

# A population-based analysis of French transfusion practices for women experiencing severe postpartum hemorrhage

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1	A retrospective analysis of French transfusion practices for women experiencing severe
2	postpartum hemorrhage
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#### 36 Abstract

37 *Background*: Transfusion is a major therapy for severe postpartum hemorrhage but there are

38 few population-based descriptions of practice. The objective of this retrospective French

- 39 population-based study was to describe transfusion practices in women with severe
- 40 postpartum hemorrhage and the compliance with guidelines.
- 41 *Methods:* Study data were sourced from a prior prospective population-based study of 182
- 42 309 deliveries in France between 2012 and 2013. Transfusion practices and compliance with
- 43 French national guidelines were described for all women with severe postpartum hemorrhage
- 44 who had been transfused with red blood cells.
- 45 *Results:* In 1495 women with severe postpartum hemorrhage (0.8% of all deliveries), 35.1%
- 46 were not transfused, 50.0% were transfused during active bleeding and 14.9% exclusively
- 47 after control of bleeding. Among 697 women with a hemoglobin level <7 g/dL, 21.4% were
- 48 not transfused. In 747 women transfused during active bleeding, 68.8% also received fresh
- 49 frozen plasma (fresh frozen plasma to red blood cell ratio between 0.5 and 1 in 80.4%). Forty-
- 50 four percent received fibrinogen concentrate (including 37.4% with a plasma fibrinogen level
- 51 >2 g/L) and 8.6% had a massive transfusion. Among 223 women transfused after bleeding
- 52 was controlled, 5.4% received fresh frozen plasma and 13% had a hemoglobin level >7 g/dL.
- 53 *Conclusions:* One in five women with severe postpartum hemorrhage and a low hemoglobin
- 54 concentration did not receive blood transfusion, which does not comply with French national
- recommendations. Over-transfusion occurred in women in whom bleeding had been
- 56 controlled. The use of tools to help clinicians with transfusion decision-making should be
- 57 developed.
- 58

#### 59 Keywords

- 60 Postpartum hemorrhage, severe; Transfusion; Guidelines; Epidemiology
- 61

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- 68 Obstetric Anesthesia (CARO).

69

#### 70 Introduction

71 Severe postpartum hemorrhage (SPPH) occurs in 1% of deliveries in high-resource countries

72 and is the leading cause of severe maternal morbidity and mortality worldwide.<sup>1-3</sup> Individual

risk factors are poor predictors of postpartum hemorrhage (PPH).<sup>4</sup> Consequently, interest has

74 focused on care practices, since changes in management may affect maternal morbidity and

75 mortality.<sup>5</sup> Blood transfusion is an essential component of SPPH management by maintaining

the circulating blood volume and tissue oxygenation, and for hemostatic support.<sup>6</sup>

77 There are few prospective population-based studies on transfusion practices in SPPH.

78 Previous studies are monocentric<sup>7,8</sup> or retrospective based on hospital databases,<sup>9-12</sup> while

79 population-based studies focus on massive transfusion<sup>13</sup> or are older.<sup>14</sup> Population-based and

80 prospectively-collected data could provide a snapshot of transfusion practices in SPPH, assist

81 clinicians in decision-making and identify areas that are performed well or poorly.

82 International and national transfusion guidelines for SPPH differ depending on whether the

83 bleeding is active or has been controlled.<sup>15-17</sup> However, transfusion practices in obstetric

84 hemorrhage have not been described according to the status of bleeding. The EPIMOMS

study, a French population-based study of severe acute maternal morbidity performed in 2012

and 2013, provided prospective data on women with SPPH and detailed information about

87 transfusion management and active or controlled bleeding.<sup>18,19</sup>

88 The objective of this retrospective study was to describe transfusion practices in women with

89 SPPH based on data from a prospective population-based study. Women in whom transfusion

90 started during active bleeding and those in whom transfusion started only after the control of

91 bleeding were analyzed separately. The study evaluated the compliance with some specific

92 components of transfusion management from contemporary French national guidelines,

93 endorsed by the French National Agency for the Safety of Medicines and Health Products

94 (ANSM) <sup>16, 20</sup> and by the National College of French Gynecologists and Obstetricians

**95** (CNGOF).<sup>17,21</sup>

96

#### 97 Methods

98 The source population was extracted from the EPIMOMS study, a prospective observational

99 population-based study of severe acute maternal morbidity, defined by expert consensus using

a national Delphi process, and conducted during one year in 119 maternity units and 136

101 intensive care units of six French regions (April 2012 to November 2013; 182 309

102 deliveries).<sup>18, 19</sup> Caregivers prospectively identified women with severe acute maternal

- 103 morbidity and the completeness of case ascertainment was validated by a review of delivery
- 104 logbooks, birth registers, hospital discharge databases and laboratory records. Detailed
- 105 information on sociodemographic characteristics, medical and obstetric history, antenatal

106 care, delivery and obstetric hospitalization was collected from medical charts.

