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1 **Title page**

2

3 **Title:**

4 Comparison of quantitative and calculated postpartum blood loss after vaginal delivery

5

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30 years. The other authors report no conflict of interest.

31

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40 TRACOR, CYTOCINON, and TRAAP trials (ClinicalTrials.gov numbers respectively
41 NCT01044082, NCT01113229, and NCT02302456).

42 These three trials were respectively approved by the Paris-Ile de France III Committee for
43 the Protection of Research Subjects in September 2009 (n°B90885-20), by the Ethics
44 Committee of Poissy Saint-Germain Hospital on October 20, 2009 (n°09049), and by the
45 West II Committee for the Protection of Research Subjects on August 21, 2014 (2014/09)
46 associated with the approval of the French Health Products Safety Agency on August 6, 2014
47 (2014-001748-39).

48 All individuals provided written informed consent to participate in each trial.

49

50 **Presentation:**

51 This work was presented (abstract and poster) at the 42nd Annual Pregnancy Meeting of the
52 Society for Maternal-Fetal Medicine, January 31–February 5, 2022, Orlando, Florida.

53

54

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59

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64 **Author Contributions:**

65 Catherine Deneux-Tharaux and François Goffinet conceptualized and developed the
66 methodology for the TRACOR trial.

67 Patrick Rozenberg conceptualized and developed the methodology for the CYTOCINON trial.

68 Catherine Deneux-Tharaux and Loïc Sentilhes conceptualized and developed the
69 methodology for the TRAAP trial.

70 Hugo Madar, Loïc Sentilhes, Catherine Deneux-Tharaux, François Goffinet and Patrick

71 Rozenberg contributed to data acquisition.

72 Hugo Madar, Catherine Deneux-Tharaux and Loïc Sentilhes designed the study question and
73 analytic plan.

74 Hugo Madar, Catherine Deneux-Tharaux and Loïc Sentilhes conducted data analysis,
75 generated the tables and figures and drafted the manuscript.

76 Catherine Deneux-Tharaux, Loïc Sentilhes, François Goffinet, Marie-Pierre Bonnet and
77 Patrick Rozenberg provided analytic oversight and edited the manuscript.

78 All authors have read and agreed to the final version of the manuscript.

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90

91

92 **Manuscript text**

93

94 **Title:**

95 Comparison of quantitative and calculated postpartum blood loss after vaginal delivery

96

97 **Condensation:**

98 After vaginal delivery, quantitative blood loss is lower than calculated blood loss and the
99 difference tends to rise as blood loss increases.

100

101 **Short title:**

102 Comparison of quantitative and calculated postpartum blood loss after vaginal delivery

103

104 **AJOG MFM at a Glance:**

105

106 **A. Why was this study conducted?**

- 107
- 108 • No consensus in methods exists to assess postpartum blood loss.
 - 109 • Quantitative blood loss has been proposed to overcome the limitations of intervention-
110 based outcomes, but remains partly subjective and potentially biased by amniotic fluid or
111 missed out-of-bag losses.
 - 112 • Calculated blood loss based on laboratory parameters could be an objective assessment
113 method, but few studies have compared these methods' results.

113

114 **B. What are the key findings?**

- 115 • After vaginal delivery, quantitative and calculated blood loss were significantly but
116 moderately correlated (Spearman coefficient=0.44).
- 117 • Median quantitative blood loss (100 mL, interquartile range (IQR) 50-275) was significantly
118 lower than median calculated blood loss (260 mL, IQR 0-630), and the difference tended
119 to increase with blood loss.
- 120 • Negative calculated values occurred but almost always corresponded to quantitative
121 values ≤ 500 mL.

122

123 **C. What does this study add to what is already known?**

- 124 • Description and quantification of the difference between quantitative and calculated
125 blood loss after vaginal delivery.

126

127 **Word count (abstract): 444**

128 **Word count (main text): 3636**

129

130 **Conflict of Interest:**

131 Author 2 has carried out consultancy work and been a lecturer for Ferring Laboratories,
132 GlaxoSmithKline and Bayer, and been a lecturer for Norgine in the previous 3 years. Author 4
133 carried out consultancy work and was a lecturer for Ferring Laboratories in the previous 3
134 years. The other authors report no conflict of interest.

135

136 **Keywords:** postpartum hemorrhage, vaginal delivery, blood loss, calculated blood loss,
137 measured blood loss, postpartum blood loss assessment method.

138 **Abstract**

139

140 **Background:**

141 Because there is no consensual method of assessing postpartum blood loss, the comparability
142 and relevance of the postpartum hemorrhage-related literature is questionable. Quantitative
143 blood loss assessment using a volumetric technique with a graduated collector bag has been
144 proposed to overcome limitations of intervention-based outcomes but remains partly
145 subjective and potentially biased by amniotic fluid or missed out-of-bag losses. Calculated
146 blood loss based on laboratory parameters has been published and used as an objective
147 method expected to reflect total blood loss, but few studies have compared quantitative with
148 calculated blood loss.

149 **Objective:**

150 This study aimed to compare the distribution of postpartum blood loss after vaginal delivery
151 assessed by two methods – quantitative and calculated blood loss – and the incidence of
152 abnormal blood loss with each method.

153 **Study Design:**

154 The data came from the merged database of 3 multicenter, randomized controlled trials, all
155 testing different interventions to prevent postpartum blood loss in individuals with a singleton
156 live fetus ≥ 35 weeks, born vaginally. All 3 trials measured blood loss volume by using a
157 graduated collector bag. Hematocrit was measured in the eighth or ninth month of gestation
158 and on day 2 postpartum. The two primary outcomes were: quantitative blood loss defined
159 by the total volume of blood loss measured in a graduated collector bag, and calculated blood
160 loss mathematically defined from the peripartum hematocrit change (estimated blood volume
161 $\times [(antepartum\ hematocrit - postpartum\ hematocrit)/antepartum\ hematocrit]$, where

162 estimated blood volume (mL) = booking weight (kg) × 85). We modelled the association
163 between positive quantitative blood loss and positive calculated blood loss with polynomial
164 regression and calculated the Spearman correlation coefficient.

