Maternal morbidity and mortality in the Netherlands and their association with obstetric interventions

Kallianidis, A.F.

Management of major obstetric haemorrhage prior to peripartum hysterectomy and outcomes across nine European countries

A.F. Kallianidis, A. Maraschini, J. Danis, L.B. Colmorn, C. Deneux-Tharaux, Serena Donati, M. Gissler, M. Jakobsson, M. Knight, A. Kristufkova, P.G. Lindqvist, G. Vandenberghe, T. van den Akker

On behalf of the International Network of Obstetric Survey Systems

Acta Obstetricia et Gynecologica Scandinavica. 2021;100(7):1345-1354.

7

ABSTRACT

Introduction: Peripartum hysterectomy is applied as a surgical intervention of last resort in case of major obstetric haemorrhage. It is performed in an emergency setting except for women with a strong suspicion of placenta accreta spectrum (PAS) where it may be anticipated before caesarean section. The aim of this study was to compare management strategies in case of obstetric haemorrhage leading to hysterectomy between nine European countries participating in the International Network of Obstetric Survey Systems (INOSS), and to describe pooled maternal and neonatal outcomes following peripartum hysterectomy.

Material and methods: We merged data from nine nationwide or multi-regional obstetric surveillance studies performed in Belgium, Denmark, Finland, France, Italy, the Netherlands, Slovakia, Sweden and the United Kingdom collected between 2004 and 2016. Hysterectomies performed from 22 gestational weeks up to 48 hours postpartum due to obstetric haemorrhage were included. Stratifying women with and without PAS, procedures performed in the management of obstetric haemorrhage prior to hysterectomy between countries were counted and compared. Prevalence of maternal mortality, complications after hysterectomy and neonatal adverse events (stillbirth or neonatal mortality) were calculated.

Results: A total of 1,302 women with peripartum hysterectomy were included. In women without PAS who had major obstetric haemorrhage leading to hysterectomy, uterotonics administration was lowest in Slovakia (48/73, 66%) and highest in Denmark (25/27, 93%), intrauterine balloon use was lowest in Slovakia (1/72, 1%) and highest in Denmark (11/27, 41%) and interventional radiology varied between none in Denmark and Slovakia to 11/59 (79%) in Belgium. In women with PAS, uterotonics administration was lowest in Finland (5/16, 31%) and highest in the UK (84/103, 82%), intrauterine balloon use varied between none in Belgium and Slovakia to 29/103 (28%) in the UK. Interventional radiology was lowest in Denmark (0/16) and highest in Finland (9/15, 60%). Maternal mortality occurred in 14/1,226 (1%), commonest complications were hematologic (95/1,202, 8%) and respiratory (81/1,101, 7%). Adverse neonatal events were observed in 79/1259 (6%) births.

Conclusions: Management of obstetric haemorrhage in women who eventually underwent peripartum hysterectomy varied greatly between these nine European countries. This potentially life-saving procedure is associated with substantial adverse maternal and neonatal outcome.

INTRODUCTION

Being the most invasive surgical procedure peripartum and non-reversible in terms of fertility, peripartum hysterectomy is applied as an intervention of last resort in the course of major obstetric haemorrhage. When all other management interventions such as uterotonics, surgical or interventional radiology procedures have failed, peripartum hysterectomy can be a live-saving procedure. It has therefore been included as a maternal near miss event by the World Health Organization (WHO).[1] However, the optimal timing of peripartum hysterectomy in the course of haemorrhage and its order in the chain of interventions, remain subject of discussion.

Prevalence of peripartum hysterectomy differs considerably between countries, but little is known as to whether similar differences are present in terms of management strategies applied during major obstetric haemorrhage prior to resorting to hysterectomy.[2, 3] After unsuccessful medical management, proceeding to surgical interventions starting with the least invasive and most readily accessible intervention is a common strategy. However, data comparing effectiveness of different medical and surgical interventions are scarce and hampered by differences in timing and clinical setting resulting in low quality evidence.[4, 5] Relating management strategies in major obstetric haemorrhage to prevalence of hysterectomy and maternal outcomes may provide new insights into which strategies are most successful in preventing both maternal mortality and potentially preventable hysterectomies. We postulated that management of major obstetric haemorrhage would vary considerably between countries, given the lack of international clinical guidance and controlled trials comparing management interventions.

Peripartum hysterectomy, in most women, will be unplanned, taking place in an emergency setting of severe obstetric haemorrhage. However, in women with antenatally suspected placenta accreta spectrum (PAS), planned caesarean hysterectomy can be anticipated management.[6, 7] PAS was found to be the second most common indication for peripartum hysterectomy in European countries, occurring in 34.8% women who underwent hysterectomy.[3] The diagnosis of PAS, however, is notoriously difficult with up to 70% of PAS remaining undiagnosed antenatally.[8]

Primary aim of this study was to compare management interventions performed in the course of major obstetric haemorrhage ultimately leading to peripartum hysterectomy between nine European countries. Additionally, we aimed to pool together a large dataset of peripartum hysterectomies to obtain more robust calculations of prevalence of maternal mortality and complications, as well as neonatal adverse events.

