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1 **Conservative Management or Cesarean Hysterectomy for Placenta Accreta Spectrum:**
2 **the PACCRETA Prospective Study**

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74

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77

78 **Condensation**

79 Conservative management was associated with a lower incidence of more than 4 units of
80 packed red blood cells within 6 months compared with cesarean-hysterectomy.

81

82 **Short title:** Conservative management or cesarean hysterectomy for placenta accreta
83 spectrum

84

85 **AJOG at a Glance:**

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

87 Cesarean-hysterectomy in women with placenta accreta spectrum is widely practiced but its
88 maternal outcomes have not been thoroughly compared with conservative management.

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

90 Compared with cesarean-hysterectomy, conservative management was associated with lower
91 rates of more than 4 units of packed red blood cells, hysterectomy, total estimated blood loss
92 exceeding 3000 ml, any blood product transfusion, adjacent organ injury, and with higher
93 rates of embolization, endometritis, and readmission within 6 months.

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

95 This large prospective multicenter study using propensity-score weighting to account for
96 potential indication bias suggests that conservative management compared with cesarean-
97 hysterectomy is associated with lower rates of severe bleeding and hysterectomy, but with
98 higher rates of embolization and endometritis within 6 months.

99

100

101 **Abstract**

102 **Background:** Placenta accreta spectrum is a life-threatening condition that has increased
103 dramatically in recent decades alongside cesarean rates worldwide. Cesarean-hysterectomy in
104 women with placenta accreta spectrum is widely practiced but its maternal outcomes have not
105 been thoroughly compared with alternatives such as conservative management.

106 **Objective:** Our objective was to compare severe maternal outcomes in women with placenta
107 accreta spectrum treated by a cesarean-hysterectomy and those by conservative management
108 leaving the placenta in situ.

109 **Study design:** From a source population of 520,114 deliveries in 176 hospitals (PACCRETA
110 study), we designed an observational cohort of women with placenta accreta spectrum who
111 had either a cesarean-hysterectomy or conservative management (placenta left in situ) during
112 cesarean delivery. Clinicians prospectively identified women meeting the inclusion criteria
113 and included them at delivery. Data collection started only after women had received
114 information and agreed to participate in the study in the immediate postpartum period. The
115 primary outcome was the transfusion of more than 4 units of packed red blood cells within 6
116 months postpartum. Secondary outcomes were other maternal complications within 6 months.
117 We used propensity-score weighting to account for potential indication bias.

118 **Results:** 86 women had conservative management and 62 cesarean-hysterectomy for placenta
119 accreta spectrum during cesarean delivery. The primary outcome occurred in 14 of 86 women
120 in the conservative management group (16.3%) and 36 of 61 (59.0%) in the cesarean-
121 hysterectomy group (risk ratio in propensity score weighted model, 0.29; 95% confidence
122 interval 0.19 to 0.45). Rates of hysterectomy, total estimated blood loss exceeding 3000 ml,

123 any blood product transfusion, adjacent organ injury, and non-postpartum hemorrhage-related
124 severe maternal morbidity were lower with conservative management than with cesarean-
125 hysterectomy (all adjusted, $P \leq 0.02$); rates of arterial embolization, endometritis, and
126 readmission within 6 months of discharge were higher.

127 **Conclusion:** Among women with placenta accreta spectrum and cesarean delivery, compared
128 with cesarean-hysterectomy, conservative management was associated with a lower risk of
129 transfusion of more than 4 units of packed red blood cells within 6 months.

130 **Key words:** placenta accreta spectrum, cesarean-hysterectomy, conservative management,
131 postpartum hemorrhage, transfusion.

132

133

134 **Introduction**

135 Placenta accreta spectrum (PAS) is defined by trophoblast invasion into the myometrium
136 where villous tissue attaches (placenta accreta) or penetrates (placenta increta) the
137 myometrium and sometimes reaches and penetrates the uterine serosa or an adjacent organ
138 (placenta percreta).¹ It can cause heavy blood loss during delivery and is thus associated with
139 such severe maternal morbidity as massive transfusion, hysterectomy, coagulopathy,
140 multisystem organ failure, and death.^{1,2} The incidence of this life-threatening condition has
141 increased dramatically in recent decades alongside cesarean rates worldwide; it ranges from
142 1.7 to 4.6 per 10,000 deliveries in prospective population-based studies.³⁻⁵

143 Cesarean-hysterectomy is considered the principal and preferred option for delivery for
144 women with PAS.^{1,6-8} Nevertheless, some authors have proposed alternative approaches,
145 globally called "conservative management" with the primary aim of decreasing maternal
146 morbidity and the secondary aim of preserving the woman's uterus and thus her fertility.^{1,2,9-17}
147 One of these approaches involves leaving the placenta in situ, that is, totally or partially inside
148 the uterus awaiting complete resorption.^{1,2,9-15} A retrospective multicenter study of 167
149 women with PAS managed with this approach reported that while 6% had severe maternal
150 morbidity, in particular delayed infection or bleeding, only 42% had transfusions, and 78%
151 avoided a hysterectomy.¹¹ Follow-up showed that some of them became pregnant and had
152 healthy children.¹² Accordingly, some experts recommend leaving the placenta in situ as a
153 possible strategy, especially for women wishing to preserve their fertility.^{15,18-21} Nevertheless,
154 only three small retrospective single-center studies have compared maternal outcomes for
155 women managed by either cesarean-hysterectomy or leaving the placenta in situ; their results
156 showed better outcomes for the latter, but their study designs had important limitations.²²⁻²⁴
157 The feasibility of recruiting women for a large randomized controlled trial to determine the

158 safest management for this rare life-threatening condition seems improbable. Observational
159 population-based cohort studies offer the best compromise for assessing outcomes associated
160 with the planned mode of delivery in an unselected population of women with this disorder.
161 We conducted this prospective multiregional study to compare severe maternal outcomes in
162 two groups of women with PAS: those treated by a cesarean-hysterectomy and those by
163 conservative management leaving the placenta in situ. Propensity score analysis was used to
164 ensure the comparability of the study groups and to minimize selection bias.

