Obstetric hemorrhage: improving care by collaborating across borders

Vries, P.L.M. de

Part 2

Obstetric hemorrhage: Reducing preventable severe maternal outcome by exploring subgroups of women with obstetric hemorrhage

Chapter 6

Trends in maternal mortality from obstetric hemorrhage in France: 15 years of confidential enquiry into maternal deaths

M. Bonnet**, P.L.M. de Vries**, S. Levet, M. Saucedo, E. Morau, M. Dreyfus, F. Goffinet, C. Deneux-Tharaux, on behalf of the ENCMM Study Group

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Abstract

Objectives: To assess temporal trends in incidence and underlying cause of maternal deaths from obstetric hemorrhage in France and to describe clinical care before and after implementation of the first national guidelines published in 2004 and updated in 2014.

Methods: Data from all hemorrhage-related maternal deaths between 2001-2015 were extracted from the French Confidential Enquiry into Maternal Deaths. We compared the maternal mortality ratio (MMR), cause of obstetric hemorrhage and death preventability by triennium. Critical care, transfusion and obstetric management among women who died were described for 2001-2003 and 2013-2015.

Results: The MMR from obstetric hemorrhage significantly decreased over time from 2.3/100,000 livebirths (54/2,391,551) in 2001-2003 to 0.8/100,000 livebirths (19/2,412,720) in 2013-2015. In 2001-2003, uterine atony accounted for 50% (27/54) of maternal deaths versus 21% (4/19) in 2013-2015. As compared to 2001-2003, an increased proportion of women had hemodynamic continuous monitoring in 2013-2015 (30%, 9/30 versus 47%, 8/18), and received vasopressor infusion therapy (57% 17/30 versus 72% 13/18) and a smaller proportion was extubated during active hemorrhage (17%, 5/30 versus 0/18). Transfusion therapy was initiated more frequently and earlier in 2013-2015 (71 versus 58 minutes). In 2013-2015, 88% of maternal deaths due to hemorrhage remained preventable. Main identified improvable care factors were related to delays in diagnosis and surgical management, particularly after caesarean delivery.

Conclusion: Maternal mortality by obstetric hemorrhage decreased dramatically in France between 2001 and 2015, particularly mortality due to uterine atony. Among women who died, we detected fewer instances of substandard transfusion management or critical care. Nevertheless, opportunities for improvement were observed in most of the recent cases.

Introduction

Maternal mortality (MM), although rare in high-income countries, remains a key indicator of maternal health in those settings. Obstetric hemorrhage is one of the leading causes of MM, and is considered as a specific marker of the quality of obstetric care.(1) In depth analysis of maternal deaths through permanent confidential enquiries has proven to be an efficient method to identify improvable care factors related to both organizational and clinical components of care.(2)

In France, maternal mortality has been explored since 1995 through a permanent confidential enquiry into maternal deaths (ENCMM).(3) The first publications of this enquiry reported obstetric hemorrhage as the primary cause of MM, with a maternal mortality ratio (MMR) due to obstetric hemorrhage twice that of neighboring high-income countries. (4,5)

These findings led to a broad commitment of stakeholders to develop and implement national multidisciplinary guidelines to prevent and treat postpartum hemorrhage, and to reduce variation in local care policies. Therefore, the French College of Gynecologists and Obstetricians (CNGOF) and the French Society of Anesthesia and Critical Care (SFAR) published the first national guidelines in 2004,(6) updated in 2014.(7) These national multidisciplinary recommendations addressed obstetric, anesthetic and critical care management, including transfusion (Table 1). They were widely disseminated in France, notably through numerous presentations at national and regional congresses. They have also been widely implemented at regional and local levels into care protocols, as well as by perinatal networks. Finally, these recommendations have been used in simulation training sessions for clinicians. Five process quality indicators (COMPAQ-HPST) were defined by the French National Authority for Health (HAS) in 2012 for the prevention and early management of obstetric hemorrhage and implemented in maternity units (supplemental Table S1).(8)

It is important not only for France, but also for other countries, to know whether this general mobilization around the quality of obstetric hemorrhage management has translated into any improvement in mortality on a national scale. (Supplemental Figure S1).(9) Therefore, we aimed to assess temporal trends in incidence and underlying causes of maternal deaths from obstetric hemorrhage between 2001 and 2015 in France and to describe their clinical care before and after implementation of the first national guidelines.