MATERIAL AND METHODS

We performed a multi-country, population-based study combining data from nine countries of the International Network of Obstetric Survey Systems (INOSS).[9-16] INOSS is an international collaboration of national survey systems, aiming to improve management of uncommon obstetric complications.[17] Data from obstetric surveillance studies on peripartum hysterectomy were collected from: the Belgian Obstetric Surveillance System (B.OSS), *Epidemiologie de la Morbidite Maternelle Severe* (EPIMOMS) in France, the Italian Obstetric Surveillance System (ItOSS), *Landelijke studie naar Etnische determinanten van Maternale Morbiditeit* (LEMMoN) in The Netherlands, the Nordic Obstetric Surveillance System (NOSS) from Denmark, Finland and Sweden, the Slovak Obstetric Survey System (SOSS) and the UK Obstetric Surveillance System (UKOSS). All studies were nationwide except for EPIMOMS which included six regions of France (Alsace, Auvergne, Basse-Normandie, Île-de-France, Lorraine and Rhône-Alpes) covering 20% of national births and ItOSS, which encompassed six regions in Italy (Campania, Emilia-Romagna, Lazio, Piedmont, Sicily and Tuscany) representing 49% of national births.

Methods of data collection for all individual survey studies have previously been described more extensively.[18-23] In short, all countries performed prospective national or multi-regional obstetric survey studies on peripartum hysterectomy, except for Slovakia, where data were collected retrospectively. Duration of studies varied between 12 and 36 months over different periods between 2004 and 2016. In Belgium, Sweden, Italy and the UK, monthly mailing to an appointed clinician was used to identify women who underwent peripartum hysterectomy. Further details were requested through a case report form and a 'nothing to report' response was requested when there was no reported case. In Denmark and Finland appointed clinicians in each maternity unit reported peripartum hysterectomies by means of electronic or paper data collection forms. In Sweden, Denmark and Finland, who jointly performed a previous NOSS hysterectomy study, validation and identification of additional cases was performed after cross-checking health registers and hospital databases (Hospital Discharge Register, Medical Birth Register and delivery logbooks). In The Netherlands and France, registration studies identified women with severe maternal morbidity in a similar manner and within those, women who had a peripartum hysterectomy. In Slovakia, women who underwent peripartum hysterectomy in the year before were identified after correspondence with all maternity units. Except for France and Slovakia, all countries have previously published national data on peripartum hysterectomies.[9, 10, 14-16, 19]

To overcome differences in case selection between studies, we included women who underwent hysterectomy performed from the 22nd week of gestation up to 48 hours postpartum performed due to obstetric haemorrhage. This was the broadest overlapping definition between all studies. A more detailed description

of methods used for case selection and background characteristics of women have been described previously. [3]

The main outcome of this study was to describe the frequency of management interventions performed in the train of events leading to peripartum hysterectomy in the nine countries. These were: administration of uterotonics, performance of arterial ligation, manual removal of the placenta, vaginal or uterine packing, balloon tamponade, uterine compression sutures, curettage, suturing the placental bed, leaving the placenta in situ in women with PAS and interventional radiology. Interventional radiology was not always available in hospitals where hysterectomies were performed. In addition, transfusion of blood products and counts were described. For women with PAS, information was not available as to whether the hysterectomy was anticipated prior to caesarean section or took place in an emergency setting. Therefore, we decided to stratify outcomes according to the indication of hysterectomy into women with and without PAS.

Secondary outcomes were maternal mortality and complication rates after hysterectomy, and adverse neonatal outcome. Complications were coded by the lead investigators of each study according to the following options: hematologic, febrile/infection, genitourinary, wound, respiratory, renal, gastrointestinal, thromboembolic, cardiovascular, psychological, neurologic, endocrinologic. Adverse neonatal outcome was defined as stillbirth or neonatal mortality including deaths up to 28 days postpartum.

After receiving all nine de-identified national datasets, these were merged and analyzed at Leiden University Medical Centre, The Netherlands. If data for a specific variable were not available for a country or had more than 50% missing values, data were presented as "not reported", since quality of the data for that variable was then considered unreliable. Variables are presented descriptively as numbers with corresponding percentages. In the calculation of percentages missing values are subtracted from the denominator, since it was impossible to identify them as positive or negative, which would have led to considerable under- or overestimation. Cumulative percentages were calculated using a fixed-effects model in order to take into account differences in study sample size. Analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, USA) and R for Statistics (https://www.r-project.org/).

Ethical approval

All national and multiregional studies were previously approved by their national or local Ethics Committees. (Supplementary material, Table S1)

RESULTS

A total of 1,302 peripartum hysterectomies were identified amongst 2,498,013 births (5.2/10,000 births).

Variation in management of women without PAS between countries

Of 849 women who underwent peripartum hysterectomy for an indication other than PAS, 671/849 (79%) received uterotonics. In Belgium, Italy and Slovakia fewer than 80% received uterotonics. In Slovakia, use of oxytocin and prostaglandins was lower than in other countries, whilst the proportion of women receiving ergometrin was highest (42/73, 59%). The most frequently performed surgical procedure was suturing the placental bed in case of placenta previa (44/157, 28%), varying from 0/59 (0%) in the Netherlands to 22/27 (82%) in Denmark. Vaginal and/or uterine packing was performed in 102/301 (34%) women in Italy to 5/40 (13%) women in Belgium. Intrauterine balloon tamponade varied considerably, ranging between 1/71 (1%) in Slovakia and 11/27 (41%) in Denmark, with a proportion of 116/528 (22%) overall. Arterial ligation was applied much more frequently in France 35/75 (47%) compared to all other countries. Use of uterine compression sutures was highest in Denmark 10/27 (37%) and lowest in Slovakia 0/71 (0%). Interventional radiology procedures were not performed in Denmark and Slovakia while in the Netherlands and Belgium these were performed in 7/59 (12%) and 11/59 (19%) respectively. Curettage was performed in 89/301 (30%) women in Italy while in only one other woman in the Netherlands. (Table 1) The number of women in whom no surgical interventions were performed before peripartum hysterectomy varied between 70/73 (96%) in Slovakia to 2/27 (7%) in Denmark. (Table 2)