165

166 **Methods**

167 **Study Design**

168 The PACCRETA study was a multiregional observational study conducted in 8 regions and
169 176 maternity units in France.²⁵ Its aim was to include women at risk of PAS to investigate
170 population-based incidence of PAS, characteristics of women, clinical profiles, prenatal
171 detection, maternal outcomes according the management; the large majority of data of PAS
172 before 2013 coming from retrospective studies of referral centers that may bias those
173 outcomes.^{2,5,25} Women eligible for the cohort had a stillbirth or live-born infant at or after 22
174 weeks of gestation between November 1, 2013, and October 31, 2015, and either PAS or the
175 combination of a low-lying placenta or placenta previa with at least one previous cesarean.
176 Clinicians prospectively identified women meeting the inclusion criteria and included them at
177 delivery. Data collection started only after women had received information and agreed to
178 participate in the study in the immediate postpartum period. Clinical research midwives
179 consulted the delivery logbook and computerized databases at each center to verify
180 exhaustiveness. Details of the rationale and design of the cohort study have been published
181 previously.^{5,26} The PACCRETA study was funded by the French Health Ministry under its

182 Hospital Clinical Research Program and by the Angers University Hospital. The funders had
183 no role in the study design, data collection and analysis, decision to publish, or preparation of
184 the manuscript. The Committee for the Protection of Patients (AOR12156), the Consultative
185 Committee on the Treatment of Personal Health Data for Research Purposes, and the National
186 Data Protection Authority (CNIL n° DR-2013-427) approved the study protocol. The source
187 population was 520,114 deliveries, that is, about 30% of all deliveries in France during the
188 two-year study period, with characteristics similar to the national profile of parturients.^{5,26}

189

190 **Study population**

191 This study included women in the PACCRETA cohort with PAS who had a cesarean delivery
192 and either conservative management (defined by the obstetrician's decision to leave the
193 placenta partially or totally in situ) or a cesarean-hysterectomy, with or without attempted
194 placental removal. We excluded women with vaginal deliveries to ensure comparability
195 between the two groups, as well as women with cesareans who were not treated by either
196 conservative management or cesarean-hysterectomy.

197 PAS was defined by the presence of at least one among the following clinical or histological
198 criteria:²⁵ 1) partial or total impossibility of manual removal of the placenta and no cleavage
199 plane between part or all of the placenta and the uterus; 2) massive bleeding from the
200 implantation site after forced placental removal and no other cause of postpartum
201 hemorrhage; 3) histological confirmation of PAS on a hysterectomy specimen; and 4) finding
202 signs of PAS at laparotomy in women with suspected PAS on prenatal imaging. All
203 histological reports of hysterectomy specimens were reviewed by a senior pathologist with
204 specific expertise in PAS histopathology (SP). All women were followed up until six months
205 postpartum.

206

207 **Study outcomes**

208 The primary outcome was the incidence of women transfused with more than 4 units of
209 packed red blood cells within 6 months postpartum. We chose this outcome as primary
210 because (i) massive blood transfusion is consensually recognized as a marker of PPH-related
211 severe maternal morbidity,²⁷ (ii) this outcome appears more relevant than blood loss volume
212 that remains highly subjective in particular for high volumes,^{28,29} (iii) the incidence of this
213 outcome was reported after cesarean-hysterectomy and conservative treatment in reports^{2,11}
214 published before the beginning of the PACRRETA study,²⁵ which informed our hypotheses
215 for sample size calculation regarding this outcome (see below), and (iv) it is sufficiently
216 frequent to be able to detect a significant difference between the two groups. Moreover, other
217 outcomes possibly pertinent in the context of postpartum hemorrhage are not in the context of
218 PAS with comparison of cesarean-hysterectomy and conservative management, such as
219 hysterectomy.

220 Secondary outcome measures describing postpartum blood loss and other maternal
221 complications within 6 months were: proportion of women with estimated blood
222 loss >3000 ml (total, within and then after the first 24 hours), proportion of women who
223 underwent vessel ligation and/or uterine compression sutures, arterial embolization,
224 hysterectomy (total, primary, and delayed, the latter two defined as hysterectomy respectively
225 within and then after the first 24 hours),¹¹ any transfusion of packed red blood cells (total,
226 within and then after the first 24 hours), fresh frozen plasma, platelets, or fibrinogen, inotropic
227 agents, adjacent organ injury, septic shock defined as a positive blood culture (sepsis)
228 associated with need for vasopressors to reverse sepsis-induced hypotension,³⁰ endometritis,
229 defined as maternal fever at least 38.0°C (100.4°F) with vaginal discharge and/or pelvic pain,

230 postpartum thromboembolic events, readmission within 6 months of delivery, non-postpartum
231 hemorrhage-related severe maternal morbidity, and maternal death. Non-postpartum
232 hemorrhage-related severe maternal morbidity was a composite outcome defined as any of the
233 following within 6 months postpartum: sepsis, septic shock, peritonitis, uterine necrosis,
234 postpartum uterine rupture, fistula, injury to adjacent organs, acute pulmonary edema, acute
235 kidney failure, deep vein thrombophlebitis or pulmonary embolism, or maternal death.¹¹
236 Specific outcomes were also collected for the women treated by conservative management:
237 proportion of women lost to follow-up, women who had secondary curettage or operative
238 hysteroscopy, and the greatest diameter and vascularization of the retained tissues on
239 ultrasonography at 1-2 months and 3-6 months after delivery.
240 The obstetrician handling the delivery prospectively collected information about the
241 procedures used during surgery and the third stage of labor, and clinical outcomes identified
242 before discharge. A research assistant, independent of the local medical team, collected all
243 other data from medical charts.

