



Universiteit  
Leiden  
The Netherlands

## **Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously**

Henriquez, D.D.C.A.

### **Citation**

Henriquez, D. D. C. A. (2020, December 1). *Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously*. Retrieved from <https://hdl.handle.net/1887/138245>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/138245>

**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/138245> holds various files of this Leiden University dissertation.

**Author:** Henriquez, D.D.C.A.

**Title:** Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously

**Issue date:** 2020-12-01

# PART 1

Women with postpartum  
haemorrhage:  
what issues to resolve?



# 2

## A total blood volume or more transfused during pregnancy or after childbirth: individual patient data from six international population-based observational studies

*Stephen J McCall, Dacia Henriquez, Hellen McKinnon Edwards, Thomas van den Akker, Johanna van der Bom, Marie-Pierre Bonnet, Catherine Deneux-Tharaux, Serena Donati, Ada Gillissen, Jennifer J Kurinczuk, Zhuoyang Li, Alice Maraschini, Aurélien Seco, Elizabeth Sullivan, Simon Stanworth, Marian Knight*

(submitted)



# Abstract

## Background

This study aimed to compare incidence, management and outcomes of women who had been transfused their blood volume or more within 24 hours.

## Methods

Combined analysis of individual patient data, prospectively collected in six international population-based studies (France, United Kingdom, Italy, Australia, the Netherlands and Denmark). Massive transfusion in major obstetric haemorrhage was defined as transfusion of eight or more units of red blood cells within 24 hours in a pregnant or postpartum woman. Causes, management and outcomes of women with massive transfusion were compared across countries using descriptive statistics.

## Findings

The incidence of massive transfusion was approximately 20 women per 100,000 maternities for The United Kingdom, Australia and Italy; by contrast Denmark, the Netherlands and France had incidences of 82, 66 and 70 per 100,000 maternities, respectively. There was large variation in obstetric and haematological management across countries. Fibrinogen products were used in 87% of women in Australia, while the Netherlands and Italy reported lower use at 35-37% of women. Tranexamic acid was used in 75% of women in the Netherlands, but in less than half of women in the UK and Italy. In all countries, women received large quantities of colloid/crystalloid fluids during resuscitation (>3.5 litres). There was large variation in the use of compression sutures, embolisation and hysterectomy across countries. There was no difference in maternal mortality; however, variable proportions of women had cardiac arrests, renal failure and thrombotic events from 0-16%.

## Interpretation

There was considerable variation in the incidence of massive transfusion associated with major obstetric haemorrhage across six high-income countries. There were also large disparities in both transfusion management and obstetric management between these countries. There is a requirement for detailed evaluation of evidence underlying current guidance and cross-country comparison may empower countries to benchmark their clinical care against that of other countries.

## Funding:

SM was funded by the Medical Research Council (UK) and the Nuffield Department of Population Health, University of Oxford. EPIMOMS was funded by a grant from the French National Research Agency (ANR) and the Ile-de-France Regional Health Agency. The Italian study was funded by the Italian Ministry of Health. The original AMOSS study Life-threatening massive obstetric haemorrhage requiring rapid, high-volume blood transfusion was funded by the Australian Red Cross Blood Service and the Royal Hospital for Women Foundation.

## Introduction

The most common form of major obstetric haemorrhage (MOH), postpartum haemorrhage (PPH), which occurs in 3-7% of deliveries in high-income settings <sup>1</sup>; and remains a major cause of maternal mortality and morbidity. In France, Italy and the United States, haemorrhage is the leading cause of maternal mortality responsible for 11%, 15% and 14% of maternal deaths, respectively <sup>2-4</sup> and haemorrhage related mortality in the United Kingdom (UK) nearly doubled during the period 2010-12 to 2013-15 <sup>5</sup>. Major obstetric haemorrhage (MOH) is a common reason for admission to intensive care <sup>6</sup>.

Management of MOH, often defined pragmatically as transfusion of a total body blood volume (8-10 units of red blood cells) or more within 24 hours of delivery <sup>7-9</sup> and also referred to as massive transfusion, focusses on transfusion and fluid resuscitation, alongside planning for definitive obstetric and surgical interventions <sup>10</sup>. The literature in major haemorrhage caused by trauma has emphasised the importance of damage control resuscitation, including timely transfusion support, early use of coagulation factors and minimising use of crystalloids, all contributing to improved clinical outcomes, although it is unclear how far these protocols should be applied in an obstetric setting <sup>11</sup>.

Multiple guidelines to direct transfusion practice in MOH exist and these vary in terms of when blood components should be given and the dose. The reasons for variation in practice are unclear but are likely in part to reflect lack of high-quality data <sup>12,13</sup>. A number of national studies have reported the transfusion management of PPH <sup>14,15</sup>, but there has been little comparison reported at a national level, to explore regional variations in practice. As part of an initiative to inform the research agenda, this study was planned to describe and compare the incidence, characteristics, aetiology, management and outcomes of pregnant or postpartum women who have been transfused their total blood volume or more within 24 hours, based on regional or national data collection systems across six countries.

## Methods

### Study description

This international population-based study of massive transfusion in MOH, used secondary analysis of data from six population-based studies from Australia, Denmark,

France, Italy, the Netherlands and the UK.

### **Overall description**

In each country, data were collected either nationally or from a number of regions on a population basis. A detailed explanation of the methodology for each country can be found in the supplementary section and is summarised in Box 1. In short, these population-based studies collected data, using enhanced systems, from the medical records of the women who met the case definition for each of the respective studies. Danish data were solely based on information entered into the Danish Medical Birth Registry and the Danish Transfusion Database, which included data from all hospitals in Denmark. Four of the included datasets were national except for the Netherlands, France, and Italy. The TeMpOH-1 study in the Netherlands collected data from 75% of national births. Italy collected data from six regions namely Piedmont, Emilia-Romagna, Tuscany, Lazio, Campania and Sicily; these regions represent 49% of births in Italy and the EPIMOMS study in France collected data from six regions: Alsace, Lorraine, Auvergne, Rhone-Alpes, Ile-de-France and Basse-Normandie and these regions represented 18% of national births.

### **Case definition**

Massive transfusion in major obstetric haemorrhage was defined as a receipt of eight or more units of red blood cells within 24 hours in a pregnant or postpartum woman of at least 20 weeks of gestation.