Erythrocytes were administered to 752/837 (90%) women, ranging from 38/55 (69%) in Belgium to 100% in Finland and Sweden. Number of erythrocyte units transfused varied greatly with women in the Netherlands receiving a median of 16 units (IQR 11-24) vs. four in both Belgium (IQR 0-8) and Italy (IQR 2-6). (Table 3)

Variation in management of women with PAS between countries

In 453 women indication for hysterectomy was PAS, diagnosed either before or during surgery; 58/453 (13%) women had a vaginal birth. Uterotonics were administered to 265/453 (59%) women. Proportions of women in Italy and Finland receiving uterotonics were 71/188 (38%) and 5/16 (31%) respectively, much lower than in other countries. Interventional radiology procedures were performed in 79/451 (17.5%) women overall and not performed at all in Denmark, vs. in 9/15 (60%) in Finland. Intrauterine balloon tamponade was applied in 39/446 (9%) women overall, again with great variance between countries: none in Belgium and Slovakia vs. 29/103 (28%) in the UK. Leaving the placenta in situ was commonly performed in France (10/23, 44%) unlike other countries (only performed in one other woman, in Belgium). Manual removal of the placenta occurred in 10/13 (77%) women in

Belgium and 6/16 (38%) women in Denmark, vs. none in Finland and Sweden. (Table 4) The number of women in whom no surgical interventions were performed before hysterectomy varied between 25/30 (83%) in Slovakia and 21/26 (81%) in Sweden to 1/14 (7%) in Belgium. (Table 2)

A total of 399/451 (89%) women received transfusion of erythrocytes, 264/445 (59%) fresh frozen plasma and 136/448 (30%) thrombocytes. Women in Denmark and Finland received relatively high numbers of erythrocyte units: 13 (IQR 5-22) and 12 (IQR 6-12) respectively. (Table 3)

Outcomes and complications

Maternal mortality occurred in 14/1,272 women, giving a case fatality rate of 1%. The commonest complications following peripartum hysterectomy were hematologic (95/1,202, 8%) or respiratory (81/1,101, 7%). (Table 5) Admission into the Intensive Care Unit (ICU) occurred for 760/1,272 (60%) women. In Slovakia only 20/103 (20%) were admitted into an ICU. The total duration of admission into ICU and the total duration of hospital stay were comparable between countries that had such data available. Neonatal adverse outcome occurred in 79/1259 (6%) births, likely associated with the considerable proportion of preterm births (487/1302, 37%).[3] (Table 6)

Table 1. Management of women with obstetric haemorrhage for indications other than placenta accreta spectrum.

Country	BE n = 59	DK n = 27	FI n = 56	FR n = 75	UK n = 173	IT n =301	NL n = 59	SK n =73	SE n = 26	Total n = 849
Uterotonics	42 (71)	25 (93)	49 (88)	63 (84)	156 (90)	219 (73)	48 (81)	48 (66)	21 (81)	671 (79)
Oxytocin	38 (78)	25 (96)	49 (88)	40 (53)	151 (89)	207 (69)	43 (73)	46 (65)	21 (81)	620 (74)
missing	10 (17)	1 (4)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	16 (2)
Prostaglandins	31 (65)	22 (85)	36 (67)	58 (77)	110 (65)	153 (51)	45 (76)	14 (20)	11 (42)	480 (58)
missing	11 (19)	1 (4)	2 (4)	0 (0)	3 (2)	0 (0)	0 (0)	2 (3)	0 (0)	19 (2)
Ergometrin	16 (35)	N/R*	N/R	N/R	91 (54)	N/R	9 (15)	42 (59)	5 (19)	163 (44)
missing	13 (22.0)				3 (2)		0 (0)	0 (0)	0 (0)	16 (4)
Surgical Intervention										
Suturing placental bed	14 (31)	22 (82)	N/R	N/R	N/R	N/R	0 (0)	N/R	8 (31)	44 (28)
missing	14 (23.7)	0 (0)					0 (0)		0 (0)	14 (8)
Vaginal/Uterine Packing	5 (13)	N/R	18 (32)	11 (15)	22 (13)	102 (34)	8 (14)	N/R	6 (23)	172 (24)
missing	19 (32)		0 (0)	0 (0)	3 (2)	0 (0)	0 (0)		0 (0)	22 (3)
Balloon Tamponade	8 (18)	11 (41)	17 (30)	18 (24)	44 (26)	N/R*	13 (22)	1 (1)	4 (15)	116 (22)
missing	15 (25)	0 (0)	0 (0)	0 (0)	3 (2)		0 (0)	2 (3)	0 (0)	20 (4)
Curettage	N/R	N/R	N/R	N/R	0 (0)	89 (30)	1 (2)	N/R	0 (0)	90 (17)
missing					3 (2)	0 (0)	0 (0)		0 (0)	3 (0.1)
Manual Removal of Placenta	20 (47)	3 (11)	4 (7)	N/R	N/R	N/R	4 (7)	N/R	0 (0)	31 (15)
missing	16 (27)	0 (0)	0 (0)				0 (0)		0 (0)	16 (7)
Arterial Ligation	3 (6)	0 (0)	5 (9)	35 (47)	21 (12)	N/R	8 (14)	2 (3)	1 (4)	75 (14)
missing	12 (20)	0 (0)	0 (0)	0 (0)	3 (2)		0 (0)	2 (3)	0 (0)	17 (3)
Uterine Compression Sutures	3 (8)	10 (37)	8 (14)	13 (17)	38 (22)	29 (10)	3 (5)	0 (0)	4 (15)	108 (13)
missing	19 (32)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	2 (3)	0 (0)	24 (3)
Interventional radiology	11 (19)	0 (0)	3 (5)	7 (9)	6 (4)	2 (1)	7 (12)	0 (0)	1 (4)	37 (4)
missing	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)	2 (3)	0 (0)	5 (0.6)