165 **Results:**

166 Among the 8341 individuals included in this analysis, the median quantitative blood loss (100
167 mL, interquartile range 50-275) was significantly lower than the median calculated blood loss
168 (260 mL, interquartile range 0-630) ($P<.05$). The incidence of abnormal blood loss was lower
169 with quantitative blood loss than calculated blood loss for blood loss ≥ 500 mL, ≥ 1000 mL and
170 ≥ 2000 mL, respectively, it was 9.6% (799/8341) vs 32.3% (2691/8341), 2.1% (176/8341) vs
171 11.5% (959/8341), and 0.1% (10/8341) vs 1.4% (117/8341); ($P<.05$). Quantitative blood loss
172 and calculated blood loss were significantly but moderately correlated (Spearman
173 coefficient=0.44; $P<.05$). The association between them was not linear, and their difference
174 tended to increase with blood loss. Negative calculated blood loss values occurred in 23%
175 (1958/8341) of individuals; among them, more than 99% (1939/1958) had quantitative blood
176 loss ≤ 500 mL.

177 **Conclusion:**

178 Quantitative and calculated blood loss were significantly but moderately correlated after
179 vaginal delivery. However, clinicians should be aware that quantitative blood loss is lower than
180 calculated blood loss, with a difference that tended to rise as blood loss increased.

181

182 **Main text**

183

184 **Introduction**

185

186 Postpartum hemorrhage (PPH) remains one of the leading causes of severe maternal
187 complications, accounting for more than 25% of maternal deaths or near misses worldwide.<sup>1-
188 3</sup> It is most commonly defined by blood loss at or over a given threshold within 24 hours after
189 birth. Although the World Health Organization defines this threshold as a blood loss of 500
190 mL,⁴ it can vary up to 1000 mL according to the guidelines and route of delivery.⁵⁻¹¹ Although
191 this standard threshold-based definition appears simple, the heterogeneity of methods used
192 to assess postpartum blood loss likely contributes to the wide variation in the reported
193 incidences of PPH across studies and trials (from 5% to 14% according to the blood loss
194 assessment methods or the study design).¹²⁻¹⁴

195 Visual estimation of postpartum blood loss, the historical assessment method,¹⁵ is known
196 to be operator-dependent and often inaccurate, underestimating large volumes and
197 overestimating small ones.¹⁵⁻²⁷ Hence, direct quantitative blood loss assessment methods
198 using a volumetric technique with a graduated collector bag or a gravimetric technique by
199 weighing blood-soaked textiles have been proposed.^{7, 8, 28-30} These quantitative methods
200 appear more accurate and reproducible than visual estimation and lead to higher reported
201 incidence rates of PPH.^{14, 28, 31, 32} However, their routine use has not been demonstrated to
202 improve maternal outcomes,³³ and their reliability remains questionable, given the possibility
203 of uncollected blood loss in particular after bag removal or contamination with amniotic fluid
204 in the measured volume.^{20, 21, 26, 34} Other blood loss-related clinical outcomes based on
205 interventions, such as additional uterotonic, transfusion, or invasive procedures, are also used

206 in research studies but are limited by their subjective dimension as they involve clinical
207 judgment and the local care organization and resources.¹² In response to these limitations of
208 PPH-related clinical outcomes, some authors have proposed the use of calculated blood loss
209 (CBL), in particular in interventional studies.^{15, 25, 35, 36} CBL, based on laboratory parameters,
210 notably pre-and post-delivery hematocrit, is therefore objective since it is independent of
211 clinical judgment, and expected to reflect total blood loss.^{25, 36-39} Few studies, however, have
212 compared and assessed the correlation between calculated laboratory-based parameters and
213 clinically quantified blood loss in an obstetric context.^{25, 39, 40} In addition, their methodological
214 limitations related to their single-center design, small sample sizes, and heterogeneous
215 calculation methods, hamper the generalizability of their results.^{25, 39, 40} Determining whether
216 quantitative blood loss (QBL) and CBL estimate blood loss similarly and have comparable
217 incidences remains of importance in particular because a recent meta-analysis combined
218 these outcomes to assess the impact of intervention to reduce blood loss.⁴¹ Because three
219 large recent trials assessing different interventions for PPH prevention collected clinically QBL
220 and blood parameters to calculate CBL for each participant, they offer the opportunity to
221 analyze QBL as well as CBL in a large dataset of vaginal deliveries.⁴²⁻⁴⁴

222 Our primary objective was to compare the distribution of postpartum blood loss after
223 vaginal delivery assessed by two methods — quantitative blood loss (QBL) and calculated
224 blood loss (CBL) — and the incidence of abnormal blood loss (≥ 500 mL, ≥ 1000 mL, ≥ 2000 mL)
225 with each. Our secondary objective was to analyze the correlation between QBL and CBL.

226

227

228 **Materials and methods**

229

230 *Population*

231

232 We conducted a secondary analysis of the combined population of individuals who
233 participated in the TRACOR (TRAction of the CORd),⁴² CYTOCINON (combination of CYTOtec
234 and SyntoCINON to prevent PPH),⁴³ and TRAAP (TRANexamic Acid for Preventing PPH after
235 vaginal delivery)⁴⁴ randomized controlled trials (RCTs) (ClinicalTrials.gov numbers respectively
236 NCT01044082, NCT01113229, and NCT02302456), respectively approved by the Paris-Ile de
237 France III Committee for the Protection of Research Subjects in September 2009 (n°B90885-
238 20), by the Ethics Committee of Poissy Saint-Germain Hospital on October 20, 2009 (n°09049),
239 and by the West II Committee for the Protection of Research Subjects on August 21, 2014
240 (2014/09) associated with the approval of the French Health Products Safety Agency on
241 August 6, 2014 (2014-001748-39). All individuals provided written informed consent to
242 participate in each trial. Participants were not involved in the development of the research.

243

244 These three French RCTs were multicenter and intended to compare an intervention
245 for the prevention of blood loss after vaginal delivery (controlled cord traction [yes/no] for
246 TRACOR⁴² in 2010-2011) or a drug (misoprostol versus placebo for CYTOCINON⁴³ in 2010-
247 2013; tranexamic acid versus placebo for TRAAP⁴⁴ in 2015-2016) in several French maternity
248 units (five in TRACOR, three in CYTOCINON, and 15 in TRAAP; some hospitals participated in
249 one, two, or three of them). None showed a significantly lower PPH rate in the intervention
250 group.⁴²⁻⁴⁴ The TRAAP and CYTOCINON trials were modelled on TRACOR with a similar
251 methodology, in particular, their inclusion and exclusion criteria, methods for assessing blood

252 loss, and outcome definitions. Except for the intervention tested, practices related to the
253 management of the third stage of labor were similar among the participating centers, with a
254 routine prophylactic intravenous injection of oxytocin (5 or 10 IU) at delivery of the anterior
255 shoulder; practices for the management of PPH were also similar and consistent with national
256 guidelines.^{6, 45} Participants were individuals ≥ 18 years who gave birth vaginally to a singleton
257 live fetus at 35 or more weeks of gestation; individuals were excluded if they had placenta
258 previa, coagulation disorders, an in utero fetal death, multiple gestation, or if they did not
259 understand French. All three trials measured the volume of blood loss by using a graduated
260 (100 mL graduation) collector bag placed just after delivery of the child and kept in place until
261 the birth attendant considered that the bleeding had stopped (a minimum of 15 minutes for
262 all).^{42-44, 46} Externalization of the amniotic fluid was achieved before the bag was placed and
263 the birth attendant transferred the blood from blood-soaked gauze swabs into the graduated
264 collector bag by squeezing them.