Table 1. French CNGOF-SFAR guidelines on prevention and management of obstetric hemorrhage: main content

	2004 guidelines	**2014 guidelines updates**
Definition of postpartum hemorrhage	Blood loss ≥ 500 mL after birth regardless route of delivery	No change
Definition of severe postpartum hemorrhage	Severe PPH: Not defined	**Severe PPH defined by a blood loss ≥ 1000 mL, regardless of the route of delivery**
Prevention hemorrhage		
Hemorragic risk assessment	PPH risk factors are not globally predictive. In women at risk for PPH, multidisciplinary discussion of the site of birth is necessary and must take into account the nature of the risk and the speed of access to blood products If prenatal anaemia: iron supplementation	No change No change
Prophylactic uterotonic Manual removal of the placenta in the absence of abnormal bleeding	Oxytocin 5-10 UI slow IV infusion (over 1 minute for women without cardiovascular and over 5 minutes for women with cardiovascular risk factors) or IM just after birth between 30 and 60 min after birth	No change No change
Initial management of hemorrhage		
Quantification of blood loss	Not mentioned	**Collector bag recommended once PPH diagnosed** (optional before)
First line uterotonic Assessment of the genital tract	Oxytocin 5-10UI IV or IM Within 30 min after obstetric hemorrhage diagnosis	No change No change
Manual uterine exploration	Within 30 min after obstetric hemorrhage diagnosis	No change
Second line uterotonics		
Sulprostone	Sulprostone maximum 500 µg in 500ml/h. Timing: within 30 min of PPH diagnosis, should oxytocin be ineffective	No change
Other second-line uterotonics[1]	Association of sulprostone with other second-line uterotonic not recommended	No change

Table 1. (continued)

	2004 guidelines	2014 guidelines updates
Nonpharmacological management		
Uterine tamponade	Not mentioned	**Use left to the clinician's choice. Timing: after failure of second line uterotonic and before surgical or radiological embolization**
Embolization	Cesarean: preference to proceed immediately to conservative surgical management after failure of second line uterotonics Vaginal birth: option in hemodynamically stable patients after failure of second line uterotonics.	No change
Conservative surgery[2]	Cesarean: Recommended in case of failure of second line uterotonics Vaginal birth: recommended after failure of second line uterotonics in case of hemodynamically unstable patients No type of compression suture or vascular ligation suture is recommended over another.	No change
Hysterectomy	Surgical approach: subtotal hysterectomy Timing: In case of failure of compression sutures/vascular ligation or embolization	**Surgical approach depending on surgeon's preference** No change in timing
Resuscitation and transfusion management		
Coagulation screening	Regularly after failure of initial management of PPH, bedside haemoglobin testing optional.	No change
Fluid replacement therapy	Crystalloids and then colloids in case of severe obstetric hemorrhage Timing: start in case of obstetric hemorrhage	Crystalloids. Colloids can be given in case of severe obstetric hemorrhage Timing: start after 500 mL of blood loss
Red blood cells	Start transfusion to maintain a hemoglobin between 7 and 10 g/dL if bleeding persists.	**Maintain a haemoglobin level $\geq$ 8g/dL** **Timing: initiate based on clinical signs of hemorrhage severity**

Table 1. (continued)

	2004 guidelines	2014 guidelines updates
Fresh frozen plasma	In case of coagulopathy associated to persistent bleeding FFP (10 a 15mL/kg) can be used.	**Depending on the severity of the hemorrhage or coagulopathy**
Platelets	Cesarean birth: supplement if platelets $\leq 50 \times 10^9$/L Vaginal birth: supplement if platelets $\leq 30 \times 10^9$/L	Maintain above 50×10^9/l regardless mode of birth
rFVIIa	Not mentioned	**Only for uncontrolled haemorrhage after failure of conventional treatment and after having attempted to correct platelet levels and other haemostasis indicators**
Fibrinogen concentrate	Not mentioned	**Maintain fibrinogenemia $\geq$ 2.0 g/L. In ongoing bleeding with > 2000 mL and in the absence of laboratory results, a dose of 2 gr Fibrinogen can be given.**
Tranexamic acid	Not mentioned	**Left to the clinicians 'choice 1 gram IV, could be repeated 30 min later in case of persistent bleeding**
Organization of care		
Call for help Documentation	At the diagnosis of obstetric hemorrhage Not mentioned	At the diagnosis of obstetric hemorrhage **The management and monitoringsteps for obstetric hemorrhage must be recorded on a special monitoring form**
Inter hospital transfer	Recommended if patient hemodynamically stable	No change
Leadership	Senior anaesthesiologist in the lead of resuscitation management. Senior obstetrician in the lead of obstetric management	No change
Multidisciplinary training	Not mentioned	**Each department is responsible for training all professionals likely to deal with patients with PPH to manage this situation**

Methods

In this study, the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) statement was followed.(10)

