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General obstetrics

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

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Objective To ascertain the incidence of massive transfusion (MT) in obstetrics in the UK, and describe its management and clinical outcomes.

Design A population-based cross-sectional study conducted through the UK Obstetric Surveillance System (UKOSS).

Settings All UK hospitals with consultant-led maternity units.

Population Any pregnant woman at ≥20 weeks of gestation receiving ≥8 units of red blood cells within 24 hours of giving birth, from July 2012 to June 2013.

Methods Prospective case identification through the monthly mailing of UKOSS.

Results We identified 181 women who had undergone MT, making the estimated incidence of MT associated with postpartum haemorrhage (PPH) 23 per 100 000 maternities (95% confidence interval 19–26) per year. The median estimated blood loss was 6 l (interquartile range 4.5–8.0 l). The majority of women presented outside working hours (63%), 40% had had previous caesarean sections and 3% had normal vaginal births without risk factors. The main cause for MT was uterine atony (40%) and the main mode of birth was caesarean section (69%). Of the 181 women, 15 received >20 units of red blood cells. In total, 45% of women underwent hysterectomy, and among all causes of PPH, placenta accreta had the highest hysterectomy rate. Two women died, 82% were admitted to intensive care/high-dependency units, and 28% developed major morbidities.

Conclusion Massive transfusion due to PPH is associated with high rates of morbidity and hysterectomy. Clinical and research efforts should focus on approaches to recognise and optimise timely resuscitation and management of these severe cases.

Keywords management, massive transfusion, outcome, postpartum haemorrhage.

Tweetable abstract Massive transfusion due to postpartum haemorrhage is associated with high rates of morbidity and hysterectomy.

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Introduction

Postpartum haemorrhage (PPH) remains a common cause of maternal morbidity and mortality worldwide.[1–3] There is no universally accepted definition for PPH between countries, and therefore its incidence varies depending on how it is defined. In Scotland the incidence of severe PPH —defined as >2500 ml blood loss or ≥5 units of red blood cells (RBC) within 24 hours of giving birth—has risen over the years with its incidence being reported as 3.7 per 1000

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maternities in the 2003–05 triennium and 5.9 per 1000 maternities in the 2009–12 triennium.[4] The rise in the frequency of severe PPH has also been evident in other resource-rich countries.[5–7] Although the mortality rate from PPH remains low in these countries the rates of severe adverse outcomes associated with PPH have increased. The reasons for this include associated factors such as advanced maternal age, multiple birth, obesity, increased obstetric intervention and higher rates of caesarean section.[3,5] The treatment of PPH is multifactorial and involves timely identification and supportive resuscitation, alongside the use of pharmacological, mechanical and surgical methods to arrest bleeding.[8] Early identification of PPH risk factors is considered an important part of antepartum and peripartum care, but there are few prospective data to inform strategies for optimal management of PPH.

In this respect little is known about the incidence, management and clinical outcome of massive transfusion (MT) in obstetrics. Although there is no agreed definition for MT worldwide, researchers have applied transfusion of ≥10 units of RBC within 24 hours, 50% blood volume loss within 3 hours, or transfusion of ≥4 RBC units within 1 hour.[9] The overall objectives of this study, undertaken through the United Kingdom Obstetric Surveillance System (UKOSS), were to ascertain the incidence of MT in obstetrics in the UK, and describe the current management practices and clinical outcome of these cases. In this study, MT was defined pragmatically as any pregnant woman at ≥20 weeks of gestation receiving ≥8 units of RBC transfusion within 24 hours of giving birth.

Methods

This was a national cross-sectional descriptive study conducted in the UK from July 2012 to June 2013 and undertaken through UKOSS. The study was approved by the UK Research Ethical Committee London—City & East (REC reference 12/LO/0689). Over the last 10 years, UKOSS has developed a reliable and straightforward method to study rare disorders of pregnancy. Anonymous descriptive, case–control and cohort studies are conducted through a prospective monthly case collection scheme, achieving a 92–95% response rate.[10]