265

266 *Outcomes*

267

268 In this study, the two primary outcomes were postpartum blood loss assessed by two
269 methods, QBL and CBL. QBL was defined by the total volume of blood loss in the graduated
270 collector bag when removed. CBL was defined by the following formula: estimated blood
271 volume \times [(antepartum hematocrit – postpartum hematocrit)/antepartum hematocrit],
272 where estimated blood volume (mL) = booking weight (kg) \times 85.^{36, 38} In France, two blood
273 counts are routinely performed during pregnancy, one between the fifth and seventh months
274 to detect anemia, and one in the eighth or ninth month, before the mandatory
275 anesthesiologist visit. In our CBL formula, the antepartum hematocrit measurement refers in

276 the first place to that measured at the eighth or ninth month. This hematocrit was considered
277 to best reflect the maternal status, compared with the blood sample taken in the delivery
278 room before delivery, which is not performed routinely in France at vaginal birth but only in
279 situations that are probably not physiological and therefore subject to indication bias. If not
280 available from the eighth or ninth month, antepartum hematocrit was that measured
281 between the fifth and seventh month. If this was unavailable, we used that measured in the
282 delivery room, if available. Postpartum hematocrit was measured on day 2 after delivery
283 according to the trial protocols.^{42, 43, 46} If missing, it was measured on day 3. If no blood sample
284 was available from day 2 or 3, postpartum hematocrit was assessed from a day-1 blood sample
285 if available.^{42, 43, 46} In individuals transfused before planned postpartum hematocrit
286 measurement, the value of the postpartum hematocrit reflecting blood loss was estimated as
287 follows: value of the hematocrit measured after transfusion (%) – (3 × number of red blood
288 cell units transfused).^{47, 48}

289

290 *Statistical analysis*

291

292 We described the characteristics of our study population, as well as those of individuals
293 who had a missing value for the primary outcomes, whether QBL or CBL, who thus could not
294 be included in our analysis. We calculated and compared the incidence of abnormal blood loss
295 based on QBL and CBL according to three thresholds of blood loss: ≥ 500 mL, ≥ 1000 mL and \geq
296 2000 mL.

297 We described the distribution of QBL and CBL in the whole study population. We
298 calculated Spearman correlation coefficient to analyze the correlation between positive QBL
299 and CBL. Indeed, individuals with QBL values equal to zero mL and CBL values less than or

300 equal to 0 mL were clinically implausible and therefore were excluded from this analysis. We
301 used a polynomial regression model to estimate the predicted QBL according to the CBL in the
302 population of individuals with strictly positive values of QBL and CBL. We further explored the
303 relation between QBL and CBL by plotting a Bland-Altman plot of difference between QBL and
304 CBL against the mean of the two blood loss assessment methods.⁴⁹

305

306 We conducted several sensitivity analyses. First, to explore the potential impact of
307 variations in the calculation method of CBL, we compared the distribution of CBL calculated
308 with two other previously published formulas:^{25, 37, 39, 50}

- 309 - CBL Formula 2: estimated blood volume \times [(antepartum hematocrit – postpartum
310 hematocrit)/antepartum hematocrit], where estimated blood volume (mL) = $0.75 \times$
311 $[(\text{height (inches)} \times 50) + (\text{booking weight (pounds)} \times 25)]$,^{25, 39}
- 312 - CBL Formula 3: estimated blood volume \times [(antepartum hematocrit – postpartum
313 hematocrit)/antepartum hematocrit], where estimated blood volume = 2680 mL/m^2 of
314 body surface area and body surface area (m^2) = $0.0071843 \times \text{booking weight (kg)}^{0.4253}$
315 $\times \text{height (cm)}^{0.725}$.^{37, 50}

316 Second, we conducted the analyses within four different subpopulations of individuals to
317 assess the impact of options taken for the calculation of CBL on the relation between QBL and
318 CBL: (i) in the whole population including individuals with QBL values equal to zero mL and
319 CBL values less than or equal to 0 mL, (ii) among individuals with antepartum hematocrit
320 measured at the eighth or ninth month of pregnancy, (iii) among individuals with antepartum
321 hematocrit measured at admission in the delivery room before delivery, (iv) and among
322 individuals without any transfusion between delivery and postpartum blood sample. The chi-
323 square test was used to compare proportions. The medians of paired continuous observations

324 were compared with the sign test. $P < .05$ was considered statistically significant. Analyses
325 were completed with STATA software v14.1 (StataCorp, College Station, TX).

326 Results

327

328 *Population description*

329

330 Among the pooled population of the three trials, 12.7% (1211/9552) had a missing
331 value for either QBL or CBL and were excluded. Our study population comprised 8341
332 individuals with a vaginal delivery (Fig. 1). Their mean age was 30.2 (± 5.0) years. They were
333 mainly of European origin (82.5%) and nulliparous (53.8%); 7.4% were obese. Overall, 5.5%
334 had a previous caesarean and 3.4% a previous PPH. Nearly 20% had labor induced, and less
335 than 20% had an operative vaginal delivery. Almost all — 98.4% — received a prophylactic
336 injection of oxytocin. The postpartum blood loss was collected in the collector bag for a
337 median duration of 27 minutes (interquartile range [IQR] 17-39) (Table 1). The characteristics
338 of individuals excluded for missing values for QBL or CBL were similar to those of the study
339 population (Table 1). No individuals were transfused before delivery.