Study population

We conducted a retrospective study of all maternal deaths due to obstetric hemorrhage in France between 2001 and 2015 identified through the French Confidential Enquiry into Maternal Deaths (Enquête Nationale Confidentielle sur les Morts Maternelles, ENCMM). Ethical approval for the ENCMM was granted by the French Commission on Information Technology and Liberties (CNIL) on June 26, 2018, DR-2018-157 and informed consent was waived. Collected data are fully anonymized with no identifying features of individual patients or healthcare providers. We analyzed maternal deaths from all France, including overseas departments (Réunion, Guadeloupe, Martinique and French Guyane) except those in Mayotte, as this territory was not part of France over the complete study period. The ENCMM has been set up in 1996 under the authority of the national Public Health Agency (Santé Publique France) and the national institute for health research (Institut National de la Santé et de la Recherche Médicale) to identify and document all maternal deaths in France.(3,11) In the ENCMM, deaths of women while pregnant or within 1 year after the end of pregnancy, regardless of the cause of death, defined as pregnancy-associated deaths, are identified through four sources: 1) spontaneous notifications by clinicians; 2) death certificates with any cause of death coded in the pregnancy chapter of the International Classification of Diseases, 10th revision (ICD-10), or any mention of pregnancy or puerperium in the text, or when the pregnancy checkbox was ticked; 3) computer-based national linkage of the death register with the birth register; and 4) the national hospital discharge database. This method has been described in detail elsewhere.(3),(12) For each identified pregnancy-associated death, a team of two assessors (an obstetrician or midwife and anesthetist) conducts a confidential enquiry, using a standardized questionnaire to collect relevant information about the case via on-site interviews and manual review of medical records and autopsy reports. The team of assessors is recruited on a voluntary basis after validation by professional bodies and members of the expert committee. When a confidential enquiry is not possible, information from the death certificate and hospital discharge summary is analyzed. Each death is then anonymously reviewed in a plenary session by the national expert committee of the ENCMM which aims to agree unanimously on 1) the underlying cause of death; 2) whether it was a maternal death, defined as the death of a woman during pregnancy or within 1 year of its end regardless of the

duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management (but not accidental or incidental);(11) and 3) the quality of care (optimal or non-optimal) and maternal death preventability (probably or possibly preventable, not preventable, undetermined) referring to any event in management, organization or patient behavior that might have prevented fatal outcome. Among probably or possibly preventable maternal deaths, contributing factors may be related to (a) care provided, (b) organization of care and (c) patient and health care system interaction (in non-exclusive categories). The committee's assessment is collected using a standardized form for each death. The main characteristics of the woman, her pregnancy and care pathway, as well as the conclusions of the expert committee are entered in an electronic permanent database.

Overall, the maternal death enquiry process remained essentially the same during the study period. The main changes include: 1) the introduction of the computer-based national linkage of the death register with the birth register in 2007 to improve maternal death identification; this improvement mostly concerned late maternal deaths and maternal deaths from indirect causes, and very few maternal deaths from obstetric hemorrhage; and 2) improvement in cooperation and trust from local clinical teams yielded a greater proportion of deaths for which detailed information was collected to support a reliable confidential enquiry.

For this study, we identified all maternal deaths from obstetric hemorrhage (based on the underlying cause of death selected by the national expert committee) from 2001-2015 (most recent available year of complete data when this analysis was conducted).

Studied variables

We collected the following maternal, pregnancy and delivery characteristics from the ENCMM database: maternal age, country of birth, body mass index (BMI), parity, prior obstetric hemorrhage, prior uterine scar, multiple pregnancy, term of delivery, labor induction, mode of delivery, and the number of annual births in the maternity unit of delivery. Conditions causing obstetric hemorrhage were also collected (uterine atony, abnormal placentation, placenta abruption, uterine rupture, genital tract trauma, cesarean surgical trauma, other/undetermined). Characteristics of obstetrical, and critical and care and transfusion management were also collected: use of prophylactic uterotonics, initial management of obstetric hemorrhage (additional intravenous access, volume replacement, manual placenta removal or manual exploration of the uterus, anesthetist and obstetrician

called at the time of the diagnosis), use of second-line uterotonics (administration of sulprostone and timing between diagnosis and sulprostone), radiological and surgical procedures (third line interventions such as arterial embolization, uterine compressive sutures, pelvic artery ligation, and the timing between obstetric hemorrhage diagnosis and any of these procedures, hysterectomy, and the timing between diagnosis and hysterectomy), monitoring of the women (central venous access, invasive arterial blood pressure, blood test performed, and timing between diagnosis of obstetric hemorrhage and first blood test), major aspects of resuscitation and anesthesia (use of vasopressors infusion after the onset of hemorrhage onset, inappropriate tracheal extubating while active hemorrhage, cardiac arrest at the induction of general anesthesia), blood transfusion (no blood transfusion, transfusion of ≥10 red blood cells (RBC), total number of RBC, timing between diagnosis of obstetric hemorrhage and first RBC transfused, fresh frozen plasma (FFP) transfusion, total number of FFP transfused, platelet transfusion), and use of procoagulant agents (fibrinogen concentrate, tranexamic acid, recombinant factor seven activated (rFVIIa)). The timing between diagnosis of obstetric hemorrhage and maternal death was also extracted.

Statistical analysis

MMR was calculated as the number of maternal deaths per 100,000 live births, overall and from obstetric hemorrhage, for each triennium between 2001 and 2015. We described the distribution of the underlying cause of obstetric hemorrhage and preventability of maternal deaths from obstetric hemorrhage for each triennium.

As we aimed to evaluate the trends since the publication of the French national guidelines on obstetric hemorrhage in 2004, we described women's characteristics (analyzed as the proportion of women in high risk subgroups), obstetrical and critical care and transfusion management, for the women who died before (2001-2003) and those who died after guideline implementation (2013-2015, most recent data available); this second part of the analysis was done among the women for whom a confidential enquiry was conducted and provided those detailed data.

