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Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial

M. Cortet[1,2,3,4]*, C. Deneux-Tharaux[5], C. Dupont[6,7], C. Colin[8], R.-C. Rudigoz[9], M.-H. Bouvier-Colle[5] and C. Huissoud[2,9,10]

[1] Hospices civils de Lyon, Service de Biostatistique, F-69003, Lyon, France
[2] Université de Lyon, F-69000, Lyon, France
[3] Université Lyon 1, F-69100, Villeurbanne, France
[4] CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, F-69100, Villeurbanne, France
[5] INSERM U953 Epidemiological Research Unit on Perinatal Health and Women's and Children's Health, UPMC Paris 6, Paris, France
[6] Aurore Perinatal Network, Hopital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France
[7] Université de Lyon, EA Santé-Individu-Société 4129, F-69002 Lyon Cedex 03, France
[8] Hospices civils de Lyon, Pôle Information Médicale Evaluation Recherche, F-69003 Lyon, France
[9] Hospices civils de Lyon, Service de Gynécologie-Obstétrique de l'Hôpital de La Croix-Rousse, F-69000 Lyon, France
[10] INSERM U846, Stem Cell and Brain Research Institutes, F-69500 Bron, France

* Corresponding author. E-mail: marion.cortet@chu-lyon.fr

Editor's key points

- The aim of the study was to observe whether the fibrinogen level at diagnosis of postpartum haemorrhage (PPH) is associated with the severity of bleeding.
- This study suggests that a low fibrinogen level at PPH diagnosis is associated with a higher risk of severe PPH, independently of the other laboratory indicators.

Background. The aim of the study was to determine whether the fibrinogen level at diagnosis of postpartum haemorrhage (PPH) is associated with the severity of bleeding.

Methods. This is a secondary analysis of a population-based study in 106 French maternity units identifying cases of PPH prospectively. PPH was defined by a blood loss exceeding 500 ml during the 24 h after delivery or a peripartum haemoglobin decrease of more than 20 g litre^{-1}. This analysis includes 738 women with PPH after vaginal delivery. Fibrinogen levels were compared in patients whose PPH worsened and became severe and those whose PPH remained non-severe. Severe PPH was defined as haemorrhage by occurrence of one of the following events: peripartum haemoglobin decrease $\geq$40 g litre^{-1}, transfusion of concentrated red cells, arterial embolization or emergency surgery, admission to intensive care, or death.

Results. The mean fibrinogen concentration at diagnosis was 4.2 g litre^{-1} [standard deviation (SD)=1.2 g litre^{-1}] among the patients without worsening and 3.4 g litre^{-1} (SD=0.9 g litre^{-1}) ($P<0.001$) in the group whose PPH became severe. The fibrinogen level was associated with PPH severity independently of other factors [adjusted odds ratio=1.90 (1.16–3.09) for fibrinogen between 2 and 3 g litre^{-1} and 11.99 (2.56–56.06) for fibrinogen $<$2 g litre^{-1}].

Conclusions. The fibrinogen level at PPH diagnosis is a marker of the risk of aggravation and should serve as an alert to clinicians.

Keywords: blood coagulation; fibrinogen; postpartum haemorrhage

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Postpartum haemorrhage (PPH) remains a major cause of maternal mortality throughout the world,[1] including in France.[2] Specific guidelines describe preventive and curative treatments for PPH.[3–5] Its risk factors have been well identified and studied repeatedly.[6–9] The risk factors for its aggravation, however, have been studied much less.[10]

Coagulation plays an important role in postpartum haemostasis. Primary and especially secondary coagulation disorders are risk factors for PPH that have not been sufficiently evaluated. Pregnancy-induced hypercoagulability tends to reduce the risk of haemorrhage naturally. Pregnancy-related coagulation changes are expressed by a progressive and significant increase in the fibrinogen level, while the standard indicators, such as prothrombin time (PT) and activated coagulation time (ACT), vary little.[11]

Coagulation disturbances are frequent and occur rapidly during PPH. There is, however, no consensus about the thresholds that should trigger specific management, but maintaining the plasma fibrinogen concentration is important for limiting excessive blood loss.[12 13] Because fibrinogen

is usually available more rapidly than other blood products that might correct coagulation, it can be—and often is—administered faster. Nonetheless, the benefits of this early treatment have never been evaluated.