Women were eligible for inclusion in the study if they were pregnant at ≥20 weeks of gestation and if they had received ≥8 units of RBC transfusion within 24 hours of giving birth. Cases were identified and reported to UKOSS by the obstetric units in participating hospitals (obstetricians, midwives, anaesthetists and perinatal risk management/risk coordinator or equivalent). On receiving the case report, UKOSS dispatched a pre-piloted paper case report form to the reporting clinicians. The case report form sought confirmation of the appropriate case definition and additional information on demographics, cause of PPH, management of PPH and clinical outcomes of women and babies. Clinical data on cases were collected from the woman's case notes by the clinical team looking after the woman, and no personally identifiable data (i.e. names, addresses, hospital/NHS numbers) were submitted to UKOSS. Each case was allocated a unique UKOSS identification number and hospitals were asked to keep their own record of the unique study number and the patient identifiers in order to facilitate elimination of duplicate reports.

Analysis

All analyses were performed using the statistical software SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous data were summarised as medians with the 25 and 75th centiles, and discrete data as frequencies and percentages.

Results

During the study period a total of 277 cases were reported to UKOSS from 212 hospitals in the UK. Of these, case report forms were received for 210; 34 cases were subsequently reported by the clinicians not to be valid cases, no data were received for 18, five were duplicates, five delivered outside the study period, and in five cases records were lost. Of the 210 case report forms received, 29 did not fulfil the study inclusion criteria, leaving a total of 181 confirmed cases in which women had received ≥8 units of RBC within 24 hours of delivery for management of PPH. During the study period there were an estimated 787 105 deliveries in the UK, making the estimated incidence of MT due to PPH 23 per 100 000 maternities (95% confidence interval [95% CI] 1.9–2.6).

Characteristics of women requiring massive transfusion

Table 1 describes the demographic and baseline clinical features of women, including details of the index pregnancy. The median (interquartile range [IQR]) age and BMI for all women were 33 years (29–36) and 25 kg/m^2 (22–29 kg/m^2), respectively. The median (IQR) gestational age (n = 175 cases) was 38 weeks (37–40 weeks). In our cohort, 18% and 8% of women were of Asian and Black ethnicity, respectively: the former is a recognised risk factor for PPH,[8] and the latter requires further investigation.

Details of haemorrhage

The median (IQR) estimated blood loss for 178 women with bleeding and requiring ≥8 units of RBC (data missing for three women) was 6 l (4.5–8.0 l) (see Figure S1). Of these, 176 women fulfilled the Royal College of Obstetricians and Gynaecologists (RCOG) -defined criteria for severe PPH (i.e. >2 l estimated blood loss).[8]

Table 1. Characteristics of cases and details of pregnancy and birth

Characteristics (*n* = denominator)	*n* (%)
BMI (kg/m^2) (*n* = 181)	
<25	87 (48%)
25–35	83 (46%)
>35	11 (6%)
Ethnicity (*n* = 181)	
White	128 (71%)
Mixed	1 (<1%)
Asian or Asian British	32 (18%)
Black or Black British	14 (8%)
Chinese or other ethnic group	6 (3%)
Number of previous completed pregnancies beyond 24 weeks (*n* = 180)	
0	68 (38%)
1–3	93 (52%)
≥4	19 (10%)
Previous caesarean section (*n* = 181)	73 (40%)
Previous post-partum haemorrhage (*n* = 181)	25 (14%)
Other pre-existing medical conditions (*n* = 181)	37 (20%)
Multiple pregnancy (*n* = 181)	8 (4%)
Miscarriage (*n* = 181)	2 (1%)
Termination of pregnancy (*n* = 181)	3 (2%)
Induced birth (*n* = 176)	61 (35%)
Premature labour (*n* = 175)	41 (23%)
Mode of birth (*n* = 181)	
Spontaneous	36 (20%)
Instrumental	21 (12%)
Caesarean	124 (69%)*

The denominator varies for several reasons, including some which were 'not reported'. Mode of birth refers to the most invasive mode for multiple births where the mode of birth differed between the babies.
*Includes one hysterotomy at 22 weeks and one hysterotomy at an unreported time.