340

341 *Distribution of QBL and CBL*

342

343 The distribution of QBL did not follow a normal curve (Fig. 2.A). Mean QBL was 211 mL
344 (± 252) and median QBL 100 mL (IQR, 50-275) with a range of 0 mL to 6000 mL (Fig. 2.A). The
345 CBL distribution pattern was close to normal with a mean value of 319 mL (± 615), a median
346 value of 260 mL (IQR, 0-630) and a range of -3023 mL to 8138 mL (Fig. 2.B). QBL was equal to
347 0 mL for 2.0% of individuals (165/8341). CBL was equal to 0 mL for 11.3% of individuals
348 (940/8341) and was less than 0 mL for 23.5% of individuals (1958/8341), including 1.1% of
349 individuals (89/8341) with both QBL equal to 0 mL and CBL ≤ 0 mL. Negative values of CBL

350 were explained by a postpartum hematocrit value higher than their antepartum value. More
351 than 99% (1939/1958) of individuals with negative CBL had a QBL less than or equal to 500
352 mL.

353

354 *Association between QBL and CBL*

355

356 Figure 3 shows the distribution of individual positive values of both QBL and CBL (64.3%
357 of individuals (5367/8341)). The correlation between QBL and CBL was statistically significant
358 but moderate, with a Spearman coefficient equal to 0.44 ($P<.001$). The association between
359 QBL and CBL was not linear, in particular for high volumes, with a difference between QBL and
360 CBL that tended to increase as CBL rose. QBL values predicted by polynomial regression were
361 always lower than observed CBL values (Fig. 3). The Bland-Altman plot shows a mean
362 difference (bias) of -370 mL between QBL and CBL with a difference that tended to increase
363 with blood loss (Fig. 4).

364

365 *Incidence of abnormal blood loss*

366

367 The incidence of abnormal blood loss was lower with QBL than CBL for all three
368 thresholds considered ($P<.05$): ≥ 500 mL, respectively 9.6% (799/8341) and 32.3%
369 (2691/8341); ≥ 1000 mL, 2.1% (176/8341) and 11.5% (959/8341); and ≥ 2000 mL, 0.1%
370 (10/8341) and 1.4% (117/8341) (Fig. 2).

371

372 *Sensitivity analyses*

373

374 The distribution of CBL was similar regardless of the calculation formula used (Fig. A.1).
375 In the four subpopulations of individuals, (i) all individuals, (ii) individuals with antepartum
376 hematocrit measured at the eighth or ninth month, (iii) individuals with antepartum
377 hematocrit measured in delivery room and (iv) individuals without any transfusion, the
378 analysis of the relation between QBL and CBL yielded results similar to the main analysis (Figs.
379 A.2, A.3, A.4, A.5). In particular, negative CBL values occurred in 14.9% of individuals
380 (257/1723) in the subgroup of individuals with antepartum hematocrit measured in the
381 delivery room before delivery (Fig. A.4).

382

383 **Comment**

384

385 *Principal Findings*

386

387 In this large population of individuals with vaginally delivered singleton live fetuses at
388 35 or more weeks of gestation, QBL and CBL were significantly but moderately correlated.
389 Their relation was not linear. Median QBL (100 mL, IQR 50-275) was significantly lower than
390 median CBL (260 mL, IQR, 0-630) with a difference that tended to increase with blood loss.
391 Thus, the incidence of abnormal blood loss was lower with QBL than CBL for each standard
392 blood loss threshold. Negative CBL values occurred in 23% of individuals, more than 99% of
393 whom had a QBL of 500 mL or less.

394

395 *Results in the Context of What is Known*

396

397 To our knowledge, few studies have compared measured or visual estimated blood
398 loss with CBL, and they all had methodological limitations related mainly to their small sample
399 size, single-center design, and failure to detail how blood loss was collected.^{25, 39, 40, 51} We
400 found that median measured QBL was significantly lower than median CBL, which provides
401 robust evidence to support the results of 2 previous single-center studies in the USA.^{25, 39}
402 However, in these studies CBL was compared to visually estimated blood loss which cannot
403 be rigorously compared to our QBL outcome.^{25, 39} In a sample of 446 individuals with vaginal
404 deliveries, Stafford et al. reported a median visually estimated blood loss of 250 mL (IQR, 200-
405 350), lower than the 574 mL (IQR, 237-903) median CBL.²⁵ Similarly, Conner et al. found a
406 median estimated blood loss of 300 mL (IQR, 300-350), in their single-center prospective

407 cohort of 3969 individuals with vaginal deliveries, lower than the median CBL of 442 mL (IQR,
408 210-751).³⁹ An original finding of our study is the non-linear relationship between QBL and
409 CBL,^{39, 51} with the difference between the two measures tending to rise as blood loss increases.
410 This result reinforces the point made in the earlier study by Gharoro et al. of a small
411 prospective cohort of 211 deliveries in Benin.⁵¹ It is important to know that the gap between
412 the two measures is greater in the abnormal ranges of postpartum blood loss. This non-linear
413 relationship between QBL and CBL was not highlighted by Kahr et al. who found a good
414 correlation between QBL and CBL (Pearson coefficient equal to 0.68) in a small single-center
415 prospective study of 461 vaginal deliveries.⁴⁰ However, their results were limited by the lack
416 of standardization for the CBL assessment with possible different timings for the postpartum
417 blood samples.⁴⁰
418 Interestingly, we found that negative values of CBL existed and occurred in 23% of individuals.
419 These cases were not mentioned in the study by Stafford et al.²⁵ and were excluded by Conner
420 et al., although they represented nearly one third of the population.³⁹ Gharoro et al. pointed
421 out that they occurred only in individuals with visually estimated blood loss less than 500 mL.⁵¹
422 These negative CBL values can be partially explained by the timing of antepartum and
423 postpartum hematocrit, as discussed below, and possibly physiological peripartum changes
424 including hemoconcentration and autotransfusion.⁵²

425

426 *Clinical Implications*

427

428 After vaginal delivery, the ongoing assessment of blood loss should remain
429 quantitative to guide daily practice with the use of direct measurement of blood loss (QBL).³⁰

430 Clinicians should be aware that there are differences between QBL and CBL, with QBL lower

431 than CBL, and these differences tend to increase with blood loss. However, these findings may
432 not apply to the cesarean context and would merit further assessment.⁵³

433 By definition, CBL, only available here two days after delivery, is not a clinical tool useful for
434 guiding management of individuals with an ongoing PPH. To our knowledge, there are no data
435 in the obstetrics setting on real-time measurement of CBL by direct measurements of
436 hematocrit levels from capillary (e.g., finger prick) blood samples.