Fibrinogen decreases during PPH may be an important stage in the perpetuation of a haemorrhage. Accordingly, in a series of 128 women, Charbit and colleagues[14] showed that an early reduction in the fibrinogen level during PPH was the best early biological marker for predicting the risk of severity.

As part of the PITHAGORE6 trial,[15] a cohort of patients with PPH was set up and the clinical and organizational risk factors for aggravation were studied.[10] Information about laboratory factors was not studied at that time. The objective of this study was to determine whether the fibrinogen level at PPH diagnosis was associated with subsequent aggravation to severe PPH.

Methods

Patients

This *post hoc* analysis includes patients from the PITHAGORE6 study,[15] which included women with PPH diagnosed from December 2004 through November 2006 in one of the 106 maternity units of the six participating perinatal networks (maternity units and perinatal networks are listed in Supplementary Appendix S1). The Southeast III Institutional Review Board and the French Data Protection Agency (CNIL) both approved the study. Because the study involved no experimental intervention but only standard care, and the outcome data used were routinely collected at the maternity units and were transmitted anonymously, individual consent is not required under French law.

All patients with PPH were included prospectively. PPH was defined by a blood loss exceeding 500 ml during the 24 h after delivery or a peripartum haemoglobin decrease of more than 20 g litre^{-1}. Severe PPH was defined by the occurrence of one of the following events: peripartum haemoglobin decrease $\geq$40 g litre^{-1}, transfusion of concentrated red cells, arterial embolization or emergency surgery (hysterectomy, arterial ligation, or other surgery for haemostasis), admission to intensive care, or death.

The PITHAGORE6 study included 9365 women with PPH from a total of 146 876 deliveries (6.4%). For this study, we included only patients with vaginal deliveries. We also excluded any case with causes for the haemorrhage that could be described as surgical: uterine rupture, wound of birth canal, placenta accreta, and placenta praevia. This reduced the population to 6324 patients, including 1037 (16.4%) with severe PPH. Finally, only patients whose fibrinogen level was measured in 2 h after diagnosis of PPH were selected, that is, 738 women (Fig. 1) from 89 maternity units.

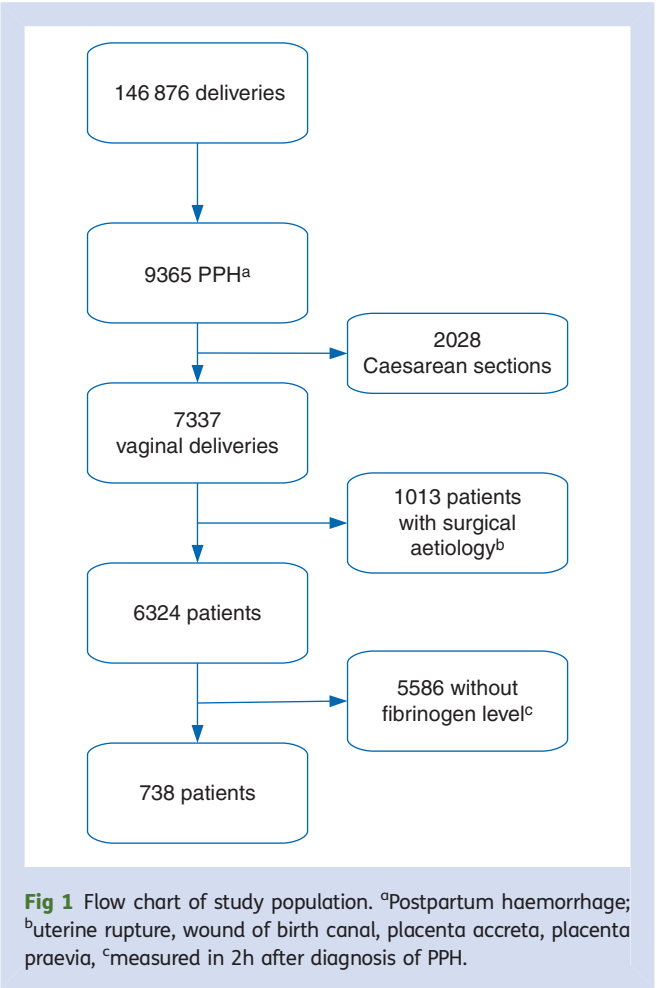

Fig 1 Flow chart of study population. [a]Postpartum haemorrhage; [b]uterine rupture, wound of birth canal, placenta accreta, placenta praevia, [c]measured in 2h after diagnosis of PPH.