Qualitative data were expressed as number (percentage) and quantitative variables as median (range). Because we studied the entire population of interest rather than a sample, inferential statistical methods such as hypothesis tests were not used. Statistical analyses were performed using Excel and Stata® v16 software.

Results

During the 15-year study period, MMR from obstetric hemorrhage significantly decreased from 2.3/100,000 livebirths (54/2,391,551) in 2001-2003 to 0.8/100,000 livebirths (19/2 412 720) in 2013-2015 (Table 2).

Table 2. Maternal mortality due to obstetric hemorrhage by 3-year periods in France: ratios (MMR)[1] and distribution of causal conditions

	2001-2003	2004-2006	2007-2009	2010-2012	2013-2015
Maternal deaths from all causes					
Live births	2391551	2 468 315	2 472 650	2 477 240	2 412 720
All maternal deaths up to 42 days	235	203	234	225	186
MMR (/100 000 live births)	9.8	8.3	9.5	9.1	7.7
Maternal mortality due to obstetric hemorrhage[2]					
n	54	44	39	29	19
MMR (/100 000 live births)	2.3	1.8	1.6	1.2	0.8
% of maternal deaths up to 42 days[3]	22.1	21.7	16.2	12.9	9.7
Maternal mortality due to obstetric hemorrhage by uterine atony					
n	27	32	21	12	4
MMR (/100 000 live births)	1.1	1.3	0.8	0.5	0.2
% of all maternal deaths up to 42 days	11.5	15.8	9.0	5.3	2.2
Underlying conditions causing obstetric hemorrhage in maternal deaths n (%)					
All	n=54	n=44	n= 39	n=29	n=19
Uterine atony	27 (50)	32 (73)	21 (54)	12 (41)	4 (21)
Abnormal placentation[4]	4 (7)	4 (9)	9 (23)	2 (7)	4 (21)
Placental abruption	4 (7)	2 (5)	3 (8)	1 (3)	3 (16)
Uterine rupture	11 (20)	2 (5)	3 (8)	6 (21)	2 (11)
Genital tract trauma	2 (4)	2 (5)	1 (3)	0	0
Surgical injury during caesarean section	1 (2)	0	2 (5)	6 (21)	4 (21)
Others/ Undetermined	5 (9)	2 (5)	0.0	2 (7)	2 (11)

Table 2. (continued)

	2001-2003	2004-2006	2007-2009	2010-2012	2013-2015	
Preventability of maternal deaths n (%)						
Preventability assessment possible	30 (55)	27 (61)	26 (70)	23 (79)	18 (95)	
Preventability of hemorrhage related maternal deaths (%) (probably or possibly)	97	89	89	100	88	0.5

[1]MMR=maternal mortality ratio

[2] Including 4 women for whom hemorrhage occurred in the immediate postpartum but who died >42 d after birth due to long stay in intensive care unit (n = 2 in 2001–2003, n = 1 in 2007–2009, n = 1 in 2013–2015). Those 4 deaths were not included in the calculation of the "% of all maternal deaths up to 42 d."

[3]Not including the 4 women who died >42 d after birth: n = 2 in 2001–2003, n = 1 in 2007–2009, n = 1 in 2013–2015.

[4]Placenta accreta spectrum (2001–2003: n = 4, 2004–2006: n = 4, 2007–2009: n = 7, 2010–2012: n = 2, 2013–2015: n = 2) and placenta previa (2001–2003: n = 0, 2004–2006: n = 0, 2007–2009: n = 2, 2010–2012: n = 0, 2013–2015: n = 2

The proportion of uterine atony as primary underlying cause of obstetric hemorrhage decreased from 50% (27/54) in 2001-2003 to 21% (4/19) in 2013-2015, while the proportion of surgical lesion in the context of cesarean delivery increased from 2% (1/54) to 21% (4/19). Preventability of hemorrhage-related deaths remained high during the whole study period (97% in 2001-2003 and 88% in 2013-2015).

The characteristics of the women who died are presented for 2001-2003 and 2013-2015 in supplemental Table S2. Confidential enquiry was not available for 24 women in 2001-2003 and for 1 woman in 2013-2015. As compared to the 2001-2003 period, women in the most recent time period were more often older than 35 years (61% (11/18) versus 43% (13/30)), obese (33% (6/18) versus 14% (4/30)) and with prior uterine scar (55% (10/18) versus 27% (8/30)). More than two thirds of the women who died had a caesarean delivery in both time periods.

The proportion of women who died within the first 12 hours after obstetric hemorrhage diagnosis decreased from 63% to 39% between the two time periods. Nonetheless, 66% (8/12) and 75% (3/4) of maternal deaths from obstetric hemorrhage due to uterine atony occurred within 12 hours after the diagnosis in 2001-2003 and 2013-2015, respectively (Table 3).

