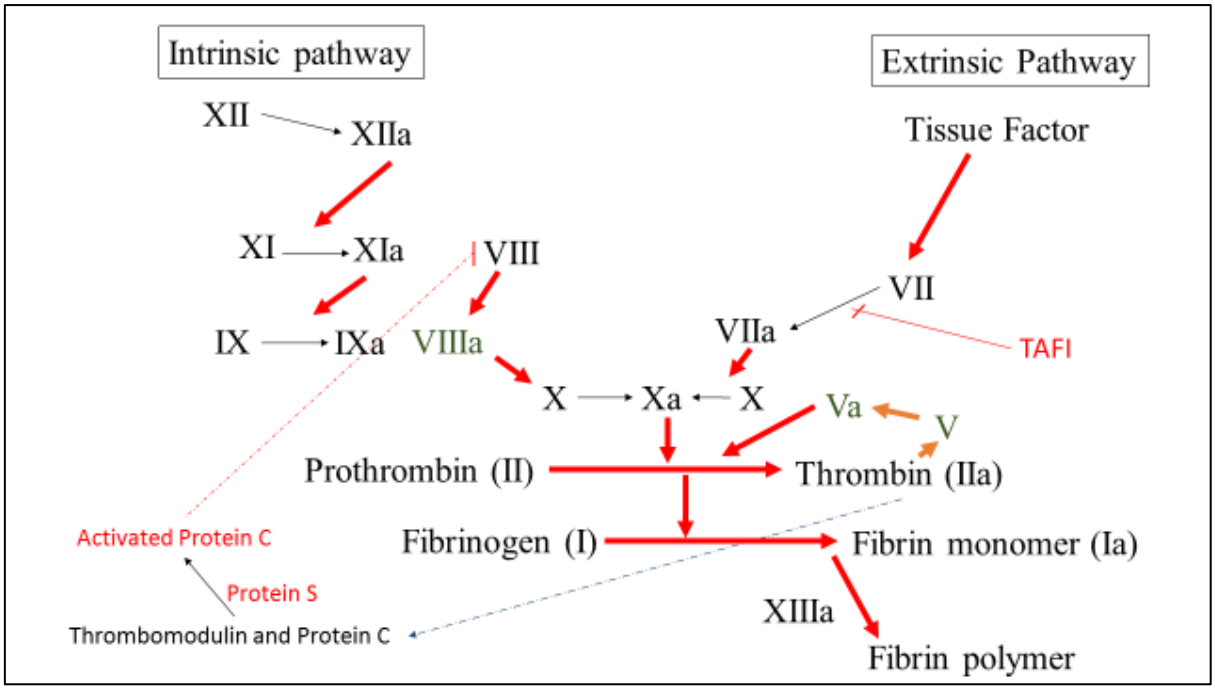
Haemostasis is the normal physiological response to vessel injury and is a process in which a clot or haemostatic plug is formed to stop haemorrhage. It involves a complex set of interactions between the coagulation cascade, fibrinolysis, platelets and the endothelium (Rasche, 2001, McKinnon-Edwards, 2017, Palta et al., 2014) (see Figure 1).

An overview of the haemostatic changes that occur during pregnancy is required to understand the necessary haematological management in major obstetric haemorrhage. A common diagrammatic representation of the coagulation cascade is illustrated in Figure 1. After injury to the endothelium, collagen is exposed and alongside tissue factor the coagulation cascade is initiated. Through a number of enzymatic reactions this results in thrombin formation which converts fibrinogen to fibrin. Pregnancy is a hypercoagulable state as there is a rise in procoagulation factors such as fibrinogen, factors VII, VIII, X, XII and von Williebrand factor (Baird, 2017, Szecsi et al., 2010, Hellgren, 2003). There is also a decline in anticoagulation factors (protein S) and fibrinolysis (Szecsi et al., 2010). Due to an increased plasma volume and consumption of platelets at the placenta, there is a decrease in overall platelet count (Aster, 1990, Hellgren, 2003, Reese et al., 2018). In addition, platelet turnover appears to be normal during pregnancy (Hellgren, 2003).

At 37 weeks of gestation, fibrinogen levels are 4-6g/l which is considerably higher than in the non-pregnant population (normal range 2-4g/l) (Allard et al., 2014). Haemostasis is regulated via the placental bed which releases tissue factor and thrombomodulin and plasminogen (Thachil and Toh, 2009). Blood flow to the placental bed is at 750ml/min (Assali et al., 1953) and the total circulating blood volume at term is approximately 7 litres (Vricella et al., 2015). Vessel constriction and uterine contraction is required to stop

bleeding when the placenta is expelled (Burton-Brown, 1949). Simultaneously, after separation of the placenta, large amounts of tissue factor are expressed from the placental bed, which activate procoagulants resulting in haemostasis of the placental 'scar'. In an uncomplicated delivery, haemostasis results in little blood loss during the third stage of labour.

Figure 1. Coagulation cascade.



1.2.2.5 Major obstetric haemorrhage (MOH)

1.2.2.5.1 Definition

There is no universally agreed definition of MOH, which leads to varying incidence estimates between regions. This variation may also be the result of different methods of assessing PPH; a systematic review illustrated that there was a 3% prevalence of PPH using an objective measurement while this was reduced to 1.7% using a subjective measurement (Carroli et al., 2008). In Scotland, MOH was been defined by Scottish Confidential Audit of Severe Maternal Morbidity (SCASMM) as >2500ml blood loss or administration of ≥5 units of red blood cells (RBC) within 24 hours of giving birth and the

estimated incidence was 5.9 per 1000 live births in 2011 (SCASMM, 2013). However, it remains unclear what constituents (haemoglobin level, amount of blood loss or transfusions) of PPH are predictors of poor maternal outcomes (Waterstone et al., 2001).

In order to account for the measurement bias that is associated with assessing blood loss (Schorn, 2010, Dildy III et al., 2004), selected studies have used massive transfusion (MT) as a method to define MOH (McKinnon-Edwards, 2017, Green et al., 2016b). However, MT does not have a universally agreed definition. Pragmatically it has been defined as transfusion of one body blood volume within 24 hours of delivery (Levi et al., 2011), although both approaches are retrospective definitions, based on what has occurred, rather than a prospective assessment of bleeding.

1.2.2.6 Major obstetric haemorrhage and coagulopathy

1.2.2.6.1 Coagulopathy and disseminated intravascular coagulopathy

Coagulopathy occurs when the clotting ability of the blood is impaired (Hunt, 2014). It results from the combination of blood loss, consumption of coagulation factors, fibrinolysis and haemodilution from resuscitation products (Hunt et al., 2015). Traumatic uncontrolled bleeding results in consumptive coagulopathy which occurs when a high expression of tissue factor leads to the initiation of the coagulation process, use of platelets and procoagulation factors. This results in consumption of coagulants and thus the haemostatic mechanisms are no longer able to stop further bleeding. Lack of perfusion results in hypoxia and consequent acidosis; in addition, hypothermia further exacerbates the coagulopathy (Rossaint et al., 2016). The subsequent management with crystalloids, colloids and red blood cell transfusion results in haemodilution which may exacerbate disseminated intravascular coagulation (DIC) (Davenport, 2013).

DIC is an uncontrolled systemic activation of the coagulation cascade which results in microvascular thrombosis which compromises systemic blood supply (Erez et al., 2015, Levi and ten Cate 1999). In an exsanguinating patent, the lethal triad which is a combination of DIC alongside hypothermia and acidosis will result in a downward spiral in physiological condition (Rotondo and Zonies, 1997, Sagraves et al., 2006). Without surgical and haemostatic correction, it will result in hypovolemic shock, multiple organ failure and death.

1.2.2.6.1.1 Haemostatic changes during major obstetric haemorrhage

Knowledge of the pathophysiological response to haemorrhage in the obstetric setting is required to understand the resuscitation needed. Due to the hypercoagulable state in pregnancy, women have higher levels of procoagulants than the general population, which suggests that data from trauma research in non-pregnant populations cannot be directly applied to MOH (Allard et al., 2014). Current evidence suggests that the haemostatic impairment is different between trauma induced bleeding and obstetric haemorrhage (Collis and Collins, 2015). In particular, previous research has shown that prothrombin (PT) and activated prothrombin times (aPTT) were normal in severe PPH bleeds, whilst fibrinogen decline appeared to have a direct relationship with increased blood loss (Collins et al., 2014, Charbit et al., 2007, de Lloyd et al., 2011).

1.2.2.6.1.2 Haemostatic impairment according to aetiology

Current evidence suggests that haematological impairment varies according to the aetiology of MOH (Collis and Collins, 2015, Green et al., 2016a).

Placental abruption is complete or partial premature placental separation before delivery (Thachil and Toh, 2009). It is the result of the rupture of maternal decidual arteries causing separation of the decidual-placental interface (Tikkanen, 2010). Consequently it will result

in a large release of tissue factor and subsequent consumptive coagulopathy while appearing outwardly that women have relatively low blood loss (Thachil and Toh, 2009). Placental abruption presents with hypofibrinogenaemia and thrombocytopenia from the onset and in severe cases leads to DIC (Green et al., 2016a, Collis and Collins, 2015). In a number of studies, women with abruption have had the lowest fibrinogen levels compared to women with other causes of MOH (Collins et al., 2014, Green et al., 2016a). Women with amniotic fluid embolism will have similarly poor haemostatic features as it is characterised by acute DIC (Thachil and Toh, 2009).

The most common causes of MOH, uterine atony and genital tract trauma or surgical lacerations, are unlikely to lead to severe coagulopathy or DIC unless there is massive uncontrolled blood loss (Collis and Collins, 2015, Collins et al., 2014). Green et al. (2016a) found that fibrinogen and platelet levels remained slightly higher in women with haemorrhage caused by trauma than other causes (Green et al., 2016a). Similarly, in women with trauma, atony or retained placenta, after a PPH of 1000-1500mls, the fibrinogen level was 3.9 g/l and PT/aPPT was normal in 98.4% and 98% of patients respectively (Collins et al., 2014). This variation in haemostatic impairment according to aetiology has only been shown in small studies and further work is required to determine whether these findings can be replicated in larger studies.

1.2.2.7 Management of major obstetric haemorrhage

Management of MOH can be subdivided broadly into obstetric management and haematological management. Haematological management, including blood transfusion and fluid resuscitation, aims to stabilise the patient and allow planning of definitive obstetric and surgical interventions.

1.2.2.7.1 Current obstetric management of major obstetric haemorrhage

Obstetric treatment of MOH can be further subdivided into medical and surgical management. Medical management includes the use of uterotonics or prostaglandins and surgical management includes interventional radiology, surgical interventions, intrauterine balloon tamponade, uterine compression sutures and hysterectomy. There is significant variation in PPH guidelines across international obstetric societies (Dahlke et al., 2015) and often management is based on limited evidence with expert opinion filling in the gaps when there is a lack of high quality evidence (Mavrides et al., 2016, RANZCOG, 2017, Sentilhes et al., 2016, American College of Obstetricians Gynecologists, 2006). This also reflected in differences in surgical management of PPH across countries. The first line surgical management of PPH in the United Kingdom in 2007-2009 was uterine compression sutures (B-lynch) (Kayem et al., 2011), while in France and the Netherlands the first line invasive treatment was arterial embolisation during a similar period (Kayem et al., 2016, Zwart et al., 2010a). There has been no international study to compare whether differences in surgical management are reflected in variations in maternal and perinatal outcomes across nations.

1.2.2.7.2 Obstetric management by aetiology of MOH

Some guidelines have suggested that the first line of treatment in MOH should be uterotonics aimed at treating uterine atony as it is the most common cause of PPH (Abdul-Kadir et al., 2014). While the administration of uterotonics occurs, other causes of haemorrhage may be explored (Abdul-Kadir et al., 2014). Appropriate management will be guided by the aetiology of the haemorrhage, for example, attempts will be made to remove retained products and traumatic injury will be sutured (RANZCOG, 2017).

However, tailoring management to the aetiology of haemorrhage is not a feature of most current international guidelines (Mavrides et al., 2016, RANZCOG, 2017, Sentilhes et al., 2016, American College of Obstetricians Gynecologists, 2006). Green et al. (2016b) showed that there is, in practice, clear variation between aetiology and obstetric management. The largest proportion of women who had a hysterectomy were those with AIP in comparison to all other causes of haemorrhage (93% of women with AIP vs. 45% women with other causes). In contrast, uterine balloons and compression sutures were more commonly used to manage uterine atony (Green et al., 2016b).

1.2.2.8 Haematological management and fluid resuscitation in MOH

There is even more limited evidence to guide the management of haemostatic impairment during PPH (Mavrides et al., 2016); however, appropriate fluid resuscitation and blood product transfusion aims to maintain circulating blood pressure and volume to ensure tissue perfusion while averting coagulopathy. Table 3 summarises the haematological management of major haemorrhage from a number of international guidelines. The threshold for the commencement of blood components remains unclear and haematological management in obstetric haemorrhage is not described as a first-line intervention in guidelines (Hunt et al., 2015). Unlike non-pregnant patients with haemorrhage due to general trauma, pregnant women have up to 40% higher circulating blood volume (Abbassi-Ghanavati et al., 2009). In addition, expansion in plasma volume results in haemodilution (fall in haemoglobin, haemocrit and RBC count) (Soma-Pillay et al., 2016), therefore, compared to general trauma patients, pregnant woman can sustain a higher blood loss. Accordingly, in women with an obstetric haemorrhage vital signs may not deteriorate until a significant amount of their circulating blood volume has been lost, which may be the result of having a higher circulating volume and being a young and

healthy population (Norman and Clark, 2016). Rather than administering a set number of units of RBC, fresh frozen plasma (FFP) and platelets for resuscitation through a major haemorrhage protocol (MHP), the trauma guideline by the British Committee for Standards in Haematology (BCSH) (Hunt et al., 2015) recommends that resuscitation through blood components should be guided by the haemostatic changes that occur during ongoing haemorrhage.

Table 3. Summary of haematological guidelines for the management of postpartum haemorrhage from international societies and expert consensus groups.

Guideline	**France - CNGOF & SFAR (Sentilhes et al., 2016)**	**United Kingdom – RCOG (Mavrides et al., 2016)**	**United Kingdom - BSCH (Hunt et al., 2015)***	**Australia and New Zealand - RANZCOG (RANZCOG,, 2017) and National Blood Authority**	**Collis and Collins authors' strategy. (Collis and Collins, 2015)**
Transfusion	Fluid resuscitation when PPH worsens after failure of first line management.	No firm criteria for resuscitation.	Provide transfusion management in any clinical scenario	Early replacement of clotting factors is essential in severe PPH.**	Bleeding >1000ml and ongoing run point of care tests.
Red blood cells	Clinical signs on severity of PPH. No amount given.	Indication is a clinical and haematological assessment. Give emergency group O RhD negative blood.	RBC transfusion guided by blood loss and haemodynamic stability. Group-O or group specific emergency supplies.	Given in response to haemodynamic changes and estimated blood loss. No target ratio given.	-
RBC therapeutic goals	Hb 80 g/L	Hb > 80g/L	Maintain high enough Hb for adequate perfusion.	-	-
Plasma	FFP can be given without waiting for laboratory results if PPH is severe.	FFP should be guided by haemostatic testing and if haemorrhage is continued. If no haemostatic results and continued bleeding transfuse FFP after 4 units of RBC at 12/15 ml/kg.	Transfuse at a ratio 1:2 FFP:RBC in initial resuscitation until haemostatic results return. Should be guided by abnormalities in aPTT/PT. Give 15-20 ml/kg.	FFP: 15 mL/kg	FFP: 15/kg/L if FIBTEM <12mm or PT/aPTT abnormal. Increase volume of FFP if >1.5x normal. Needs to be actively bleeding regardless of tests.
Clotting therapeutic goal	-	PT < 1.5 x normal	PT / aPTT < 1.5 x normal	PT <1.5 × normal aPTT <1.5 × normal	PT/aPTT <1.5 x normal FIBTEM >12mm
Platelets	No dosage given.	1 pool of platelets if PPH is ongoing and platelet count <75 X 10^9/ L	Usually required after the loss of 1-1.5 blood volumes. 1 pool when platelet count falls below >50 X 10^9/L	1 adult therapeutic dose if platelet count < 50 X 10^9/ L	Yes – unlikely to only occur in placental abruption or amniotic fluid embolus. Multiple platelet transfusions are not justified.

Guideline	France - CNGOF & SFAR (Sentilhes et al., 2016)	United Kingdom – RCOG (Mavrides et al., 2016)	United Kingdom - BSCH (Hunt et al., 2015)*	Australia and New Zealand - RANZCOG (RANZCOG,, 2017) and National Blood Authority	Collis and Collins authors' strategy. (Collis and Collins, 2015)
Platelets therapeutic goal	PLT count >50 X 10^9/ L	PLT count >75 X 10^9/ L	PLT count >50 X 10^9/ L	PLT count >50 X 10^9/ L	>75 X 10^9/ L
Fibrinogen	Active bleeding and <2 g/L transfuse fibrinogen. No dosage given or type of fibrinogen product.	Transfuse 2 pools of cryoprecipitate (10 units) if PPH continued and fibrinogen <2g/L.	Fibrinogen < 1 usually occurs after the loss of 1-1.5 time blood volumes. 2 pools of cryoprecipitate (2 pools = 10 donor units contains 3-6 g of fibrinogen). It will raise fibrinogen level by 1g/L.	Administer cryoprecipitate (3-4g) or fibrinogen concentrate when fibrinogen level <1.5-2g/L.*	One pool of cryoprecipitate would raise fibrinogen level by 0.5g/L.
Fibrinogen therapeutic goal	Maintain fibrinogen level >2 g/L	Fibrinogen level >2 g/L	Fibrinogen level >1.5 g/L	Fibrinogen level >2 g/L	FIBTEM >11mm Fibrinogen level >1-1.5 g/L
Antifibrinolytics	Tranexamic acid may be useful – use at the clinician's discretion. Not for prophylaxis. Before Woman trial.	Consider use of tranexamic acid in PPH. No dosage or indication given. Before Woman trial.	Tranexamic acid should be given as soon as possible after injury at dose of 1g over 10min. Before Woman trial.	1 g of tranexamic acid in PPH is appropriate when considering other interventions and haemostatic features of patient. * Tranexamic acid may be considered within 3 hours of severe PPH.	Yes – no dose suggested. Before Woman trial.
Factor VIIa	No recommended use.	Routine use of FVIIa is not recommended.	Use of Factor VIIa is not recommended.	Considered in life threatening haemorrhage only after conventional measures have failed.	Should be used in life threatening PPH: fibrinogen > 1 g/l and platelet count >20 X 10^9/ L.
Fluid replacement	Plasma expansion by crystalloids.	Warm fluid replacement to prevent hypothermia. Maximum 2 L isotonic crystalloid and maximum 1.5 L colloid until blood arrives.	Not mentioned in guideline.	Not mentioned in either guideline.	Use of colloids such as hydroxyethyl starches may interfere with fibrin clot strength.

Adapted and updated table from: Shalyor et al. National and international guidelines for patient blood management in obstetrics: a qualitative review. Anesthesia-analgesia. 2017:124(1). Pages: 219-232. BSCH: British Committee for Standards in Haematology; CNOF: French college of Gynaecologists and Obstetricians (CNGOF); SFAR: French Society of Anaesthesiology; RCOG: Royal College of Obstetricians and Gynaecologists; RANZCOG: Royal Australian and New Zealand College of Obstetricians and Gynaecologists.
* Not pregnancy specific **updated RANZCOG 2017 guideline.

1.2.2.8.1 Blood components and haemostatic agent replacement in pregnancy

1.2.2.8.1.1 Fibrinogen

There is a growing body evidence that suggests fibrinogen should be replaced sooner than other procoagulants (Collis and Collins, 2015). Green et al. (2016a) showed that the median fibrinogen level fell to <2 g/L for women with massive transfusion (8 units or more of RBC within 24 hours of delivery). Other observational studies have shown that an early fibrinogen level <2 g/L was associated with the final severity of PPH, poor patient outcomes and mortality (Charbit et al., 2007, Cortet et al., 2012, Rourke et al., 2012, McQuilten et al., 2017) which supports the notion of early replacement of fibrinogen. In contrast, the results from a recent randomised control trial showed that early administration of fibrinogen concentrate (2g) did not reduce postpartum blood loss in patients with PPH (Wikkelsø et al., 2015). However, the FIB-PPH trial used a low dose of fibrinogen and only elevated the circulating volume of fibrinogen by 0.4 g/L in the intervention arm. Table 3 highlights the variations in international guidelines for the therapeutic goals, amount of products to be given and use of cryoprecipitate or fibrinogen. No study has identified the optimum level of fibrinogen to be administered during MOH or what the appropriate therapeutic goal should be.

1.2.2.8.1.2 Plasma or Fresh Frozen Plasma

Coagulation testing through PT/aPTT does not appear to be correlated with increased blood loss in the obstetric setting and appears to be normal in the majority of causes of PPH (de Lloyd et al., 2011, Green et al., 2016a). These tests are weakly correlated to plasma concentrations of thrombin and Xa inhibitors, and they were not designed to predict bleeding (Adcock and Gosselin, 2017, Kitchens, 2005). In addition to the increased risk of circulatory overload, BCSH guidelines recommend that FFP should be guided by laboratory results (Hunt et al., 2015).

1.2.2.8.1.3 Antifibrinolytics

Antifibrinolytics have been shown to be efficacious in reducing premature mortality after bleeding in trauma as shown by the CRASH-2 randomised control trial (RCT) (CRASH-2 collaborators, 2010). Tranexamic acid (TXA) binds to plasminogen and inhibits the degradation of fibrin thus encouraging further clotting. The recent WOMAN trial showed that use of tranexamic acid (TXA) reduced maternal mortality in women with PPH (WOMAN Trial Collaborators, 2017). All the current obstetric guidelines, excluding RANZCOG, were written before the publication of the WOMAN trial results so recommendations are likely to change and encourage the use of TXA in the management of MOH. However, Collis and Collins (2015) have argued that TXA may have no benefit for women with hypofibrinogenaemia or MOH as the participants in the WOMAN study were unlikely to have a major coagulopathy.

1.2.2.8.2 Context of haematological management

Despite having the same availability of evidence to all clinicians, it is clear that obstetric management differs internationally (Kayem et al., 2016, Zwart et al., 2010a, Kayem et al., 2011). Reasons for these differences are often the result of variations in clinical opinion. There is also significant variation in the guidelines for haemostatic management of obstetric haemorrhage (Table 3). This is likely to be mirrored in clinical practice; although, this has yet to be shown.

Table 3 highlights that haematological management guidelines are not tailored to the aetiology of obstetric haemorrhage despite there being recorded differences in haemostatic impairment. As a result, it is unclear if the amount of blood components and haemostatic agents administered differ in practice according to aetiology of PPH.

The study described in chapter four aims to compare haematological management across a number of countries and to assess if these differ by aetiology of PPH.

1.2.2.9 Clinical questions

There are a number of unanswered scientific questions about massive transfusion in major obstetric haemorrhage. Multinational studies offer the opportunity to replicate findings across nations, in particular to first address the questions of whether haemostatic impairment varied according to aetiology of PPH; second, whether haematological management varies across countries; and if so, whether maternal outcomes vary across countries.

1.2.3 Clinical background and rationale: abnormally invasive placenta

1.2.3.1 Abnormally invasive placenta

AIP is a placenta that cannot be removed manually without causing severe bleeding (Chantraine and Langhoff-Roos, 2013). AIP is a spectrum disorder inclusive of all three subtypes of invasive placentae, which are: placenta accreta, increta and percreta. These subtypes are determined by the depth of trophoblast invasion into the myometrium. Placenta accreta is where the chorionic villi adheres directly to the myometrium without the decidua (Chantraine and Langhoff-Roos, 2013). While placenta increta occurs when the chorionic villi invade into the myometrium but do not emerge through the outside of the uterus. The most severe is placenta percreta, this is where the chorionic villi invade through the myometrium and serosa, and in some cases to neighbouring organs. AIP becomes a clinical problem after delivery when the placenta does not physiologically detach from the uterus and is followed by massive obstetric haemorrhage (MOH) leading to further morbidity and risk of maternal death (Committee on Obstetric Practice, 2012, Fitzpatrick et al., 2014a).

1.2.3.2 Risk factors and morbidity

The main risk factors for AIP are previous caesarean section and previous uterine surgery. In addition, placenta praevia and in vitro fertilisation (IVF) are also known risk factors (Fitzpatrick et al., 2012). Internationally, the incidence of AIP is increasing, (Wu et al., 2005) which is thought to be the result of an increasing rate of caesarean section (Bateman et al., 2012). This is concerning as AIP is often associated with very poor maternal outcomes with an average estimated blood loss of between three and five litres (Hudon et al., 1998), which, without medical intervention, would result in maternal death (Geller et al., 2004). An increase in the incidence of AIP will

lead to an increasing trend of severe maternal haemorrhage and maternal mortality (Solheim et al., 2011). This trend is unfortunately being reflected in the United Kingdom; the most recent report into the confidential enquiry into maternal deaths in the United Kingdom showed a doubling in the maternal deaths as a result of haemorrhage during the period 2014-2016 and this increase was the direct consequence of deaths caused by abnormal placentation (Knight et al., 2017).

1.2.3.3 Difficulty in detection and diagnosis

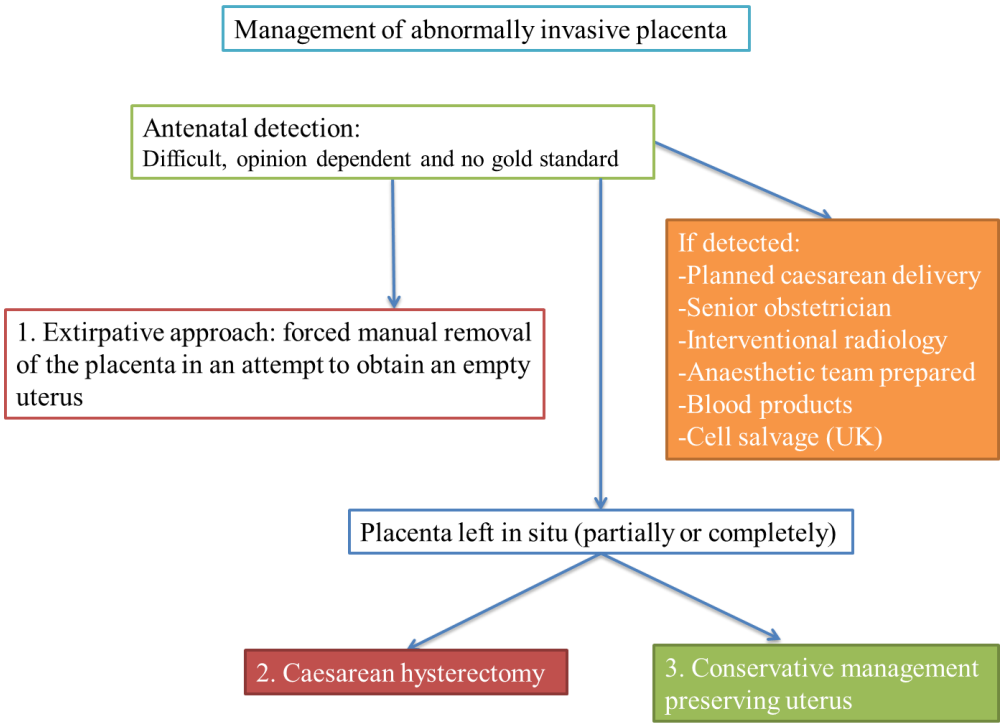
The gold standard diagnosis for AIP is histological confirmation of the chorionic villi attached to the myometrium without the presence of the decidua (Tantbirojn et al., 2008). This confirmation can only occur after hysterectomy or death (Garmi and Salim, 2012). Antenatal imaging is used to inform clinical management (Alkazaleh et al., 2004, Pilloni et al., 2016). However, no gold standard diagnostic technique exists to diagnose AIP in the antenatal period and diagnostic techniques are based on expert opinion, which are prone to error (Collins et al., 2015). Subsequently, in about half of women with AIP, AIP is not suspected prior to delivery (Fitzpatrick et al., 2012).

The sensitivity of antenatal screening is higher for percreta than that for accreta or increta (Marcellin et al., 2018, Pilloni et al., 2016). Placenta percreta is much easier to distinguish at ultrasound (Marcellin et al., 2018) and at delivery because the invasion has broken through the serosa. However, it is more difficult to differentiate between a placenta resistant to manual delivery and a truly invasive placenta that has not invaded through the serosa (accreta/increta). This is problematic, as a false positive could lead to a hysterectomy and its associated morbidities when surgery was not required. On the other hand, a false negative could result in a catastrophic haemorrhage when an invasive placenta is forcibly removed (Eller et al., 2009).

1.2.3.3.1 Management and outcomes of an antenatal suspicion of AIP

Previous research has shown that maternal outcomes are better for women who have had an antenatal suspicion of AIP compared to AIP being discovered at delivery (Eller et al., 2009, Shamshirsaz et al., 2015). In particular, women with an increta or percreta without antenatal suspicion had a larger blood loss compared to those with antenatal suspicion (Fitzpatrick et al., 2014a). Antenatal suspicion enables appropriate management with a multi- disciplinary team within a well-equipped centre. Preparedness for the major complication of AIP has been shown to improve maternal outcomes (Warshak et al., 2010, Eller et al., 2011, Kong et al., 2017, Shamshirsaz et al., 2015, Brennan et al., 2015). Therefore, antenatal suspicion of AIP is an important factor when analysing outcomes of women with AIP because management has been shown to differ.

Figure 2. Flow diagram showing the management of abnormally invasive placenta.



1.2.3.4 Management of AIP

After the delivery of the infant, management of AIP can be broadly subdivided into three approaches as shown in figure 2. These are the forced manual removal of the placenta (extirpative approach), conservative approaches or peripartum hysterectomy.

1.2.3.4.1 Forced manual removal approach

A forced manual removal or an extirpative approach involves forcibly removing or excising the placenta after delivery in order to obtain an empty uterus (Sentilhes et al., 2010a, Kayem et al., 2004). The approach is associated with greater blood loss and morbidity compared to leaving the placenta in situ and proceeding to an immediate peripartum hysterectomy (Eller et al., 2009, Shamshirsaz et al., 2015).

In addition, the extirpative approach has poorer maternal outcomes compared to a conservative approach that does not forcefully remove the placenta. Kayem et al. (2004) compared two managements over two time periods (1993-1997 vs. 1997-2002); the first time period used an immediate removal of placenta material and the second time period left the placenta in situ as a conservative approach to conserve the uterus. Kayem et al. (2004) found that during the period of 1997-2002 (conservatively managed group) compared to the 1993-1997 (forced manual removal) there was a lower rate of hysterectomy, a lower mean estimated blood loss, and there were fewer women with disseminated intravascular coagulation.

The extirpative approach is unlikely to be used as a planned management for AIP and is more common in women where AIP has not been suspected in the antenatal period (Eller et al., 2009).

1.2.3.4.1.1 Gentle removal of placenta

To protect against a false positive (Bowman et al., 2014, Weiniger et al., 2016), where the accreta has been suspected antenatally, an obstetrician may attempt gentle cord traction alongside the administration of oxytocin to deliver the placenta (Sentilhes et al., 2018, Sentilhes et al., 2013). The rationale for this approach is to guarantee that it is a true case of AIP, which requires further management to prevent a potentially unnecessary hysterectomy. However, with any attempt to remove an accreta there is the risk of major obstetric haemorrhage (Sentilhes et al., 2018). A case series showed that an attempted removal of the placenta was possible without severe maternal morbidity and it prevented fifteen percentage of hysterectomies (Weiniger et al., 2016). Approximately, half of women in this study were false positives and there were no details on the level of placental invasion.

1.2.3.4.2 Peripartum hysterectomy

1.2.3.4.2.1 Peripartum hysterectomy morbidity

Peripartum hysterectomy is considered the gold standard approach to manage AIP (Sentilhes et al., 2018, Eller et al., 2009). Previous studies have shown it to be lifesaving treatment for women where other uterus conserving surgeries fail (Angstmann et al., 2010, Knight and UKOSS, 2007). Reassuringly, it has a low mortality rate of 0.6% in the United Kingdom; however, hysterectomy was associated with severe maternal morbidities such as major haemorrhage, bladder or ureter damage, pulmonary embolism and red cell transfusion of the total blood volume or greater (Knight and UKOSS, 2007, Allen et al., 2018). This approach has an significant long term impact on women who have had their uterus removed and lost their future fertility; as a result, peripartum hysterectomy is associated with post-surgery depression and anxiety (Ewalds-Kvist et al., 2005).

1.2.3.4.3 Conservative management or placenta 'left in situ'

Although an extirpative approach aims to conserve the uterus through forceful removal of the placenta, others have used an approach where the placenta is left in situ either partially or completely without forceful removal (Sentilhes et al., 2010a, Sentilhes et al., 2018, Kayem et al., 2004). This approach is the most common method of conservative management (Silver and Branch, 2018). This would only be considered if the patient was haemodynamically stable and not septic. These women require close monitoring for subsequent haemorrhage or sepsis and, if successful, it is anticipated that the placenta will be partially shed.

The physiological rationale for the 'left in situ' approach is that after the delivery, blood flow to the uterus and placenta will decrease as the uterus involutes. The reduced blood flow and oxygen to the placenta will cause necrosis of the villous tissue and subsequent detachment of the placenta from the uterine wall (Sentilhes et al., 2018).

1.2.3.4.4 Other conservative approaches

In addition, there are other conservative approaches that use surgical methods to preserve the uterus (Sentilhes et al., 2018). The 'the Triple-P procedure' involves resecting the area of the myometrium containing the invasive placenta then suturing around this area to reconstruct the uterus (Teixidor Viñas et al., 2015). The 'one-step conservative surgery' includes removing the portion of the uterus containing the adherent placenta in a single procedure (Sentilhes et al., 2018, Palacios-Jaraquemada, 2008). The results from these studies suggest that local resection was associated with fewer post-surgical complications; however, in this study there was a high risk of selection bias towards less severe cases (Clausen et al., 2014). The evidence for both surgical approaches is limited due to the lack of population-based studies and small

samples size (Teixidor Viñas et al., 2015, Shabana et al., 2015, Palacios-Jaraquemada, 2008).

1.2.3.4.4.1 Evidence for conservative management

Table 4 highlights selected studies that have examined uterus preserving management by leaving the placenta in situ. Fitzpatrick et al. (2014a) showed that use of transfusion products was lower in a group that had the placenta left completely intact compared to those who had immediate placenta removal. Successful conservative management has been shown to preserve future fertility (Sentilhes et al., 2010b); however, there was still associated morbidity. These women required longer monitoring for complications due to risk of haemorrhage and sepsis. Those who had unsuccessful preservation of the uterus had a hysterectomy at a median of 51 days (range: 6–97 days) in the United Kingdom and 22 weeks (IQR: 9-45 weeks) in France after delivery (Sentilhes et al., 2010a, Fitzpatrick et al., 2014a). Despite the United Kingdom study being the only population-based study there were not enough cases to fully describe the outcomes associated with a conservative approach with any degree of confidence. Table 4 highlights that there is a lack of high quality population-based evidence examining a conservative 'left in situ' approach compared to a peripartum hysterectomy, which makes it an area of debate (Sentilhes et al., 2013). In particular, the secondary hysterectomy and infection rate after conservative delivery have yet to be estimated robustly in a population-based design.

1.2.3.5 Clinical research questions

The main clinical research question remains to ascertain whether there is a difference in maternal and infant outcomes between the modalities of management, and in this case a hysterectomy compared to a uterus conserving approach.

Table 4. Selected studies examining approaches to conservative management.

Authors, date and location	Study design and aim	Case definition	Comparison groups	Sample size	Outcomes
Bretelle et al. 2007. Two teaching hospitals. Marseille, France. (Bretelle et al., 2007)	Case series. To investigate the management of abnormally invasive placenta (AIP)	Diagnosis of placenta accreta based on clinical and histological findings	A) Standard treatment consisted of either a surgical non-conservative approach with a primary total hysterectomy or resection and extraction of the placenta (extirpative approach). Primary immediate hysterectomy was always indicated in cases of life-threatening haemorrhage. B) Conservative approach to leave the placenta in situ.	N=50. A)24 cases had normal approach (management of haemorrhage and if fails, hysterectomy). B) 26 cases had Conservative treatment.	A) In (n=24) normal approach group 15 woman had a hysterectomy. B) In the conservative group 5 women had a hysterectomy, 10 (38%) had a transfusion and 3 had disseminated intravascular blood coagulation (12%). No direct comparison between management groups was made.
Kayem et al. 2004. One tertiary centre. France (Kayem et al., 2004)	Case series. To compare historical management approaches to AIP.	Placenta accreta according to clinical or histologic criteria.	A) Systematic manual removal of the placenta to leave the uterine cavity empty, even if force was required. Then undertake a hysterectomy if required. B) Conservative treatment. No antenatal suspicion: removal of the placenta was not forced; the conservative treatment left the placenta, in part or entirely, in the uterus when the patient's haemodynamic status was stable and no septic risk was present. With antenatal suspicion: similar approach was taken but was planned with obstetrical team.	N=33. A) n=13 B) n=20	Hysterectomy: group A vs. group B (n=11 (85%) vs. n=3 (15%), respectively); Amount transfused: Group A vs. group B (3,230mls vs. 1,560, respectively). Sepsis group A vs. group B (n=0 vs. n=3 (15%), respectively).

Authors, date and location	Study design and aim	Case definition	Comparison groups	Sample size	Outcomes
Fitzpatrick et al. 2014. United Kingdom. (Fitzpatrick et al., 2014a)	Population-based cohort study. Describe current management and associated outcomes of AIP.	Placenta accreta, increta, and percreta diagnosed histologically following hysterectomy, or post-mortem, or an abnormally adherent placenta, requiring active management, including conservative approaches where the placenta is left in situ.	A) Women who had no attempt to remove placenta around time of delivery B) Women who had an attempt to remove placenta around time of delivery C) No attempt made to remove placenta in an attempt to conserve the uterus	N=134. A) n=32 B) n=102 C) n=18	Hysterectomy: Group A vs. group B, (n=26 (66%) vs. n=58 (57%), respectively); Estimated total blood loss in ml (range): group A vs. group B - 1750 (range: 200–15 000mls) vs. 3700 (range: 500–24 000mls), respectively. Blood products given: group A vs. group B: (n=17 (57%) vs. n=87 (86%), respectively). C) 11 (73%) of these women it was successful, 5 women underwent a hysterectomy a median of 51 days (range 6–97 days) after delivery.
Sentilhes et al. 2010. France. (Sentilhes et al., 2010a)	French multicentre retrospective study. Describe the outcomes of woman managed conservatively.	Diagnosed using a clinical and histologic criteria. Conservative management in case of placenta accreta was defined by the decision of the obstetrician to leave the placenta partially or totally in situ, with no attempt to remove it forcibly.	A) Women with conservative management	N=167	Hysterectomy: n=18 (11%); median time of 22 days (IQR: 9–45); blood transfusion n=70 (42%); transfused more than 5 units of RBC n=25 (15%); Infection including fever symptoms n=47 (28%).
Pather et al. 2014. Short communication. Sidney, Australia (Pather et al., 2014)	Case series and review of the literature. Describe the conservative management in cases of percreta.	Cases of placenta accreta with a conservative approach. Placental attachment to either the bladder, rectum, omentum and other surrounding structures.	A) Women with placenta percreta and left in situ	N=3 case series N=57 from literature review	Hysterectomy: n=25 (44%) of women. 42% had major complications such as sepsis (n=4), major haemorrhage (11), pulmonary embolism (n=1), fistula (n=1) and coagulopathy (n=6).

Authors, date and location	Study design and aim	Case definition	Comparison groups	Sample size	Outcomes
Clausen et al. 2014. Review of literature up to 2013. (Clausen et al., 2014) [Includes: Kayem et al. 2004 & Sentilhes et al. 2013]	Review of the literature to describe the management of placenta percreta.	Studies were included if they included placenta percreta cases confirmed histologically or during surgery.	A) Women with placenta left in situ B) Local resection of placenta and/or uterus C) Primary hysterectomy	N= 36 left in situ N=17 local resection N=66 hysterectomy	Hysterectomy in left in situ n=18 (50%), local resection (n=0). Subsequent complication rate in 24hrs was n=9 (25%) in left in situ, n=2 in local resection and n=19 (30%) in hysterectomy group.

1.2.4 Clinical background and rationale: anaphylaxis in pregnancy

1.2.4.1 Incidence and trends

There is very little information regarding the incidence of anaphylaxis in pregnancy globally. A study in the U.S.A suggested an incidence of 2.7 cases per 100,000 deliveries (Mulla et al., 2010). It has been proposed that anaphylaxis is increasing in the general population but still remains a very rare event (Simons and Schatz, 2010, Ewan P.W and for the for the British Society for Allergy and Clinical Immunology, 2006, Harper et al., 2018). This may be the case in pregnancy due to an increase in exposure to potential allergens; however, there are no data available to assess this. The elevated rates of caesarean delivery globally will result in an increased exposure to anaesthetic drugs and antibiotics during delivery (Betrán et al., 2016), which might be reflected in an increasing incidence of peripartum anaphylaxis.

1.2.4.1.1 Anaphylaxis

Anaphylaxis is a potentially fatal systemic hypersensitivity reaction, which is rapid in onset (Johansson et al., 2001). It is characterised by life-threatening airway, breathing or circulatory problems often with skin or mucosal changes. It commonly occurs when allergens trigger an IgE mechanism causing mast cell activation, resulting in an anaphylactic reaction (Simons and Schatz, 2010).

1.2.4.2 Causative agents

Anaphylaxis can be caused by a number of agents such as food, latex, insect stings and medication (Sengupta and Kohli, 2008, Khan et al., 2008, Shingai et al., 2002, Sheikh, 2007, Cuciti et al., 2005). Antibiotics and anaesthetic agents have been shown to be important causes of reactions in the medical setting (Jao et al., 2006, Mulla et al., 2010, Dunn et al., 1999). Exposure to antibiotics is common in the pregnant population through

the use of prophylactic antibiotics before elective caesarean delivery; intrapartum antibiotic prophylaxis for group B streptococcal (GBS) carriage to prevent neonatal transmission; and the use of other antibiotics to treat infection (Sengupta and Kohli, 2008, Khan et al., 2008). National differences in antenatal screening and prevention policies for GBS between the United Kingdom, European countries and the United States may be reflected in variations in the causal agents between countries, which has yet to be examined (Royal College of Obstetricians and Gynaecologists, 2012, Kenyon et al., 2004).

1.2.4.3 Management

There are no specific guidelines for the management of maternal anaphylaxis so it is likely that women with anaphylaxis in pregnancy are treated in the same way as the general population (Resuscitation council, 2008, The Association of Anaesthetists of Great Britain & Ireland, 2009, Lieberman et al., 2005). Management is characterised by a rapid assessment of life threatening cardio-respiratory compromise, which is usually treated with epinephrine (adrenaline), hydrocortisone (steroid), chlorphenamine (antihistamine), oxygen and fluids (Soar et al., 2008). While drugs are being administered, an airway must be established and high flow oxygen should be given to the patient. Despite international variations in these guidelines, epinephrine, oxygen and fluid administration form the mainstay components of management (Lieberman et al., 2005, Alrasbi and Sheikh, 2007).

1.2.4.4 Outcomes

Outcomes of anaphylaxis in pregnancy can be very severe, as shown by case reports of maternal and neonatal mortality (Cooper et al., 2005, Berenguer et al., 2013). Outcomes have also been reported to include maternal cardio-respiratory compromise resulting in cardiac arrest and hypoxic brain injury in the neonate. However, it is unclear how representative these case reports are of all women with anaphylaxis in pregnancy. This

highlights the need for a population-based study to provide a reliable estimate of not only the incidence but the maternal and perinatal outcomes associated with anaphylaxis in pregnancy.

1.2.4.5 Prospective study of rare complication of pregnancy

Anaphylaxis in pregnancy is a very rare complication of pregnancy; as a result, a single country's data may not provide sufficient numbers of cases to provide a stable estimate of the incidence and outcomes of the condition. Consequently, the pooling of data from multiple nations will provide a more robust estimate.

1.2.4.6 Clinical research objectives

The main research objectives are to provide a valid and precise estimate of the incidence of anaphylaxis in pregnancy, and to describe the causative agents, management and outcomes of anaphylaxis in pregnancy.

1.3 Aim and objectives

1.3.1 Aim

To explore the utility of international collaborative studies to address clinical questions in pregnancy where the exposures, management and/or outcomes are rare.

1.3.2 Objectives

1. To examine the feasibility of pooling together data from two national studies (UK and Australia) of a rare complication of pregnancy, to enable the examination of rare outcomes and a rare exposure, using the example of extreme maternal obesity.
2. To describe the clinical characteristics associated with a rare severe maternal morbidity across five countries (UK, Australia, the Netherlands, France and Italy), using the example of massive transfusion in major obstetric haemorrhage.
3. To undertake a pooled analysis of binational data (UK and France) to enable the assessment of an uncommon management of a severe complication of pregnancy, using the example of abnormally invasive placenta.
4. To complete a prospective multinational study (UK, France, the Netherlands, Finland and Belgium) of a very rare complication of pregnancy to identify associated causes and outcomes, using the example of anaphylaxis in pregnancy.

Chapter 2. An examination of rare outcomes and an uncommon exposure: a pooled analysis of extreme maternal obesity

2.1 Introduction

2.1.1 Feasibility of multinational studies of rare complications of pregnancy

Previous research pooling together international data on rare complications in pregnancy has been limited due to heterogeneity of definitions, methods and populations (Knight et al., 2009). To address these limitations the obstetric surveillance systems in Australia and the United Kingdom were designed to be compatible to allow the pooling of data. In Australia and the United Kingdom, obesity during pregnancy is a common comorbidity and these obstetric surveillance systems set out to examine extreme maternal obesity. As highlighted in chapter one, a potential benefit of multinational studies of severe and rare complication of pregnancy is the pooling together of data; however, in order for this method to be valid, an assessment of comparability between datasets must be completed. The process and feasibility of harmonising datasets, with the view of combining the datasets, from the INOSS collaboration has yet to be undertaken.

For the purposes of this chapter, extreme maternal obesity (BMI $\geq$50 kg/m^2) was chosen to assess the feasibility of combining two national studies that collected data on a rare exposure, using similar methodology and definitions. This study further examined whether the two extremely obese populations were similar enough in terms of baseline characteristics to allow the pooling of data. If data could be pooled this would allow further study into the epidemiology of extreme maternal obesity on a larger population. In particular, it would enable the examination of both rare outcomes associated with this complication and an uncommon exposure group, which was defined by a higher BMI cut-off.

2.1.2 Rare outcomes

Table 2 highlighted that none of the identified studies were able to robustly examine the association between extreme maternal obesity and the most uncommon outcomes, such as perinatal death, stillbirth and shoulder dystocia. In particular, previous research has been limited by inadequate sample size, thus increasing the likelihood of type II errors when examining extreme obesity and rare outcomes. In the general population in the UK, 4 per 1000 of babies were stillborn and the perinatal mortality rate was 5.6 per 1000 births in 2016 (Office for National Statistics, 2017b, Draper ES et al., 2018), in Australia 7.2 per 1000 of all babies were stillborn between 2005-2009 and there was a perinatal mortality rate of 9.6 per 1000 births in 2012 (Hilder et al., 2014). The pooling of the two incidences from the UK and Australia provided an incidence of 6 per 1000 for stillbirth and 8 per 1000 births for perinatal mortality. Table 5 illustrates the impact of increasing the sample size on the minimum detectable odds ratio between extreme obesity and stillbirth and perinatal mortality, given an incidence of 0.6% for stillbirth and 0.8% for perinatal mortality in the non-extremely obese population (Fleiss et al., 2013). Thus the combination of two national studies provides the opportunity to add to the evidence base by increasing the sample size to examine rare outcomes.

Table 5. The change in study power according to an increase in sample size for the minimum detectable odds ratio of rare outcomes (stillbirth and perinatal death).

Number of extremely obese women	**Number of women in the comparison group**	**Minimum detectable odds ratio for stillbirth**	**Minimum detectable odds ratio for perinatal death**
AMOSS study: 315	AMOSS study: 621	5.83	4.90
UKOSS study: 617	UKOSS study: 611	4.9	4.10
1000	1000	3.73	3.18
Combined: 932	Combined: 1232	3.55	3.05
2000	2000	2.69	2.40

2.1.3 Uncommon exposure

The pooling of two national studies will allow the examination of a more uncommon exposure, and as an illustrative example this chapter examined a higher BMI cut-off. At the time of the writing of the study protocol, there were no published data that had examined the outcomes of pregnancy for extremely obese women any higher than ≥50 kg/m^2 . Kim et al. (2017) used a multicentre retrospective study over a 10 year period to report on 39 women with a BMI ≥60 kg/m^2 . Similar to Kim et al. (2017), there were too few women with a BMI≥60 kg/m^2 in either UK or Australian national study to allow a robust examination of this subgroup. Consequently, the larger sample size, through the combination of the two national studies, will allow an examination of women with a BMI ≥60 kg/m^2 compared to BMI >50-59 kg/m^2.