- 107 The study population included all the women from the EPIMOMS study who had SPPH,
- 108 defined as a hemorrhage with at least one of the following criteria: blood loss >1500 mL,
- 109 transfusion of four red blood cell (RBC) units or more, arterial embolization, conservative
- 110 uterine surgery (arterial ligation or uterine compression sutures), hysterectomy, acute organ
- 111 dysfunction (cardiovascular, respiratory, renal, hepatic or neurologic dysfunction), admission
- to an intensive care unit, acute severe postpartum anemia (hemoglobin (Hb) level <7 g/dL) in
- 113 the absence of chronic anemia, acute thrombocytopenia  $<50.10^{9}$ /L, disseminated intravascular
- 114 coagulopathy (DIC), or maternal death.<sup>18, 19</sup>
- 115 During the study period, 1655 women had SPPH (0.9% of deliveries, Fig. 1). For this
- analysis, women with congenital bleeding disorders or antepartum diagnosis of morbidly
- adherent placenta were excluded because specific transfusion strategies were planned in
- advance for those patients. Secondary SPPH, occurring more than 24 h after delivery, was
- 119 excluded because its causes and management, including transfusion strategy, differ from
- 120 primary PPH. The analysis was therefore restricted to women with primary SPPH for whom
- transfusion strategy was not anticipated (n=1495).
- 122 The time when bleeding was controlled (corresponding to the cessation of the bleeding as
- diagnosed by the clinicians) and the time when RBC transfusion was started were specifically
- 124 collected in the EPIMOMS study. Women with SPPH were included in the "transfusion
- started during active bleeding" group if RBC transfusion started prior to the control of
- 126 bleeding, and in "transfusion started after bleeding control" if RBC transfusion started after
- the time of bleeding control. Women transfused before and after bleeding control were
- 128 classified in the group "transfusion started during active bleeding".
- 129 Maternal demographics, pregnancy, delivery and hospital markers of the severity of PPH
- 130 (total blood loss; nadir Hb level; nadir plasma fibrinogen level; hemorrhagic shock as defined
- in the EPIMOMS study by a systolic blood pressure <90 mmHg for >60 min or unresponsive
- to plasma expansion); DIC as defined in the EPIMOMS study by a platelet count  $<50.10^{9}/L$
- and/or a prothrombin time <60% and/or a serum fibrinogen level <2 g/L; components of PPH
- 134 management; and causes of SPPH such as placenta accreta, placenta previa, placental
- abruption, uterine rupture, amniotic fluid embolism, surgical causes, perineal trauma or
- episiotomy, placental retention, uterine atony, other causes and unidentified causes) were

- 137 collected. If SPPH arose from multiple causes, only one was recorded in the order of priority138 mentioned above.
- 139 Transfusion practices were explored: type and total quantity of blood products administered,
- 140 the intervals between the diagnosis of PPH and the start of RBC transfusion and between the
- 141 first administration of RBC and of fresh-frozen plasma (FFP) or fibrinogen concentrate (FC),
- the FFP:RBC ratio administered within three hours of the first RBC transfusion, and last Hb
- 143 level measured before transfusion.
- 144 At the time of the study, French national guidelines were available for transfusion in SPPH, as
- 145 part of general guidelines on blood transfusion <sup>16, 20</sup> and as a specific section of obstetric
- 146 guidelines on the management of PPH.<sup>17,21</sup> These guidelines were similar to those in Europe
- 147 and North America at the time.<sup>22, 23</sup> The transfusion strategies differed according to the
- 148 presence or absence of active bleeding. In adults with acute anemia not associated with active
- 149 bleeding and without cardiovascular disease, the transfusion trigger was a Hb level <7 g/dL.
- 150 In adults with active bleeding, RBC were indicated if the patient was hemodynamically
- unstable and/or to keep Hb 7–10 g/dL, but were usually not indicated when the Hb
- 152 concentration was >10 g/dL.
- 153 French guidelines advocate the monitoring of the plasma fibrinogen level both to predict the
- severity of PPH and to guide the administration of coagulation factors. In SPPH, FFP
- transfusion is recommended early using a FFP:RBC ratio between 1:2 and 1:1.
- 156 Administration of fibrinogen concentrate or FFP is also suggested if the plasma fibrinogen
- 157 level is <2 g/dL. Non-compliance with French transfusion guidelines was considered to have
- 158 occurred if there had been no RBC transfusion despite a Hb level <7 g/dL, RBC transfusion
- despite a Hb level >10 g/dL, early FFP and RBC transfusion with a FFP:RBC ratio lower than
- 160 1:2, absence of FFP or fibrinogen concentrate administration in women with a fibrinogen
- 161 level <2 g/dL or DIC, and administration of fibrinogen concentrate to women with a
- 162 fibrinogen level  $\geq 2$  g/dL.
- 163 The characteristics of the women, pregnancy, labor, delivery, the maternity unit, PPH
- severity, PPH management and causes of SPPH were collected and described separately for
- 165 women with RBC transfusion started during active bleeding, women with RBC transfusion
- 166 started after the control of bleeding, and women without a RBC transfusion. Transfusion
- 167 practices and their compliance with French guidelines were described accordingly.
- 168 Values are expressed as n (%), means (SD), or medians (IQR) as appropriate. Analyses were
- 169 performed using STATA version 13.1 (College Station, TX, USA).