Table 2. Characteristics of PPH cases requiring massive transfusion

Characteristics	
Primary cause of bleed (*n* = 181), *n* (%)	
Uterine atony	71 (40)
Placenta abnormalities	59 (33)
Placenta accreta	29/59 (49)
Placental abruption	17/59 (29)
Placenta praevia	13/59 (22)
Laceration/extension//tears	34 (19)
Trauma	26/34 (76)
Uterine rupture	8/34 (24)
Other	17 (9)
Location of the woman at the onset of haemorrhage (*n* = 180) *n* (%)	
Labour/Delivery room	48 (27)
Obstetric theatre/recovery room	103 (57)
Home/Community	17 (9)
Other	12 (7)
Onset of bleed outside working hours* (*n* = 114) *n* (%)	
Uterine atony	49 (43)
Placenta abnormalities	32 (28)
Placenta accreta	11/32 (34)
Placental abruption	13/32 (41)
Placenta praevia	8/32 (25)
Laceration/extension/tears	22 (19)
Trauma	18/22 (82)
Uterine rupture	4/22 (18)
Other	11 (10)
Time of birth to onset of bleed (minutes) (*n* = 169), median (IQR)	13 (0–63)
Onset of bleeding before childbirth (antenatal and intrapartum) (*n* = 34)	67 (17–259)
Postnatal (*n* = 135)	24 (7–87)

The denominator varies for several reasons, including occasional not reported.
*Working hours were defined as any time from 9:00 am to 6:00 pm Monday to Friday excluding bank holidays and weekends.

Table 2 summarises the causes of bleeding in women requiring ≥8 units of RBC, and aspects of their presentation, such as location at time of bleed. The most common cause was uterine atony, followed by placenta accreta and trauma. There were 17 'other' cases, which were reported as arterial tears ($n = 8$), amniotic fluid embolism ($n = 2$), retained products ($n = 2$), uterine inversion ($n = 1$), uterine infection ($n = 1$), clotting disorder ($n = 1$) and unknown ($n = 2$). Of the 180 women (data not available for one), many (63%) presented outside working hours—defined as weekends, bank holidays and overnight from 6:01 pm to 8:59 am. Seventeen (9%) women were in the community/home at the onset of bleed and 103 (57%) were in theatre and/or recovery room. Of the 17 cases that were in the community/home at the onset of bleeding, 14 started to haemorrhage outside working hours, two within working hours and for one it was not possible to determine the time of bleeding. The causes of haemorrhage for these 17 women included: atony ($n = 3$), placenta praevia ($n = 5$), placenta abruption ($n = 5$), accreta ($n = 2$) uterine rupture ($n = 1$) and trauma ($n = 1$).

As shown in the (Figure S2), the causes of bleeding in women requiring ≥8 units of RBC were grouped by total amount of RBC transfused into three categories: moderate (8–12 units, $n = 125$); high (13–20 units, $n = 39$); and massive (>20 units, $n = 15$). Placenta accreta was the most common cause of massive bleeds (40%), whereas uterine atony was the most common cause for moderate severity bleeds (45%). Factor VIIa and tranexamic acid were administered to 15 (8%) and 84 (46%) women, respectively.

Mode of birth by aetiology

According to the bleeding, risk factors and mode of birth, women were categorised into five groups which were: (1) normal vaginal birth, with no risk factors ($n = 5$); (2) normal vaginal birth with risk factors ($n = 31$); (3) operative vaginal birth ($n = 21$); (4) elective caesarean section ($n = 36$); and (5) emergency caesarean section ($n = 88$). Risk factors included previous pregnancy with PPH or caesarean section, previous pregnancy stillbirth, parity of >4, induction, pre-eclampsia, antepartum haemorrhage, intrapartum haemorrhage, or anaemia.[11] The causes of PPH for each of these groups are depicted in Figure 1.

Apart from elective caesarean section, where placenta accreta was the main cause of PPH (47%), uterine atony was the most common for other categories. Further, out of all placenta accreta cases, 24 (83%) delivered via caesarean section, of which 17 were elective. Of the five women who underwent normal vaginal birth without risk factors, two gave birth in a midwifery-led birth unit and three delivered in a hospital setting. Two were nulliparous. Four had an atonic uterus and received 8, 10, 10 and 13 units of RBC transfusion. The remaining woman who bled due to trauma received 9 units of RBC. Two of the five women had major morbidities, and both developed respi-