244

245 **Statistical analysis**

246 The total number of deliveries expected in the participating hospitals for the PACCRETA
247 study was 540,000. We speculated that the incidence of PAS would be at least 1 in 4700
248 deliveries, for at least 115 women with this disorder.²⁵

249 Previous results justified an assumption of a 50% incidence of the primary outcome in the
250 cesarean-hysterectomy group.² To show a relative reduction of at least 50% in this incidence
251 in the conservative management group—that is, an incidence of 25% or less in this arm, a

252 hypothesis consistent with the literature,¹¹ with $\alpha = 0.05$, $1-\beta = 0.80$, and a bilateral test, the
253 study required 58 women in each group.

254 Descriptive statistics were used to compare the baseline characteristics of the study
255 participants, management, and organization during delivery before the surgical procedure.
256 Quantitative variables are expressed, as appropriate, as means with standard deviations,
257 compared by Student's t-tests, or as medians with interquartile ranges, compared by Wilcoxon
258 rank-sum tests. Chi-square or Fisher's exact tests were used as appropriate to compare
259 categorical variables.

260 In the main analysis we used inverse probability of treatment weighting based on a propensity
261 score to control for factors that might influence both management choice and outcome.^{31,32}
262 Propensity score was defined as the women's probability of having conservative management
263 based on their individual characteristics and was estimated with a multivariate logistic
264 regression model including the following covariates: age, body mass index, notable
265 preexisting condition, parity, previous curettage, number of previous cesarean deliveries,
266 placenta previa or low-lying at the last ultrasound, prenatal suspicion of PAS, multiple
267 pregnancy, and transfer to a referral center, all having the adequate resources to be considered
268 centers of excellence for PAS.³³ We assigned women who had conservative management a
269 weight of $1/(\text{propensity score})$ and those who had cesarean-hysterectomy a weight of
270 $1/(1-\text{propensity score})$. Balance among covariates was checked by using standardized
271 differences.

272 Primary and secondary outcomes were compared between the two groups and results were
273 expressed as risk ratios with 95% confidence intervals. We report results of univariate and
274 multivariate weighted log-binomial regression models adjusted for the attempted removal of

275 the placenta. This characteristic of delivery was not included in the propensity score as it is
276 one of the components of PAS management and not a baseline characteristic, but might have
277 influenced the outcome if unbalanced between the two groups.^{34,35} To avoid inflation of type I
278 error risk, we selected specific secondary outcomes for which statistical comparisons were
279 made with adjustment for multiple comparisons by the Benjamini–Hochberg procedure,
280 corrected p values were reported for them.³⁶

281 Primary and secondary outcomes were also examined in the prespecified subgroup of women
282 with prenatally suspected PAS, because this situation is a daily practice that differs from the
283 management of PAS diagnosed intraoperatively.

284 Propensity scores could not be calculated for 9 women (6.1%) due to missing data for a
285 variable included in the score. Six (7.0%) had conservative management and 3 (4.8%) had
286 cesarean hysterectomy. We used Stata software, version 15.0 (StataCorp) for all analyses.

287 Graphics were created with the R ‘ggplot2’ package.

288

289

290 **Results**

291 **Study population**

292 During the study period, 520,114 women gave birth in the 176 centers, and 660 were included
293 in the PACCRETA study. We excluded 407 women who had a low-lying placenta or placenta
294 previa associated with one previous cesarean but without PAS, 7 who declined participation
295 or were lost to follow-up, and 35 with a PAS who had vaginal deliveries. Of the remaining
296 211 women with PAS and cesarean deliveries, 63 were not treated by either conservative
297 management or cesarean-hysterectomy and were therefore excluded from this analysis (their

298 inclusion criteria for PAS, baseline characteristics, management of delivery, and maternal
299 outcomes are synthesized in Tables S1 to S3 in the Supplementary Appendix). The study
300 population accordingly included 148 women, 86 in the conservative management group and
301 62 in the cesarean-hysterectomy group (Figure 1).

302 Women receiving conservative management were significantly younger and had lower parity
303 than those with cesarean-hysterectomy (Table 1). Differences in women's characteristics
304 present at baseline were well balanced between the two groups after propensity score
305 weighting, with all standardized differences less than 10% (Figure 2).

306 During delivery, diagnosis of placenta percreta with bladder invasion at laparotomy was more
307 frequent in the conservative management than the cesarean-hysterectomy group. Inversely,
308 conversion to general after regional anesthesia and attempted placental removal occurred
309 more often in the cesarean-hysterectomy group (Table 2).

310 **Outcomes**

311 The primary outcome, transfusion of more than 4 units of red blood cells up to 6 months
312 postpartum, occurred in 14 of 86 (16.3%) women in the conservative management group and
313 36 of 61 (59.0%) in the cesarean-hysterectomy group (adjusted risk ratio (aRR), 0.29; 95%
314 confidence interval (CI), 0.19 to 0.45; in the propensity score weighted model adjusted for
315 attempted placenta removal) (Table 3). Women with conservative management compared
316 with women with cesarean-hysterectomy, had lower rates of the following outcomes:
317 hysterectomy (22.1% (19/86) versus 100% (62/62); $P < 0.001$), estimated blood loss exceeding
318 3000 ml, both total (10.7% (9/84) versus 45.8% (27/59); aRR, 0.27; 95% CI, 0.15 to 0.47;
319 $aP < 0.001$) and within 24 hours (7.1% (6/85) versus 45.8% (27/59); aRR, 0.19; 95% CI, 0.10