2.2 Aim and objectives

2.2.1 Study aim

To examine the feasibility of pooling together two national datasets of a rare complication of pregnancy, to enable the examination of rare outcomes following a rare exposure: extreme maternal obesity.

2.2.2 Objectives

To achieve the study aim by conducting a combined study of extreme maternal obesity in Australia and the United Kingdom.

1. To assess the comparability between datasets from the Australian data source (AMOSS) and the United Kingdom data source (UKOSS).
2. To describe and compare the characteristics, management and outcomes of women with extreme maternal obesity in Australia and the United Kingdom.
3. To examine the association between extreme maternal obesity and rare maternal and perinatal outcomes.
4. To compare the characteristics, management and outcomes between women who have a BMI $\geq$ 60 kg/m^2 and women who have a BMI >50-59 kg/m^2.

2.3 Methods

2.3.1 Study design

This study was an international population-based cohort study, using data from two national cohort studies of extremely pregnant obese women, which were undertaken in Australia and the United Kingdom (Sullivan et al., 2015, Knight et al., 2010). The primary exposure in this cohort study was extreme maternal obesity, defined as a BMI >50 kg/m^2 at any point during pregnancy. The unexposed comparison cohorts were pregnant women with a BMI < 50 kg/m^2. In a secondary analysis, the exposure group was restricted to those who had a BMI ≥60 kg/m^2 and were compared to those with a BMI >50-59 kg/m^2.

In each country, anonymous data were prospectively collected using a national obstetric surveillance system (United Kingdom Obstetric Surveillance System (UKOSS) or Australasian Maternity Outcomes Surveillance System (AMOSS)). Populations of extremely obese women were identified from obstetric units using the respective national case definitions (see Box 1). These data had already been collected and were accessed for the purposes of the study reported here. A uniform definition was created by excluding UKOSS obese women with an exact BMI of 50 kg/m^2 as these women were not included in the extremely obese definition in the AMOSS study.

Box 1. Definitions used to identify extremely obese women by country.

United Kingdom: Women who weighed >140kg at any point in pregnancy or had a BMI ≥50 kg/m^2 at any point in pregnancy or any women whose weight exceeded the capacity of the hospital scales.

Australia: Women who weighed >140kg at any point in pregnancy or had a BMI > 50 kg/m^2 at any point in pregnancy.

Uniform case definition:

Women who had a BMI >50 kg/m^2 at any point in pregnancy.

2.3.2 Exposure groups

2.3.2.1 Identification of comparison cohort

The United Kingdom comparison cohort was identified as the two women who delivered immediately before the extremely obese women. The United Kingdom comparison cohort had a similar data collection form to the extremely obese cohort.

Australia's comparison cohort was identified from two different AMOSS studies (placenta accreta and peripartum hysterectomy) as the two women delivering immediately prior to the identified cases of placenta accreta or peripartum hysterectomy. A general questionnaire was used to collect data about both the comparison and obese groups, while the obese group had an additional questionnaire. The general questions contained information about BMI; thus allowing a comparison cohort with a BMI < 50 kg/m^2 to be identified.

2.3.3 Data collection

The data were collected in the original studies using the standard surveillance system methods in each country. Anonymised clinical and demographic data were extracted from the case notes from both exposure groups in each country. Clinicians completed the data collection form using information from the patient's medical records; therefore, only anonymous data were obtained after the pregnancy event.

2.3.4 Comparability of the datasets

Similar to individual patient data meta-analyses, the comparability of the datasets were assessed prior to pooling the data. Data forms included information about sociodemographic factors, previous medical history, previous obstetric history and details of the current pregnancy such as peripartum management and outcomes for mother and child. On examination of the data collection forms, there were some differences between the questions asked and the coding of the responses between the UKOSS and AMOSS studies. A mapping exercise was used to assess the availability of desired variables and comparability of questions between the AMOSS and UKOSS datasets.

First, the data collection forms were examined to assess if the desired covariates and outcomes identified from the literature were available in each dataset. Secondly, the questions and coding were assessed for their comparability. On occasions, where the coding differed, harmonisation of the coding was devised and applied. This resulted in uniform values and labels of variables across both datasets. In instances where definitions differed, a comparable definition value was devised.

An assessment was made to determine whether the variables were measuring the same clinical phenotype in similar ways. If a variation in a characteristic or outcome was the result of different clinical thresholds or diagnostic criteria, it could not be harmonised and

it was excluded from the analysis. Only those variables where there were comparable data were pooled.

2.3.5 Covariates and outcomes

Potential covariates and outcomes were identified from the literature. These characteristics, confounders and outcomes were then selected from those variables that were available in both the UKOSS and AMOSS datasets.

2.3.6 Missing data

Previous studies using UKOSS data have shown that the distribution of missing data for each variable was not missing at random; as a result, multiple imputation was not considered appropriate (Lindquist et al., 2013). A proxy category was created for each variable to account for the missing data. In a sensitivity analysis, complete case analysis was used to assess the impact of using a proxy (missing) variable.

2.3.7 Power

2.3.7.1 BMI>50 kg/m^2 analysis

The sample size was predetermined by the size of the existing studies; therefore the sample was fixed at 932 women who had a BMI >50 kg/m^2 and 1232 women who had a BMI <50 kg/m^2. For the lowest frequency outcome (stillbirth), which had an incidence of 0.6% in the unexposed group, given the sample size the minimum detectable odds ratio at the 5% significance level was 3.55. For the highest frequency outcome, which had an incidence of 26.9% (caesarean delivery) in the unexposed group, the minimum detectable odds ratio at the 5% significance level was 1.31.

2.3.7.2 BMI ≥60 kg/m^2 analysis

Similarly, the fixed sample size was 111 women who had a BMI ≥60 kg/m^2 and 821 women who had a BMI >50-<60 kg/m^2. For the lowest frequency outcome (perinatal death), which had an incidence of 1.2% in the unexposed group, given the sample size the minimum detectable odds ratio at the 5% significance level was 5.63. For the highest frequency outcome, which had an incidence of 23% (any hypertension disorder during pregnancy) in the unexposed group, the minimum detectable odds ratio at the 5% significance level was 1.89.

2.3.8 Harmonisation and univariable analysis

After variable harmonisation, the UKOSS and AMOSS datasets were merged. An initial examination of the proportions was used to assess comparability between the datasets. Histograms were used to assess normality in continuous variables. Normally distributed continuous variables were summarised as means with standard deviations; skewed continuous variables were summarised as medians with interquartile ranges. Descriptive analyses were undertaken using the Chi Square test or Wilcoxon rank-sum test to assess whether there was a difference in characteristics, management and outcomes between (a) obese women in Australia and the United Kingdom (b) Australian and United Kingdom comparison women.

2.3.9 Univariable and multivariable analysis examining the association between extreme maternal obesity and outcomes.

Univariable analysis was undertaken to examine the association between extreme maternal obesity and outcomes for both mother and baby using the pooled AMOSS and UKOSS datasets. Continuous variables were tested for departure from linearity by entering both a continuous and categorical version of the same variable into two separate models. These

were then compared statistically using log-likelihood tests. Each outcome was individually modelled in a univariable analysis using an unconditional logistic regression model, with results presented as odds ratios with 95% confidence intervals. The exposure variable in each model was extreme obesity. To account for clustering of infants within mothers' robust estimates of variance were calculated.

2.3.10 Multivariable analysis examining the association between extreme maternal obesity and outcomes.

Only outcomes that were statistically significant at the univariable level ($P<0.05$) were assessed in the multivariable analysis. A restrictive p-value <0.05 was chosen to reduce the chance of a type I error. Prior to multivariable analysis, collinearity was assessed using Pearson's correlation coefficient. Variables were considered highly correlated if they had correlation coefficient greater than 40. Credible interactions with each outcome were identified from the literature, these included: preeclampsia and parity, caesarean section and parity, induction of labour and parity. None of these interactions were found to be statistically significant at the 5% level.

In the multivariable analysis, potential explanatory variables were sequentially added to the univariable model in a forward stepwise method with an examination of the results as each variable was added. Variables were added sequentially in order of p-value, lowest first. An explanatory variable was included in the final model if it was associated with the exposure and outcome (P-value for Wald test<0.05) and significantly improved the model fit assessed by likelihood ratio tests at the 5% significance level.

2.3.11 Maternal outcomes and confounders

The maternal outcomes examined in multivariable models were preeclampsia, hypertension during pregnancy, pregnancy induced hypertension, wound infection and

caesarean delivery. Data about gestational diabetes were not comparable between the datasets due to differences in clinical thresholds, and therefore could not be included in the analyses. The incidence of thrombotic events was too low to allow a multivariable analysis to be conducted robustly.

Informed by the literature, each outcome had plausible additional explanatory variables added to each model. The literature was presented in table 2. In addition, where information was incomplete a scoping search was performed to examine the literature examining each outcome and maternal extreme obesity (>50 kg/m^2) or maternal obesity (>30kg/m^2). In the hypertension during pregnancy, pregnancy induced hypertension and preeclampsia models, other potential explanatory variables were parity, age and smoking status during pregnancy. In the caesarean delivery model, potential explanatory variables were previous caesarean delivery, previous pregnancy problems and parity. In the wound infection model, potential explanatory variables were smoking status and pre-existing diabetes.

2.3.11.1 Perinatal outcomes

The infant outcomes investigated were perinatal death (< 7 days postpartum), stillbirth, macrosomia (birthweight >4500grams), infant respiratory distress and Apgar score <7 at 5 minutes. Data about admission for neonatal intensive care were not comparable between the datasets and could not be included in the analysis.

2.3.11.2 Perinatal outcomes and explored explanatory variables

For the model of macrosomia, potential confounders included were smoking and gestational age at delivery. For the models of Apgar <7 at five minutes and respiratory problem, potential confounders were gestational age at delivery, parity and previous pregnancy problems.

2.3.11.3 Sensitivity analysis

In addition to the complete case analysis, the comparison group was also restricted to women who had a BMI < 30 kg/m^2 to assess the impact on the magnitude of identified associations in the multivariable analysis. To allow sufficiently powered estimates to be calculated, a non-obese population was chosen using BMI < 30 kg/m^2 as a cut-off instead of a normal weight population (<25 kg/m^2).

2.3.12 Statistical analysis examining women with a BMI ≥60 kg/m^2

A univariable analysis was conducted to compare the management, maternal and perinatal outcomes between women with a BMI ≥60 kg/m^2 and women with a BMI >50 -59 kg/m^2. Unconditional logistic regression was used to compare the outcomes for these two groups of women. Variables were only included in the multivariable model if the association between obesity and outcome was statistically significant (5%) in the univariable analysis. Only preeclampsia was statistically significant in the univariable analysis and the following covariates were examined in the multivariable model of the preeclampsia: smoking status, pre-existing diabetes, parity and age.

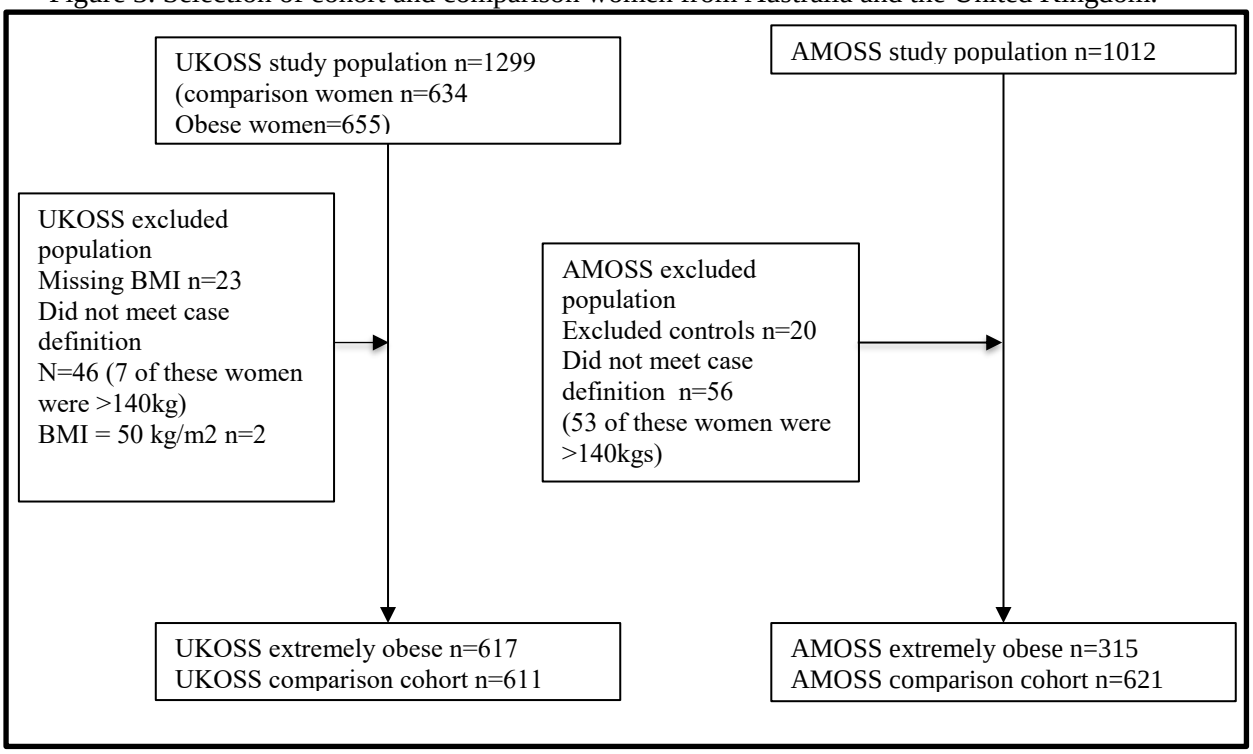
2.3.13 Ethics committee approval

The Australian collaborators gained approval for the study from the Human Research Ethics Committee (HREC), New South Wales, Australia. Ethics committee approval for secondary analysis of United Kingdom data was not required. The Australia data were securely transferred, stored and analysed at the NPEU, University of Oxford.

2.4 Results

Figure 3 shows the derivation of the study population from the national population-based cohort studies in Australia and the United Kingdom. During the period September 2007-August 2008, 617 women with a BMI>50 kg/m^2 were identified through the United Kingdom Obstetric Surveillance System. Between January - October 2010, 315 women with a BMI>50 kg/m^2 were identified using the Australasian Maternity Outcomes Surveillance System.

Figure 3. Selection of cohort and comparison women from Australia and the United Kingdom.



2.4.1 Availability of desired variables

Table 2, which examined the literature, presents the availability of desired variables and comparability of the wording and coding of questions from each study.

2.4.2 Comparability of variables

Table 6 shows that the majority of the variables were collected using very similar questions, which allowed coding to be uniform across variables in the two datasets. In instances where questions were asked to a subset of the women in one country and not the other, the question was restricted to that subset across both populations; for example, wound infection was restricted to women who had caesarean deliveries. Questions were combined to ensure that the same characteristics or outcomes were being measured, for example, the AMOSS question on maternal admission to an intensive care unit (ICU) was combined with admission to a high dependency unit (HDU) to make it comparable with the UKOSS question. Within the AMOSS data there were differences between the items collected for the obese women and comparison women, for example, there were instances where a specific variable was collected for only extremely obese women. In this situation, the free text was used to obtain values for the comparison group.

Table 6. Examination of the availability of desired variables and comparability of questions from the AMOSS and UKOSS datasets.

Desired variable	Available (UKOSS extremely obese/ comparison group)	Available (AMOSS extremely obese/ comparison group)	Included in study	If included, what were the questions used from AMOSS and UKOSS questionnaire				Details on harmonisation or comment
				UKOSS wording	AMOSS wording	UKOSS question number	AMOSS form (GF or EMO*), question number	
Sociodemographic characteristics								
Age	*Yes*	*Yes*	*Yes*	Age in years	Year of birth	1.1	GF: 1.1	
BMI at booking	*Yes*	*Yes*	*Yes*	Body Mass Index	Calculated from height and weight	1.8	GF: 1.8 and 1.9	
Max recorded BMI	*Yes*	*No comparison*	*No*					
Weight gain during pregnancy	*No*	*No*	*No*					
Smoking status	*Yes*	*Yes*	*Yes*	Smoking status: never, gave up prior to pregnancy, gave up during pregnancy and current smoker	Smoking status: never, quit before pregnancy, quit <20 weeks gestation, quit >19 weeks gestation, current smoker and unknown	1.9	GF: 1.10	Recoded into smoking during pregnancy and did not smoke during pregnancy
Ethnicity	*Yes*	*No*	*No*					No ethical approval for inclusion of ethnicity data
Country of birth	*No*	*Yes*	*No*					
Socioeconomic status	*No*	*Yes*	*No*					
Employment status	*Yes*	*No*	*No*					
Drug use	*No*	*Yes*	*No*					
Known previous medical history								
Previous pregnancy problems	*Yes*	*Yes*	*Yes*	Previous pregnancies: pregnancy problems?	Any medical/obstetric problems in a prior pregnancy?	2.2	GF: 2.3	
Previous cardiac disease	*Yes*	*Yes*	*Yes*	Please specify previous pregnancy problems	Please specify previous pregnancy problems	2.2	GF: 2.3	Extracted and coded from the free text
Previous renal problems	*Yes*	*Yes*	*Yes*					

Desired variable	Available (UKOSS extremely obese/ comparison group)	Available (AMOSS extremely obese/ comparison group)	Included in study	If included, what were the questions used from AMOSS and UKOSS questionnaire				Details on harmonisation or comment
				UKOSS wording	AMOSS wording	UKOSS question number	AMOSS form (GF or EMO*), question number	
Previous mental health issues	*Yes*	*Yes*	*Yes*					
Previous asthmatic condition	*Yes*	*Yes*	*Yes*					
Previous caesarean delivery	*Yes*	*Yes*	*Yes*	Did this woman have a prior caesarean delivery	Previous abdominal surgery. If yes please specify	3.3	GF:2.4	Extracted the code from previous abdominal surgery
How many previous caesareans	*No*	*Yes*	*No*					
Parity	*Yes*	*Yes*	*Yes*	Number of completed pregnancies over 24 weeks	The number of pregnancies resulted in a live birth or stillbirth	2.1	GF:2.1b	AMOSS parity includes pregnancies >20 weeks gestation vs. ≥24 in UKOSS
Hypertension medication prior to pregnancy	*Yes*	*Yes*	*Yes*	Essential hypertension requiring treatment	Please list any regularly taken prescribed medication that the woman was on prior to pregnancy	3.2	GF:3.2	Extracted and coded hypertensive medications from the free text in AMOSS dataset
Pre-existing diabetes	*Yes*	*Yes*	*Yes*	Diabetes mellitus	Diabetes mellitus present prior to pregnancy / pre-existing medical problems	3.1	GF: 3.1 EMO: 1.2	Data on AMOSS comparison group were extracted from free text
Insulin dependent	*Yes*	*Yes*	*Yes*	If yes, is this insulin dependent?	What therapy was used to treat diabetes mellitus prior to pregnancy / list any prescribed medication	3.1	EMO: 1.2 GF: 3.1	
Details of current pregnancy and complications								
Gestational Diabetes	*Yes*	*Yes*	*Yes*	Did the women develop gestational diabetes in this pregnancy?	Obese women: Did the women develop gestational diabetes in this pregnancy? Comparison: Were there any obstetric / medical problems in this pregnancy	4.7	EMO: 2.5 GF 4.4 & 4.5	Data on AMOSS comparison group were extracted from free text from two questions

Desired variable	Available (UKOSS extremely obese/ comparison group)	Available (AMOSS extremely obese/ comparison group)	Included in study	If included, what were the questions used from AMOSS and UKOSS questionnaire				Details on harmonisation or comment
				UKOSS wording	AMOSS wording	UKOSS question number	AMOSS form (GF or EMO*), question number	
Hypertensive disorder during pregnancy	*Yes*	*Yes*	*Yes*	Any hypertensive disorder in this pregnancy? Pregnancy induced hypertension (PIH)/ Preeclampsia (hypertension and proteinuria) / Eclampsia / Others	Obese women: Did the women develop any hypertensive disorder in this pregnancy? PIH/ Preeclampsia imposed on chronic hypertension/ Preeclampsia/ Eclampsia / Other Comparison: Were there any obstetric / medical problems in this pregnancy	4.8	EMO: 2.6 GF: 4.4 &4.5	Merged preeclampsia imposed onto chronic hypertension and preeclampsia
Pregnancy induced hypertension	*Yes*	*Yes*	*Yes*					
Preeclampsia and eclampsia	*Yes*	*Yes*	*Yes*					
Multiple pregnancy	*Yes*	*Yes*	*Yes*	Was this a multiple pregnancy?	Was this a multiple pregnancy?	4.4	GF: 4.3	
Induced	*Yes*	*Yes*	*Yes*	Was delivery induced?	Was labour induced?	5.2	5.1a	
Caesarean delivery	*Yes*	*Yes*	*Yes*	Was delivery by caesarean section?	Was the baby born by caesarean section?	5.4	5.2	
Thromboprophylaxis usage antenatal	*Yes*	*No comparison*	*Yes****	Did the woman receive any antenatal thromboprophylaxis in this pregnancy?	Did the women receive any antenatal thromboprophylaxis?	2.2	EMO:2.2	No AMOSS comparison data
Scan problems	*Yes*	*No comparison*	*Yes****	Were there any difficulties reported with undertaking detailed scans?	Were there any reported difficulties with undertaking a scan during this pregnancy?	4.11	EMO:2.8	No AMOSS comparison data
Thromboprophylaxis postnatal	*Yes*	*No comparison*	*Yes****	Were thromboprophylactic measures used after delivery	Did the woman receive any thromboprophylaxis postpartum?	5.9	4.2	No AMOSS comparison data
Maternal outcomes								
ICU/HDU	*Yes*	*Yes*	*Yes*	Was the woman admitted to ITU/HDU?	Was the woman admitted to ICU? / Was the woman admitted to HDU?	6a.1	GF: 6.1 & 6.2	Combined HDU and ITU in both studies

Desired variable	Available (UKOSS extremely obese/ comparison group)	Available (AMOSS extremely obese/ comparison group)	Included in study	If included, what were the questions used from AMOSS and UKOSS questionnaire				Details on harmonisation or comment
				UKOSS wording	AMOSS wording	UKOSS question number	AMOSS form (GF or EMO*), question number	
Wound infection in those with caesarean delivery	*Yes*	*Yes*	*Yes*	Did the woman have a documented post-operative wound infection or other operative complication?	Wound infection? Free text - did any major maternal morbidity occur, if yes please specify?	5.4	EMO: 4.1 GF: 5.4	Removed women without caesarean sections and wound infection was extracted from free text in comparison groups
Postpartum haemorrhage	*Yes*	*Yes*	*Yes*	Did any major morbidity occur?	Large postpartum haemorrhage (>1000ml) OR Did any major maternal morbidity occur?	6a.2	GF: 5.4	
Thrombotic event	*Yes*	*Yes*	*Yes*	Did any major morbidity occur?	Did the woman experience a thrombotic event during this pregnancy?	5.4	EMO: 2.3	AMOSS obese women have own question; UKOSS extracted from free text. AMOSS comparison group extracted from free text
	Infant outcomes							
Perinatal death**	*Yes*	*Yes*	*Yes*	Did the infant die & was the infant stillborn	Infant's condition at birth and separation status (died)	6b.4 & 6b.9	GF: 7.7 & 7.8	Death up to 7 days in United Kingdom and up to 28 days in Australia. Removed deaths accordingly. AMOSS stillbirths were restricted to those over 24 weeks gestation due to differing definition
Stillbirth **	*Yes*	*Yes*	*Yes*	Was the infant stillborn	Infant's condition at birth and separation status (died)	6b.4	GF: 7.7	
NICU	*Yes*	*Yes*	*Yes*	Was the infant admitted to the neonatal unit?	Was the infant admitted to the neonatal unit?	6b.6	GF: 7.7b	

Desired variable	Available (UKOSS extremely obese/ comparison group)	Available (AMOSS extremely obese/ comparison group)	Included in study	If included, what were the questions used from AMOSS and UKOSS questionnaire				Details on harmonisation or comment
				UKOSS wording	AMOSS wording	UKOSS question number	AMOSS form (GF or EMO*), question number	
Gestation weeks	*Yes*	*Yes*	*Yes*	Date of delivery and estimated date of delivery	Date of delivery and estimated date of delivery	4.1 &6b.1	GF: 4.1 &7.1	
Birthweight	*Yes*	*Yes*	*Yes*	Birthweight	Birthweight	6b.3	GF: 7.5	
Shoulder dystocia	*Yes*	*No*	*Yes****	Was shoulder dystocia documented?	Was shoulder dystocia documented?	5.8	EMO: 3.3	No AMOSS comparison data and not in caesarean deliveries
Congenital abnormality	*Yes*	*Yes*	*Yes*	Did any other infant congenital anomaly?	Was the baby born with congenital malformations?	6b.7	GF: 7.8	
Infant respiratory problem	*Yes*	*Yes*	*Yes*	Major infant complications occur?	Major infant complications occur?	6b.8	7.7d	Extracted from free text and given code
Apgar score <7 @ 5min	*Yes*	*Yes*	*Yes*	5 min Apgar	What was the 5 minute Apgar score?	6b.5	7.7a	

* GF: General form; EMO: Data collection form for extremely obese women **To ensure comparable definition across countries stillbirths <24weeks gestation were excluded.***Only included in the comparison of BMI >50-59 kg/m2 vs. ≥60 kg/m2.

2.4.3 Comparability of populations between Australia and the United Kingdom

2.4.3.1 Characteristics and previous medical history

Table 7-9 presents an assessment of the comparability of the AMOSS and UKOSS populations. For the majority of characteristics there were no statistically significant differences between the obese women; this was also true for the comparison groups. One exception is that both the AMOSS extremely obese women and comparison group had a larger proportion with previous pregnancy problems than UKOSS women. This difference was statistically significant for the obese women. On the basis that the data were collected using similar questions it was concluded that this represented a real difference and not an artefact of data collection.

AMOSS obese women had also a greater frequency of previous caesarean deliveries compared to UKOSS obese women (32.1% vs. 16.5%, P<0.001). There was also a difference between the UKOSS and AMOSS comparison women (8.3% vs. 18.5%, P<0.001).

2.4.3.2 Hypertension and diabetes

Table 8 shows the comparability between the UKOSS and AMOSS datasets for hypertension and diabetes. As noted earlier, gestational diabetes was not considered comparable between the United Kingdom and Australian populations. Variations in proportions reported between UKOSS and AMOSS were likely to be due to differences in threshold of screening women for gestational diabetes (Nankervis et al., 2014, National Institute for Health and Care Excellence, 2015). Reassuringly of those with hypertensive disorders in pregnancy, the proportions of women receiving hypertension medication prior to pregnancy were very similar between the UKOSS and AMOSS studies despite using free text to provide data for the AMOSS study. Pre-existing diabetes was more prevalent

in the AMOSS obese women than the UKOSS obese women (14% vs. 4.9%, P<0.001, respectively). There was also a difference between the comparison groups (2% vs. 0%, P<0.001, respectively).

2.4.3.3 Details of current pregnancy and complications

Table 9 presents the comparability of the UKOSS and AMOSS datasets for details during the index pregnancy. Notably, the United Kingdom and Australia have different admission thresholds for ICU/HDU; therefore, ICU/HDU admission was not comparable between the datasets (Pollock et al., 2010). Similarly, it was likely that variations in postpartum haemorrhage (PPH) were the result of measurement heterogeneity between the United Kingdom and Australia. As a result PPH was excluded as an outcome to be examined (Knight et al., 2009).

There were no statistically significant differences in the frequency of caesarean deliveries, wound infection in those with a caesarean delivery or thrombotic events between the UKOSS and AMOSS obese women. The AMOSS comparison women had a significantly higher proportion of caesarean deliveries than the UKOSS comparison women (31.7% vs. 22.1%, P<0.001, respectively).

Table 7. Assessing the comparability between the AMOSS and UKOSS datasets: characteristics and previous medical history.

		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=617)	AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)	P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) n=611	AMOSS: n(%) comparison women (BMI < 50 kg/m^2) n=621	P-value (between comparison group)	Comparability (Y/N)	Comment
Sociodemographic characteristics									
Age	*Mean (S.D.)*	30.4 (5.6)	30.8 (5.78)	0.318	28.94 (6.21)	30.28 (5.76)	<0.001	Yes	
BMI at booking	*Median (IQR)*	52.85 (51-55.9)	53.88 (50.9-56.4)	0.089	24 (22.1-28.0)	24.8 (21.95-28.96)	0.07	Yes	
Max recorded BMI	*Median (IQR)*	52.98 (51.02-56.3)	53.4 (51.5-56.3)		24.87 (22.1-29.0)			No	No AMOSS comparison group
Smoking status	*Never/ex-smoker*	457 (74.1)	227 (72.1)		461 (75.5)	484 (77.9)			
	Smoked during pregnancy	158 (25.6)	72 (22.9)	0.599	146 (23.9)	100 (16.1)	0.003	Yes	
	Missing	2 (0.3)	16 (5.1)		4 (0.7)	37 (6)			
Known previous medical history									
Previous pregnancy problems	*None*	233 (37.8)	81 (25.7)		240 (39.3)	222 (35.7)			
	Yes	167 (27.1)	132 (41.9)	<0.001	101 (16.5)	129 (20.8)	0.099	No	The questions differ as the AMOSS population contains previous medical problems as well
	Primigravid	213 (34.5)	93 (29.5)		268 (43.9)	251 (40.4)			
	Missing	4 (0.6)	9 (2.9)		2 (0.3)	19 (3.1)			
Previous cardiac disease	*None*	613 (99.4)	308 (97.8)		609 (99.7)	603 (97.1)			
	Yes	1 (0.2)	6 (1.9)	0.004	1 (0.2)	7 (1.1)	0.033	Yes	Only comparable if used data extracted from free text
	Missing	3 (0.5)	1 (0.3)		1 (0.2)	11 (1.8)			

		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=617)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) n=611		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) n=621		P-value (between comparison group)	Comparability (Y/N)	Comment
Previous renal disease	*None*	613	(99.4)	306	(97.1)		609	(99.7)	604	(97.3)			
	Yes	1	(0.2)	8	(2.5)	<0.001	1	(0.2)	6	(1)	0.058	Yes	Only comparable if free text is used
	Missing	3	(0.5)	1	(0.3)		1	(0.2)	11	(1.8)			
Previous mental health issues	*None*	571	(92.5)	284	(90.2)		585	(95.7)	570	(91.8)			
	Yes	43	(7)	30	(9.5)	0.172	25	(4.1)	40	(6.4)	0.056	Yes	
	Missing	3	(0.5)	1	(0.3)		1	(0.2)	11	(1.8)			
Previous asthma	*None*	540	(87.5)	278	(88.3)		583	(95.4)	576	(92.8)			
	Yes	74	(12.0)	36	(11.4)	0.793	27	(4.4)	35	(5.6)	0.300	Yes	
	Missing	3	(0.5)	1	(0.3)		1	(0.2)	10	(1.6)			
Previous caesarean section	*None*	301	(48.8)	118	(37.5)		292	(47.8)	250	(40.3)			
	Yes	102	(16.5)	101	(32.1)	<0.001	51	(8.3)	115	(18.5)	<0.001	Yes	
	Primigravid	213	(34.5)	93	(29.5)		268	(43.9)	251	(40.4)			
	Missing	1	(0.2)	3	(1)		0	(0)	5	(0.8)			
Parity	*Nulliparous*	213	(34.5)	93	(29.5)		268	(43.9)	251	(40.4)	0.221	Yes	
	Multiparous	403	(65.3)	222	(70.5)	0.12	343	(56.1)	370	(59.6)			
	Missing	1	(0.2)	0	(0)		0	(0)					

Table 8. Assessing the comparability between the AMOSS and UKOSS datasets: diabetes and hypertension.

Characteristic		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=617)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) n=611		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) n=621		P-value (between comparison group)	Comparability (Y/N)	Comment	
Hypertension tension medication prior to pregnancy	*None*	577	(93.5)	293	(93)	0.763	607	(99.3)	613	(98.7)	0.990	Yes	In AMOSS maybe under ascertained as AMOSS collected using free text while UKOSS had specific question	However, the AMOSS and UKOSS comparison women have similar proportions
	Yes	38	(6.2)	21	(6.7)		3	(0.5)	3	(0.5)				
	Missing	2	(0.3)	1	(0.3)		1	(0.2)	5	(0.8)				
Pre-existing diabetes	*None*	587	(95.1)	271	(86.0)	<0.001	610	(99.8)	601	(96.8)	<0.001	Yes	Data on AMOSS obese women and UKOSS study was collected using a specific question as AMOSS comparison group are collected using free text	More pre-existing diabetes in Australian data; this may be due to an ethnicity effect or definition issues.
	Yes	30	(4.9)	44	(14.0)		0	(0)	15	(2.4)				
	Missing	0	(0)	0	(0)		1	(0.2)	5	(0.8)				
Insulin dependent diabetes	*Yes*	14	(2.3)	7	(2.2)	0.960	0	(0)	5	(0.8)	0.030	Yes	Although the proportions receiving insulin are similar amongst the countries	
Gestational Diabetes	*No*	514	(83.3)	225	(71.4)	Omitted	602	(98.5)	574	(92.4)	Omitted	No	Large difference between United Kingdom and Australia that was likely to be due to definitions	Both AMOSS obese women and the UKOSS study were collected using a specific question. AMOSS comparison women were collected using free text.
	Yes	64	(10.4)	45	(14.3)		9	(1.5)	19	(3.1)				
	N/A	30	(4.9)	44	(14)		0	(0)	15	(2.4)				
	Missing	9	(1.5)	1	(0.3)		0	(0)	13	(2.1)				

Characteristic		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=617)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) n=611		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) n=621		P-value (between comparison group)	Comparability (Y/N)	Comment	
Hypertensive disorder during pregnancy	*No*	473	(76.7)	235	(74.6)		581	(95.1)	586	(94.4)				
	Yes	137	(22.2)	79	(25.1)	0.358	30	(4.9)	22	(3.5)	0.265			
	Missing	7	(1.1)	1	(0.3)		0	(0)	13	(2.1)				
PIH	*No*	530	(85.9)	266	(84.4)		595	(97.4)	600	(96.6)				
	Yes	80	(13)	48	(15.2)	0.365	16	(2.6)	8	(1.3)	0.102	Yes	AMOSS obese women and UKOSS study were collected using a question as AMOSS comparison were collected using free text	However, the AMOSS and UKOSS comparison women have similar proportions
	Missing	7	(1.1)	1	(0.3)		0	(0)	13	(2.1)				
Pre-eclampsia	*No*	553	(89.6)	283	(89.8)		597	(97.7)	594	(95.7)				
	Yes	57	(9.2)	31	(9.8)	0.796	14	(14)	14	(2.3)	0.989			
	Missing	7	(1.1)	1	(0.3)		0	(0)	13	(2.1)				

Statistical comparisons only presented for comparable data.

Table 9. Assessing the comparability between the AMOSS and UKOSS datasets: details of current pregnancy and complications.

Characteristic		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=617)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) (n=611)		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) (n=621)		P-value (between comparison group)	Comparability (Y/N)	Comment
Multiple pregnancy	*No*	600	(97.2)	308	(97.8)		603	(98.7)	608	(97.9)	0.385		
	Yes	17	(2.8)	7	(2.2)	0.627	8	(1.3)	12	(1.9)		Yes	
	None	0	(0)	0	(0)		0	(0)	1	(0.2)			
Induced	*No*	386	(62.6)	189	(60)		469	(76.8)	486	(78.3)			
	Yes	221	(35.8)	122	(38.7)	0.646	142	(23.2)	129	(20.8)	0.187	Yes	
	Missing	10	(1.6)	4	(1.3)		0	(0)	6	(1)			
Oxytocin	*No*	199	(32.3)	182	(57.8)		369	(60.4)	460	(74.1)			
	Yes	202	(32.7)	128	(40.6)	0.001	151	(24.7)	153	(24.6)	0.341	Yes	
	Missing	216	(35)	5	(1.6)		91	(14.9)	8	(1.3)			
Caesarean section	*No*	303	(49.1)	143	(45.4)		476	(77.9)	424	(68.3)			
	Yes	304	(49.3)	169	(53.7)	0.241	135	(22.1)	197	(31.7)	<0.001	Yes	
		10	(1.6)	3	(1)		0	(0)	0	(0)			
Thromboprophylaxis usage antenatal	*No*	499	(80.9)	291	(92.4)		597	(97.7)	-	-			
	Yes	112	(18.2)	16	(5.1)	Omitted	14	(2.3)	-	-	Omitted	See comment	No data for comparison group BMI <50 kg/m^2
	Missing	6	(1)	8	(2.5)		0	(0)	-	-			
Scan problems	*No*	173	(28)	85	(27)		591	(96.7)	-	-			
	Yes	428	(69.4)	189	(60)	Omitted	15	(2.5)	-	-	Omitted	No	No data for comparison group
	Missing	16	(2.6)	41	(13)		5	(0.8)	-	-			

Characteristic		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=617)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) (n=611)		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) (n=621)		P-value (between comparison group)	Comparability (Y/N)	Comment
Thromboprophylaxis post	*No*	167	(27.1)	112	(35.6)		470	(76.9)	-	-			
	Yes	435	(70.5)	196	(62.2)	Omitted	141	(23.1)	-	-		See comment	No data for comparison group BMI <50 kg/m^2
	Missing	15	(2.4)	7	(2.2)		0	(0)	-	-			
ICU/HDU	*No*	592	(95.9)	294	(93.3)		607	(99.3)	613	(98.7)			
	Yes	17	(2.8)	20	(6.3)	Omitted	4	(0.7)	8	(1.3)	Omitted	No	Different thresholds for admission used
	Missing	8	(1.3)	1	(0.3)		0	(0)	0	(0)			
PPH	*No*	598	(96.9)	294	(93.3)		607	(99.3)	578	(93.1)			Different measurement criteria
	Yes	11	(1.8)	16	(5.1)	Omitted	4	(0.7)	9	(1.4)		No	
	Missing	8	(1.3)	5	(1.6)		0	(0)	34	(5.5)			
Wound infection in those with caesarean	*No*	251	(40.7)	140	(44.4)	0.459	127	(20.8)	183	(29.5)	0.018		
	Yes	48	(7.8)	23	(7.3)		6	(1)	1	(0.2)		Yes	
	N/A	313	(50.7)	146	(46.3)		476	(77.9)	424	(68.3)			
	Missing	5	(0.8)	6	(1.9)		2	(0.3)	13	(2.1)			
Thrombotic event	*No*	607	(98.4)	305	(96.8)		611	(100)	578	(93.1)			Data on AMOSS obese women and in the UKOSS study were collected using a specific question AMOSS comparison data were collected using free text
	Yes	3	(0.5)	4	(1.3)	0.186	0	(0)	1	(0.2)	0.304	Yes	
	Missing	7	(1.1)	6	(1.9)		0	(0)	42	(6.8)			

Statistical comparisons only presented in comparable data.

Table 10. Assessing the comparability between the AMOSS and UKOSS datasets: perinatal outcomes.

Characteristic		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=625)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) (n=619)_		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) (n=621)		P-value (between comparison group)	Comparability
Perinatal death	*No*	614	(98.2)	313	(99.1)		614	(99.2)	625	(99.2)		
	Yes	9	(1.4)	3	(0.9)	0.491	5	(0.8)	4	(0.6)	0.874	Yes, those >7 days removed.
	Missing	2	(0.3)	0	(0)		0	(0)	1	(0.2)		
Stillbirth ≥24weeks gestation	*No*	617	(98.7)	313	(99.1)		614	(99.2)	625	(99.2)		
	Yes	6	(1)	3	(0.9)	0.98	5	(0.8)	3	(0.5)	0.465	Yes
	Missing	2	(0.3)	0	(0)		0	(0)	2	(0.3)		
NICU admission	*No*	551	(89)	236	(75.4)		579	(94.3)	524	(83.6)		
	Yes	66	(10.7)	74	(23.6)	Omitted	35	(5.7)	95	(15.2)	Omitted	No
	Missing	2	(0.3)	3	(1)		0	(0)	8	(1.3)		
Preterm birth	*No*	550	(88.9)	281	(89.8)		569	(92.7)	566	(90.3)		
	Yes	65	(10.5)	32	(10.2)	0.77	43	(7)	60	(9.6)	0.089	Yes
	Missing	4	(0.6)	0	(0)		2	(0.3)	1	(0.2)		
Very preterm birth	*No*	606	(97.9)	309	(98.7)		608	(99)	621	(99)		
	Yes	9	(1.5)	4	(1.3)	0.56	4	(0.7)	5	(0.8)	0.425	Yes
	Missing	4	(0.6)	0	(0)		2	(0.3)	1	(0.2)		
Birthweight (grams)	*Mean (S.D.)*	3622	(732)	3595.6	(695.4)	0.856	3357.5	(586.1)	3326	(638.3)	0.277	
Macrosomia	*No*	558	(90.1)	286	(91.4)		603	(98.2)	618	(98.6)		
	Yes	59	(9.5)	27	(8.6)	0.64	11	(1.8)	6	(1)	0.211	Yes
	Missing	2	(0.3)	0	(0)		0	(0)	3	(0.5)		

Characteristic		UKOSS: n(%) of obese women (BMI >50 kg/m^2) (n=625)		AMOSS: n(%) of obese women (BMI >50 kg/m^2) (n=315)		P-value (between obese group)	UKOSS: n(%) comparison women (BMI <50 kg/m^2) (n=619)_		AMOSS: n(%) comparison women (BMI < 50 kg/m^2) (n=621)		P-value (between comparison group)	Comparability
Shoulder dystocia*	*No*	292	(46.7)	132	(41.7)		462	(97.3)	-	-		No data about AMOSS comparison women
	Yes	13	(2.1)	8	(5.8)	0.50	13	(2.7)	-	-	Omitted	
	Missing	320	(51.2)	176	(55.7)		0	(0)	-	-		
Congenital abnormality	*No*	608	(98.2)	296	(94.6)		605	(98.5)	602	(97.6)		
	Yes	8	(1.3)	8	(2.6)	0.146	13	(1.5)	13	(2.1)	0.398	Yes
	Missing	3	(0.5)	9	(2.9)		12	(0)	2	(0.3)		
Infant respiratory problem	*No*	596	(96.3)	285	(91.1)		601	(97.9)	620	(98.9)		
	Yes	21	(3.4)	7	(2.2)	0.41	13	(2.1)	0	(0)	<0.001	Yes
	Missing	2	(0.3)	21	(6.7)		0	(0)	7	(1.1)		
Apgar score @ 5min <7	*No*	582	(94)	301	(96.2)		588	(95.8)	613	(97.8)		
	Yes	18	(2.9)	9	(2.9)	0.935	10	(1.6)	9	(1.4)	0.751	Yes
	Missing	19	(3.1)	3	(1.0)		16	(2.6)	5	(0.8)		

*Denominator only vaginal or instrumental deliveries and not available in AMOSS comparison women. Statistical comparisons only presented in comparable data.

2.4.4 Comparability of the perinatal outcomes

Table 10 shows the comparability of the perinatal outcomes. The majority of the outcomes occurred with a similar frequency in the two datasets and were comparable. One exception was, Neonatal Intensive Care Unit (NICU) admission; this was excluded due to the issues of the variability of the measure between different settings (Wiegerinck et al., 2014).

2.4.4.1 Combined Australia and the United Kingdom analysis (BMI >50 vs. BMI <50 kg/m^2)

Table 11 presents the characteristics and outcomes of the pooled cohorts of extremely obese women (BMI >50 kg/m^2) and comparison women (BMI <50 kg/m^2) from Australia and the United Kingdom. The median BMI was 53 kg/m^2 (interquartile range (IQR) 51-56) in the obese cohort while the median BMI in the comparison cohort was 25 kg/m^2 (IQR: 21.8-28.4). Obese women were on average slightly older (31 vs. 30, P<0.001, respectively) compared to comparison women. A statistically significantly higher proportion of obese women had previous pregnancy problems (32.1% vs. 18.7%); antihypertensive medications prior to pregnancy (6.3% vs. 0.5%); mutliparious (67.1% vs. 57.9%); a history of previous caesarean deliveries (21.8% vs. 13.5%); and pre-existing diabetes (7.9% vs. 1.2%).

2.4.4.2 Unadjusted associations with maternal outcomes

Table 12 compares the current pregnancy characteristics and maternal outcomes in the pooled extremely obese cohort with the comparison group in a univariable analysis. Women with extreme obesity had statistically significantly increased odds of caesarean delivery (unadjusted odds ratio (uOR):2.87 (95%CI: 2.40-3.44)) and a statistically significantly higher odds of induction of labour (uOR):2.1 (95%CI: 1.74-2.54)) than the comparison group.

The presence of extreme obesity significantly increased the odds of hypertensive disorders during pregnancy (uOR: 6.84 (95%CI: 4.99-9.40)), pregnancy induced hypertension (uOR: 8.01 (95%CI: 5.13-12.50)) and preeclampsia (uOR: 4.47 (95%CI: 2.99-6.91)) compared to women with a BMI <50 kg/m^2.

In those with caesarean deliveries, extremely obese women had a statistically significantly increased odds of wound infection (uOR: 8.04 (95%CI: 3.65-17.73)). Obese women also had a nine-fold (uOR: 9.13 (95% CI: 1.12-74.31) increase in the odds of thrombotic events compared to those with a BMI <50 kg/m^2.

2.4.4.3 Unadjusted associations between extreme obesity and perinatal outcomes

Twelve of the infants born to extremely obese women died in the early neonatal period or were stillborn. These associations were not statistically significant probably due to small numbers and low study power, extreme obesity was associated with raised odds of perinatal death (uOR: 1.78 (95%:0.75-4.25)) and stillbirth (uOR: 1.50 (95%CI: 0.58-3.90)) compared to women of lower BMI (<50) kg/m^2. Although all had raised odds preterm birth, very preterm births and congenital abnormalities did not have a statistically significant association with extreme maternal obesity (see Table 13).

In the univariable analysis, extremely obese women had a statistically significantly increased odds of having a macrosomic baby (uOR: 7.32 (95% CI: 4.32-12.40)), an infant with respiratory distress syndrome (uOR: 2.18 (95%CI: 1.02-4.66)) and an infant with a low Apgar score (uOR: 1.93 (95%CI: 1.07-3.50)) compared to women with a BMI <50 kg/m^2.

Table 11. Combined Australian and United Kingdom cohort data comparing obese women (BMI >50 kg/m2) with the comparison women (BMI<50 kg/m2): sociodemographic characteristics, previous medical problems.

Sociodemographic characteristics		**Number (%) of obese women (n=932)**		**Number (%) of comparison women (n=1232)**		**P-value**
Age	*Mean (S.D.)*	31	(5.7)	30	(6.0)	<0.001
BMI at booking	*Median (IQR)*	53	(51-56)	24.5	(21.8-28.4)	<0.001
Smoking status	*Never/ex-smoker*	684	(73.4)	945	(76.7)	0.014
	Smoked during pregnancy	230	(24.7)	246	(20)	
	Missing	18	(1.9)	41	(3.3)	
Known previous medical history						
Previous pregnancy problems	*None*	314	(33.7)	462	(37.5)	<0.001
	Yes	299	(32.1)	230	(18.7)	
	Not applicable	306	(32.8)	519	(42.1)	
	Missing	13	(1.4)	21	(1.7)	
Previous cardiac disease	*None*	921	(98.8)	1,212	(98.4)	0.786
	Yes	7	(0.8)	8	(0.6)	
	Missing	4	(0.4)	12	(1)	
Previous renal disease	*None*	919	(98.6)	1,213	(98.5)	0.290
	Yes	9	(1)	7	(0.6)	
	Missing	4	(0.4)	12	(1)	
Previous mental health issues	*None*	855	(91.7)	1,155	(93.8)	0.017
	Yes	73	(7.8)	65	(5.3)	
	Missing	4	(0.4)	12	(1)	
Previous asthma	*None*	818	(87.8)	1,159	(94.1)	<0.001
	Yes	110	(11.8)	62	(5)	
	Missing	4	(0.4)	11	(0.9)	
Previous caesarean deliveries	*None*	419	(45)	542	(44)	<0.001
	Yes	203	(21.8)	166	(13.5)	
	Not applicable	306	(32.8)	519	(42.1)	
	Missing	4	(0.4)	5	(0.4)	
Current pregnancy						
Parity	*Nulliparous*	306	(32.8)	519	(42.1)	<0.001
	Multiparous	625	(67.1)	713	(57.9)	
	Missing	1	(0.1)	0	(0)	
Multiple pregnancy	*No*	908	(97.4)	1,211	(98.3)	0.121
	Yes	24	(2.6)	20	(1.6)	
	Missing	0	(0)	1	(0.1)	
Hypertension prior to pregnancy	*None*	870	(93.3)	1,220	(99)	<0.001
	Yes	59	(6.3)	6	(0.5)	
	Missing	3	(0.3)	6	(0.5)	
Pre-existing diabetes	*None*	858	(92.1)	1,211	(98.3)	<0.001
	Yes	74	(7.9)	15	(1.2)	
	Missing	0	(0)	6	(0.5)	
Insulin dependent	*Yes*	21	(2.3)	5	(0.4)	0.062

Table 12. Combined Australian and United Kingdom data comparing obese women (BMI >50 kg/m^2) with the comparison women (BMI<50 kg/m^2): current pregnancy details and complications.

