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Original article

Postpartum hemorrhage with transfusion: Trends, near misses, risk factors and management at the scale of a perinatal network

Hémorragie du post-partum avec transfusion : tendances, near-miss*, facteurs de risqué et prise en charge à l'échelle d'un réseau périnatal*

M. Marocchini [a,*], J. Lauféron [a], C. Quantin [b], P. Sagot [a]

[a] *Department of obstetrics and gynecology, university hospital, Dijon, France*
[b] *Department of biostatistics and bioinformatics, university hospital, Dijon, France*

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ABSTRACT

Objectives. – To analyze temporal trends and management of postpartum hemorrhage (PPH) with transfusion and its related maternal near-miss (MNM) cases between 2006 and 2014 and to study risk factors.
Material and methods. – This retrospective cohort study from two prospective databases included 156,047 women giving birth in all the maternity hospitals of Burgundy. We analyzed temporal trends and the distribution of PPH with transfusion, the circumstances of transfer of patients between hospitals and factors associated with PPH with transfusion. PPH with massive blood transfusion and/or non-medical treatment was defined as MNM. Statistical analysis included Chi^2 tests and logistic regression for multivariate analysis.
Results. – The overall rate of PPH with transfusion was 7.3‰ and globally increased during the study period whereas the MNM rate did not. MNM represented 37% of patients with PPH with transfusion and 71% of transferred patients, but surgical treatments were performed before transfer. Factors associated with PPH with transfusion were maternal age > 35 years (odds ratio [OR] = 1.3), prematurity (OR = 5.0), cesarean section (OR = 4.8), placenta previa (OR = 22.0), twin pregnancy (OR = 6.6), HELLP syndrome (OR = 17.9) and severe small-for-gestational-age infants (OR = 2.0). The first four were also associated with MNM.
Conclusion. – MNM cases of PPH rates were steady in Burgundy while rates of PPH with transfusion increased moderately.

Mots clés :
Hémorragie du post-partum
Transfusion sanguine
Réseau périnatal
Morbidité maternelle
Near-miss

RÉSUMÉ

But. – Analyser l'épidémiologie et la prise en charge des hémorragies du post-partum (HPP) avec transfusion et des cas de *near-miss* en Bourgogne entre 2006 et 2014.
Matériels et méthodes. – Cent cinquante-six mille quarante-sept femmes ayant accouché dans toutes les maternités de Bourgogne ont été incluses. Les données ont été extraites des bases du Réseau périnatal de Bourgogne et de l'établissement français du sang. Nous avons analysé l'évolution dans le temps et la répartition des HPP sévères, les circonstances de transferts interhospitaliers et les facteurs associés à l'HPP avec transfusion. Un cas d'HPP accompagnée d'une polytransfusion et/ou d'un traitement invasif définissait un *near-miss*.
Résultats. – Le taux global d'HPP avec transfusion était de 7,3 ‰ et augmentait globalement au cours de la période d'étude, contrairement au taux de *near-miss*. Les *near-miss* constituaient 37 % des HPP avec transfusion et 71 % des patients transférées, l'ensemble des traitements chirurgicaux étant réalisés avant

* Corresponding author. Maternité du Bocage, 14, rue Paul-Gaffarel, 21079 Dijon cedex, France.
E-mail address: michael.marocchini@hotmail.fr (M. Marocchini).

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transfert. Les facteurs associés à l'HPP avec transfusion étaient l'âge maternel supérieur à 35 ans (*odds ratio* [OR] = 1,3), la prématurité (OR = 5,0), la césarienne (OR = 4,8), le placenta prævia (OR = 22,0), la grossesse gémellaire (OR = 6,6), le HELLP syndrome (OR = 17,9) et le petit poids pour l'âge gestationnel sévère (OR = 2,0). Ces quatre premiers facteurs étaient associés aux *near-miss*.
Conclusion. – Le taux de *near-miss* était stable en Bourgogne et celui d'HPP avec transfusion augmentait modérément.