170 The French Data Protection Authority and the French Advisory Committee on Information

171 Processing in Research in the field of Health approved the EPIMOMS study (CNIL 912210,

172 CCTIRS 12.060). All the women were informed of anonymized data collection during the

173 EPIMOMS study.

174

#### 175 **Results**

176 Of the 1495 women with SPPH, 970 (64.9%) were transfused; 747 (50.0%) had RBC

transfusion started during active bleeding and 223 (14.9%) had RBC transfusion started onlyafter control of bleeding (Fig. 1).

179 The proportions of sub-Saharan African women, multiparous women, women with previous

180 PPH, multiple pregnancy, emergency cesarean delivery, and women who did not receive

181 prophylactic uterotonic drugs were higher among women with RBC transfusion started during

active bleeding than among women transfused only after control of bleeding (Table 1). The

183 proportions of women under 30 years of age, primiparous, having antepartum anemia, and

having an operative vaginal delivery were higher among women transfused after control of

185 bleeding than among women with RBC transfusion started during active bleeding.

186 Uterine atony was the commonest etiology of SPPH not only overall but also in each

187 subgroup according to transfusion management (Table 2). Clinical and biologic markers of

188 PPH severity and invasive procedures were frequently observed in women with RBC

transfusion started during active bleeding (Table 2). Among these women, two-thirds received

190 FFP, 43.9% received FC and 8.6% had a massive transfusion ( $\geq 10$  RBC units) (Table 3a).

191 Among women with RBC transfusion started after control of bleeding, 5.4% received FFP

and 4.0% FC.

193 Regarding non-compliance with guidelines, for women with SPPH and a nadir Hb <7 g/dL,

194 21.4% were not transfused (Table 3b), while in women with RBC transfusion started during

active bleeding, 47.6% had a nadir Hb <7 g/dL. In this subgroup of women with transfusion

started during active bleeding, the FFP:RBC ratio within the first three hours of RBC

transfusion was <0.5 in 10.3% of women transfused with both RBC and FFP, and the plasma

198 fibrinogen was  $\geq 2$  g/L in 37.4% of those who received FC. Among women with RBC

transfusion started after control of bleeding, 13.0% had a nadir Hb between 7 and 10 g/dL.

200

#### 201 Discussion

202 In women with severe postpartum hemorrhage, half had RBC transfusion started during active

bleeding, 15% were transfused exclusively after bleeding control and 35% were not

- transfused. A fifth of the women with SPPH and a Hb level <7 g/dL were not transfused with
- **205** RBC. Conversely, one in eight women with Hb level  $\geq 7$  g/dL and control of bleeding
- 206 received RBC. Two-thirds of women with transfusion started during active bleeding were
- treated with FFP, including 80% with an FFP:RBC ratio between 1:2 and 1:1. Fibrinogen
- 208 concentrate was also used in almost half of these women, but this included only a third of
- those with a plasma fibrinogen of  $\leq 2 \text{ g/dL}$ .
- 210 The characteristics of patients and transfusion practices in SPPH differed between women in
- 211 whom transfusion was started during active bleeding and those transfused only after control
- of bleeding. Women transfused during active bleeding were more frequently from sub-
- 213 Saharan Africa, multiparous and delivered by a cesarean. In addition, they received more
- diverse types of blood products and in larger quantities than women in whom transfusion was
- started after the control of bleeding. These results suggest the need to explore transfusion
- 216 practices separately in these two different contexts.
- 217 The gap between clinical practice and the French transfusion guidelines suggests under-
- transfusion, as a fifth of the women with SPPH and a nadir Hb <7 g/dL were not transfused.
- 219 A restrictive transfusion strategy, considering RBC transfusion indicated for patients with a
- 220 Hb level <7 g/dL, is recommended in obstetric and non-obstetric settings.<sup>22, 23, 24</sup> Severe
- 221 maternal anemia is associated with increased maternal mortality and morbidity, and should be
- corrected.<sup>25</sup> Our results show that this transfusion trigger and the need for RBC transfusion in
- 223 SPPH with severe anemia should be regularly communicated to practitioners.
- 224 In the context of transfusion started during active bleeding, two-thirds of the women had a Hb
- level >7 g/dL at the start of transfusion, which is consistent with the 2004 French guidelines.<sup>21</sup>
- 226 Half the women transfused during active bleeding had a nadir Hb <7 g/dL during their
- 227 management, which may reflect the severity of PPH but also the clinical challenge of
- transfusion decision-making. In ongoing SPPH, maintenance of Hb levels between 7 and 10
- 229 g/dL is recommended but may be difficult to achieve. Monitors providing real-time perfusion
- 230 indices, such as tissue oxygen saturation (StO<sub>2</sub>) measured by near-infrared spectroscopy,
- coupled with laboratory data, are probably the next frontier in the management of
- hemorrhagic shock.<sup>26</sup> Delays in transfusing blood products are also possible, but this remains
- 233 speculative in the absence of data showing that transfusions were specifically triggered after a
- Hb <7 g/dL had been confirmed.
- The administration of FFP was observed in 68.8% of women with SPPH and transfusion
- started during active bleeding, and in agreement with 2012 French guidelines it was used in a
- FFP:RBC ratio between 0.5 and 1 in 80% of these women.<sup>20</sup> Fixed FFP:RBC ratios for initial