Maternal outcomes		Number (%) of obese women (n=932)		Number (%) of comparison women (n=1232)		Unadjusted Odds Ratios	95% Confidence intervals	P-value
Hypertensive disorder during pregnancy	*No*	708	(76)	1,167	(94.7)	1		
	Yes	216	(23.2)	52	(4.2)	6.85	(4.99-9.40)	<0.001
	Missing	8	(0.9)	13	(1.1)			
Pregnancy induced hypertension	*No*	796	(85.4)	1,195	(97)	1		
	Yes	128	(13.7)	24	(1.9)	8.01	(5.13-12.50)	<0.001
	Missing	8	(0.9)	13	(1.1)			
Preeclampsia	*No*	836	(89.7)	1,191	(96.7)	1		
	Yes	88	(9.4)	28	(2.3)	4.48	(2.99-6.91)	<0.001
	Missing	8	(0.9)	13	(1.1)			
Induction of labour	*No*	575	(61.7)	955	(77.5)	1		
	Yes	343	(36.8)	271	(22)	2.1	(1.74-2.54)	<0.001
	Missing	14	(1.5)	6	(0.5)			
Caesarean delivery	*No*	446	(47.9)	900	(73.1)	1		
	Yes	473	(50.8)	332	(26.9)	2.87	(2.40-3.44)	<0.001
	Missing	13	(1.4)	0	(0)			
Wound infection in those with caesarean	*No*	391	(42)	310	(25.2)	1		
	Yes	71	(7.6)	7	(0.6)	8.04	(3.65-17.73)	<0.001
	N/A	459	(49.2)	900	(73.1)			
	Missing	11	(1.2)	15	(1.2)			
Thrombotic event	*No*	912	(97.9)	1,189	(96.5)	1		
	Yes	7	(0.8)	1	(0.1)	9.13	(1.12-74.31)	0.04
	Missing	13	(1.4)	42	(3.4)			

Table 13. Combined Australian and United Kingdom data comparing obese women (BMI >50 kg/m^2) with the comparison women (BMI<50 kg/m^2): perinatal outcomes.

		Number (%) of infants from obese women		Number (%) of infants from comparison women		Unadjusted Odds Ratios	95% Confidence intervals	P-value
Perinatal death*	*No*	927	(98.5)	1,239	(99.2)	1		
	Yes	12	(1.3)	9	(0.8)	1.78	(0.75-4.25)	0.192
	Missing	2	(0.2)	1	0.1			
Still birth >24weeks gestation	*No*	930	(98.8)	1,239	(99.2)	1		
	Yes	9	(1)	8	(0.6)	1.50	(0.58-3.90)	0.407
	Missing	2	(0.2)	2	(0.2)			
Preterm birth	*No*	831	(89.2)	1,135	(91.5)	1		
	Yes	97	(10.4)	103	(8.3)	1.29	(0.93-1.78)	0.126
	Missing	4	(0.4)	3	(0.2)			
Very preterm birth	*No*	915	(98.2)	1,229	(99)	1		
	Yes	13	(1.4)	9	(0.7)	1.94	(0.76-4.94)	0.164
	Missing	4	(0.4)	3	(0.2)			
Birthweight (grams)	*Mean (StD)*	3613	(24.1)	3,342	(17.82)	-		-
Macrosomia	*No*	844	(90.6)	1,221	(98.4)	1		
	Yes	86	(9.2)	17	(1.4)	7.32	(4.32-12.40)	<0.001
	Missing	2	(0.2)	3	(0.2)			
Congenital abnormality	*No*	904	(97)	1,207	(97.3)	1		
	Yes	16	(1.7)	22	(1.8)	0.97	(0.50-1.88)	0.931
	Missing	12	(1.3)	12	(1.0)			
Infant respiratory problem	*No*	906	(97.2)	1,221	(98.4)	1		
	Yes	21	(2.3)	13	(1.0)	2.18	(1.02-4.66)	0.045
	Missing	5	(0.5)	7	(0.6)			
Apgar score <7 @ 5 minutes	*No*	883	(94.7)	1,201	(96.8)	1		
	Yes	27	(2.9)	19	(1.5)	1.93	(1.07-3.50)	0.03
	Missing	22	(2.4)	21	(1.7)			

*These are fetal and neonatal deaths that have occurred after ≥24 weeks of gestational age and before 7 completed days after birth, respectively.

2.4.5 Adjusted associations between extreme obesity (>50 BMI) and outcomes for mother and infant

Table 14 presents the multivariable logistic regression results examining the association between maternal and infant outcomes with extreme maternal obesity. Each outcome was adjusted for factors that could have plausibly confounded the relationship between extreme maternal obesity and outcome. Compared with women with a BMI <50 kg/m^2, extremely obese women had more than a fourfold increase in the odds of preeclampsia (adjusted odds ratio (aOR): 4.88 (95% CI: 3.11-7.65)) and a nine fold increase in the odds of pregnancy induced hypertension (aOR: 9.09 (95% CI: 5.75-14.38)), after adjusting for smoking status, pre-existing diabetes and parity. Women with a BMI >50 kg/m^2 had triple the odds of having a caesarean delivery (aOR: 3.15 (95% CI: 2.55-3.88)), after adjusting for previous caesarean delivery and previous pregnancy problems. In those with a caesarean delivery, the odds of having a wound infection were seven times higher for extremely obese women (aOR: 7.25, 95% CI: 3.28-16.07), after controlling for pre-existing diabetes.

Infants born to women with a BMI>50 kg/m^2 were eight times more likely to have macrosomia (aOR: 8.05 (95% CI: 4.70-13.78)) and a twofold (2.03 (95% CI: 1.13-3.66) higher odds of a low Apgar score at 5 minutes, after adjusting for gestational age at delivery. There were raised odds of having an infant with a respiratory problem/respiratory distress syndrome adjusted for gestational after at delivery (aOR: 2.00 (0.91-4.42), although this was not statistically significant. The sensitivity analyses shown in model B (which restricted the comparison to women with a BMI <30 kg/m^2) and C (proxy variable model to deal with missing data) did not materially change the results (Table 14).

Table 14. Multivariable result of the association between extreme obesity (>50BMI) for maternal and infant outcomes.

	Model A			Model B			Model C		
Maternal outcomes	**aOR**	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**	**aOR**	**95% CI**	**P-value**
Preeclampsia & eclampsia									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	4.88	(3.11-7.65)	<0.001	6.53	(3.76-11.34)	<0.001	4.81	(3.06-7.55)	<0.001
Pregnancy induced hypertension									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	9.09	(5.75-14.38)	<0.001	8.45	(5.07-14.09)	<0.001	8.61	(5.44-13.64)	<0.001
Caesarean delivery									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	3.15	(2.55-3.88)	<0.001	3.23	(2.57-4.05)	<0.001	3.07	(2.49-3.79)	<0.001
Induction of labour									
BMI <50 kg/m²	1		.	1			1		
BMI >50 kg/m²	2.45	(2.00-2.99)	<0.001	2.64	(2.12-3.29)	<0.001	2.48	(2.02-3.03)	<0.001
Wound infection									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	7.25	(3.28-16.07)	<0.001	11.72	(3.63-37.80)	<0.001	7.25	(3.28-16.07)	<0.001
Perinatal outcomes									
Macrosomia*									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	8.05	(4.70-13.78)	<0.001	9.75	(5.06-18.81)	<0.001	8.05	(4.70-13.78)	<0.001
Apgar @ 5min <7*									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	2.03	(1.13-3.66)	0.02	2.13	(1.12-4.07)	0.02	2.03	(1.13-3.66)	0.02
Respiratory problem*									
BMI <50 kg/m²	1			1			1		
BMI >50 kg/m²	2.00	(0.91-4.42)	0.09	1.77	(0.76-4.13)	0.18	2.00	(0.91-4.42)	0.09

Model A: proxy variable for missing values. Model B: comparison group BMI <30. Model C: complete case analysis. Pre-eclampsia and pregnancy induced hypertension: adjusted for smoking status, pre-existing diabetes and parity. Caesarean delivery: adjusted for previous caesarean delivery, previous pregnancy problems. Wound infection: adjusted for pre-existing diabetes. Macrosomia: adjusted for gestational age. Apgar < 7 @ 5min: adjusted for gestational age and parity. Respiratory problem: gestational age at delivery. *Calculated using robust standard errors.

2.4.6 Comparison of the management, maternal and perinatal outcomes of women with a BMI ≥60 kg/m^2 to those with a BMI > 50-59.

Table 15 shows the characteristics and previous medical problems across both the extreme obesity exposure groups. Apart from age, the sociodemographic characteristics and previous medical histories were otherwise similar between women with a BMI ≥60kg/m^2 and women with a BMI >50-59 kg/m^2 (P>0.05).

Table 16 shows the maternal management and outcomes across the two groups. Women with a BMI ≥60 kg/m^2 had a raised odds of preeclampsia (uOR: 1.91 (95%CI: 1.08-3.39)), and a raised odds of receiving either thromboprophylaxis antenatally (uOR: 2.25 (95%CI: 1.39-3.64)) or postnatally (uOR: 1.68 (95%CI: 1.04-2.70)) compared to those with a BMI >50-59kg/m^2. Although there were no other statistically significant differences, there was a higher proportion of most adverse infant and maternal outcomes in the BMI ≥60 kg/m^2 group.

The presence of a BMI ≥60 kg/m^2 was associated with a twofold increase in the odds of having preeclampsia (aOR: 1.83 (95%CI: 1.01-3.30)) compared to those with a BMI >50-59 kg/m^2, after adjusting for smoking status, pre-existing diabetes and parity.

Table 17 shows the perinatal outcomes between those with a BMI ≥60 kg/m^2 and those with a BMI >50-59 kg/m^2. Severe adverse outcomes such as perinatal death were uncommon in both groups (n=2 (18 per 1000 births), BMI≥60 kg/m^2 vs. n=10 (12 per 1000 births), BMI ≥50-59kg/m^2) thus limiting the power of these comparisons. All perinatal outcomes were similar between both obesity groups.

Table 15. Combined Australian and United Kingdom data comparing obese women with a BMI ≥60 kg/m^2 to women with a BMI between >50- 59 kg/m^2: characteristics and previous medical problems.

Characteristic		Number (%) of obese women BMI 60 kg/m^2 or greater (n=111)		Number (%) of women BMI 50 - 59.9 kg/m^2 (n=821)		p-value
Sociodemographic characteristics						
Age	*Mean (S.D.)*	31.7	(5.51)	30.3	(5.67)	0.017
BMI at booking	*Median (IQR)*	61.7	(60-64.9)	52.3	(50.8-54.9)	<0.001
Max recorded BMI	*Median (IQR)*	62.9	(61-66.8)	52.7	(50.9-55.0)	<0.001
Smoking status	*Never/ex-smoker*	85	(76.6)	599	(73)	0.42
	Smoked during pregnancy	24	(21.6)	206	(25.1)	
	Missing	2	(1.8)	16	(1.9)	
Known previous medical history						
Previous pregnancy problems	*None*	41	(36.9)	273	(33.3)	0.713
	Yes	33	(29.7)	266	(32.4)	
	Not applicable	35	(31.5)	271	(33.0)	
	Missing	2	(1.8)	11	(1.3)	
Known cardiac disease	*None*	109	(98.2)	812	(98.9)	0.200*
	Yes	2	(1.8)	5	(0.6)	
	Missing	0	(0)	4	(0.5)	
Known renal disease	*None*	110	(99.1)	809	(98.5)	0.999*
	Yes	1	(0.9)	8	(1.0)	
	Missing	0	(0)	4	(0.5)	
Known mental health issues	*None*	99	(89.2)	756	(92.1)	0.219
	Yes	12	(10.8)	61	(7.4)	
	Missing	0	(0)	4	(0.5)	
Known asthma	*None*	98	(88.3)	720	(87.7)	0.961
	Yes	13	(11.7)	97	(11.8)	
	Missing	0	(0)	4	(0.5)	
Previous caesarean delivery	*None*	53	(47.7)	366	(44.6)	0.297
	Yes	22	(19.8)	181	(22.0)	
	Not applicable	35	(31.5)	271	(33.0)	
	Missing	1	(0.9)	3	(0.4)	
Parity	*Nulliparous*	35	(31.5)	271	(33.0)	0.803
	Multiparous	75	(67.6)	550	(67.0)	
	Missing	1	(0.9)	0	(0)	
Current pregnancy						
Multiple pregnancy	*Singleton*	108	(97.3)	800	(97.4)	0.928
	Twin pregnancy	3	(2.7)	21	(2.6)	
Known hypertension prior to pregnancy requiring treatment	*None*	103	(92.8)	767	(93.4)	0.693
	Yes	8	(7.2)	51	(6.2)	
	Missing	0	(0)	3	(0.4)	
Known pre-existing diabetes prior to pregnancy	*None*	101	(91.0)	757	(92.2)	0.657
	Yes	10	(9.0)	64	(7.8)	
	Missing	-	-	-	-	
Insulin dependent diabetes	*Yes*	4	(3.6)	17	(2.1)	0.705*

*Fisher's exact test

Table 16. Combined Australian and United Kingdom comparing women with a BMI ≥60 kg/m^2 to women with a BMI between >50-59 kg/m^2: maternal outcomes.

		Number (%) of women BMI 60 kg/m^2 or greater (n=111)		Number (%) of women BMI >50-59.9 kg/m^2 (n=821)		Unadjusted odds ratio	95% Confidence interval	P-value
Management								
Difficulties undertaking ultrasounds	*No*	30	(27.0)	228	(27.8)	1		
	Yes	78	(70.3)	539	(65.7)	1.10	(0.70-1.72)	0.678
	Missing	3	(2.7)	54	(6.6)			
Induced	*No*	70	(63.1)	505	(61.5)	1		
	Yes	40	(36)	303	(36.9)	0.95	(0.63-1.44)	0.817
	Missing	1	(0.9)	13	(1.3)			
Caesarean delivery	*No*	48	(43.2)	398	(48.5)	1		
	Yes	62	(55.9)	411	(50.1)	1.25	(0.84-1.87)	0.274
	Missing	1	(0.9)	12	(1.5)			
Thromboprophylaxis usage in antenatal period	*No*	84	(75.7)	706	(86.0)	1		
	Yes	27	(24.3)	101	(12.3)	2.25	(1.39-3.64)	0.001
	Missing	0	(0)	14	(1.7)			
Thromboprophylaxis postpartum period	*No*	24	(21.6)	255	(31.1)	1		
	Yes	86	(77.5)	545	(66.4)	1.68	(1.04-2.70)	0.033
	Missing	1	(0.9)	21	(2.6)			
Maternal Outcome								
Wound infection in those with caesarean	*No*	47	(42.3)	344	(41.9)	1		
	Yes	14	(12.6)	57	(6.9)	1.80	(0.93-3.48)	0.081
	N/A	49	(44.1)	410	(49.9)			
	Missing	1	(0.9)	10	(1.2)			
Venous thromboembolism	*No*	111	(100)	807	(98.3)	1		
	Yes	0	(0)	7	(0.9)	0	(0.0-4.00)	0.325
	Missing	0	(0)	7	(0.9)			
Hypertensive disorder during pregnancy	*No*	77	(69.4)	631	(76.9)	1		
	Yes	33	(29.7)	183	(22.3)	1.48	(0.95-2.29)	0.082
	Missing	1	(0.9)	7	(0.9)			
Pregnancy induced hypertension	*No*	94	(84.7)	702	(85.5)	1		
	Yes	16	(14.4)	112	(13.6)	1.07	(0.61-1.88)	0.823
	Missing	1	(0.9)	7	(0.9)			
Pre-eclampsia/eclampsia	*No*	93	(83.8)	743	(90.5)	1		
	Yes	17	(15.3)	71	(8.6)	1.91	(1.08-3.39)	0.026
	Missing	1	(0.9)	7	(0.9)			

Table 17. Combined Australian and United Kingdom data comparing obese women BMI ≥60 kg/m^2 to women with a BMI between >50-59 kg/m^2: perinatal outcomes.

		Number (%) of women BMI 60 kg/m^2 or greater		Number (%) of women BMI >50-59.9 kg/m^2		Unadjusted odds ratio	95% CI	P-value
Perinatal death*	*No*	112	(98.2)	815	(98.5)	1		
	Yes	2	(1.8)	10	(1.2)	1.46	(0.31-6.74)	0.631
	Missing	0	(0)	2	(0.2)			
Still birth ≥24weeks gestation*	*No*	112	(98.2)	818	(98.9)	1		
	Yes	2	(1.8)	7	(0.8)	2.09	(0.43-10.19)	0.363
	Missing	0	(0)	2	(0.2)			
Preterm birth	*No*	101	(90.2)	730	(89.0)	1		
	Yes	10	(8.9)	87	(10.6)	0.83	(0.36-1.94)	0.668
	Missing	1	(0.9)	3	(0.4)			
Very preterm birth	*No*	111	(99.1)	804	(98.0)		Omitted	
	Yes	0	(0)	13	(1.6)			
	Missing	1	(0.9)	3	(0.4)			
Birthweight	*Mean (S.D.)*	3683.0	(752.1)	3603.7	(715.0)		Omitted	
Macrosomia (>4500grams)	*No*	98	(87.5)	746	(91.0)	1		
	Yes	14	(12.5)	72	(8.8)	1.48	(0.80-2.74)	0.211
	Missing	0	(0)	2	(0.2)			
Shoulder dystocia	*No*	44	(39.3)	373	(45.5)	1		
	Yes	1	(0.9)	19	(2.3)	0.45	(0.06-3.42)	0.438
	Missing	67	(59.8)	428	(52.2)			
Congenital abnormality	*No*	107	(95.5)	797	(97.2)	1		
	Yes	3	(2.7)	13	(1.6)	1.72	(0.48-6.14)	0.404
	Missing	2	(1.8)	10	(1.2)			
Infant respiratory problem	*No*	109	(97.3)	797	(97.2)	1		
	Yes	3	(2.7)	18	(2.2)	1.22	(0.35-4.21)	0.755
	Missing	0	(0)	5	(0.6)			
Apgar score <7 @ 5min	*No*	105	(93.8)	778	(94.9)	1		
	Yes	2	(1.8)	25	(3.0)	0.59	(0.14-2.54)	0.482
	Missing	5	(4.5)	17	(2.1)			

Odds ratios are estimated using robust standard errors. *Denominator is total births n=941. Denominator in the remainder of the table is live births (including multiple births).

2.5 Discussion

2.5.1 Main findings

This study has shown that combining data collected from two national obstetric surveillance systems using similar methodologies and definitions, can be undertaken to allow a detailed comparison of extremely obese pregnant women in Australia and the United Kingdom. Although the populations differed in terms of age, previous medical history and pregnancy problems they were otherwise comparable, which allowed the pooling of data.

2.5.2 Rare outcomes

This study has shown that the combination of two national studies increased the statistical power of the studies and precision of the estimates of the incidence of more common maternal and infant outcomes in extremely obese women. These included, hypertensive disorders, wound infection, macrosomia, and poor infant condition. This added weight to the suggestion that the examination of rare outcomes through an increased sample size is an added benefit of multinational studies (Knight and INOSS, 2014). Nevertheless, this study illustrates that there must be an even larger study of relatively uncommon exposures, such as extreme obesity, to assess whether an association exists with very rare maternal and infant outcomes. For example, in order to detect as statistical significant a difference in perinatal mortality between the two cohorts, a future study would require 4000 extremely obese women and 6000 comparison women, assuming the effect estimate was (uOR) 1.78 and prevalence of perinatal mortality in the unexposed group was 0.8%. A future study would require the inclusion of eight countries, if each country provided data on 500 extremely obese women. Alternatively, a smaller number of countries would be required if each country extended the period with which cases were collected.

Furthermore, the majority of odds for these rare outcomes were in a positive direction suggesting that an association may exist but this study did not have the power to exclude the role of chance for a substantial number of outcomes and these tended, not surprisingly, to be the rarer outcomes.

In addition, not all rare outcomes, which were highlighted in the literature, were available in the Australian comparison women, such as shoulder dystocia. Thus shoulder dystocia could not be explored in the comparison between extremely obese women and women with a BMI <50 kg/m^2. As a result, this objective could not be fully answered incorporating the Australian data.

2.5.3 Extremely obese women and BMI ≥60 kg/m^2

One of the novel benefits of a multinational study was the ability to examine a subset at the most extreme end of the BMI spectrum. This demonstrated that women with a BMI>60kg/m^2 had very similar characteristics and received similar management compared to women with a BMI>50 -59 kg/m^2. Interestingly, the BMI>60 kg/m^2 group had an increased risk of preeclampsia, which supports the hypothesis of a 'dose response' relationship between obesity and preeclampsia (Marshall et al., 2012). The BMI>60 kg/m^2 cohort does not appear to have an excess burden of perinatal risk compared to women with BMI >50-<60 kg/m^2; although, the role of chance could not be excluded for most outcomes even when pooling the data from these two national studies. The trend of the results has highlighted that further research is required to fully investigate the association between a BMI>60 kg/m^2 and adverse maternal and perinatal outcomes.

2.5.4 Feasibility of combining two national datasets and significance for future studies

2.5.4.1 Definitions

Although both AMOSS and UKOSS systems completed similar studies they used slightly different definitions. Despite this drawback, AMOSS and UKOSS used definitions which sufficiently similar to allow the creation of a uniform definition. The unified definition resulted in the exclusion of only two women. Nevertheless, this issue highlights the importance and benefit of using uniform definitions for future studies. Ideally, studies should run in parallel to ensure the definition remains constant.

2.5.4.2 Methods

The AMOSS and UKOSS data about extremely obese women were collected using a near complete national coverage of maternity units within the respective countries. UKOSS data were collected from all consultant-led obstetric centres, which is where all such women would be managed, while AMOSS data were collected from 66% of hospitals with over 50 births per year in Australia (Halliday et al., 2013). AMOSS has a large coverage at a national level therefore we considered it population-based, alongside UKOSS which covers all births.

Similar data collection forms resulted in the majority of desired variables being available in both datasets. However, a number of potentially useful sociodemographic characteristics were unavailable, such as ethnicity, due to data sharing limitations. The AMOSS obese women had an additional questionnaire to that of the Australian comparison women. Thus, a number of variables were therefore not available for the comparison cohort, such as maximum-recorded BMI, thromboprophylaxis use (antenatally, postnatally), scan

problems and shoulder dystocia. Future studies should aim to use identical data collection forms for both the exposed and comparison group to overcome this limitation.

2.5.4.3 Populations

In comparison with the United Kingdom extremely obese cohort, the Australian cohort was slightly older and had a higher median BMI. These women were more likely to be multiparous, to have had more previous caesarean sections in the past and had more previous pregnancy problems. However, as these characteristics could be accounted for in the analysis, the two populations were considered similar enough to combine.

Ethnic differences between the United Kingdom and Australian populations were anticipated (Hilder et al., 2014, McClaren, 2015). However, this could not be assessed due to the unavailability of the ethnicity variable in the AMOSS dataset that was shared. This would have required separate ethical approvals due to the disclosure of aboriginal status, which were not sought. As a result, differences in outcomes that may have related to ethnicity were not accounted for in the analysis.

There were some outcomes and morbidities that were not considered comparable between the populations. Differences in the definitions used for postpartum haemorrhage (PPH) between nations were likely to make the comparison invalid (Knight et al., 2009). In Australia, the definition of PPH is a haemorrhage at least 500 millilitres in a women with a vaginal delivery and 1000 millilitres in a women undergoing a caesarean delivery (National Centre for Classification in Health, 2006). By contrast, the PPH definition in the United Kingdom is 500 millilitres or more within 24 hours after birth, inclusive of all modes of birth (Falagas and Kompoti, 2006).

Differences in the screening methods for gestational diabetes between the United Kingdom and Australia resulted in an incomparable variable between the datasets (Nankervis et al.,

2014, National Institute for Health and Care Excellence, 2015). Australia screens all women for gestational diabetes, whilst in the United Kingdom, most hospitals only test women for gestational diabetes if they are at increased risk of gestational diabetes. Furthermore, Australian uses a lower threshold for diagnosis than in the United Kingdom (Australia defines gestational diabetes as a fasting plasma glucose level >5.1 mmol/litre vs. United Kingdom: >5.6 mmol/litre).

2.5.5 Strengths, limitations and significance for future studies

2.5.5.1 Strengths

This study has shown that it is feasible to combine data from two nations examining a rare exposure in pregnancy. This has a number of added benefits over national studies. First, this study increased the sample size and the precision of the estimates of effect. Second, the increased study population of a rare exposure (extreme obesity) allowed the examination of a subset of this exposure group; to date this is the largest study to examine the BMI ≥60 kg/m^2 group. The examination of the extreme end of the BMI continuum has shown that women with higher BMIs have a higher risk of adverse maternal and infant outcomes than those at the lower ends of the continuum.

2.5.5.2 Limitations and significance for future studies

The combining of two independent studies from different maternal populations had a number of limitations. First, the definition of extreme obesity was not identical, which led to the exclusion of two women from the dataset. Future studies should aim to make sure that definitions are uniform or ensure that both studies use common elements enabling the development of a set of comparable cases. This would be best done by designing the studies simultaneously and running them in parallel.

Second, some of the desired variables identified from the literature were not available in both datasets or were collected using different definitions. This led to an analysis based on only those variables present in both datasets. Data about outcomes that were not collected uniformly across countries need to be interpreted with caution. In addition, the comparison data in Australia were collected differently to the exposed cohort; as a consequence, shoulder dystocia could not be examined in the comparison between extremely obese women and women with a BMI <50 kg/m^2. This was a major limitation as this chapter set out to examine rare outcomes such as shoulder dystocia. To increase the number of clinical features that can be compared between exposed and unexposed groups the data collection forms should be as similar as possible for the two groups.

Third, the extremely obese populations of the United Kingdom and Australia had slightly different characteristics; for example, the Australian population had a larger proportion of slightly older multiparous women with a larger comorbidity burden. However, with information about these factors they could be accounted for in the analysis and therefore did not limit the comparison. Although as with all non-randomised evidence it is still possible these estimates were biased by unmeasured confounders.

2.5.6 Conclusion

This chapter showed that pooled analysis using studies from different nations is feasible and has substantial benefits in allowing more precise estimates of outcomes associated with rare exposures during pregnancy. However, even two national studies did not provide a large enough study population to robustly examine the most uncommon outcomes. Therefore, future international studies on rare complications of pregnancy in combination with rare outcomes will need to aim to include more countries to maximise the size of the study population and/or carried out over longer periods of time.

Chapter 3. Multinational study showing the characteristics of women with a severe complication of pregnancy: massive transfusion in major obstetric haemorrhage.

3.1 Introduction

3.1.1 Severe complications of pregnancy and combined analysis

The benefits of multi-country studies of severe complications of pregnancy have been highlighted as being able to complete comparative and combined analyses on these conditions in order to guide policy and clinical practice (Knight and INOSS, 2014). The majority of these studies have been binational studies (Schaap et al., 2014). Thus there remains an opportunity to explore the potential benefits of multi-country studies by completing a comparative and combined analysis that focuses on clinical management across multiple countries. Variation between countries in obstetric management of haemorrhage has already been demonstrated (Kayem et al., 2016, Zwart et al., 2010a). It is also known that haematological management guidelines vary between countries (see Table 3) (Shaylor et al., 2017), yet it is not unknown whether differences in haematological management of PPH varies between countries. Current studies of haemorrhage have defined severe haemorrhage by the number of units of red blood cells transfused. This chapter, which examined massive transfusion, offered the opportunity to explore differences in the use of blood components and haemostatic agents across countries, and to examine their potential impact on outcomes.

3.1.2 Replication and comparison of management

Multinational studies also offer the opportunity to replicate findings across nations. In light of the criteria proposed by Hill (Hill, 1965), the replication of haematological phenomenon across multiple countries would uphold the consistency criterion. Guidelines for haematological management is currently not tailored according to the aetiology of the haemorrhage (see Table 3) despite evidence to suggest that haemostatic features differ according to aetiology. In particular, a previous study have shown that platelet and fibrinogen levels differ according to the cause of PPH; however, this study was not population based (Collins et al., 2014). In order to strengthen the evidence, a multinational study will allow examination of whether the results of this research in the UK can be replicated internationally. Consequently, the replication of findings will provide a stronger argument and evidence base to change clinical practice with regards to tailored haematological management.

3.2 Study aim

To examine the international variation in the epidemiology, haemostatic features, obstetric and haematological management and maternal and perinatal outcomes for women with major obstetric haemorrhage (MOH).

3.2.1 Cross-country comparisons

1. To identify a set of cases using a common definition based of MOH on the number of units of red blood cells transfused during a specified time period.

2. To compare the epidemiology, haemostatic features, management, causes and outcomes of MOH requiring massive transfusion across the participating INOSS countries.

3.2.2 Pooled data comparisons

3. To examine whether patterns in haemostatic features and haematological and obstetric management were sufficiently similar between the United Kingdom and other countries to allow pooled comparisons.

4. To describe the management and haemostatic features and outcomes according to the aetiology of haemorrhage.

5. To investigate any association between transfusion management and clinical outcomes.

3.3 Methods

3.3.1 Study description

This was an international population-based study of massive transfusion in MOH, using a secondary data analysis of five population-based studies from Australia, France, Italy, the Netherlands and the United Kingdom. In this study, massive transfusion in major obstetric haemorrhage was defined as a pregnant or postpartum women (at least 20 weeks of gestation) who had received eight or more units of RBC within 24 hours.

3.3.2 Overall description

In each country, data were collected either nationally or from a number of regions on a population basis within the country. Data were prospectively collected using a national obstetric surveillance system:

- UK Obstetric Surveillance System (UKOSS)
- Australasian Maternity Outcomes Surveillance System (AMOSS))

A population-based multi-regional surveillance system:

- Italian Obstetric Surveillance System (ItOSS)
- Épidémiologic de la Morbidité Maternelle Sévère study (EPIMOMS in France)

Retrospective cohort study:

- Transfusion strategies in women during Major Obstetric Haemorrhage study (TeMpOH-1 in the Netherlands).

These data had already been collected and were accessed and analysed for the purpose of the study reported here.

3.3.2.1 Case definition

From the studies included, a subsample of women meeting a unified case definition were extracted. To be included, pregnant or postpartum women had to have received eight or more units of red blood cells within 24 hours. Women who were less than 20 weeks pregnant were excluded.

3.3.3 Data collection

3.3.3.1 United Kingdom and Australia

The methods for UKOSS and AMOSS data collection systems have been previously described in chapter two (Knight et al., 2005, Halliday et al., 2013). Both countries used a national surveillance system to identify cases of massive transfusion from consultant led obstetric units nationally in the United Kingdom and from hospitals with over 50 births per year in Australia. Reporters were asked to complete a data collection form using the medical records of the women. Data were collected anonymously. The findings from the United Kingdom study have been published previously (Green et al., 2016a, Green et al., 2016b).

During the period 2014-2015, AMOSS identified women who had 5 or more units of RBC transfused within 24 hours at 20 weeks gestation or more. Between June 2013- July 2014, women who had 8 or more units of RBCs transfused within 24 hours at 20 weeks' gestation or more were identified using the United Kingdom Obstetric Surveillance System.

3.3.3.2 France (EPIMOMS)

This study included data from the EPIMOMS study that prospectively identified cases of severe maternal morbidity from 6 regions in France: Alsace Champagne-Ardenne,

Lorraine, Auvergne, Rhone-Alpes, Ile-de-France and Normandy. Cases were identified for a year between 2012-2013 from 113 intensive care units and 118 maternity units. Selected maternal morbidities were identified by a local reporter in each hospital. Data about demographics, previous medical history, current pregnancy, causes, management and maternal and perinatal outcomes were collected from the case notes of each women.

Major obstetric haemorrhage was one of the severe maternal morbidities in the EPIMOMS study. To be included as a MOH case, women had to be at least 22 weeks' of gestation or more and had to meet one of the following criteria: ≥1500mls blood loss, blood transfusion ≥ 4 RBC, uterine artery embolisation, ligation or compressive uterine sutures or have an emergency peripartum hysterectomy (Deneux-Tharaux and Bouvier-Colle, 2017).

3.3.3.3 Italy

The Italian Obstetric Surveillance (ItOSS) system in Italy identified women who had 4 or more units of RBCs transfused at 22 weeks' of gestation or greater. This prospective population-based study identified women during 2014-2016 from six regions in Italy, namely Piedmont and Emilia-Romagna, Tuscany, Lazio, Campania and Sicily, which represent 49% of births in Italy. The clinical reporter from each facility identified and collected data on women with PPH, uterine rupture, abnormally invasive placenta and peripartum hysterectomy. Clinical and demographic data were collected from the woman's medical records and entered into an online data collection form. The completeness of the reported cases was verified through the Hospital Discharge Database.

3.3.3.4 The Netherlands

TeMpOH-1 was a national retrospective cohort study conducted between January 2011 and January 2013 in the Netherlands, which included all hospitals. Women were identified using records from blood transfusion services and birth registries of participating hospitals.

Women were included if they had received four units or more of RBC or FFP and/or platelets in addition to RBCs as a result of obstetric haemorrhage. Data were collected from medical records and included information about previous medical history, current pregnancy, causes of haemorrhage, haematological parameters, blood components, fluid resuscitation and surgical and medical management.

3.3.4 Comparability of datasets

With reference to the literature, the clinical and demographic variables required to answer the objectives were requested from the participating countries. Using data dictionaries from each country, each variable was mapped to assess the availability and comparability between datasets (see Table 18). If the components of a particular variable were not comparable between the datasets, then a common definition for that variable was created. If this was not possible the variable was excluded from the analysis. In the instance of obstetric management, the differences in variables are indicated in the Tables.

A mapping exercise was completed to assess whether the coding matched; where coding differed a harmonised coding was devised and applied. The units used for the haematological parameters were assessed. In instances where they differed they were converted to the same units; however, if this was not possible the variable was excluded from the analysis.

Table 18. Availability of variables from each respective dataset.

Desired variable	United Kingdom (UKOSS)	Australia (AMOSS)	Italy (ItOSS)	the Netherlands (TeMpOH-1)	France (EPIMOMS)	Included in analysis	Comment
Sociodemographic characteristics							
Age	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Height	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Weight	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
BMI at booking	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Smoking status	*Yes*	*Yes*	*No*	*No*	*Yes*	Yes	
Ethnicity	*Yes*	*No*	*No*	*Yes*	*No*	No	
Country of birth	*No*	*No*	*Yes*	*No*	*Yes*	No	
Socioeconomic status	*No*	*Yes*	*No*	*No*	*No*	No	
Employment status	*Yes*	*No*	*No*	*No*	*No*	No	
Drug use	*No*	*No*	*No*	*No*	*Yes*	No	
Previous medical history							
Parity	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Previous caesarean section	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Number of previous caesareans	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Previous pregnancy problems	*Yes*	*Yes*	*No*	*Yes*	*Yes*	Yes	
Previous postpartum haemorrhage	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	Yes	
Inherited bleeding disorders	*Yes*	*Yes*	*No*	*Yes*	*Yes*	Yes	
Thrombocytopenia	*Yes*	*Yes*	*No*	*No*	*Yes*	Yes	
Pre-existing medical problems	*Yes*	*See comment*	*No*	*Yes*	*Yes*	Yes	*Used a singular code on previous medical problems*
Anaemia before pregnancy/ before bleeding event	*Yes*	Yes	*No*	*No*	*Yes*	No	*Not comparable between countries*
Known infection	*Yes*	Yes	*No*	*Yes*	*Yes*	Yes	
Known hypertension	*Yes*	Yes	*No*	*Yes*	*Yes*	Yes	
Current pregnancy characteristics							
Multiple pregnancy	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	

Desired variable	United Kingdom (UKOSS)	Australia (AMOSS)	Italy (ItOSS)	the Netherlands (TeMpOH-1)	France (EPIMOMS)	Included in analysis	Comment
Induction of labour	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Use of uterotonics in vaginal deliveries	*No*	*Yes*	*No*	*Yes (not complete)*	*Yes*	*No*	*Was not comparable between countries*
Caesarean delivery	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Abnormal placentation during pregnancy	*Yes*	*Yes (from coding)*	*Yes*	*No*	*Yes*	*No*	*Was not included as it was captured in the primary cause*
When did the haemorrhage occur?	*Yes*	*Yes*	*No*		*Yes*	*Yes*	
Primary cause of the bleed	*Yes*	*Yes*	*Yes*	*Yes*	*Yes see comment*	*Yes*	*Did not include a primary cause so women had multiple causes*
Haematological features							
First Hb value after onset	*Yes (g/dL)*	*Yes (g/L)*	*Yes*	*Yes (g/dL)*	*Yes (g/L)*	*Yes*	*All Dutch haematological features variables are based on the best and worst values*
Worst Hb value after onset	*Yes (g/dL)*	*Yes (g/L)*	*Yes*	*Yes (g/dL)*	*Yes (g/L)*	*Yes*	
Initial Platelet count (x10^9/L) after onset	*Yes(x10^9/L)*	*Yes(x10^9/L)*	*No*	*Yes (mmol/L)*	*Yes(10³/mm³)*	*Yes*	
Worst Platelet count (x10^9/L) after onset	*Yes(x10^9/L)*	*Yes(x10^9/L)*	*No*	*Yes (mmol/L)*	*Yes(10³/mm³)*	*Yes*	
Initial prothrombin time after onset (sec)	*Yes -PT (sec)*	*Yes used PT or INR*	*No*	*Yes -PT (sec)*	*Yes (PT %)*	*Yes*	*French data not comparable*
Worst prothrombin time after onset (sec)	*Yes -PT (sec)*	*Yes used PT or INR*	*No*	*Yes -PT (sec)*	*Yes (PT %)*	*Yes*	*French data not comparable*
Initial activated prothrombin time after onset (sec)	*Yes (sec)*	*Yes (sec)*	*No*	*Yes (sec)*	*Yes (sec)*	*Yes*	
Worst activated prothrombin time after onset (sec)	*Yes (sec)*	*Yes (sec)*	*No*	*Yes (sec)*	*Yes (sec)*	*Yes*	
Initial Fibrinogen after onset g/L	*Yes (g/L)*	*Yes (g/L)*	*No*	*Yes (g/L)*	*Yes (g/L)*	*Yes*	
Worst Fibrinogen after onset g/L	*Yes (g/L)*	*Yes (g/L)*	*No*	*Yes (g/L)*	*Yes (g/L)*	*Yes*	
Blood products given							
Number of units of RBC	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Fresh Frozen Plasma	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Platelets	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	

Desired variable	United Kingdom (UKOSS)	Australia (AMOSS)	Italy (ItOSS)	the Netherlands (TeMpOH-1)	France (EPIMOMS)	Included in analysis	Comment
Cryoprecipitate	*Yes*	*Yes*	*Yes*	*Not used*	*Not used*	*Yes*	*Included as interesting difference between countries*
Fibrinogen	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Cell Saver	*Yes*	*Yes*	*No*	*No*	*No*	*Yes*	*Included as interesting difference between countries*
Factor VIIa	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	
Tranexamic acid	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	
Colloid (ml)	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	
Crystalloid (ml)	*Yes*	*No*	*Yes*	*Yes*	*Yes*	*Yes*	
Time of first unit	*No*	*Yes*	*No*	*Yes*	*No*	*No*	
Time of eighth unit	*No*	*Yes*	*No*	*Yes*	*No*	*No*	
Medical Management							
Oxytocin	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Italian data limited to vaginal births*
Ergometerine	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	
Prostaglandin	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	
Misoprostol	*Yes*	*Yes*	*No*	*Yes*	*Yes*	*Yes*	
Management surgical							
Suturing	*Yes*	*No*	*No*	*No*	*No*	*No*	
Placenta removal	*Yes*	*No*	*No*	*No*	*Yes*	*No*	
Intraabdominal packing	*Yes*	*Yes*	*No*	*Yes (not comparable)*	*Yes*	*No*	*Was not considered a relevant management*
Balloons	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Intrauterine packing	*Yes*	*Yes*	*No*	*No*	*No*	*Yes*	
Embolisation and ligation	*Yes*	*Yes*	*Yes see comment*	*Yes*	*Yes*	*Yes*	*Embolisation and ligation combined due to the UK data*
Intra-arterial balloons	*Yes*	*Yes*	*No*	*No*	*No*	*Yes*	
Uterine compression sutures	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Hysterectomy	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	
Maternal morbidity							
Death	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	

Desired variable	United Kingdom (UKOSS)	Australia (AMOSS)	Italy (ItOSS)	the Netherlands (TeMpOH-1)	France (EPIMOMS)	Included in analysis	Comment
Serious maternal morbidity	*Yes*	*Yes*	*Yes*	*No*	*See comment*	*No*	*Excluded outcomes were as a result of a lack of validity and case ascertainment*
Respiratory distress syndrome	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	
Coagulopathy	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	
Kidney failure	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	
Cardiac arrest	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	
Pulmonary oedema	*No*	*Yes*	*Yes*	*No*	*Yes*	*No*	
Thrombotic event	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	
Multiple organ failure	*Yes*	*Yes*	*Yes*	*No*	*See comment*	*No*	*French data not comparable*
Septicaemia	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*Yes*	
Required ventilation	*No*	*Yes*	*Yes*	*No*	*Yes*	*No*	*Not relevant or valid outcomes*
Pelvic injury	*No*	*Yes*	*No*	*No*	*Yes*	*No*	
Reaction to transfusion	*No*	*Yes*	*No*	*No*	*Yes*	*No*	
Other morbidity	*No*	*Yes*	*No*	*No*	*No*	*No*	
ITU admission	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	

3.3.5 Missing data

Previous studies using obstetric surveillance data have showed that the distribution of missing data for each variable was not missing at random; therefore, multiple imputation was not considered suitable (Lindquist et al., 2013). In analyses stratified by country, missing data were included as a 'missing' category for categorical variables. Complete case analysis was used for continuous variables. The analysis stratified by aetiology used a complete case analysis to aid with comparison across groups. Haematological or obstetric management variables missing in three or more countries were excluded from the stratified analysis by aetiology.

3.3.6 Statistical analysis

3.3.6.1 Case selection

This study used methods similar to an individual patient data meta-analysis where each country was analysed individually then pooled together (Riley et al., 2010). A harmonised case definition was identified using the minimum comparable number of units of red blood cells available across all countries. Although there was a slight difference in the number of weeks of gestation for inclusion, this was deemed unlikely to significantly affect the results. There were only two women who had a MOH as a result of abnormal placentation at 21 weeks of gestation and these women did not have different haematology compared to women at 22 weeks, as a result they were included. However, women with missing gestational age or gestational age less than 20 weeks were excluded from the study.

3.3.6.2 Descriptive analyses

Descriptive analyses used the following tests where appropriate: Analysis of Variance (ANOVA), Wilcoxon rank-sum test, Kruskal-wallis test and chi square tests or the Fisher's

exact test, if 20% of cells had a value of less than 5. In order to reduce the risk of a type I error a p-value <0.01 was used to determine statistical significance.

3.3.6.3 Cross-country analysis

Proportions, means and medians of patient characteristics, medical history, haematological features, obstetric and haematological management and perinatal and maternal outcomes were compared across countries. Normality was assessed using histograms. Normally distributed continuous variables were presented as means with standard deviations and skewed continuous variables were presented as medians with interquartile ranges. The exact binomial distribution was used to estimate confidence intervals for proportions. Statistical hypothesis testing was carried out to test for statistical difference between the countries and the respective characteristics, haematological features, management and outcomes.

3.3.6.4 Analyses stratified by aetiology of major obstetric haemorrhage

The numbers within each category of aetiology was small per country, as a result, cross country analysis stratified by aetiology was deemed unfeasible. To account for this, the aetiology of major obstetric haemorrhage was categorised into causes with similar mechanisms. Groups were categorised thus: women with a primary cause of atony; women with either a traumatic cause (laceration, genital tract trauma or uterine rupture); women with abnormal placentation (either abnormally invasive placenta, retained placenta or placenta praevia); and women with placental abruption.

France had multiple causes of PPH coded so a primary cause was devised using a hierarchical approach. The primary cause was defined in the following order: first those with abnormal placentation, second women with abruption, and third women with trauma and lastly those with atony.

3.3.6.4.1 Replication analysis: United Kingdom vs. Combined (Australia, France, the Netherlands and Italy)

In the first analysis, a pooled analysis was limited to a comparison between the United Kingdom and combined data for France, the Netherlands, Italy, and Australia. This allowed an assessment to check whether the United Kingdom was comparable to the other countries before pooling the data further.

A stratified analysis by aetiology compared the haematological features, obstetric and haematological management and maternal and perinatal outcomes in the United Kingdom to a combined cohort of countries. Statistical hypothesis testing assessed whether there was statistical difference between the United Kingdom and a combined cohort of countries, for each respective aetiology. The Italian data lacked information about most of the haematological features so was excluded from the haematological comparison. Other than death and intensive therapy unit (ITU) admission, The Netherlands did not collect outcome data so the country's cases were excluded from the denominator of the relevant analyses.

3.3.6.4.2 Complete pooled analysis

The second analysis compared the aetiology of major obstetric haemorrhage to the haematological features, obstetric and haematological management and perinatal and maternal outcomes in a pooled cohort across all countries. Proportions and medians were compared across the aetiologies of major obstetric haemorrhage. Hypothesis tests assessed for difference between the aetiology of PPH and the respective characteristics, haematological features, management and outcomes.

3.3.6.5 Exploratory analysis: haematological management and association with maternal outcomes

This exploratory analysis sought to examine the influence of haematological management on maternal outcomes.

3.3.6.5.1 Outcome

The definitions of maternal morbidities varied greatly between countries and it was unclear if any of these had any objective measures (e.g. acute lung injury or overall maternal morbidity) or met specific clinical criteria (e.g. disseminated intravascular coagulopathy). Perinatal outcomes were unlikely to be impacted by the majority of causes of haemorrhage so were not considered appropriate to explore. As a result, the most objective and reliable outcomes from the available data were hysterectomy and maternal mortality. Hysterectomy and maternal mortality were likely to be associated with the exposures in the same direction, as the amount of blood components used were likely to be higher in both outcomes. Therefore, they were combined *a priori* to create a composite outcome of hysterectomy and maternal mortality.

3.3.6.5.2 Exposures: haematological management and covariates

Blood components and haemostatic agents used were included as exposures. The number of RBC, FFP and platelets were treated as continuous variables. Tranexamic acid, colloid and crystalloid were included as binary variables: used/did not use. A combined variable to determine use of any concentrated source of fibrinogen was created using cryoprecipitate and fibrinogen: used/ did not use. There was variation in the type of fibrinogen products used between countries and this provided a measure of 'any use of fibrinogen'. Informed by the general obstetric haemorrhage literature identified through the scoping review, age and parity were identified as potential confounders and the aetiology of major obstetric haemorrhage was anticipated to act as an effect modifier.

3.3.6.6 Power

This size of the study population was predetermined according to the individual datasets making up the study; as a result, the sample was fixed at 287 women with MT/MOH who either had a hysterectomy or died and 332 women with MT/MOH did not have a hysterectomy and survived. This provided 80% power to detect an odds ratio of 1.60 or greater at the 5% significance level in the lowest prevalence exposure in the comparison group (52.8% source of fibrinogen concentrate).

3.3.6.7 Statistical techniques

Blood components, haemostatic agents used were presented as proportions and medians with interquartile ranges according to their distribution across the composite outcome. Maternal mortality plus hysterectomy as the outcome was modelled individually with each blood component and haemostatic agent in a univariable analysis using unconditional logistic regression. Results were presented as odds ratios and 95% confidence intervals calculated using robust estimates of variance because of likely clustering within countries. In this exploratory analysis, a p-value of <0.05 was used to represent statistical significance. A multivariable analysis was carried out adjusting for maternal age and parity. In continuous exposures, departure from linearity with the outcome was assessed by fitting two separate models with and without the categorical term of the categorised continuous variable. A likelihood ratio test was used to assess if the models were nested within each other. An interaction between the aetiology of major obstetric haemorrhage and the exposure was tested for each model. Interaction terms were fitted in the fully adjusted model and statistical significance was assessed by likelihood ratio testing. There were no interactions identified between blood components or haemostatic agents and the aetiology of major obstetric haemorrhage.

3.3.7 Ethics approval and data sharing agreements

Data sharing agreements between the University of Oxford and each country were executed to facilitate the transfer and analysis of data in the United Kingdom. The Netherlands, France and Australia signed data sharing agreements with the University of Oxford. No data sharing agreement was required to access the Italian data. The French data collaborators gained approval from the EPIMOMS steering committee at INSERM, Paris. The TeMpOH-1 (the Netherlands) and ItOSS steering committees approved the study protocol and agreed to participate. The Australian collaborators gained approval for the study from the Human Research Ethics Committee, New South Wales, Australia. Ethics committee approval for the secondary analysis of United Kingdom data was not required.