320 to 0.38; aP<0.001), any transfusion of blood products (38.4% (33/86) versus 86.9% (53/61);
321 aRR, 0.45; 95% CI, 0.33 to 0.63; aP<0.001), of fresh frozen plasma (30.2% (26/86) versus
322 75.4% (46/61); aRR, 0.42; 95% CI, 0.32 to 0.55; aP<0.001), of platelets (9.3% (8/86) versus
323 29.5% (18/61); aRR, 0.46; 95% CI, 0.25 to 0.84; aP=0.02) and of fibrinogen (18.6% (16/86)
324 versus 65.0% (39/60); aRR, 0.32; 95% CI, 0.22 to 0.45; aP<0.001), use of inotropic agents
325 (10.5% (9/86) versus 25.0% (15/60); aRR, 0.50; 95% CI, 0.28 to 0.91; aP=0.02), adjacent
326 organ injury (4.7% (4/86) versus 12.9% (8/62); aRR, 0.29; 95% CI, 0.11 to 0.79; aP=0.02),
327 and non-PPH related severe maternal morbidity (5.8% (5/86) versus 16.1% (10/62); aRR,
328 0.41; 95% CI, 0.19 to 0.86; aP=0.02).

329 But they had higher rates of arterial embolization (24.4% (21/86) versus 3.2% (2/62); aRR,
330 12.07; 95% CI, 3.79 to 38.38; aP<0.001), endometritis (10.8% (9/83) versus 0% (0/59);
331 P=0.02), and 6-month readmission (28.9% (24/83) versus 3.4% (2/59); aRR, 12.07; 95% CI,
332 3.90 to 37.37; aP<0.001))) (Table 3).

333 Specific follow-up outcomes in the 80 women who had conservative management without a
334 hysterectomy in the first 24 hours are described in Table S4 in the Supplementary Appendix.
335 The median greatest diameter of retained tissue was 71 mm (interquartile range, 37-108) at 1-
336 2 months post-delivery and 34 mm (interquartile range, 17-60) at 3-6 months.

337

338 **Subgroup analysis**

339 Among women with prenatally suspected PAS, baseline characteristics did not differ
340 significantly between those in the conservative management (n=58) and cesarean-
341 hysterectomy (n=33) groups (Tables S5 to S6 in the Supplementary Appendix). Differences in

342 women's characteristics present at baseline were well balanced between the two groups after
343 propensity score weighting (Figure S1 in the Supplementary Appendix). The primary
344 outcome occurred in 12 of 58 (20.7%) women in the conservative management group and 15
345 of 33 (45.5%) women in the cesarean-hysterectomy group (adjusted risk ratio, 0.58; 95% CI,
346 0.36 to 0.95). Women with conservative management had lower rates than those with
347 cesarean-hysterectomy of the following outcomes: hysterectomy, estimated blood loss
348 exceeding 3000 ml, both total and within 24 hours, any transfusion of blood products except
349 for platelets (all adjusted, $P \leq 0.03$) (Table S7 in the Supplementary Appendix). Follow-up
350 descriptive results were similar to those in the main analysis (Table S8 in the Supplementary
351 Appendix).

352 **Comment**

353 **Principal findings**

354 In this large prospective multiregional study including women with PAS, conservative
355 management was associated with lower rates than cesarean-hysterectomy of the primary
356 outcome—transfusion of more than 4 units of red blood cells—and of several secondary
357 outcomes, such as hysterectomy and total estimated blood loss exceeding 3000 ml.
358 Nevertheless, conservative treatment was also associated with higher rates of arterial
359 embolization, endometritis, and 6-month readmission than those reported after cesarean-
360 hysterectomy. These findings were consistent in the subgroup of women with prenatally
361 suspected PAS.

362 **Results in the Context of What is Known**

363 Our results are consistent with those of three small studies that reported lower mean estimated
364 blood loss and hysterectomy rates after conservative management (leaving the placenta in
365 situ) compared with cesarean-hysterectomy.²²⁻²⁴ Those findings however were weakened by
366 methodologic limitations, including the retrospective single-center design and small sample.

367 Other relevant data in the literature come from indirect comparisons based on retrospective
368 studies assessing maternal outcomes after either conservative treatment or cesarean-
369 hysterectomy.^{2,15} A previous French multicenter retrospective study of 167 women with PAS
370 managed conservatively showed the following rates: transfusion with more than 5 units of
371 packed red blood cells 15.0%, total hysterectomy 21.6%, any transfusion 41.9%, endometritis
372 9%, and severe maternal morbidity 6%.¹¹ Among the largest series assessing maternal
373 outcomes after cesarean-hysterectomy for PAS, the rate of transfusion of at least 4 units of
374 packed red blood cells ranged from 42 to 70%;^{34,37,38} bladder and ureteral injury rates ranged
375 respectively from 17 to 29% and 3.3% to 6.5%,^{34,37,38} and one study reported any transfusion
376 for 82%.³⁴ Maternal outcome rates were also similar in subgroups of women with prenatally
377 suspected PAS.^{20,34,37,38} Thus, the results for maternal outcomes are consistent with our
378 findings for the cesarean-hysterectomy group in both the main and subgroup populations.
379 These indirect comparisons all suggest the unlikelihood of bias in our groups by the inclusion
380 of the most severe PAS cases in the cesarean-hysterectomy group and less severe ones in the
381 conservative management group.

382 **Clinical Implications**

383 The trade-off between a lower risk of severe blood loss and of hysterectomy and a longer-
384 term follow-up with higher endometritis and readmission rates should be discussed with
385 women with suspected PAS to enable shared decision-making about delivery management.

386 **Research Implications**

387 Further studies are required to determine what factors predict the success or failure of
388 conservative treatment to help obstetricians/physicians identify women who would benefit
389 most from this approach.