transfusion in major bleeding are extrapolated from the trauma and cardiovascular surgery 238 literature,<sup>27</sup> but there are few data on its use in SSPH and its relevance is currently 239 challenged.<sup>28</sup> The transfusion strategy based on FFP:RBC ratio greater than 1:2 in ongoing 240 241 bleeding may not be appropriate for all clinical settings, in particular in the absence of 242 coagulation factor deficiencies. Recent studies in major obstetric hemorrhage suggest that 243 prothrombin time and activated partial thromboplastin time (as markers of coagulopathy) are 244 poorly correlated with blood loss and are abnormal in a minority of women with very large blood losses.<sup>13,29</sup> A systematic review including randomized controlled trials that compared 245 the use of point-of-care thromboelastometry or thromboelastography with usual care, to guide 246 247 transfusion strategy in bleeding patients, concluded that these devices reduced the proportion of patients transfused with RBC, FFP or platelets and may reduce mortality.<sup>30</sup> However, this 248 249 review did not include obstetric patients and its results were mainly based on elective cardiac 250 surgery. There was a high risk of bias due to heterogeneity. Goal-directed coagulation factor 251 therapy based on visco-elastic algorithms for the treatment of coagulopathy in SPPH should be evaluated further.<sup>31</sup> 252

253 An increasing use of pro-hemostatic agents was seen in women transfused during active 254 bleeding: both FC and tranexamic acid were administered to more than 40% of the women 255 with a transfusion started during active bleeding. Changes in transfusion practice have anticipated changes in guidelines.<sup>32</sup> Fibrinogen concentrate was given before the first RBC 256 unit in half the cases, which may be explained by its immediate availability while awaiting 257 258 delivery of FFP or RBCs. It could also be explained by knowledge about publications that 259 have highlighted the association between an early fall in plasma fibrinogen and progression to SPPH.<sup>33,34</sup> 260

261 For women transfused after bleeding control, a minority was transfused when above the

recommended transfusion triggers: 13% received RBC despite a Hb >7 g/d, and 5.4%

received FFP and 4.0% FC. The use of FFP or FC after bleeding has been controlled is not in

accordance with the French guidelines.<sup>20</sup> Clinicians may have used these products to correct

265 biological abnormalities or out of concern about a recurrence of bleeding. The results

highlight the need for improving postpartum anemia management in France and may be a

comment on the limited guidelines with respect to patient blood management in obstetrics.

268 The recent NATA patient blood management guidelines in obstetrics are a step forward as

they recommend the administration of intravenous iron to women with postpartum Hb level

270 of 6–9 g/L.<sup>24</sup>

271

This study has several strengths. We used a large population-based cohort of pregnant women 272 with characteristics comparable to the national profile,<sup>35</sup> and the definition of SPPH was 273 274 reproducible and easily applied. The prospective inclusion of women using predefined SPPH 275 criteria ensured the completeness of the cases in the source population. The design allowed 276 differentiation between women transfused during active bleeding and those exclusively 277 transfused after control of bleeding. However, the study also has limitations. Despite detailed 278 data having been collected on transfusion practice in SPPH, some data on timing of 279 subsequent blood products administered (including platelet transfusions) were not recorded. 280 The time period between the last pre-transfusion Hb measurement after delivery and the onset 281 of RBC transfusion was not standardized as data were extracted from an observational study. 282 Also, we did not have access to hematological indices closest to the time of hospital 283 discharge, so we could not determine the extent of anemia or hemostatic derangement among 284 these patients in the early postpartum period. We did not have patient-centric information to 285 assess whether patients with anemia were symptomatic. We were also unable to determine 286 provider-specific transfusion decision-making and whether providers used other point-of-care 287 technologies, such as visco-elastic testing in their transfusion decision-making. 288 In conclusion, our findings suggest that moderate variability exists in French transfusion 289 practices during the acute period of bleeding and after arrest of bleeding for women with 290 SPPH. Further research is needed to explore decision-making approaches to transfusion and 291 to examine the degree to which these are influenced by national guidelines. Although 292 standardizing practices may be challenging during the dynamic period of blood loss, there is a 293 need to study the impact of patient blood management practices for the treatment of 294 postpartum anemia after SPPH.

295

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297

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307 **References** 

#### 308

Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V. Identifying
 regional variation in the prevalence of postpartum haemorrhage: a systematic review and
 meta-analysis. *PlosOne* 2012;7:e41114.