3.4 Results

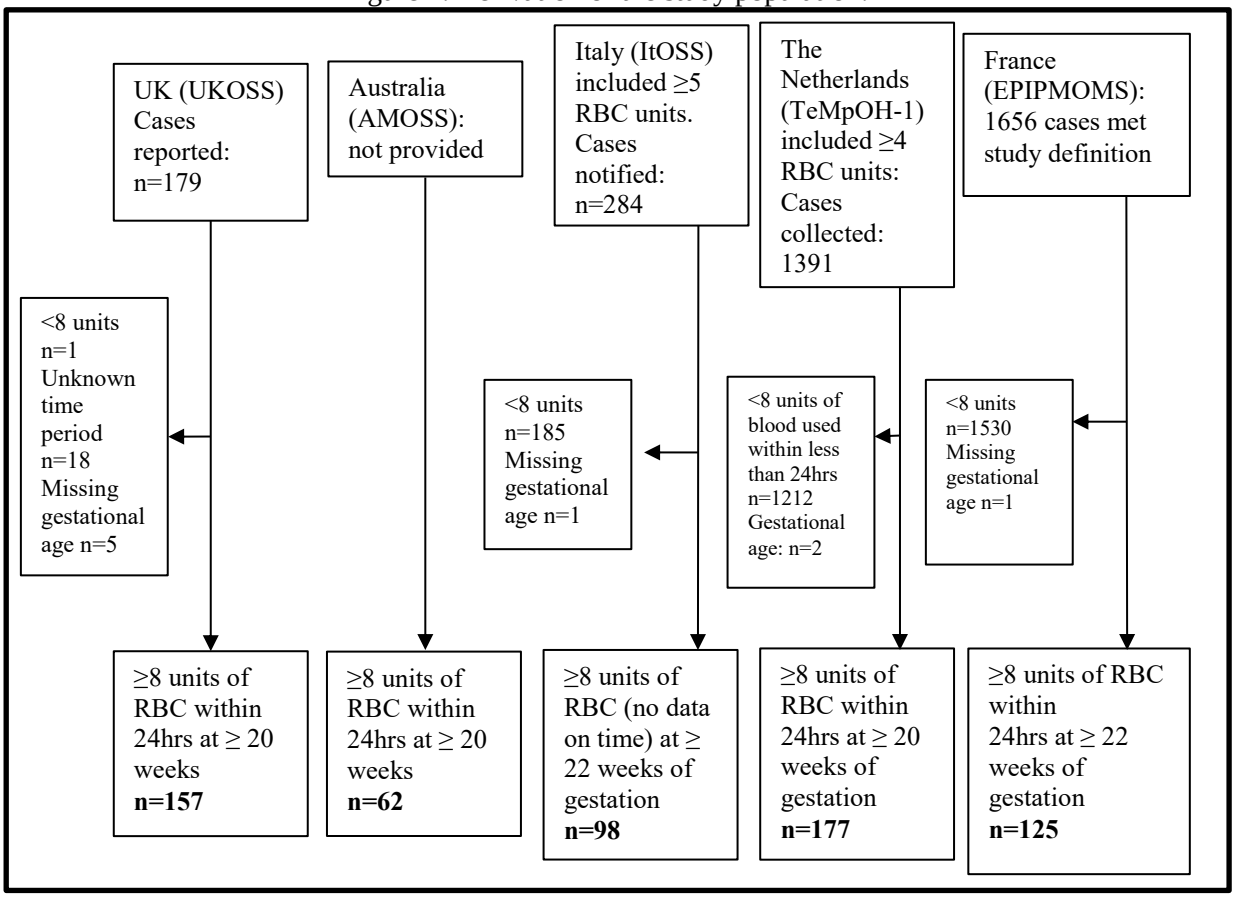
3.4.1 Study population

The derivation of the study population from the United Kingdom, Australia, Italy, the Netherlands and France is shown in Figure 4. During a 1 year period, 157 women who met the definition were identified (Box 2) using the United Kingdom Obstetric Surveillance System; 62 women were identified using the Australian Maternity Outcomes Surveillance System and a further 125 women were collected in France through the EPIMOMS study. Over a 2 year period, 177 women were identified retrospectively in the Netherlands through the TeMpOH-1 study and 98 women were identified using the Italian Obstetric Surveillance System.

Box 2. Unified case definition

The unified case definition for this study was classified as being women who were transfused 8 or more units of red blood cells within 24 hours and at 20 weeks' of gestation or more.

Figure 4. Derivation of the study population.



3.4.2 Dataset comparability

The availability of questions was assessed in Table 18 and the comparability of variables was assessed through data dictionaries. The majority of data items were collected using the same questions and in a manner that allowed uniform variables to be created across datasets. However, there were several key differences in the data collected across datasets. ItOSS did not collect data about haematological parameters other than haemoglobin level; AMOSS did not collect data about fluid resuscitation and haemostatic agents such as factor VIIa or tranexamic acid; in addition, the Netherlands did not collect data about maternal outcomes other than maternal death and ITU admission.

3.4.3 Cross-country comparison

3.4.3.1 Incidence

The estimated incidence of massive transfusion, defined as 8 or more units of RBCs in 24 hours at ≥20 weeks of pregnancy within each country is presented in Table 19. The United Kingdom, Australia and Italy had a similar incidence of massive transfusion at 20 women per 100,000 deliveries; the Netherlands had the highest incidence of massive transfusion at 92 women per 100,000 deliveries (95% CI: 79.2-107.0); followed by France with an incidence of approximately 70 women per 100,000 deliveries (see Table 19).

Table 19. Incidence of massive transfusion (transfused eight or more units within 24 hours).

Country	Number of women	Maternities denominator	Rate per 100,000 maternities (95% CI)
United Kingdom	157	787,105	20.0 per 100,000 maternities (17.0-23.3)
Australia	62	302,666	20.5 per 100,000 maternities (15.7-26.3)
Italy	98	474,562	20.9 per 100,000 maternities (16.8-25.2)
The Netherlands	177	270,101	65.5 per 100,000 maternities (56.2-75.9)
France	125	182,309	68.6 per 100,000 maternities (57.1-81.7)

3.4.3.2 Previous medical history and current pregnancy characteristics

Table 20 shows the previous medical history and current pregnancy characteristics of women who had a massive transfusion. The mean age of the women with massive transfusion was approximately 32 years old; Italy had the oldest women at a mean of 35 years old. The median BMI was similar across countries ranging from 23kg/m^2 in Italy and the Netherlands to 25kg/m^2 in the United Kingdom. Across all countries, the majority of

women who had massive transfusion were multiparous (>50%). However, age and parity differed statistically by country, P<0.01.

Among those with massive transfusion, the rate of previous caesarean section was 24% in France and the Netherlands, 28% in Italy, 36% in Australia and 40% in the UK and this difference was statistically significant (P <0.01). In addition, the women who had massive transfusion from the United Kingdom and Australia had a higher proportion of previous postpartum haemorrhages compared to other countries (13-15% vs. 4%) although differences were not statistically significant. In the current pregnancy, women who had massive transfusion in France had over double the proportion of multiple pregnancies (14%) compared to 4-7% in the United Kingdom, Italy, Australia and the Netherlands; however, these differences were not statistically significant.

In women who had massive transfusion, France had a higher proportion of cases induced at 58% compared to 21-35% in the remaining countries. In France, United Kingdom, Italy and Australia the majority of cases who had massive transfusion were delivered by caesarean section (58%-68%); the Netherlands had the lowest proportion of caesarean deliveries at 41%. These differences were statistically significant across countries (P<0.01).

Table 20. The sociodemographic, previous medical history and current pregnancy characteristics of women with massive transfusion according to country.

Characteristics		**United Kingdom n=157**		**Australia n=62**		**Italy n=98**		**the Netherlands n=177**		**France n=125**		**P-value**
Age	*Mean (S.D.)*	32.4	(5.9)	32.8	(5.2)	34.9	(6.0)	32.2	(5.3)	32.90	(5.9)	0.001
BMI	*Median (IQR)*	24.9	(22-28.7)	24.8	(21-28)	23.0	(21-25.4)	23.0	(20.8-26.0)	24.00	(21-26.8)	<0.001
Smoking status	*Never/ex-smoker*	130	(82.8)	50	(80.6)	-	-	-	-	95	(76)	0.832
	Smoked during pregnancy	27	(17.2)	8	(12.9)	-	-	-	-	18	(14.4)	
	Missing	0	(0)	4	(6.5)	-	-	-	-	12	(9.6)	
Previous medical history												
Previous pregnancy problems	*None*	62	(39.5)	42	(67.7)	-	-	-	-	57	(45.6)	0.005
	Yes	34	(21.7)	8	(12.9)	-	-	-	-	11	(8.8)	
	No previous pregnancies	61	(38.9)	7	(11.3)	48	(49)	84	(47.5)	55	(44)	
	Missing	0	(0)	5	(8.1)	-	-	-	-	2	(1.6)	
Previous caesarean section	*None*	34	(21.7)	24	(54.5)	21	(21.4)	51	(28.8)	38	(30.4)	0.014
	Yes	63	(40.1)	16	(36.4)	27	(27.6)	42	(23.7)	30	(24)	
	No previous pregnancies	60	(38.2)	4	(9.1)	48	(49)	84	(47.5)	55	(44)	
	Missing	0	(0)	18		2	(2)	0	(0)	2	(1.6)	
Parity	*Nulliparous*	60	(38.2)	4	(6.5)	48	(49)	84	(47.5)	55	(44)	<0.001
	Multiparous	96	(61.1)	41	(66.1)	50	(51)	93	(52.5)	69	(55.2)	
	Missing	1	(0.6)	17	(27.4)	0	(0)	0	(0)	1	(0.8)	
Previous postpartum haemorrhage	*None*	74	(47.1)	29	(76.3)	40	(40.8)	84	(47.5)	64	(51.2)	0.008
	Yes	23	(14.6)	5	(13.2)	4	(4.1)	8	(4.5)	5	(4)	
	No previous pregnancies	60	(38.2)	4	(10.5)	48	(49)	84	(47.5)	55	(44)	
	Missing	0	(0)	24		6	(6.1)	1	(0.6)	1	(0.8)	
Current pregnancy												
Current pregnancy problems	*None*	79	(50.3)	-	-	57	(58.2)	130	(73.4)	-	-	<0.001
	Yes	78	(49.7)	-	-	41	(41.8)	47	(26.6)	-	-	
	Missing	0	(0)	-	-	0	(0)	0	(0)	-	-	

Characteristics		United Kingdom n=157		Australia n=62		Italy n=98		the Netherlands n=177		France n=125		P-value
Hypertension prior to pregnancy or current problem	*None*	156	(99.4)	60	(96.8)	93	(94.9)	151	(85.3)	123	(98.4)	
	Yes	1	(0.6)	2	(3.2)	5	(5.1)	26	(14.7)	1	(0.8)	<0.001
	Missing	0	(0)	0	(0)	0	(0)	0	(0)	1	(0.8)	
Infection in current pregnancy	*No*	156	(99.4)	57	(91.9)	-	-	177	(100)	117	(93.6)	
	Yes	1	(0.6)	3	(4.8)	-	-	0	(0)	3	(2.4)	
	Missing	0	(0)	2	(3.2)	-	-	0	(0)	5	(4)	0.094*
Inherited bleeding disorders	*No*	155	(98.7)	56	(90.3)	-	-	-	-	120	(96)	
	Yes	2	(1.3)	1	(1.6)	-	-	-	-	4	(3.2)	
	Missing	0	(0)	5	(8.1)	-	-	-	-	1	(0.8)	0.069*
Multiple pregnancy	*No*	150	(95.5)	59	(95.2)	91	(92.9)	166	(93.8)	107	(85.6)	
	Yes	7	(4.5)	3	(4.8)	7	(7.1)	10	(5.6)	18	(14.4)	
	Missing	0	(0)	0	(0)	0	(0)	1	(0.6)	0	(0)	0.014
Use of augmentation during labour	*No*	15	(9.6)	14	(22.6)	-	-	-	-	70	(56)	
	Yes	40	(25.5)	24	(38.7)	-	-	-	-	52	(41.6)	
	Missing	102	(65)	24	(38.7)	-	-	-	-	3	(2.4)	
Induced	*None*	102	(65)	21	(33.9)	56	(57.1)	115	(65)	52	(41.6)	
	Yes	55	(35)	17	(27.4)	19	(19.4)	62	(35)	73	(58.4)	
	Missing	0	(0)	24	(38.7)	23	(23.5)	0	(0)	0	(0)	<0.001
Delivery type	*Vaginal delivery*	50	(31.8)	26	(41.9)	36	(36.7)	104	(58.8)	47	(37.6)	
	Caesarean delivery	107	(68.2)	36	(58.1)	62	(63.3)	72	(40.7)	78	(62.4)	
	N/A Pregnancy loss	0	(0)	0	(0)	0	(0)	1	(0.6)	0	(0)	<0.001

Not applicable excluded from estimate *Using Fisher's exact test. Australian missing data excluded from percentages of previous caesarean section and previous postpartum haemorrhage.

3.4.3.3 Haematology management cross country analysis

The blood components and haemostatic agents given during the management of major haemorrhage are shown in Table 21. Use of blood components varied across countries, Italy used a smaller amount of fresh frozen plasma (FFP) and platelets compared to everywhere else. France had the highest use of FFP with a median of 7 units (IQR: 5-9) compared to the other countries, which ranged from 4 units in Italy to 6 units in United Kingdom, the Netherlands and Australia. The difference between use of FFP was statistically significant ($P<0.01$).

Different sources of fibrinogen were used, the United Kingdom and Australia mainly administered cryoprecipitate while France, Italy and the Netherlands used fibrinogen concentrate. The highest proportion of women receiving a fibrinogen product was in Australia (84%), while the Netherlands and Italy had a lowest use of a fibrinogen product (36-37%) compared to the other countries (63%-84%). These differences between countries were unlikely to be due to chance.

Between 13-16% of women received factor VIIa in the Netherlands, Italy and France while the United Kingdom had a lower use at 8%, although this difference was not statistically significant. Use of tranexamic acid (TXA) also varied between countries, the Netherlands used TXA in 75% of major bleeds while it was used in less than a half of women in the United Kingdom and Italy, and these differences were statistically significant. The majority of women received either a colloid or crystalloid for fluid resuscitation. Large amounts of fluids were transfused; the median transfusion of crystalloids was 2.5 litres (IQR: 2-3.5litres) in Italy and the Netherlands and this was higher in the United Kingdom at a median of 3 litres.

Table 21. Haematological management by country.

Blood products		United Kingdom n=157		Australia n=62		Italy n=98		the Netherlands n=177		France n=125		P-value
Number of RBC units	*Median (IQR)*	10	(8-14)	11	(9-14)	9	(8-11)	11	(9-15)	10	(9-12)	<0.001
FFP	*Median (IQR)*	6	(4-8)	6	(4-8)	4	(2-8)	6	(4-8)	7	(5- 9)	<0.001
Platelets	*Median (IQR)*	1	(1-2)	1	(1-2)	0	(0-2)	2	(1-3)	1	(1- 3)	<0.001
Source of concentrated fibrinogen administered	*No*	58	(36.9)	8	(12.9)	61	(62.2)	114	(64.4)	27	(21.6)	
	Yes	99	(63.1)	52	(83.9)	37	(37.8)	63	(35.6)	93	(74.4)	<0.001
	Missing	0	(0)	2	(3.2)	0	(0)	0	(0)	5	(4)	
Fibrinogen concentrate used	*No*	147	(93.6)	54	(87.1)	61	(62.2)	114	(64.4)	27	(21.6)	
	Yes	10	(6.4)	0	(0)	37	(37.8)	63	(35.6)	93	(74.4)	<0.001
	Missing	0	(0)	8	(12.9)	0	(0)	0	(0)	5	(4)	
Cryoprecipitate used	*No*	55	(35)	8	(12.9)	-	-	-	-	-	-	
	Yes	95	(60.5)	52	(83.9)	-	-	-	-	-	-	0.001
	Missing	7	(4.5)	2	(3.2)	-	-	-	-	-	-	
Number of units of cryoprecipitate	*Median (IQR)*	2	(0-2)	1	(1-2)	-	-	-	-	-	-	0.096
Use of cell salvage	*No*	112	(71.3)	46	(74.2)	-	-	-	-	-	-	
	Yes	39	(24.8)	6	(9.7)	-	-	-	-	-	-	0.038
	Missing	6	(3.8)	10	(16.1)	-	-	-	-	-	-	
If Yes, amount transfused (ml)	*Median (IQR)*	900	(500-1900)	630	(500-780)	-	-	-	-	-	-	0.49
Factor VIIa	*No*	145	(92.4)	-	-	85	(86.7)	149	(84.2)	102	(81.6)	
	Yes	12	(7.6)	-	-	13	(13.3)	28	(15.8)	18	(14.4)	0.127
	Missing	0	(0)	-	-	0	(0)	0	(0)	5	(4)	
Tranexamic acid	*No*	85	(54.1)	-	-	56	(57.1)	44	(24.9)	46	(36.8)	
	Yes	72	(45.9)	-	-	42	(42.9)	133	(75.1)	73	(58.4)	<0.001
	Missing	0	(0)	-	-	0	(0)	0	(0)	6	(4.8)	
Colloid (ml)	*No*	17	(10.8)	-	-	1	(1)	5	(2.8)	18	(14.3)	
	Yes	135	(86)	-	-	48	(49)	159	(89.8)	87	(69.1)	0.001
	Missing	5	(3.2)	-	-	49	(50)	13	(7.3)	21	(16.7)	
If Yes, amount transfused (ml)	*Median (IQR)*	1000	(1000-2000)	-	-	1000	(500-1500)	1500	(1000-2000)	-	-	<0.001
Crystalloid (ml)	*No*	7	(4.5)	-	-	0	(0)	41	(23.2)	5	(4)	
	Yes	148	(94.3)	-	-	49	(50)	136	(76.8)	102	(81.6)	0.033
	Missing	2	(1.3)	-	-	49	(50)	-	-	18	(14.4)	
If Yes, amount transfused (ml)	*Median (IQR)*	3000	(2000-4000)	-	-	2500	(1700-3500)	2500	(1600-4300)	-	-	0.001

3.4.3.4 Obstetric management of major obstetric haemorrhage in each country

Medical management of massive haemorrhage involving the use of ergometrine, oxytocin, prostaglandin and misoprostol ranged from 88% of cases in France to 99% in the Netherlands. Medical management did not appear to differ significantly between countries. Italy only collected data about uterotonics given in vaginal births and 93% received uterotonics or prostaglandins to stop the bleeding. The types of drugs that were used was statistically significantly different across each country, oxytocin had higher use in the United Kingdom and Australia and prostaglandin was used more commonly in France and the Netherlands (see Table 22).

The use of surgical techniques and interventional radiology also varied between countries. Intrauterine balloons were used in half of all women with haemorrhage except in France where it was only used in a third of women with major bleeds. Use of embolisation and ligation differed also, both France and the Netherlands had high proportions of embolisation and ligation use with 68.8% and 52.5 % of women respectively, while in the United Kingdom and Italy they were used in 7.9% and 15.9% of women, respectively. These differences between countries were statistically significant ($P<0.01$)

Use of uterine compression sutures ranged from 14% in Italy and the Netherlands to a third of women in Australia. Use of hysterectomy varied greatly according to country. In Italy 74% of women with a major bleed had a hysterectomy, compared with approximately a half of women in the United Kingdom, France and Australia, and a third of women in the Netherlands. These surgical interventions differed statistically between countries.

Table 22. Obstetric management by country.

		United Kingdom n=157		Australia n=62		Italy n=98		the Netherlands n=177		France n=125		P-value
Medical management												
Oxytocin	*No*	5	(3.2)	7	(11.3)	-	-	63	(35.6)	47	(37.6)	<0.001
	Yes	152	(96.8)	54	(87.1)	-	-	114	(64.4)	71	(56.8)	
	Missing	0	(0)	1	(1.6)	-	-	0	(0)	7	(5.6)	
Ergometrine	*No*	67	(42.7)	32	(51.6)	-	-	158	(89.3)	-	-	<0.001
	Yes	90	(57.3)	26	(41.9)	-	-	19	(10.7)	-	-	
	Missing	0	(0)	4	(6.5)	-	-	0	(0)	-	-	
Prostaglandin	*No*	63	(40.1)	30	(48.4)	-	-	29	(16.4)	16	(12.8)	<0.001
	Yes	94	(59.9)	28	(45.2)	-	-	148	(83.6)	101	(80.8)	
	Missing	0	(0)	4	(6.5)	-	-	0	(0)	8	(6.4)	
Misoprostol	*No*	71	(45.2)	29	(46.8)	-	-	115	(65)	117	(93.6)	<0.001
	Yes	86	(54.8)	28	(45.2)	-	-	62	(35)	1	(0.8)	
	Missing	0	(0)	5	(8.1)	-	-	0	(0)	7	(5.6)	
Any medical management*	*No*	4	(2.5)	3	(4.8)	2	(2)	12	(1)	9	(7.2)	0.374
	Yes	153	(97.5)	58	(93.5)	30	(93.8)	165	(99)	110	(88.0)	
		0	(0)	1	(1.6)	66	#	0	(0)	6	(4.8)	
Surgical management												
Intrauterine balloons**	*No*	66	(42.0)	26	(41.9)	45	(45.9)	76	(42.9)	87	(69.6)	<0.001
	Yes	91	(58.0)	33	(53.2)	53	(54.1)	101	(57.1)	34	(27.2)	
	Missing	0	(0)	3	(4.8)	0	(0)	0	(0)	4	(3.2)	
Intra-abdominal packing***	*No*	142	(90.4)	48	(77.4)	-	-	-	-	108	(86.4)	0.405
	Yes	15	(9.6)	9	(14.5)	-	-	-	-	12	(9.6)	
	Missing	0	(0)	5	(8.1)	-	-	-	-	5	(4)	
Intrauterine packing	*No*	137	(87.3)	48	(77.4)	-	-	-	-	-	-	0.27
	Yes	20	(12.7)	11	(17.7)	-	-	-	-	-	-	
	Missing	0	(0)	3	(4.8)	-	-	-	-	-	-	

		United Kingdom n=157		Australia n=62		Italy n=98		the Netherlands n=177		France n=125		P-value
Embolisaton or ligation	*No*	132	(84.1)	41	(66.1)	94	(95.9)	84	(47.5)	35	(28)	
	Yes	25	(15.9)	21	(33.9)	4	(4.1)	93	(52.5)	86	(68.8)	<0.001
	Missing									4	(3.2)	
Intra-arterial balloons	*No*	152	(96.8)	58	(93.5)	-	-	-	-	-	-	
	Yes	5	(3.2)	2	(3.2)	-	-	-	-	-	-	0.956
	Missing	0	(0)	2	(3.2)	-	-	-	-	-	-	
Compression sutures	*No*	120	(76.4)	39	(62.9)	85	(86.7)	152	(85.9)	89	(71.2)	
	Yes	37	(23.6)	21	(33.9)	13	(13.3)	25	(14.1)	32	(25.6)	0.001
	Missing	0	(0)	2	(3.2)	0	(0)	0	(0)	4	(3.2)	
Hysterectomy	*No*	86	(54.8)	30	(48.4)	26	(26.5)	125	(70.6)	65	(52.0)	
	Yes	71	(45.2)	32	(51.6)	72	(73.5)	52	(29.4)	55	(44.0)	<0.001
	Missing	-	-	-	-	-	-	-	-	5	(4.0)	

*Italian data is for vaginal births only. ** Italian data includes intrauterine packing ***the Netherlands; intra-abdominal packing was used after hysterectomy. Any type of medical management included: ergometrine, Oxytocin, misoprostol and prostaglandin #Excluded missing from percentage

3.4.3.5 Aetiology of major obstetric haemorrhage

The aetiology of major obstetric haemorrhage is presented in an expanded form and condensed form (see Table 23). The most common cause in all countries was atony, with a prevalence ranging from 38.9% of MOH cases in the United Kingdom to 62.7% in the Netherlands. The second leading cause was abnormal placentation with a prevalence ranging from 22.4% in Italy to 32% in Australia. The least common cause was placental abruption with prevalence ranging from 2% in the Netherlands to 9% in the United Kingdom. Aetiology of haemorrhage was significantly different across countries (P<0.01).

Table 23. Aetiology of major obstetric haemorrhage by country.

	Primary cause of PPH	**United Kingdom n=157**		**Australia n=62**		**Italy n=98**		**the Netherlands n=177**		**France n=125**	
	Atony	61	(38.9)	25	(40.3)	55	(56.1)	111	(62.7)	80	(64)
Abnormal placentation	Placenta Praevia	12	(7.6)	4	(6.5)	*	*	4	(2.3)	11	(9.1)
	Abnormally invasive placenta	26	(16.6)	12	(19.4)	20	(20.4)	17	(9.6)	15	(11.9)
	Placenta abruption	14	(8.9)	4	(6.5)	3	(3.1)	4	(2.3)	10	(8.2)
Trauma	Uterine rupture	5	(3.2)	2	(3.2)	3	(3.1)	*	*	5	(4.1)
	Retained placenta	1	(0.6)	4	(6.5)	2	(2)	18	(10.2)	13	(10.7)
	Laceration	22	(14)	7	(11.3)	6	(6.1)	21	(11.9)	20	(15.9)
	Other	15	(9.6)	3	(4.8)	8	(8.2)	2	(1.1)	11	(9)
	Missing	1	(0.6)	1	(1.6)	1	(1)	0	(0)	11	(9)
	Atony	61	(38.9)	25	(40.3)	55	(56.1)	111	(62.7)	51	(40.8)
	Abnormal placentation	39	(24.8)	20	(32.3)	22	(22.4)	39	(22)	31	(24.8)
	Trauma	27	(17.2)	9	(14.5)	9	(9.2)	21	(11.9)	20	(16)
	Abruption	14	(8.9)	4	(6.5)	3	(3.1)	4	(2.3)	8	(6.4)
	Other	15	(9.6)	3	(4.8)	8	(8.2)	2	(1.1)	4	(3.2)
	Missing	1	(0.6)	1	(1.6)	1	(1)	0	(0)	11	(8.8)

Abnormal placentation group included: abnormally invasive placenta, placenta praevia and retained placenta. Trauma group included: rupture and genital tract lacerations, tears and surgical wounds. French causes were categorised into one cause per woman using a hierarchy (1st abnormal placentation, 2nd abruption, 3rd trauma and 4th atony). *Not collected. The other group contained: amniotic fluid embolism, DIC and haematoma.

3.4.3.6 Maternal outcomes by country

The maternal outcomes are presented in Table 24. Overall there were nine maternal deaths which gave a case fatality rate of 1.5% (95% CI: 0.67-2.7) and the distribution of deaths was not statistically different between countries (P>0.01). There were 14 women with thrombotic events and France had about double the proportion of these events compared to the United Kingdom and Australia (8% vs. 3%, respectively), although this was not statistically significant. Over 80% of women were admitted to an ITU in the United Kingdom, Italy, Australia and the Netherlands while France had 65% of women admitted to an ITU (P<0.001).

Table 24. Maternal outcomes by country.

		United Kingdom n=157		AMOSS n=62		Italy n=98		the Netherlands n=177		France n=125		P-value
Maternal outcome												
Maternal death	*No*	155	(98.7)	62	(100)	95	(96.9)	173	(97.7)	122	(97.6)	0.695
	Yes	2	(1.3)	0	(0)	3	(3.1)	4	(2.3)	3	(2.4)	
Cardiac problem*	*No*	149	(94.9)	58	(93.5)	93	(96.9)	-	-	13	(10.4)	0.626
	Yes	8	(5.1)	2	(3.2)	5	(3.1)	-	-	10	(8)	
	Missing	0	(0)	2	(3.2)	0	(0)	-	-	102	(81.6)	
Infection**	*No*	152	(96.8)	57	(91.9)	96	(97.9)	-	-	113	(90.4)	0.421
	Yes	5	(3.2)	2	(3.2)	2	(2.1)	-	-	8	(6.4)	
	Missing	0	(0)	3	(4.8)	0	(0)	-	-	4	(3.2)	
Thrombotic event	*No*	153	(97.5)	58	(93.5)	98	(100)	-	-	113	(90.4)	0.268***
	Yes	4	(2.5)	2	(3.2)	0	(0)	-	-	8	(6.4)	
	Missing	0	(0)	2	(3.2)	0	(0)	-	-	4	(3.2)	
ITU admission	*No*	29	(18.5)	3	(4.8)	15	(15.5)	32	(18.1)	44	(35.2)	<0.001
	Yes	128	(81.5)	59	(95.2)	82	(84.5)	145	(81.9)	81	(64.8)	

*Cardiac problem: United Kingdom: cardiac arrest, cardiac infection, cardioversion and inotropic support; United Kingdom, Australia and France: cardiac arrest.
Infection: United Kingdom: chest infection, septicaemia, septic shock, sepsis, enterococcus infection, necrotising fasciitis, c difficile, abscess, suspected tuberculosis or meningitis, wound infection and wound dehiscence. Australia: sepsis. Italy and France: septicaemia.*Italy removed from estimate.

3.4.4 United Kingdom compared to France, the Netherlands, Italy and Australia

3.4.4.1 Analysis by aetiology: haematological parameters (excluding Italy)

Table 25 shows the haematological parameters according to the aetiology of the bleed in the United Kingdom compared to the combined cohort of women from France, the Netherlands and Australia. Within each category of cause of haemorrhage, there were very similar values when comparing the haematological features in the United Kingdom to the other combined countries. Prothrombin times across all causes were similar comparing women from the United Kingdom to the combined cohort. The lowest median values of fibrinogen at diagnosis and at worst were for haemorrhages caused by abruption in both the United Kingdom (United Kingdom initial: median 0.6 (IQR: 0.6-1.6), worst: median 0.6 (IQR: 0.3-0.6) and the combined cohort (France, the Netherlands, Australia initial: median 1.1 (IQR: 0.7-2.8), worst: median 0.8 (IQR: 0.6-1.6)). However, there were a few notable differences; for women with abnormal placentation, the United Kingdom had a lower median platelet count at diagnosis than the combined countries. In addition, women with massive transfusion in the UK had a lower haemoglobin at diagnosis compared to other countries, however, the lowest recorded values of haemoglobin were similar between the two regions.

3.4.4.2 Analysis by aetiology: haematological management

The haematological management according to the aetiology of haemorrhage in the United Kingdom compared to a combined cohort of women from France, the Netherlands, Italy and Australia is shown in Table 26. In atony, trauma, abruption and other causes of haemorrhage, the United Kingdom and the combined cohort received similar amounts of RBCs and platelets, with no evidence of a statistical difference (P>0.01). For abnormal placentation, the United Kingdom used statistically more units of RBCs with a median of

14 unit of RBCs (IQR: 10-17) compared to 10 units (IQR: 9-13) in the combined cohort, P<0.01.

The use of a source of concentrated fibrinogen product (either cryoprecipitate or fibrinogen concentrate) differed between the United Kingdom and the combined cohort according to the cause of haemorrhage. In atony and abruption, a larger proportion of women received fibrinogen in the United Kingdom compared to the combined cohort (Atony 72% vs. 50% respectively P<0.01; abruption 86% vs. 69% respectively, P >0.01). This difference was statistically significant for the atonic bleeds but not for the bleeds caused by abruption. In general, the combined cohort received more tranexamic acid than the United Kingdom in most causes of haemorrhage other than abruption where the cohort in the United Kingdom had a greater use of tranexamic acid (57% vs. 40%), however, this difference was not statistically significant.

Table 25. Haematological parameters by aetiology in United Kingdom vs. France, the Netherlands and Australia .

Haematological parameters		Atony					Abnormal placentation				
		United Kingdom n=61		Fr, NL and Aus. n=187		P-value	United Kingdom n=39		Fr, NL and Aus. n=90		P-value
Haemoglobin at diagnosis (g/L)	*Mean (S.D.)*	90.6	(23.6)	102.3	(22.2)	<0.001	85.3	(22.7)	97.2	(22.3)	0.008
Worst value of haemoglobin (g/L)	*Mean (S.D.)*	68.7	(12.8)	62.2	(16.5)	0.135	71.3	(18.3)	66.3	(19.4)	0.479
Platelets at diagnosis (x10^9/L)	*Median (IQR)*	135	(106.5-186.0)	143	(107.0-191.0)	0.884	94	(63.0-199.0)	139.5	(107.0-185.0)	0.004
Platelets worst (x10^9/L)	*Median (IQR)*	68	(52.0-96.0)	65	(46.5-89.0)	0.183	57	(37.5-90.5)	74.5	(46.0-94.0)	0.123
PT at diagnosis (sec)	*Median (IQR)*	13.1	(11.0-17.5)	13.6	(11.3-15.1)	0.774	13	(11.0-14.0)	13	(11.1-16.0)	0.646
PT at worst (sec)	*Median (IQR)*	14.9	(12.4-19.0)	17	(13.6-21.0)	0.086	14	(12.0-16.6)	17	(13.2-20.0)	0.045
APTT at diagnosis (sec)	*Median (IQR)*	32.3	(30.0-43.0)	34.2	(30.0-40.0)	0.873	33	(27.8-41.4)	35	(30.0-42.0)	0.408
APTT at worst (sec)	*Median (IQR)*	38	(31.6-47.5)	45	(38.0-60.0)	0.005	37	(33.0-52.0)	42	(35.0-50.0)	0.354
Fibrinogen at diagnosis (g/L)	*Median (IQR)*	1.9	(1.1-2.5)	2.2	(1.5-3.0)	0.104	1.8	(1.2-2.5)	2.1	(1.6-3.0)	0.074
Fibrinogen at worst (g/L)	*Median (IQR)*	1.4	(1.0-2.2)	1.4	(1.0-1.8)	0.124	1.3	(0.9-2.1)	1.5	(1.2-2.1)	0.172

Haematological parameters		Trauma					Abruption					Other				
		United Kingdom n=27		Fr, NL and Aus. n=50		P-value	United Kingdom n=14		Fr, NL and Aus. n=16		P-value	United Kingdom n=15		Fr, NL and Aus. n=9		P-value
Haemoglobin at diagnosis (g/L)	*Mean (S.D.)*	79.8	(23.6)	96.2	(22.1)	0.003	86.3	(17.3)	90.9	(25.7)	0.579	82.1	(19.7)	98.5	(18.8)	0.057
Worst value of haemoglobin (g/L)	*Mean (S.D.)*	67.3	(17.1)	61.7	(18.9)	0.204	63.3	(11.2)	60.2	(11.4)	0.182	66	(13.7)	76.3	(18.9)	0.006
Platelets at diagnosis (x10^9/L)	*Median (IQR)*	141.5	(96.0-204.0)	154	(113.0-193.0)	0.760	137.5	(98.0-242.0)	159	(113.0-181.0)	0.359	122	(99.0-202.0)	136	(110.0-175.0)	0.858
Platelets worst (x10^9/L)	*Median (IQR)*	83	(68.0-108.0)	64	(38.0-92.0)	0.027	50.5	(33.0-78.0)	72.5	(58.0-87.0)	0.093	60	(50.0-99.0)	53	(31.0-96.0)	0.421
PT at diagnosis (sec)	*Median (IQR)*	13	(11.0-15.0)	13	(11.0-16.2)	0.836	14.2	(11.9-19.0)	16.6	(14.1-20.0)	0.175	13.8	(12.1-19.5)	16.5	(14.1-18.9)	0.584
PT at worst (sec)	*Median (IQR)*	14	(13.0-17.0)	16.5	(13.6-21.5)	0.324	17.9	(14.5-21.0)	19.1	(19.0-24.7)	0.257	15.9	(13.7-25.6)	34.8	(15.1-43.9)	0.112
APTT at diagnosis (sec)	*Median (IQR)*	32	(26.0-39.0)	34	(29.0-51.0)	0.202	35	(30.9-56.5)	39.5	(31.0-46.0)	0.837	36.5	(32.3-48.5)	29	(24.7-32.0)	0.031
APTT at worst (sec)	*Median (IQR)*	36	(28.8-44.5)	46	(40.0-64.0)	0.004	52	(41.0-81.0)	43	(38.0-46.0)	0.473	39.6	(31.1-67.0)	39	(25.9-97.0)	0.933
Fibrinogen at diagnosis (g/L)	*Median (IQR)*	2.7	(1.7-4.1)	2.2	(1.5-3.2)	0.228	0.6	(0.6-1.6)	1.1	(0.7-2.8)	0.117	1.9	(1.2-2.9)	2	(1.5-3.6)	0.393
Fibrinogen at worst (g/L)	*Median (IQR)*	1.7	(1.0-2.7)	1.5	(0.8-2.0)	0.172	0.6	(0.3-0.6)	0.8	(0.6-1.6)	0.057	1.3	(0.6-2.3)	1.3	(1.0-1.6)	0.867

Table 26. Haematological management by aetiology of PPH in United Kingdom vs. other countries.

Haematological management		Atony					Abnormal placentation					Trauma				
		UK n=61		Fr, NL, Aus and It n=242		P-value	UK n=39		Fr, NL, Aus and It n=112		P-value	UK n=27		Fr, NL, Aus and It n=59		P-value
Number of RBC units	*Median (IQR)*	10	(8-12)	10	(8-13)	0.467	14	(10-17)	10	(9-13)	0.003	10	(8-12)	10	(9-15)	0.313
FFP	*Median (IQR)*	6	(4- 8)	6	(4- 8)	0.951	7	(4- 8)	6	(4- 8)	0.250	4	(4- 8)	6	(4-11)	0.050
Platelets	*Median (IQR)*	1	(0- 2)	1	(1- 2)	0.614	2	(1- 2)	2	(1- 2)	0.981	1	(1- 2)	1	(1- 3)	0.289
Used a source of concentrated fibrinogen	*No*	17	(27.9)	127	(52.7)	0.001	16	(41)	46	(41.8)	0.931	15	(55.6)	24	(40.7)	0.198
	Yes	44	(72.1)	114	(47.3)		23	(59)	64	(58.2)		12	(44.4)	35	(59.3)	
Used Fibrinogen concentrate	*No*	58	(95.1)	145	(60.4)	<0.001	38	(97.4)	62	(57.4)	<0.001	26	(96.3)	30	(53.6)	<0.001
	Yes	3	(4.9)	95	(39.6)		1	(2.6)	46	(42.6)		1	(3.7)	26	(46.4)	
Factor VIIa	*No*	53	(86.9)	187	(86.2)	0.887	38	(97.4)	80	(87)	0.107	26	(96.3)	41	(82)	0.090
	Yes	8	(13.1)	30	(13.8)		1	(2.6)	12	(13)		1	(3.7)	9	(18)	
Tranexamic acid	*No*	30	(49.2)	73	(33.8)	0.028	24	(61.5)	35	(38)	0.013	15	(55.6)	18	(36)	0.098
	Yes	31	(50.8)	143	(66.2)		15	(38.5)	57	(62)		12	(44.4)	32	(64)	
Colloid	*No*	6	(10.5)	12	(6.1)	0.255	5	(12.8)	5	(6.8)	0.281	1	(3.8)	5	(11.1)	0.404
	Yes	51	(89.5)	184	(93.9)		34	(87.2)	69	(93.2)		25	(96.2)	40	(88.9)	
Crystalloid	*No*	3	(5)	1	(0.6)	0.060	0	(0)	1	(1.6)	0.999	0	(0)	1	(2.5)	0.999
	Yes	57	(95)	162	(99.4)		38	(100)	63	(98.4)		27	(100)	39	(97.5)	

Table continued.

Haematological management		Abruption				Other				
		UK n=14		Fr, NL, Aus and It n=19		P-value	UK n=15		Fr, NL, Aus and It n=17		P-value
Number of RBC units	*Median (IQR)*	10	(9-14)	10	(8-12)	0.413	10	(8-20)	10	(8-12)	0.801
FFP	*Median (IQR)*	9	(4-12)	6	(4- 9)	0.341	8	(4-14)	6	(6-12)	0.939
Platelets	*Median (IQR)*	2	(1- 3)	2	(1- 4)	0.982	1	(0- 3)	1	(0- 4)	0.594
Used a source of concentrated fibrinogen	*No*	2	(14.3)	6	(31.6)	0.252	7	(46.7)	4	(23.5)	0.169
	Yes	12	(85.7)	13	(68.4)		8	(53.3)	13	(76.5)	
Used Fibrinogen concentrate	*No*	11	(78.6)	9	(47.4)	0.087	13	(86.7)	7	(41.2)	0.012
	Yes	3	(21.4)	10	(52.6)		2	(13.3)	10	(58.8)	
Factor VIIa	*No*	14	(100)	13	(86.7)	0.483	13	(86.7)	8	(61.5)	0.198
	Yes	0	(0)	2	(13.3)		2	(13.3)	5	(38.5)	
Tranexamic acid	*No*	6	(42.9)	9	(60)	0.356	9	(60)	7	(53.8)	0.743
	Yes	8	(57.1)	6	(40)		6	(40)	6	(46.2)	
Colloid	*No*	2	(14.3)	2	(14.3)	0.999	3	(20)	0	(0)	0.250
	Yes	12	(85.7)	12	(85.7)		12	(80)	10	(100)	
Crystalloid	*No*	1	(7.1)	0	(0)	0.999	3	(20)	1	(12.5)	0.999
	Yes	13	(92.9)	12	(100)		12	(80)	7	(87.5)	

3.4.4.3 Medical and surgical management in United Kingdom vs. combined cohort

3.4.4.4 Medical management

For every cause of haemorrhage, the United Kingdom had a higher overall use of uterotonics and prostaglandins than the combined cohort. However, not every woman in the combined cohort with an atonic cause of haemorrhage received an uterotonic (see Table 27).

3.4.4.5 Surgical management

According to aetiology, surgical management differed between the United Kingdom and the combined cohort of countries. For women with atony, 80% were treated with an intrauterine balloon in the United Kingdom compared to 60% in the combined cohort ($P<0.01$). Nearly a half of women were treated by embolisation or ligation to surgically manage bleeds caused by atony or abnormal placentation in the combined cohort compared to 13% in the United Kingdom; these differences were statistically significant ($P<0.001$). For abnormal placentation, nearly 90% underwent a hysterectomy in the United Kingdom while this was 63% in the combined cohort, which was statistically significantly different ($P<0.001$) (see Table 27).

3.4.4.6 Maternal outcomes in United Kingdom vs. combined cohort

The maternal outcomes in the United Kingdom compared to a combined cohort stratified by aetiology are shown in Table 28. The total number of maternal deaths and morbidities was very small so the United Kingdom comparison with the combined cohort is limited. There was no evidence of a statistically significant relationship with any of the outcomes between United Kingdom and the combined cohort by cause of haemorrhage. However, the United Kingdom had a higher proportion of women admitted to ITU for abnormal placentation than the combined cohort (90 vs. 70%, $P>0.01$).

Table 27. Obstetric management by aetiology in United Kingdom vs. all other countries.

Obstetric management		Atony n=303					Abnormal placentation n=151					Trauma n=86					Abruption n=33					Other n=32				
		UK n=61		Fr, NL, Aus and It n=242		P-value	UK n=39		Fr, NL, Aus and It n=112		P-value	UK n=27		Fr, NL, Aus and It n=59		P-value	UK n=14		Fr, NL, Aus and It n=19		P-value	UK n=15		Fr, NL, Aus and It n=17		P-value
Oxytocin	*No*	0	(0)	50	(26.7)	<0.001	2	(5.1)	33	(37.5)	<0.001	2	(7.4)	21	(42)	0.002	0	(0)	6	(40)	0.017	1	(6.7)	3	(37.5)	0.103
	Yes	61	(100)	137	(73.3)		37	(94.9)	55	(62.5)		25	(92.6)	29	(58)		14	(100)	9	(60)		14	(93.3)	5	(62.5)	
Ergometrine	*No*	16	(26.2)	114	(83.8)	<0.001	23	(59)	46	(80.7)	0.020	15	(55.6)	23	(76.7)	0.091	6	(42.9)	4	(66.7)	0.329	7	(46.7)	3	(60)	0.999
	Yes	45	(73.8)	22	(16.2)		16	(41)	11	(19.3)		12	(44.4)	7	(23.3)		8	(57.1)	2	(33.3)		8	(53.3)	2	(40)	
Prostaglandin	*No*	13	(21.3)	22	(11.8)	0.065	25	(64.1)	29	(33)	0.001	14	(51.9)	15	(30)	0.059	5	(35.7)	5	(38.5)	0.883	6	(40)	4	(50)	0.685
	Yes	48	(78.7)	164	(88.2)		14	(35.9)	59	(67)		13	(48.1)	35	(70)		9	(64.3)	8	(61.5)		9	(60)	4	(50)	
Misoprostol	*No*	17	(27.9)	121	(64.7)	<0.001	27	(69.2)	76	(87.4)	0.015	13	(48.1)	40	(80)	0.004	7	(50)	12	(92.3)	0.033	7	(46.7)	6	(75)	0.379
	Yes	44	(72.1)	66	(35.3)		12	(30.8)	11	(12.6)		14	(51.9)	10	(20)		7	(50)	1	(7.7)		8	(53.3)	2	(25)	
Medical management in vaginal births	*No*	0	(0)	8	(3.8)	0.205	1	(2.6)	10	(10.9)	0.172	2	(7.4)	6	(11.1)	0.712	0	(0)	4	(25)	0.103	1	(6.7)	1	(7.7)	0.999
	Yes	61	(100)	201	(96.2)		38	(97.4)	82	(89.1)		25	(92.6)	48	(88.9)		14	(100)	12	(75)		14	(93.3)	12	(92.3)	
Intrauterine balloons	*No*	12	(19.7)	96	(39.7)	0.004	24	(61.5)	63	(56.8)	0.603	16	(59.3)	42	(71.2)	0.273	7	(50)	14	(82.4)	0.121	7	(46.7)	14	(82.4)	0.062
	Yes	49	(80.3)	146	(60.3)		15	(38.5)	48	(43.2)		11	(40.7)	17	(28.8)		7	(50)	3	(17.6)		8	(53.3)	3	(17.6)	
Intra-abdominal packing	*No*	59	(96.7)	64	(85.3)	0.037	33	(84.6)	46	(92)	0.324	24	(88.9)	26	(92.9)	0.669	13	(92.9)	2	(100)	0.538	12	(80)	5	(71.4)	0.999
	Yes	2	(3.3)	11	(14.7)		6	(15.4)	4	(8)		3	(11.1)	2	(7.1)		1	(7.1)	0	(0)		3	(20)	2	(28.6)	
Embolisaton and ligation	*No*	53	(86.9)	131	(54.1)	<0.001	34	(87.2)	60	(53.6)	<0.001	18	(66.7)	31	(52.5)	0.220	14	(100)	13	(68.4)	0.027	12	(80)	13	(76.5)	0.999
	Yes	8	(13.1)	111	(45.9)		5	(12.8)	52	(46.4)		9	(33.3)	28	(47.5)		0	(0)	6	(31.6)		3	(20)	4	(23.5)	
Uterine compression sutures	*No*	39	(63.9)	179	(74)	0.119	34	(87.2)	100	(90.1)	0.612	23	(85.2)	49	(83.1)	0.999	11	(78.6)	16	(88.9)	0.631	12	(80)	13	(76.5)	0.999
	Yes	22	(36.1)	63	(26)		5	(12.8)	11	(9.9)		4	(14.8)	10	(16.9)		3	(21.4)	2	(11.1)		3	(20)	4	(23.5)	
Hysterectomy	*No*	39	(63.9)	144	(59.5)	0.527	4	(10.3)	42	(37.5)	0.001	21	(77.8)	34	(57.6)	0.071	7	(50)	13	(72.2)	0.198	14	(93.3)	7	(41.2)	0.003
	Yes	22	(36.1)	98	(40.5)		35	(89.7)	70	(62.5)		6	(22.2)	25	(42.4)		7	(50)	5	(27.8)		1	(6.7)	10	(58.8)	

Table 28. Maternal outcomes by aetiology of haemorrhage in the United Kingdom vs all other countries.