437

438 *Research Implications*

439

440 CBL is mainly interesting for research purposes but its usefulness remains to be
441 demonstrated. It offers an objective assessment of blood loss in comparative trials, in contrast
442 to the limitations of clinical markers of blood loss or intervention-based outcomes (such as
443 additional uterotonic use, transfusion, second-line therapy, surgery), all likely to vary by
444 provider judgment, organization of care, and resource availability. This aspect is underlined in
445 the core outcome set recently developed for studies evaluating interventions for PPH.⁵⁴
446 Moreover, the finding that the difference between QBL and CBL tends to increase with blood
447 loss suggests that CBL could be a complementary relevant outcome without the limitations of
448 clinically-assessed blood loss-related outcomes, such as QBL, known to underestimate high
449 volumes of blood loss.²⁵ Nevertheless, one issue of combining different approaches to assess
450 blood loss in intervention trials is that interpretation may be challenging in case of conflicting
451 results. Thus, our results advocate against combining QBL and CBL within a single so called
452 'blood loss' outcome in research studies or meta-analyses.

453 Negative CBL values, by definition clinically impossible, appear inherent in the CBL indicator
454 whatever the formula used for the calculation, likely related to incompressible variability of

455 hematocrit. Although it appears that these negative CBL values were found in women with
456 low QBL, this is an important limitation and advocates for not using CBL as the only blood loss
457 outcome in research studies. We also found in our exploratory analysis that hematocrit
458 measured in the delivery room before delivery did not satisfactorily control for this limitation
459 with still 15% negative CBL values (Fig. A.4)

460 Further studies could evaluate the added value of blood loss assessment by CBL in other
461 populations, especially those for whom QBL is considered even more subjective and less
462 accurate — individuals with cesarean deliveries or severe PPH. Thus, interventional trials and
463 prospective studies related to PPH prevention or treatment might be encouraged to provide
464 clinical but also laboratory blood loss markers to help providers interpret the generalizability
465 of their results. Finally, automated tools for real-time quantification of postpartum blood loss
466 are under development and need to be evaluated.⁵⁵⁻⁵⁷

467

468 *Strengths and Limitations*

469

470 The main strength of our study is its large population, including individuals from three
471 recent multicenter RCTs with reliable data collection, focused on postpartum blood loss and
472 reflecting current obstetric practices.⁴²⁻⁴⁴ Except for the intervention tested (without
473 significant effect on PPH incidence), the third stage of labor was managed similarly for all
474 individuals. QBL and CBL were assessed similarly within the three trials, with blood loss
475 collected in a collector bag for the former, with a postpartum hematocrit on day 2 for 97%
476 (8069/8341) of the individuals for the latter. Volume resuscitation during and after delivery
477 may alter maternal physiologic blood volume changes and modify hematologic values in
478 particular through hemodilution.^{58, 59} We acknowledge that information on hydration status

479 and loading volumes during and after delivery was not available in our study. Nevertheless,
480 contrary to the majority of studies comparing measured or visual estimated blood loss and
481 CBL for which CBL was assessed few hours after delivery, CBL was measured on day 2, limiting
482 the risk of bias measurement of CBL in our study.^{25,39}

483 Nevertheless, this study has several limitations. The generalizability of our results is
484 limited for high blood loss volumes, given the low number of individuals in this range which
485 should lead to confirm the curvilinear relationship between QBL and CBL. Despite the efforts
486 to standardize the QBL, we acknowledge that QBL was assessed until the birth attendant
487 judged that bleeding had stopped and may be underestimated by missing occult blood loss
488 that may occur after bag removal.⁶⁰ Similarly, despite the efforts to standardize the CBL, there
489 was still heterogeneity in the timing and place of antepartum hematocrit measurements as
490 they were part of routine antenatal care. However, antepartum hematocrit was measured
491 during the eighth or ninth month in 87% (7255/8341) of individuals – routinely performed
492 blood sample during pregnancy in France and then not subject to indication bias –, and the
493 sensitivity analysis limited to this subgroup of individuals yielded results similar to the main
494 analysis. Another limitation of our study was the 12.7% of missing data for blood loss (QBL or
495 CBL); however, the similarity of the characteristics of individuals with missing blood loss data
496 to those of individuals included in our study suggests the risk of selection bias is limited.

497

498 *Conclusion*

499

500 In this large study of individuals with vaginal deliveries we found that quantitative and
501 calculated blood loss were significantly but moderately correlated. Median QBL was lower

502 than median CBL, and the difference tended to increase with blood loss. Negative values of
503 CBL occurred but corresponded almost always to low QBL values of less than 500 mL.

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670 **Table 1. Maternal, labor, and delivery characteristics of individuals in the study population**
 671 **and of those excluded because of a missing value for quantitative or calculated blood loss**

Characteristics	Study population (N=8341)	Individuals excluded because of a missing value for QBL or CBL (n=1211) ^a
Maternal characteristics		
Age (years)	30.2 ± 5.0	31.0 ± 5.1
Geographic origin		
European	6,727 (82.5)	950 (81.8)
North Africa	669 (8.2)	104 (8.9)
Sub-Saharan Africa	307 (3.8)	45 (3.9)
Asia	172 (2.1)	21 (1.8)
French overseas territories	144 (1.8)	25 (2.1)
Other	128 (1.6)	17 (1.5)
Body mass index before pregnancy (kg/m ²)		
< 18.5	604 (7.3)	84 (7.3)
18.5-24.9	5,688 (68.4)	793 (68.9)
25-29.9	1,405 (16.9)	186 (16.2)
≥ 30	616 (7.4)	88 (7.6)

Chronic hypertension	54	(0.7)	15	(1.3)
Pre-existing diabetes	42	(0.5)	5	(0.4)
Nulliparous	4,489	(53.8)	632	(52.5)
History of caesarean section	459	(5.5)	73	(6.1)
History of PPH	280	(3.4)	41	(3.4)

Labor and delivery characteristics

Labor induction	1,650	(19.8)	245	(20.3)
Spontaneous delivery	6,814	(81.7)	954	(78.8)
Operative vaginal delivery	1,527	(18.3)	257	(21.2)
Prophylactic oxytocin	8,210	(98.4)	1,163	(97.3)
Perineal trauma 3rd/4th degree	114	(1.4)	20	(1.7)
Additional uterotonic due to bleeding	634	(7.6)	94	(7.8)
Transfusion	59	(0.7)	10	(0.8)
Second-line interventions for PPH ^b	38	(0.5)	8	(0.7)
Duration of collector bag ^c	27	[17-39]	29	[18-42]
Available measurement of antepartum hematocrit				
5 th -7 th month hematocrit	4248	(50.9)	307	(25.4)
8 th -9 th month hematocrit	7255	(87.0)	619	(51.1)