3122.Dupont C, Touzet S, Colin C, et al. Incidence and management of postpartum

haemorrhage following the dissemination of guidelines in a network of 16 maternity units in
France. Int J Obstet Anesth 2009;18:320-7.

315 3. GBD Maternal Mortality collaborators. Global, regional, and national levels of

316 maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study

317 2015. Lancet 2016;388:1775-812.

318 4. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum

hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg* 2010;110:1368-73.

320 5. Driessen M, Bouvier-Colle MH, Dupont C, Khoshnood B, Rudigoz RC, Deneux-

321 Tharaux C. Postpartum hemorrhage resulting from uterine atony after vaginal delivery:

322 factors associated with severity. *Obstet Gynecol* 2011;117:21-31.

323 6. Chandraharan E, Krishna A. Diagnosis and management of postpartum haemorrhage.
324 *BMJ* 2017;358: j3875.

325 7. Parker J, Thompson J, Stanworth S. A retrospective one-year single-centre survey of
326 obstetric red cell transfusions. *Int J Obstet Anesth* 2009;18:309-13.

8. Butwick AJ, Aleshi P, Fontaine M, Riley ET, Goodnough LT. Retrospective analysis
of transfusion outcomes in pregnant patients at a tertiary obstetric center. *Int J Obstet Anesth*2009;18:302-8.

So-Osman C, Cicilia J, Brand A, Schipperus M, Berning B, Scherjon S. Triggers and
appropriateness of red blood cell transfusions in the postpartum patient--a retrospective audit. *Vox Sang* 2009;98:65-9.

Blood transfusion during pregnancy, birth,
and the postnatal period. *Obstet Gynecol* 2014;123:126-33.

Cauldwell M, Shamshirsaz A, Wong TY, et al. Retrospective surveys of obstetric red
cell transfusion practice in the UK and USA. *Int J Gynaecol Obstet* 2017;139:342-5.

337 12. Mhyre JM, Shilkrut A, Kuklina EV, et al. Massive blood transfusion during

hospitalization for delivery in New York State, 1998-2007. Obstet Gynecol 2013;122:1288-

**339** 94.

Green L, Knight M, Seeney F, et al. The haematological features and transfusion 340 13. 341 management of women who required massive transfusion for major obstetric haemorrhage in 342 the UK: a population based study. Br J Haematol 2016;172:616-24. 343 Bonnet MP, Deneux-Tharaux C, Dupont C, Rudigoz RC, Bouvier-Colle MH. 14. 344 Transfusion practices in postpartum hemorrhage: a population-based study. Acta Obstet 345 Gynecol Scand 2013;92:404-13. 346 15. Abdul-Kadir R, McLintock C, Ducloy AS, et al. Evaluation and management of 347 postpartum hemorrhage: consensus from an international expert panel. Transfusion 348 2014;54:1756-68. 349 Agence française de sécurité sanitaire des produits de santé (afssaps). Transfusion de 16. 350 globules rouges en situation d'urgence hémorragique, d'anesthésie et de réanimation-351 recommandations de bonne pratique. Available at: 352 http://wwwafssapsfr/var/afssaps\_site/storage/original/application/67bca30279b4b95b00cf19a 353 e44c3a8cepdf 2002. Accessed June 2019. 354 17. Boulay G, Hamza J. [Anesthesic practices in patients with severe postpartum 355 hemorrhage with persistent or worsening bleeding]. J Gynecol Obstet Biol Reprod (Paris) 356 2004;33(8 Suppl):4S80-84S88. 357 18. Korb D, Goffinet F, Seco A, Chevret S, Deneux-Tharaux C, Group ES. Risk of severe 358 maternal morbidity associated with cesarean delivery and the role of maternal age: a 359 population-based propensity score analysis. CMAJ 2019;191:E352-E360. 360 19. Madar H, Goffinet F, Seco A, Rozenberg P, Dupont C, Deneux-Tharaux C. Severe 361 acute maternal morbidity in twin compared with singleton pregnancies. Obstet Gynecol 362 2019;133:1141-50. 363 Haute Autorité de Santé-Agence Nationale de Sécurité du Médicament (HAS-ANSM). 20. 364 Transfusion de plasma thérapeutique: produits, indications. 2012. Available at: 365 https://ansm.sante.fr/var/ansm\_site/storage/original/application/872563885f6ef900fd735283e 366 334d31e.pdf. Accessed June 2019. 367 21. Goffinet F, Mercier F, Teyssier V, et al. [Postpartum haemorrhage: recommendations 368 for clinical practice by the CNGOF (December 2004)]. Gynecol Obstet Fertil 2005;33:268-369 74. 370 22. Rossaint R, Bouillon B, Cerny V, et al. Management of bleeding following major 371 trauma: an updated European guideline. Crit Care 2010;14:R52.