Maternal outcomes		Atony					Abnormal placentation					Trauma					Abruption n=30					Other n=36				
		UK n=61		Fr, NL, Aus and It n=242		P-value	UK n=39		Fr, NL, Aus and It n=112		P-value	UK n=27		Fr, NL, Aus and It n=59			UK n=14		Fr, NL, Aus and It n=19		P-value	UK n=15		Fr, NL, Aus and It n=17		P-value
Maternal death	*No*	61	(100)	238	(98.3)	0.587	39	(100)	110	(98.2)	0.999	27	(100)	57	(96.6)	0.999	13	(92.9)	18	(94.7)	0.999	14	(93.3)	16	(94.1)	0.999
	Yes	0	(0)	4	(1.7)		0	(0)	2	(1.8)		0	(0)	2	(3.4)		1	(7.1)	1	(5.3)		1	(6.7)	1	(5.9)	
Cardiac problem	*No*	59	(96.7)	123	(93.9)	0.508	37	(94.9)	69	(95.8)	0.999	26	(96.3)	38	(100)	0.415	11	(78.6)	13	(92.9)	0.596	15	(100)	11	(73.3)	0.100
	Yes	2	(3.3)	8	(6.1)		2	(5.1)	3	(4.2)		1	(3.7)	0	(0)		3	(21.4)	1	(7.1)		0	(0)	4	(26.7)	
Sepsis	*No*	60	(98.4)	125	(95.4)	0.434	37	(94.9)	70	(95.9)	0.999	27	(100)	38	(100)	-	14	(100)	13	(100)	-	13	(86.7)	12	(80)	0.999
	Yes	1	(1.6)	6	(4.6)		2	(5.1)	3	(4.1)		0	(0)	0	(0)		0	(0)	0	(0)		2	(13.3)	3	(20)	
Thrombotic event	*No*	59	(96.7)	127	(96.9)	0.999	39	(100)	70	(95.9)	0.550	27	(100)	35	(92.1)	0.260	12	(85.7)	13	(100)	0.481	15	(100)	15	(100)	-
	Yes	2	(3.3)	4	(3.1)		0	(0)	3	(4.1)		0	(0)	3	(7.9)		2	(14.3)	0	(0)						
ITU admission	*No*	11	(18)	44	(18.2)	0.978	4	(10.3)	33	(29.7)	0.017	5	(18.5)	8	(13.6)	0.551	4	(28.6)	4	(21.1)	0.695	4	(26.7)	2	(11.8)	0.383
	Yes	50	(82)	198	(81.8)		35	(89.7)	78	(70.3)		22	(81.5)	51	(86.4)		10	(71.4)	15	(78.9)		11	(73.3)	15	(88.2)	

Denominator for maternal mortality and ITU admission is atony n=303; abnormally invasive placenta n=151; trauma n=86; abruption n=33; other n=32.
Denominator for other maternal morbidities have excluded the Netherlands. Denominator is atony n=192; abnormally invasive placenta n=112; trauma n=65; abruption n=29 and other n=30. Missing excluded from percentage.

3.4.5 Pooled comparison analyses

3.4.5.1 Haematological parameters in a pooled comparison

The haematological parameters among women with each aetiology of haemorrhage in a pooled comparison are presented in Table 29. There was no statistically significant difference between aetiology of MOH and haemoglobin (at worst), platelets or coagulation parameters (PT/aPTT) at either diagnosis or worst value (P>0.01). However, fibrinogen did differ by aetiology, the median fibrinogen value at diagnosis was significantly lower for women with abruption compared to other causes of haemorrhage (0.8g/L (IQR: 0.6-1.8) vs. 2.1g/L (IQR: 1.4-3.0), P<0.001). Similarly, fibrinogen value at worst was significantly lower for women with abruption compared to other causes (median: 0.6g/L (IQR: 0.6-1.8) vs. 1.4g/L (IQR: 1-2), P<0.001).

Across all causes there was a large reduction in the platelet count at diagnosis to platelet count at worst (median at diagnosis: $140x10^9$ (IQR: 104-191) to median at worst: $68x10^9$ (IQR: 47-92)). There was only a small increase in the median clotting time across all causes with a 2 second increase in PT from diagnosis to worst and 8 seconds in aPTT. The fibrinogen level was low at diagnosis of haemorrhage with a median of 2.1g/L (IQR: 1.4-3.0) in all causes except abruption where it was even lower.

3.4.5.2 Haematological management in a pooled cohort

The use of blood components and haemostatic agents according to the aetiology of haemorrhage are presented in Table 30. The use of RBC, FFP and platelets did not statistically differ according to aetiology, P>0.01. The majority of women received a source of concentrated fibrinogen, the highest proportion receiving fibrinogen was in those women with an abruption (76%) and the lowest usage were in bleeds caused by atony (52%). Use of factor VIIa differed according to aetiology, it was highest in the 'other' causes group (28%), although these differences were not statistically significant. Similarly, the use of TXA differed according to the cause of haemorrhage, 63% of women received TXA in the atony group and 46% of women received the antifibrinolytic in the abruption group, although this difference was not statistically significant (P>0.01). There was consistently high use of colloid and crystalloid across all causes of haemorrhage.

Table 29. Haematological parameters by aetiology of PPH in combined analysis.

Haematological management		Atony		Abnormal placentation		Trauma		Abruption		Other		P-value	All causes	
Haemoglobin at diagnosis (g/L)	*Mean (S.D.)*	97.7	(23.3)	93.5	(22.8)	90.8	(23.7)	88.7	(22.0)	87.9	(19.0)	0.003	95.1	(23.2)
Worst value of haemoglobin (g/L)	*Mean (S.D.)*	62.9	(16.0)	67.9	(19.1)	63.9	(18.2)	61.8	(11.2)	68.4	(15.5)	0.092	65	(17.0)
Platelets at diagnosis (x10^9/L)	*Median (IQR)*	142	(107.0-188.0)	131	(95.0-186.0)	147	(109.0-195.0)	153	(111.0-181.0)	135	(104.5-188.5)	0.463	140	(104.0-191.0)
Platelets worst (x10^9/L)	*Median (IQR)*	65	(49.0-90.5)	67.5	(43.0-93.0)	73	(48.0-99.0)	68.5	(45.5-85.0)	59	(38.5-97.5)	0.911	68	(47.0-92.0)
PT at diagnosis (sec)	*Median (IQR)*	13.5	(11.0-15.3)	13	(11.1-15.2)	13	(11.0-16.0)	14.5	(12.8-19.0)	14.1	(12.1-19.0)	0.230	13.4	(11.3-15.7)
PT at worst (sec)	*Median (IQR)*	16	(13.4-20.1)	15	(12.4-19.0)	14.8	(13.0-19.6)	18.5	(15.0-24.7)	16.8	(13.8-29.0)	0.126	15.6	(13.4-20.0)
APTT at diagnosis (sec)	*Median (IQR)*	33.5	(30.0-42.0)	34	(29.0-42.0)	34	(28.0-44.0)	36.1	(31.0-49.0)	33.5	(30.0-45.0)	0.642	34	(29.2-42.0)
APTT at worst (sec)	*Median (IQR)*	43	(37.0-58.5)	42	(33.1-50.0)	43.1	(35.0-56.0)	44.5	(41.0-81.0)	39	(26.0-74.0)	0.329	42	(35.0-57.0)
Fibrinogen at diagnosis (g/L)	*Median (IQR)*	2.1	(1.3-2.9)	2.1	(1.5-2.8)	2.3	(1.6-3.4)	0.8	(0.6-1.8)	1.9	(1.3-3.4)	<0.001	2.1	(1.4-3.0)
Fibrinogen at worst (g/L)	*Median (IQR)*	1.4	(1.0-1.9)	1.4	(1.1-2.1)	1.6	(1.0-2.2)	0.6	(0.4-1.4)	1.3	(0.9-2.3)	<0.001	1.4	(1.0-2.0)

Abnormal placentation group includes: abnormally invasive placenta, placenta praevia and retained placenta. Trauma groups includes: rupture and genital tract lacerations, tears and surgical wounds. Italy only included in haemoglobin.

Table 30. Haematological management by aetiology of PPH in a pooled analysis including all countries.

Blood products		Atony n=303	Abnormal placentation n=151	Trauma n=86	Abruption n=33	Other n=33	P-value*	All causes
Number of RBC units	*Median (IQR)*	10 (8-13)	11 (9-14)	10 (9-14)	10 (8-12)	10 (8-12)	0.227	10 (8-13)
FFP	*Median (IQR)*	6 (4- 8)	6 (4- 8)	6 (4- 8)	7 (4-12)	6 (4-12)	0.169	6 (4-8)
Platelets	*Median (IQR)*	1 (1- 2)	2 (1- 2)	1 (1- 2)	2 (1- 3)	1 (0- 3)	0.521	1 (1-2)
Source of concentrated fibrinogen	*No*	144 (47.7)	62 (41.6)	39 (45.3)	8 (24.2)	11 (33.3)	0.066	264 (43.8)
	Yes	158 (52.3)	87 (58.4)	47 (54.7)	25 (75.8)	22 (66.7)		339 (56.2)
Fibrinogen concentrate	*No*	203 (67.4)	100 (68)	56 (67.5)	20 (60.6)	20 (60.6)	0.859	399 (66.8)
	Yes	98 (32.6)	47 (32)	27 (32.5)	13 (39.4)	13 (39.4)		198 (33.2)
Cryoprecipitate	*No*	21 (25.6)	15 (26.8)	15 (42.9)	3 (16.7)	7 (41.2)	0.174	61 (29.3)
	Yes	61 (74.4)	41 (73.2)	20 (57.1)	15 (83.3)	10 (58.8)		147 (70.7)
Factor VIIa	*No*	240 (86.3)	118 (90.1)	67 (87)	27 (93.1)	21 (72.4)	0.108	473 (86.9)
	Yes	38 (13.7)	13 (9.9)	10 (13)	2 (6.9)	8 (27.6)		71 (13.1)
Tranexamic acid	*No*	103 (37.2)	59 (45)	33 (42.9)	15 (51.7)	17 (58.6)	0.109	227 (41.8)
	Yes	174 (62.8)	72 (55)	44 (57.1)	14 (48.3)	12 (41.4)		316 (58.2)
Colloid	*No*	18 (7.1)	10 (8.8)	6 (8.5)	4 (14.3)	3 (11.5)	0.703	41 (8.4)
	Yes	235 (92.9)	103 (91.2)	65 (91.5)	24 (85.7)	23 (88.5)		450 (91.6)
Crystalloid	*No*	4 (1.8)	1 (1)	1 (1.5)	1 (3.8)	4 (16.7)	0.006	11 (2.5)
	Yes	219 (98.2)	101 (99)	66 (98.5)	25 (96.2)	20 (83.3)		431 (97.5)

*Comparing blood products across aetiology.

3.4.5.3 Obstetric management in a pooled comparison

3.4.5.3.1 Medical management

The obstetric management according to the aetiology of haemorrhage is presented in Table 31. The overall proportion of women given uterotonics or prostaglandins was 94% in every cause of haemorrhage. A high proportion of women with atonic bleeds received uterotonics or prostaglandins compared with those women who had abruption related haemorrhage (97% vs. 87%). Any medical management appeared to differ statistically according to aetiology.

3.4.5.3.2 Surgical management

The proportion of women undergoing hysterectomy was just over a third for every cause excluding abnormal placentation where over two thirds of women had a hysterectomy. Intrauterine balloons were used more in atony (64%) than other causes of haemorrhage (51%). Uterine compression sutures had a higher use in atonic bleeds than other causes (28% vs. 21%). Embolisation was used more commonly in women with bleeds caused by atony, abnormal placentation and trauma than women with bleeds caused by abruption or other causes (40% vs. 20%). This difference between aetiology and surgical management was statistically significant.

3.4.5.4 Maternal outcomes in a pooled comparison

The pooled comparison of maternal outcomes according by aetiology of haemorrhage is presented in Table 32. Maternal case fatality was not statistically significantly different by aetiology of haemorrhage. However, a larger proportion of women with abruption as a cause of haemorrhage died compared to all causes (6% vs. 2%, P>0.01). There were more cardiac arrests in the abruption group than all other causes (14% vs. 6%). Thrombotic events appeared to be equally distributed amongst the causes groups at 3%. There was a very high frequency of admission to an ITU at approximately 80% across all causes. However overall, there were no statistically significant differences between the outcomes and aetiology (P>0.01).

Table 31. Obstetric management by aetiology of PPH in a pooled analysis including all countries.

		Atony n=303		Abnormal placentation n=151		Trauma n=86		Abruption n=33		Other n=33		P-value	All causes	
Medical management														
Oxytocin	*No*	50	(20.2)	35	(27.6)	23	(29.9)	6	(20.7)	4	(17.4)	0.282	118	(23.4)
	Yes	198	(79.8)	92	(72.4)	54	(70.1)	23	(79.3)	19	(82.6)		386	(76.6)
Ergometrine	*No*	130	(66)	69	(71.9)	38	(66.7)	10	(50)	10	(50)	0.196	257	(65.9)
	Yes	67	(34)	27	(28.1)	19	(33.3)	10	(50)	10	(50)		133	(34.1)
Prostaglandin	*No*	35	(14.2)	54	(42.5)	29	(37.7)	10	(37)	10	(43.5)	<0.001	138	(27.5)
	Yes	212	(85.8)	73	(57.5)	48	(62.3)	17	(63)	13	(56.5)		363	(72.5)
Misoprostol	*No*	138	(55.6)	103	(81.7)	53	(68.8)	19	(70.4)	13	(56.5)	<0.001	326	(65.1)
	Yes	110	(44.4)	23	(18.3)	24	(31.2)	8	(29.6)	10	(43.5)		175	(34.9)
Any medical management	*No*	8	(3)	11	(8.4)	8	(9.9)	4	(13.3)	2	(7.1)	0.031	33	(6.1)
	Yes	262	(97)	120	(91.6)	73	(90.1)	26	(86.7)	26	(92.9)		507	(93.9)
Surgical management														
Intrauterine balloons	*No*	108	(35.6)	87	(58)	58	(67.4)	21	(67.7)	22	(66.7)	<0.001	296	(49.1)
	Yes	195	(64.4)	63	(42)	28	(32.6)	10	(32.3)	11	(33.3)		307	(50.9)
Intra-abdominal packing	*No*	123	(90.4)	79	(88.8)	50	(90.9)	20	(87)	17	(77.3)	0.454	289	(88.9)
	Yes	13	(9.6)	10	(11.2)	5	(9.1)	3	(13)	5	(22.7)		36	(11.1)
Embolisaton or ligation	*No*	184	(60.7)	94	(62.3)	49	(57)	27	(81.8)	26	(78.8)	0.032	380	(62.7)
	Yes	119	(39.3)	57	(37.7)	37	(43)	6	(18.2)	7	(21.2)		226	(37.3)
Uterine compression sutures	*No*	218	(71.9)	134	(89.3)	72	(83.7)	27	(84.4)	26	(78.8)	<0.001	477	(79)
	Yes	85	(28.1)	16	(10.7)	14	(16.3)	5	(15.6)	7	(21.2)		127	(21)
Hysterectomy	*No*	183	(60.4)	46	(30.5)	55	(64)	20	(62.5)	21	(63.6)	<0.001	325	(53.7)
	Yes	120	(39.6)	105	(69.5)	31	(36)	12	(37.5)	12	(36.4)		280	(46.3)

Table 32. Maternal outcomes by aetiology of haemorrhage in a pooled analysis including all countries.

Maternal outcome		Atony		Abnormal placentation		Trauma		Abruption		Other		P-value	All causes	
Maternal death	*No*	299	(98.7)	149	(98.7)	84	(97.7)	31	(93.9)	31	(93.9)	0.096	594	(98)
	Yes	4	(1.3)	2	(1.3)	2	(2.3)	2	(6.1)	2	(6.1)		12	(2)
Cardiac arrest	*No*	182	(94.8)	106	(95.5)	64	(98.5)	24	(85.7)	27	(87.1)	0.049	403	(94.4)
	Yes	10	(5.2)	5	(4.5)	1	(1.5)	4	(14.3)	4	(12.9)		24	(5.6)
Infection	*No*	185	(96.4)	107	(95.5)	65	(100)	27	(100)	26	(83.9)	0.012	410	(96)
	Yes	7	(3.6)	5	(4.5)	0	(0)	0	(0)	5	(16.1)		17	(4)
Thrombotic event	*No*	186	(96.9)	109	(97.3)	62	(95.4)	25	(92.6)	31	(100)	0.512	413	(96.7)
	Yes	6	(3.1)	3	(2.7)	3	(4.6)	2	(7.4)	0	(0)		14	(3.3)
ITU admission	*No*	55	(18.2)	37	(24.7)	13	(15.1)	8	(24.2)	6	(18.2)	0.352	119	(19.7)
	Yes	248	(81.8)	113	(75.3)	73	(84.9)	25	(75.8)	27	(81.8)		486	(80.3)

3.4.6 Exploratory analysis: haematological management association with maternal outcomes

The odds ratios of hysterectomy and death according to the use of blood components and haemostatic agents is presented in Table 33. A one unit increase in RBC was associated with a 13% increase in the adjusted odds of hysterectomy and/or death (adjusted odds ratio aOR: 1.13 (95%CI:1.08-1.18); the adjusted odds of hysterectomy and/or death increased by 9% per unit increase of FFP (aOR:1.09 (95%CI: 1.02-1.17); there was an 12% increase in the odds of hysterectomy and death for a one unit increase in platelets (aOR: 1.12 (95%CI:1.04-1.21). There was no statistically significant evidence of an association between hysterectomy and/or death with the use of crystalloids, colloids, tranexamic acid and fibrinogen concentrate.

Table 33. Odds ratios with 95% confidence intervals of hysterectomy and/or death for blood components and haemostatic agents given.

		No hysterectomy or death n=332		Hysterectomy or death n=287		Unadjusted Odds Ratio	95% Confidence interval	P-value	Adjusted odds ratio**	95% Confidence interval *	P-value
Red blood cells	*Median (IQR)*	10	(8-12)	11	(9-15)	1.12	(1.07-1.17)	<0.001	1.13	(1.08-1.18)	<0.001
FFP	*Median (IQR)*	6	(4- 8)	6	(4-10)	1.09	(1.01-1.17)	0.019	1.09	(1.02-1.17)	0.016
Platelets	*Median (IQR)*	1	(1- 2)	2	(1- 3)	1.12	(1.04-1.19)	0.001	1.12	(1.04-1.21)	0.004
Source of concentrated fibrinogen n(%)	Not used	154	(47.2)	114	(39.9)	1			1		
	Used	172	(52.8)	172	(60.1)	1.35	(0.85-2.16)	0.208	1.31	(0.86-2.01)	0.206
Tranexamic acid use n(%)	Not used	120	(40.3)	111	(43.9)	1			1		
	Used	178	(59.7)	142	(56.1)	0.86	(0.47-1.58)	0.633	0.82	(0.48-1.40)	0.475
Colloid n(%)	Not used	28	(9.7)	13	(6.1)	1			1		
	Used	262	(90.3)	200	(93.9)	1.64	(0.47-5.70)	0.433	1.76	(0.62-5.01)	0.289
Crystalloid n(%)	Not used	6	(2.4)	6	(3)	1			1		
	Used	244	(97.6)	191	(97)	0.78	(0.40-1.55)	0.482	0.78	(0.43-1.43)	0.426

*robust estimates of variance were calculated to account for clustering via countries **adjusted for age and parity

3.5 Discussion

3.5.1 Main methodological findings

This chapter has illustrated that a uniform case definition can be achieved across different multinational studies to facilitate the examination of massive transfusion in MOH.

3.5.1.1 Cross-country comparison

A multinational study has enabled the comparative analysis of haematological management and obstetric management across countries. This work has highlighted that despite the same evidence being available to clinicians and guideline writers, each country has its own clinical management approach. Furthermore, it has allowed the detailed examination of different haematological management and their potential impact on outcomes. Despite differences in the use of blood components and haemostatic agents there did not appear to be differences in maternal outcomes across countries. Even in a study across five countries, adverse outcomes were rare and this limited the power to detect as statistically significant some of the clinically important differences suggested by the analysis.

3.5.1.2 Replication

Multiple population-based studies across different countries allowed the replication of findings from previous smaller studies. Across all causes of haemorrhage, prothrombin time remained close to normal while fibrinogen was low in all causes. In particular, the observed haematological parameters in the United Kingdom were replicated in Australia, the Netherlands and France.

3.5.1.3 Pooled analyses

The combination of studies examining massive transfusion has allowed a pooled analysis stratified by aetiology of PPH. This showed that despite differences in haemostatic features by aetiology there did not appear to be any differences in the use of blood components or haemostatic agents or maternal outcomes.

3.5.2 Clinical utility of the chapter

Haemostatic features differed according to aetiology of haemorrhage; the lowest values of fibrinogen were in abruption, and trauma had the highest values of platelet count and fibrinogen. This suggests that use of blood products should be tailored to the cause of haemorrhage. The main blood components administered (RBC, FFP and platelets) did not differ according to aetiology. However, women with abruption received a greater amount of fibrinogen, which is reassuring since they had the lowest fibrinogen values. Despite differences in haemostatic management, maternal outcomes across countries did not appear to materially differ. Even with the pooling of five large population-based studies, numbers were too small to assess difference in maternal morbidities and mortality by aetiology of haemorrhage. Nevertheless, the proportion of women undergoing hysterectomy varied, in particular and not surprisingly, women with abnormal placentation had double the proportion of hysterectomies compared to women with other causes of haemorrhage.

3.5.2.1 Haematological management

This study has shown international variation in the use of blood components and haemostatic agents. Previous research has illustrated that guidelines for the blood management of haemorrhage varies by country and by medical speciality (Shaylor et al., 2017). Consequently, it is not surprising that clinical practice and use of blood

components differed by country. The key differences were variations in the use of fibrinogen concentrate and tranexamic acid.

3.5.2.2 Haematological management and outcomes

Although the use of blood components and haemostatic agents varied between countries this did not appear to be reflected in differing maternal or perinatal outcomes across countries. Furthermore, even though there was no tailored haematological management according to aetiology, there did not appear to be differences in the outcomes that were assessed across aetiologies. However, very few women died so this study is limited in its ability to assess this with certainty.

3.5.2.2.1 Replications of haematological parameters

The results across all countries replicated the findings from the United Kingdom study (Collis and Collins, 2015). Previous research has shown that fibrinogen drops to lower values sooner than other haemostatic features (de Lloyd et al., 2011). A number of studies have shown that a low fibrinogen is predictive of severe PPH, while PT and aPTT remain normal and unsensitised to further bleeding (Charbit et al., 2007, de Lloyd et al., 2011, Collins et al., 2014, Simon et al., 1997). Collis and Collins (2015), combined over 1700 women from five studies and showed that a baseline clauss fibrinogen of <3 g/L and <2g/L was predictive of severe PPH while >4g/L was not. The findings from this study are consistent with previous research, which found that the initial coagulation test fibrinogen was low at 2 g/L compared to the normal pregnancy values (4-6g/L), and PT and aPTT were only marginally elevated. This result emphasises the importance of the administration of fibrinogen as it appears to more sensitive to major haemorrhage than other haemostatic factors.

3.5.2.2.2 Haematological parameters by aetiology

The haematological findings by aetiology from this international study were consistent with previous research. Fibrinogen levels tended to be lower in women with abruption compared to other causes of haemorrhage (Collins et al., 2014) and women with haemorrhage caused by trauma had a higher platelet count and fibrinogen levels compared to other causes. Confirming known findings that consumption of coagulation factors differs according to aetiology (Collins et al., 2014). This result has important implications for practice as it can be argued that haematological management should mirror the coagulopathic changes during haemorrhage (Collins et al., 2014, Allard et al., 2014, Hunt et al., 2015).

3.5.2.3 Exploratory analysis of blood components and maternal outcomes

This study showed that increased use of blood components such as red blood cells, fresh frozen plasma and platelets were associated with increased odds of death and/or hysterectomy. This result is likely to reflect the severity of the haemorrhage, as those with poor outcomes such as hysterectomy and/or death were likely to require more blood products.

3.5.3 Limitations and issues with observational research in transfusion medicine

This analysis should be interpreted in the context of the limitations. Observational studies examining the association between haematological management and outcomes are prone to indication bias i.e. those who received an intervention appear to have worse outcomes (Del Junco et al., 2013) and this is reflected in the relationship between the use of blood components and poor outcomes. This analysis was also susceptible to survival bias, as those women who died or had a hysterectomy before they received 8 units of RBC would not have been included in the study population.

However, whilst bearing these limitations in mind there are important messages from the findings.

Transfusion research is difficult to conduct due to the time varying element of the treatment and coagulation tests. For example, patients who received the same number of units within 24hr may differ according to the acuteness of the bleed i.e. someone who is transfused 8 units within an hour would be very different to a patient who received 8 units over 24 hours.

To overcome these limitations and to prevent survival bias, future studies should either define this population as ‘any women who required the activation of a massive transfusion protocol’ or use a composite of inclusion criteria, which would include death from haemorrhage related causes, received several RBC units in a short period of time or received a threshold number of units of RBC. Furthermore, time varying treatment bias can be prevented by documenting timings of each blood product given (Del Junco et al., 2013).

It is known that laboratories have different reference ranges for haematological parameters. This may be the result of differences in characteristics between populations such as gender or age (Lugada et al., 2004, Wakeman et al., 2007). However, differences in reference ranges may be the result of variations in procedures between laboratories that process blood such as transportation time, the time take to process the sample, (Kristal et al., 2005) and storage temperature (van Balveren et al., 2017). In countries that provided haematological data, there was no difference between the ages of women with massive transfusion. Nevertheless, information on transportation times and temperature of storage was not available, as a consequence, these variations could not be accounted for in the analysis. There may be variations in

reference ranges between laboratories within countries, however, it cannot be determined whether these variations in reference ranges were different between countries.

This study was unique in its ability to compare who had all been transfused at least their total blood volume or more. These findings have a number of strengths: first, a comparative analysis across countries using a uniform case definition was completed; second, a pooled analysis with a meaningful number of women allowed the aetiology of PPH to be compared by management and outcomes; third, this multinational study replicated the findings across nations.

3.6 Conclusion

Large multinational studies of rare exposures and rare outcomes can be carried out and they allow in depth comparisons of different management approaches across countries. In particular, in this case, despite women having similar haematological features and causes of haemorrhage across countries, there did not appear to be a consistent use of blood products or haemostatic agents across countries. The use of blood products and haemostatic agents varied significantly between countries and did not appear to be evidence based. Furthermore, this multinational study enabled a pooled analysis, which described different clinical phenotypes of women that bleed. In this case, haematological features varied according to the aetiology of the haemorrhage, yet, the use of blood components did not appear to vary according the aetiology. Consequently, future research into obstetric haemorrhage should take into consideration the aetiology of the haemorrhage when examining its management.

Chapter 4. An uncommon modality of management in a rare and severe complication of pregnancy: abnormally invasive placenta

4.1 Introduction

4.1.1 Chapter in context

4.1.1.1 Randomised controlled trials and observational evidence

In emergency situations during delivery it may be difficult to conduct a randomised controlled trial (RCT) because of ethical and practical considerations. If ethical considerations of obtaining consent in an emergency can be overcome, it remains extremely challenging to conduct RCTs in emergency situations where the obstetric condition is rare. This is because of the small number eligible participants that would be distributed in a large geographic area. As a result, most guidelines and recommendations are based upon evidence derived from observational studies.

Observational evidence that uses retrospective data may be prone to a number of limitations such as information bias and indication bias when considering differences in management. When using routine data sources there is a particular concern over whether included cases are true cases due to the limited ability to check medical records to ensure correct case definitions are met. Bespoke case notification and data collection systems of rare and severe complications of pregnancy are designed to overcome these limitations (Kayem et al., 2013, Knight et al., 2005, Knight and INOSS, 2014).

4.1.1.2 Management of severe complications in pregnancy

The previous chapter on massive transfusion illustrated that haematological and obstetric management of major obstetric haemorrhage varies between countries. In addition, it demonstrated that obstetric management, including surgical approaches, should be guided by the cause of haemorrhage (Belghiti et al., 2011, Mavrides et al., 2016). However, many of these causes of major haemorrhage are individually rare, and for reasons discussed above, it is difficult to conduct RCTs during the intrapartum period. As a result, the evidence for optimal management of these severe complications is limited. This is the case for major haemorrhage caused by abnormally invasive placenta (AIP). AIP is a placenta that that does not detach physiologically and cannot be removed manually without causing severe bleeding (Chantraine and Langhoff-Roos, 2013). Conservative management for AIP is used infrequently with hysterectomy being the preferred approach. However, there is a lack of high quality evidence comparing the modalities of management due the rarity of AIP and the uncommon use of conservative management.

4.1.1.3 International variation in guidelines

Despite the lack of high quality evidence there are guidelines for the management of AIP (American College of Obstetricians and Gynecologists, 2006, Sentilhes et al., 2018, Royal College of Obstetricians and Gynaecologists, 2011, Silver and Branch, 2018). These guidelines are based off expert opinion and provide a pragmatic approach to managing AIP; however, these guidelines vary in terms of the recommendations given. Many of the guidelines recommend that peripartum hysterectomy is the primary management for women with AIP (American College of Obstetricians and Gynecologists, 2006, Royal College of Obstetricians and Gynaecologists, 2011, Silver

and Branch, 2018, American College of Obstetricians Gynecologists, 2012). However, the guidelines do allow for a conservative approach to be taken if the women has a strong preference for preserving her fertility and is consulted about the subsequent risks of sepsis and secondary hysterectomy. The International Federation of Gynecology and Obstetrics (FIGO) have offered two guidelines on both the non-conservative approach (hysterectomy) and the conservative approaches that aim to preserve the uterus (Sentilhes et al., 2018, Allen et al., 2018). The variation between the two FIGO guidelines has illustrated that the question over the optimal management for abnormally invasive placenta remains unanswered.

4.1.2 International variation in management approaches to abnormally invasive placenta (AIP)

Despite peripartum hysterectomy being the preferred treatment for AIP, there is international variation in its use in clinical practice; for example, 66% of women who required a massive transfusion as a result of AIP underwent a hysterectomy in the Netherlands (Ramler et al., 2017). Whereas, in the United Kingdom, 93% of women who had a massive transfusion for AIP had a hysterectomy compared to 6-76% of women with other causes of haemorrhage (Green et al., 2016b). Thus, the primary management for AIP in the United Kingdom is peripartum hysterectomy (Royal College of Obstetricians and Gynaecologists, 2011).

Chapter three that examined massive transfusion showed that France has a much lower hysterectomy rate in women with AIP than the United Kingdom for all causes. It also showed that women with AIP were transfused a significantly higher amount of units of RBC in the UK than in France, the Netherlands and Australia than other causes of PPH. A case series of 167 women with AIP from a number of tertiary centres in France highlighted that conservative management is increasing and was used in 25% of women with AIP in 2007 (Sentilhes et al., 2010a). Accordingly, the literature suggests that French obstetricians are more willing to undertake a uterus conserving approach than United Kingdom obstetricians. This variation offers an opportunity to study and compare the outcomes from two countries with contrasting approaches to managing AIP to inform future guidelines. In addition, if the populations of both countries were similar this would allow the pooling of data to provide a means to explore this uncommon modality of management in a rare complication of pregnancy.

4.2 Aim and objectives

Aim

To investigate the utility of data from two countries to examine an uncommon management approach to a rare and severe complication of pregnancy: abnormally invasive placenta

Objectives

1. To create a uniform set of cases by harmonising the case definition of the studies completed in the United Kingdom and France.
2. To compare the epidemiology, characteristics, management and outcomes of women with abnormally invasive placenta in France and the United Kingdom.
3. To undertake a pooled analysis to compare a planned conservative management to a planned hysterectomy.

4.3 Methods

4.3.1 Study population

This was an international population-based study of abnormally invasive placenta using secondary data analysis of two population-based cohort studies from the United Kingdom and France. The data were collected nationally in the United Kingdom and from a number of regions within France. Data were prospectively collected using a national obstetric surveillance system in the UK (UKOSS) and a prospective cohort study in France (PACCRETA).

4.3.2 Case definition

Abnormally invasive placenta was defined as a placenta accreta/increta/percreta that was either diagnosed histologically after a hysterectomy, or at post-mortem or was an abnormally adherent placenta that required active management including a conservative approach where the placenta was left in situ. Women who had a difficult manual delivery of the placenta but did not require active management were not included in the study as there was no evidence to confirm AIP.

4.3.3 UKOSS

The United Kingdom data were collected using the UKOSS system and the UKOSS methods have been previously described (Knight et al., 2005). In brief, women meeting the case definition were identified nationally in the United Kingdom during the period of May 2010 to April 2011. Women with abnormally invasive placenta were identified using the case definition shown in Box 3. Anonymised data were collected using a paper data collection form and a nominated reporter in each hospital completed this form using the woman's hospital records. The UKOSS data have been published previously (Fitzpatrick et al., 2014a, Fitzpatrick et al., 2012).

Box 3. Case definitions from the respective studies.

UKOSS study case definition	PACCRETA study case definition
Women were included as having abnormally invasive placenta if they met either of the following criteria: **1.** Placenta accreta/increta/percreta diagnosed histologically following hysterectomy or postmortem. **Or** **2.** An abnormally adherent placenta, **requiring active management**, including conservative approaches where the placenta is left in situ. **Excluded** women who had a manual placental removal with minimal or moderate difficulty but required no additional active management. **Active management:** this is when some other manipulation is required to remove the placenta and the placenta can only be partially removed or is removed piecemeal with clear documentation that the clinician did not feel it was fully removed.	The diagnosis of placenta accreta, increate, percreta was made if at least one of the following clinical and histological criteria were met: **1.** Manual delivery of the placenta impossible or incomplete with partial or total absence of a plane of cleavage between the placenta and the myometrium. **2.** Massive bleeding of the site of placental insertion after difficult manual delivery of the placenta. **3.** Histologic confirmation of the placentation anomaly from the hysterectomy (uterine) or placental specimens. **4.** Prenatal diagnosis of placenta accreta confirmed at delivery.
Harmonised definition for study	
Women were included as having abnormally invasive placenta if they met either of the following criteria: **1.** Placenta accreta/increta/percreta diagnosed histologically following hysterectomy or postmortem. **Or** **2.** An abnormally adherent placenta, **requiring active management**, including conservative approaches where the placenta is left in situ.	

4.3.4 PACCRETA

The methodology of the PACCRETA study has been described in the published protocol (Kayem et al., 2013). In summary, this population-based study identified women meeting the case definition, as shown in Box 3 , from 182 centres across in eight regions of France, where there were approximately 540,000 deliveries over the two-year study period. Each centre had a nominated clinician that identified women who met the case definition. In addition, delivery logs and electronic records were checked to maximise case ascertainment. Data collected from the medical records of each woman were entered onto a paper based data collection form.

4.3.5 Comparability of datasets

The PACCRETA data collection form was translated into English and all data items in the UKOSS date collection form were mapped to the PACCRETA data collection form. The characteristics, management and outcomes of interest were identified from the literature and if these were available and comparable between datasets they were extracted. For variables where there was a not a uniform definition, a common definition was generated. If this was not possible then the variable was excluded from the analysis.

4.3.5.1 Specific classification for variables

4.3.5.1.1 Exposure groups

The grading of abnormal invasive placenta (accreta, increta and percreta) was classified into two categories: placenta percreta and a category containing both placenta increta and accreta, on the basis these are largely indistinguishable clinically. Any history of uterine surgery was combined into a variable that included previous caesarean section, myomectomy, cavity breach, dilation and curettage, previous termination of pregnancy and evacuation of retained products of conception. Utertonics for treatment of haemorrhage contained misoprostol, ergometrine, syntocinon or prostaglandin.

4.3.6 Maternal and infant outcomes

Outcomes were explored for both mother and infant. The maternal outcomes were maternal death, postpartum infection, damage to the bowel, urinary tract or bladder and ITU admission. Blood loss was reported both as a continuous outcome and as two categorical variables: postpartum haemorrhage (≥1500mls) (Rath, 2011, Cameron, 2006, Coker and Oliver, 2012) and severe postpartum haemorrhage (≥2000mls)

(Schaap et al., 2017). Damage to the urinary tract, bowel or bladder was combined into one category. Infant outcomes included perinatal death, Apgar score less than 7 at five minutes and mean birthweight.

4.3.7 Missing data

Previous UKOSS studies have shown that the distribution of missing data was not at random. As a result, multiple imputation was not considered suitable (Lindquist et al., 2013). Complete case analysis was used for continuous variables except for blood loss, as those in France who did not have a diagnosed postpartum haemorrhage did not have a blood loss value. There was a variable to indicate if these women had an abnormal bleed and the median blood loss for women without an abnormal bleed was 500mls and this was assumed for these women.

4.3.8 Statistical analysis

4.3.8.1 Case selection

This study used methods similar to an individual patient data meta-analysis where each country was analysed individually then pooled together (Riley et al., 2010). A harmonised case definition was selected using the cases from the PACCRETA study that met the stricter UKOSS definition (see Box 3). The UKOSS definition did not include women who had a haemorrhage as a result of a manual removal of placenta, therefore, these women were removed from the study. In those who only met the fourth criteria of the PACCRETA study (antenatal diagnosis), their PACCRETA forms were checked to assess if they met the UKOSS definition. These cases were included if they had a placenta percreta or surgical management for haemorrhage which included a hysterectomy, conservative surgical management.

4.3.8.2 Descriptive analyses

The following statistical tests were used where appropriate: student's T-test, Wilcoxon rank-sum test, Kruskal-wallis test and chi square tests or the Fisher's exact test, if 20% of cells had a value of less than 5. A p-value <0.05 was used to determine statistical significance. Normality was assessed using histograms. Normally distributed continuous variables were presented as means with standard deviations and skewed continuous variables were presented as medians with interquartile ranges.

4.3.8.3 Between country analysis

The incidence of AIP was calculated per 10,000 deliveries according to the estimated number of deliveries that occurred during the study period. The confidence intervals were estimated using the exact binomial distribution.

A comparative analysis was undertaken in the AIP population comparing both differences between countries. The women's characteristics, medical history, obstetric and haematological management and perinatal and maternal outcomes were compared between France and the United Kingdom. Hypothesis testing was carried out to test for statistical difference between the United Kingdom and French AIP populations for each of the respective characteristics, haematological features, management and outcomes.

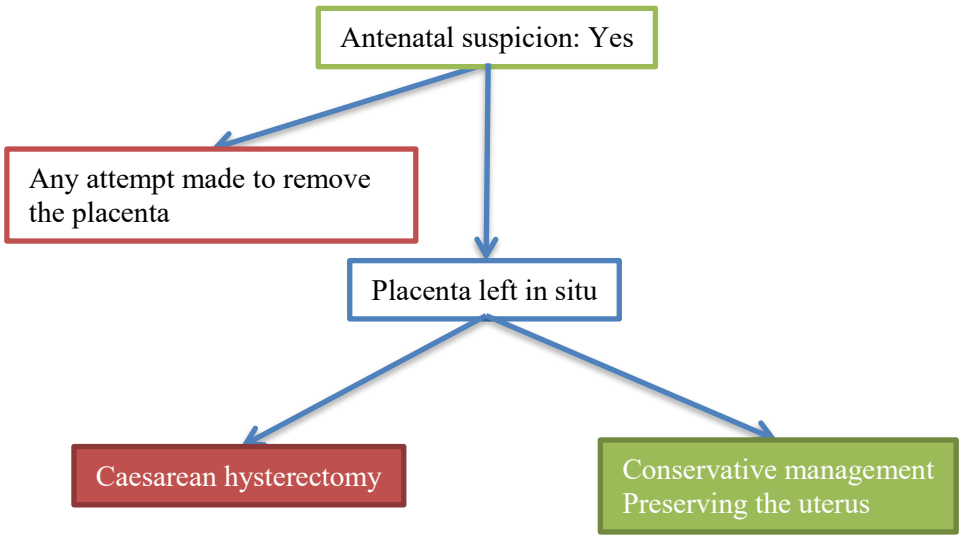
4.3.8.3.1 Exploratory analysis

A comparative analysis was undertaken in women who had an antenatal suspicion of AIP according to whether they had an attempted manual removal of placenta. Selected management and outcomes were compared between the United Kingdom and France. This analysis was undertaken to understand if some of the observed differences in outcomes were explained by an attempted manual delivery of placenta.

4.3.8.4 Pooled analysis

The comparison groups in the pooled analysis are shown in Figure 5. This analysis included a subgroup of women who had both an antenatal suspicion of AIP and no attempt to remove the placenta after delivery. The characteristics, management and maternal and infant outcomes were compared between women who had a planned hysterectomy and those who had their placenta left completely in situ with no planned hysterectomy.

Figure 5. Illustration of the comparison management.

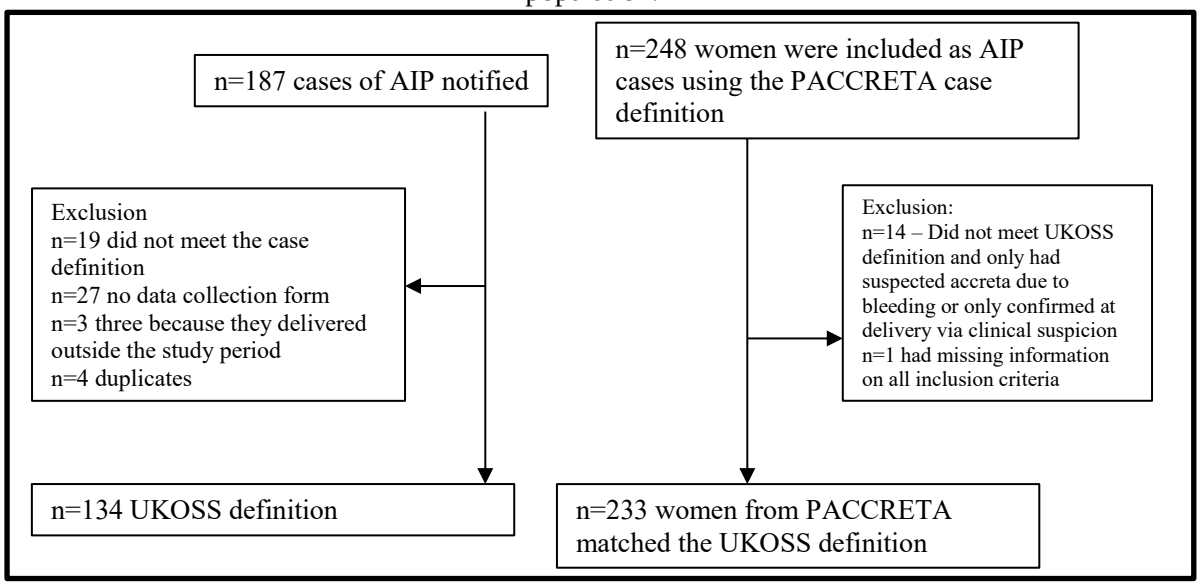


4.4 Results

4.4.1 Study population and incidence

The derived study population in the United Kingdom and France is shown in Figure 6. In the United Kingdom there were 134 women with abnormally invasive placenta who met the case definition during the period May 2010 to May 2011, in 798,634 deliveries. This gave an estimated incidence of AIP in 1.7 women per 10,000 maternities (95%CI: 1.4-2.0). After harmonisation of definitions, 233 women in the PACCRETA study met the same case definition over a two-year period in 2013-2015. In the PACCRETA study, 17 women were referred to centres included in the study from outside the population areas. They have been removed from the incidence estimate but included in the remainder of the analysis. During this period, the study population was drawn from 537, 794 women giving birth; this gave an estimated incidence of AIP of 4.0 women per 10,000 maternities (95% CI: 3.4-4.6).

Figure 6. Selection of women with AIP from each study to create a uniformly defined population.



4.4.2 Between-country analysis

4.4.2.1 Characteristics and previous pregnancy characteristics

The characteristics and previous pregnancy features of women with AIP according to country are presented in Table 34. In women with AIP the mean age at delivery was 34 years and approximately a fifth of women were obese in both the United Kingdom and France. There were no statistically significant differences between the mean age at delivery, proportion of obese women and proportion of women who smoked during pregnancy between the AIP cohorts in the United Kingdom and France. The United Kingdom cohort had a lower proportion of nulliparous women compared to the French cohort (9% vs. 17%), although this difference was not statistically significant.

In women who had AIP, the United Kingdom had a statistically significantly higher proportion of women with at least one previous caesarean section than France (93% vs. 79%), while France had a higher proportion of women who had other previous uterine surgery compared to the United Kingdom (42% vs. 29%), which was statistically significant. When these risk factors for AIP were combined into one variable, there was no statistically significant difference between the two countries; the majority of women had some form of previous uterine surgery.

4.4.2.2 Current pregnancy characteristics

The characteristics of the current pregnancy and of the AIP are presented in Table 35. In both the United Kingdom and France, two thirds of women with AIP had placenta praevia suspected prior to delivery and approximately a half of women had AIP suspected prior to delivery. There was no statistically significant difference in the grade of AIP between France and the United Kingdom; in women with AIP, 29% and 22% had a final diagnosis of placenta percreta in the United Kingdom and France, respectively.

Table 34. Characteristics of women with AIP in United Kingdom and France.

		United Kingdom n(%) n=134		France n(%) n=233		P-value	Comparability issues
Age mean (SD)		34.6	(5.6)	34.3	(5.0)	0.606	None
BMI category	*<25*	60	(45.8)	128	(56.4)		
	≥25-<30	42	(32.1)	51	(22.5)	0.093	
	≥30	29	(22.1)	48	(21.1)		
	Missing	3		6			
Smoking status	*Did not smoke during pregnancy*	107	(80.5)	176	(78.9)	0.730	
	Smoked during pregnancy	26	(19.5)	47	(21.1)		
	Missing	1		10			
Country of birth	*France*	-	-	91	(41.9)	-	No data from the United Kingdom
	Not France	-	-	126	(58.1)		
	Missing			16			
Ethnicity binary	*White*	99	(74.0)	-	-		
	Black and minority ethnic	34	(26.0)	-	-		
	Missing	1					
Parity	*Zero*	12	(9.0)	39	(16.7)		
	1	39	(29.1)	70	(30.0)	0.087	
	2+	83	(61.9)	124	(53.2)		
History of PPH							
	No	111	(91.0)	154	(79.4)	0.006	Specific question in France and extracted data from general question in UKOSS
	Yes	11	(9.0)	40	(20.6)		
	Not applicable (nulliparous)	12		39			
Previous caesarean section	*Zero*	9	(7.4)	40	(20.6)		
	1	63	(51.6)	85	(43.8)	0.007	
	2+	50	(41.0)	69	(35.6)		
	Not applicable (nulliparous)	12		39			
Previous uterine surgery excluding previous caesarean delivery	*No*	94	(70.7)	136	(58.4)	0.019	Includes: myomectomy, cavity breached, dilation & curettage, previous TOP, and ERPC
	Yes	39	(29.3)	97	(41.6)		
	Missing	1					
Any history of uterine surgery including caesarean section	*No*	5	(3.7)	16	(6.9)	0.213	
	Yes	129	(96.3)	217	(93.1)		

Table 35. Current pregnancy characteristics of women with AIP.

Current pregnancy		**United Kingdom n(%) n=134**		**France n(%) n=233**		**P-value**	**Comparability issues**
Hypertensive disorder during pregnancy	*No*	125	(95.4)	213	(91.4)	0.155	None
	Yes	6	(4.6)	20	(8.6)		
	Missing	3					
Placenta praevia suspected prior to delivery	*No*	47	(35.3)	81	(34.9)	0.935	None
	Yes	86	(64.7)	151	(65.1)		
	Missing	1		1			
Multiple pregnancy	*Yes*	4	(3)	9	(3.9)	0.776	None
	No	130	(97)	224	(96.1)		
Abnormally invasive placenta							
AIP suspected prior to delivery	*Yes*	66	(49.6)	118	(53.4)	0.492	None
	No	67	(50.4)	103	(46.6)		
	Missing	1		12			
AIP type	*Placenta accreta/ increta*	94	(70.7)	175	(78.5)	0.098	None
	Placenta percreta	39	(29.3)	48	(21.5)		
	*Conservative vaginal **			8			
	Missing	1		2			
Delivery and management		**United Kingdom n(%) n=134**		**France n(%) n=233**		**P-value**	**Comparability issues**
Termination of pregnancy	*No*	130	(98.5)	232	(99.6)	0.297	None
	Yes	2	(1.5)	1	(0.4)		
	Missing	2					
Planned caesarean delivery							None
	No	22	(16.7)	88	(37.8)	<0.001	
	Yes	110	(83.3)	145	(62.2)		
	Missing	2					
Gestational age at delivery							None
	<34 Weeks	23	(17.2)	44	(18.9)		
	≥34-<37	43	(32.1)	77	(33)	0.867	
	≥37	68	(50.7)	112	(48.1)		
Caesarean delivery							None
	Yes	118	(88.1)	198	(85.0)	0.411	
	No	16	(11.9)	35	(15.0)		

*Delivered vaginally and left part or all of the placenta in the uterus with no histology

4.4.2.3 Delivery and management of women with AIP

Approximately a half of women with AIP were delivered at less than 37 weeks of gestation and the majority of women had a caesarean delivery (88% vs. 85%, respectively) in both the United Kingdom and France (Table 35). A larger proportion of women had a planned caesarean delivery in the United Kingdom compared to France (83% vs. 62%, P<0.001). In those with an antenatal suspicion prior to delivery, a statistically significantly larger proportion of women had a planned caesarean section in the UK compared to France (97% vs. 87%, P=0.021).

The United Kingdom had a significantly larger proportion of women who had a hysterectomy compared to France (59% vs. 34%, P<0.001) (Table 36). In women who had a hysterectomy, approximately 90% of women had a hysterectomy within 48 hours in both the United Kingdom and France. The United Kingdom had a much lower proportion of women who had their placenta left in situ with 28% compared to 47% in France, which was statistically significantly different. In those who had their placenta left in situ there was no statistically significant difference in the proportion of women who had their placenta left completely in situ between the United Kingdom and France.

4.4.2.4 Surgical and haematological management of women with AIP

Other types of surgical and haematological management of women with AIP in the United Kingdom and France are presented in Table 37. In both countries, approximately 20% of women with AIP underwent embolisation. The United Kingdom had a statistically significantly higher proportion of use of uterine compression sutures and uterine balloon tamponade compared to France with 13% vs. 5% and 25% vs. 14%, respectively.