Table 3. Critical care and transfusion management in maternal deaths from obstetric hemorrhage in France, 2001-2003 and 2013-2015

	2001-2003 N=30 n (%)	**2013-2015 N=18 n (%)**
Monitoring		
Central venous access	16 (53)	10 (59) •
Invasive arterial blood pressure	9 (30)	8 (47) •
Blood test performed	27 (90)	16 (94) •
Time between obstetric hemorrhage diagnosis and first blood test – minutes (median (min-max))	25 (0-270)	30 (5-240) •
Resuscitation		
Vasopressors[1]	17 (57)	13 (72)
Tracheal extubation while active hemorrhage	5 (17)	0
Cardiac arrest at the induction of general anaesthesia	3 (10)	1 (6) •
Transfusion		
No blood transfusion	2 (7)	1 (6) •
Transfusion of ≥ 10 RBC	12 (40)•	10 (59) •
Total number of RBC transfused (median (min-max))	9 (2-64)•	14 (2-41) •
Time between hemorrhage diagnosis and first RBC transfusion in minutes (median (min-max))	71 (0-135)	48 (5-390) •
FFP transfusion	23 (77)	15 (88) •
Total number of FFP transfused (median (min-max))	8 (2-67)•	14 (2-46) •
Platelets Transfusion	12 (40)	14 (82) •
Pro-coagulant agents		
Fibrinogen concentrate	13 (43)	14 (82) •
Tranexamic acid	0	8 (47) •
rFVIIa	0	7 (41) •

Table 3. (continued)

	2001-2003 N=30 n (%)	2013-2015 N=18 n (%)
Delay between obstetric hemorrhage diagnosis and maternal death		
Time between hemorrhage diagnosis and maternal death-minutes- (median (min-max))		
Overall group of women	360 (1h-150 days)	1920 (2h40-265 days)
Women with obstetric hemorrhage due uterine atony	351 (2h20-6 days)	501 (6h-17 days)
Death < 12h from hemorrhage diagnosis n (%)		
All women	19 (63)	7 (39)
Women with obstetric hemorrhage due to uterine atony	8 (66)	3 (75)

[1]excepting vasopressors for cardiac arrest
•1 missing datum
Abbreviations: RBC: red blood cells; FFP: fresh frozen plasma; max, maximum; min, minimum; rFVII1, recombinant factor 7 activate

No difference was observed in prophylactic and initial obstetric hemorrhage management between the two time periods (supplemental Table S3).

Around 30% of women died without a hysterectomy in both time periods (Table 4). All the six women who died without hysterectomy in 2013-2015 gave birth by emergency cesarean delivery. In three of these six women the obstetrician did not have the surgical skills to perform hemostatic surgery, resulting in a time delay while waiting for a more experienced surgeon. ln the three other women, for two of them hysterectomy was not performed as diagnosis of hemorrhage came too late (patient already in cardiac arrest before relaparotomy), and for one woman, surgeons first aimed to perform conservative surgery, and she died during this procedure.

Table 4. Obstetric management in maternal deaths from obstetric hemorrhage in France, 2001-2003 and 2013-2015
Abbreviations: min, minimum; max, maximum; OH, obstetric hemorrhage

	All causes 2001-2003 N=30	All causes 2013-2015 N=18	Atony 2001-2003 N=12	Atony 2013-2015 N=4
Second line uterotonics				
Sulprostone administration n (%)	16 (53)	9 (50)	8 (67)	4 (100)
Time OH-diagnosis and sulprostone < 30min n (%)	6 (20)	5 (28)	4 (33)	3 (75)
Time OH-diagnosis and sulprostone - minutes (median (min-max))	34 (0-110)	15 (0-375)	38 (0-105)	9 (0-35)
Radiological and surgical procedures				
Any third line procedure n (%)	8 (27)	6 (33)	4 (33)	2 (50)
arterial embolization	6	2	2	2
Uterine compressive sutures	1	2	0	2
Pelvic artery ligation	6	3	2	2
Time OH-diagnosis and third-line procedure - minutes (median (min-max))	50 (5-210)	60 (44-320)	50 (5-260)	265 (44-320)
Hysterectomy n (%)	21 (70)	12 (67)	9 (75)	4 (100)
Preceded by third line intervention	7	3	4	2
Followed by selective artery embolization	3	1	0	0
Delay OH-diagnosis and hysterectomy (median (min-max))	126 (37 - 935)	240 (85-840)	210 (70-570)	180 (85-365)
Hysterectomy alone	123 (37-395)	260 (110-840)	145 (70-376)	180 (180-180)
After conservative third line procedure	145 (90-360)	120 (85-365)	345 (210-570)	225 (85-365)

For the subgroup of women with obstetric hemorrhage due to uterine atony, second-line uterotonics were used more frequently in the most recent triennium and median delay before their administration decreased from 38 minutes in 2001-2003 to 9 minutes in 2013-2015.

In the 2013-2015 triennium, critical care interventions and transfusion therapy were applied earlier and more frequently (Table 3). Hemodynamic continuous monitoring with invasive arterial blood pressure increased from 30% (9/30) to 47% (8/18) and the use of vasopressors after the onset of hemorrhage (excluding those used to manage cardiac arrest) increased from 17/30 (57%) to 12/18 (70%). While in 2001-2003, five of 30 (17%) obstetric hemorrhage-related maternal deaths were extubated during active hemorrhage, this did not happen in 2013-2015. The proportions of women transfused with red blood cells (RBC), fresh frozen plasma (FFP) and platelets increased with time and delay before the start of transfusion was reduced by one third between the two time periods. During the course of obstetric hemorrhage, the FFP:RBC ratio remained greater than 0.6 in the most recent time period (Figure 1). The use of fibrinogen concentrate doubled (from 13/30 women (43%) in 2001-2003 to 14/18 women (82%) in 2013-2015). Tranexamic acid and rFVIIa, that were never used during the first study period, were administered in 47% and 41% of women respectively in 2013-2015. Point of care hemostatic testing was unavailable for use at either time point at any of the hospitals where maternal deaths occurred during the 2 time periods.