Presented as n (%). Percentages calculated after excluding missings.
BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden. N/R= Not Reported. *Not reported due to ≥50% missing values.

Table 2. Number of surgical interventions, including radiological intervention, performed during the management before peripartum hysterectomy.

Country	BE *n* = 59	DK *n* = 27	FI *n* = 56	FR *n* = 75	UK *n* = 173	IT *n* = 301	NL *n* =59	SK *n* =73	SE *n* = 26	Total *n* = 849
Women without PAS										
0	18 (31)	2 (7)	28 (50)	20 (27)	80 (46)	140 (47)	30 (51)	70 (96)	13 (50)	401 (47)
1	19 (32)	9 (33)	8 (14)	30 (40)	54 (31)	36 (12)	14 (24)	3 (4)	6 (23)	179 (31)
2	12 (20)	6 (22)	14 (25)	21 (28)	31 (18)	36 (12)	10 (17)	0 (0)	4 (15)	134 (16)
3	2 (3)	6 (22)	5 (9)	4 (5)	7 (4)	33 (11)	4 (7)	0 (0)	3 (12)	64 (8)
≥4	8 (14)	4 (15)	1 (2)	0 (0)	1 (1)	56 (19)	1 (2)	0 (0)	0 (0)	71 (8)
Country	**BE** *n* = 14	**DK** *n* = 17	**FI** *n* = 16	**FR** *n* = 23	**UK** *n* = 103	**IT** *n* = 188	**NL** *n* = 36	**SK** *n* = 30	**SE** *n* = 26	**Total** *n* = 453
Women with PAS										
0	1 (7)	2 (12)	7 (44)	4 (17)	56 (54)	90 (48)	24 (67)	25 (84)	21 (81)	230 (51)
1	8 (57)	5 (29)	7 (44)	7 (30)	29 (28)	76 (40)	7 (19)	4 (13)	4 (15)	147 (33)
2	4 (29)	5 (29)	1 (6)	10 (44)	16 (16)	19 (10)	4 (11)	1 (3)	1 (4)	61 (14)
3	0 (0)	3 (18)	1 (6)	2 (9)	2 (2)	3 (2)	1 (3)	0 (0)	0 (0)	12 (3)
≥4	1 (7)	2 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)

Presented as n (%). BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden, PAS= Placenta accreta spectrum.

Table 3. Proportions and numbers of transfusion of blood products.

Country	**BE n = 59**	**DK n = 27**	**FI n = 56**	**FR n = 75**	**UK n = 173**	**IT n = 301**	**NL n = 59**	**SK n = 73**	**SE n = 26**	**Total n = 849**
Women without PAS										
Erythrocytes	38 (69)	25 (93)	54 (100)	69 (96)	166 (98)	251 (83)	58 (98)	65 (89)	26 (100)	752 (90)
Median n (IQR)	4 (0-8)	15 (9-22)	12 (8.75-18)	8 (5.25-10.75)	11 (7-18)	4 (2-6)	16 (11-24)	N/R	11.5 (9-18.25)	7 (4-12)
missing	4 (7)	0 (0)	2 (4)	3 (4)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	12 (1)
Fresh Frozen Plasma	40 (74)	24 (89)	48 (100)	62 (87)	137 (81)	157 (52)	45 (85)	41 (56)	21 (91)	575 (70)
Median n (IQR)	2 (0-5.25)	8 (4-14)	8 (4.25-13.5)	6 (4-9)	4 (2-6)	1 (0-3)	6 (3-10)	N/R	6 (2-15)	4 (0-6)
missing	5 (9)	0 (0)	8 (14)	4 (5)	3 (2)	0 (0)	6 (10)	0 (0)	3 (12)	29 (3)
Thrombocytes	25 (50)	24 (89)	38 (75)	27 (39)	76 (45)	39 (13)	38 (68)	41 (57)	16 (67)	324 (39)
Median n (IQR)	0 (0-2)	3 (2-5)	16 (0-24)	0 (0-1)	0 (0-2)	0 (0-0)	2 (0-2)	N/R	1 (0-2)	0 (0-2)
missing	9 (15)	0 (0)	5 (9)	5 (7)	3 (2)	0 (0)	3 (5)	0 (0)	2 (8)	27 (3)
Country	**BE n = 14**	**DK n = 17**	**FI n = 16**	**FR n = 23**	**UK n = 103**	**IT n = 188**	**NL n = 36**	**SK n = 30**	**SE n = 26**	**Total n = 453**
Women with PAS										
Erythrocytes	8 (62)	14 (82)	15 (100)	22 (96)	100 (97)	157 (84)	35 (97)	25 (83)	23 (89)	399 (89)
Median No (IQR)	4 (0-13.5)	13 (4.5-21.5)	12 (6-19)	8 (5-10)	10 (6-16)	3 (2-4)	11 (5.25-16)	N/R	7 (2-17)	5 (2-10)
missing	1 (7)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.4)
Fresh Frozen Plasma	10 (77)	13 (77)	11 (100)	22 (96)	73 (71)	69 (37)	27 (79)	22 (73)	17 (65)	264 (59)
Median No (IQR)	3.5 (0.75-10)	8 (0.5-15)	8 (6-11)	4 (3-7)	4 (0-6)	0 (0-2)	3.5 (2-6.25)	N/R	4 (0-9)	2 (0-9.25)
missing	1 (7)	0 (0)	5 (31)	0 (0)	0 (0)	0 (0)	2 (5.6)	0 (0)	0 (0)	8 (2)
Thrombocytes	6 (46)	13 (77)	8 (53)	10 (44)	43 (42)	10 (5)	13 (38)	22 (73)	11 (44)	136 (30)
Median No (IQR)	1 (0-5.5)	2 (1-5.5)	8 (0-24)	0 (0-2)	0 (0-2)	0 (0-0)	0 (0-1)	N/R	0 (0-2)	0 (0-1.5)
missing	1 (7)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	1 (4)	5 (1)