373 updated report by the American Society of Anesthesiologists Task Force on Perioperative 374 Blood Transfusion and Adjuvant Therapies. Anesthesiology 2006;105:198-208. 375 24. Munoz M, Stensballe J, Ducloy-Bouthors AS, et al. Patient blood management in 376 obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus 377 statement. Blood Transfus 2019;17:112-36. 378 25. Daru J, Zamora J, Fernandez-Felix BM, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Global 379 380 Health 2018;6:e548-e554. 381 26. Duret J, Pottecher J, Bouzat P, et al. Skeletal muscle oxygenation in severe trauma 382 patients during haemorrhagic shock resuscitation. Crit Care 2015;19:141. 383 27. Rahouma M, Kamel M, Jodeh D, et al. Does a balanced transfusion ratio of plasma to 384 packed red blood cells improve outcomes in both trauma and surgical patients? A meta-385 analysis of randomized controlled trials and observational studies. Am J Surg 2018;216:342-386 50. 387 28. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. 388 Anaesthesia 2015;70 Suppl 1:78-86, e27-78. 389 29. Gillissen A, van den Akker T, Caram-Deelder C, et al. Coagulation parameters during 390 the course of severe postpartum hemorrhage: a nationwide retrospective cohort study. Blood 391 *Adv* 2018;2:2433-42. 392 30. Wikkelso A, Wetterslev J, Moller AM, Afshari A. Thromboelastography (TEG) or 393 rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding 394 patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia 395 2017;72:519-31. 396 Collins PW, Cannings-John R, Bruynseels D, et al. Viscoelastometry guided fresh 31. 397 frozen plasma infusion for postpartum haemorrhage: OBS2, an observational study. Br J 398 Anaesth 2017;119:422-34. 399 32. Sentilhes L, Vayssiere C, Deneux-Tharaux C, et al. Postpartum hemorrhage: 400 guidelines for clinical practice from the French College of Gynaecologists and Obstetricians 401 (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care 402 (SFAR). Eur J Obstet Gynecol Repro Biol 2016;198:12-21. 403 Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early 33.

Practice guidelines for perioperative blood transfusion and adjuvant therapies: an

372

23.

404 predictor of the severity of postpartum hemorrhage. J *Thromb Haem* 2007;5: 266-73.

- 405 34. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level
  406 and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J*
- *Anaesth* 2012;108:984-9.
- 408 35. Blondel B, Lelong N, Kermarrec M, Goffinet F. Trends in perinatal health in France
- from 1995 to 2010. Results from the French National Perinatal Surveys. *J Gynecol Obstet*
- *Biol Reprod (Paris)* 2012;41:e1-e15.

#### 415 Appendix A

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- 417 The following are members of the EPIMOMS study group:
- 418 For the Naître en Alsace perinatal network: Bruno Langer
- 419 For the Rhône-Alpes Aurore perinatal network: Corinne Dupont, René-Charles Rudigoz
- 420 For the Auvergne perinatal network: Françoise Vendittelli
- 421 For the Basse-Normandie perinatal network: Gaël Beucher
- 422 For the MYPA perinatal region, Ile de France region: Patrick Rozenberg
- 423 For the Naître dans l'Est Francilien network, Ile de France region: Lionel Carbillon
- 424 For the Paris Nord perinatal network: Elie Azria, Nathalie Baunot
- 425 For the 92 Nord perinatal network, Ile de France region: Catherine Crenn-Hebert, Gilles
- 426 Kayem
- 427 For the Lorraine perinatal network: Jeanne Fresson
- 428 For the Société Française d'Anesthésie Réanimation (SFAR): Alexandre Mignon
- 429 For the Pôle Santé Publique, Hospices Civils de Lyon: Sandrine Touzet
- 430 For the Inserm Epopé research team: Marie-Pierre Bonnet, Marie-Hélène Bouvier-Colle,
- 431 Anne Chantry, Coralie Chiesa-Dubruille, Catherine Deneux-Tharaux, Aurélien Seco.
- 432
- 433

#### Fig.1. Study population



SPPH: severe postpartum hemorrhage. RBC: red blood cell.

**Table 1**. Characteristics of women with severe postpartum hemorrhage, stratified by use of red blood cell transfusion.