### **Statistical analysis**

Women's characteristics, medical history, haematological features, obstetric and transfusion management and perinatal and maternal outcomes were compared across countries. Normality was assessed using histograms. Normally distributed continuous variables are presented as means with standard deviations and skewed continuous variables are 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 differences between countries and respective characteristics, management and outcomes of women undergoing massive transfusion. . 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-Freeman-Halton's test. In order to reduce the risk of a type I error a p-value <0.01 was used to indicate statistical significance. Missing data were included as a 'missing' category for categorical variables. Complete



case analysis was used for continuous variables.

### **Categorisation of aetiology of MOH**

France had multiple causes of MOH 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, third women with trauma and lastly those with atony.

### **Ethics approval and data sharing agreements**

The French data collaborators gained approval from the EPIMOMS steering committee at INSERM, Paris for this analysis. The TeMpOH-1 (the Netherlands) study was approved by the ethics committee of the Leiden University Medical Center and by the institutional review board of each participating hospital; the TeMpOH-1 and ItOSS steering committees approved the study protocol and the data transfer agreement. Approval for the obtained secondary use of Australia data obtained was from the Human Research Ethics Committee, New South Wales, Australia and from Human Research Ethics Committee for individual sites across Australia. Ethics committee approval for the secondary analysis of UK data was not required. The Danish collaborators acquired permission from the Danish Data Protection Agency (J.nr: HGH-2016-066), no permission was required from the Danish Ethics Committee according to Danish law.

### **Role of the funding source**

The funder had no role in the data collection, analysis, interpretation or the writing of the manuscript. They had no decision to publish. SM the corresponding author had full access to the data in the study and the final responsibility for the decision to submit for publication.

## **Results**

### **Incidence**

Denmark reported the highest incidence of massive transfusion at 82 (95% CI: 73-92) women per 100,000 deliveries; followed by the France and the Netherlands with an incidence of approximately 70 per 100,000 deliveries (95% CI: 57-82) and 65 per 100,000 deliveries (95% CI: 56-76), respectively. The UK, Australia and Italy had a similar incidence of massive transfusion at 21 women per 100,000 deliveries; (Table 1). These variable rates are seen despite many similarities in baseline characteristics

of women presenting with PPH, including age and BMI.

### **Previous medical history and current pregnancy characteristics**

Mean age of women with massive transfusion was 32 years (SD  $\pm 5.7$ ) and the majority were multiparous (57%) (Table 1). Amongst women with a previous pregnancy, there were differences in the proportion of women with previous caesarean section and a previous postpartum haemorrhage between countries (previous caesarean section: highest in the UK (65%) and lowest in France (45%)).

Amongst cases, there were differences in the proportions of women with multiple pregnancies between countries (Denmark 30% and France 14%, respectively). In addition, the majority of women were delivered by caesarean section in each country (range excluding the Netherlands: 58%-68%), while the Netherlands had the lowest proportion of caesarean deliveries at 42%.

### **Aetiology of major obstetric haemorrhage**

The most common cause of MOH in all countries was atony, with a prevalence ranging from 40% in the UK to 63% in the Netherlands (Supplementary Table 2). The second leading cause was abnormal placentation with a prevalence ranging from 22% in Italy to 32% in Australia. The least common cause was placental abruption with a proportion ranging from 3% in the Netherlands to 9% in the UK.

### **Transfusion management cross country analysis**

Use of blood components varied across countries, Italy had a smaller median use of fresh frozen plasma (FFP) and platelets compared to other countries (Table 2). France had the highest use of FFP with a median of 7 units (IQR: 5-9) compared with the other countries. The inter country difference in use of FFP was statistically significant ( $P < 0.01$ ).

Different concentrated sources of fibrinogen were used, the UK 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 (35-37%) compared to the other countries (64%-87%).

Between 13-16% of women received factor VIIa in the Netherlands, Italy and France while the United Kingdom reported the lowest 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 women with massive transfusion while it was used in less than a half of women in the UK and Italy, and these differences were statistically significant. The majority of women received either a colloid or crystalloid for fluid resuscitation. Large amounts of colloid and crystalloid fluids were transfused; the median fluid transfusion was between 3.5 and 4.5 litres in Italy, the Netherlands and the UK.

### **Obstetric management of major obstetric haemorrhage in each country**

Medical management of massive haemorrhage due to atony involving the use of ergometrine, oxytocin, prostaglandin and misoprostol ranged from 88% of cases in France to 97% in the UK. The types of drugs that were used was statistically significantly different between each country; oxytocin was more frequently used in the UK and Australia and prostaglandin used more commonly in France and the Netherlands (Table 3).

The use of surgical techniques and interventional radiology also varied between countries. An intrauterine balloon was used in half of all women with massive transfusion except in France where a balloon was only used in a third. Use of arterial embolisation and major vessel ligation was more common in France and the Netherlands (70% and 52 % of women, respectively) compared to the UK and Italy (16% and 4% of women, respectively).

Uterine compression sutures were more commonly used in Australia, France and the UK (35%-24%) compared to the remaining countries (11-14%). In Italy, 74% of women with a massive transfusion had a hysterectomy, compared with less than half of women in the United Kingdom, France, and a third of women in the Netherlands.

### **Maternal outcomes by country**

Overall there were nine maternal deaths which gave a case fatality of 1.5% (95% CI: 0.67-2.7) (Table 4). Nevertheless, maternal mortality was rare across all countries. Fourteen women had a thrombotic event; women in France had about double the proportion of these events compared to the UK and Australia (8% vs. 3-5%, respectively). In addition, France had a higher proportion of renal failure compared to other countries (16% vs. ~1-2%, respectively). Furthermore, France had slightly higher proportion of cardiac arrests compared to other countries (8% vs. ~1-5%). The majority of women were admitted to intensive treatment/care unit (ITU/ICU) in every country.

## **Discussion**

### **Main findings**

This population-based study has shown a five-fold variation in the incidence of massive transfusion across six high-income countries. Despite the same primary evidence being available to clinicians and guideline writers, in each country different obstetric and haematological management is provided for the management of women undergoing transfusion in major obstetric haemorrhage. Although there were no differences in maternal mortality between countries, these numbers are low, and there was evidence of highly variable rates of cardiac arrest, thrombotic events and renal failure. The greatest variation in resuscitation was seen for use of fibrinogen products, tranexamic acid and factor VIIa. Again, there was striking variation in obstetric management including the use of intrauterine balloons, embolisation and hysterectomy between countries.