Introduction

The performance of a perinatal healthcare network should not be restricted to the study of neonatal morbidity and mortality alone; maternal issues have to be taken into account as well. Maternal mortality is a common indicator of the quality of obstetrical care. Although it is interesting at the scale of a country and for international comparisons, it is nowadays too low to be relevant when it comes to the assessment of a regional network, especially in developed countries, where it is increasingly complemented by near-miss audits [1].

Postpartum hemorrhage (PPH) is still the leading cause of maternal mortality worldwide, representing 19.7% of maternal deaths [2]. In France, the maternal mortality rate is 9.6 per 100 000 births, with PPH implicated in up to 16% of deaths, of which more than 80% are considered avoidable [2,3]. While maternal deaths consecutive to obstetrical hemorrhage are exceptional, PPH is frequent and an increase has been observed worldwide over the last 2 decades [4–6]. It can be life-threatening and is responsible for considerable morbidity and health expenditure, most of which is avoidable. From this point of view, halting the increase in the PPH rate is a leading public health issue in obstetrics. The incidence of PPH is, however, difficult to determine, partly because blood loss at delivery is underestimated [7] and partly because the diagnosis is often missing from patients' hospital discharge abstracts. This is why it has been suggested to focus rather on PPH requiring blood transfusion [7]. Sagot et al. [8] showed that linkage between administrative data on blood transfusion from the national French Blood Service (FBS) and the Burgundy Perinatal Network (BPN) database allowed the complete identification of all PPH severe enough to justify a blood transfusion. The rigorous traceability of blood products thus secures an exhaustiveness in the listing of concerned patients.

Since 1995, the BPN has been promoting the training of perinatology professionals as well as periodical clinical practice reviews. It has been issuing obstetrics protocols regularly, including a protocol about the management of PPH as soon as 2004, which has been updated several times since and transmitted to all maternity hospitals of Burgundy. Among other things, it states the successive steps of PPH management, summarily volume expansion, manual removal of the placenta, oxytocin, sulprostone, transfusion and additional treatments.

There are many well-known risk factors for PPH such as cesarean section, placenta retention, pregnancy hypertensive disorders, obstetrical trauma, placenta previa, induction of labor, multiple pregnancies, polyhydramnios and fetal macrosomia [9,10]. Even though these are neither necessary nor sufficient to cause PPH, a higher level of vigilance for women who are most at risk allows better reactivity and quicker and more efficient management. It is thus important to be aware of predictive factors of PPH with transfusion.

Considering this criterion of maternal morbidity, which though rare is sufficiently frequent to be used at the scale of a regional network, our objectives were to assess the quality of maternal care following the implementation of PPH management protocols within the BPN by analyzing the management of PPH with transfusion and related maternal near-misses occurring between 2006 and 2014, and to identify risk factors for severe PPH.

Material and methods

This study included all women who had delivered in one of the 17 maternity hospitals in Burgundy between 01 January 2006 and 12 décembre 2014. All these hospitals are part of the Burgundy Perinatal Network (BPN), whose aim is to improve the quality of perinatal care in Burgundy, a French region which accounts for around 17,000 births annually. Medical conventions between hospitals were signed to improve the coordination of admissions, transfers of patients and the use of technical facilities.

The hospitals were categorized according to their level of maternal and neonatal care: 10 primary, 6 secondary and 1 tertiary hospital (university hospital).

Data were obtained from the cross-analysis of two prospective databases: the BPN and the FBS databases [11]. The population-based BPN database records information regarding the clinical history and labor management of all patients giving birth in Burgundy from compulsory hospital discharge abstracts produced for each hospital stay and classified according to the International classification of diseases, 10th revision. The FBS is the organization in charge of the delivery and traceability of every labile blood product in France and its database is considered a gold standard. Missing and incomplete data were directly checked after reviewing the patients' medical records. The Anonymat software system was used for anonymization and linkage of the BPN and the FBS databases to determine accurately the quantity and the time of delivery of the units of packed red blood cells (RBC) to each patient [12]. Transfusions prior to the delivery were not taken into account.

PPH with transfusion was defined by the delivery of at least one unit of packed RBC was transfused as a result of PPH within the 42 days following childbirth.

Women with PPH with transfusion were defined as maternal near misses (MNM) in accordance with criteria from the World health organization maternal death and near-miss classification [13]: massive blood transfusion (≥ 4 RBC) and/or additional treatment.