	All women Women receiving Women receiving RBC during active RBC after bleeding bleeding control					Women not receiving RBC						
	(n=1,495)			(n=747)			(n=223)			(n=525)		
	n	n	(%)	n	n	(%)	n	n	(%)	n	n	(%)
Patient characteristics	-	_				-	_	_	-	_		
Age (y)	1495			747			223			525		
<30		628(4	12.0)		302(40	0.4)		113(50	0.7)		213	(40.6)
30-39		779(5	52.1)		401(53	3.7)		99(44	4.4)		279	(53.1)
≥40		88	(5.9)		44 (5	5.9)		11 (4	4.9)		33	(6.3)
Nationality	1405			700			213			492		
European		1141(8	31.2)		551(78	3.7)		177(83	3.1)		413	(84.0)
North African		95	(6.8)		47 (6	5.7)		9 (4	4.2)		39	(7.9)
Sub-Saharan African		108	(7.7)		63 (9	9.0)		14 (6	6.6)		31	(6.3)
Other (Asian, American)		61	(4.3)		39 (5	5.6)		13 (6	6.1)		9	(1.8)
Parity	1483			739			221			523		
primiparous		712(4	18.0)		340(46	5.0)		126(5	7.0)		246	(47.1)
multiparous without previous CD		507(3	34.2)		260(35	5.2)		58(2	6.3)		189	(36.1)
multiparous with previous CD		264(1	L7.8)		139(18	3.8)		37(1	6.7)		88	(16.8)
Previous PPH	1495	90	(6.0)	747	49 (6	5.6)	223	6 (2	2.7)	525	35	(6.7)
Multiple pregnancy	1494	140	(9.4)	747	76(10	).2)	222	13 (!	5.9)	525	51	(9.7)
Antepartum anemia	1423	374(2	26.3)	699	193(27	7.6)	216	81(3	7.5)	508	100	(19.7)
Labor induction or augmentation	1495	763(5	51.0)	747	381(51	1.0)	223	125(5	6.1)	525	257	(49.0)
Mode of delivery	1495			747			223			525		
spontaneous vaginal delivery		575(3	38.5)		273(36	5.6)		95(42	2.6)		207	(39.4)
operative vaginal delivery		250(1	L6.7)		125(16	5.7)		59(20	6.5)		66	(12.6)
emergency CD during labor		302(2	20.2)		160(21	1.4)		28(1)	2.5)		114	(21.7)
emergency CD before labor		162(1	LO.8)		92(12	2.3)		21 (9	9.4)		49	(9.3)
scheduled CD before labor		206(1	L3.8)		97(13	3.0)		20 (	9.0)		89	(17.0)
Prophylactic uterotonic drug	1495	1334(8	39.2)	747	651(87	7.1)	223	209(93	3.7)	525	474	(90.3)
Maternity unit characteristics												
Status	1495			747			223			525		
university hospital		658(4	14.0)		314(42	2.0)		92(4)	1.2)		252	(48.0)
non-university public hospital		624(4	11.7)		326(43	3.7)		90(40	0.4)		208	(39.6)
private hospital		213(1	L4.3)		107(14	1.3)		41(1	8.4)		65	(12.4)
Number of deliveries per year	1495			747			223			525		
≥3000		421(2	28.2)		196(26	5.2)		54(24	4.2)		171	(32.6)
1500-2999		672(4	14.9)		344(46	5.1)		97(43	3.5)		231	(44.0)
<1500		402(2	26.9)		207(27	7.7)		72(32	2.3)		123	(23.4)

Data presented as n (%).

The total number of women may vary slightly from one characteristic to another because of missing data. RBC: red blood cells. CD: cesarean delivery. PPH: postpartum hemorrhage.

**Table 2.** Etiology and management of women with severe postpartum hemorrhage, stratified by use of red blood cell transfusion.

Ī	Women receiving RBC during active bleeding		Women re after blee	eceivin ding co	g RBC ontrol	Women not receiving RBC			
	(n=747)		(n=223)			(n=525)			
	n	n	(%)	n	n	(%)	n	n	(%)
Cause of PPH <sup>a</sup>	747	_	_	223	_		525	_	
Uterine atony		335	(44.8)		66	(29.6)		198	(37.7)
Placental retention		80	(10.7)		46	(20.6)		85	(16.2)
Perineal wound or episiotomy		82	(11.0)		56	(25.1)		62	(11.8)
Surgical cause		71	(9.5)		21	(9.4)		78	(14.9)
Amniotic fluid embolism		14	(1.9)		0	(0.0)		0	(0.0)
Uterine rupture		21	(2.8)		1	(0.5)		7	(1.3)
Placental abruption		33	(4.4)		7	(3.1)		9	(1.7)
Placenta previa		19	(2.5)		0	(0.0)		22	(4.2)
Placenta accreta		32	(4.3)		1	(0.5)		5	(0.9)
Others		14	(1.9)		7	(3.1)		4	(0.8)
Unidentified		46	(6.2)		18	(8.1)		55	(10.5)
Characteristics of PPH severity									
Total blood loss (mL)	588	(150	1750 0,2200)	165	(75	1000 (0,1500	468	(110	1500 0,1700)
Nadir s. fibrinogen level (g/L)	670			140			338		
<1		61	(9.1)		2	(1.4)		3	(0.9)
1-1.9		169	(25.2)		15	(10.7)		30	(8.9)
≥2		440	(65.7)		123	(87.9)		305	(90.2)
Hemorrhagic shock	747	104	(13.9)	223	12	(5.4)	525	21	(4.0)
DIC	747	302	(40.4)	223	28	(12.6)	525	38	(7.2)
Characteristics of PPH managemen	t								
Tranexamic acid	747	338	(45.2)	223	33	(14.8)	525	118	(22.5)
Arterial embolization	747	138	(18.5)	223	10	(4.5)	525	27	(5.1)
Conservative uterine surgery	747	173	(23.2)	223	1	(0.4)	525	67	(12.8)
Peripartum hysterectomy	747	83	(11.1)	223	2	(0.9)	525	5	(1.0)

Data presented as n (%), median [interquartile range]

The total number of women may vary slightly from one characteristic to another because of missing data. <sup>a</sup> In exclusive categories.