The most common preventability factors found in 2001-2003 and in 2013-2015 are summarized in supplemental Table S4.

Discussion

Over 15 years, maternal mortality from obstetric hemorrhage in France has decreased by two thirds. Over time, fewer women died from uterine atony while the contribution of maternal deaths from surgical injury in the context of cesarean birth increased. Concomitantly, critical care and transfusion management, as well as obstetric management for uterine atony, improved among the women who died from hemorrhage. Nonetheless, most maternal deaths from obstetric hemorrhage across the entire study period including the most recent triennium were deemed preventable, warranting further evaluation of diagnosis, surgical and resuscitation management strategies.

Strengths of our study are the detailed data obtained through the ENCMM system, allowing us to reliably determine the cause of death, and to describe management strategies before and since the implementation of the national guidelines. We were able to explore timing, chronology of diagnosis and interventions in the course of obstetric hemorrhage, all being important determinants of obstetric hemorrhage-related severe maternal outcomes.(13) Thanks to the national population-based design, selection bias was absent, guaranteeing representativeness of our results.

This study had also some limitations. The number of women included remained small, inherent to the rarity of the maternal death event; studies on women with obstetric hemorrhage-related severe maternal morbidity would usefully complement our analysis, but such detailed clinical data are unavailable at a national level. Some maternal deaths occurring in 2001-2003 could not be analyzed due to insufficient available clinical data; we cannot make assumptions on the quality of care in those cases and how they would modify our findings. French guidelines on obstetric hemorrhage management were marginally updated in 2014, in particular regarding transfusion management (Table 1),(7) and some women in the 2013-2015 period were included before this update. However, we consider the implementation of guidelines as a continuous process of practice improvement, and we aimed to compare the period before the publication of the first guidelines with the period of the most recent data available, corresponding to 2013-2015. Finally, temporal changes in management observed in maternal deaths may not be extrapolated to all cases of obstetric hemorrhage as deaths are, by definition, extreme events with cumulative management failure. Nevertheless, management of these deceased women improved over time.

The 65% decrease in MMR due to obstetric hemorrhage we observed provides further evidence of important improvements in management strategies over time in France. Unlike obstetric management, critical care and transfusion management are independent from the underlying cause of hemorrhage and therefore reliable markers to evaluate to which extent guidelines have changed practices. Over the last ten years, transfusion management among trauma and surgical patients has fundamentally evolved, with earlier balanced RBC transfusion, FFP and platelets and increased use of fibrinogen concentrate and tranexamic acid. Moreover, massive transfusion protocols were implemented as a standard of care.(14–16) In France, anesthetists are the physicians mainly in charge of critical care management for women with hemorrhagic shock from obstetric hemorrhage, as for surgical and trauma patients. This explains why guidelines on transfusion management in women with obstetric hemorrhage were based on those used in surgical and trauma patients and probably why these changes have been rapidly translated into obstetric hemorrhage management.(6,7) We reported improvements in hemodynamic continuous monitoring with more frequent use of invasive monitoring of the women with active bleeding. Indeed, besides providing continuous accurate blood pressure monitoring, an arterial line facilitates access for repetitive blood sampling. Short length central venous access provides secure venous access for vasopressor infusion and for massive transfusion in patients with hemorrhagic shock.(5,17)

Point of care viscoelastic testing was unavailable in maternity units where these maternal deaths occurred. Expanding access to point-of-care might have a positive impact in the future on transfusion management as suggested by an observational study(18), but this remains to be confirmed by adequately powered randomized controlled trials.

General practice in obstetrics improved in France during the study period, with standardization of human resources(19), development of quality indicators by the French National Authority for Health for maternity units' certification, and improvement in overall obstetrics care content and organization. These advancements in general practice might have contributed to the improved management of women with obstetric hemorrhage during the study period. Despite these positive trends, the MMR from obstetric hemorrhage in France remains higher as compared to some neighboring countries, as reported in a recent paper comparing MMR in European countries with enhanced systems for MM surveillance.(20) As compared to guidelines from neighboring countries, French guidelines do not recommend as second-line uterotonic drugs the association of ergot alkaloids with sulprostone; they recommend that uterine tamponade use, as well as tranexamic acid administration, to be left to the clinician's choice as they were published before evidence for these 2 interventions become available; finally, while most guidelines specify the presence of a senior obstetrician in case of arterial ligation, in particular in case of internal iliac artery ligation, this is not the case in the French guidelines.(21)

The proportion of preventable deaths in France remained very high in the most recent period (88%), stressing further improvement of maternity care in women with obstetric hemorrhage is necessary. The profile of maternal deaths from obstetric hemorrhage we report for the last period suggests that future research should focus on some subgroups, such as women suffering from surgical lesion in the context of cesarean delivery, which now appears as one of the main underlying causes of fatal cases in France.