390 **Strengths and Limitations**

391 The main strength of our study is its prospective multiregional design including a large
392 population of women with PAS; the exhaustiveness of the recruitment was checked in the 176
393 centers in all 8 regions by clinical research midwives; PAS and the outcomes were predefined.
394 PAS cases were followed up until 6 months postpartum, as part of their standard care. To
395 control for the indication bias, we performed a propensity score analysis to take into account
396 imbalance of potential confounding factors between the two groups, specifically factors
397 related to the type of treatment chosen and the maternal outcome. Finally, to limit type I error,
398 adjustment for multiplicity was performed as planned for secondary outcomes.

399 Nevertheless, this study has some limitations, most importantly the absence of histologic
400 confirmation of PAS for the cases without hysterectomies. However, this lack of histological
401 confirmation affects all studies investigating any strategy other than hysterectomy.^{1,2,9-17} The
402 prospective design, prespecified definitions, and results consistent with the literature for both
403 arms strongly suggest that the risk of selection bias is low. In addition, as there is evidence
404 that prenatal suspicion of PAS is associated with better maternal outcomes,^{30,33} we conducted
405 a subgroup analysis of women with suspected PAS. In this subgroup analysis, findings were
406 consistently similar to those in the main analysis, thereby reinforcing its reliability and
407 validity. Nevertheless, as in all observational studies, the main limitation of ours is

408 uncontrolled confounders, particularly indication bias that may persist even with the use of a
409 propensity score analysis. This is why our results still have to be interpreted with caution.

410 **Conclusions**

411 These limitations notwithstanding, among women with PAS and a cesarean delivery,
412 conservative management, compared with cesarean-hysterectomy, was associated with lower
413 rates of severe bleeding, hysterectomy, and non-postpartum hemorrhage-related severe
414 maternal morbidity. It was also however associated with higher rates of embolization,
415 endometritis, and readmission.

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429

430

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532 morbidly adherent placenta treated with and without a standardized multidisciplinary
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534 **Table 1.** Participants' Characteristics at Baseline.

Characteristics of the participants	Women with conservative management N=86		Women with cesarean hysterectomy N=62		P
	n/N	%	n/N	%	
Maternal characteristics					
Age (yr) – Mean ± sd	N=86 33.9 ± 4.4		N=62 35.7 ± 4.7		0.02
Age>35 yr	37/86	43.0	34/62	54.8	0.16
BMI (kg/m ²) – Mean ± sd	N=83 26.0 ± 5.9		N=61 26.4 ± 6.4		0.69
BMI ≥ 30 kg/m ²	19/83	22.9	19/61	31.1	0.27
Notable preexisting condition*	6/86	7.0	9/62	14.5	0.13
Nulliparous	12/86	14.0	4/62	6.5	0.18
Parity					0.03
0-1	39/86	45.3	17/62	27.4	
2 or more	47/86	54.7	45/62	72.6	
At least one previous uterine surgery†	76/86	88.4	55/62	88.7	0.95
Curettage	31/85	36.5	16/61	26.2	0.19
Myomectomy	3/86	3.5	3/62	4.8	0.70
Previous cesarean delivery	67/86	77.9	51/62	82.3	0.52
0	19/86	22.1	11/62	17.7	0.91
1	32/86	37.2	24/62	38.7	
2	17/86	19.8	12/62	19.4	
3 or more	18/86	20.9	15/62	24.2	
Previous PAS	4/86	4.7	3/62	4.8	>0.99
Previous PPH	17/86	19.8	9/62	14.5	0.41
IVF	2/84	2.4	6/61	9.8	0.07
Multiple pregnancy	1/86	1.2	3/62	4.8	0.31
Bleeding during pregnancy	50/83	60.2	35/61	57.4	0.73
PPROM	11/86	12.8	7/62	11.3	0.78
Hospitalization during pregnancy	59/86	68.6	39/62	62.9	0.47
Transfusion during pregnancy	2/86	2.3	1/62	1.6	>0.99
Placenta previa or low-lying at the last ultrasound	65/86	75.6	51/62	82.3	0.33
Placenta previa	50/65	76.9	38/50	76.0	0.91
Low-lying placenta	15/65	23.1	12/50	24.0	
Placenta previa or low-lying with previous cesarean delivery	58/86	67.4	44/62	71.0	0.65
Prenatal suspicion of PAS	58/84	69.0	33/61	54.1	0.07
Woman transferred to a referral center	32/86	37.2	23/62	37.1	0.99

535

536 BMI, body mass index; PPH, postpartum hemorrhage; IVF, in vitro fertilization; PPRM, preterm

537 premature rupture of membranes; PAS, placenta accreta spectrum

538 *Chronic hypertension, preexisting diabetes, thromboembolism event, or other significant chronic

539 disease † Curettage, myomectomy or previous cesarean delivery

540

541 **Table 2.** Characteristics of Delivery Management

Characteristics of delivery management	Women with conservative management N=86		Women with cesarean hysterectomy N=62		P
	n/N	%	n/N	%	
Gestational age at delivery (wk)					0.61
22-27	6/86	7.0	2/62	3.2	
28-31	7/86	8.1	3/62	4.8	
32-36	42/86	48.8	30/62	48.4	
≥ 37	31/86	36.0	27/62	43.5	
Referral center of excellence for PAS	58/86	67.4	43/62	69.4	0.81
Adult intensive care unit onsite	80/86	93.0	53/62	85.5	0.13
Peripartum management					
Surgeon(s) other than OB-GYN present at cesarean	10/84	11.9	12/62	19.4	0.21
Anesthesia management					0.001
Regional only	42/86	48.8	14/62	22.6	
General only	31/86	36.0	25/62	40.3	
Regional then general	13/86	15.1	23/62	37.1	
Preoperative ureteral stent placement*	22/75	29.3	13/57	22.8	0.40
Preoperative internal iliac occlusion balloon catheter placement*	0/75	0.0	1/57	1.8	>0.99
Diagnosis of placenta percreta at laparotomy	30/85	35.3	16/61	26.2	0.24
Diagnosis of placenta percreta with bladder invasion at laparotomy	19/85	22.4	5/61	8.2	0.02
Attempted removal of the placenta	32/86	37.2	37/62	59.7	0.007
Placenta left in situ					
Partially	41/86	47.7	-	-	
Entirely	45/86	52.3	-	-	
Prophylactic uterotonic administration	34/86	39.5	34/59	57.6	0.03

542 OB-GYN, obstetrician-gynecologist; PAS, placenta accreta spectrum

543 *Among women with prelabor cesarean. Data were not collected for women with induction or

544 spontaneous onset of labor.