Presented as n (%). BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden, IQR= Interquartile range, PAS= Placenta accreta spectrum.

Table 4. Management of women with obstetric haemorrhage due to placenta accreta spectrum.

Country	BE n = 14	DK n = 17	FI n = 16	FR n = 23	UK n = 103	IT n = 188	NL n = 36	SK n = 30	SE n = 26	Total n = 453
Uterotonics	9 (64)	13 (77)	5 (31)	17 (74)	84 (82)	71 (38)	29 (81)	18 (60)	19 (73)	265 (59)
Oxytocin	7 (54)	13 (81)	5 (33)	12 (52)	84 (82)	68 (36)	26 (72)	17 (57)	18 (69)	250 (56)
missing	1 (7)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.7)
Prostaglandins	7 (58)	9 (60)	2 (13)	13 (57)	47 (46)	27 (14)	20 (56)	9 (30)	2 (8)	136 (30)
missing	2 (21)	2 (12)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)
Ergometrin	1 (10)	N/R	N/R	N/R	38 (37)	N/R	7 (19)	15 (50)	1 (4)	62 (30)
missing	4 (29)				0 (0)		0 (0)	0 (0)	0 (0)	4 (2)
Surgical Interventions										
Suturing Placental Bed	2 (20)	13 (77)	N/R	N/R	N/R	N/R	0 (0)	N/R	3 (12)	18 (20)
missing	4 (28.6)	0 (0)					0 (0)		0 (0)	4 (4)
Interventional Radiology	4 (29)	0 (0)	9 (60)	3 (13)	3 (3)	50 (27)	4 (11)	1 (3)	5 (19.6)	79 (17.5)
missing	0 (0)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.4)
Arterial Ligation	1 (10)	5 (6)	0 (0)	12 (52)	12 (12)	N/R	1 (3)	4 (13)	0 (0)	35 (14)
missing	4 (29)	0 (0)	1 (6)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	5 (2)
Manual Removal of Placenta	10 (77)	6 (38)	0 (0)	N/R	N/R	N/R	8 (22)	N/R	0 (0)	24 (12)
missing	1 (7)	1 (6)	1 (6)				0 (0)		0 (0)	3 (3)
Placenta Left in Situ	1 (8)	N/R	N/R	10 (44)	N/R	N/R*	0 (0)	N/R	0 (0)	11 (12)
missing	1 (7)			0 (0)			0 (0)		0 (0)	1 (1)
Vaginal/Uterine Packing	2 (22)	N/R	1 (7)	1 (4)	15 (15)	22 (12)	2 (6)	N/R	1 (4)	44 (11)
missing	5 (36)		1 (6)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	6 (2)
Uterine Compression Sutures	2 (20)	1 (7)	1 (7)	6 (26)	8 (8)	22 (12)	0	1 (3)	0 (0)	41 (9)
missing	4 (29)	1 (6)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)
Balloon Tamponade	0 (0)	1 (6.7)	3 (21)	1 (4)	29 (28)	N/R*	3 (8)	0 (0)	2 (8)	39 (9)
missing	5 (35.7)	1 (6.3)	1 (6.3)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	7 (3)
Curettage	N/R	N/R	N/R	N/R	0 (0)	8 (4)	0 (0)	N/R	0 (0)	8 (2)
missing					0 (0)	0 (0)	0 (0)		0 (0)	0 (0)

Presented as n (%). Percentages calculated after excluding missings. BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT= Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden. N/R= Not Reported. *Not reported due to ≥50% missing values

Table 5. Complications of peripartum hysterectomy.

