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

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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

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(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.

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Introduction

The most common form of major obstetric haemorrhage (MOH), postpartum haemorrhage (PPH), which occurs in 3-7% of deliveries in high-income settings [1]; 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 [2-4] and haemorrhage related mortality in the United Kingdom (UK) nearly doubled during the period 2010-12 to 2013-15 [5]. Major obstetric haemorrhage (MOH) is a common reason for admission to intensive care [6].

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 [7-9] and also referred to as massive transfusion, focusses on transfusion and fluid resuscitation, alongside planning for definitive obstetric and surgical interventions [10]. 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 [11].

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 [12,13]. A number of national studies have reported the transfusion management of PPH [14,15], 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 ±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 (≥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 [13]. 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 [16] 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 [17] or did not have the power to examine safety issues of the drug [18]. The findings of the WOMAN trial have now been published and it would be of interest to understand how this trial changes TXA use [19].

Recombinant Factor VIIa

In the majority of countries, current guidelines recommend that factor VIIa should not be given in obstetric haemorrhage [20-22]. 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 [23]. 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 [24]. 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 [15,25-27]. 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 [15]. 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 [28] 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 transfsuion 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.

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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
Australia	Australasian Maternity Outcomes Surveillance System (AMOSS). [29]	National obstetric surveillance system. Collected data from hospitals with more than 50 births per year.	One year (July 2014-June 2015)
Denmark	Danish Medical Birth Registry and the Danish Transfusion Database	Routinely collected national data on both birth and transfusions.	Five years (2010-2015)
France	Épidémiologic de la Morbidité Maternelle Sévère study (EPIMOMS) [30]	Prospective Population-based study from all maternity units in 6 regions.	One year (2012-2013)
Italy	Italian Obstetric Surveillance System (ItOSS)	Population-based study from all maternity units in 6 regions in Italy.	Two years (September 2014-August 2016)
The Netherlands	Transfusion strategies in women during Major Obstetric Haemorrhage study (TeMpOH-1) [31]	Collected data from 75% of national births	Two years (January 2011 and January 2013)
United Kingdom	United Kingdom Obstetric Surveillance System (UKOSS) [32]	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
National denominator		787,105	302,666	458,995	270,101	182,309	349,998	
Incidence per 100,000 maternities		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)	
Age	*Mean (Std)*	33 (5·9)	33 (5·3)	35 (6·0)	32 (5·3)	33 (5·9)	32 (5·30)	<0·001
BMI	*Median (IQR)*	25 (22-29)	25 (21-28)	23 (21-25)	23 (21-26)	24 (21-27)	23 (21-23·3)	<0·001
Previous medical history								
Parity	*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)	0·185
	Missing	1	0	0	0	1	5	
Previous caesarean section	*None*	35 (34·3)	24 (60)	22 (44·9)	51 (53·7)	38 (55·9)	111 (48·1)	0·023
	Yes	67 (65·7)	16 (40)	27 (55·1)	44 (46·3)	30 (44·1)	101 (51·9)	
	Nulliparous	60	20	48	84	56	176	
	Missing	0	1	2	0	2		
Number of previous caesarean section	*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		
Previous postpartum haemorrhage	*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		
Current pregnancy								
Hypertension prior to pregnancy or gestational hypertension	*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		
Infection in current pregnancy	*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		
Inherited bleeding disorders	*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		
Multiple pregnancy	*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	
Induced	*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		
Delivery type	*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		UK n=162	Australia n=61	Italy n=99	The Netherlands n=179	France n=126	Denmark n=288	P-value
Number of RBC units	*Median (IQR)*				(9-15)	10 (9-12)	11 (8-15)	<0·001
Received Fresh frozen plasma	*n (%)*	162 (100)	59 (96·7)	84 (84·8)	179 (100)	126 (100)	247 (85·8)	<0·001
Fresh frozen plasma	*Median (IQR)*	6 (4-8)	6 (4- 8)	4 (2-8)	6 (4-8)	7 (5- 9)	6 (4-8)	<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)	- -	
	Missing	0	2	0	0	5	- -	
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)	- -	
	Missing	0	7	0	0	5	- -	
Cryoprecipitate used	*No*	55 (35·5)	8 (13·6)	- -	- -	- -	- -	0·002
	Yes	100 (64·5)	51 (86·4)	- -	- -	- -	- -	
	Missing	7	2	- -	- -	- -	- -	
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)	- -	- -	- -	- -	
	Missing	7	7	- -	- -	- -	- -	
If Yes, amount transfused (ml)	*Median (IQR)*	1150 (500-1900)	884 (565-1377)	- -	- -	- -	- -	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)	- -	
	Missing	0	8	0	0	5	- -	
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)	- -	
	Missing	0	6	0 0	0	6	- -	
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)	- -	
	Missing	1	42	44	12	18	- -	
Total amount (ml)		4000 (3000-6000)		3500 (3000-5000)	4500 (3000-6000)			0·204
Colloid	*Yes*	139 (88·5)	- -	49 (98)	160 (96·4)	87 (82·9)	- -	<0·001
	Missing	5	- -	49	13	21	- -	
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	- -	
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·

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
Medical management								
	No	6 (3·7)	7 (11·7)	26 (26·3)	65 (36·3)	47 (39·5)	- -	<0·001
Syntocinon	*Yes*	156 (96·3)	53 (88·3)	73 (73·7)	114 (63·7)	72 (60·5)	- -	
	Missing		1	0		7	- -	
	No	69 (42·6)	32 (56·1)	- -	160 (89·4)	- -	- -	
Ergometrine	*Yes*	93 (57·4)	25 (43·9)	- -	19 (10·6)	- -	- -	<0·001
	Missing		4				- -	
	No	64 (39·5)	30 (52·6)	49 (49·5)	30 (16·8)	16 (13·6)	- -	
Prostaglandin	*Yes*	98 (60·5)	27 (47·4)	50 (50·5)	149 (83·2)	102 (86·4)	- -	<0·001
	Missing		4	0		8	- -	
	No	73 (45·1)	29 (51·8)	- -	117 (65·4)	118 (99·2)	- -	
Misoprostol	*Yes*	89 (54·9)	27 (48·2)	- -	62 (34·6)	1 (0·8)	- -	<0·001
	Missing		5				- -	
	No	5 (3·1)	3 (5)	21 (21·2)	13 (7·3)	9 (7·5)	- -	
Any utertonic treatment*	*Yes*	157 (96·9)	57 (95)	78 (78·8)	166 (92·7)	111 (92·5)	- -	<0·001
	Missing		1			6	- -	
Surgical management								
Intrauterine balloons	*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		
Intra-abdominal packing	*No*	147 (90·7)	47 (83·9)	- -	- -	109 (90·1)	- -	
	Yes	15 (9·3)	9 (16·1)	- -	- -	12 (9·9)	- -	0·344
	Missing		5	- -	- -	5	- -	
Embolisaton or ligation	*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		
Compressive sutures	*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		
Hysterectomy	*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)	
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.

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