545

Table 3. Primary and Secondary Outcomes in Women with Placenta Accreta Spectrum Treated by Conservative Management or Cesarean-Hysterectomy

Outcomes	Overall Population						Weighted population				
	Women with conservative management N=86		Women with cesarean hysterectomy N=62		Difference (95% CI)	Unadjusted Risk ratio (95% CI)	P*	Unadjusted Risk Ratio (95% CI)	P*	Adjusted Risk Ratio (95% CI) [†]	P*
	n/N	%	n/N	%							
Packed RBCs transfused > 4 units	14/86	16.3	36/61	59.0	-42.7 (-57.3 to -28.1)	0.28 (0.16-0.47)	<0.001	0.27 (0.18-0.41)	<0.001	0.29 (0.19-0.45)	<0.001
Hysterectomy	19/86	22.1	62/62	100.0	-77.9 (-86.7 to -69.1)	0.22 (0.15-0.33)	<0.001	-	-	-	-
Primary hysterectomy [‡]	6/86	7.0	62/62	100.0	-93.0 (-98.4 to -87.6)	0.07 (0.03-0.15)	<0.001	-	-	-	-
Delayed hysterectomy [‡]	13/86	15.1	0/62	0.0	15.1 (7.5 to 22.7)	-	0.001	-	-	-	-
Interval from delivery to delayed hysterectomy (d)	N=13 44 (20-61)		-		-	-	-	-	-	-	-
Placenta accreta spectrum on hysterectomy specimen	19/19	100.0	62/62	100.0	-	-	-	-	-	-	-
Total EBL > 3000 ml	9/84	10.7	27/59	45.8	-35.0 (-49.4 to -20.7)	0.23 (0.12-0.46)	<0.001	0.24 (0.13-0.42)	<0.001	0.27 (0.15-0.47)	<0.001
EBL > 3000 ml within 24 hours	6/85	7.1	27/59	45.8	-38.7 (-52.5 to -24.9)	0.15 (0.07-0.35)	<0.001	0.17 (0.09-0.34)	<0.001	0.19 (0.10-0.38)	<0.001
EBL > 3000 mL after 24 hours	4/84	4.8	0/61	0.0	4.8 (0.2 to 9.3)	-	0.16	-	-	-	-
Vessel ligation and/or uterine compression sutures	11/86	12.8	19/62	30.6	-17.9 (-31.3 to -4.4)	0.42 (0.21-0.81)	0.01	0.64 (0.39-1.04)	0.07	0.68 (0.42-1.13)	0.13
Pelvic arterial embolization	21/86	24.4	2/62	3.2	21.2 (11.1 to 31.3)	7.6 (1.8-31.1)	<0.001	11.70 (3.70-37.04)	<0.001	12.07 (3.79-38.38)	<0.001
Any RBC transfusion	33/86	38.4	53/61	86.9	-48.5 (-61.8 to -35.2)	0.44 (0.33-0.59)	<0.001	0.44 (0.32-0.61)	<0.001	0.45 (0.33-0.63)	<0.001
RBC transfusion within 24	27/85	31.8	49/57	86.0	-	-	-	-	-	-	-

hours											
RBC transfusion after 24 hours	7/85	8.2	0/57	0.0	-	-	-	-	-	-	-
Number of packed RBC units	N=33 4 (3-12)		N=53 7 (4-10)		-	-	-	-	-	-	-
Any transfusion of fresh frozen plasma	26/86	30.2	46/61	75.4	-45.2 (-59.7 to -30.7)	0.40 (0.28-0.57)	<0.001	0.41 (0.31-0.54)	<0.001	0.42 (0.32-0.55)	<0.001
Number of units of fresh frozen plasma	N=26 3 (2-8)		N=46 6 (4-8)		-	-	-	-	-	-	-
Any transfusion of platelets	8/86	9.3	18/61	29.5	-20.2 (-33.2 to -7.2)	0.32 (0.15-0.68)	0.003	0.38 (0.20-0.70)	0.003	0.46 (0.25-0.84)	0.02
Number of units of platelets	N=8 2 (2-4)		N=18 1 (1-1)		-	-	-	-	-	-	-
Any transfusion of fibrinogen	16/86	18.6	39/60	65.0	-46.4 (-61.0 to -31.8)	0.29 (0.18-0.46)	<0.001	0.31 (0.22-0.44)	<0.001	0.32 (0.22-0.45)	<0.001
Total transfusion of fibrinogen	N=16 3 (1.8-6)		N=39 3 (3-6)		-	-	-	-	-	-	-
Inotropic agents\$	9/86	10.5	15/60	25.0	-14.5 (-27.2 to -1.8)	0.42 (0.20-0.89)	0.03	0.45 (0.25-0.81)	0.01	0.50 (0.28-0.91)	0.02
Adjacent organ injury	4/86	4.7	8/62	12.9	-8.3 (-17.7 to 1.2)	0.36 (0.11-1.14)	0.15	0.34 (0.13-0.94)	0.04	0.29 (0.11-0.79)	0.02
Bladder injury	3/86	3.5	7/62	11.3	-	-	-	-	-	-	-
Ureteral injury	0/86	0.0	2/62	3.2	-	-	-	-	-	-	-
Fistula	1/86	1.2	0/62	0.0	-	-	-	-	-	-	-
Colon injury	1/86	1.2	0/62	0.0	-	-	-	-	-	-	-
Septic shock	0/83	0.0	1/60	1.7	-1.7 (-4.9 to 1.6)	0	0.42	-	-	-	-
Endometritis	9/83	10.8	0/59	0.0	10.8 (4.2 to 17.5)	-	0.02	-	-	-	-
Deep vein thrombophlebitis or pulmonary embolism#	0/83	0.0	1/60	1.7	-1.7 (-4.9 to 1.6)	0	0.42	-	-	-	-
Readmission within 6 months	24/83	28.9	2/59	3.4	25.5	8.53	<0.001	12.43		12.07	<0.001