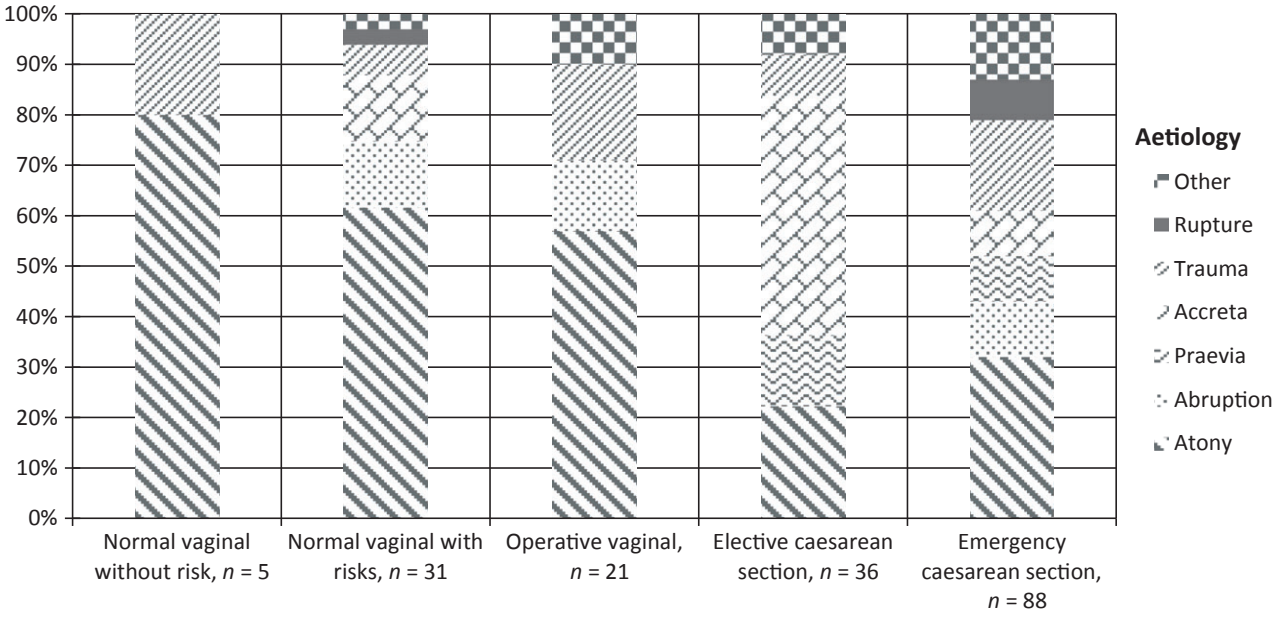

Figure 1. Distribution of aetiology, by mode of birth.

Table 3. Obstetric interventions: percentage of women receiving each treatment, by bleeding causes (women who received more than one treatment are counted multiple times)

	Atony ($n = 71$)	Abruption ($n = 17$)	Praevia ($n = 13$)	Accreta ($n = 29$)	Trauma ($n = 26$)	Rupture ($n = 8$)	Other ($n = 17$)	Total ($n = 181$)
Syntocinon infusion	99	100	100	86	88	100	94	95
Ergometrine	73	59	31	41	38	63	47	56
Prostaglandin F2α	77	65	38	31	54	38	59	59
Misoprostol	70	53	23	31	46	50	53	53
Intra-abdominal packing	4	6	8	17	12	0	18	9
Intrauterine balloons	82	53	54	31	46	13	47	57
Intrauterine packing	15	12	15	7	15	13	12	13
Vessel embolisation/ligation	15	0	23	7	31	25	18	16
Intra-arterial balloons	1	6	0	7	0	0	6	3
B-lynch or other brace suture	37	24	23	7	12	25	24	24
Hysterectomy	35	41	76	93	31	38	6	45

ratory/ventilatory failure. None of the five required interventional surgery.