Additional treatment of PPH comprised ligation of pelvic vessels (LPV), embolization of pelvic vessels (EPV) and hysterectomy. EPV was only available in one secondary hospital and the university hospital. We did not include the use of the Bakri balloon since it was not properly codified in the BPN guidelines during the study period. Data about patients who underwent one or several of these treatments were extracted thanks to their corresponding codes within the French classification of medical acts.

The intrinsic characteristics studied were: maternal age in years (< 25; 25–34; ≥ 35), gestational age at delivery in weeks of gestation (WG) (< 37; 37–40; 41–42), mode of delivery (vaginal delivery and cesarean section), plurality (singleton and twins),

severe small-for-gestational-age infant (SGA) (< 3rd percentile based on Burgundy customized growth charts [14]), placenta previa and the incidence of HELLP syndrome.

Approval for the study was obtained from the French data protection agency.

Rates were estimated for PPH with transfusion and MNM for each year within the period 2006–2014. Temporal trends were examined across all the years in the study using a Chi^2 test for linear trends in proportions. Statistical significance of differences was assessed based on two-sided *P*-values and a *P*-value < 0.05 was considered statistically significant. Odds ratios (OR) with 95% confidence intervals (95% CI) for a difference in proportions concerning risk factors were calculated using a Chi^2 test by logistic regression. All the aforementioned variables were adjusted for in the multivariate logistic regression model.

Results

A total of 156,047 women who gave birth between 2006 and 2014 in Burgundy were included in our study. There were 21.7% (n = 33,855) of deliveries in primary, 62.3% (n = 97,212) in secondary and 16.0% (n = 24,980) in tertiary maternity hospitals. The rates for the studied characteristics were: 23.4% for maternal age < 25 years, 59.6% for 25–34 years and 16.9% for ≥ 35 years; 6.9% for prematurity and 18.4% for prolonged pregnancy; 1.7% for twin pregnancy; 17.9% for cesarean section; 0.4% for placenta previa; 0.2% for HELLP syndrome; 3.0% for severe SGA (Table 1).

There were 1136 (7.3‰) women who suffered PPH with transfusion: 138 (4.1‰) in primary, 696 (7.2‰) in secondary and 302 (12.1‰) in tertiary maternity hospitals. MNM represented 37% (n = 424) of them; the respective rates in primary, secondary and tertiary hospitals were 0.8‰, 2.7‰ and 4.8‰ ($P < 0.05$) (Fig. 1). The rates therefore increased significantly with the increasing level of the maternity hospitals. The rate of severe PPH was not significantly different from 1 year to another from 2006 to 2011, but subsequently increased (Fig. 2).

At least one additional treatment was administered to 15% (n = 173) of transfused women, for a total of 192 procedures: 68 women with EPV, 83 with hysterectomy, 41 with LPV. There was a downward trend for additional treatments especially in the second half of the study period. When additional treatment was needed, there was a significant difference between vaginal delivery and cesarean section for the rate of surgical treatments (43% vs. 80%, $P < 0.05$), which varied considerably depending on the place of delivery (14% vs. 63% for the tertiary hospital; 59% vs. 88% for primary and secondary hospitals; $P < 0.05$).

All the women who delivered in the university hospital were exclusively managed there. Regarding peripheral hospitals, 98% of hysterectomies and 100% of LPV were performed on the premises while 75% of women who required EPV where transferred to the university hospital. A proportion of 12% (n = 97) of women who delivered in peripheral hospitals was transferred to a higher-level hospital for more advanced care, with 71% of them presenting at least one criterion of MNM.

Massive blood transfusion was associated with a higher risk of hospitalization in an intensive care unit (OR 6.8, 95% CI 4.8–14.6) and additional treatment (OR 9.9, 95% CI 6.5–15.1).

Among the obstetrical characteristics we studied, those significantly associated with PPH with transfusion were, in ascending order: maternal age > 35 years, severe SGA, cesarean section, prematurity, twin pregnancy, HELLP syndrome and placenta previa. On the contrary, maternal age < 25 years was a protective factor (Table 1).