### **Findings in context**

#### **Incidence**

The variation in incidence between countries is likely to be multifactorial. Variations in obstetric management may be a relevant factor. More timely recognition, and control of bleeding may prevent worsening to more severe bleeds ( $\geq 8$  units), and therefore factors that delay presentation and definitive management need to be explored between countries. National support for robust MOH protocols through appropriate fluid and haematological management may also control the bleeding at earlier stages.

Other factors include variation in risk factors such as the caesarean section rate and rate of multiple pregnancies; for example, a third of the mothers in the Danish massive transfusion cohort had a multiple pregnancy. However, the data collected in each country did not include information about the general obstetric population so there may be other differences in background risks for PPH between countries, which have not been captured. Alternatively, the variation in incidence of massive transfusion may be a reflection of differential transfusion policies.

#### **Transfusion management**

Guidelines for the haematological and fluid resuscitation management of haemorrhage vary by country and medical speciality<sup>13</sup>. Consequently, it is not surprising that clinical practice and use of blood components differed by country.

## **Fibrinogen and cryoprecipitate**

Clinicians in the UK and Australia mainly used cryoprecipitate as a source of concentrated fibrinogen while in Italy, France and the Netherlands clinicians only used fibrinogen concentrate. There is a paucity of evidence regarding the efficacy of optimal source and dose of fibrinogen. The recent FIB-PPH trial compared the use of fibrinogen concentrate to placebo in the initial treatment of PPH but the intervention did not reduce the primary outcome of postpartum bleeding <sup>16</sup> and this study explored the efficacy of fibrinogen concentrate among a wide range of cases including non-severe PPH. A comparison of cryoprecipitate to fibrinogen concentrate for both efficacy and safety in pregnant or postpartum women has yet to be undertaken. Whilst the study has focused on sources of concentrated fibrinogen, FFP is also a source of fibrinogen; however there is no evidence in the pregnant population for the most efficacious source of fibrinogen.

## **Tranexamic acid**

At the time of the data collection for this study there was a lack of high quality evidence about the use of TXA in the treatment of obstetric haemorrhage, and there was variation in use. Trials were either too small to detect a statistically significant difference in the primary outcome <sup>17</sup> or did not have the power to examine safety issues of the drug <sup>18</sup>. The findings of the WOMAN trial have now been published and it would be of interest to understand how this trial changes TXA use <sup>19</sup>.

## **Recombinant Factor VIIa**

In the majority of countries, current guidelines recommend that factor VIIa should not be given in obstetric haemorrhage <sup>20-22</sup>. A Cochrane review reported no evidence to support the efficacy of Factor VIIa across a range of clinical setting as prophylaxis or therapeutically; but with evidence to indicate an increased risk of thromboembolic events <sup>23</sup>. French guidelines allow for the use of recombinant FVIIa as a “compassionate treatment” to avoid a hysterectomy in nulliparous women or if the vital prognosis is engaged <sup>24</sup>. Overall, despite lack of evidence of benefit alongside risks and high costs, approximately 12% of women across all 6 countries received the pro-haemostatic agent in this international study.

## **Obstetric management**

Previous research has shown that obstetric management of PPH varies internationally <sup>15,25-27</sup>. The findings from this study are consistent with this, as embolisation use was

higher in France and the Netherlands in comparison to the UK. This most likely reflects the availability of the infrastructure required to provide an embolisation service. The intrauterine balloon is the most common second stage management of MOH and its lower use in France most likely reflects high use of embolisation.

This study also 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 and less than a fifth in Denmark. Consistent with previous research, a similar proportion of women in the UK and France had a hysterectomy <sup>15</sup>. With no difference in maternal mortality between countries, this suggests that the future fertility of some of these women could have been saved.

### **Maternal outcomes**

There was no difference in maternal mortality between countries. However, this study may have not been adequately powered to test for this difference in this rare event. A higher number of women with massive transfusion in France had renal failure, cardiac arrest and thrombotic events. The reasons are unclear but higher rates of pro-haemostatic agents were reported. However, EPIMOMS had specific questions on these outcomes within their data collection form, which may have resulted in better ascertainment than the UK, Italy and Australia. Although all studies, excluding Denmark, used the medical notes to complete the data collection form.

### **Strengths**

This study was unique in its ability to compare all women between populations, based on national or regional studies with women who had been transfused at least eight of more units of red blood cells. This study used similar methods to an individual patient data meta-analysis. This methodology allowed the harmonisation of definitions and creation of comparable datasets, which in turn allowed robust comparisons between nations. All countries except for Denmark had tailored data collection forms, which collected detailed information about each woman, and enabled this unique comparison.

### **Limitation**

This analysis should be interpreted in the context of the limitations. Each national study collected slightly different items. To reduce errors due to misclassification all countries had their cases cross-checked against hospital records, other than Denmark,

which was solely based on ICD-10-CM codes

Observational studies examining the association between haematological management and outcomes are prone to confounding by indication i.e. those who received an intervention appear to have worse outcomes<sup>28</sup> 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. Furthermore, there may have been a lack of power to assess difference in maternal mortality between countries.

The findings on patterns of transfusion and haematological fluid resuscitation are limited by incomplete data for timing. 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 clinically very different to a patient who received 8 units over 24 hours.

## **Conclusion**

There was a large variation in the incidence of massive transfusion associated with major obstetric haemorrhage between countries. This was likely to be the result of disparities in timely management of less severe bleeds between countries or differences in transfusion policies. Obstetric management and the use of blood products and haemostatic agents varied substantially. However, despite these variations in management, the rate of maternal mortality was similar. Therefore, there is need for a detailed evaluation of the evidence underlying current guidance, including fibrinogen concentrate and other prothrombotic agents. In addition, this comparison may empower countries to benchmark their clinical care against that of other countries, and provide a challenge to improve current practice, in particular, improved uptake of TXA, immediate use of intrauterine balloons and timely but judicious use of hysterectomy.

## **Summary**

In the absence of high-level evidence, each country has a preferred treatment regime, which may lead to the use of unnecessary costly haematological products, exposure of women to potential adverse effects and radical management such as hysterectomy. With wide variation in obstetric practice, including hysterectomy and embolisation,

significant improvement in the evidence base is required particularly if a women's future fertility could be otherwise preserved. In extreme scenarios there is a delicate balance between saving a women's life and her fertility, however, with a 40% difference in use of hysterectomy between Italy and the Netherlands and no difference in maternal mortality, there must be an examination and comparison of the clinical pathway.