Management of women requiring massive transfusion

The details of obstetric management by causes of PPH are listed in Table 3. The most common uterotonic agent administered was syntocinon (95%), followed by prostaglandin F2α (59%) and ergometrine (56%): 140 (77%) women were given a syntocinon infusion as their first line of treatment with 22 (12%) receiving it as a second line. Of the nine (5%) women who did not receive syntocinon infusion, four presented with placenta accreta and three with trauma. Ergometrine was the most frequently administered second treatment, given to 65 (36%) women. Intrauterine balloons were used in 57% of women, of whom 56% presented with atony and 12% with trauma. In total, 45% of women underwent hysterectomy, and of these 54% had placental abnormalities (27 placenta accreta, ten placenta praevia and seven placental abruption). Placenta accreta and placenta praevia were associated with high rates of hysterectomy (93% and 76%, respectively) compared with other groups (all $\leq$41%).

Outcomes of women and their infants

Two women (1%) died (both of amniotic fluid embolism), 149 (82%) were admitted to level 3 intensive care, 81 (45%) had a hysterectomy and 51 (28%) developed major morbidity: of the latter, 12 women developed respiratory/ventilatory failure, ten had cardiac complications, six developed infection, and 38 had other complications, such as delivery complications, coagulopathy, retained products, paralytic ileus and Sheehan syndrome (some had more than one of the stated complications). According to the mode of delivery, of the 81 women whose management proceeded to hysterectomy, 16 (20%) had normal vaginal births with risk factors, five (6%) had operative vaginal births, 24 (20%) gave birth by elective caesarean section and 36 (44%) by emergency caesarean section. None had normal vaginal births without risk factors.

In total there were 184 infants, 166 (90%) live infants, 16 (9%) stillborn and two (1%) infant deaths. The median birthweight for the live infants (n = 162) was 3230 g (2710–3610) and the median (IQR) for the 5-minute Apgar score (n = 158) was 9 (8–10). Of the 166 infants, 14 (8%) had major infant complications, which were primarily respiratory complications (79%).

The experience of staff involved in the management of PPH is an important factor that can affect the outcome for women; this was not assessed in this study but is an important variable that merits further investigation.

Discussion

Main findings

The estimated incidence of MT associated with PPH, defined in this study as any pregnant woman of $\geq$20 weeks of gestation receiving $\geq$8 units of RBC transfusion within 24 hours of birth was 23 per 100 000 maternities (95% CI 19–26). The vast majority of these women had had previous caesarean section and presented outside working hours. Only 3% of women had normal vaginal births without risk factors. The main cause of MT was uterine atony and the main mode of birth was caesarean section. Almost half of the women underwent hysterectomy to control bleeding, and among all causes of PPH, placenta accreta had the highest hysterectomy rate.

Strengths and limitations

One key strength of our study was the prospective nature of data collection using patients' clinical notes, as opposed to obtaining information from databases or coded discharge data. Furthermore, we adopted a definition of MT during PPH based on the quantity of RBC transfused—an objective and easily ascertained indicator—rather than more subjective and imprecise methods of quantification (e.g. estimation of blood loss).

A potential limitation of the study was that we could not be absolutely certain that we had captured all cases—perhaps through logistical and administrative lapses—no matter how much we have tried to facilitate case identification and how well-implemented the monthly UKOSS reminder system is. However, previous studies using the UKOSS reporting scheme have indicated high rates of detection and no systematic bias in their reporting scheme.[12]

Interpretation of results

Our findings were based on a large population-based study. Given that our study was of severe PPH, we can expect that such cases would have been managed in consultant-led maternity units, and so would have been reported to UKOSS through their monthly regular reminders. Therefore we believe that our study has captured the majority of cases, and that our estimate of the incidence of MT during PPH in the UK is a robust one. One retrospective cross-sectional study reported that the MT rate (defined as transfusion of $\geq$10 units of RBC during the admission for birth)[13] in New York between 1998 and 2007 was 60 per 100 000 hospitalised deliveries. Notwithstanding the higher threshold for RBC transfusion used to define MT, the higher rate of MT observed in that study is possibly due to the inclusion of all pregnancy-related haemorrhage (compared with our criterion of >20 weeks of gestation).

Of the 181 women with MT, only five (3%) had normal births without risk factors. These represent women who are

encouraged to give birth at home or in midwifery units and represent about 36% of all UK births (45.3% of women are 'low risk' at the start of labour, of whom 21% are reassigned intrapartum when they develop complications).[14,15] The number of these births each year in the UK is ~250 000 giving a risk of haemorrhage requiring MT of about 1:50 000. These data will continue to provide considerable reassurance to those who have argued that home delivery of low-risk women is safe.