The frequency of criteria defining MNM cases in transfused women was as follows: 33% (n = 372) of massive blood transfusion and 15% (n = 173) of additional treatment. Risk factors among MNM cases were maternal age ≥ 35 years (OR 1.9, 95% CI 1.4–2.6), cesarean section (OR 1.5, 95% CI 1.2–1.9), prematurity (OR 1.6, 95% CI 1.2–2.1) and placenta previa (OR 2.0, 95% CI 1.3–3.1) (Table 2).

All the obstetrical characteristics, except severe SGA, were identified as risk factors for PPH with transfusion after multivariate analysis when the studied characteristics were adjusted for one

Table 1
Obstetrical characteristics of the population of study.
Caractéristiques obstétricales de la population d'étude.

Variables	Population of study (n = 156,047) (%)	PPH with transfusion (n = 1136) (%)	OR (95% CI)
Maternal age			
< 25 years	36,532	209	0.8[a]
	(23.4)	(18.4)	(0.7–0.9)
25–34 years	93,074	694	1
	(59.6)	(61.1)	
≥ 35 years	26,441	233	1.3[a]
	(16.9)	(20.5)	(1.1–1.5)
Term of delivery			
< 37 WG	10,805	293	5.0[a]
	(6.9)	(25.8)	(4.4–5.8)
37–40 WG	116,373	641	1
	(74.6)	(56.4)	
≥ 41 WG	28,869	202	1.3
	(18.5)	(17.8)	(1.1–1.5)
Twin pregnancy	2628	111	6.6[a]
	(1.7)	(9.8)	(5.4–8.0)
Cesarean section	27,489	572	4.8[a]
	(17.6)	(50.4)	(4.3–5.4)
Placenta previa	645	84	22.0[a]
	(0.4)	(7.4)	(17.3–27.9)
HELLP syndrome	273	31	17.9[a]
	(0.2)	(2.7)	(12.3–26.2)
Severe SGA	3706	53	2.0
	(3.0)	(4.7)	(1.5–2.7)

NS: not significant.
[a] Significant risk factors for MNM after multivariate analysis.

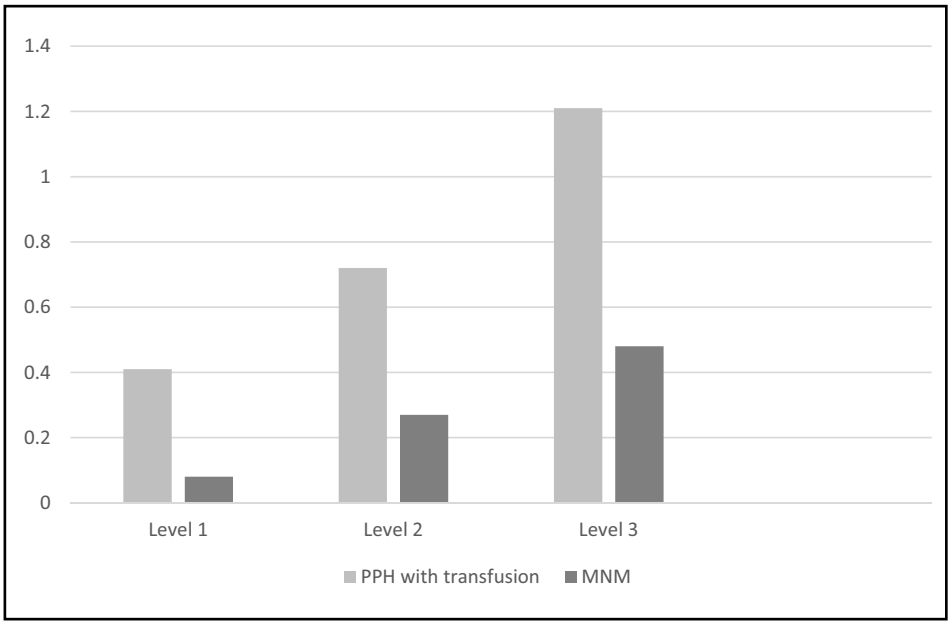

Fig. 1. Rates of PPH with transfusion and MNM according to the level of maternity hospital (%).
Taux d'HPP avec transfusion et de near-miss *selon le niveau des maternités (%).*