Approximately three quarters of women with AIP received a red blood cell (RBC) transfusion in the United Kingdom while a half of women received a RBC transfusion in France; this difference was statistically significantly different. In addition, women who received a RBC transfusion the United Kingdom had a higher median number of RBC units transfused compared to France (7 RBC units (IQR 4-12) vs. 3 RBC unit (IQR 0-6), respectively); this was statistically significantly different. The proportion of women receiving fresh frozen plasma and platelets in the United Kingdom was higher than France; these differences were statistically significant.

Table 36. Obstetric management of women with AIP in United Kingdom and France.

Medical management		**United Kingdom n(%) n=134**		**France n(%) n=233**		**P-value**	**Comparability issues**
Uterotonics used as treatment or prophylaxis*	*Not used*	25	(18.7)	61	(26.3)	0.097	None
	Used	109	(81.3)	171	(73.7)		
	Missing	0		1			
Management							
Hysterectomy	*Yes*	79	(59.0)	79	(33.9)	<0.001	None
	No	55	(41.0)	154	(66.1)		
Hysterectomy planned							
	Yes	38	(48.1)	11	(13.9)	<0.001	None
	No	41	(51.9)	68	(86.1)		
Time between delivery and hysterectomy							
	≤48hrs	73	(92.4)	73	(92.4)	0.999	None
	>48hrs	6	(7.6)	6	(7.6)		
No attempt to remove placenta at time of delivery							
	Attempt	102	(76.1)	132	(57.6)	<0.001	None
	No attempt	32	(23.9)	97	(42.4)		
Placenta left in situ	*Yes*	38	(28.4)	108	(47.2)	<0.001	None
	No	96	(71.6)	121	(52.8)		
	Unknown	0		4			
How much left in situ							
	Complete	26	(68.4)	58	(53.7)	0.114	None
	Partial	12	(31.6)	50	(46.3)		
Had hysterectomy after left in situ							
	No	18	(47.4)	77	(71.3)	0.008	None
	Yes	20	(52.6)	31	(28.7)		
Time between delivery and hysterectomy							None
	≤48hrs	15	(75.0)	25	(80.7)	0.632	
	>48hrs	5	(25.0)	6	(19.4)		
Methotrexate used							
	No	31	(81.6)	107	(100)	<0.001	None
	Yes	7	(18.4)	0	(0)		
	Missing			1			

* Use of misoprostol, ergometrine, Oxytocin or prostaglandin.

Table 37. Management of women with AIP in United Kingdom and France.

Management of haemorrhage		**United Kingdom n(%) n=134**		**France n(%) n=233**		**P-value**	**Comparability issues**
Embolisation	*Not used*	101	(75.4)	183	(78.5)	0.485	None
	Used	33	(24.6)	50	(21.5)		
Uterine artery ligation							
	Not used	132	(98.5)	219	(94)	0.060	None
	Used	2	(1.5)	14	(6)		
Iliac ligation artery							
	Not used	125	(93.3)	220	(94.4)	0.659	None
	Used	9	(6.7)	13	(5.6)		
Uterine compression sutures							
	Not used	116	(86.6)	221	(94.8)	0.005	None
	Used	18	(13.4)	12	(5.2)		
Uterine balloon tamponade							
	Not used	101	(75.4)	200	(85.8)	0.012	None
	Used	33	(24.6)	33	(14.2)		
Haematological management							Comparability issues
Whole blood or red blood cells received n (%)		102	(76.1)	115	(49.4)	<0.001	None
In women who received whole blood or red blood cells	*median (IQR) unit*	7	(4-12)	3	(0-6)	<0.001	
FFP received n (%)		69	(51.5)	91	(39.1)	0.021	None
In women who received FFP	*median (IQR) units*	4	(4-7)	2	(0-5)	0.031	
Platelets received n (%)		43	(32.1)	30	(12.9)	<0.001	
In women who received platelets	*median (IQR) units*	2	(1-2)	0	(0-1)	0.031	
Fibrinogen received e.g. cryoprecipitate or fibrinogen conc.	*Not used*	100	(74.6)	162	(69.5)	0.298	None
	Used	34	(25.4)	71	(30.5)		
Factor VIIa used	*No*	129	(96.3)	230	(98.7)	0.147	None
	Yes	5	(3.7)	3	(1.3)		

4.4.2.5 The maternal and infant outcomes of women with AIP

The maternal and infant outcomes for women with AIP are shown in Table 38. Only one woman died who had AIP and she was in the French cohort. The cause of death was haemorrhagic shock and the secondary factors that led to death were an attempted manual removal of the placenta and a failed embolisation. The median estimated blood loss for women with AIP was 3050 millilitres (mls) (IQR: 1700-6500 mls) in the United Kingdom while it was lower in France with a median of 1000 mls (IQR: 500-2500 mls), this difference was statistically significant. Approximately three quarters of women with AIP in the United Kingdom had a PPH ≥2000mls while there was only a third of women in France experienced this level of haemorrhage ($P<0.001$); this difference was statistically significant. There was a lower proportion of women in the United Kingdom with an infection than in France (2% vs. 6%), although this difference was not statistically significant. There were similar proportions of women who had either damage to their bowel, urinary tract or bladder in the United Kingdom and France. Between the two countries there were no statistically significant differences in any of the outcomes of infants born to women with AIP.

Table 38. Outcomes of women with AIP in United Kingdom and France.

Maternal outcomes		**United Kingdom n(%) n=134**		**France n(%) n=233**		**P-value**	**Comparability issues**
Woman died	*No*	134	(100)	232	(99.6)	0.999	None
	Yes	0	(0)	1	(0.4)		
Amount of blood loss*	*Median (IQR)*	3050	(1700-6500)	1000	(500-2500)	<0.001	France assumed a median value of 500mls to women who did not have documented PPH.
Postpartum haemorrhage							
	<1500 mls	25	(18.7)	130	(58.3)	<0.001	None
	≥1500 mls	109	(81.3)	93	(41.7)		
	Missing			10			
Severe postpartum haemorrhage	*<2000 mls*	37	(27.6)	152	(68.2)	<0.001	None
	≥2000 mls	97	(72.4)	71	(31.8)		
	Missing			10			
Post-delivery infection (excluding those who only had symptoms of fever)**	*No*	131	(97.8)	216	(94.3)	0.184	United Kingdom variable will only capture those with severe infection
	Yes	3	(2.2)	13	(5.7)		
	Missing	0		4			
Damage to bowel, urinary tract or bladder	*No*	124	(92.5)	213	(93)	0.865	Extracted from free text in the UK – likely to be underreported in UK
	Yes	10	(7.5)	16	(7)		
	Missing	0		4			
ITU admission	*No*	42	(31.3)	166	(71.9)	<0.001	
	Yes	92	(68.7)	65	(28.1)		
	Missing	0		2			
Infant outcomes		United Kingdom n(%) n=138		France n(%) n=242			
Perinatal mortality	*No*	132	(98.5)	235	(98.7)	0.999	None
	Yes	2	(1.5)	3	(1.3)		
	Missing	4		4			
Apgar score at 5 minutes	*≥7*	120	(87)	210	(87.9)	0.797	None
	<7	18	(13)	29	(12.1)		
Birthweight	*Mean (S.D.)*	2620.8	(762.3)	2674.1	(764.5)	0.518	None

*France missing n=10. ** United Kingdom data were extracted from free text of "did woman have any other morbidity?" and French data were based from specific questions on infective symptoms, haematological culture, symptoms of fever and aseptic shock.

4.4.3 Placenta percreta comparison between the United Kingdom and France

4.4.3.1 Medical management of women who had placenta percreta

Table 39 presents details on the delivery and management of women with placenta percreta. The United Kingdom had a statistically significantly lower proportion of women with placenta percreta suspected in the antenatal period than France (59% vs. 87%, P<0.001). In the United Kingdom, 61% of women with placenta percreta underwent a hysterectomy while 50% of women in France had a hysterectomy, although this difference was not statistically significant. Nearly half of women had their placenta left in situ in the United Kingdom, while over three quarters of women had this approach in France, this difference was statistically significant. In both countries where women had the placenta left in situ, over 80% of women had the complete placenta left in situ rather than having a partial removal.

There was no statistically significant difference in the use of embolisation in women who had placenta percreta between France and the United Kingdom. Furthermore, the United Kingdom had a higher proportion of women who had any conservative surgical treatment compared to France (28% vs. 6%, p=0.008); this difference was significant at the 1% level. There were no statistically significant differences in the proportion of blood products given to women with placenta percreta between the United Kingdom and France.

4.4.3.2 Maternal and infant outcomes for women with placenta percreta

The maternal and infant outcomes for women with placenta percreta by country are presented in Table 40. One woman who had placenta percreta died. The median estimated blood loss for women with placenta percreta was 3000 mls (IQR: 1500-9000 mls) in the United Kingdom while it was lower in France with 1500 mls (IQR: 500-3100mls, P=0.002). Over two thirds of women with placenta percreta had a PPH ≥2000mls in the United Kingdom, while this was two fifths of women in France (P=0.013). There were no women that diagnosed with intrapartum infection in the United Kingdom, in contrast, 17% of women were diagnosed with an infection in France (P=0.008). There were similar proportions of women who had either damage to their bowel, urinary tract or bladder in the United Kingdom and France. There were no statistically significant differences in the outcomes of infants delivered by mothers with placenta percreta in France and the United Kingdom.

Table 39. Medical management of women with placenta percreta.

Management		United Kingdom n(%) n=39		France n(%) n=48		P-value
AIP suspected prior to delivery	*Yes*	23	(59)	41	(87.2)	0.003
	No	16	(41)	6	(12.8)	
	Missing			1		
Caesarean delivery	*Yes*	36	(92.3)	48	(100)	0.086
Hysterectomy						
	Yes	24	(61.5)	24	(50)	0.282
	No	15	(38.5)	24	(50)	
Time between delivery and hysterectomy	*≤48hrs*	21	(87.5)	21	(87.5)	0.999
	>48hrs	3	(12.5)	3	(12.5)	
No attempt to remove placenta after delivery	*Attempt*	19	(48.7)	10	(21.7)	
	No attempt	20	(51.3)	36	(78.3)	0.009
	Missing			2		
Placenta left in situ						
	Yes	18	(46.2)	35	(76.1)	
	No	21	(53.8)	11	(23.9)	0.005
	Unknown	0		2		
How much left in situ	*Complete*	16	(88.9)	29	(82.9)	
	Partial	2	(11.1)	6	(17.1)	0.701
Had hysterectomy after left in situ	*No*	9	(50)	22	(62.9)	
	Yes	9	(50)	13	(37.1)	0.368
Time between delivery and hysterectomy	*≤48hrs*	6	(66.7)	10	(76.9)	
	>48hrs	3	(33.3)	3	(23.1)	0.655
Methotrexate used	*Yes*	5	(27.8)	0	(0)	0.003
Management of haemorrhage		United Kingdom n(%) n=39		France n(%) n=48		
Embolisation	*Not used*	25	(64.1)	26	(54.2)	
	Used	14	(35.9)	22	(45.8)	0.349
Any conservative surgical management						
	Not used	28	(71.8)	45	(93.8)	
	Used	11	(28.2)	3	(6.3)	0.008
Haematological management						
Whole blood or Red blood cells received n (%)		28	(71.8)	31	(64.6)	0.474
In women who received whole blood or Red blood cells	*median (IQR) unit*	8	(6-14)	3	(0-10)	0.003
FFP received n (%)		20	(51.3)	27	(56.3)	0.644
In women who received FFP	*median (IQR) units*	4	(4-8)	2	(0-7)	0.195
Platelets received n (%)		13	(33.3)	8	(16.7)	0.071
In women who received platelets	*median (IQR) units*	2	(1-2)	0	(0-1)	0.212
Fibrinogen received e.g. cryoprecipitate or fibrinogen conc.	*Not used*	29	(74.4)	29	(60.4)	
	Used	10	(25.6)	19	(39.6)	0.170

Table 40. Outcomes of those with placenta percreta.

Maternal outcomes		**United Kingdom n(%) n=39**		**France n(%) n=48**		**P-value**
Woman died	*Yes*	0	(0)	1	(2.1)	0.999
Amount of blood loss	*Median (IQR)*	3000	(1500-9000)	1500	(500-3200)	0.002
Postpartum haemorrhage						
	<1500 mls	8	(20.5)	23	(48.9)	0.006
	≥1500 mls	31	(79.5)	24	(51.1)	
	Missing	0		1		
Severe postpartum haemorrhage						
	<2000 mls	12	(30.8)	27	(57.4)	0.013
	≥2000 mls	27	(69.2)	20	(42.6)	
	Missing	0		1		
Post-delivery infection[†]						
	No	39	(100)	40	(83.3)	0.008
	Yes	0	(0)	8	(16.7)	
Damage to bowel, urinary tract or bladder						
	No	33	(84.6)	40	(83.3)	0.871
	Yes	6	(15.4)	8	(16.7)	
ITU admission						
	No	8	(20.5)	23	(47.9)	0.008
	Yes	31	(79.5)	25	(52.1)	
Infant outcomes		United Kingdom n(%) n=39		France n(%) n=48		
Perinatal mortality	*No*	35	(97.2)	47	(100)	0.434
	Yes	1	(2.8)	0	(0)	
	Missing	3		1		
Apgar score at 5 minutes	*≥7*	32	(82.1)	36	(75)	0.429
	<7	7	(17.9)	12	(25)	
Birthweight	*Mean (S.D.)*	2481.8	(772.5)	2673.3	(675.1)	0.229

[†] United Kingdom data were extracted from free text of "did woman have any other morbidity?" and French data were based from specific questions on infective symptoms, haematological culture, symptoms of fever and aseptic shock.

4.4.3.3 Between-country comparison according to attempted manual removal of placenta

The outcomes for women with AIP antenatally suspected by country are presented according to whether there was an attempted manual removal of the placenta (see Table 41). Women in both countries had a higher mean estimated blood loss when there was an attempted manual removal of the placenta compared to women who had no attempted manual removal of the placenta (United Kingdom: 1500 vs. 4000mls; France: 500ml vs. 1500ml), these differences were statistically significant.

There appeared to be a difference between countries according to whether an attempted manual delivery of the placenta occurred. In those who had no attempted manual delivery, the United Kingdom had a higher median blood loss compared to France (1500mls (IQR: 400-5000) vs. 500mls (IQR: 500 (500-1500)); however, this difference was not statistically significant. In those who had no attempted manual delivery, the United Kingdom had a statistically significantly higher proportion of women who had a severe postpartum haemorrhage than in France (44% vs. 23%, respectively).

In those who had an attempted manual removal, women in the United Kingdom had a higher median blood loss compared to France (4000mls (IQR: 1950-8000) vs. (1800 (IQR: (900-3500)) and this difference was statistically significant. Women who had an attempted manual removal, in the United Kingdom had a statistically significantly higher incidence of severe postpartum haemorrhage than women in France (74% vs. 48%, respectively).

Table 41. Maternal outcomes of women with antenatal suspicion of AIP in the United Kingdom and France according to attempted manual removal of placenta.

		Suspected antenatally and no attempted removal of placenta					**Suspected antenatally and had an attempted removal of the placenta**				
		United Kingdom n=27		**France n=74**		**P-value**	**United Kingdom n=39**		**France n=41**		**P-value**
Placenta accreta		9	(34.6)	40	(56)	0.067	33	(84.6)	34	(82.9)	0.838
Placenta percreta		17	(65.4)	32	(44.4)		6	(15.4)	7	(17.1)	
RBC transfusion		13	(48.1)	35	(47.3)	0.940	32	(82.1)	29	(70.7)	0.234
FFP transfusion		9	(33.3)	26	(35.1)	0.866	24	(61.5)	23	(56.1)	0.621
Platelet transfusion		4	(14.8)	7	(9.5)	0.445	15	(38.5)	10	(24.4)	0.175
Hysterectomy	*Yes*	16	(59.3)	30	(40.5)	0.095	27	(69.2)	20	(48.8)	0.063
Amount of blood loss	*Median (IQR)*	1500	(400-1500)	500	(500-1500)	0.440	4000	(1950-8000)	1800	(900-3500)	0.001
Postpartum haemorrhage	*<1500*	13	(48.1)	52	(73.2)	0.019	7	(17.9)	15	(36.6)	0.062
	≥1500	14	(51.9)	19	(26.8)		32	(82.1)	26	(63.4)	
Severe postpartum haemorrhage	*<2000*	15	(55.6)	55	(77.5)	0.032	10	(25.6)	21	(51.2)	0.019
	≥2000	12	(44.4)	16	(22.5)		29	(74.4)	20	(48.8)	
Post-delivery infection	*No*	27	(100)	66	89.2	0.105	39	(100)	37	(92.5)	0.241
	Yes	0	(0)	8	(10.8)		0	(0)	3	(7.5)	
Damage to bowel, urinary tract or bladder	*No*	23	(85.2)	65	87.8	0.743	35	(89.7)	38	(95)	0.432
	Yes	4	(14.8)	9	(12.2)		4	(10.3)	2	(5)	
ITU admission	*No*	7	(25.9)	53	(71.6)	<0.001	6	(15.4)	22	(53.7)	<0.001
	Yes	20	(74.1)	21	(28.4)		33	(84.6)	19	(46.3)	
Woman died	*No*	27	(100)	74	(100)	-	39	(100)	40	(97.6)	0.999
	Yes	0	(0)	0	(0)		0	(0)	1	(2.4)	

4.4.4 Pooled analysis: comparing a planned conservative management to a planned hysterectomy.

The derivation of comparison groups of hysterectomy and a conservative approach are given in Figure 7. This analysis was restricted to women who had an antenatal suspicion of AIP and had no attempted removal of the placenta after the delivery. The comparison was made between those who had a planned hysterectomy (n=27) and those who had their placenta left completely in situ (n=42).

4.4.4.1 Pooled analysis: a comparison of characteristics between women in the conservative management and hysterectomy group

There were no statistically significant differences in the proportion of women who were obese, smoked during pregnancy, had a previous caesarean section, had previous uterine surgery, had placenta praevia diagnosed before delivery and the grade of AIP comparing the primary hysterectomy and conservative management groups (Table 42). Due to the small number of women within each group this precluded a multivariable analysis.

Figure 7. Study population for planned conservative management compared to planned hysterectomy.

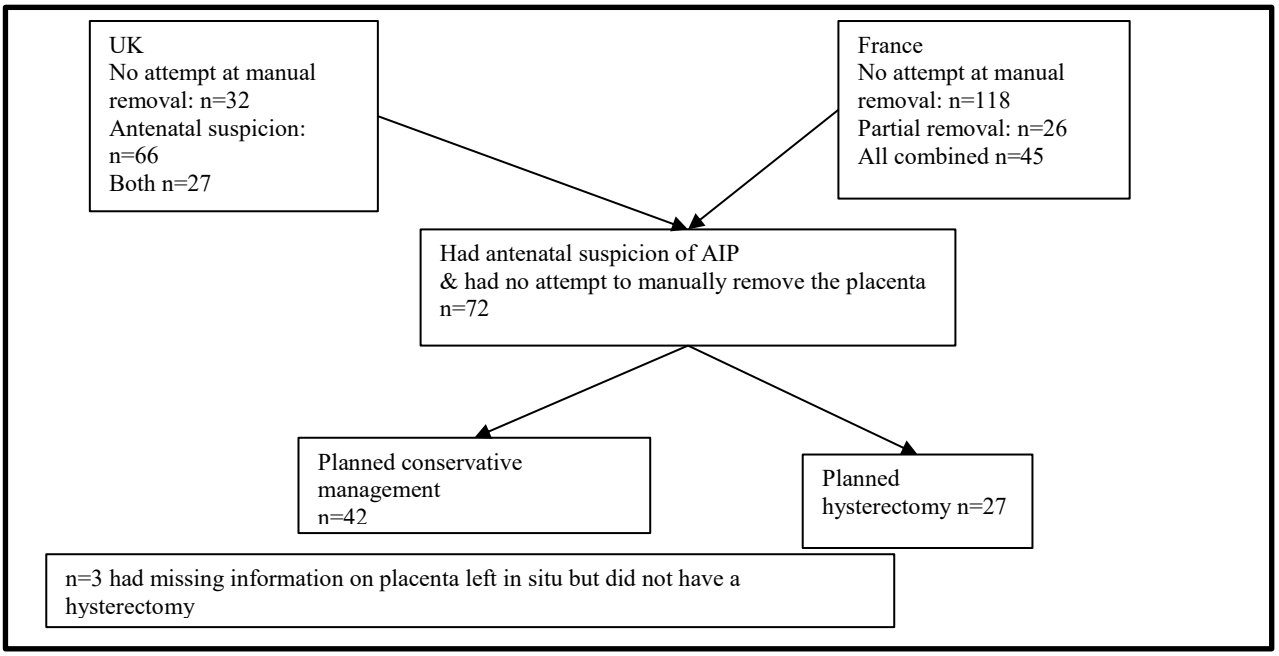


Table 42. Characteristics of women who had a planned hysterectomy compared to planned conservative management.

		Planned hysterectomy n=27		Conservative management n=42		P-value
Age Mean(SD)		34.9	(5)	34.3	(4.4)	
BMI category	<25	10	(40)	22	(53.7)	
	>=25-<30	10	(40)	8	(19.5)	0.193
	>=30	5	(20)	11	(26.8)	
	Missing	2		1		
Smoking Status						
	Did not smoke during pregnancy	22	(84.6)	31	(77.5)	0.543
	Smoked during pregnancy	4	(15.4)	9	(22.5)	
	Missing	1		2		
Parity						
	Zero	0	(0)	0	(0)	
	1	3	(11.1)	11	(26.2)	0.219
	2+	24	(88.9)	31	(73.8)	
History of PPH						
	No	24	(88.9)	37	(88.1)	0.999
	Yes	3	(11.1)	5	(11.9)	
Previous caesarean section						
	Zero	1	(3.7)	0	(0)	
	1	8	(29.6)	18	(42.9)	0.299
	2+	18	(66.7)	24	(57.1)	
Previous uterine surgery						
	No	20	(74.1)	28	(66.7)	0.514
	Yes	7	(25.9)	14	(33.3)	
Any history of uterine surgery including caesarean section	No	0	(0)	0	(0)	-
	Yes	27	(100)	42	(100)	
Current pregnancy						
Hypertensive disorder during pregnancy						
	No	27	(100)	38	(90.5)	0.150
	Yes	0	(0)	4	(9.5)	
Placenta praevia suspected prior to delivery	No	1	(3.7)	1	(2.4)	0.999
	Yes	26	(96.3)	41	(97.6)	
Multiple pregnancy						
	Yes	0	(0)	0	(0)	-
	No	27	(100)	42	(100)	
AIP type						
	Placenta accreta/ increta	12	(46.2)	18	(43.9)	0.857
	Placenta percreta	14	(53.8)	23	(56.1)	
	Missing	1		0		

4.4.4.2 Pooled analysis: a comparison of management of women in the conservative and hysterectomy groups

For both management groups approximately a half of the women were delivered between 34 to 37 weeks of gestational age. In the planned conservative management group, half of the women had embolisation while this was undertaken in a 15% of women with a planned hysterectomy; this was statistically significantly different. The use of any conservative surgical technique did not differ between the two management approaches. Conservative management failed in just over a quarter (n=12) of women, and these women progressed on to have a hysterectomy (see Table 43). A half of these women had failed conservative management during the first 48 hours after delivery.

4.4.4.3 Pooled analysis: a comparison of maternal and infant outcomes between women managed by conservative management and primary hysterectomy

No women who had a planned hysterectomy or conservative management died. Women who were managed by a planned hysterectomy had a blood loss of 2250mls (IQR: (500-1300) compared to 500mls (IQR: 500-1300, P=0.002) in those who were managed conservatively; in addition, over a half of women who were managed by a planned hysterectomy had a severe postpartum haemorrhage (≥2000mls) while this only occurred in a quarter of women with conservative management (P=0.012). There was a higher proportion of postpartum infection in those who had their placenta left in situ compared to hysterectomy (7% vs. 4%), although this difference was not statistically significantly different (see Table 44).

In women where the preservation of the uterus failed (n=12), six women had a hysterectomy within 48 hours and thereafter the median number of days to hysterectomy was 40 days (IQR: 19-102); the median estimated blood loss was 3100 mls (IQR: 1600-

5750 mls); the median number of RBC units transfused was 9 (IQR: 4-15). None of these women had sepsis.

No infants born to women who had a planned hysterectomy or conservative management died. A higher proportion of infants born to women with a planned hysterectomy had an Apgar score less than seven at five minutes compared to infants born to women who had a conservative management (44% vs. 21%, $P<0.05$) , this difference was statistically significant (see Table 44).

Table 43. Delivery and management of women who had a planned hysterectomy compared to planned conservative management.

Delivery and management		**Planned hysterectomy n=27**		**Conservative management n=42**		**P-value**
Gestational age at delivery						
	<34 Weeks	5	(18.5)	13	(31)	
	<=34->37	13	(48.1)	21	(50)	0.309
	>=37	9	(33.3)	8	(19)	
Caesarean delivery	No					
	Yes	27	(100)	42	(100)	
Medical management						
Uterotonics used as treatment or prophylaxis*						
	Not used	12	(44.4)	18	(42.9)	0.897
	Used	15	(55.6)	24	(57.1)	
Methotrexate used						
	No	9	(100)	38	(90.5)	0.999
	Yes	0	(0)	4	(9.5)	
Management of haemorrhage						
Embolisation						
	Not used	23	(85.2)	20	(47.6)	0.002
	Used	4	(14.8)	22	(52.4)	
Conservative surgical technique						
	Not used	24	(88.9)	37	(88.1)	0.999
	Used	3	(11.1)	5	(11.9)	
Uterine balloon tamponade						
	Not used	26	(96.3)	41	(97.6)	0.999
	Used	1	(3.7)	1	(2.4)	
Hysterectomy						
	Yes	27	(100)	12	(28.6)	<0.001
	No	0	(0)	30	(71.4)	
Time between delivery and hysterectomy						
	<48hrs	27	(100)	6	(50)	<0.001
	>48hrs	0	(0)	6	(50)	
Haematological management						
Whole blood or Red blood cells received n(%)		15	(55.6)	16	(38.1)	0.155
In women who received whole blood or Red blood cells	median (IQR) unit	7	(4-10)	8	(4- 14)	0.950
FFP received n(%)		13	(48.1)	10	(23.8)	0.036
In women who received FFP	median (IQR) units	2	(1-7)	4	(4 -7)	0.236
Platelets received n(%)		6	(22.2)	2	(4.8)	0.049
In women who received platelets	median (IQR) units	1	(1-2)	1	(1-1)	0.635
Fibrinogen received e.g cryoprecipitate or fibrinogen conc.	Not used	19	(70.4)	34	(81)	0.309
	Used	8	(29.6)	8	(19)	

* Use of misoprostol, ergometrine, Oxytocin or prostaglandin.

Table 44. Maternal and infant outcomes of women who had a planned hysterectomy compared to planned conservaitve management.

Maternal outcomes		**Planned hysterectomy n=27**		**Conservative management n=42**		**P-Value**
Woman died	No	27	(100)	42	(100)	-
	Yes	0	(0)	0	(0)	
Amount of blood loss*	Median (IQR)	2250	(500-5000)	500	(500-1300)	0.007
Postpartum haemorrhage						
	<1500	10	(38.5)	32	(76.2)	0.002
	>=1500	16	(61.5)	10	(23.8)	
	Missing	1		0		
Severe postpartum haemorrhage						
	<2000	12	(46.2)	32	(76.2)	0.012
	>=2000	14	(53.8)	10	(23.8)	
	Missing	1		0		
Post-delivery infection (excluding those who only had symptoms of fever)†	No	26	(96.3)	39	(92.9)	0.999
	Yes	1	(3.7)	3	(7.1)	
ITU admission						
	No	15	(55.6)	23	(54.8)	0.948
	Yes	12	(44.4)	19	(45.2)	
Damage to bowel, urinary tract and bladder						
	No	22	(81.5)	37	(88.1)	0.446
	Yes	5	(18.5)	5	(11.9)	
Infant outcomes						
Perinatal mortality	*No*	0	(0)	0	(0)	-
Apgar score at 5 minutes	*>=7*	15	(55.6)	33	(78.6)	0.043
	<7	12	(44.4)	9	(21.4)	
Birthweight	Mean (S.D.)	2615.3	(143.3)	2386.3	(112.9)	0.212

4.5 Discussion

4.5.1 Main findings

4.5.1.1 Chapter in context

This binational study enabled the assessment of different approaches to the management of a severe and rare complication of pregnancy in a medical setting where an RCT would be challenging. This study demonstrated that observational multinational studies can allow the study of an uncommon management of a rare and severe complication of pregnancy, which in this case was abnormally invasive placenta. This use of two large population-based studies enabled a pooled analysis of women with abnormally invasive placenta, the findings showed that a conservative approach of leaving the placenta in situ was associated with a lower estimated blood loss compared to a planned hysterectomy.

4.5.1.1.1 In context to other chapter and literature

Similar to the previous chapter on major obstetric haemorrhage, this chapter illustrated that management of a severe complication of pregnancy can be compared between countries. Systematic reviews have been limited due to heterogeneity between studies (Gagnier et al., 2012) and previous international comparisons of complications of pregnancy have been restricted to discussions around differences in definitions (Knight and INOSS, 2014). In this chapter, the access to individual patient data from two national studies allowed the creation of a population-based set of cases with a uniform definition. This has provided an informative comparison as any differences in outcomes, between countries with homogeneous definitions, can only be explained by variation in risk factors or management between countries.

4.5.1.1.2 Pooled analysis

The added benefit of a multinational study of AIP is that through the pooling of data it enabled the comparison of an uncommon approach to management. In rare conditions it is difficult to study differences in management in pregnancy due to small sample sizes. Furthermore, it is even more difficult to examine approaches to management that are rarely used such as a conservative approach. To overcome this limitation either the condition must be studied for a long period of time or the sampling area must be increased. However, if a long period of time is chosen it is likely that the management or other aspects of care may change over that period. As a result, the most appropriate action is to increase the study population via a multinational study.

Observational evidence is considered less robust than RCTs due to issues around confounding (Hennekens and Buring, 1987). As a result, RCTs are at the top of the evidence-based pyramid for studying the impact of an intervention on outcomes. Murad et al. (2016) argued that a well conducted case-control study or cohort study has a similar or better validity to a poorly conducted RCT. Furthermore, in a contested area such as the management of AIP, observational data has to be relied on to provide evidence for clinical practice. This robust study showed that planned conservative management was more commonly used in France while a planned hysterectomy without an attempted conservative approach was more commonly used in the United Kingdom. This natural experiment provided an opportunity to pool the data to study the differences in outcomes between these different approaches to management of AIP.

4.5.1.2 Clinical findings

There was a twofold difference in the incidence of AIP between the United Kingdom and France. In both countries, approximately half of all women had an antenatal suspicion of AIP and over a fifth of women had placenta percreta. The majority of women with AIP were managed with hysterectomy in the United Kingdom, while in France, a left in situ approach to conserve the uterus was more commonly attempted. There was a large difference in blood loss for women managed in the two countries. In particular, women from the United Kingdom had a median blood loss of approximately more than 2 litres greater than French women. As a consequence, the United Kingdom had a larger proportion of women who had a severe postpartum haemorrhage, while more women in France had a postpartum infection. This between country difference in severe postpartum haemorrhage was also reflected in women who had placenta percreta.

The difference in outcomes between the United Kingdom and France was partially explained by differential use of an extirpative approach, which was more routinely used in the United Kingdom. After stratification by attempted manual placental delivery, the proportion of women who had a severe postpartum haemorrhage remained different between France and the United Kingdom, which suggested that there were other factors explaining the difference in associated blood loss experienced by women in the two countries.

In a pooled analysis, this population-based study that compared a planned hysterectomy to a planned conservative approach and showed that a planned conservative management, where there has been no attempted removal of the placenta, was successful in 75% of women and, if successful, it avoided severe postpartum haemorrhage and loss of fertility. Although there was an increased incidence of sepsis, which may impact future fertility.

4.5.1.3 Incidence

France had over twice the apparent incidence of AIP compared to the United Kingdom. Whether this difference was a result of artefact or reflects a true difference in incidence is unclear. Previous national studies have shown that the United Kingdom has a slightly higher incidence of caesarean section than France with 24-29% rate in the United Kingdom and 21% in France (MacFarlane et al., 2016). Previous caesarean section is a risk factor for AIP (Fitzpatrick et al., 2014b), which would suggest that the United Kingdom should have a higher incidence of AIP than France.

Another important risk factor is previous uterine surgery, which appeared to be more common in the French AIP cases. However, without other data it is difficult to know whether the French pregnant population as a whole had a higher prevalence of previous uterine surgery than the UK population. If the French pregnant population had a higher prevalence of previous uterine surgery than the United Kingdom population then it may be possible that the difference in incidence was true.

4.5.1.3.1 Non-differential bias

Both France and the United Kingdom had slightly different definitions; the unmodified French definition was more liberal than the United Kingdom, despite attempts to make them comparable it is possible the difference in definitions may explain the variation in incidence. It is not known how clinicians in each country interpreted the definition, particularly in a condition where there is no uniformly agreed diagnostic criteria and where histological confirmation will only occur in those with a hysterectomy or at post mortem (Comstock, 2005) .

It is only possible to speculate that the French study may have been better at ascertaining cases of AIP than the UKOSS system in the UK. The French study had a dedicated funded

clinician at each site to complete the data collection forms, which may have encouraged a more complete participation in the study. In addition, the French study collected every woman with a previous uterine scar and placenta praevia, that is to say, all women at risk of AIP were identified in France, whereas the United Kingdom data were only collected for women with AIP.

Differences in routine ultrasound screening for AIP may also be a possible explanation for the variation in incidence between the two countries. The United Kingdom does not routinely screen for AIP (Sargent and Collins, 2017) and the last routine ultrasound scan is in the second trimester (21 weeks), while in France there are three routine ultrasound screenings at 12 weeks, 22 weeks and 32 weeks of gestational age and there is routine screening for AIP (de Vigan and Khoshnood, 2010). This again would suggest France may be better at ascertaining women with AIP than the United Kingdom. Nevertheless, it is interesting to note that there were similar proportions of women with AIP suspected antenatally and with placenta percreta, which might suggest cases from each of the two countries were of similar severity.

4.5.2 Limitations

Both the United Kingdom and French study had different case definitions so even with considerable effort to harmonise the definitions of the two studies it was likely that the populations were slightly different. Future studies should adopt the same definition or be designed together in a prospective study, and this will allow an easy comparison.

Despite pooling there were nevertheless still small numbers of women who had planned conservative management or a planned hysterectomy. This limited the complexity of analyses which could be completed using these data. Notwithstanding this limitation, there was still a statistically significant difference shown between these uncommon modalities of management and outcomes.

After the analysis was completed in Paris, it came to light that the French centres were referred cases from areas outside the study region, which may have explained the higher incidence within France. These referred cases were severe cases of AIP that required specialist care. As a result, this study was not strictly population-based with their inclusion in the study. However, excluding 17 women from the incidence provided a population based incidence.

Indication bias is a potential limitation of any observational studies examining the relationship between a management modality and an outcome. A randomised controlled trial is the most robust method to examine the causal effect of management on outcome but this would be difficult to conduct in this clinical scenario. In this study, the severity of invasion was not different between the groups, which suggests that our results may show a true difference between management and severe postpartum haemorrhage. Furthermore, when the between country analysis was restricted to women with placenta percreta there was still a difference in the estimated blood loss between the countries.

4.5.3 Strengths

This study focused on two countries with differing management of AIP and utilised studies where the definitions could be harmonised to provide a set of cases with a uniform case definition. Each study collected enough data to provide detailed information about the women with AIP.

This is the first binational study to compare conservative management to a hysterectomy. The findings of this observational study add important evidence to managing AIP, which is an area of clinical care that lacks robust evidence.

4.6 Conclusion

A binational study enabled a pooled analysis to examine uncommon modalities of management of a rare complication of pregnancy. Uterine preserving management resulted in a greater number of women retaining their potential fertility and reduced the likelihood of a life threatening haemorrhagic event. However, if the conservative management approach fails it is likely to result in severe maternal morbidity so these women need to be monitored very closely. In addition, future fertility may be compromised due to infection of retained products. Furthermore, this binational study showed that difference in blood loss and infection between the countries was likely to be the result of differences in management. For outcomes to improve in both countries there should be no forced removal of the placenta if the AIP is suspected in the antenatal period, and particularly for cases of placenta percreta. To overcome the methodological differences of comparability of definitions and data items, future multinational studies should be designed prospectively.

Chapter 5. The utility of different methodological approaches to the investigation of a very rare and severe complication of pregnancy: anaphylaxis in pregnancy

5.1 Introduction

5.1.1 Chapter in context

5.1.1.1 Prospective study of a very rare condition using obstetric surveillance systems

The INOSS collaboration was established for the rigorous study of rare and severe complications of pregnancy by using uniform definitions and common data collection methods to create comparable datasets in different countries. The collaboration also set out to complete prospective studies of rare and severe complications of pregnancy using this rigorous methodology (Knight and INOSS, 2014). However, to date there have been no completed prospective studies through the INOSS. The UKOSS study of anaphylaxis in pregnancy, which was carried out in 2012-2015, offered an opportunity to scale up the study to an international level. All INOSS collaborating countries were invited to participate, and the following agreed to: Finland, France, Belgium and the Netherlands. The definition and data collection form developed for the previous UKOSS study was used to ensure uniform data collection. The study reported in this chapter aimed to examine the feasibility of such collaborative prospective international studies and the clinical questions these studies could answer.

5.1.2 Enhanced data collection through routine data sources

5.1.2.1 Overview

There was an opportunity to contrast different types of data collection methodologies to study rare complications of pregnancy. Finland offered a retrospective registry while the U.S.A. has a large routinely collected administrative database. Alongside the prospective study, these different methodologies allowed comparisons to be made between each methodology. Using these different approaches to conduct a clinical study to enable examination of the benefits and limitations of each methodology when studying a rare complication of pregnancy.

5.1.2.2 Registry and medical records (Finland)

The Finnish birth registry is a member of the INOSS collaboration. These Finnish registries provided the opportunity to identify, retrospectively, women with severe complications. The medical birth registry provides a wealth of data on exposures, sociodemographic information and previous pregnancy history; medical birth registries also provide identifiers allowing cases to be linked with hospital records (Gissler et al., 1997). Finnish collaborators agreed to take part in the study of anaphylaxis. The combination of medical birth registry data and individual hospital records allowed for the validation of the diagnosis in women with a coded record of anaphylaxis. Furthermore, the combination of hospital records and registry data enabled tailored data extraction. This allowed data derived from the Finnish registry to be harmonised with the prospective study.

5.1.2.3 Routinely available data (U.S.A.)

Routinely collected administrative data have the advantage of providing a large quantity of data with relative ease of access. However, routine data sources in England have been shown to be poor at identifying rare morbidities in pregnancy (Nair et al., 2016b). Nair et al. (2016b) illustrated mismatches between the incidence rates provided from routine sources compared to more reliable population-based studies, which used primary data collection. The data collected in the National Inpatient Sample (N.I.S.) in the U.S.A. is regarded as a good source to study rare diseases (Healthcare Cost and Utilization Project (HCUP). 2015). The N.I.S. provided another aspect to the investigation of different methodological approaches to the study of rare conditions in pregnancy. In particular, it allowed a comparison of its utility with other data sources through the examination of anaphylaxis.

5.1.3 Rationale for the study of anaphylaxis

Out of many severe complications, anaphylaxis in pregnancy was chosen for international study because it is a very rare complication with an estimated incidence the of order of 1.1-2.1 per 100,000 maternities (McCall et al., 2018, Mulla et al., 2010). Anaphylaxis in pregnancy is a potentially fatal systemic hypersensitivity reaction, which is rapid in onset. This condition was chosen for both scientific and practical considerations. First, the scientific reasons were, that anaphylaxis is a very rare condition so that any additional cases to those collected from a single national study would increase the precision of point estimates (See Table 45). It was also chosen due to practical considerations because this DPhil had limited funding. Second, it was felt that clinicians would participate in the study due to the low workload of a very rare complication of pregnancy without additional funding.

5.1.3.1 Increased power

The UKOSS study estimated the incidence of anaphylaxis as 1.6 (95% CI: 1.1-2.1) per 100,000 maternities. In a cohort of 37 cases collected from the United Kingdom, there were 2 maternal deaths giving a case fatality rate of 5.4% (95 CI: 0.7-18.2%). Using the UKOSS study as an estimate of the case fatality rate, as an example, Table 45 presents the confidence intervals around a point estimate of 5% for different sample sizes. Table 46 shows the estimated number of cases for the included countries, assuming they occur with the same incidence as the United Kingdom.

Table 45. The variation in confidence intervals according to sample size using case fatality as an example.

Number of cases	**Number of maternal deaths (case fatality)**	**95% Confidence interval for the case fatality**
37 (current estimate)	2 (5.4%)	0.7-18.2
80	4 (5.0 %)	1.4 – 12.3
100	5 (5.0 %)	1.6 – 11.3
200	10 (5.0 %)	2.4 – 9.0

Table 46. The estimated number of cases for each country in the study period.

Country	**Estimated number of live births in study period**	***A pirori* estimated number of cases**
France (October 2016 – March 2018)	1,200,000	19
Belgium (September 2016-February 2018)	190,000	3
The Netherlands (July 2017-July 2018)	192,397	3
Finland (2004-2014)	642,430	10

Based on the incidence rate from the United Kingdom.

5.2 Aim and objectives

5.2.1 Aim

The study reported in this chapter aimed to investigate the utility of multinational studies by conducting an international prospective study and compare its utility to other methodological approaches to studying a very rare complication of pregnancy: anaphylaxis in pregnancy

5.2.2 Objectives

1. To conduct an international population-based study to identify cases of anaphylaxis in pregnancy using both prospective and retrospective data collection methods.
2. To investigate the extent to which different methodologies can address the following clinical objectives:
    a. To estimate and compare the incidence of anaphylaxis in pregnancy between nations.
    b. To describe and compare the causative agents, management and outcomes of anaphylaxis in pregnancy.
    c. To identify potential risk factors for anaphylaxis in pregnancy.

5.3 Methods

5.3.1 Data sources

This multinational study of anaphylaxis in pregnancy used data from a variety of sources over varying time periods. These are presented in Table 47.

5.3.1.1 Routine data sources – United States of America & Finland

Anaphylaxis during pregnancy was defined as a hospital admission during pregnancy or delivery that had a coded anaphylactic reaction. Finland identified women with anaphylaxis in pregnancy using ICD-10-CM codes from the Finnish Medical Birth Registry. Then the medical records were used to confirm whether the women met the definition presented in Box 4.

Table 47. Data sources for the study of anaphylaxis in pregnancy.

Country	Study type	Population	System	Data entry
United Kingdom*	Secondary data analysis of prospectively collected data: October 2012 – September 2015	Population based. All maternities in consultant-led maternity units.	United Kingdom Obstetric Surveillance System.	Paper UKOSS forms entered in Oxford
France*	Prospective: October 2016 – March 2018	All maternities in France	Network of a anaesthetists and centralised laboratories	Online data collection form (INOSS data collection form (DCF))
Belgium*	Prospective: September 2016 – February 2018	All pregnancies in Belgium	Belgium Obstetric Surveillance System	Online data collection form (INOSS DCF)
The Netherlands*	Prospective: June 2017 – June 2018	All pregnancies in the Netherlands	Netherland Obstetric Surveillance System	Online data collection form (INOSS DCF)
Finland*	Retrospective: 2004-2014	All live births and stillbirths in Finland at 22 weeks of gestation or more or delivery >500g	Finnish Medical Birth Registry and linked medical records	Online data collection form (INOSS DCF)
United States of America	Retrospective: 2004-2014	Approximately a 20% sample of all hospital admissions	Routine data source. National Inpatient Sample and Nationwide Inpatient Sample	Not tailored: data provided as download of dataset

*Tailored studies with Box 4 case definition.

5.3.2 Case definition

5.3.2.1 Studies using obstetric surveillance systems and case notes

Anaphylaxis was defined as a severe, life-threatening generalised or systemic hypersensitivity reaction (Resuscitation council, 2008). Cases had to have at least one of the criteria defined in Box 4.

The condition had to have a sudden onset with rapid progression of symptoms, irrespective of skin or mucosal changes.

Box 4. Definitions of clinical criteria for anaphylaxis.

The presence of at least one of the following:
1. A life-threatening airway problem is taken to include:
- Laryngeal or pharyngeal oedema
- Hoarse voice
- Stridor

2. A life-threatening breathing problem is taken to include:
- Shortness of breath and raised respiratory rate
- Wheeze (laryngospasm or bronchospasm)
- Decreased oxygen saturations
- Confusion secondary to hypoxia
- Cyanosis
- Respiratory exhaustion or respiratory arrest

3. A life-threatening circulatory problem is taken to include:
- Signs of shock such as faintness, pallor or clammy skin
- Tachycardia >100bpm
- Systolic BP <90mmHg or Diastolic BP<60mmHg or measured hypotension
- Decreasing level of consciousness
- Signs of ischaemia on ECG
- Cardiac arrest

5.3.3 Case notification

5.3.3.1 United Kingdom

The methods for UKOSS have been previously described in detail (Knight et al., 2005). The United Kingdom used a national surveillance system to identify cases of anaphylaxis in pregnancy occurring in consultant-led obstetric units throughout the United Kingdom during October 2012- September 2015. Reporters were asked to complete a data collection form using information from the patients' medical records. Data were collected anonymously. Data included in the study reported here have been previously published (McCall et al., 2018) and this was a secondary data analysis.

5.3.3.2 France

Women with anaphylaxis during pregnancy in France were prospectively identified from obstetric centres on a monthly basis via email reminders to two groups of professionals. The first was the national French network of anaesthetists working in maternity units ("Club des Anesthésistes Réanimateurs en Obstétrique CARO"). The second was a network of laboratories in which serum tryptase levels were tested ("Allergobionet"); here cases were identified by an elevated tryptase level result and a clinical suspicion of anaphylaxis in women whose blood samples were sent from an obstetric unit. The subsequent obstetric unit was contacted for data collection.

5.3.3.3 Belgium and The Netherlands

In Belgium and the Netherlands the cases were notified through the respective Belgium Obstetric Surveillance System (B.OSS) and Netherland Obstetric Surveillance System (NethOSS). A monthly email was sent to the nominated reporting clinicians. The clinicians reported cases of anaphylaxis in pregnancy through the online B.OSS or NethOSS case notification systems.

5.3.3.4 Finland –Finnish Medical Birth Registry

The study identified cases of anaphylaxis in pregnancy using the Finnish Medical Birth Registry (MBR). The MBR collects data about live births and stillbirths in Finland from 22 completed gestational weeks or any infant delivered weighing >500g (Gissler and Shelley, 2002). The following International Classification of Diseases, Tenth Revision, Clinical Modification codes (ICD-10-CM) were used to identify women with anaphylaxis: T78.2, T78.0, T88.2, T88.6 and T80.5. The medical records of each case identified in the registry were requested from Finnish hospitals. These records were used to determine if the woman actually met the case definition and to extract clinical data.

5.3.4 Data collection

Newsletters were used to keep clinicians informed about the progress of the study. A modified version of the UKOSS data collection form was converted into an online version. Anonymised information about maternal characteristics, previous medical history, the suspected causes of anaphylaxis, maternal and perinatal outcomes of notified cases that met the definition were entered into a customised online data collection form. The online data collection was conducted using the OpenClinca system, an accompanying study specific guide and video was produced to aid the entering of data.

5.3.4.1 Routine data source - United States

This was a population-based study using discharge data from the Nationwide Inpatient Sample over the period 2004-2014 and the Nationwide Inpatient sample (N.I.S.) (2012 onwards) from the U.S.A. (HCUP Nationwide Inpatient Sample, 2011, HCUP National Inpatient Sample, 2012). The database was renamed after the sampling frame was restructured in 2012 and for the purposes of this analysis it will be described as the N.I.S. This data source formed part of the Healthcare Cost and Utilization Project (HCUP),

Agency for Health Care Research and Quality, and is the largest all-payer publicly available dataset in the United States. From 2004-2011, the N.I.S. was a 20% stratified sample of hospital discharges from U.S.A. community hospitals and annually contained data on approximately 8 million hospitalisations from 1000 hospitals in 45 States. From 2012, the database was redesigned to contain a more representative sample of hospitals, which took into account urban-rural location, teaching hospitals, size and patient related factors. The N.I.S. has been validated against the National Hospital Discharge Survey and the Medicare Provider Analysis and Review, which showed that basic epidemiology characteristics were similar between large routine databases (Bekkers et al., 2014, Houchens and Elixhauser, 2012).