The burden of obstetric hemorrhage due to surgical complications of cesarean with hemoperitoneum we observed in this study has also been reported by the UK and the Netherlands.(22,23) Recognition of obstetric hemorrhage after cesarean delivery with postoperative hemoperitoneum can indeed be challenging.(24,25) Specific guidance seems needed to optimize the monitoring of parturients at the recovery ward after caesarean. Bedside abdominal ultrasounds should be readily available and systematically performed in case of hemodynamic instability after a cesarean without vaginal bleeding to detect a hemoperitoneum as recommended,

(26). Inferior vena cava ultrasound evaluation by the anesthesiologist can also be helpful in the extremely rare cases where retroperitoneal bleeding is suspected. In addition, next national guidelines update should consider bedside abdominal ultrasound to be performed by either obstetricians or anesthesiologists, as they are both trained for ultrasound diagnosis of hemoperitoneum. Good interdisciplinary collaboration is particularly important in this postoperative context.

The observed lack of surgical skills to perform hemostatic surgery leading to significant delay in hysterectomy has also been reported in national surveys among French residents and among obstetricians.(27,28) This emphasizes the need to involve an experienced obstetrician when hemostatic surgery is needed.(29,30) As peripartum hysterectomies remain rare events, attending planned complex surgical procedures and simulation trainings might be interesting tools to improve and maintain these skills.(31,32)

We found no change in the total number of maternal deaths due to placenta accreta spectrum, which currently appears as a marginal contributor to obstetric hemorrhage mortality in France. Although this might result from a relatively low prevalence of placenta accreta spectrum risk factors in France, in particular previous caesarean, it might also be explained by different management strategies for placenta accreta spectrum between countries, with conservative management in a third of women affected in France.(23,33,34) (35)

The main opportunities of care improvement among preventable maternal deaths by obstetric hemorrhage in the 2013-2015 are summarized in supplemental Table S5.

Conclusion

MM by obstetric hemorrhage dramatically decreased by two-thirds in France between 2001 and 2015, in particular mortality from uterine atony, which dropped by 80%. Among women who died, increased resuscitative efforts in the last triennium suggest that proactive hemorrhage management is improving over time. Nonetheless, maternal death occurred despite better efforts and with an ongoing preventability rate stable over time, which warrants continued emphasis on improving care. Further evaluation of practices in the prevention and treatment of hemorrhage after cesarean delivery seems necessary to guide future guidelines and training targeting this context.

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Supplemental information

https://www.has-sante.fr/upload/docs/application/pdf/2012-12/ipaqss-rapport-hpp-v3.pdf

Supplemental Table S1. COMPAQ indicators related to the quality of prevention and early management of postpartum hemorrhage, defined by the French national Authority for Health (HAS) in 2012

PPH prevention at delivery	Indicator 1: Prophylactic injection of oxytocin and placental examination in accordance with the national guidelines
	Indicator 2: Clinical monitoring of the woman after delivery with: measurements of heart rate, and blood pressure, assessment of uterine tonicity and assessment of blood loss at least twice within the 2 hours following delivery
PPH initial management	Indicator 3: PPH diagnosis: timing of PPH diagnosis blood loss quantification (in mL) at the time of PPH diagnosis
	Indicator 4: Manual endo-uterine exploration
	Indicator 5: Antibiotic prophylaxis in accordance with national guidelines

Supplemental Table S2. Characteristics of women who died from obstetric hemorrhage in France, 2001-2003 and 2013-2015

	2001-2003	**2013-2015**
	N=30 n	**N = 18**
	n (%)	**n (%)**
Maternal characteristics		
Age > 35 years	13 (43)	11 (61)
Born abroad	17 (57)	10 (59)•
BMI >=30kg/m^2	4 (14)•	6 (33)•
Parity		
P1	4 (13)	5 (28)
P2	6 (20)	8 (44)
P3 or more	20 (67)	5 (28)
Prior obstetric hemorrhage	1 (3)•	1 (6)
Prior uterine scar	8 (27)	10 (55)

Supplemental Table S2. (continued)

	2001-2003	2013-2015
	N=30 n	N = 18
	n (%)	n (%)
Pregnancy and delivery characteristics		
Multiple pregnancy	3 (10)	0
Preterm delivery	7 (24)	7 (44)
Labour induction	6 (20)	5 (31)
Mode of delivery		
Cesarean delivery	21 (70)	12 (66)
Operative vaginal birth	3 (10)	0
Spontaneous vaginal birth	5 (17)	4 (22)
Numbers of annuals births in maternity unit of birth		
< 1000 deliveries/year	3 (10)	4 (22)
1001-2000 deliveries/year	12 (40)	3 (17)
> 2000 deliveries/year	15 (50)	11 (61)

• 1 missing datum

Supplemental Table S3. Prophylactic and initial management in women who died from obstetric hemorrhage