Delivery room hematocrit	1723	(20.7)	114	(9.4)
Antepartum hematocrit (%) ^d	35.5	± 2.8	35.1	± 2.9
5 th -7 th month hematocrit (%)	34.2	± 2.7	34.1	± 2.8
8 th -9 th month hematocrit (%)	35.5	± 2.8	35.2	± 2.9
Delivery room hematocrit (%)	36.1	± 3.0	35.2	± 3.4
Postpartum hematocrit (%) ^e	33.3	± 4.2	33.2	± 4.2
Day-1 hematocrit (%)	30.6	± 4.4	30.8	± 4.7
Day-2 hematocrit (%)	33.4	± 4.0	33.3	± 4.1
Day-3 hematocrit (%)	31.3	± 5.1	33.6	± 3.1

672

673 Data are presented as numbers and percentages, and otherwise as means ± standard

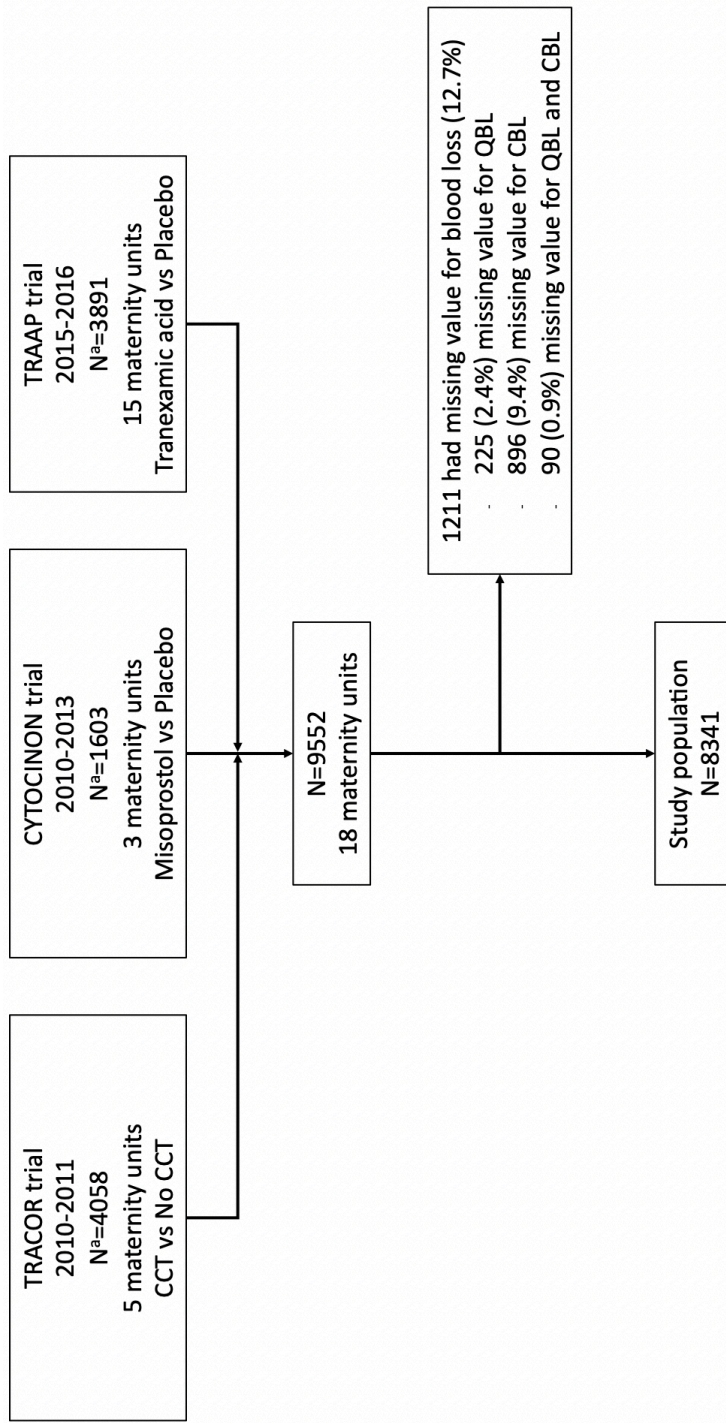
674 deviations.

675 QBL: Quantitative blood loss; CBL: Calculated blood loss; PPH: Postpartum hemorrhage.

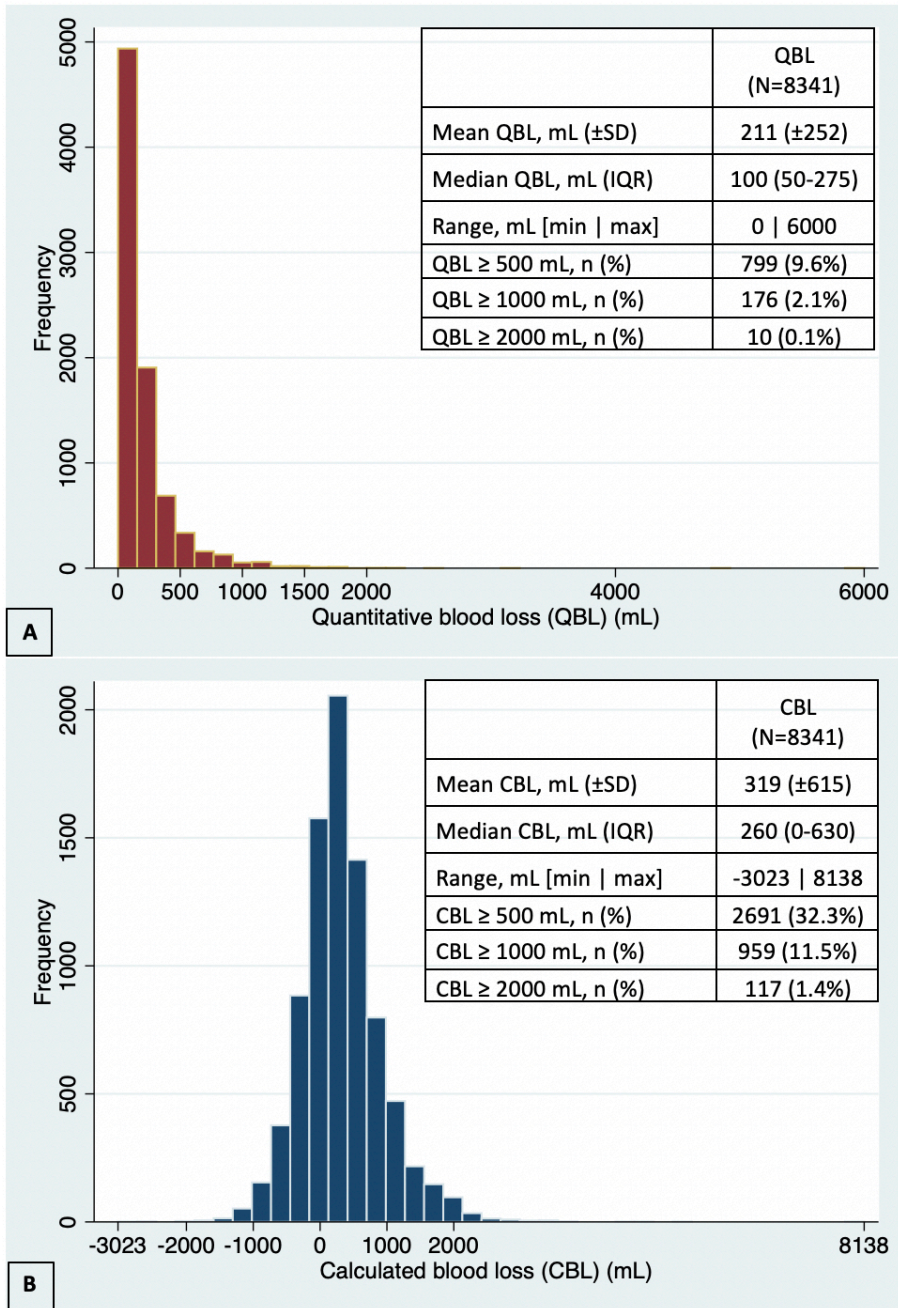
676 ^a 225 individuals had a missing value for QBL, 896 for CBL, and 90 for both QBL and CBL.677 ^b intrauterine tamponade, pelvic arterial embolization, vessel ligation, uterine compression
678 sutures, hysterectomy.679 ^c duration of collector bag presented as median with its interquartile range.680 ^d Among the study population, antepartum hematocrit refers to that measured at the eighth
681 or ninth month for 7,255 (87.0%) individuals, to that measured between the fifth and
682 seventh month for 772 individuals (9.2%) and to that measured in the delivery room for 314
683 individuals (3.8%)