Variables

Patient characteristics (age, parity, medical history, labour, and delivery) were recorded in both groups (non-severe and severe PPH) as were their laboratory results (haemoglobin, coagulation data, platelet count, and fibrinogen concentration) and the time blood samples were obtained, to calculate the time relative to haemorrhage diagnosis. Fibrinogen assays were performed with the Clauss fibrinogen method, which has a low coefficient of variation (6–12%).[16]

The cause of the haemorrhage was recorded from the medical chart, as reported by the medical team that cared for the patient. Several causes could be mentioned for the same patient.

Statistical analysis

Patients' characteristics were compared with Student's *t*-test for the normally distributed quantitative variables and with Wilcoxon's rank test for the quantitative variables not normally distributed. The distributions of the qualitative variables were compared with the χ^2 test. The mean fibrinogen levels at diagnosis were compared according to PPH outcome with Student's *t*-test, and the timing of the fibrinogen assays with Wilcoxon's rank test. A non-parametric receiver operating characteristic (ROC) curve and its area under the curve were estimated to evaluate the accuracy of the fibrinogen level for assessing the severity of PPH.

A multivariate logistic regression model was adjusted to estimate the independent association between severe PPH and the fibrinogen level, analysed as a categorical variable

with cut-off points at 2 and 3 g litre^{-1}. Covariables included the time between diagnosis and the blood sample, haemoglobin, platelets, PT and ACT as continuous variables, and the clinical characteristics significantly associated with severe PPH in the univariate analysis. A *P*-value of <0.05 was defined as significant. The analyses were performed with R software (R Development Core Team, *R: A Language and Environment for Statistical Computing*, 2008) and with the Diagnosis Med package (Pedro Brasil, 2009, Diagnosis test accuracy assessment for medical professionals. R package version 0.2.2.1).

Results

PPH was severe for 323 of the 738 (43.8%) women included, but not for 415 (56.2%). Among the women with severe haemorrhages, 52 women required embolization, 12 ligation of the uterine arteries, and 17 hysterectomy; 63 were transferred to intensive care, 136 received transfusions, and 263 had a postpartum haemoglobin level that decreased more than 40 g litre^{-1}. None of the women died.

The patients' characteristics at diagnosis are compared in Table 1. The mean age was 29.8 yr for the women with non-severe PPH and 30.2 yr for those with severe PPH ($P=0.320$); deliveries occurred at median gestational ages of 40.0 and 40.1 weeks ($P=0.680$). Table 2 presents the causes of the haemorrhages, determined retrospectively. Uterine atony was the most common cause, either alone or in combination with another cause.

At the first blood sample after PPH diagnosis, the mean fibrinogen level was 4.2 g litre^{-1} [standard deviation (SD)=1.2] in the group with non-severe PPH and 3.4 g litre^{-1} (SD=0.9) in the group with severe PPH ($P<0.001$). Figure 2A illustrates the distribution of the fibrinogen levels in the two groups. The median time until the blood sample for the fibrinogen assay was 45 min after diagnosis of PPH for the non-severe group and 40 min for the severe group ($P=0.04$) (Fig. 2B).

Figure 3 shows the sensitivity (True Positive Rate) and specificity (1-False Positive Rate) of the fibrinogen level at diagnosis for an outcome of severe PPH. The specificity of a fibrinogen level <2 g litre^{-1} for the prediction of severe PPH was 99.3% [95% confidence interval (CI)=(98.4–1.00)], with a sensitivity of 12.4% [95% CI=(8.79–15.98)]; for a threshold <3 g litre^{-1}, the specificity was 89.9% [95% CI=(85.9–91.9)] for a sensitivity of 35.5% [95% CI=(30.7–41.1%)].