### **Authors' contribution**

**SM** contributed to study conception, design, co-ordinated the project, data analysis and wrote the first draft of the manuscript. **TA** interpreted the data, commented on the manuscript. **JB** was the principal investigator of the TeMpOH-1 project. **MPB XXXX** with **EPIMOMS**. **CDT** was the principal investigator of **EPIMOMS**. **SD** was the principal investigator of **ITOSS**. **AM** performed the data analysis of the Italian data. **HME** gained ethical approval for use of Danish data, gained access to the Danish registry, data management of Danish data. **AG XXXX** with **TeMpOH-1**, data management of Dutch data. **DH** set up and conducted the **TeMpOH-1** study, and coordinated data management of Dutch data. **ZL** was responsible for the data management of the Australian data and gained ethical approval for the transfer of Australian data. **AS** was with **EPIMOMS**, data management of the French data. **ES** was the principal investigator of **AMOSS**. **MK** was the principal investigator of **UKOSS**.

### **All authors interpreted the data and commented on the manuscript.**

**SS**, **JK** and **MK** contributed to the study conception, design and supervised the project.

Declaration of interests: No conflicts of interest to disclose.

**Acknowledgements:** This formed part of **SM's** DPhil in Population Health, University of Oxford.



**Research in context**

There is a lack of high quality evidence underlying guidelines for the management of obstetric haemorrhage, which has resulted in variation in surgical practices across countries. A number of bi-national analyses have shown that surgical management of severe postpartum haemorrhage varied across countries, with a preference for vessel embolisation in France and the Netherlands and compression sutures in the UK. Furthermore, transfusion management guidelines differ across countries; for example, there are different thresholds for transfusion of blood components and use of haemostatic agents and the type and quantity of product given also differs. It is not clear whether these differences in transfusion guidelines are reflected in clinical practice. In addition, if differences exist in terms of management (surgical and transfusion), whether these difference impact maternal mortality or severe maternal morbidity.

Box 1. Summary of data collection systems and data collected.

| Country                | Name of system or dataset                                                                          | Type of system                                                                                           | Date collected                            |
|------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Australia</b>       | Australasian Maternity Outcomes Surveillance System (AMOSS). <sup>29</sup>                         | National obstetric surveillance system. Collected data from hospitals with more than 50 births per year. | One year (July 2014-June 2015)            |
| <b>Denmark</b>         | Danish Medical Birth Registry and the Danish Transfusion Database                                  | Routinely collected national data on both birth and transfusions.                                        | Five years (2010-2015)                    |
| <b>France</b>          | Épidémiologie de la Morbidité Maternelle Sévère study (EPIMOMS) <sup>30</sup>                      | Prospective Population-based study from all maternity units in 6 regions.                                | One year (2012-2013)                      |
| <b>Italy</b>           | Italian Obstetric Surveillance System (ItOSS)                                                      | Population-based study from all maternity units in 6 regions in Italy.                                   | Two years (September 2014-August 2016)    |
| <b>The Netherlands</b> | Transfusion strategies in women during Major Obstetric Haemorrhage study (TelmpOH-1) <sup>31</sup> | Collected data from 75% of national births                                                               | Two years (January 2011 and January 2013) |
| <b>United Kingdom</b>  | United Kingdom Obstetric Surveillance System (UKOSS) <sup>32</sup>                                 | Obstetric surveillance system which collected data nationally from all consultant-led hospitals.         | One year (June 2013- July 2014)           |

Table 1. Sociodemographic, previous medical history and current pregnancy information in women undergoing massive transfusion for major obstetric haemorrhage.