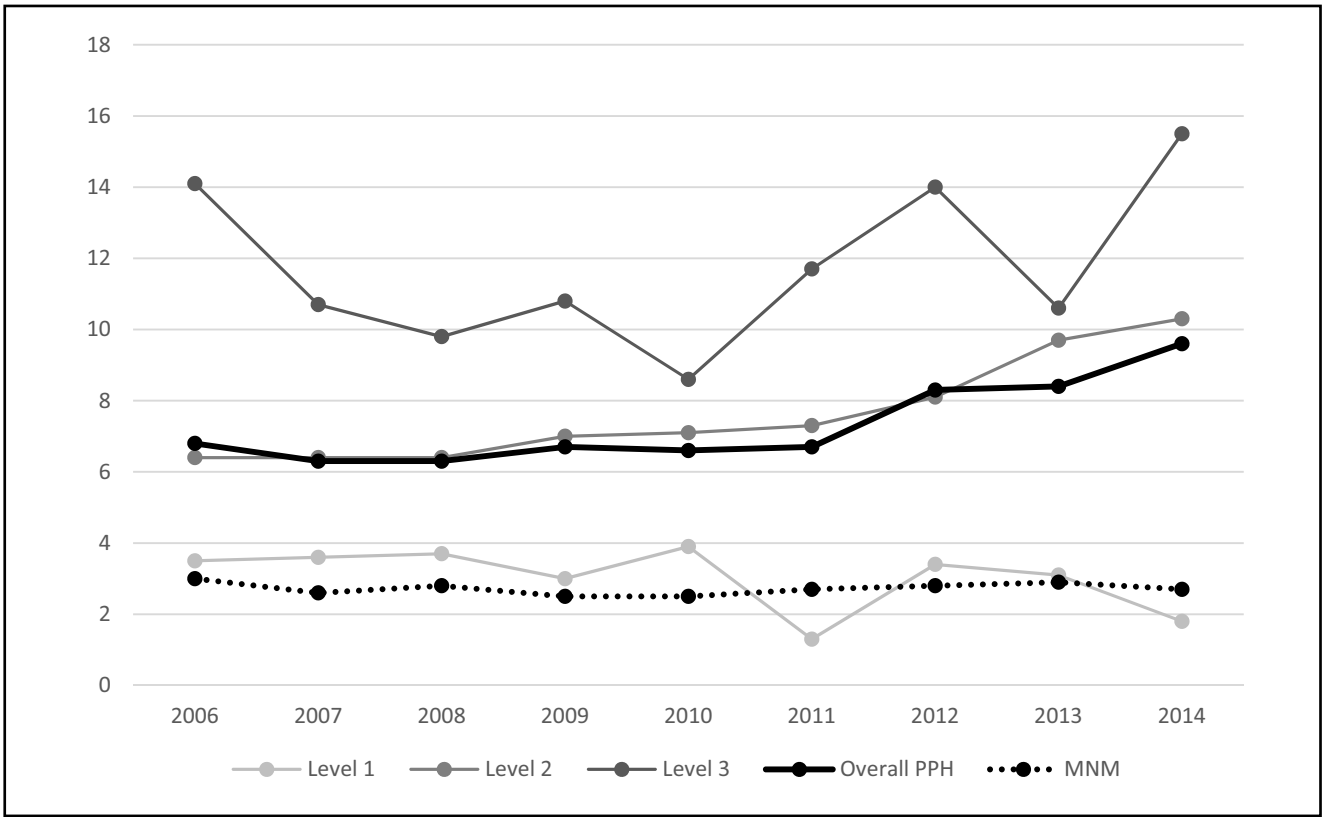

Fig. 2. Temporal trends for PPH with transfusion and MNM rates (‰).
Évolution des taux d'HPP avec transfusion et de near-miss *(‰).*

another. Likewise, maternal age $\geq$ 35 years, cesarean section and placenta previa remained risk factors for PPH-related MNM.