Table 3 presents the other laboratory indicators. In a multivariate logistic model including the laboratory variables for coagulation, haemoglobin, type of delivery, perineal tears, episiotomy, and time between diagnosis and blood sample, the fibrinogen level was independently associated with the severity of PPH. Compared with fibrinogen >3 g litre^{-1}, the odds ratio of severe PPH was 1.90 (1.16–3.09) for fibrinogen between 2 and 3 g litre^{-1} and 11.99 (2.56–56.06) for fibrinogen <2 g litre^{-1}.

Discussion

This study suggests that a low fibrinogen level at PPH diagnosis is associated with a higher risk of severe PPH, independently of the other laboratory indicators. Fibrinogen is one of

Table 1 Maternal characteristics.*Non-severe PPH. †Severe PPH. ‡χ^2 test

Variable	Item	All (*n*=738)	NSPPH* (%) (*n*=415)	SPPH† (%) (*n*=323)	*P*-value‡
Parity	Primiparous	316	169 (40.7)	147 (45.5)	0.22
	Multiparous	422	246 (59.3)	176 (54.5)	
Previous coagulation disorder	No	732	410 (98.8)	322 (99.7)	0.35
	Yes	6	5 (1.2)	1 (0.3)	
Uterine scar	No	702	398 (95.9)	304 (94.1)	0.34
	Yes	36	17 (4.1)	19 (5.9)	
Previous haemorrhage	No	677	379 (91.3)	298 (92.3)	0.75
	Yes	61	36 (8.7)	25 (7.7)	
Twinning	Singleton	707	400 (96.4)	307 (95.5)	0.45
	Twins	31	15 (3.6)	16 (4.5)	
Delivery	Simple vaginal delivery	606	356 (85.8)	250 (77.4)	0.004
	Instrumental vaginal delivery	132	59 (14.2)	73 (22.6)	
Episiotomy	No	439	268 (64.6)	171 (52.9)	0.002
	Yes	299	147 (35.4)	152 (47.1)	
Severe perineal tears	No	699	399 (96.4)	300 (92.9)	0.05
	Yes	38	15 (3.6)	23 (7.1)	
Active management of third stage of labour	No	228	127 (30.6)	101 (31.3)	0.91
	Yes	510	288 (69.4)	222 (68.7)	
Delivery of placenta	Manual	189	91 (21.93)	98 (30.34)	0.005
	Complete	453	276 (66.51)	177 (54.80)	
	Incomplete	96	48 (11.57)	48 (14.86)	

Table 2 Causes of PPH. *Non-severe PPH. †Severe PPH. ‡χ^2 test. ¶Defined as default in coagulation proteins. §Fisher's exact test. ‖χ^2 test with Yates' correction

Cause	All (n=738)	NSPPH* [n=415 (100%)]		SPPH† [n=323 (100%)]		P-value
		n	%	n	%	
Uterine atony	438	231	55.66	207	64.09	0.02‡
Incomplete delivery of placenta	158	86	20.72	72	22.29	0.67‡
Placental retention	101	49	11.81	52	16.1	0.11‡
Coagulopathy¶	11	1	0.24	10	3.09	0.001§
Preeclampsia	2	2	0.48	0	0	
No identified	144	95	22.89	49	15.17	0.01‡
Other	11	4	0.96	7	2.16	0.30‖

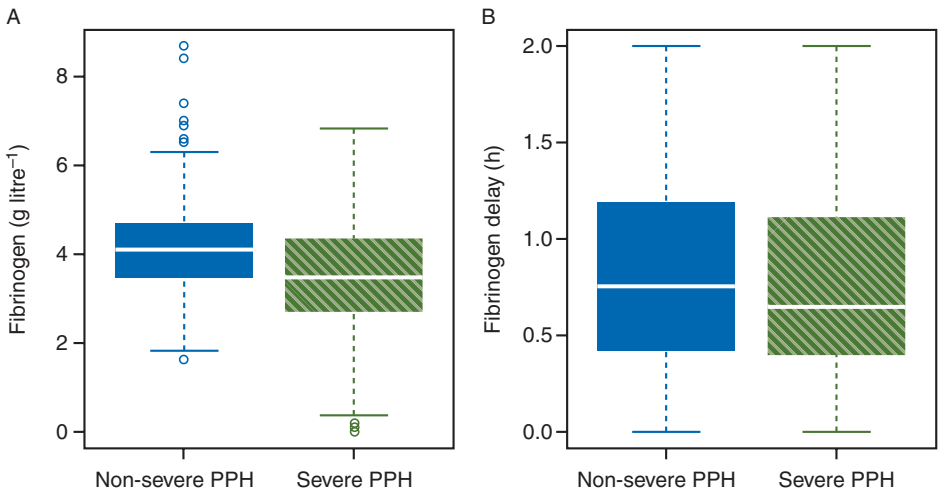

Fig 2 Distribution of (A) fibrinogen level and (B) time until blood samples were obtained (quartiles and medians) for non-severe PPH and severe PPH.