The majority of randomised trials of PPH prevention and management have been carried out on low-risk women undergoing vaginal birth. However, this study shows that these women very rarely require MT, and demonstrates the importance of research into the management of PPH during complex births. Although logistically more complex to carry out, these are the women who have high morbidity and where intervention is crucial to prevent maternal death. This is also likely to be true for low-resource settings where there may be more to be gained from improving the management of complex births than from the provision of universal PPH prophylaxis.[16]

Most women requiring MT had had previous caesarean delivery, and presented outside working hours. The main cause of MT in our study was uterine atony. These findings are consistent with other studies,[3,6] although one study has reported placental abnormalities as the most common cause of PPH.[13] The main mode of birth in our cohort was caesarean section. Almost half of the women underwent hysterectomy to control bleeding, consistent with current recommendations for early recourse to hysterectomy,[8] and among all causes of PPH, placenta accreta had the highest hysterectomy rate and received the greatest number of RBC transfusions.

The overall rate of hysterectomy in our study was high (45%)—unsurprising perhaps given the high rates of previous caesarean deliveries in our cohort. One population-based case–control study in the UK showed that previous, and ongoing, caesarean deliveries are risk factors for peripartum hysterectomy (odds ratio 3.52, 95% CI 2.35–5.26 and odds ratio 7.13, 95% CI 3.71–13.7, respectively), and that the odds increased with the number of previous caesarean deliveries.[12] Another important observation was the fact that women with placenta accreta, compared with all other PPH causes, had the highest hysterectomy rate (93%). This contrasts with a hysterectomy rate of 59% observed in a previous UKOSS study of placenta accreta,[17] reflecting a difficulty in controlling bleeding among the group included in this study. Given that the RCOG guideline for the management of PPH recommends that hysterectomy be administered 'sooner rather than later' in women with placenta accreta,[8] it is unsurprising that most of these women with massive haemorrhage have undergone hysterectomy. It is also interesting to note that placenta accreta cases made up almost half of women delivered by elective caesarean section (47%), for which multidisciplinary expertise and forward planning would have been in place to cope with and manage all contingencies. The fact that a disproportionately high number of women ($n = 6$) with placenta accreta went on to receive >20 units of RBC, reiterates the potential severity of PPH associated with this particular aetiology.

In resource-rich countries, the rate of mortality associated with PPH is very low. Between 1994 and 2014 in the UK, the direct haemorrhage death rate has remained relatively unchanged (0.39–0.9 per 100 000 maternities).[18] In our study, the mortality rate from MT was comparably low (0.23 per 100 000 maternities), and the main cause of death for the two mortalities was amniotic fluid embolism. On the other hand, the morbidity rate was high, with more than 80% of women being transferred to high dependency or intensive care units; almost half of the women with MT underwent hysterectomy and a third of them developed other morbidities, such as respiratory failure and cardiac complications. The high rate of morbidity due to PPH in developed countries has been recognised by other studies[3,5] and our study's findings are consistent with theirs. Early recognition of PPH,[19] and forward antenatal planning for women who are at high risk of bleeding, are key to improving outcome and preventing these women from requiring MT.

Conclusion

Our findings have established the on-going burden of morbidity associated with MT of PPH and identified a range of clinical and organisational factors associated with presentation. Further, research should focus on approaches to recognise and optimise timely resuscitation and management in women with more severe PPH. By comparison, in trauma, morbidity/mortality associated with MT are also high[20] and there is considerable interest in testing whether different strategies for blood transfusion may reduce mortality and morbidity.[21]

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

LG designed the study, carried out the analysis and wrote the first draft. MK designed the study, carried out the analysis and contributed to the writing of the article. FMS and CH analysed and validated the data and contributed to the writing of the article. PWC, REC, NAB and AW contributed to the design of the study and writing of the article. SSS designed the study, carried out the analysis and wrote the first draft.

Details of ethics approval

The study was approved by the UK Research Ethical Committee London—City & East (REC reference 12/LO/0689).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of the estimated blood loss volumes.

Figure S2. Distribution of aetiology, by severity of bleed (data shows % of women in each severity category who had various aetiologies). ■

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