5.3.4.2 Selection of women with pregnancy or delivery

Hospitalisations of women giving birth were identified using an enhanced method of identifying obstetric deliveries using the International Classification of Diseases, Ninth Revision, Clinical Modification procedure and diagnosis codes (ICD-9 CM) (Kuklina et al., 2008). Maternities were identified using the following ICD-9-CM diagnosis codes: V270 to V279 (outcome of pregnancy) and 650 (normal pregnancy). In addition, maternities were also identified using these procedure codes: 720, 721, 7221, 7229, 7231, 7239, 724, 726 (forceps); 7251, 7252, 7253, 7254 (breech extraction); 7271, 7279 (vacuum extraction); 728, 729 (other specified and unspecified delivery); 7322 (internal and combined version and extraction); 7359 (other manually assisted deliveries); 736 (episiotomy); and 740 to 749.9 (caesarean section). Diagnosis-related group (DRG) delivery codes were also used to identify maternities and these codes were: 370 (caesarean section) to 375 (vaginal delivery within operation room).

This study was not only concerned with deliveries but any hospitalisation during pregnancy so additional ICD-9 CM diagnosis codes were used in combination, these included: 630 (hydatidiform mole), 631(abnormal products of conception), 633 (ectopic pregnancy), abortion (632-639). Those individuals who were older than 55 years or younger than 12 years old or who were coded as male were excluded from the sample. In addition, this analysis excluded hospitalisations without any ICD-9 CM diagnosis or procedure code.

5.3.4.3 Selection of anaphylaxis

Women with anaphylaxis during pregnancy were identified using the following ICD-9 CM diagnosis codes: 995.0 (anaphylactic shock or reaction unspecified), 995.60 to 995.69 (food reactions) and 999.4 (anaphylactic reaction to serum). The codes to identify cases of anaphylaxis are consistent with those used previously (Ma et al., 2014). Hospitalisations were excluded if they did not have an ICD-9-CM code.

5.3.4.4 Covariates and characteristics

The N.I.S. included information about the following medical characteristics and sociodemographic factors: age, race, income (reported as the quartile classification of the estimated median income of residents in the patient's ZIP code), insurance status (Medicaid and Medicare, private insurance, self-pay, no charge and other) and admission at the weekend. Hospitalisations with a caesarean section were identified using the ICD-9-CM procedure codes: 740 to 749.9. Hospitalisations with a coded medical history of allergic reactions were identified using the ICD-9-CM codes: V140 to V150.9 and V727.

5.3.4.5 Maternal outcomes

The N.I.S. contained a variable to indicate if death occurred during the hospitalisation. Cardiac arrest during hospitalisation was identified using the ICD-9-CM code: 427.5.

5.3.5 Statistical Analysis

5.3.5.1 Harmonisation of data from obstetric surveillance systems and Finland

The following countries had uniform data collection methods: Finland, France, the Netherlands and Belgium. The online data collection form was a modified version of the UKOSS data collection form and the majority of variables were the same. Additional questions were added to the online form after analysis of the United Kingdom data and input from international collaborators to add clinical utility. These included questions about tryptase results and skin testing.

5.3.5.2 Statistical analysis of data from obstetric surveillance systems and Finland

The incidence of anaphylaxis in pregnancy was estimated for each participating country. The incidence was presented as a rate per 100,000 maternities with 95% confidence intervals estimated using the binomial distribution. The characteristics, causal agents, management and outcomes are presented as absolute values and proportions to describe the characteristics, causative agent, and outcomes of cases. Initially the characteristics, management, causal agents and outcomes between the countries were checked to assess comparability. If there were no statistically significant differences between the countries they were presented as a combined cohort. Management was identified as differing between the United Kingdom and the mainland European study and as a consequence results were presented separately. Cases were categorised according to when the anaphylactic reaction occurred in relation to the delivery. These groups included: antenatal (not in delivery suite or theatre), intrapartum (immediately before delivery), post-delivery

(up to 48 hours after delivery). Women were categorised into these clinical timing groups using the time of anaphylaxis and time of delivery, suspected causal and additional information included in the case notes. It is possible that management and causal agents may have changed over a ten year period, so a sensitivity analysis was carried out in Finnish women who had anaphylaxis before 2012 to assess any difference in the management and causal agents.

5.3.5.3 Statistical analysis: routine data source – U.S.A.

The unit of analysis was individual hospitalisation rather than per woman. The sampling design was taken into consideration. Weights provide an accurate discharge estimate for the entire U.S.A. population. Discharge weights were provided by HCUP for each year. HCUP created the weights by stratifying the N.I.S. hospitals by the factors that created the sample (these included: census division, teaching status, bed size, urban/rural location and ownership). A weight for each stratum was calculated by dividing the national number of discharges (universe discharges) in that strata by the number of N.I.S. discharges in that stratum. Weights were then imported for each year into STATA and the "svy" STATA command were used to weight the data.

5.3.5.3.1 Incidence – United States

Both the incidence from the N.I.S. sample and U.S.A. population estimate are presented. These were calculated as per 100,000 pregnancy hospitalisations for the period 2004-2014 with 95% confidence intervals. In addition, yearly rates of anaphylaxis in pregnancy were estimated and the rate of anaphylaxis in pregnancy in those who had a caesarean delivery was also estimated. The risk of an anaphylactic reaction in a caesarean delivery compared to a vaginal delivery is presented as an incidence rate ratio with 95% confidence intervals.

5.3.5.3.2 Risk factors for anaphylaxis – U.S.A,

Unconditional logistic regression analysis was conducted to compare the characteristics, medical history and management of those with and without anaphylaxis during a pregnancy hospitalisation. Potential risk factors available in the dataset were: age, race, socioeconomic measures, history of allergy, caesarean delivery and weekend admission. The rationale for the inclusion for each of these risk factors is shown in table 48. These studies were identified through the scoping search. However, no study identified in the review had examined an association between admission date and race with anaphylaxis. Collinearity was assessed by a Pearson's correlation coefficient and no covariates were considered to be collinear (correlation coefficient <0.30). There was no statistically significant interaction between caesarean delivery and race (P<0.05). Age did not have a linear relationship with the outcome variable (anaphylaxis in pregnancy) so was included as a categorical variable. A forward stepwise regression method was used to select variables for the multivariable model using a P-value <0.1 as a cut-off. Variables were added sequentially in order of p-value, lowest first. Each potential risk factor was modelled against anaphylaxis (Yes/No) and was included in the final model if it was associated with the outcome (P-value for Wald test <0.05) and improved the fit of the data, which was assessed by likelihood ratio tests at the 5% significance level. The forward stepwise regression was an iterative process and was completed manually.

Table 48. Rationale for risk factors included in the United States of America (U.S.A.) analysis.

Potential risk factor	Rationale
Age	Demonstrated to be a risk factor for anaphylaxis (Turner et al., 2017).
Socioeconomic measures	Socioeconomic disparities have been documented in many areas in health including obstetrics. There is no reason to suspect this may be different with anaphylaxis.
Race	Racial disparities have been documented in many areas in health including obstetrics. There is no reason to suspect this may be different with anaphylaxis. (Bryant et al., 2010)
Caesarean delivery	Shown to be associated with anaphylaxis (Mulla et al., 2010, Simons and Schatz, 2010).
Admission at weekend	Poor hospital outcomes have been associated with weekends. There may be an increased risk of medical mistakes at weekend such as giving a wrong antibiotic to someone with an allergy. (Palmer et al., 2015)
History of allergy	Shown to be highly prevalent in those who have had anaphylaxis in pregnancy. (McCall et al., 2018)

5.3.5.3.3 Missing data

A similar approach was taken to missing data as in previous chapters. A proxy category for each variable was created to include the missing data. Complete case analysis was used in the univariable and multivariable models for the N.I.S. analysis. A proxy variable model was created to assess the impact of using complete case analysis in the N.I.S. A further sensitivity analysis using two separate models, categorised the missing data of race into the "white category" and "black category", respectively, to assess the impact of the missing data on the final multivariable model.

5.3.6 Ethics committee approval

Permission for the use and sharing of registry and medical records was obtained from the National Institute for Health and Welfare (THL), Finland. Approval was acquired from the Belgium Obstetric Surveillance System and Netherland Obstetric Surveillance System steering committee for the data collection and sharing of data for this anaphylaxis study. The Central University Research Ethics Committee (CUREC), University of Oxford gave approval to complete a prospective observational study [Reference: R46400/RE001]. There was no required approval for the secondary data analysis of UKOSS data. Data approval for the N.I.S. data was obtained through the HCUP website.

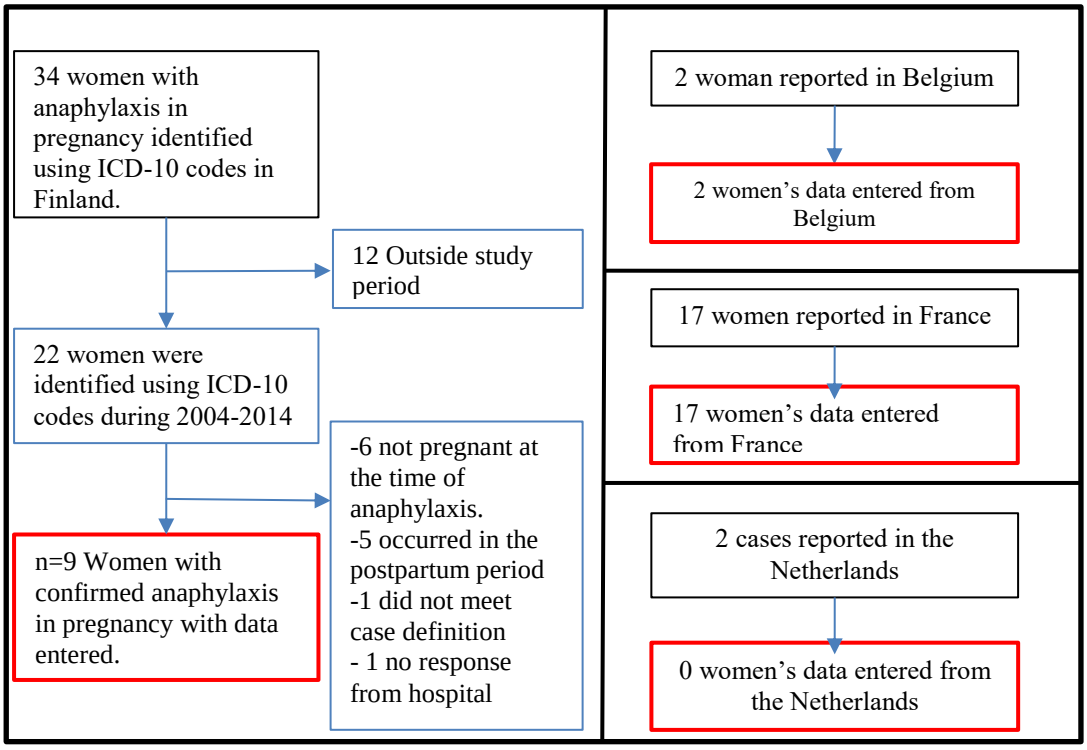
5.4 Results

5.4.1 Selection and identification of the study population in the European study

The selection of the study population is shown in Figure 8. In Finland, 22 women were identified as having anaphylaxis during pregnancy from the Finnish Medical Birth Registry in the years 2004-2014. After inspection of available hospital records, nine women actually met the case definition.

Data were collected for 19 women in Belgium and France during the period September 2016-February 2018. In addition, data had already been collected on 37 women from the United Kingdom, two of these women gave birth outside the study period (>48hrs), giving 35 women from the United Kingdom and a total of 63 cases of anaphylaxis in pregnancy available for analysis.

Figure 8. Prospective and registry based study using Finnish registry data 2004-2014 and prospective studies in Belgium, France and the Netherlands.



5.4.2 Incidence

The incidence of anaphylaxis in pregnancy ranged from 1.1 – 1.5 per 100,000 maternities in Finland, France, United Kingdom, Belgium and the Netherlands (Table 49). Before validation, Finland had an incidence of 3.4 per 100,000; this declined to 1.4 per 100,000 after validation. For the European study this gave a combined incidence of 1.5 anaphylactic reactions per 100,000 maternities. There was no validation of cases in the U.S.A. and the estimated incidence of 3.8 per 100,000 pregnancy related hospitalisations was higher, which was based off a weighted estimate for the entire U.S.A. population.

Table 49. Incidence of anaphylaxis in pregnancy across countries.

Country	Anaphylaxis in pregnancy	Denominator*	Rate per 100,000
United Kingdom	35	2,324,522	1.5 (95%CI: 1.1-2.1)
France	17	1,125,495	1.5 (95% 0.9-2.4)
Finland	9	642,430	1.4 (95%CI: 0.6-2.7)
The Netherlands	2	173,013	1.1 (95% CI: 0.1-4.2)
Belgium	2	180,660	1.1 (95% CI: 0.1-4.0)
Combined	65	4,446,120	1.5 (95% CI: 1.1-1.9)
United States of America**	354 (1722)	9,268,853 (44,548,412)	3.8 (95% CI: 3.4-4.2)

*Denominator number of maternities unless otherwise stated **Unit of analysis was pregnancy hospitalisation. Bracketed denominator is the weighted estimation for the entire U.S.A. population. The incidence and 95% confidence interval was based off the weighted estimate and provided a national estimate for the U.S.A. population. Finland only included births >22 weeks of gestation, while cases from the USA and other countries were not restricted by gestational age.

5.4.2.1 Longitudinal incidence using National Inpatient Sample in United States.

The derivation of the U.S.A study population is shown in Figure 9. The overall incidence of anaphylaxis in pregnancy was estimated as 3.8 (95% CI: 3.4-4.2) per 100,000 pregnancy related hospitalisations. The incidence of anaphylaxis in those who were delivered by caesarean was 7.7 per 100,000 caesarean deliveries (95%: 6.7-8.7). Those who had a caesarean delivery had nearly quadruple the risk of an anaphylactic reaction compared to those who did not [Rate ratio: 3.8 (95%CI: 3.1-4.8)] (see Table 50).

Figure 9. Derivation of study population for the National Inpatient Sample, U.S.A.

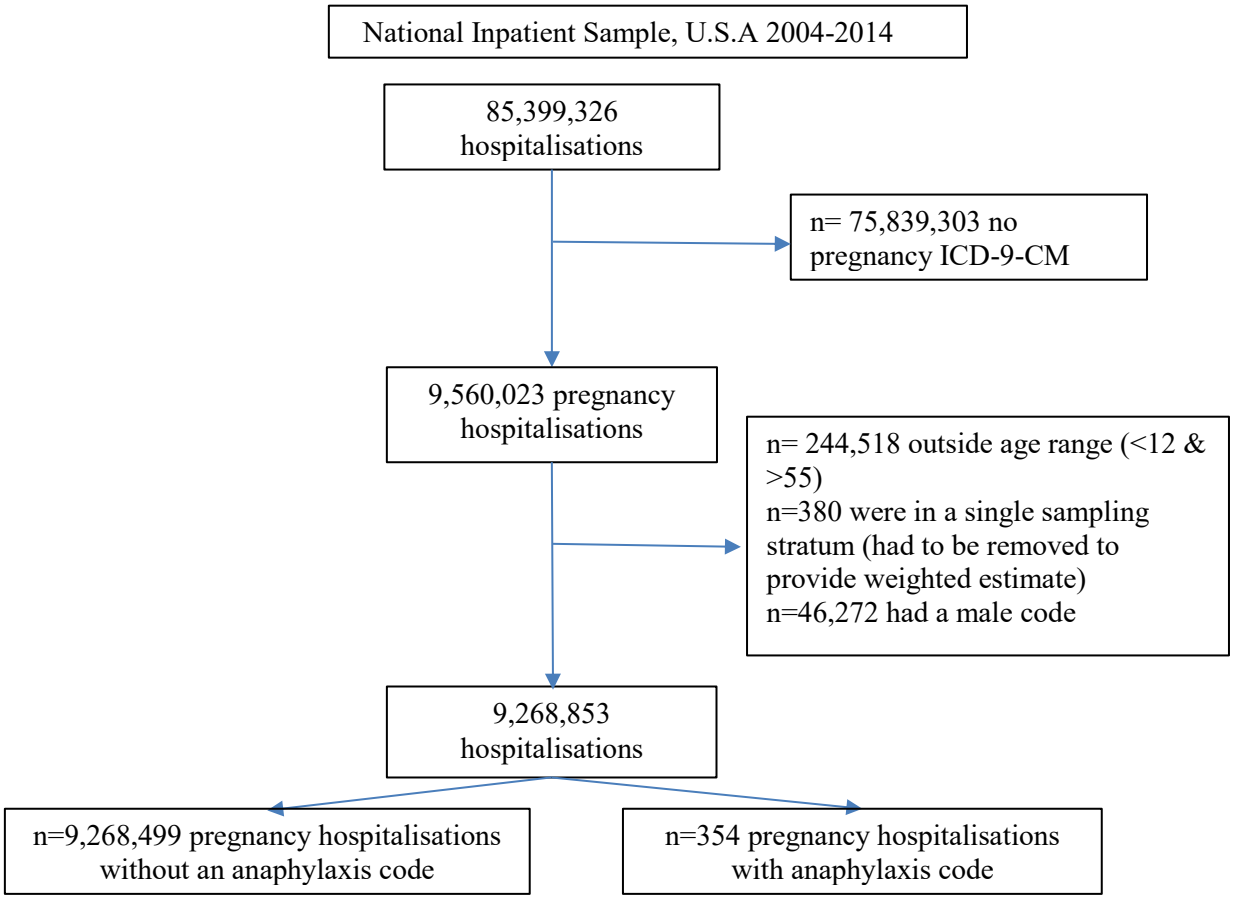


Table 50. Incidence of anaphylaxis in pregnancy combined with those delivered by caesarean section in United States of America during 2004-2014.

2004-2014	Unweighted	Weighted	Rate	95% CI	Unweighted		Weighted	
					Incidence rate ratio	95% CI	Incidence rate ratio	95% CI
Total number of hospitalisations	9,268,853	44,323,268						
Anaphylaxis in pregnancy	354	1694	3.8	(3.4-4.2)				
No caesarean section	126	607			1		1	
In those with caesarean sections*	228	1086	7.7	(6.7-8.7)	3.9	(3.1-4.8)	3.8	(3.1-4.8)

*2004-2014: 2,944,090 caesarean sections (unweighted).

5.4.2.2 Temporal trend of anaphylaxis during pregnancy in United States of America

The incidence of anaphylaxis in pregnancy remained between 3 to 5 per 100,000 pregnancy related hospitalisations during the period 2004 to 2014 (Table 51, Figure 10)Figure 10. Trend of anaphylaxis in pregnancy as rate per 100,000 hospitalisations.. In 2010, there was an apparent reduction to 2.5 per 100,000 (95%CI: 1.4-3.6) pregnancy related hospitalisations; however this difference was not statistically significant (see Table 51, Figure 11).

Table 51. Incidence of anaphylaxis in pregnancy in the U.S.A. during 2004-2014.

Year	Unweighted number of hospital records	Weighted number of hospital records	Number of anaphylaxis episodes	Weighted sample	Rate per 100,000 hospitalisations	95% CI
2004	894589	4,181,660	31	143	3.4	(2.3-4.6)
2005	875702	4,139,434	29	132	3.2	(2.0-4.4)
2006	895518	4,214,792	32	149	3.5	(2.4-4.7)
2007	948092	4,468,572	32	158	3.5	(2.3-4.8)
2008	888796	4,146,832	35	163	3.9	(2.7-5.2)
2009	840729	4,037,117	37	173	4.3	(2.9-5.7)
2010	796916	3,809,515	19	94	2.5	(1.4-3.6)
2011	816475	3,765,168	40	186	4.9	(3.3-6.6)
2012	770955	3,854,776	35	175	4.5	(3.0-6.1)
2013	764959	3,824,793	37	185	4.8	(3.3-6.4)
2014	776122	3,880,610	27	135	3.5	(2.2-4.8)

Figure 10. Trend of anaphylaxis in pregnancy as rate per 100,000 hospitalisations.

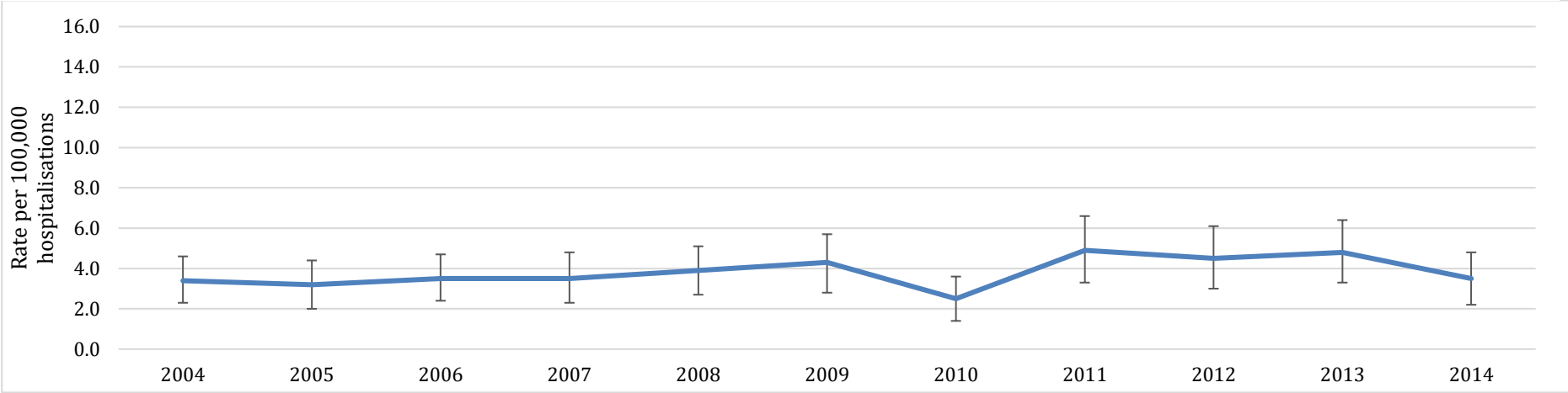


Figure 11. Trend of anaphylaxis in pregnancy in those who had caesarean deliveries as rate per 100,000 hospitalisations.

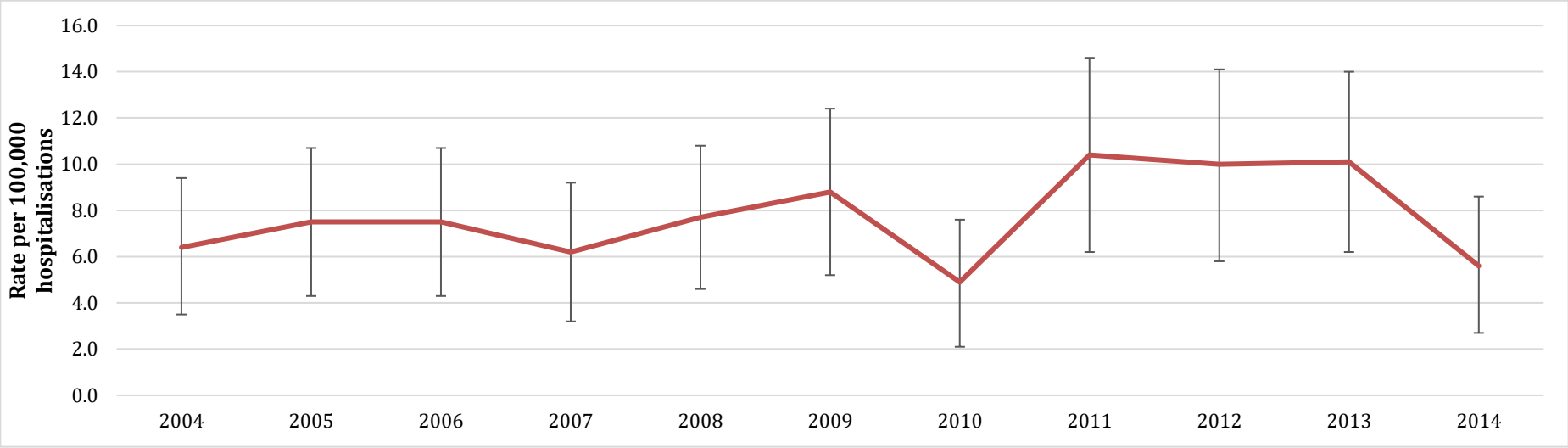


Table 52. Incidence of anaphylaxis in pregnancy in those with caesarean section in the United States of America during 2004-2014.

	Number of Caesareans	N. of anaphylaxis episodes with caesarean sections	Weighted number of anaphylaxis number of caesareans	Rate	95% CI	Rate ratio	95% CI	Weighted Rate ratio	95% CI
2004	265,181	17	79	6.4	(3.5-9.4)	2.9	(1.4-5.8)	3.0	(1.4-6.2)
2005	266,595	21	95	7.5	(4.3-10.7)	6.0	(2.7-13.5)	5.8	(2.6-12.8)
2006	278,049	21	98	7.5	(4.3-10.7)	4.2	(2.0-8.8)	4.3	(2.1-9.0)
2007	305,139	18	89	6.2	(3.2-9.2)	2.7	(1.3-5.4)	2.7	(1.3-5.6)
2008	283,929	22	102	7.7	(4.6-10.8)	3.6	(1.8-7.2)	3.5	(1.8-7.0)
2009	275,427	25	117	8.8	(5.2-12.4)	4.3	(2.1-8.5)	4.2	(2.0-8.9)
2010	256,217	12	60	4.9	(2.1-7.6)	3.6	(1.4-9.2)	3.6	(1.4-9.3)
2011	265,445	28	127	10.4	(6.2-14.6)	4.8	(2.5-9.5)	4.5	(2.3-8.8)
2012	251,357	25	125	10.0	(5.8-14.1)	5.2	(2.5-10.8)	5.2	(2.4-10.9)
2013	248,025	25	125	10.1	(6.2-14.0)	4.3	(2.2-8.6)	4.3	(2.2-8.6)
2014	248,667	14	70	5.6	(2.7-8.6)	2.3	(1.1-4.9)	2.3	(1.1-4.8)

*the rate ratio comparing reactions in caesarean delivery to vaginal delivery.

5.4.2.3 Anaphylaxis in caesarean deliveries in United States of America

The timing of the anaphylaxis cannot be determined from the database so the causal relationship between anaphylaxis and caesarean delivery remains unclear in the N.I.S. The incidence of anaphylaxis in those who had a caesarean delivery was at least double compared to anaphylaxis in all pregnancy related hospitalisations for each year (Table 52).

5.4.2.4 Characteristics of women with anaphylaxis in pregnancy – European study

The characteristics of women from the European countries are presented in Table 53. There were no statistical differences in the characteristics between the United Kingdom and France, Belgium and Finland (data not shown); accordingly results are presented as a combined cohort. The mean age of the study population was 32 (SD ±7) years old, approximately a fifth smoked during pregnancy and there was a median gestational age at delivery of 39 weeks (Interquartile range (IQR): 37-40) and the median BMI was 26 (Interquartile range (IQR): 23-29). Approximately a third of women were nulliparous and a third had a previous pregnancy problem. Over a tenth of women had a previous anaphylactic reaction and a third of women had a known drug allergy with the most common being a penicillin allergy.

Table 53. Characteristics of women with anaphylaxis in pregnancy in the INOSS study.

Characteristics		**INOSS n=63**	
Mean Age (SD) n=62		31.7	(6.7)
Smoking status			
	Never/ex-smoker	45	(77.6)
	Smoked during pregnancy	13	(22.4)
	Missing	5	
Median Gestational age at delivery (IQR)* n=56		39	(37-40)
Median BMI (IQR) n=59		26	(23-29)
Previous Obstetric History			
Parity			
	0	20	(31.7)
	1 or more	43	(68.3)
Previous Pregnancy Problem			
	Yes	20	(31.7)
	No	43	(68.3)
Previous Medical History			
Previous anaphylactic reaction			
	Yes	7	(11.1)
	None	56	(88.9)
Known drug allergy			
	Yes	19	(30.6)
	None	43	(69.4)
	Missing	1	
Type of drug allergy			
	Penicillin based	14	(73.7)
	Other	5	(26.3)
History of atopy			
	Yes	20	(32.8)
	No	41	(67.2)
	Missing	2	
History of any allergic reaction			
	Yes	34	(54)
	None	29	(46)
History of any allergic reaction or atopy			
	Yes	38	(60.3)
	No	25	(39.7)

5.4.3 Management of anaphylaxis

The United Kingdom and mainland European countries had similar proportions of women receiving oxygen and IV fluid to manage the reaction. There was a difference in the proportion of women receiving epinephrine between Finland, Belgium and France and the United Kingdom (68% vs. 93%, P<0.05, respectively). In a sensitivity analysis, women who had a reaction earlier than 2012 were excluded. In this restricted cohort, 85% (n=44) received epinephrine and corticosteroid (n=45, 88%) while 67% (n=29) of women received antihistamine (Table 54).

Table 54. Management of anaphylaxis in pregnancy in United Kingdom compared to European nations.

Managements		**France, Belgium, and Finland (n=28)**		**United Kingdom (n=35)**		**Combined n=63**		**Combined without Finland <2012 n=58**	
High flow O_2	*Yes*	22	(88)	27	(79.4)	49	(83.1)	46	(83.6)
	No	3	(12)	7	(20.6)	10	(16.9)	9	(16.4)
IV fluids	*Yes*	25	(92.6)	30	(85.7)	55	(88.7)	50	(87.7)
	No	2	(7.4)	5	(14.3)	7	(11.3)	7	(12.3)
Epinephrine	*Yes*	19	(67.9)	27	(93.1)	46	(80.7)	44	(84.6)
	No	9	(32.1)	2	(6.9)	11	(19.3)	8	(15.4)
Antihistamine *	*Yes*	3	(20)	26	(86.7)	29	(64.4)	29	(67.4)
	No	12	(80)	4	(13.3)	16	(35.6)	14	(32.6)
Corticosteroid**	*Yes*	17	(77.3)	32	(97)	49	(89.1)	45	(88.2)
	No	5	(22.7)	1	(3)	6	(10.9)	6	(11.8)
Tryptase levels tested Yes		14	(53.8)	30	(85.7)	44	(72.1)	44	(78.6)
Had abnormal tryptase levels		11	(84.6)	8	(32.0)	19	(50)	19	(50)

Percentages are calculated for those with complete data.

5.4.4 Suspected causal agents

More reactions occurred before delivery than after (36 vs. 27, respectively) with 16 occurring in the antenatal period (not at delivery) and 20 occurring just before delivery. Immediately post-delivery reactions made up over a third of all of all reactions. (Figure 12, Table 55). Three of the fourteen women who had a known penicillin allergy were given a penicillin-based antibiotic resulting in an anaphylactic reaction.

The majority of reactions that were immediately before delivery occurred in women undergoing a caesarean delivery (n=19). Eight reactions were as a result of prophylactic antibiotics before caesarean section, two reactions were the result of antibiotics administered for premature rupture of membranes, three reactions were as a result of prophylactic antibiotics for GBS infection and five occurred after administration of anaesthetic agents and two reactions occurred as a result of other agents.

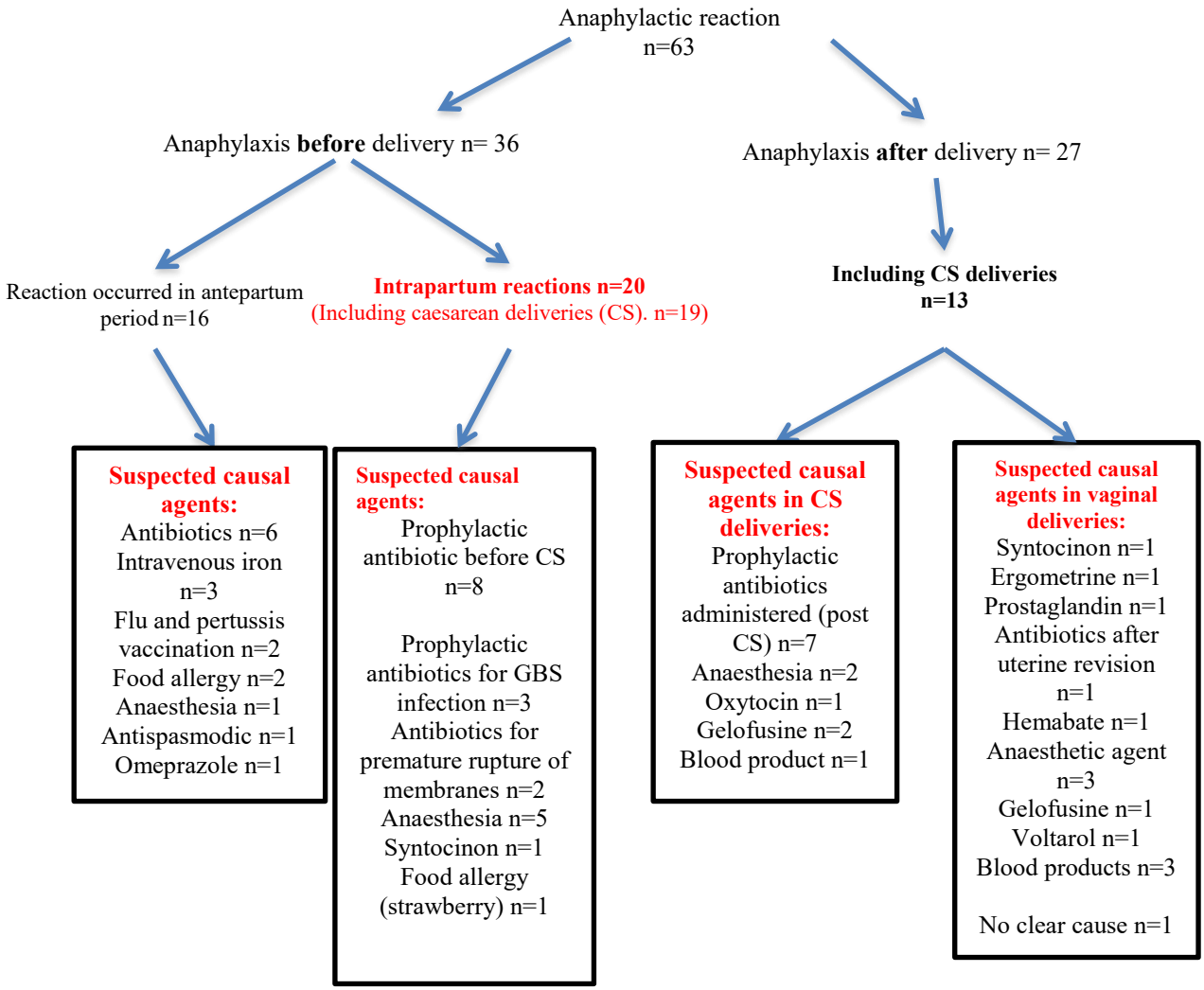
In those who had reactions after delivery, approximately a half of women (n=12, 44%) had a reaction to an agent given for the management or resuscitation of a postpartum haemorrhage.

Overall there were eleven reactions related to anaesthesia (Figure 12). The agents included suxamethonium (n=6), suxamethonium and thiopentone (n=1), lidocaine (n=1), sugammadex (n=1) and unspecified agent but temporally related to anaesthesia (n=2).

Table 55. Timing of anaphylactic reaction

Timing of delivery (n=63) n(%)		
Anaphylactic reaction occurred before delivery	36	(57.1)
Reaction occurred in antepartum period	16	(25.4)
Reaction occurred in intrapartum reaction	20	(31.7)
Caesarean delivery	19	(30.0)
Anaphylactic reaction occurred after delivery	27	(42.9)
Vaginal deliveries	14	(22.2)
Caesarean deliveries	13	(20.6)

Figure 12. Suspected causal agents in the INOSS study population by time of reaction according to delivery.



5.4.5 Maternal outcomes

Overall, two women died giving a case fatality rate of 3.2% (95% CI: 3.9-11.0) in women who had anaphylaxis during pregnancy and over a tenth of women had a severe maternal morbidity. The most common morbidity was a cardiac arrest (n=3). In addition, approximately a half of women with anaphylaxis in pregnancy were admitted to ITU and/or required ventilation (see Table 56).

5.4.6 Perinatal outcomes in infants born after an anaphylactic reaction

There were no perinatal deaths or stillbirths to mothers who had anaphylaxis before delivery. In infants born after a maternal anaphylactic reaction, the rate of neonatal encephalopathy was 9.1% (95% CI: 1.9-24.3) with 4 out of 5 the infants known to have been cooled. Over a third of infants were admitted to NICU and 16% of infants had an Apgar score at 5 minutes that was less than 7 (see Table 57).

5.4.6.1 Maternal and perinatal outcomes in the United States of America

The number of outcomes in the sample was too small to be presented in this chapter and have been suppressed according to the N.I.S. analytic requirements. For the period 2004-2014, the national estimated number of cardiac arrests and/or deaths that occurred during an admission related to anaphylaxis was 19 women (95% CI: 0-36.8%). The maternal hospitalisation was not linked to the infant's record so no perinatal outcomes were available.

Table 56. Maternal outcomes in the INOSS study.

Maternal outcomes		INOSS n=63	
Maternal death		2	(3.2)
Severe maternal morbidity*		7	(11.1)
	Cardiac arrest	3	(4.8)
	Thrombotic event	2	(3.2)
	*Other***	3	(4.8)
ITU admission		30	(47.6)
Intubation required***		13	(48.0)

*Morbidities that resulted in maternal deaths included
**acute renal injury, acute cardiac failure and thrombopenia (n=1); respiratory arrest (n=1) and stress cardiomyopathy (n=1)
***Only collected in France, Belgium and Finland

Table 57. Perinatal outcomes of those who had a reaction before delivery in the INOSS study.

Neonatal outcomes		Combined (n=37)*	
Perinatal death	*Yes*	0	(0)
	No	33	(100)
	Missing	4	
Neonatal ICU admission			
	Yes	12	(35.3)
	No	22	(64.7)
	Missing	3	
Neonatal encephalopathy			
	Yes	5	(14.3)
	No	30	(85.7)
	Missing	2	
Baby cooled			
	Yes	4	(80.0)
	Unknown	1	(20.0)
Apgar @ 5min < 7			
	No	26	(83.9)
	Yes	5	(16.1)
	Missing	6	

*Two infants had no known delivery information these are included in the missing category

5.4.7 Risk factors for anaphylaxis in pregnancy

5.4.7.1 Characteristics of anaphylaxis in pregnancy in the N.I.S.

The characteristics of women and risk factors for anaphylaxis in pregnancy are presented in Table 58. Women who had anaphylaxis during a pregnancy related hospitalisation tended to be slightly older, have a “black” or “other” racial identity, have had a caesarean delivery during the hospitalisation, had a prior history of an allergic reaction, received Medicaid and had been admitted during a weekday. There appeared to be no difference in the distribution of median household income according to anaphylaxis status.

The results of the multivariable unconditional logistic regression analysis are presented in Table 59**Error! Reference source not found.**. After adjustment, three factors were statistically significantly associated with anaphylaxis in pregnancy. Women who had a history of an allergy had four times the odds of having an anaphylactic reaction [aOR: 4.05 (95%CI: 2.64-6.23)] compared to women with no history of an allergy. Women who had a caesarean birth had over four times the odds of having an anaphylactic reaction compared to women who did not have a caesarean birth [aOR:4.19 (95% CI:3.21-5.35)]. The odds of anaphylaxis during a pregnancy related hospitalisation were 1.57 times higher in black women [aOR: 1.57 (95% CI: 1.15-2.15)] and women of other racial identity [aOR: 1.9 (95% CI: 1.08-2.63)] compared to white women. The results for the proxy variable model or the two sensitivity analyses did not materially change the results.

Table 58. Characteristics and risk factors for anaphylaxis in pregnancy.

		No Anaphylaxis in pregnancy (n= 9,268,499)		Anaphylaxis in pregnancy (n=354)		Unadjusted Odds Ratio	95% CI	P-value
Age	*mean (sd)*	28	(6.24)	28.8	(6.07)	1.02	(1.01-1.04)	0.003
Race								
	White	4,021,467	(52.2)	135	(45.9)	1.00		
	Black	1,069,795	(13.9)	57	(19.4)	1.57	(1.15-2.15)	0.005
	Hispanic	1,787,349	(23.2)	58	(19.7)	0.94	(0.69-1.29)	0.717
	Asian or Pacific Islander	394,592	(5.1)		*		*	0.102
	Native American	60,938	(0.8)		*		*	0.498
	Other	371,882	(4.8)	21	(7.1)	1.62	(1.04-2.52)	0.035
	Missing	1,562,476		60				
Caesarean Section								
	No	6,324,696	(68.2)	126	(35.6)	1.00		
	Yes	2,943,803	(31.8)	228	(64.4)	3.84	(3.09-4.78)	<0.001
History of allergy code								
	No	9,082,778	(98)	326	(92.1)	1.00		
	Yes	185,721	(2)	28	(7.9)	4.13	(2.76-6.18)	<0.001
Primary expected payer								
	Medicare	64,763	(0.7)		*	*		0.31
	Medicade	3,936,464	(42.5)	174	(49.2)	1.00		
	Private Insurance	4,672,033	(50.5)	150	(42.4)	0.72	(0.58-0.90)	0.003
	Self Pay	310,077	(3.4)	16	(4.5)	1.14	(0.70-1.86)	0.592
	No charge	18,535	(0.2)		*	*		0.808
	Other	250,528	(2.7)	12	(3.4)	1.09	(0.60-1.95)	0.784
	Missing	16,099		0				
Admitted on weekend								
	No	7,469,510	(80.6)	307	(86.7)	1.61	(1.19-2.19)	0.001
	Yes	1,798,987	(19.4)	47	(13.3)	1.00		
	Missing		*	0				
Median household income								
	Lowest quartile	2,024,018	(27.5)	82	(28.3)	1.00		
	Quartile 2	1,872,337	(25.4)	77	(26.6)	1.02	(0.75-1.40)	0.895
	Quartile 3	1,811,405	(24.6)	70	(24.1)	0.98	(0.71-1.35)	0.889
	Highest quartile	1,650,873	(22.4)	61	(21)	0.93	(0.66-1.29)	0.649
	Missing	1,909,866		64				

*numbers suppressed

Table 59. Risk factors for anaphylaxis in pregnancy using a multivariable model.

		Main model			Proxy variable model			Sensitivity 2*			Sensitivity 3†		
		Odds ratio	95% CI	P-Value	Odds ratio	95% CI	P-Value	Odds ratio	95% CI	P-Value	Odds ratio	95% CI	P-Value
History of allergy code	No	1			1			1			1		
	Yes	4.05	(2.64-6.23)	<0.001	3.90	(2.60-5.87)	<0.001	3.83	(2.55-5.75)	<0.001	3.93	(2.61-5.92)	<0.001
Caesarean Section	No	1			1			1			1		
	Yes	4.19	(3.28-5.35)	<0.001	3.78	(3.04-4.70)	<0.001	3.77	(3.03-4.69)	<0.001	3.79	(3.05-4.72)	<0.001
Race	White	1			1			1			1		
	Black	1.57	(1.15-2.15)	0.005	1.57	(1.15-2.15)	0.005	1.48	(1.10-1.99)	0.010	1.38	(1.07-1.79)	0.013
	Hispanic	1.00	(0.73-1.38)	0.977	1.00	(0.73-1.37)	0.993	0.94	(0.70-1.27)	0.684	1.00	(0.73-1.37)	0.991
	Asian or Pacific Islander	1.58	(0.97-2.57)	0.066	1.57	(0.97-2.56)	0.068	1.48	(0.92-2.38)	0.109	1.57	(0.97-2.56)	0.068
	Native American	1.55	(0.49-4.87)	0.452	1.55	(0.49-4.85)	0.455	1.45	(0.47-4.54)	0.520	1.55	(0.49-4.85)	0.455
	Other	1.69	(1.08-2.63)	0.021	1.68	(1.08-2.63)	0.022	1.58	(1.02-2.44)	0.039	1.68	(1.08-2.63)	0.022
	Missing	-	-	-	1.24	(0.91-1.70)	0.171	-	-	-	-	-	-

Adjusted for history of allergy, caesarean section and race. *Missing included in the white category of race. ** Missing included in the black category of race.

5.5 Discussion

5.5.1 Main findings

5.5.1.1 European countries

This chapter established that a multinational study using data collected through surveillance systems and a combination of medical records and registry data was feasible and allowed the study of a rare complication of pregnancy, such as anaphylaxis in pregnancy. This chapter provided a more accurate estimation of the causal agents and outcomes of anaphylaxis. The Finnish study, using both a registry and case notes, highlighted that relying solely on ICD-10-CM codes may provide inaccurate estimates of incidence, as about half of cases proved to be ineligible when cases notes were examined (1.5 per 100,000 maternities (95% CI: 1.1-1.9) . The use of a uniform case definition and data collection system allowed the cases and data to be comparable across countries. As a result, a rigorous population-based study has been completed across four European countries.

5.5.1.2 United States of America

The use of the N.I.S. from the United States of America provided much larger numbers of women with anaphylaxis in pregnancy. Unlike the Finnish study, there was no verification of the cases included so it is likely that this incidence estimate contains false positives. The incidence from the U.S.A., which used routine data sources, was over twice that of the European incidence. On the other hand, the dataset provided an ideal population-based comparator allowing the risk factors for anaphylaxis to be examined. However, the dataset was limited in the granularity of the information provided, in particular, it lacked details about causal agents or outcomes.

5.5.2 Chapter in context

5.5.2.1 Prospective study (Belgium, France, the Netherlands and United Kingdom) benefits and challenges

5.5.2.1.1 Benefits

This is the first prospective study to be completed using an international collaboration to study anaphylaxis in pregnancy. This multinational study which included three countries with obstetric surveillance systems and two other countries using other similar methodologies has provided a large-scale study of a very rare complication of pregnancy.

The prospective study design has the added advantage of being able to use a uniform case definition across nations, which overcame some of the limitations of the previous chapters. This helped to ensure that comparisons were robust and enabled a combined analysis. In addition, the use of an online data collection system and identical questions ensured that all data were the same, allowing a thorough comparison to be made between countries and facilitating ease of analysis.

5.5.2.2 Challenges

Prospective studies have the same limitations as national surveillance systems as they rely on reporters to identify cases within each maternity unit; as a result this study was susceptible to under ascertainment. In the case of the Netherlands, we did not have any reported cases entered onto the data entry system; as a result, they were not included in any of the descriptive analyses other than incidence. The French data collection system relied on reporting from either an anaesthetist or a positive tryptase result. However, all women who deliver in France are visited by an anaesthetist, making it

likely that there is high case ascertainment in France and it is also highly likely that an anaesthetist will be involved in the resuscitation of a woman with anaphylaxis. Due to the rigorous case definition, the study population is unlikely to have contained very many false positive cases. With no comparison group other than the background population numbers, it was not possible to calculate estimates for risk factors.

5.5.2.3 Combination of registry data and hospital records (Finland)

5.5.2.3.1 Benefits

This method allowed routinely identified cases of anaphylaxis to be validated against the hospital records and this prevented false positives from being included in the study population. Extraction of data and entry into a tailored data collection form allowed the Finnish retrospective data to be comparable with the data from the prospective studies.

The Finnish registry data is useful when studying rare complications as it can take years to accrue enough cases for a robust epidemiological study using prospective methods. The retrospective registry allowed immediate access to many cases that would normally take a decade to collect in Finland. The cases were analysed in one cohort over 10 years, as there was a relatively small number of births each year.

5.5.2.3.2 Challenges

Similar to the National Inpatient Sample this method relied on ICD-10-CM codes for the identification of cases with anaphylaxis. Consequently, the sample was still vulnerable to false negatives and was reliant on the accuracy of the coding of clinical data for the identification of women with anaphylaxis. The validation of cases resulted in the removal of over a half of women identified using ICD-10-CM codes. Also, as the sample was retrospective, it is possible that the management of anaphylaxis was

historically different to that during the period of the prospective study. To account for this limitation, a sensitivity analysis excluded Finnish cases that occurred before the start of the United Kingdom study. This analysis showed that there was no material difference in excluding the Finnish cases.

In addition, Finland only included births >22 weeks of gestation, while other countries' cases were not restricted by gestational age. As a result, the incidence of anaphylaxis in pregnancy in Finland may be an underestimate; however, only a small number of women are likely to have had anaphylaxis before 22 weeks of gestation.

5.5.2.3.3 Benefits

Use of a routine data source from the U.S.A. enabled the estimate of the incidence of this rare complication of pregnancy over a ten-year period in the whole of the United States, which represents a very large number of pregnant women. Studies that use routine data sources also benefit from relatively easy access. In addition, the N.I.S. provided an ideal comparison population to allow the risk factors for anaphylaxis to be explored.

5.5.2.3.4 Challenges of using routine data sources

The findings are only as reliable as the validity and sensitivity of the ICD-9-CM codes used to code the clinical data. The coding of anaphylaxis using the World Health Organization International Classification of Diseases may under-report the true number of cases of anaphylaxis (Tanno et al., 2017). In particular, studies have shown ICD-9-CM codes were only 66% sensitive in identifying this condition (Walsh et al., 2013). For example, cases that occurred in the community and did not need hospitalisation were not identified. This would only be a salient issue if the woman died in the

community, which would have resulted in an underestimate of the poor outcomes associated with the condition. Previous research has shown that ICD codes are not sensitive when identifying anaphylaxis, which may result in false negatives in the sample (Walsh et al., 2013, Tanno et al., 2017). Furthermore, there may have been other inaccuracies in the coding as 0.5% of the sample had a pregnancy code but were coded as male.