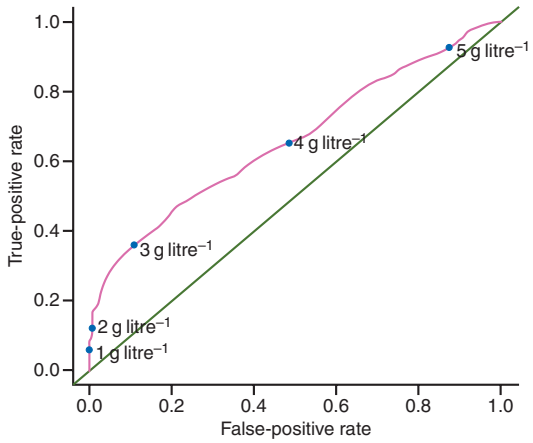

Fig 3 ROC curve of fibrinogen concentration at diagnosis for the prediction of severe PPH. Area under the curve=0.66, 95% CI=(0.64–0.68).

Table 3 Laboratory variables at the time of diagnosis. *Non-severe PPH. †Severe PPH. ‡Wilcoxon test. ¶Prothrombin ratio. §Activated Cephalin time

Variable	NSPPH* [mean (SD)]	SPPH† [mean (SD)]	P-value‡
Haemoglobin (g litre^{-1})	107 (14)	97 (18)	<0.001
Platelets (g litre^{-1})	209 (63)	194 (68)	<0.001
PR¶ (%)	91 (11)	82 (18)	<0.001
ACT§ ratio	0.98 (0.14)	1.11 (0.50)	<0.001

the most important components of coagulation. It is the principal factor for the final stage of clot formation, initiated by the intrinsic and extrinsic coagulation pathways. The fibrinogen level increases during pregnancy from the first through the third trimester.[17] This increase is part of a set of adaptations of the coagulation system that limit the risk of PPH.[17] The mean fibrinogen level during the 9th month

is ~5 g litre^{-1},[11 18] well above the 3 g litre^{-1} normally observed outside pregnancy. During PPH, the fibrinogen level decreases rapidly, influenced by two principal mechanisms: the blood loss itself, which induces depletion of coagulation factors, and the consumption of factors associated with coagulation activation.

In our study, the mean fibrinogen level in both the severe and non-severe groups can be considered to have been normal at diagnosis since the values were within the consensus range of 2–4 g litre^{-1} for non-pregnant women (i.e. 3.4 and 4.2 g litre^{-1}). Nonetheless, when we consider normal fibrinogen values among pregnant women, the values for women in the non-severe PPH group corresponded to the 15th percentile, and for the severe group, the 7th.[11] These values are close to those observed by Charbit and colleagues,[14] respectively, 4.4 and 3.3 g litre^{-1}. In our study, a fibrinogen level between 2 and 3 g litre^{-1}, usually considered normal, was nonetheless associated with a higher risk of severe PPH. The risk was multiplied by almost 12 when the fibrinogen level was <2 g litre^{-1}. This result points in the same direction as that of Charbit and colleagues,[14] who showed that fibrinogen had a positive predictive value of 100% for severe PPH at a threshold of 2 g litre^{-1}. These observations should encourage obstetrics teams not to accept fibrinogen values established outside of pregnancy as normal during pregnancy, but instead to use as their reference values measured in pregnant women, especially during the third trimester.[11 18]

In practice, bleeding persists not because of the reduced fibrinogen but because the obstetric cause has continued. The reduction in the fibrinogen level can nonetheless contribute to the continuation of the bleeding, to the extent that it is the factor that decreases fastest during major bleeding.[19] Charbit and colleagues[14] reported the speed of this decrease during PPH. In that study, as in ours, the only coagulation variable that remained independently associated with severe haemorrhage was the fibrinogen level.