|                                                                    |                    | UK n=162         | Australia n=61   | Italy n=99       | The Netherlands n=179 | France n=126     | Denmark n=288    | P-value |
|--------------------------------------------------------------------|--------------------|------------------|------------------|------------------|-----------------------|------------------|------------------|---------|
| <b>National denominator</b>                                        |                    | 787,105          | 302,666          | 455,995          | 270,101               | 182,309          | 349,998          |         |
| <b>Incidence per 100,000 maternities</b>                           |                    | 20.6 (17.5-24.0) | 20.2 (15.4-25.9) | 21.6 (17.5-26.3) | 65.5 (80.2-102.1)     | 69.5 (57.9-82.7) | 82.3 (73.1-92.4) |         |
| <b>Age</b>                                                         | Mean (Std)         | 33 (5.9)         | 33 (5.3)         | 35 (6.0)         | 32 (5.3)              | 33 (5.9)         | 32 (5.30)        | <0.001  |
| <b>BMI</b>                                                         | Median (IQR)       | 25 (22-29)       | 25 (21-28)       | 23 (21-25)       | 23 (21-26)            | 24 (21-27)       | 23 (21-23.3)     | <0.001  |
| <b>Previous medical history</b>                                    |                    |                  |                  |                  |                       |                  |                  |         |
| <b>Parity</b>                                                      |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | Nulliparous        | 60 (37.3)        | 20 (32.8)        | 48 (48.5)        | 84 (46.9)             | 56 (44.8)        | 176 (44.8)       |         |
|                                                                    | Multiparous        | 101 (62.7)       | 41 (67.2)        | 51 (51.5)        | 95 (53.1)             | 69 (55.2)        | 207 (55.2)       |         |
|                                                                    | Missing            | 1                | 0                | 0                | 0                     | 1                | 5                | 0.185   |
| <b>Previous caesarean section</b>                                  |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | None               | 35 (34.3)        | 24 (60)          | 22 (44.9)        | 51 (53.7)             | 38 (55.9)        | 111 (48.1)       |         |
|                                                                    | Yes                | 67 (65.7)        | 16 (40)          | 27 (55.1)        | 44 (46.3)             | 30 (44.1)        | 101 (51.9)       | 0.023   |
|                                                                    | Nulliparous        | 60               | 20               | 48               | 84                    | 56               | 176              |         |
|                                                                    | Missing            | 0                | 1                | 2                | 0                     | 2                |                  |         |
| <b>Number of previous caesarean section</b>                        |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | 0                  | 34 (33.7)        | 25 (61)          | 15 (36.6)        | -                     | 38 (75.8)        | (67.7)           |         |
|                                                                    | 1                  | 38 (37.6)        | 10 (24.4)        | 16 (39)          | -                     | 21 (16.9)        | (19.8)           | <0.001  |
|                                                                    | 2+                 | 29 (28.7)        | 6 (14.6)         | 10 (24.4)        | -                     | 9 (7.3)          | (12.6)           |         |
|                                                                    | Nulliparous        | 60               | 20               | 48               | -                     | 56               |                  |         |
|                                                                    | Missing            | 1                | 0                | 10               | -                     | 2                |                  |         |
| <b>Previous postpartum haemorrhage</b>                             |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | None               | 78 (76.5)        | 29 (85.3)        | 41 (91.1)        | 86 (91.5)             | 64 (92.8)        | (86.6)           |         |
|                                                                    | Yes                | 24 (23.5)        | 5 (14.7)         | 4 (8.9)          | 8 (8.5)               | 5 (7.2)          | (13.4)           | 0.007   |
|                                                                    | Nulliparous        | 60               | 20               | 48               | 84                    | 56               |                  |         |
|                                                                    | Missing            | 0                | 7                | 6                | 1                     | 1                |                  |         |
| <b>Current pregnancy</b>                                           |                    |                  |                  |                  |                       |                  |                  |         |
| <b>Hypertension prior to pregnancy or gestational hypertension</b> |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | None               | 161 (99.4)       | 59 (96.7)        | 94 (94.9)        | 153 (85.5)            | 124 (99.2)       | (94.4)           | <0.001  |
|                                                                    | Yes                | 1 (0.6)          | 2 (3.3)          | 5 (5.1)          | 26 (14.5)             | 1 (0.8)          | (5.6)            |         |
|                                                                    | Missing            | 0                | 0                | 0                | 0                     | 1                |                  |         |
| <b>Infection in current pregnancy</b>                              |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | No                 | 161 (99.4)       | 56 (94.9)        | 99 (100)         | 179 (100)             | 117 (97.5)       | (98.9)           | 0.006*  |
|                                                                    | Yes                | 1 (0.6)          | 3 (5.1)          | 0 (0)            | 0 (0)                 | 3 (2.5)          | (1.1)            |         |
|                                                                    | Missing            | 0                | 2                | 0                | 0                     | 6                |                  |         |
| <b>Inherited bleeding disorders</b>                                |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | No                 | 160 (98.8)       | 55 (98.2)        | -                | -                     | 121 (96.8)       | -                | 0.602*  |
|                                                                    | Yes                | 2 (1.2)          | 1 (1.8)          | -                | -                     | 4 (3.2)          | -                |         |
|                                                                    | Missing            | 0                | 5                | -                | -                     | 1                |                  |         |
| <b>Multiple pregnancy</b>                                          |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | No                 | 155 (95.7)       | 58 (95.1)        | 92 (92.9)        | 167 (93.8)            | 108 (85.7)       | 219 (76)         | <0.001  |
|                                                                    | Yes                | 7 (4.3)          | 3 (4.9)          | 7 (7.1)          | 11 (6.2)              | 18 (14.3)        | 69 (24)          |         |
|                                                                    | Missing            | 0                | 0                | 0                | 1                     | 0                | 0                |         |
| <b>Induced</b>                                                     |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | None               | 103 (65.2)       | 20 (54.1)        | 56 (73.7)        | 117 (65.4)            | 52 (41.6)        | 348 (60.5)       | <0.001  |
|                                                                    | Yes                | 55 (34.8)        | 17 (45.9)        | 20 (26.3)        | 62 (34.6)             | 73 (58.4)        | 227 (39.5)       |         |
|                                                                    | Missing            | 4                | 24               | 23               | 0                     | 1                |                  |         |
| <b>Delivery type</b>                                               |                    |                  |                  |                  |                       |                  |                  |         |
|                                                                    | Vaginal delivery   | 50 (31.6)        | 25 (41)          | 37 (37.4)        | 104 (58.4)            | 47 (37.6)        | 92 (31.9)        | <0.001  |
|                                                                    | Caesarean delivery | 108 (68.4)       | 36 (59)          | 62 (62.6)        | 74 (41.6)             | 78 (62.4)        | 196 (68.1)       |         |
|                                                                    | N/A Pregnancy loss | 4                | 0                | 0                | 1                     | 1                | 0                |         |

\* Used Fisher's exact test.