5.5.2.3.5 Why did the U.S.A. have a larger incidence? Other explanations?

The larger incidence within the U.S.A. may be explained by misclassification within the routinely collected data from U.S.A. The findings from the Finnish study showed an approximate halving in the confirmed number of cases of anaphylaxis after data validation, compared to those identified solely using ICD-10-CM classification codes. This suggests that validation of cases is essential when undertaking analyses of rare complications from routine data sources. Without verification from the medical records it is impossible to show how many cases were false positives. A similar finding was shown in a previous study of amniotic fluid embolism (Knight et al., 2012). Had the misclassification in the U.S.A. been at a similar level to that in Finland (60%), then the incidence would have been similar to the European estimate.

5.5.3 Findings in context

5.5.3.1 Incidence

This study suggested international variations in the incidence of anaphylaxis in pregnancy. There have been no other population-based studies in Europe to determine the incidence of anaphylaxis in pregnancy, however, the incidence of anaphylaxis in the U.S.A. was similar to a previous retrospective study in Texas, which used an obstetric database and estimated the incidence to be 2.7 per 100,000 deliveries (95% CI:1.7-4.2) (Mulla et al., 2010). Data collected nationally across five European countries suggests the incidence to be lower than estimated in the U.S.A.

5.5.3.1.1 Why did the U.S.A. have a larger incidence? Possible explanations

As discussed, it is most likely the difference in incidence between the European studies and the U.S.A was the result of misclassification and coding errors. Without verification from the medical records it is not possible to determine if this was the case. It is possible, but unlikely, that the incidence was higher in the U.S.A. than the European countries. A possible explanation for a higher incidence within the U.S.A. may be the routine bacteriological screening for GBS. This policy has increased the proportion of women receiving intrapartum antibiotics for GBS, which may have resulted in the higher incidence in the N.I.S. sample compared to the United Kingdom (Verani et al., 2010). In the United Kingdom, there is a risk-based prevention strategy for GBS infection (Di Renzo et al., 2015, Royal College of Obstetricians and Gynaecologists, 2012). Conversely, differences in GBS screening policies do not explain the differences in the incidence between France and the U.S.A. (Mereghetti et al., 2007).

The inclusion of false positives into the N.I.S. sample, may have influenced the results of the risk factors analysis. Differential misclassification would have biased the results of this analysis if they were unevenly distributed between the categories of the risk factors. Non-differential misclassification would have been evenly distributed between the categories of the risk factors and would have resulted in the wrong magnitude of point estimate.

5.6 Conclusion

The prospective study of a very rare complication of pregnancy was achieved across four European nations. A uniform case definition was used together with a single data collection system that allowed a comparable study from the onset. This study showed variation in the incidence between routine data sources and data collected using medical records either through an obstetric surveillance system or alongside a birth registry. Anaphylaxis is a very rare complication during pregnancy but has severe outcomes for both mother and baby. The majority of reactions occur at the time of delivery and is often the result of antibiotic administration or the use of anaesthetic agents. Furthermore, not every woman received epinephrine in this study, which has demonstrated that clinical management can be improved.

Chapter 6. Discussion

6.1 Main findings

The studies conducted and reported in this DPhil thesis illustrate the utility of using multinational collaborative studies to contribute evidence to the improvement of outcomes and prevention of rare and severe complications of pregnancy. The second chapter, investigating extreme maternal obesity, showed that it is feasible for data to be pooled from completed international studies on a severe and rare exposure; thus this enabled an examination of rare outcomes associated with a rare exposure. However, even data from two national studies did not provide a sample large enough to investigate the rarest of outcomes, such as perinatal death or stillbirth. The third and fourth chapter, examining massive transfusion in obstetric haemorrhage and abnormally invasive placenta, enabled cross-country comparisons of obstetric and haematological management. Furthermore, in the case of women who had a total blood volume or more transfused, between country comparison demonstrated that variation in haematological features by aetiology of haemorrhage was replicated across countries. The fourth chapter illustrated that by the pooling of data from France and the United Kingdom the comparison of uncommon modalities of management in a rare complication of pregnancy, abnormally invasive placenta, was possible.

Chapters that made use of previously collected data were limited to national studies with comparable definitions and data items. To overcome these limitations, a rigorous prospective international study was conducted using a uniform case definition and a single data collection system from the outset. The findings of this research are presented in the fifth chapter, which demonstrated the feasibility and benefits of completing a population-based study across five European countries. In particular, this

methodology doubled the number of cases of an extremely rare complication of pregnancy, namely, anaphylaxis. As a result of this increase in numbers the findings enable a more precise estimate of the frequencies of the causal agents and outcomes associated with this potentially fatal condition.

6.2 Chapter summaries

6.2.1 Methodological summary: extreme maternal obesity

6.2.1.1 Rare outcomes

This chapter has shown that the combination of two national studies increased the statistical power of testing and precision to estimate the incidence of more common maternal and infant outcomes in extremely obese women. Extreme maternal obesity was associated with an increased likelihood of a number of adverse maternal and perinatal outcomes such as hypertensive disorders, wound infection after caesarean delivery, macrosomia, and poor infant condition. However, even after combining two national cohorts, this study did not have sufficient statistical power to detect an association between extreme obesity and both perinatal death and stillbirth. Furthermore, data on shoulder dystocia was not available in the Australian comparison cohort; as a result, this rare outcome could not be assessed in this analysis.

6.2.1.2 Rare exposures

The combination of two national studies enabled the examination of a subset of the more extreme end of the BMI spectrum. Interestingly, the BMI>60 kg/m^2 group had an increased risk of preeclampsia compared to women with a BMI >50-<60 kg/m^2. The BMI>60 kg/m^2 cohort does not appear to have an excess burden of perinatal risk

compared to women with BMI >50-<60 kg/m^2 but again the role of chance could not be excluded, for most outcomes, even with the pooling of two national studies. Nevertheless, this comparison did show differential management of thromboprophylaxis between the two extremely obese groups. This demonstrates an area of delivery of clinical care that requires improvement as all extremely obese women are at increased risk of a thrombotic event.

6.2.2 Methodological summary: massive transfusion in major obstetric haemorrhage

Chapter three examined massive transfusion in major obstetric haemorrhage and it highlighted a number of benefits of multinational studies. In an attempt to overcome the limitations of chapter two, this chapter increased the number of countries included in the comparative and combined analyses. This type of multinational study provided a comparison of haematological management across countries, which showed large variation in clinical practice but there was no apparent difference in maternal outcomes. The pooling of data replicated the observed variation of haemostatic features by aetiology of haemorrhage across multiple countries.

6.2.2.1 Clinical utility of multinational studies

6.2.2.1.1 Differential management of massive transfusion

The chapter on massive transfusion in major obstetric haemorrhage illustrated the utility of a comparative analysis of haematological management across countries. Even though the same evidence on haematological management is available to clinicians and guideline writers, each country has its own preference for blood components and haemostatic agents used during resuscitation. A multinational comparison was

achieved, which described variations in haematological management and the potential impact on outcomes. In spite of variations in the use of blood components and haemostatic agents, there did not appear to be differences in maternal outcomes across countries. Even with multiple national studies, adverse outcomes were rare and therefore limited the power to detect as statistically significant some clinically important differences that were suggested by the analysis in this study. For example, women who had abruption had a higher proportion of poor outcomes such as maternal mortality but this was not statistically significantly different.

6.2.2.1.2 Replication of characteristic of haemostatic features by aetiology.

Multinational studies are useful in terms of replicating findings across multiple countries to provide stronger evidence that a phenomenon actually exists in the population of interest (Moonesinghe et al., 2007, Hill, 1965). This chapter demonstrated that haemostatic features were replicated across countries and haemostatic features differed according to the aetiology of haemorrhage. In particular, women with haemorrhage as a result of abruption had the lowest values of fibrinogen, while women with trauma had the highest values of platelet count and fibrinogen. This suggests that use of blood products should be tailored to the cause of haemorrhage. However, despite the observed differences in haematological parameters, the main blood components administered (RBC, FFP and platelets) did not differ according to aetiology.

6.2.3 Methodological summary: abnormally invasive placenta

Chapter four included a binational study that investigated abnormally invasive placenta. This binational study demonstrated the added advantage of comparing countries with different modalities of management. In addition, through a pooled analysis, the binational study enabled the examination of a rare management and its associated maternal and infant outcomes.

6.2.3.1 Clinical utility of multinational studies

6.2.3.1.1 Cross-country comparison of obstetric management

Binational studies are at their most useful when comparing countries with different modalities of management. These studies can generate hypotheses on whether differences in management are reflected in differences in outcomes. This chapter showed cross-country differences in the management of AIP between the United Kingdom and France. In particular, there was a larger proportion of women in the United Kingdom who had a manual removal of placenta and a hysterectomy than women in France. Furthermore, France had a higher proportion of women who were managed with a conservative approach than the United Kingdom. These differences in management were reflected in differences in outcomes. In particular, there was a larger proportion of women with severe postpartum haemorrhage in the United Kingdom, while in France, there was a larger proportion of women who had an infection.

6.2.3.1.2 Examination of a rare management in a rare complication

The added benefit of a multinational study on AIP is that through the pooling of data it enabled the comparison of rare modalities of management. In rare conditions it is difficult to study the impact of management on outcomes in pregnancy due to small

sample sizes. It is even more difficult to examine approaches to management that are used rarely, such as a conservative approach. This chapter completed a pooled analysis that showed a planned conservative approach was associated with a lower level of blood loss than those who had a planned hysterectomy. As a result, this chapter has provided the best available evidence where an RCT would have been extremely difficult.

6.2.4 Methodological summary: anaphylaxis in pregnancy

Chapter five was designed to overcome the limitations of comparability, which were common in the previous chapters, through a multinational prospective study. It overcame comparability issues by using a uniform case definition across all participating European nations. In addition, the use of a single online data collection system ensured that all data items were alike allowing a robust pooled analysis to be undertaken. The findings demonstrate that a multinational study using surveillance systems, and a combination of medical records and registry data, to study a rare complication, such as anaphylaxis in pregnancy, was feasible and beneficial. Multi-national studies, examining a very rare complication, provided a more accurate estimation of the causal agents and outcomes than a single national study due to the doubling of the sample size.

Furthermore, this chapter highlighted the importance of validating cases as the Finnish registry data was validated using the women's medical records. These findings showed that relying solely on ICD-10-CM codes may provide an inaccurate estimate of incidence (Knight et al., 2012).

6.3 Clinical implications

6.3.1 Extreme maternal obesity

The study of extreme maternal obesity (chapter two) showed that women who were extremely obese have a higher risk of poor maternal and infant outcomes than those with a lower BMI. The results of this study suggest that there is no threshold BMI level for poor outcomes. As a result those in the highest BMI categories may benefit from losing weight before pregnancy even if they have no possibility of regaining a normal BMI.

The BMI ≥60 kg/m^2 analysis, shows that the degree of relative obesity impacted on thromboprophylaxis practice. The RCOG's guideline states that any women with a BMI >40kg/m^2 should be considered at intermediate risk of a thrombotic event and should be considered for 10 days of thromboprophylaxis postpartum (Royal College of Obstetricians and Gynaecologists, 2015b). Within Australia there is regional variation on the guidelines concerning BMI and postpartum thromboprophylaxis. In Queensland the guideline suggests that a woman must possess three or more risk factors (BMI >30 kg/m^2 being one of these risk factors) to be given low molecular weight heparin for 6 days postnatally, while the South Australian government and current expert opinion recommends that BMI ≥30 kg/m^2 plus another major risk factor for postpartum thromboembolism requires prophylactic anticoagulation for 5 days postpartum (Mclintock et al., 2012, South Australian Maternal & Neonatal Clinical Network, 2013). As there was large variation in practice within a sub study of women with a BMI > 50 kg/m^2 this suggests that the guidelines are variably followed and there is a place for more implementation work. Nevertheless, the results suggest that BMI does

influence clinical decisions when administering thromboprophylaxis postnatally. Of note, there were no thrombotic events in the BMI ≥60 kg/m^2 group, which was the group in which the larger proportion of women received thromboprophylaxis.

6.3.1.1 Findings placed in context of literature

6.3.1.1.1 Wound infection after caesarean section

The results of this study and previous research have suggested there is an association between maternal obesity (BMI > 30kg/m^2 or BMI ≥60 kg/m^2) and wound infection after a caesarean delivery (Marchi et al., 2015, Kim et al., 2017). NICE guidance recommends that routine use of prophylactic antibiotics should be administered to all women who receive a caesarean delivery (National Institute for Health and Care Excellence, 2011). Future research should consider examining the dose extremely obese women receive. It is possible that extremely obese women who received appropriate treatment still developed a wound infection. There is currently little evidence examining weight appropriate antibiotic dosages (Falagas, 2016).

6.3.1.1.2 Hypertensive disorders of pregnancy

There is a strong body of evidence showing an association between maternal obesity and an increased risk of hypertensive disorders (Wang et al., 2013, Marchi et al., 2015); this relationship has also been shown in the extreme maternal obesity literature (Alanis et al., 2010, Marshall et al., 2012, Nieuwoudt et al., 2014). With larger numbers, the study reported here was able to more precisely estimate the size of the association, showing that extremely obese women had seven times the odds of preeclampsia compared to a lower BMI population.

6.3.1.1.3 Mode of delivery

The findings in relation to mode of delivery are consistent with the findings of a review that showed obese women were at increased risk of caesarean delivery (Chu et al., 2007) and the findings are also consistent with other studies of the extreme maternal obesity literature (Alanis et al., 2010, Nieuwoudt et al., 2014, Marshall et al., 2012). Despite an increased risk of complications from anaesthetic administered during surgical interventions, extremely obese women were more likely to be delivered by caesarean section (Rao and Rao, 2010). There are many clinical factors that may lead to the decision to deliver an obese woman by caesarean; some of these include: increased risk of shoulder dystocia, failure to progress, infant distress and previous caesarean deliveries (Chu et al., 2007). Added to this, as particularly pertinent in extremely obese women, is the fear of anaesthetic difficulty if emergency delivery is required. This emphasises that clinicians considering mode of birth for extremely obese women should ensure that there are the necessary facilities for an emergency situation, when problems with surgery are anticipated for women with planned caesarean sections.

6.3.1.1.4 Infant outcomes

Meta-analysis of observational research has shown that a high pre-pregnancy body mass is associated with infant macrosomia (Yu et al., 2013). In particular, there is a positive relationship between maternal body mass and infant birthweight. The findings of this study are consistent with both the wider literature on obesity in pregnancy (Yu et al., 2013) and extreme maternal obesity (Marshall et al., 2014). Similarly, the association between maternal obesity with poor infant's condition immediately after birth, is supported by both a wider maternal obesity review (Zhu et al., 2015) and literature on extreme maternal obesity (Alanis et al., 2010).

6.3.2 Massive transfusion in major obstetric haemorrhage

The study reported in chapter three showed that the use of blood components or haemostatic agents varied between countries. The largest variation in blood products occurred for the use of fibrinogen, tranexamic acid and factor VIIa. This may reflect the paucity of evidence available for each haemostatic agent. In the absence of concrete evidence each country has a preferred treatment regime. In spite of differences in haematological management across nations, maternal outcomes did not appear to differ although the numbers of events were small.

6.3.2.1 Use of blood products: context of findings

6.3.2.1.1 Fibrinogen and cryoprecipitate

This study showed that clinicians in the United Kingdom and Australia mainly used cryoprecipitate as a source of fibrinogen while in Italy, France and the Netherlands clinicians only used fibrinogen concentrate. There is a scarcity of evidence regarding the efficacy of administering fibrinogen concentrate; the FIB-PPH trial compared the use of fibrinogen concentrate to placebo but the intervention did not reduce the primary outcome, of postpartum bleeding (Wikkelsoe et al., 2012). A comparison of cryoprecipitate to fibrinogen concentrate has yet to be undertaken and this trial would be difficult to conduct due to the differences in the components of the agents. As a result, there is no evidence to guide practice which might explain why there are variations in the use of fibrinogen and the type of fibrinogen source used across countries.

6.3.2.1.2 Tranexamic acid

At the time of the data collection for this study there was a lack of high quality evidence on the use of TXA in the treatment of obstetric haemorrhage, and there was also variation in its use. The trials were either too small to detect a statistically significant difference in the primary outcome (Xu et al., 2013) or did not have the power to examine safety issues of the drug (Ducloy-Bouthors et al., 2011). This lack of assurance in efficacy and safety of TXA is likely to have an impact on the recommendations in guidelines and could explain the variations seen internationally at this time. The findings of the WOMAN trial have now been released which are likely to impact on future clinical practice and guidelines (WOMAN Trial Collaborators, 2017).

6.3.2.1.3 Colloids and crystalloids

In this study there were consistently large quantities of colloids and crystalloids used in resuscitation between countries and for different causes of haemorrhage. Current guidelines recommend limited use of fluids in resuscitation; the CNOG guideline in France, recommended the use of only crystalloids, whereas in this study colloids were administered (Sentilhes et al., 2016). The RCOG in the United Kingdom recommend a maximum use of 2 litres of crystalloids (Mavrides et al., 2016). The current trauma and haematology literature recommends that the use of large quantities of fluid are avoided due the increased dilution of coagulation factors leading to a reduced clot strength and potentially fatal development of DIC (Collis and Collins, 2015). Colloids, such as hydroxyethyl starches, have been shown to interfere with fibrin which reduces clot strength (Fenger-Eriksen et al., 2010). In addition, it is likely that colloids increase the require for blood transfusion; however, the use of either colloids or crystalloids did not

appear to make a difference to mortality in critically ill patients (Lewis SR et al., 2018). There remains a debate around the use of fluids in resuscitation protocols and trials in obstetric haemorrhage are yet to test the safety of fluids in resuscitation. Further work is required to determine if naturally occurring fluids such as albumin or FFP may be better alternatives for fluid resuscitation.

6.3.2.1.4 Factor VIIa

Current guidelines (Sentilhes et al., 2016, Mavrides et al., 2016, Hunt et al., 2015) recommend that factor VIIa should not be given in obstetric haemorrhage. Approximately 12% of women received the haemostatic agent in this international study. A Cochrane review showed that there was weak evidence to support the efficacy of Factor VIIa in general; and, there is evidence to suggest an increased risk of thromboembolic events with the use of the Factor VIIa (Simpson et al., 2012). This study did not have a large enough sample size to examine adverse effects; however, it is worrying that such a large number of women received this drug with known risk of thromboembolic events.

6.3.2.2 Blood components and haemostatic agents by aetiology

Current guidelines recommend that blood products should be given in accordance with haemostatic abnormalities (Hunt et al., 2015, Collis and Collins, 2015). This study showed that haemostatic features differed according to aetiology of PPH. Despite differences in haemostatic features by aetiology of haemorrhage, the use of the main blood components (RBC, FFP and platelets) did not differ significantly by the cause of haemorrhage. Reassuringly, there was a higher use of fibrinogen in the abruption group which had the lowest level of fibrinogen.

Current practice in many places uses transfusion ‘packs’ with empiric use of RBCs and FFP in high ratio, which are administered to patients as part of major haemorrhage protocols (MHPs) and this is standard across aetiologies. The current recommended management of massive haemorrhage aims to treat rapid coagulopathy though the immediate administration of RBCs, FFP and platelets (Spahn et al., 2013). However, these MHPs are not tailored to cause of the haemorrhage.

There has been some discussion about the use of MHPs in obstetrics (Allard et al., 2014, Shaylor et al., 2017) where a systematic review showed that a MHP improved survival (Vogt et al., 2012). However, these ratio based approaches are likely to give plasma and platelets to women who may not need them which may cause circulatory overload and adult respiratory distress syndrome (Inaba et al., 2010). Further evidence is required to support the use of MHPs in obstetric haemorrhage and some consideration should be given to developing haemorrhage aetiology specific MHPs.

Current trauma literature has suggested that major bleeding and coagulopathy should be treated using goal directed haemostatic resuscitation rather than ratio replacements through MHPs (Gonzalez et al., 2016, Rivers et al., 2001). The recent PPROP trial tested ratios Plasma, Platelets and RBCs 1:1:2 vs. 1:1:1 and showed no difference in all-cause mortality (Holcomb et al., 2015). An audit showed that therapy based goals in an algorithm using point of care testing (FIBTEM) in obstetric haemorrhage reduced the overall amount of RBCs, FFP, platelets and cryoprecipitate given, although this was not statistically significant (Mallaiah et al., 2015). There is an opportunity for future research to be undertaken to show the clinical impact in the haematological management of MOH.

6.3.2.3 Obstetric management

6.3.2.3.1 Medical management

There were large amounts of uterotonics and prostaglandins administered in women with all aetiologies of haemorrhage in the different countries. The proportion of women with uterine atony receiving these drugs was higher in the United Kingdom compared to other countries. There remains an opportunity to ensure that every woman with an atonic bleed receives an uterotonic drug. A Cochrane review suggested that under current evidence, oxytocin was the most effective drug at treating bleeding due to uterine atony (Mousa et al., 2014). However, a recent RCT showed that carbetocin was just as effective as oxytocin and clinical guidelines have yet to be updated (Widmer et al., 2018). However, this study highlighted large variations in the type of drug used to treat PPH and these differences are also reflected in international guidelines (Dahlke et al., 2015).

6.3.2.3.2 Surgical management

Previous research has shown that surgical management of PPH varies internationally (Kayem et al., 2016, Kayem et al., 2011, Zwart et al., 2010a). The findings from this study are consistent with previous research, as embolisation use was higher in France and the Netherlands in comparison to the United Kingdom. This most likely reflects the availability of the infrastructure required to provide an embolisation service. This study showed significant disparity in the use of hysterectomy where three quarters of women had a hysterectomy in Italy while only a third of women did so in the Netherlands. Consistent with previous research, a similar proportion of women in the United Kingdom and France had a hysterectomy (Kayem et al., 2016). There has been limited work examining the differences in obstetric management by aetiology. Across all countries hysterectomies were not surprisingly more common amongst women with abnormally invasive placenta and placenta praevia, as this is the primary management for AIP in most countries (Kayem et al., 2011, Allen et al., 2018).

6.3.3 Abnormally invasive placenta

6.3.3.1 Cross-country differences in management

6.3.3.1.1 Hysterectomy or conservative management

Similar to previous findings, this study showed that the primary management for AIP in the United Kingdom was hysterectomy (Green et al., 2016b, Royal College of Obstetricians and Gynaecologists, 2011). A smaller case series showed that conservative management of AIP in France occurred in 25% of affected women (Sentilhes et al., 2010a), while the findings from this study showed this approach is now used in half of women with AIP in France.

6.3.3.1.2 Attempted removal of the placenta

It is surprising that an attempted manual removal of the placenta occurred in women with an antenatal suspicion of AIP. Nevertheless, this occurred in a large proportion of women in both countries. These findings suggest that clinical practice in the United Kingdom and France did not adhere to the clinical guidelines of not attempting a manual removal of the placenta and leaving the placenta undisturbed (Royal College of Obstetricians and Gynaecologists, 2011, Sentilhes et al., 2013). This suggests that training around the management of AIP at delivery should be reviewed. Alternatively, this may be an issue with false positives, in particular, the clinician may not trust the antenatal diagnosis so may attempt a forcible manual removal of the placenta.

6.3.3.2 Difference in outcomes

Women with AIP in the United Kingdom had a substantially higher blood loss than women with AIP in France. More women in France had postpartum infection than in

the United Kingdom although there was no difference in the proportion of women who had damage to either the bowel, urinary tract or the bladder.

In order to assess whether there is a true difference in outcomes, an examination of bias, chance and confounding must first be undertaken.

6.3.3.2.1 Bias and confounding

Case selection bias would arise if the French cohort of women had less severe forms of AIP than women with AIP in the United Kingdom, for example, if in France there was a higher proportion of women with accreta, which is the least invasive form of AIP. Alternatively, if France had a higher proportion of women whose AIP was detected antenatally this would result in a larger proportion of women who had a planned management in a tertiary centre, which is associated with better maternal outcomes (Eller et al., 2011). Despite inward referral in regions in France, both countries had the same proportion of women who had placenta percreta and an antenatal suspicion of AIP suggesting that bias is unlikely to explain the differences in management.

Confounding would occur if women from the United Kingdom had a type of AIP or risk factors that increased the propensity for bleeding. The between-country analysis was not adjusted for potential confounders between countries. However, it appears that the risk factors for postpartum haemorrhage within the AIP population between the countries were similar and included: multiple pregnancy, caesarean delivery, severity of the invasive placenta and previous uterine surgery or caesarean delivery. However, the prevalence of risk factors for PPH in the pregnancy population was not provided. Confounding seems to be an unlikely reason for the differences in outcomes as both

AIP populations were similar in terms of risk factors for PPH. With this being said, this study was not randomised so it is possible that there was residual confounding.

6.3.3.2.2 Other explanation for the difference between the countries?

Every effort was made to develop a uniform case definition and there were similar proportions of women with AIP suspected antenatally and with placenta percreta. This would suggest that the differential management of AIP between the countries might be a possible explanation for this variation in severe postpartum haemorrhage and infection.

6.3.3.2.3 Difference in management: Attempted removal of placental tissue after delivery

The United Kingdom had a slightly higher proportion of women with an attempted manual removal of placenta than France. This might partially explain the difference in blood loss between the countries, as the proportion of women with severe postpartum haemorrhage was higher for women who had an attempted manual removal of placenta compared to women in whom no attempt was made to remove the placenta. This finding is consistent with the literature, which shows an increased blood loss for women who had an attempted manual removal of placenta compared to leaving the placenta in situ (Kayem et al., 2004, Allen et al., 2018, Sentilhes et al., 2018, Kayem et al., 2007). Conversely, the effect of an attempted removal of placenta on blood loss appears to differ by country, as there was much greater blood loss in the United Kingdom than France. This suggests that there may be other factors which may influence the larger blood loss in the United Kingdom, such as the use of hysterectomy and the lack of centralisation of AIP care in the United Kingdom.

6.3.3.2.4 Planned conservative management or hysterectomy

In women who had a planned management where there was no attempted removal of the placenta, a lower proportion of women had severe postpartum haemorrhage in those managed conservatively compared to a planned hysterectomy. This would suggest that there are other potential explanations for the differences in blood loss between the two countries. One of these explanations may be the differential use of hysterectomy and conservative management.

Consistent with previous studies, conservative management was successful in the majority of women and only 25% went on to have a secondary hysterectomy (Kayem et al., 2004, Sentilhes et al., 2010a). As a result of conservative management over 75% of these women retained their potential fertility compared to women who had an immediate hysterectomy. However, women who had a failed conservative approach had a life threatening blood loss, which is consistent with previous research (Pather et al., 2014, Sentilhes et al., 2010a). In this cohort of women, this blood loss occurred at the time of secondary hysterectomy.

6.3.3.2.5 Biological plausibility for haemorrhage

The lack of centralisation of care of AIP in the United Kingdom may be part of an explanation for the higher proportion of women with severe postpartum haemorrhage during a hysterectomy. Hysterectomies were performed in the majority of centres in the United Kingdom. Ruiz et al. (2018) showed there was a higher complication, transfusion and mortality rate for hysterectomies performed by inexperienced surgeons compared to experienced surgeons (Ruiz et al., 2018). All surgical skill requires practice to streamline the surgical technique and prevent human errors.

Conversely, lower rates of haemorrhage in women who had a conservative approach has biological plausibility. After delivery, the blood flow to the uterus will decrease that will result in necrosis of the placenta and either expulsion or re-absorption of the placenta. Without a rupture or trauma to the uterus there is less likely to be a spontaneous haemorrhage; as a result, conservative management is unlikely to result in a major obstetric haemorrhage (Sentilhes et al., 2018), while even a planned hysterectomy for a placenta percreta is likely to result in major blood loss. The surgical dissection of each chorionic villi from the neighbouring organs will result in constant blood loss, which will collectively result in a large overall blood loss. This major blood loss may not be life threatening; if the procedure is planned, there would be the appropriate products available to ensure blood and fluid replacement.

6.3.3.2.6 Infection

Previous research has shown that infection is a complication associated with this management (Sentilhes et al., 2010a, Sentilhes et al., 2013, Kayem et al., 2007, Kayem et al., 2004). This is biologically plausible, as leaving placental tissues to be reabsorbed following necrosis provides a focus for bacterial colonisation and infection. However, this study had very small numbers of women with infection and it cannot be concluded that infection differed between a planned hysterectomy and the conservative management.

6.3.4 Anaphylaxis in pregnancy

6.3.4.1 Main clinical findings

The study reported in chapter five showed that anaphylaxis during pregnancy is an extremely rare but severe complication of pregnancy. It is often the result of administration of antibiotics or anaesthetic agents and most reactions occurred at or around the time of delivery. Furthermore, anaphylaxis has very poor outcomes for a tenth of mothers and a sixth of babies.

The U.S.A. had apparently over double the incidence of anaphylaxis in pregnancy compared to European countries, but an inability to validate cases in the routine U.S.A. data leaves the possibility of false positive cases being included to an unknown extent. Both the European and the U.S.A. data showed that caesarean delivery was more common in those who had anaphylaxis compared to the background populations and that women with anaphylaxis were likely to have had a history of allergic reactions. In the European study, over a tenth of women had severe morbidity as a result of the reaction, and although there were no perinatal deaths 16% of infants had neonatal encephalopathy.

6.3.4.2 Suspected causes

The main causal agents of anaphylaxis were antibiotics and anaesthetic agents. Over a fifth of reactions were found to be the direct result of prophylactic use of antibiotics at the time of caesarean delivery which were administered to prevent postoperative infection (National Institute for Health and Care Excellence, 2011, Tita et al., 2016). Half of these reactions occurred after caesarean delivery. It is important to note that had the antibiotics been administered before surgery the burden of infant morbidity

may have been higher. In addition, three women had a reaction to an antibiotic that was a noted allergy, as a result, these reactions were completely iatrogenic thus demonstrating that anaphylaxis was entirely preventable in these women.

Similar to previous studies the most common suspected causal agent was the use of antibiotics (Mulla et al., 2010, Hepner et al., 2013). Previous studies showed women developed anaphylaxis after being given antibiotics prophylactically for GBS, (Jao et al., 2006, Mulla et al., 2010, Dunn et al., 1999) while others were given for surgical prophylaxis (Hepner et al., 2013). There were three women who had anaphylaxis following antibiotics administered for GBS in mainland Europe; two occurred in France and one in the United Kingdom. France has universal screening for GBS while there is no national screening policy for GBS in the United Kingdom or Finland (Ministry of Social Affairs and Health, 2014). The chapter showed that despite differences in policies for prophylaxis for group B streptococcus between the European countries there was no difference in incidence of this very rare complication, although this comparison had limited power.

6.3.4.3 Known drug allergies and causal agents

Three women who had known penicillin allergies were given a penicillin-based antibiotic resulting in an anaphylactic reaction. Human factors have been demonstrated to play a role in medication errors (Mahajan, 2011). This highlights that these cases were preventable and indicates that a detailed drug allergy history must be taken at booking and immediately prior to administration of any antibiotics. The introduction of allergy wristbands in the delivery suite or theatre could encourage an awareness.

6.3.4.4 Management

6.3.4.4.1 Epinephrine and other vasopressors

A recent United Kingdom National Audit Project into anaphylaxis has shown that epinephrine was used less frequently in obstetrics than other specialities (Lucas, 2018). This may be the consequence of concerns that adrenaline may cause vasoconstriction of the uterus resulting in fetal hypoxia (Chaudhuri et al., 2008). In particular, animal models show a 40% reduction in uterine blood flow after the administration of epinephrine, however this is for a short period of time (Chestnut et al., 1986). Current international guidelines in the non-pregnant population recommend immediate administration of epinephrine as soon as a diagnosis of anaphylaxis has been made (Resuscitation council, 2008, Sampson et al., 2006, Muraro et al., 2014, Alrasbi and Sheikh, 2007). The study findings show that an even lower proportion of women received epinephrine in mainland Europe compared to the United Kingdom. This may be explained by a lack of understanding and knowledge of the protocol from the attending health care professional (Pouessel et al., 2017) or concerns over the use of the drug within obstetrics.

Similar to case reports, ephedrine was used in two women to manage anaphylaxis in this study, although clinical opinion would suggest that it is less effective than epinephrine to manage severe anaphylaxis (Chaudhuri et al., 2008).

6.3.4.4.2 Steroids and antihistamines

International variations in the administration of steroids and antihistamines shown in this study may be explained by variations in guidelines for the management of anaphylaxis (Lieberman et al., 2005, Muraro et al., 2014, Alrasbi and Sheikh, 2007). If

the variation in clinical practice is the result of a lack of awareness of the drugs required for resuscitation, then the anaphylaxis algorithm should be visible in operating theatres and labour wards (Resuscitation council, 2008, The Association of Anaesthetists of Great Britain & Ireland, 2009).

6.3.4.5 Caesarean section

Previous studies have shown that most women with anaphylaxis were delivered by caesarean section; however, it was unclear whether this association with caesarean section was a cause or a consequence of the reaction (Mulla et al., 2010, Hepner et al., 2013). A previous review recommended caesarean delivery in severe cases of anaphylaxis in order to deliver the infant immediately to reduce the risk of hypoxic brain injury (Hepner et al., 2013). The findings using the U.S.A. data show that women having a caesarean delivery had a raised likelihood of having an anaphylactic reaction but there was no timing data so we cannot infer whether the caesarean was a cause or a management of the reaction. The findings from the European study showed only 5% of women had a caesarean delivery as the result of an anaphylactic reaction; these women received antibiotics for GBS prophylaxis then went on to be delivered by caesarean section. In contrast, approximately a third of reactions occurred before a caesarean delivery and the majority of these were reactions to agents given as part of routine care prior to caesarean delivery.

6.3.4.6 Maternal outcomes

Previous studies have been unable to accurately examine maternal and infant outcomes associated with this condition either due to publication bias in case reports (Hepner et al., 2013) or lack of suitable population-based data (Mulla et al., 2010). This study has

shown there are poor outcomes for women who have anaphylaxis with a 3.5% case fatality and 10% of women having a severe morbidity. The findings of the confidential enquiry into maternal deaths in the United Kingdom suggest a similar case fatality for anaphylaxis during pregnancy, with one death due to anaphylaxis during 2013–2015 (Bamber et al., 2017) .

Interestingly, the number of maternal deaths as a result of anaphylaxis in the U.S.A. was not large enough to report due to reporting restrictions to prevent a deductive disclosure. A possible explanation may be that the national inpatient sample is unlikely to capture anaphylactic reactions that occurred in the community, in accident and emergency (A&E) or is a sampling phenomenon. Jerschow et al. (2014) showed that 44% of fatal anaphylaxis cases in the general population occurred in Accident & Emergency or in the community rather than as an inpatient. However, the majority of reactions during pregnancy occurred within the hospital setting so there must be other reasons for the apparent difference in maternal deaths in the U.S.A (Lucas, 2018).

6.3.4.7 Infant outcomes

There were severe outcomes for infants with a third of infants admitted to NICU, a quarter of infants had an abnormal Apgar score and nearly one in six infants had neonatal encephalopathy that required whole body cooling. Previous research has suggested that poor outcomes have been averted by rapid diagnosis of anaphylaxis, appropriate administration of epinephrine and prompt delivery after diagnosis (within 10-15minutes) (Hepner et al., 2013).

6.4 Rationale and reflection on this methodology

Studies reported in this DPhil used similar methods to an individual patient data (IPD) meta-analysis where the individual's data from each national study were analysed rather than using aggregated data from each country in a meta-analysis. The utility of aggregated data is often limited due to heterogeneity between studies (Gagnier et al., 2012) and previous international comparisons of complications of pregnancy have been restricted to discussions around differences in definitions (Knight and INOSS, 2014), apart from the eclampsia study (Schaap et al., 2014). A methodology similar to an IPD was deemed appropriate for a number of reasons (Riley et al., 2010). First, each national study had differing definitions so required harmonisation in order to create a uniform set of cases. Second, data items that were specified in each of the protocols were not always reported within the published study or were not comparable, thus, the variables required modification in order to have a common value. Third, these findings overcame publication bias, as the majority of the data presented in the DPhil studies had not been published at its writing. Fourth, statistical analyses were standardised across studies allowing adjusted analyses using the same covariates; this would not have been possible using aggregated data. Fifth, aggregated data analysis would not have allowed the pooling of data and the examination of subgroups within studies, which is one of the major benefits of completing individual patient data analyses.

6.4.1 Choice of studies and countries – scientific or pragmatic?

The inclusion of studies in this DPhil were due to a combination of both pragmatic and scientific reasons. Only topics on rare and severe complications of pregnancy that had been completed in more than one country could be considered for inclusion. From completed studies, a variety of topics were chosen to investigate the different utilities of the collaboration.

In the context text of high-income settings, extreme maternal obesity offered an examination of rare outcomes in a rare exposure, which had not been previously examined due to small numbers. Only two countries had population-based data on women with a BMI>50 kg/m^2 and the results show that two countries' data did not provide enough power to complete this aim. Major obstetric haemorrhage offered an opportunity to compare haematological management and replicate management across countries. Abnormally invasive placenta offered an opportunity to examine a rare management for a rare complication of pregnancy; France and the United Kingdom were included as only two countries' data were required to answer the question. Australia and Italy offered data for inclusion in this study; however, their definitions could not be harmonised.

A prospective international study using the INOSS network required a very rare complication to be studied. A very rare condition was used as the area of study for two reasons, first, without funding it would be impossible to get buy-in from international partners for a large research study. Secondly, any additional cases added to study a very rare condition improved the ability to precisely determine its causes and outcomes and were therefore highly valuable. Anaphylaxis in pregnancy was chosen for several

reasons: the UKOSS study had just finished in the United Kingdom; it had an unambiguous definition; anaphylaxis in pregnancy was very rare with an estimated incidence of 1.6 per 100,000 deliveries (McCall et al., 2018). Therefore, there was an opportunity to scale up the study on anaphylaxis in pregnancy to an international level and there was interest in the study outcomes amongst international partners.

6.5 Challenges and limitations

It should be noted these limitations are not novel to multinational surveillance systems but are common epidemiological issues.

6.5.1.1 Resources

The methodology of multinational studies has some limitations; in particular, it was very person resource intensive. It required considerable time to contact the principal investigators of each national study; it required effort to encourage buy-in for participation in the study; it took time and effort to gain approval from the respective steering committees and ethics boards to set up data-sharing agreements, to harmonise the datasets, and to solve any queries which arose during the analysis (Riley et al., 2010). To complete these four large studies within three years with very limited funding was a pragmatic success of the collaboration. However, the considerable effort that was required to produce high quality multinational studies must be considered before embarking upon future international collaborative studies (Riley et al., 2010).

6.5.1.2 Definitions and datasets

Studies that used the secondary data analysis of national data were limited to those existing studies that had comparable definitions and datasets. In the extreme maternal obesity chapter, both AMOSS and UKOSS systems completed a similar study, however, they used slightly different definitions. Furthermore, the selection of studies for the abnormally invasive placenta study was limited to France and the United Kingdom. Heterogeneity in definitions was a common limitation for previous meta-analyses and studies examining maternal morbidity (Hoy et al., 2014, Knight et al., 2009).

The study of AIP (chapter four) highlighted that even with individual data, it is still difficult to harmonise two studies with differing definitions which leaves questions around the results.

A further limitation arose in the heterogeneity of data items collected. In some instances, variables were asked using a specific question while in some countries it was extracted from a global question, for example, maternal morbidity outcomes in the United Kingdom were extracted from "were there any other morbidities?". As a result, the observed differences between countries may be due to varying ascertainment rather than a true difference. Some of the desirable variables identified from the literature were not available in all the datasets or were collected using different definitions, which led to an analysis based on only those variables that existed in more than one dataset and were comparable between datasets.

6.5.1.3 Sensitivity and specificity

All of the original national studies reported in this DPhil thesis relied on reporters to identify cases within each maternity unit; as a result, the findings were susceptible to reporter fatigue and the consequent failure to report eligible cases. However, due to the rigorous case definition used in each chapter, the study populations were unlikely to have contained false positives.

6.5.1.4 Differences in populations

It is possible that differences in characteristics or risk profiles could explain some of the differences in management and outcomes between countries. For example, the Australian extremely obese cohort when compared to the United Kingdom cohort was slightly older and had a higher median BMI. The Australian women were more likely

to be multiparous, to have had more caesarean sections and pregnancy problems in past pregnancies. However, these differences between populations were accounted for in the adjusted analysis. In the abnormally invasive placenta study, women with AIP in the United Kingdom were more likely to have had a previous caesarean section than women in France. However, the French cohort had an increased proportion of women who had previous uterine surgery than the United Kingdom. It is unlikely that this variation in characteristics could explain the difference in blood loss between the two nations.

6.6 Comparison with previous international comparisons of severe and rare complications of pregnancy

Similar to the findings of this study, previous research using international collaborative and comparative studies has highlighted a number of interesting clinical questions (Knight et al., 2009, Vandenberghe et al., 2018, Schaap et al., 2014). Knight et al. (2009) showed that PPH was increasing in high-income settings; however, the study was limited to data mainly obtained from routine sources with heterogeneous definitions. This DPhil has provided a much richer and more robust comparison between countries using uniform definitions and datasets.

During the writing of this thesis a multinational descriptive study using the INOSS collaboration was published. This showed variation in the incidence of uterine rupture was related to differences in caesarean section rates and the proportion of women who had a trial of labour after a caesarean section (TOLAC) across countries (Vandenberghe et al., 2018). Similarly, the findings from this DPhil have highlighted that difference in incidence rates may be as a result of differences in management, such as, between-country differences in the incidence of haemorrhage requiring massive transfusion.

Previous multinational studies have highlighted differences in management and the incidence of a severe complication of pregnancy (Schaap et al., 2014). Schaap et al. (2014) found that the Netherlands had a higher incidence of eclampsia than the United Kingdom and this may have been related to a lower rates of administration of magnesium sulphate and antihypertensives in the Netherlands. Consequent implementation work that followed in the Netherlands resulted in a decline in the

number of women with eclampsia in the Netherlands (Schaap et al., 2018). The study that examined anaphylaxis in pregnancy was a reversal of this logic, as there was *a priori* knowledge of the differences in national policies for the use of antibiotics for prophylaxis of group B streptococcus.

6.7 Key messages for future research

6.7.1 Clinical implications of each chapter and for future research

Extreme maternal obesity: future international studies of rare complications of pregnancy aiming to examine rare outcomes will need to include more countries to maximise the size of the study population.

Massive transfusion in major obstetric haemorrhage: consumption of coagulation factors differed according to aetiology. The findings will inform future RCTs to improve intrapartum care for PPH. These findings could inform a complex aetiology specific intervention to address the growing problem of PPH.

Abnormally invasive placenta: this study has shown a clear difference in the management of AIP and the impact it can have on outcomes. These findings have important considerations for future guideline creation.

Anaphylaxis in pregnancy: the findings of this study illustrated that the incidence of anaphylaxis in all the European countries was the same despite differences in policies surrounding the use of antibiotics for the prophylaxis for group B streptococcal carriage. Although not novel, this study showed that relying solely on routinely collected data to study rare and severe complications overestimates the incidence of these conditions. In rare complications even a small number of false positives can have a significant impact on the overall incidence. Future research of rare pregnancy complications using routine data sources should ensure the validity of cases through examination of the medical records, or use a stricter coding practice, to guarantee that all cases meet a strict case definition (Knight et al., 2012).

6.7.2 Scientific recommendations for the multinational research of severe maternal morbidity

The choice of country has important implication for the research question in multinational studies. Future studies should include countries that have variations in incidence, policy, structures or management to allow multinational studies to take advantage of the natural experiments that exist. This DPhil showed that variations in management had an impact on outcomes in each country.

In order for between-country comparisons to be authentic there must be uniform definitions between countries or overlap in definitions to allow harmonisation of definitions to occur. Schaap et al. (2017) developed a set of definitions for severe maternal outcomes (core outcomes), which should be included in future research to allow appropriate comparison between studies. Furthermore, a single data collection form should be used in future research to provide a uniform dataset, such as the online data collection form used in the anaphylaxis in pregnancy study. Future international collaborations should consider consulting each other before developing a case definition and outcomes. For example, engagement with the CROWN Initiative and the development and adoption of core outcome sets for specific conditions will allow data to be compared and combined across countries (Duffy et al., 2017).

The INOSS methodology used in the ‘anaphylaxis in pregnancy’ study has already been adopted and adapted for the recent GLOSS study, which examined sepsis in pregnancy. The recently completed GLOSS study showed that prospective snapshot studies of severe complications in high income settings can be undertaken to provide an international population-based study on more common severe complications of

pregnancy (Bonet et al., 2018). Perhaps, with funding attached to these studies it may allow severe complications of pregnancy to be studied for a shorter period of time at an international level. The GLOSS study used a uniform case definition and prospectively collected data through a single online system similar to the anaphylaxis in pregnancy study. Perhaps these snapshot studies, which can examine more common complications, should be an ambition for the INOSS collaboration.

Furthermore, this study showed the benefit of examining a specific cause of haemorrhage. Abruption is a rare and severe complication of pregnancy, which has poor maternal and infant outcomes. This condition would benefit from a future international collaborative study.

6.7.3 Pragmatic recommendations for the multinational research of severe maternal morbidity

There are a number of processes that would increase the efficiency of completing international studies. The ethical approval process, requesting of data, translating of data collection forms and harmonisation of datasets are labour intensive tasks that require the active participation of all countries involved. First, the acquisition of funding would enable researchers from each country to be allocated time to work on the study. Second, the process by which data sharing agreements are made between countries is also time consuming. A more efficient process would be to have a head of terms agreement between each institution instead of a study specific data sharing agreement. This would reduce the time to acquire data for future studies as an agreement is already in place. Third, ethical approval for individual international studies could be accomplished through each national study including a clause about

future international sharing of data. Fourth, a standardised protocol for the combining of multinational data would ensure that the harmonisation of data items were uniform across INOSS studies.

6.8 Conclusion

The work in this DPhil thesis has demonstrated that international studies of severe and rare complications of pregnancy are feasible, have multiple uses for research and have the potential to improve clinical practice. First, they enable a comparison of incidence rates, which in turn allows the generation of hypotheses for the observed differences seen between countries. Binational studies are at their most useful when comparing countries with different modalities of management, where these studies can generate hypotheses about whether difference in management are reflected in differences in outcomes. Second, where numbers are too small for an analytical study to be completed in a single national study, multinational studies provide pooled data that enable the examination of outcomes following rare modalities of management. Third, international prospective studies have the added advantage of using both comparable cases and datasets from the outset. This was of real value as it doubled the size of the United Kingdom study, which enabled a more accurate estimate of the causal agents and maternal and perinatal outcomes associated with anaphylaxis in pregnancy. Finally, despite the limitations of this methodology, these studies provide rich comparisons where we can be more certain that the observed differences between countries are not the result of differences in study methodologies. They empower countries to benchmark their clinical care against that of other countries, and provide a challenge to improve current practice.

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Appendix 1

Search strategy

Box 5. Search terms for extreme maternal obesity literature search

The terms used in Medline (1996-2016 July week 2) were as follows:
(1) Exp Obesity/or obesity.mp,
(2) Exp Body Mass Index/or BMI.mp,
(3) 1 and 2,
(4) Exp Pregnancy Complications or (pregnancy adj3 complica ∗).ti,
(5) Exp Pregnancy Outcome or (pregnancy adj3 outcome*).ti

Box 6. Search terms for major obstetric haemorrhage

Search results in Medline

1. Hemorrhage/

2. Blood Transfusion/ or Blood Component Transfusion/ or Transfusion Medicine/ or Blood Transfusion, Autologous/

3. Pregnancy/ or Obstetrics/

4. Mothers/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy, Animal

5. 3 or 4

6. 1 or 2

7. major.mp.

8. large.mp.

9. severe.mp.

10. massive.mp.

11. 7 or 8 or 9 or 10

12. 6 and 11

13. 5 and 12

14. limit 13 to (english language and humans)

15. Postpartum Period/

16. 5 or 15

17. 12 and 16

18. limit 17 to humans

19. postpartum.mp. 20. 16 or "20".mp.

21. postpartum.ti.

22. postpartum.ab.

23. 3 or 4 or 15 or 22 or "23".mp.

24. 6 and 11

25. 24 and "25".mp

26. (blood adj4 unit).ab.

27. haemostatic.mp.

28. 1 or 2 or "30".mp. or "31".mp. 29. 11 and "32".mp. 30. 24 and "33".mp.

Box 7. Search terms for anaphylaxis

Search results in Medline
1. Anaphylaxis/
2. Pregnancy/ or Pregnancy Complications/ or pregnancy.mp. or Pregnancy, High-Risk/ or Pregnancy, Abdominal/ or Pregnancy Tests, Immunologic/
3. Maternal Death/ or Maternal Health/ or Maternal Mortality/ or Maternal Health Services/
4. Cesarean Section/ or Delivery, Obstetric/
5. 2 or 3 or 4
1. 1 and 4