RBC: red blood cells. PPH: postpartum hemorrhage. Shock: Systolic blood pressure <90 mmHg of duration >60 min or unresponsive to plasma expansion. DIC: Disseminated intravascular coagulopathy defined by thrombocytopenia <50 x  $10^{9}$ /L or s. fibrinogen level <2 g/L or prothrombin ratio <60%

 Table 3a. Transfusion-related data for women with severe postpartum hemorrhage transfused with red blood cells during or after active bleeding.

	Worr	nen with	RBC	Women with RBC			
	during	active ble	eeding	after ble	ontrol		
		(n=747)		(n=223)			
	n	n	(%)	n	n	(%)	
Characteristics of RBC transfusion				-	_		
Hb level before RBC transfusion (g/dL)	683			220			
<6.0		91	(13.3)		59	(26.8)	
6.0-6.9		141	(20.7)		123	(55.9)	
7.0-7.9		140	(20.5)		26	(11.8)	
≥8.0		311	(45.5)		12	(5.5)	
Time from PPH diagnosis to RBC transfusion	6901	h38 (52n	nin,2h53)	200	32h (	22h,58h)	
Total number of RBC units	743		3 (2,5)	221		2 (2,3)	
≥10 RBC units		64	(8.6)		0	(0.0)	
Characteristics of FFP transfusion							
FFP transfusion	747	514	(68.8)	223	12	(5.4)	
Time from RBC to FFP transfusion <sup>a</sup>	467	28n	nin (4,59)				
Total number of FFP units <sup>a</sup>	511		3 (2,5)				
Characteristics of FC administration							
FC administration	747	328	(43.9)	223	9	(4.0)	
Time from RBC to FC administration <sup>b</sup>	290	-1mir	n (-37,46)				
Total quantity of FC <sup>b</sup> (g)	319	3	(1.5,4.5)				
Platelets transfusion	747	132	(17.7)	223	5	(2.2)	

Data presented as n(%), median [interquartile range]

The total number of women may vary slightly from one characteristic to another because of missing data.

 $^{\rm a}$  Among women with RBC transfusion started during active bleeding and transfused with FFP (n=514).

<sup>b</sup> Among women with RBC transfusion started during active bleeding and who received FC (n=328).

RBC: red blood cells. Hb: hemoglobin. PPH: postpartum hemorrhage. FFP: fresh frozen plasma. FC: fibrinogen concentrate.

Table 3b: Anemia management and hemostatic support among women with severe postpartum hemorrhage

	Women receiving Women receiving RBC during active RBC after bleeding bleeding control						Women not receiving RBC		
	(n	=747)	(n=223)			) (		(n=525)	
	n	n	(% <sup>a</sup> )	n	n	(% <sup>a</sup> )	n	n	(% <sup>a</sup> )
RBC transfusion according to nadir Hb level									
Women with nadir Hb <7g/dL (N=697)		354 (	(50.8)		194	(27.8)		149	(21.4)
	n	n	(% <sup>b</sup> )	n	n	(% <sup>b</sup> )	n	n	(% <sup>b</sup> )
Management of acute anemia									
Nadir Hb (g/dL)	743			223			523		
<7		354 (	47.6)		194	(87.0)		149	(28.5)
7-10		360 (	48.5)		29	(13.0)		312	(59.7)
>10		29	(3.9)		0	(0.0)		62	(11.9)
Hemostatic support									
FFP:RBC within the first 3 h of RBC transfusion <sup>c</sup>	368								
<0.5		38 (	(10.3)						
0.5 - 1		296 (	80.4)						
>1		34	(9.3)						
Fibrinogen level before FC administration <sup>d</sup> (g/L)	286			7					
<2		103 (	(36.0)		2	(28.6)			
≥2		107 (	(37.4)		1	(14.3)			
not measured		76 (	26.6)		4	(57.1)			
Neither FFP nor FC transfusion despite fibrinogen <2g/L <sup>e</sup>	230	24 (	(10.4)	17	8	(47.1)			
Neither FFP nor FC transfusion despite DIC <sup>f</sup>	302	37(	(12.3)	28	17	(60.7)			

The total number of women may vary slightly from one characteristic to another because of missing data.

<sup>a</sup> Expressed as row percentage.

<sup>b</sup> Expressed as column percentage.

<sup>c</sup> Among women with RBC transfusion started during active bleeding and transfused with FFP (n=514).

<sup>d</sup> Among women transfused with RBC and who received FC (N=337).

<sup>e</sup> Among women transfused with RBC and who had a nadir fibrinogen <2g/L (n=247).

<sup>f</sup> Among women transfused with RBC and who had a DIC (N=330).

RBC: red blood cells. Hb: hemoglobin. PPH: postpartum hemorrhage. FFP: fresh frozen plasma. FC: fibrinogen concentrate. DIC: disseminated intravascular coagulopathy defined by thrombocytopenia <50 x  $10^9/L$  or fibrinogen level <2g/L or prothrombin ratio <60%.