684 ^e Among the study population, postpartum hematocrit refers to that measured at day-2 for
685 8069 (96.7%) individuals, to that measured at day-3 for 77 individuals (1.0%) and to that
686 measured at day-1 for 195 individuals (2.3%)

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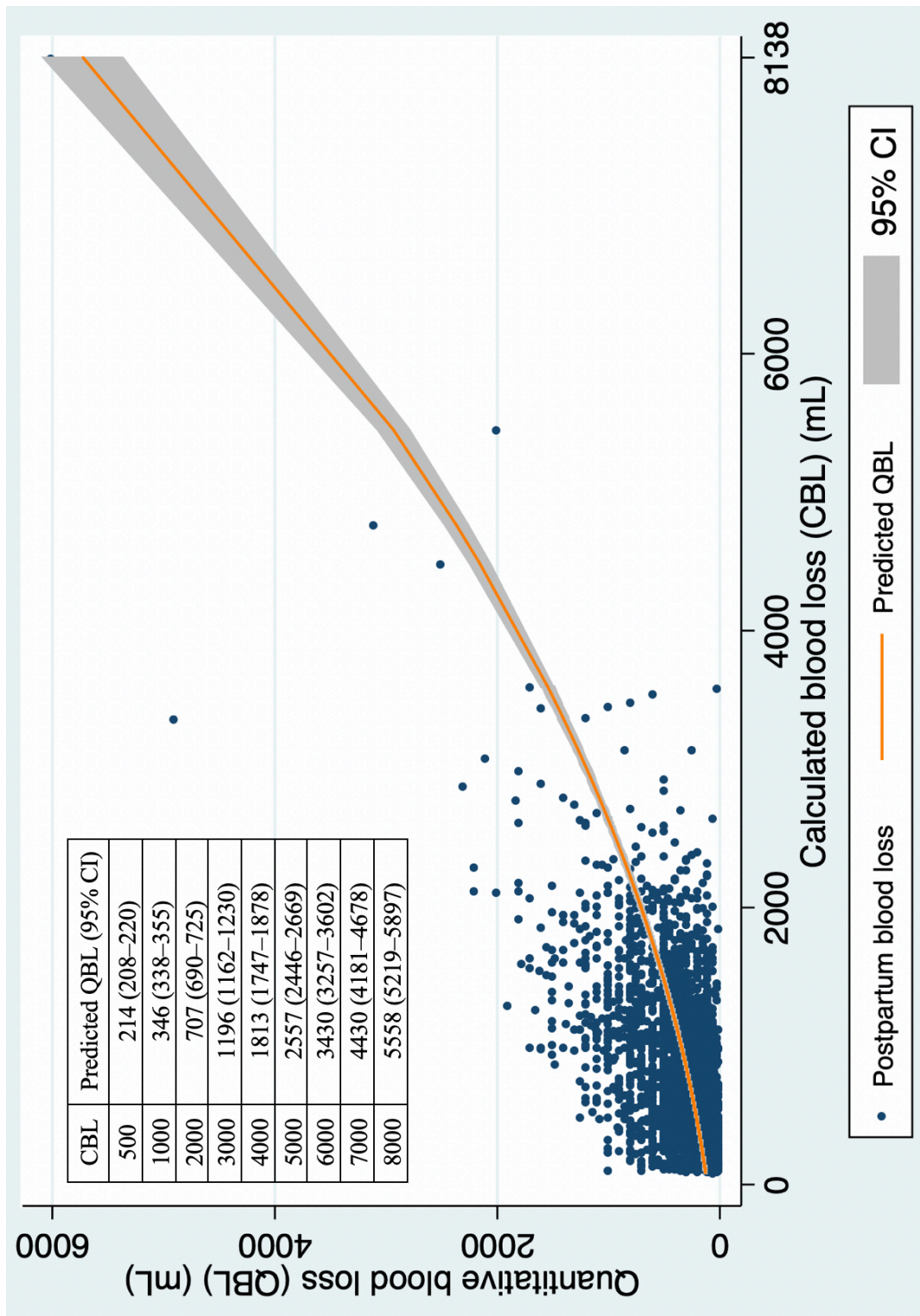
691 **Figure 2**