Table 2. Haematological management by country

| Blood products                                 |  |                  |                  |                  |                  |                  |            |                       |           |              |  |               |  |         |
|------------------------------------------------|--|------------------|------------------|------------------|------------------|------------------|------------|-----------------------|-----------|--------------|--|---------------|--|---------|
| Number of RBC units                            |  | UK n=162         |                  | Australia n=61   |                  | Italy n=99       |            | The Netherlands n=179 |           | France n=126 |  | Denmark n=288 |  | P-value |
| Received Fresh frozen plasma                   |  | Median (IQR)     |                  |                  |                  |                  |            |                       |           |              |  |               |  |         |
| n (%)                                          |  | 162 (100)        | 59 (96.7)        | 84 (84.8)        | 179 (100)        | 6 (4-8)          | 179 (100)  | 126 (100)             | 11 (8-15) | <0.001       |  |               |  |         |
| Fresh frozen plasma                            |  | Median (IQR)     | 6 (4-8)          | 4 (2-8)          | 6 (4-8)          | 179 (100)        | 126 (100)  | 247 (85-8)            | <0.001    |              |  |               |  |         |
| Received Platelets                             |  | n (%)            | 126 (77.8)       | 51 (83.6)        | 40 (40.4)        | 179 (100)        | 126 (100)  | 205 (71.2)            | <0.001    |              |  |               |  |         |
| Platelets                                      |  | Median (IQR)     | 1 (1-2)          | 1 (1-2)          | 0 (0-2)          | 2 (1-3)          | 1 (1-3)    | 2 (0-3)               | <0.001    |              |  |               |  |         |
| Source of concentrated fibrinogen administered |  | No               | 58 (35.8)        | 8 (13.6)         | 62 (62.6)        | 116 (64.8)       | 27 (22.3)  | -                     | <0.001    |              |  |               |  |         |
| Yes                                            |  | 104 (64.2)       | 51 (86.4)        | 37 (37.4)        | 63 (35.2)        | 94 (77.7)        | 94 (77.7)  | -                     | <0.001    |              |  |               |  |         |
| Missing                                        |  | 0                | 2                | 0                | 0                | 5                | 5          | -                     | <0.001    |              |  |               |  |         |
| Fibrinogen concentrate used                    |  | No               | 152 (93.8)       | 54 (100)         | 62 (62.6)        | 116 (64.8)       | 27 (22.3)  | -                     | <0.001    |              |  |               |  |         |
| Yes                                            |  | 10 (6.2)         | 0 (0)            | 37 (37.4)        | 63 (35.2)        | 94 (77.7)        | 94 (77.7)  | -                     | <0.001    |              |  |               |  |         |
| Missing                                        |  | 0                | 7                | 0                | 0                | 5                | 5          | -                     | <0.001    |              |  |               |  |         |
| Cryoprecipitate used                           |  | No               | 55 (35.5)        | 8 (13.6)         | -                | -                | -          | -                     | 0.002     |              |  |               |  |         |
| Yes                                            |  | 100 (64.5)       | 51 (86.4)        | -                | -                | -                | -          | -                     | 0.002     |              |  |               |  |         |
| Missing                                        |  | 7                | 2                | -                | -                | -                | -          | -                     | 0.002     |              |  |               |  |         |
| Number of units of cryoprecipitate             |  | Median (IQR)     | 2 (0-2)          | 1 (1-2)          | -                | -                | -          | -                     | 0.06      |              |  |               |  |         |
| Use of cell salvage                            |  | No               | 115 (74.2)       | 46 (85.2)        | -                | -                | -          | -                     | 0.098     |              |  |               |  |         |
| Yes                                            |  | 40 (25.8)        | 8 (14.8)         | -                | -                | -                | -          | -                     | 0.098     |              |  |               |  |         |
| Missing                                        |  | 7                | 7                | -                | -                | -                | -          | -                     | 0.098     |              |  |               |  |         |
| If Yes, amount transfused (ml)                 |  | Median (IQR)     | 1150 (500-1900)  | 884 (377-1377)   | -                | -                | -          | -                     | 0.92      |              |  |               |  |         |
| Recombinant Factor VIIa                        |  | No               | 149 (92)         | 48 (90.6)        | 86 (86.9)        | 151 (84.4)       | 103 (85.1) | -                     | 0.224     |              |  |               |  |         |
| Yes                                            |  | 13 (8)           | 5 (9.4)          | 13 (13.1)        | 28 (15.6)        | 18 (14.9)        | 18 (14.9)  | -                     | 0.224     |              |  |               |  |         |
| Missing                                        |  | 0                | 8                | 0                | 0                | 5                | 5          | -                     | 0.224     |              |  |               |  |         |
| Tranexamic acid                                |  | No               | 87 (53.7)        | 41 (74.5)        | 57 (57.6)        | 45 (25.1)        | 47 (39.2)  | -                     | <0.001    |              |  |               |  |         |
| Yes                                            |  | 75 (46.3)        | 14 (25.5)        | 42 (42.4)        | 134 (74.9)       | 73 (60.8)        | 73 (60.8)  | -                     | <0.001    |              |  |               |  |         |
| Missing                                        |  | 0                | 6                | 0                | 0                | 6                | 6          | -                     | <0.001    |              |  |               |  |         |
| Any fluid used during resuscitation            |  | No               | 4 (2.5)          | -                | 0 (0)            | 0 (0)            | 0 (0)      | -                     | <0.001*   |              |  |               |  |         |
| Yes                                            |  | 157 (97.5)       | 12 (22.2)        | 55 (100)         | 167 (100)        | 108 (100)        | 108 (100)  | -                     | <0.001*   |              |  |               |  |         |
| Missing                                        |  | 1                | 42               | 44               | 12               | 18               | 18         | -                     | <0.001*   |              |  |               |  |         |
| Total amount (ml)                              |  | 4000 (3000-6000) | 3500 (3000-5000) | 4500 (3000-6000) | 4500 (3000-6000) | 87 (82.9)        | 87 (82.9)  | -                     | 0.204     |              |  |               |  |         |
| Colloid                                        |  | Yes              | 139 (88.5)       | -                | 49 (98)          | 160 (96.4)       | 21         | -                     | <0.001    |              |  |               |  |         |
| Missing                                        |  | 5                | -                | 49               | 13               | 21               | 21         | -                     | <0.001    |              |  |               |  |         |
| If Yes, amount transfused (ml)                 |  | Median (IQR)     | 1000 (650-2000)  | -                | 1000 (500-1500)  | 1500 (1000-2000) | -          | -                     | <0.001    |              |  |               |  |         |
| Crystalloid                                    |  | Yes              | 152 (95)         | -                | 49 (100)         | 137 (100)        | 103 (95.4) | -                     | 0.025     |              |  |               |  |         |
| Missing                                        |  | 2                | -                | 50               | 42               | 18               | 18         | -                     | 0.025     |              |  |               |  |         |
| If Yes, amount transfused (ml)                 |  | Median (IQR)     | 3000 (1500-4000) | -                | 2500 (1700-3500) | 2500 (1600-4300) | -          | -                     | 0.442     |              |  |               |  |         |

\*Australia only recorded use of 5 and 25% albumin administration-

\*Australia only recorded use of 5 and 25% albumin administration.