Comment

In recent years, numerous authors have shown a clear increase in PPH rates in developed countries [10,15,16] mainly related to uterine atony, in spite of the implementation of guidelines recommending the active management of the third stage of labor. Our mean rate of PPH with transfusion was 7.3‰, which stands in the lower range of the literature, which ranges from 0.2% to 2.27%, and our mean annual increase rate was the lowest at 4.4% (Table 3). It is noticeable that there were no maternal deaths consecutive to PPH in study period.

Table 2
Maternal near miss by obstetrical characteristics.
Caractéristiques obstétricales des near-miss.

Variables	PPH with transfusion ($n=1136$) (%)	≥4 RBC ($n=367$) (%)	OR (95% CI)	Additional treatment ($n=173$) (%)	OR (95% CI)	MNM ($n=424$) (%)	OR (95% CI)
Maternal age							
<25 years	209 (18.4)	42 (11.4)	0.5 (0.4–0.7)	13 (7.5)	0.3 (0.2–0.6)	47 (11.1)	0.5[a] (0.4–0.7)
25–34 years	694 (61.1)	229 (62.4)	1	112 (64.7)	1	254 (59.9)	1
≥35 years	233 (20.5)	96 (26.2)	1.4 (1.1–1.9)	48 (27.7)	NS	123 (29.0)	1.9[a] (1.4–2.6)
Term of delivery							
<37 WG	243 (21.4)	100 (27.2)	1.7 (1.3–2.3)	39 (22.5)	NS	113 (26.7)	1.6 (1.2–2.1)
37–40 WG	691 (60.8)	200 (54.5)	1	102 (59.0)	1	237 (55.9)	1
≥41 WG	202 (17.8)	67 (18.3)	NS	32 (18.5)	NS	74 (17.5)	NS
Twin pregnancy	111 (9.8)	33 (9.0)	NS	21 (12.1)	NS	41 (9.7)	NS
Cesarean section	571 (50.3)	218 (59.4)	1.7 (1.3–2.2)	100 (57.8)	1.4 (1.0–2.0)	238 (59.1)	1.5[a] (1.2–1.9)
Placenta previa	83 (7.3)	37 (10.1)	1.8 (1.1–2.8)	25 (14.5)	2.6 (1.6–4.4)	44 (10.4)	2.0[a] (1.3–3.1)
HELLP syndrome	31 (2.7)	13 (3.5)	NS	4 (2.3)	NS	13 (3.2)	NS
Severe SGA	53 (4.7)	22 (6.0)	NS	6 (3.5)	NS	23 (5.4)	NS

NS: not significant.
[a] Significant risk factors for MNM after multivariate analysis.

Table 3
Summary of the literature regarding PPH with transfusion and mean annual increase rates.
Revue de la littérature à propos des taux annuels d'HPP avec transfusion.

First author	Period of study	Number of deliveries	PPH with transfusion rate (%)	Mean annual increase rate (%)
Balki, 2008 [22]	2000–2005	33,631	0.31	NA
Roberts, 2009 [23]	1999–2004	500,603	0.8–1.07	5.1
Bateman, 2010 [24]	2004	876,641	0.26	–
Callaghan, 2010 [5]	1994–2006	10,481,197	0.2	NA
Holm, 2012 [25]	2001–2008	382,266	1.92	NA
Jakobsson, 2012 [15]	2006–2008	171,731	1.83–2.27	11.4
Kramer, 2013 [10]	1999–2008	8,371,209	0.21	>8.0
Ford, 2015 [16]	2003–2011	818,965	0.75–1.21	6.1
Marocchini, 2017	2006–2014	156,047	0.63–0.96	4.4

NA: not available.

In our study, the rate of PPH with transfusion remained stable from 2006 to 2009 and then increased. It is nonetheless interesting to point out that the rate of MNM remained stable throughout the study period. This stability was contemporary to the implementation within the BPN of PPH management protocols, which were inspired by the 2004 French guidelines. We can hypothesize that the increase in rates of PPH with transfusion in recent years may arise from the increase in induction and augmentation of labor and uterine scars [9], and the rate of MNM may not have been affected thanks to the implementation of a comprehensive protocol. Some studies [17,18] have shown indeed that maternal morbidity decreased after similar actions within a single obstetrics unit in the short term. One can however as well wonder about a potential liberalization of transfusion practices, which could account for a part of this increase. Still, the French College of obstetricians and gynecologists consider in their 2016 quality directive that transfusion and hemostatic surgery are relevant indicators for the assessment of maternal morbidity.