Country	BE n=73	DK n=44	FI n=72	FR n=98	UK n=276	IT n=489	NL n=95	SK n=103	SE n=52	Total n=1302
Hematologic	12 (16)	2 (5)	0 (0)	N/R	16 (6)	46 (9)	2 (2)	17 (17)	0 (0)	95/1,202 (8)
Respiratory	3 (4)	5 (11)	0 (0)	N/R	26 (9)	35 (7)	5 (5)	N/R	7 (14)	81/1,101 (7)
Genito-Urinary	3 (4)	0 (0)	3 (4)	N/R	0 (0)	N/R	13 (14)	5 (6)	4 (8)	29/713 (4)
Cardiovascular	0 (0)	4 (9)	2 (3)	9 (9)	7 (3)	15 (3)	5 (5)	N/R	1 (2)	43/1,195 (4)
Gastro-Intestinal	2 (3)	1 (2)	2 (3)	N/R	N/R	N/R	4 (4)	1 (1)	0 (0)	10/437 (2)
Endocrinological	0 (0)	1 (2)	0 (0)	N/R	N/R	N/R	6 (6)	N/R	0 (0)	7/336 (2)
Wound-related	0 (0)	0 (0)	0 (0)	5 (5)	0 (0)	N/R	4 (4)	4 (4)	0 (0)	13/808 (2)
Thromboembolic	0 (0)	1 (2)	1 (1)	3 (3)	4 (1)	1 (0.2)	1 (1)	N/R	2 (4)	13/1,196 (1)
Infection	1 (1)	0 (0)	0 (0)	5 (5)	0 (0)	1 (0.2)	9 (10)	N/R	1 (2)	17/1,196 (1)
Renal	1 (1)	0 (0)	1 (1)	N/R	3 (1)	7 (1)	2 (1)	N/R	0 (0)	14/1,101 (1)
Psychological	1 (1)	0 (0)	0 (0)	N/R	N/R	N/R	2 (2)	N/R	0 (0)	3/336 (0.9)
Neurological	2 (1)	2 (5)	0 (0)	0 (0)	0 (0)	5 (1)	0 (0)	N/R	0 (0)	8/1,196 (0.7)

Presented as n (%). Denominator in totals calculated after subtracting missing or not reported values. BE= Belgium, DK= Denmark, FI=Finland, FR=France, UK= United Kingdom, IT=Italy, NL=The Netherlands, SK=Slovakia, SE=Sweden.

Table 6 . Maternal and neonatal outcome after peripartum hysterectomy.

Country	BE n = 73	DK n = 44	FI n = 72	FR n = 98	UK n = 276	IT n = 489	NL n = 95	SK n = 103	SE n = 52	Total n = 1302
Maternal mortality	1 (1)	1 (2)	0 (0)	3 (3)	2 (0.7)	5 (1)	2 (2)	0 (0)	0 (0)	14 (1)
missing	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	28 (6)	0 (0)	0 (0)	0 (0)	30 (2)
Mother admitted into ICU	48 (67)	26 (59)	34 (48)	49 (50)	231 (84)	230 (50)	81 (85)	20 (20)	41 (79)	760 (60)
missing	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	27 (6)	0 (0)	1 (1)	0 (0)	30 (2)
ICU (days)*	3 (2-4)	N/R	N/R	3 (1-4)	2 (1-3)	2 (1-3)	2 (1-3)	2 (2-3)	N/R	2 (1-3)
Hospital stay (days)*	9 (7-12)	N/R	N/R	8 (7-13)	N/R	N/R	8 (6-13)	7 (5-8)	N/R	8 (6-11)
Neonatal adverse events	7 (10)	5 (11)	5 (7)	6 (6)	8 (3)	31 (7)	6 (6)	7 (7)	4(8)	79 (6)
missing	1 (1)	0 (0)	0 (0)	0 (0)	4 (1)	36 (7)	1 (1)	1 (1)	0 (0)	43 (3)

Presented as n (%). * Presented as median (interquartile range). BE= Belgium, DK= Denmark, FI= Finland, FR= France, UK= United Kingdom, IT=Italy, NL= The Netherlands, SK= Slovakia, SE= Sweden, ICU= Intensive Care Unit.

DISCUSSION

The main finding of our study was the considerable inter-country variation in the management of major obstetric haemorrhage ultimately leading to hysterectomy for women with as well as without PAS. Use of uterotonics, surgical procedures and transfusion rates all varied considerably between nine European countries. In women who underwent peripartum hysterectomy substantial rates of maternal mortality, complications and neonatal adverse outcomes were observed.

Many differences in management were found. In Slovakia, intrauterine balloon tamponade, uterine compression sutures and interventional radiology procedures were almost never performed. Low rates of interventional radiology are in line with low availability, with only two hospitals in the country performing interventional radiology for obstetric indications. At the same time Slovakia had the second highest prevalence of peripartum hysterectomy of included countries (7 per 10,000 births), which may reflect a practice of performing hysterectomy in a relatively early stage in the course of haemorrhage.[3] In the Nordic countries, interventional radiology is also not available in every hospital and use varies with the highest rate in Finland.[9] In Denmark, combining intrauterine balloon tamponade with uterine compression sutures ('the sandwich model') appears to be frequently used.[24] Conservative management, such as leaving the placenta in situ in women with PAS, appears to be common practice in France. In women with PAS, clinicians in Sweden, the Netherlands and Slovakia performed almost no other surgical intervention before performing hysterectomy. This contrasts starkly with clinical practice in the UK, Finland and Belgium where multiple other interventions are attempted to stop bleeding and preserve the uterus. Use of surgical procedures other than interventional radiology and administration of blood products will be less susceptible to availability and accessibility but rather reflect differences in preference between countries. These differences underline the results of a previous international review of hysterectomy, where in-depth audit revealed possible differences in management between countries.[25]

In a previous systematic review and meta-analysis, maternal mortality within women undergoing peripartum hysterectomy was 1.4% in high-income settings, comparable to our results.[2] The same meta-analysis demonstrated different rates of complications, the most prominent being hematologic (26%) and infectious (19%) complications versus hematologic (8%) and respiratory (7%) in our study. That study included hysterectomies up to six weeks postpartum, thereby also including indications such as infection, which are more likely to occur beyond the 48-hour time limit.