after discharge from delivery stay					(14.7 to 36.3)	(2.10-34.71)		(4.04-38.25)	<0.001	(3.90-37.37)	
Time to readmission after discharge from delivery stay (d)	N=23 51 (20-75)		N=2 37 (31-43)		-	-	-	-	-	-	-
Death	0/86	0.0	1/62 †	1.6	-1.6 (-4.7 to 1.5)	0	0.42	-	-	-	-
Non-PPH-related severe maternal morbidity**	5/86	5.8	10/62	16.1	-10.3 (-20.7 to 0.1)	0.36 (0.13-1.00)	0.05	0.42 (0.20-0.89)	0.03	0.41 (0.19-0.86)	0.02

Continuous outcomes are presented as medians (IQR)

EBL, estimated blood loss; RBC, red blood cells; PPH, postpartum hemorrhage

* The P value was adjusted for multiple testing by the Benjamini–Hochberg procedure, except for the primary outcome (unadjusted P), i.e., women transfused with more than 4 units of packed red blood cells within 6 months postpartum.

† Multiple regression model with inverse probability of treatment (propensity score) weighting and also adjusted for attempted removal of the placenta

‡ A primary hysterectomy was defined as a hysterectomy that took place within the first 24 hours after delivery, whereas a delayed hysterectomy took place more than 24 hours and up to 6 months after delivery.

§ Adrenaline, noradrenaline, dobutamine

Deep vein thrombophlebitis

¶ Woman with a BMI of 41.5 and prenatally suspected placenta accreta had an emergency cesarean-hysterectomy at 32 weeks of gestation due to preeclampsia and bleeding, followed by a pelvic arterial embolization due to diffuse bleeding with coagulopathy. She died two days later of multiorgan failure.

** Non-PPH-related severe maternal morbidity is defined as any of the following: septic shock, peritonitis, uterine necrosis, postpartum uterine rupture, fistula, injury to adjacent organs, acute pulmonary edema, acute kidney failure, deep vein thrombophlebitis or pulmonary embolism, or maternal death. No peritonitis, postpartum uterine rupture, acute pulmonary edema, or acute kidney failure occurred. Four women with total EBL>3000 ml in the conservative management group and four in the cesarean-hysterectomy group also had a non-PPH related severe maternal morbidity event.

List and titles of figures

Figure 1. Flow chart of the study population

Figure 2. Absolute standardized differences of baseline characteristics between the two groups (conservative management or cesarean-hysterectomy) before and after propensity score weighting

Legend:

IPTW, inverse probability of treatment weighting using the propensity score. Weights are assigned to women, calculated as the inverse of their probability of receiving treatment estimated by the propensity score [31-32].

Absolute standardized difference is calculated as the absolute value of the mean difference between the two groups divided by the pooled standard deviation.

Triangle shapes are variables included in the propensity score and round shapes are variables not included in the propensity score

BMI, body mass index; PPH, postpartum hemorrhage; IVF, in vitro fertilization; PPRM, preterm premature rupture of membranes; PAS, placenta accreta spectrum