The rate of PPH with transfusion in the six secondary hospitals, five of which have an intensive care unit and one of which offers EPV, was twice that in primary hospitals, which did not have these resources. Unsurprisingly, the rate in the university hospital was again twice that in secondary hospitals. The university hospital manages high-risk pregnancies primarily or after in utero or postpartum transfer, and is the only hospital to provide the highest level of care for both mother and child. Concerning MNM, the differences between the different levels of hospitals were more marked, with a clear over-representation of the university hospital. It is remarkable that PPH associated with MNM occurred even in the smallest facilities (several maternity hospitals in our study carried out fewer than 500 deliveries per year).

Women who required EPV were mainly transferred to the university hospital due to the lack of trained radiologists in peripheral hospitals. EPV was promoted regardless of the route of delivery and represented more than 50% of the additional treatments performed on women delivering in the university hospital thanks to its permanent availability. The global policy of the BPN was to favor EPV rather than surgical treatments whenever hemodynamics allowed it. However, almost all of the additional surgical treatments were performed in the hospital of delivery, even for women who were to be transferred. One can deduce that all obstetricians should be trained in emergency hemostatic surgery, and there should be an experienced gynecologic surgeon in every facility. Unsurprisingly, placenta previa was the main risk factor for additional treatment.

The characteristics of the study population were comparable to those in the literature [9,10,15,16,19], except for the cesarean section rate, which varied according to local practices. It was low in

our study compared with national and international data and fell significantly from 19.1% to 16.6% during these 9 years. Maternal age ≥ 35 years, prematurity, twin pregnancy, cesarean section, placenta previa, HELLP syndrome and severe SGA proved to be risk factors for severe PPH, with a stronger association for placenta previa and HELLP syndrome. This seems coherent with the literature [9,10,16,19], although many authors preferred to take into account major blood loss rather than blood transfusion. Advanced maternal age, prematurity, cesarean section and placenta previa remained risk factors for PPH associated with MNM. It is worth noticing that the risk increased steadily with age. Cesarean section stands out by far as the most easily modifiable risk factor, which is why the indication for each one should be carefully pondered, especially in patients with several risk factors, at a time when the general trend is towards an increase in the cesarean section rate [20,21].

The design of our study is one of its key strengths. It is population-based and the BPN registry has collected exhaustive data on a large population of women over a 9-year period. Furthermore, as the deliveries occurred in all the maternity hospitals of Burgundy, all levels of neonatal care are represented, and the study population is therefore representative of the general population. We extracted data from two unique databases, thus ensuring the exact numbers of women with transfusion and RBC administered to each woman.

Antepartum anemia appears as a possible confounding factor regarding the use of transfusion as a severity criterion for PPH, since it brings forward the decision for transfusion. Furthermore, it would have been relevant to study more antepartum obstetrical characteristics such as parity, smoking, previous cesarean section and body mass index, but unfortunately these items were not systematically reported in the BPN database.

Conclusion

This work allowed us to show that, despite the rise in rates of PPH with transfusion following the increase of the prevalence of risk factors for uterine atony, the rate of PPH-related MNM was stable in Burgundy during the study period. Maternal age over 35 years, cesarean section, placenta previa, prematurity, twin pregnancy and HELLP syndrome were independent risk factors for PPH with transfusion, the first three of which were also independent risk factors for PPH-related MNM. The linkage of our two prospective databases enabled us to assert the exhaustiveness of the reported number of PPH with transfusion. Severe PPH thus appears as a sentinel criterion for the assessment of the quality of maternal care in a perinatal network: it is a source of severe morbidity and high socioeconomic costs. To our knowledge, no other study has reported the stabilization of an increasingly recognized indicator of maternal morbidity after the standardization of a comprehensive protocol at the scale of an organized perinatal network. PPH-related MNM are rare but frequent enough to justify their analysis during clinical practice reviews within each facility in order to improve the management of PPH and strive towards the goal of preventing avoidable maternal deaths.

Disclosure of interest

The authors declare that they have no competing interest.

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