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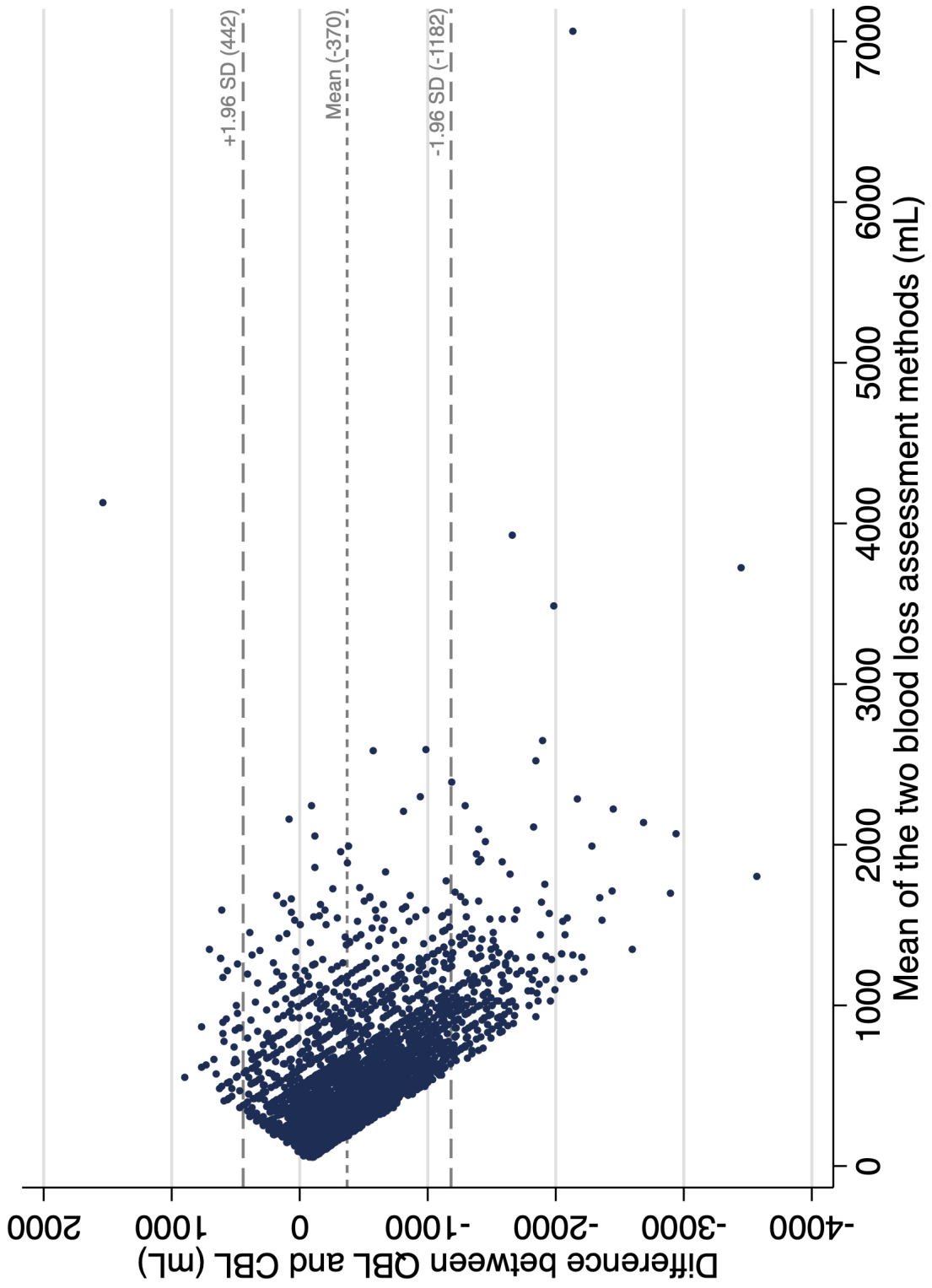
694 **Figure 3**



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697 Figure 4



699 **Figure legends**

700

701 **Figure 1. Flowchart of the study population**

702 ^a N corresponds to the intention-to-treat population in each trial.

703 TRACOR: Traction of the cord; CYTOCINON: Combined use of oxytocin and misoprostol in the

704 prevention of postpartum hemorrhage; TRAAP: Tranexamic acid for preventing postpartum

705 hemorrhage following a vaginal delivery; CCT: Controlled cord traction; QBL: Quantitative

706 blood loss; CBL: Calculated blood loss.

707

708 **Figure 2. Distribution of quantitative and calculated blood loss**

709 A: Distribution of quantitative blood loss.

710 B: Distribution of calculated blood loss.

711 QBL: quantitative blood loss; SD: Standard deviation; IQR: Interquartile range; Calculated

712 blood loss.

713

714 **Figure 3. Correlation between quantitative blood loss and calculated blood loss among**
715 **individuals with positive values of QBL and CBL.**

716 Polynomial regression model to estimate the predicted quantitative blood loss according to

717 calculated blood loss. Values of predicted quantitative blood loss with 95% confidence

718 interval according to fixed values of calculated blood loss.

719 Regression equation: $QBL = 113.5 + 169.0 * CBL + 63.9 * CBL^2$

720 Spearman coefficient: 0.44 (P<.001)

721 QBL: Quantitative blood loss; CBL: Calculated blood loss; CI: Confidence interval.

722

723 **Figure 4. Bland-Altman plot of difference between quantitative blood loss and calculated**
724 **blood loss against the mean of the two blood loss assessment methods among individuals**
725 **with positive values of QBL and CBL.**

726 Bias is represented by a short-dashed grey line, 95% limits of agreement are indicated by
727 long-dashed grey lines.

728 95% Confidence interval of the lower limit of agreement (-1.96 standard deviation): [-1202 ; -
729 1164]

730 95% Confidence interval of the upper limit of agreement (+1.96 standard deviation): [423 ;
731 461]

732 95% Confidence interval of the mean difference: [-381 ; -359]

733 QBL: Quantitative blood loss; CBL: Calculated blood loss; SD: Standard deviation

734

735

736 **Appendix A. Supplemental material**

737

738 **Figure A.1. Distribution of calculated blood loss according to different formulas**

739

740 **Figure A.2. Correlation between quantitative blood loss and calculated blood loss for all**
741 **individuals including individuals with QBL values equal to zero mL and CBL values less than**
742 **or equal to 0 mL**

743

744 **Figure A.3. Correlation between quantitative blood loss and calculated blood loss only for**
745 **individuals with antepartum hematocrit measured at the eighth or ninth month of**
746 **pregnancy**

747

748 **Figure A.4. Correlation between quantitative blood loss and calculated blood loss for**
749 **individuals with antepartum hematocrit measured in the delivery room**

750

751 **Figure A.5. Correlation between quantitative blood loss and calculated blood loss for**
752 **individuals without transfusion between delivery and postpartum blood sample**

753