Table 3. Obstetric management by country

|                                 |         | UK n=162   | Australia n=61 | Italy n=99 | The Netherlands n=179 | France n=126 | Denmark n=288 | P-value |
|---------------------------------|---------|------------|----------------|------------|-----------------------|--------------|---------------|---------|
| <b>Medical management</b>       |         |            |                |            |                       |              |               |         |
| <b>Syntodinon</b>               | No      | 6 (3-7)    | 7 (11-7)       | 26 (26-3)  | 65 (36-3)             | 47 (39-5)    | -             | <0-001  |
|                                 | Yes     | 156 (96-3) | 53 (88-3)      | 73 (73-7)  | 114 (63-7)            | 72 (60-5)    | -             |         |
|                                 | Missing |            | 1              | 0          |                       | 7            | -             |         |
| <b>Ergometrine</b>              | No      | 69 (42-6)  | 32 (56-1)      | -          | 160 (89-4)            | -            | -             | <0-001  |
|                                 | Yes     | 93 (57-4)  | 25 (43-9)      | -          | 19 (10-6)             | -            | -             |         |
|                                 | Missing |            | 4              |            |                       |              | -             |         |
| <b>Prostaglandin</b>            | No      | 64 (39-5)  | 30 (52-6)      | 49 (49-5)  | 30 (16-8)             | 16 (13-6)    | -             | <0-001  |
|                                 | Yes     | 98 (60-5)  | 27 (47-4)      | 50 (50-5)  | 149 (83-2)            | 102 (86-4)   | -             |         |
|                                 | Missing |            | 4              | 0          |                       | 8            | -             |         |
| <b>Misoprostol</b>              | No      | 73 (45-1)  | 29 (51-8)      | -          | 117 (65-4)            | 118 (99-2)   | -             | <0-001  |
|                                 | Yes     | 89 (54-9)  | 27 (48-2)      | -          | 62 (34-6)             | 1 (0-8)      | -             |         |
|                                 | Missing |            | 5              |            |                       |              | -             |         |
| <b>Any uterine treatment*</b>   | No      | 5 (3-1)    | 3 (5)          | 21 (21-2)  | 13 (7-3)              | 9 (7-5)      | -             | <0-001  |
|                                 | Yes     | 157 (96-9) | 57 (95)        | 78 (78-8)  | 166 (92-7)            | 111 (92-5)   | -             |         |
|                                 | Missing |            | 1              |            |                       | 6            | -             |         |
| <b>Surgical management</b>      |         |            |                |            |                       |              |               |         |
| <b>Intrauterine balloons</b>    | No      | 68 (42)    | 26 (44-8)      | 45 (45-5)  | 77 (43)               | 88 (72-1)    | 246 (85-4)    | <0-001  |
|                                 | Yes     | 94 (58)    | 32 (55-2)      | 54 (54-5)  | 102 (57)              | 34 (27-9)    | 42 (14-6)     |         |
|                                 | Missing | 0          | 3              | 0          | 0                     | 4            | -             |         |
| <b>Intra-abdominal packing</b>  | No      | 147 (90-7) | 47 (83-9)      | -          | -                     | 109 (90-1)   | -             | 0-344   |
|                                 | Yes     | 15 (9-3)   | 9 (16-1)       | -          | -                     | 12 (9-9)     | -             |         |
|                                 | Missing |            | 5              | -          | -                     | 5            | -             |         |
| <b>Embolisation or ligation</b> | No      | 136 (84)   | 41 (67-2)      | 95 (96)    | 86 (48)               | 36 (29-5)    | 286 (99-3)    | <0-001  |
|                                 | Yes     | 26 (16)    | 20 (32-8)      | 4 (4)      | 93 (52)               | 86 (70-5)    | 2 (0-7)       |         |
|                                 | Missing |            |                |            |                       | 4            | -             |         |
| <b>Compressive sutures</b>      | No      | 123 (75-9) | 38 (64-4)      | 86 (86-9)  | 154 (86)              | 90 (73-8)    | 247 (85-8)    | <0-001  |
|                                 | Yes     | 39 (24-1)  | 21 (35-6)      | 13 (13-1)  | 25 (14)               | 32 (26-2)    | 41 (14-2)     |         |
|                                 | Missing | 0          | 2              | 0          | 0                     | 4            | -             |         |
| <b>Hysterectomy</b>             | No      | 87 (53-7)  | 29 (47-5)      | 26 (26-3)  | 126 (70-4)            | 66 (54-5)    | 223 (77-4)    | <0-001  |
|                                 | Yes     | 75 (46-3)  | 32 (52-5)      | 73 (73-7)  | 53 (29-6)             | 55 (45-5)    | 65 (22-6)     |         |
|                                 | Missing |            | -              | -          | -                     | 5            | -             |         |

\* Italian and Danish data include intrauterine packing. The Netherlands: intra-abdominal packing was after hysterectomy.

Table 4. Maternal outcomes by country

| Maternal outcome |         | UK n=162   | Australia n=61 | Italy n=99 | The Netherlands n=179 | France n=126 | Denmark n=288 | P-value |
|------------------|---------|------------|----------------|------------|-----------------------|--------------|---------------|---------|
| Maternal death   | No      | 160 (98.8) | 61 (100)       | 96 (97)    | 175 (97.8)            | 123 (97.6)   | 286 (99.3)    | 0.37*   |
|                  | Yes     | 2 (1.2)    | 0 (0)          | 3 (3)      | 4 (2.2)               | 3 (2.4)      | 2 (0.7)       |         |
|                  | Missing |            |                |            |                       |              |               |         |
| Cardiac arrest   | No      | 154 (95.1) | 57 (96.6)      | 94 (94.9)  | -                     | 116 (92.1)   | 285 (99)      | 0.005*  |
|                  | Yes     | 8 (4.9)    | 2 (3.4)        | 5 (5.1)    | -                     | 10 (7.9)     | 3 (1)         |         |
|                  | Missing | 0          | 2              | 0          |                       |              |               |         |
| Renal failure    | No      | 160 (98.8) | 58 (98.3)      | 97 (98)    | -                     | 106 (84.1)   | 284 (98.6)    | <0.001* |
|                  | Yes     | 2 (1.2)    | 1 (1.7)        | 2 (2)      | -                     | 20 (15.9)    | 4 (1.4)       |         |
|                  | Missing |            | 2              |            |                       |              |               |         |
| Infection        | No      | 157 (96.9) | 56 (96.6)      | 97 (98)    | -                     | 118 (93.7)   | -             | 0.399*  |
|                  | Yes     | 5 (3.1)    | 2 (3.4)        | 2 (2)      | -                     | 8 (6.3)      | -             |         |
|                  | Missing | 0          | 3              | 0          |                       | 4            |               |         |
| Thrombotic event | No      | 158 (97.5) | 57 (96.6)      | 99 (100)   | -                     | 118 (93.7)   | 93.7 (287)    | <0.001* |
|                  | Yes     | 4 (2.5)    | 2 (3.4)        | 0 (0)      | -                     | 8 (6.3)      | 6.3 (1)       |         |
|                  | Missing | 0          | 2              | 0          | -                     |              |               |         |
| ITU admission    | No      | 30 (18.5)  | 2 (3.3)        | 15 (15.3)  | 32 (17.9)             | 44 (34.9)    | -             | <0.001  |
|                  | Yes     | 132 (81.5) | 59 (96.7)      | 83 (84.7)  | 147 (82.1)            | 82 (65.1)    | -             |         |
| Fisher's exact   |         |            |                |            |                       |              |               |         |

Maternal outcomes: Cardiac arrest: UK included - cardiac arrest, cardiac infection and cardioversion and inotropic support; Italy, Australia and France: cardiac arrest.