	2001-2003 N=30	2013-2015 N=18
Prevention of obstetric hemorrhage		
Prophylactic uterotonic	29 (96)	14 (82)[1]•
Initial management of obstetric hemorrhage		
Additional intravenous access	30 (100)	17 (100) •
Volume replacement therapy by crystalloids	28 (93)	16 (94) •
Manual placenta removal or exploration of the uterus	28 (93)	12 (92) •
Anaesthetist called at OH-diagnosis	28 (93)	17 (100) •
Obstetrician called at OH diagnosis	30 (100)	17 (100) •

• 1 missing datum
[1]Two of the three women without prophylactic uterotonics were women having a planned peripartum hysterectomy for placenta accreta spectrum.
Abbreviations: OH = obstetric hemorrhage

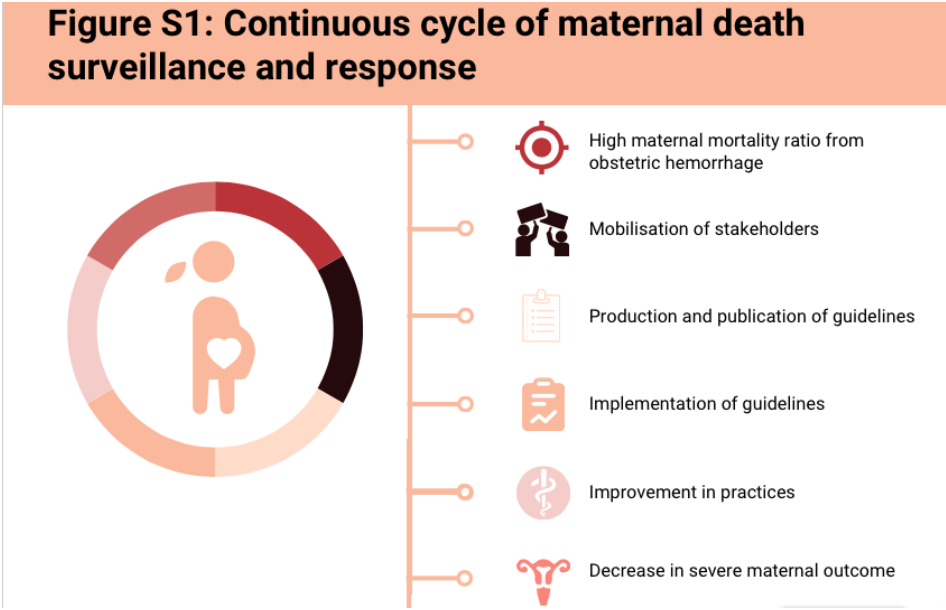
Supplemental Table S4. Main improvable care factors among women who died from obstetric hemorrhage in France in 2001-2003 as compared to 2013-2015

Main improvable care factors 2001-2003	Main improvable care factors 2013-2015
Delay in transfusion management Long delay before start transfusion management Limited number of laboratory assessments to evaluate necessity to adapt or intensify transfusion management	Delay in intra-abdominal bleeding diagnosis after cesarean delivery Late detection of abnormal vital parameters due to suboptimal postpartum surveillance particularly in the recovery ward Late or no performance of bedside ultrasound to detect intra-abdominal bleeding
Suboptimal transfusion therapy Administration of insufficient blood products and procoagulant management Inadequate FFP:RBC ratio	Delay in hemorrhage management Delay in surgical management of hemorrhage due to insufficient surgical skills to perform hemostatic surgery Delay in adequate management of hemorrhage due to underestimation of the severity of bleeding
Delay in hemorrhage management Delay before start administration second line uterotonics after failure of first-line treatment of hemorrhage Late application of invasive interventions such as arterial ligation, embolization, and hysterectomy to arrest bleeding	Delay in transfusion management Although delays before start transfusion management reduced as compared to 2001-2003, a certain delay remains present with no point of care testing available.
Inadequate hemodynamic monitoring Late application of methods to hemodynamically monitor the patient. Insufficient hemodynamic monitoring due to limited use of central venous access or invasive arterial line	

Abbreviations: FFP= fresh frozen plasma, RBC= red blood cells

Supplemental Table S5. Overview of the main opportunities of care improvement among preventable maternal deaths by obstetric hemorrhage in the most recent period

Reduce delays in diagnosis of hemorrhage – *Guidelines could include specific recommendations to optimize the monitoring of parturients at the recovery ward after cesarean delivery* – *Such recommendations could include frequency of monitoring of vital parameters and the inclusion of other parameters to evaluate hemodynamic instability such as the shock index.*
Improve diagnosis of hemorrhage among women with no exteriorized bleeding – *Abdominal ultrasound should be systematically performed to detect hemoperitoneum* – *Bedside abdominal ultrasound can be performed by either obstetricians or anesthesiologists*
Reduce delays of hemorrhage management – *Obstetricians should train their skills to perform hemostatic surgery by attending planned complex surgical procedures and surgical simulation trainings.* – *An experienced obstetrician should be always available on call.*



Supplemental Figure S1. Continuous cycle of maternal death surveillance and response