A major strength of our study is that we pooled data from seven nationwide and two multi-regional obstetric surveillance studies, which led to the largest cohort of women who had peripartum hysterectomy described in the literature, as far as we are aware. The vast majority of previous studies are from single institutions.

Management interventions in such studies are biased by availability of surgical interventions such as interventional radiology, operator preference and local protocols. By using nationwide data such local differences are diminished and national trends become noticeable. Furthermore, quality of data is high with low rates of missings, even though not all countries were able to report all variables.

Main limitation of this study remains the fact that it encompasses data from 9 studies performed during different time periods, the first starting in August 2004 and the last ending in August 2016.[3] Inevitably, obstetric practice might have changed over time such as preferences and management protocols within countries. However, recent literature has not added significant new insight into management of postpartum haemorrhage other than administration of tranexamic acid.[26] Novel surgical interventions such as local uterine segment resection known as "one-step" surgery or modified uterine compression suturing techniques were not described in our cohort. We had no information as to whether the hysterectomy was anticipated or took place in an emergency setting. Some hysterectomies will have been planned, especially in women with suspicion of PAS. However, the finding that one in eight women with PAS gave birth vaginally illustrates that a sizable proportion would have been unplanned hysterectomies. As such, women with PAS might have undergone fewer additional interventions, with lower transfusion rates and possibly fewer complications because surgery took place in a planned setting. Some women with PAS performed in planned settings, will not have experienced haemorrhage (≥1L). Given that our dataset did not include total amount of blood loss, these women will have been included in our study. This might partly explain the relatively low rates of uterotonic use and transfusion rates in some countries. Variation in use of uterotonics in women without PAS may be explained by the contribution of non-atonic bleeding, such as surgery-related bleeds around hysterectomy, and -to a limited extent- coding problems. It is clear that in case of atony, uterotonics should be first-line management. Additionally, it was impossible to identify in how many women hysterectomy initiated the haemorrhage rather than being the ultimate measure taken to stop bleeding. Also, variation in available resources, particularly with regard to interventional radiology, hampers comparisons. Finally, complications were coded by the principal investigator of each study, possibly leading to differences in definitions used. Complication rates should be interpreted with caution as these may, in some women, result from the major bleeding rather than the surgery itself. For example, thromboembolism can result from major bleeding with subsequent disseminated intravascular coagulation.

One might argue that in the management of obstetric haemorrhage in these women, all interventions performed up to the hysterectomy were unsuccessful and led to a delay that sometimes even contributed to the deaths of women whose hysterectomies were delayed too much. On the other hand, in other women hysterectomy was probably performed in an early stage of the course of bleeding. A decision to perform hysterectomy may be taken more readily in older and parous

women and by a surgically skilled obstetrician. However, we believe that the greatest contributor to the variance is the lack of international guidance on optimal management of life threatening major obstetric haemorrhage. There is no conclusive evidence about the superiority of one management intervention over another.[5, 27] Moreover, any management strategy should take into account the underlying cause of haemorrhage, and local availability and accessibility of management interventions. Implementation of standardised step-down management strategies previously has shown to reduce rates of hysterectomy and maternal mortality.[28] Finally, for women with PAS, guidelines propose a multidisciplinary approach and, although evidence for interventional radiology is limited, accessibility is recommended.[29]

To identify the optimal management strategy for every woman with major obstetric haemorrhage, further research is neccesary. Ideally, a case-control design could help establish associations between different surgical interventions and maternal outcomes or clinical parameters related to the bleeding, taking into account known risk factors.. Larger cohorts could potentially enable propensity-matched comparisons between management strategies. To gather adequate numbers of participant INOSS provides an ideal platform. A prospectively designed cohort study conducted simultaneously in multiple nationwide surveys could be a next step.

CONCLUSION

Obstetric haemorrhage remains a leading cause of maternal morbidity and mortality. Management strategies differed markedly between the nine European countries studied. The optimal management strategy remains subject of discussion.[5] Practice variation related to the use of oxytocin, balloon tamponade and interventional radiology may contribute to increased hysterectomy rates in some countries. Risk factors for haemorrhage, such as caesarean sections, are rising, translating into increased rates of peripartum hysterectomy. This illustrates the importance of optimizing management strategies in major obstetric haemorrhage.[27] This includes the timing of hysterectomy, avoiding early and preventable removal of the uterus, as well as late hysterectomies associated with severe morbidity and death.