The principal strength of our study is that its findings come from a population-based study, covering all maternity units and consequently all deliveries in a large geographic area (PITHAGORE6 study).[15] It nonetheless has two weak points in terms of interpreting the results. First, the proportion of severe PPH in our series is substantially higher than in reality or than in the PITHAGORE6 study from which our data come (43.77% severe PPH *vs* 16.40% in the PITHAGORE6 study). This high rate of severe PPH in our study is associated with the exclusion of women in the database who had not had a fibrinogen assay at diagnosis. This overrepresentation should nonetheless have only a limited impact on the interpretation of the results because it is probable that the women who did not have coagulation tests during their PPH had either a minimal or a moderate haemorrhage, with fibrinogen levels that were probably higher because of the relatively small blood loss. Secondly, we can suppose that at the moment of the fibrinogen assay, blood loss may already have been higher in the group that developed severe PPH, as the difference in their haemoglobin levels might also suggest. In these conditions, a lower fibrinogen level might simply indicate the existing development into a more severe form of PPH.

In the study by Charbit and colleagues,[14] on the other hand, the variation between the initial haemoglobin level and the level at diagnosis did not differ significantly between the two groups. In our study, the median delay before the assay was very similar in both groups, which suggests the same reaction speed by the teams, and therefore, probably, identical or very similar initial rates of bleeding. In any case, in our study, the multivariate analysis suggests that a low fibrinogen level is independently associated with an increased risk that the haemorrhage will become severe. Nevertheless, a severe PPH may occur with a normal fibrinogen level.

No study has assessed the benefits of an early fibrinogen transfusion during PPH, but increasingly, teams report using it routinely in PPH because fibrinogen is rapidly available while waiting for fresh-frozen plasma to thaw. Fibrinogen is a derivative of haemostatic blood and induces less haemodilution than fresh-frozen plasma.[20] Clinical studies in intensive care units and experimental data also suggest that the early utilization of fibrinogen makes it possible to reduce the use of other blood derivatives.[13 21] There is no consensus threshold for a fibrinogen transfusion during haemorrhage. The Royal College of Obstetricians and Gynaecologists[4 22] recommends cryoprecipitate infusion when fibrinogen is <1 g litre^{-1}. The Club d'Anesthésistes et de Réanimateurs en Obstétrique,[23] on the other hand, recommends fibrinogen infusion when the level decreases below 2 g litre^{-1}. A recent work *in vitro* shows that a concentration of at least 2 g litre^{-1} of fibrinogen is necessary for optimal clot formation.[24] The study suggests that even a threshold of 3 g litre^{-1} could be useful. In our study, a fibrinogen level below 2 g litre^{-1} multiplied the risk of development into severe PPH by 11, independently of other laboratory results.

Management of patients with PPH requires rapid multidisciplinary obstetric and medical management. Nonetheless, coagulation disorders are often underestimated and an optimal and rapid correction might improve obstetric management. The British Royal College of Obstetricians and Gynaecologists suggests calling for help from a specialist in clinical haemostasis in the case of severe PPH. Bedside tests on thromboelastometry allow rapid measurement, and even nearly continuous monitoring, of the fibrinogen level.[25] They may contribute to improving the management of secondary coagulopathies by allowing real-time evaluation. Nonetheless, the early correction of fibrinogen has never been assessed in obstetrics, and there is no consensus about it. The results of our study suggest the need to study in detail the effect of fibrinogen transfusion in PPH to determine whether this strategy, used by some European teams, does or does not reduce the risk that a PPH will become severe.

Conclusion

Coagulation disorders, like all aggravating factors for PPH, have been the object of relatively few studies. Our work

suggests that the fibrinogen level at diagnosis correlates with the course of the haemorrhage and that its low level is associated with an increased risk of aggravation (12 times higher risk of severe PPH when fibrinogen is <2 g litre^{-1}). Independent of other laboratory indicators, a fibrinogen level between 2 and 3 g litre^{-1}, usually considered normal, is also associated with a nearly doubled risk of severe haemorrhage and may constitute an early warning sign.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

None declared.

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