Infection: UK: 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.

Thrombotic: pulmonary embolism, deep venous thrombosis.

## References

1. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: A review and recommendations from the international postpartum hemorrhage collaborative group. *BMC Pregnancy and Childbirth* 2009; **9**.
2. Deneux-tharaux C, Saucedo M. Épidémiologie de la mortalité maternelle en France, 2010–2012. *Gynécologie Obstétrique Fertilité & Sénologie* 2017; **45**(12, Supplement): S8-S21.
3. Brantley M, Callaghan W, Cornell A, et al. Report from nine maternal mortality review committees. Atlanta: CDC Division of Reproductive Health, 2018.
4. Donati S, Maraschini A, Lega I, et al. Maternal mortality in Italy: Results and perspectives of record-linkage analysis. *Acta Obstet Gynecol Scand* 2018; **97**(11): 1317-24.
5. Knight M, Nair M, Tuffnell D, et al. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15. . Oxford: National Perinatal Epidemiology Unit, University of Oxford 2017.
6. Sullivan EA, Hall B, King JF. Maternal deaths in Australia 2003-2005. Sidney: AIHW National Perinatal Epidemiology Research Unit, 2007.
7. McKinnon Edwards H. Aetiology and treatment of severe postpartum haemorrhage. Copenhagen: University of Copenhagen; 2017.
8. Green L, Knight M, Seeney F, et al. The haematological features and transfusion management of women who required massive transfusion for major obstetric haemorrhage in the UK: a population based study. *Br J Haematol* 2016; **172**(4): 616-24.
9. Green L, Knight M, Seeney FM, et al. The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2016; **123**(13): 2164-70.
10. Ramler PI, van den Akker T, Henriquez DD, Zwart JJ, van Roosmalen J. Incidence, management and outcome of women requiring massive transfusion after childbirth in the Netherlands: secondary analysis of a nationwide cohort study between 2004 and 2006. *BMC pregnancy and childbirth* 2017; **17**(1): 197.
11. Henriquez DD, Bloemenkamp KW, van der Bom JG. Management of postpartum hemorrhage: how to improve maternal outcomes? *J Thromb Haemost* 2018; **16**(8): 1523-34.
12. Dahlke JD, Mendez-Figueroa H, Maggio L, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *American Journal of Obstetrics & Gynecology* 2015; **213**(1): 76.e1-e10.
13. Shaylor R, Weiniger CF, Austin N, et al. National and International Guidelines for Patient Blood Management in Obstetrics: A Qualitative Review. *Anesthesia & Analgesia* 2017; **124**(1): 216-32.
14. Ramler PI, Akker T, Henriquez DD, Zwart JJ, Roosmalen J. Incidence, management and outcome of women requiring massive transfusion after childbirth in the Netherlands: secondary analysis of a nationwide cohort study between 2004 and 2006. *BMC pregnancy and childbirth* 2017; **17**(1): 197.
15. Kayem G, Dupont C, Bouvier-Colle M, Rudigoz R, Deneux-Tharaux C. Invasive therapies for primary postpartum haemorrhage: a population-based study in France. *BJOG: An International Journal of Obstetrics & Gynaecology* 2016; **123**(4): 598-605.
16. Wikkelsø A, Edwards H, Afshari A, et al. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. *Br J Anaesth* 2015; **114**(4): 623-33.
17. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomization trial. *Arch Gynecol Obstet* 2013; **287**(3): 463-8.
18. Ducloy-Bouthors A-S, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Crit Care* 2011; **15**(2):

R117.

19. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *The Lancet* 2017; **389**(10084): 2105.
20. Sentilhes L, Vayssière C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2016; **198**: 12-21.
21. Mavrides E, Allard S, Chandrachan E, et al. Postpartum Haemorrhage, Prevention and Management (Green-top Guideline No. 52). . *BJOG: An International Journal of Obstetrics & Gynaecology* 2016; **124**:e106-e149.
22. Hunt BJ, Allard S, Keeling D, et al. A practical guideline for the haematological management of major haemorrhage. *Br J Haematol* 2015; **170**(6): 788-803.
23. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev* 2012; (3).
24. Goffinet F, Mercier F, Teyssier V, et al. Postpartum haemorrhage: recommendations for clinical practice by the CNGOF (December 2004). *Gynecologie, obstetrique & fertilite* 2005; **33**(4): 268-74.
25. Kayem G, Kurinczuk J, Alfirevic Z, Spark P, Brocklehurst P, Knight M. Specific second-line therapies for postpartum haemorrhage: a national cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2011; **118**(7): 856-64.
26. Zwart JJ, Dijk PD, van Roosmalen J. Peri-partum hysterectomy and arterial embolization for major obstetric hemorrhage: a 2-year nationwide cohort study in the Netherlands. *American Journal of Obstetrics & Gynecology* 2010; **202**(2): 150.e1-7.
27. Bonnet M-P, Basso O, Bouvier-Colle M-H, et al. Postpartum haemorrhage in Canada and France: a population-based comparison. *PLoS ONE* 2013; **8**(6): e66882.
28. Del Junco DJ, Fox EE, Camp EA, Rahbar MH, Holcomb JB. Seven deadly sins in trauma outcomes research: an epidemiologic post-mortem for major causes of bias. *The Journal of Trauma and Acute Care Surgery* 2013; **75**(1 0 1): S97.
29. Halliday LE, Peek MJ, Ellwood DA, et al. The Australasian Maternity Outcomes Surveillance System: An evaluation of stakeholder engagement, usefulness, simplicity, acceptability, data quality and stability. *Aust N Z J Obstet Gynaecol* 2012; **53**.
30. Korb D, Goffinet F, Seco A, Chevrete S, Deneux-Tharaux C. Risk of severe maternal morbidity associated with cesarean delivery and the role of maternal age: a population-based propensity score analysis. *CMAJ* 2019; **191**(13): E352-E60.
31. Henriquez DD, Bloemenkamp KW, Loeff RM, et al. Fluid resuscitation during persistent postpartum haemorrhage and maternal outcome: A nationwide cohort study. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2019; **235**: 49-56.
32. Knight M, Kurinczuk JJ, Tuffnell D, Brocklehurst P. The UK Obstetric Surveillance System for rare disorders of pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology* 2005; **112**(3): 263-5.