REFERENCES

1. Evaluating the quality of care for severe pregnancy complications: the WHO near-miss approach for maternal health. http:// apps. who. int/ iris/ bitstream/10665/ 44692/ 1/ 9789241502221_ eng. pdf2011.
2. van den Akker T, Brobbel C, Dekkers OM, Bloemenkamp KW. Prevalence, Indications, Risk Indicators, and Outcomes of Emergency Peripartum Hysterectomy Worldwide: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016;128:1281-94.
3. Kallianidis AF, Maraschini A, Danis J, et al. Epidemiological analysis of peripartum hysterectomy across 9 European countries. Acta Obstet Gynecol Scand. 2020;99:1364-1373.
4. Gilmandyar D, Thornburg LL. Surgical management of postpartum haemorrhage. Semin Perinatol. 2019;43:27-34.
5. Kellie FJ, Wandabwa JN, Mousa HA, Weeks AD. Mechanical and surgical interventions for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2020;7:CD013663.
6. Jauniaux E, Bhide A. Prenatal ultrasound diagnosis and outcome of placenta previa accreta after cesarean delivery: a systematic review and meta-analysis. Am J Obstet Gynecol. 2017;217:27-36.
7. Jauniaux E, Bunce C, Gronbeck L, Langhoff-Roos J. Prevalence and main outcomes of placenta accreta spectrum: a systematic review and metaanalysis. Am J Obstet Gynecol. 2019;221:208-218.
8. Thurn L, Lindqvist PG, Jakobsson M, et al. Abnormally invasive placenta-prevalence, risk factors and antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries. BJOG. 2016;123:1348-55.
9. Jakobsson M, Tapper AM, Colmorn LB, et al. Emergency peripartum hysterectomy: results from the prospective Nordic Obstetric Surveillance Study (NOSS). Acta Obstet Gynecol Scand. 2015;94:745-54.
10. Knight M, Ukoss. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. BJOG. 2007;114:1380-7.
11. Kristufkova A, Krobel M, Borovosky M, Danis J, Dugatova M. Analysis of severe acute maternal morbidity in Slovak Republic in year 2012. Gynekol prax. 2015;13:185-91.
12. Kristufkova A, Krobel M, Danis J, Dugatova M, Nemethova B, Borovosky M. Analysis of severe acute maternal morbidity in Slovak Republic in year 2013. Gynekol prax. 2016;14:92-8.
13. Kristufkova A, Krobel M, Danis J, Dugatova M, Nemethova B, Borovosky M. Analysis of severe acute maternal morbidity in Slovak Republic in year 2014. Gynekol prax. 2017;15:25-32.
14. Vandenberghe G, Guisset M, Janssens I, et al. A nationwide population-based cohort study of peripartum hysterectomy and arterial embolisation in Belgium: results from the Belgian Obstetric Surveillance System. BMJ Open. 2017;7:e016208.
15. Zwart JJ, Dijk PD, van Roosmalen J. Peripartum hysterectomy and arterial embolization for major obstetric haemorrhage: a 2-year nationwide cohort study in the Netherlands. Am J Obstet Gynecol. 2010;202:150 e1-7.
16. Maraschini A, Lega I, D'Aloja P, et al. Women undergoing peripartum hysterectomy due to obstetric haemorrhage: a prospective population based study. Acta Obstet Gynecol Scand. 2020;99:274-282.
17. Knight M, Inoss. The International Network of Obstetric Survey Systems (INOSS): benefits of multi-country studies of severe and uncommon maternal morbidities. Acta Obstet Gynecol Scand. 2014;93:127-31.

18. Blondel B, Coulm B, Bonnet C, Goffinet F, Le Ray C, National Coordination Group of the National Perinatal S. Trends in perinatal health in metropolitan France from 1995 to 2016: Results from the French National Perinatal Surveys. J Gynecol Obstet Hum Reprod. 2017;46:701-13.
19. Colmorn LB, Petersen KB, Jakobsson M, et al. The Nordic Obstetric Surveillance Study: a study of complete uterine rupture, abnormally invasive placenta, peripartum hysterectomy, and severe blood loss at delivery. Acta Obstet Gynecol Scand. 2015;94:734-44.
20. Knight M, Kurinczuk JJ, Tuffnell D, Brocklehurst P. The UK Obstetric Surveillance System for rare disorders of pregnancy. BJOG. 2005;112:263-5.
21. Madar H, Goffinet F, Seco A, Rozenberg P, Dupont C, Deneux-Tharaux C. Severe Acute Maternal Morbidity in Twin Compared With Singleton Pregnancies. Obstet Gynecol. 2019;133:1141-50.
22. Vandenberghe G, Roelens K, Van Leeuw V, Englert Y, Hanssens M, Verstraelen H. The Belgian Obstetric Surveillance System to monitor severe maternal morbidity. Facts Views Vis Obgyn. 2017;9:181-8.
23. Zwart JJ, Richters JM, Ory F, de Vries JI, Bloemenkamp KW, van Roosmalen J. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. BJOG. 2008;115:842-50.
24. Colmorn LB, Krebs L, Langhoff-Roos J. Potentially Avoidable Peripartum Hysterectomies in Denmark: A Population Based Clinical Audit. pLoS One. 2016;11:e0161302.
25. Jónasdóttir E, Aabakke AJM, Colmorn LB, et al. Lessons learnt from anonymized review of cases of peripartum hysterectomy by international experts: A qualitative pilot study. Acta Obstet Gynecol Scand. 2019;98:955-7.
26. 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. Lancet. 2017;389:2105-16.
27. Ahmadzia HK, Grotegut CA, James AH. A national update on rates of postpartum haemorrhage and related interventions. Blood Transfus. 2020;18:247-53.
28. Varatharajan L, Chandraharan E, Sutton J, Lowe V, Arulkumaran S. Outcome of the management of massive postpartum haemorrhage using the algorithm "HEMOSTASIS". Int J Gynaecol Obstet. 2011;113:152-4.
29. Collins SL, Alemdar B, van Beekhuizen HJ, et al. Evidence-based guidelines for the management of abnormally invasive placenta: recommendations from the International Society for Abnormally Invasive Placenta. Am J Obstet Gynecol. 2019;220:511-26.