Figure 1. Flow chart of the study population

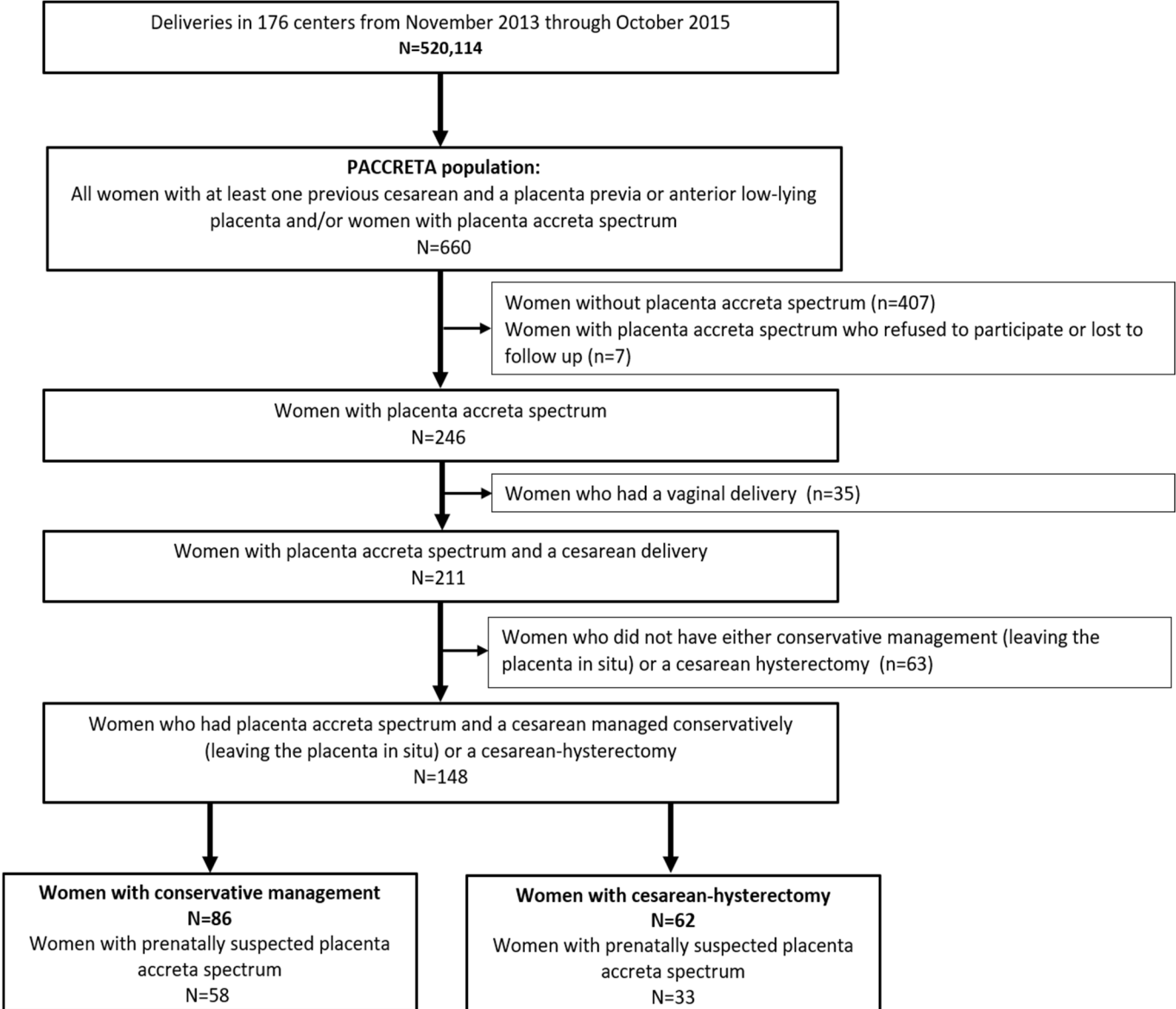
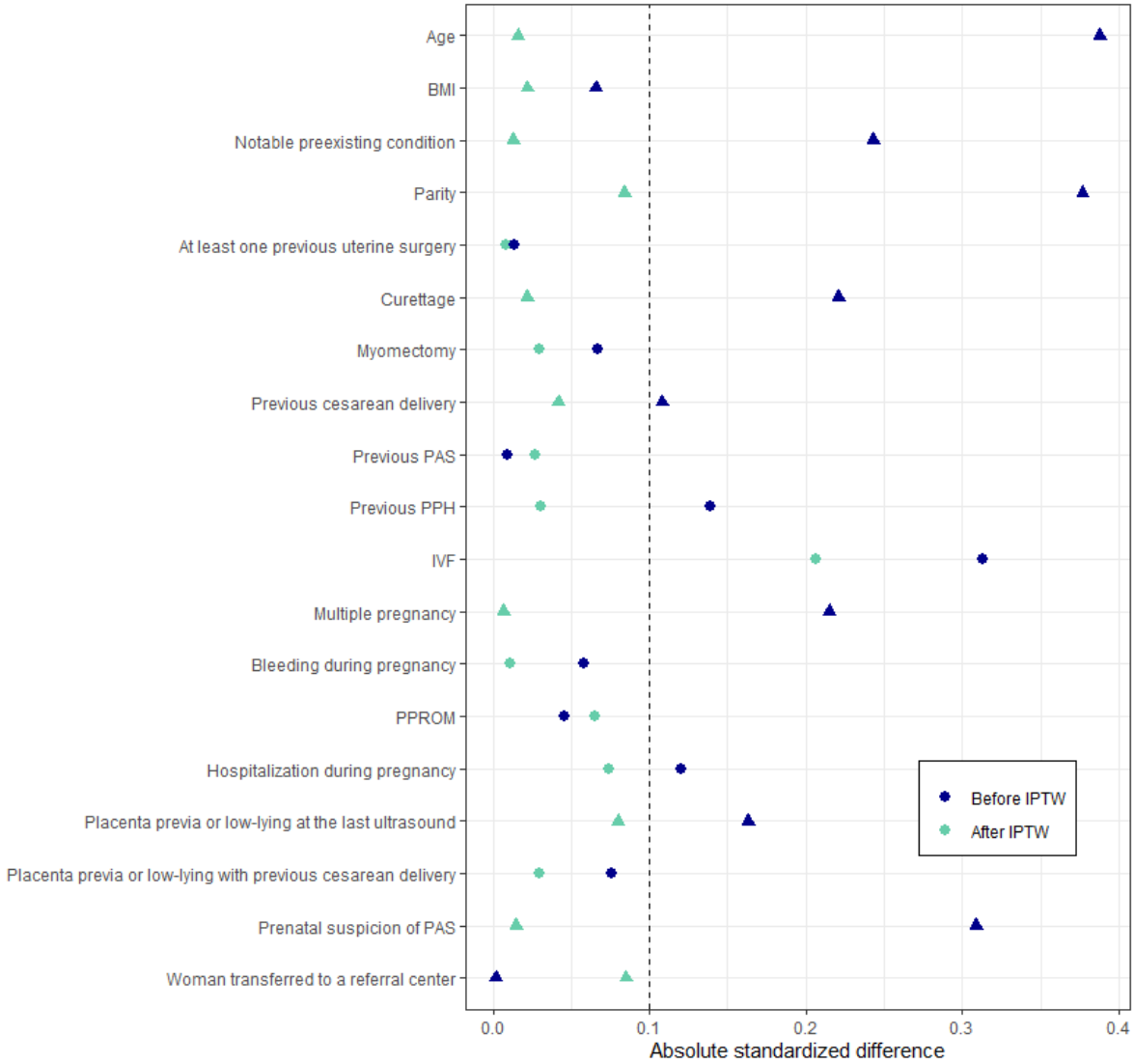


Figure 2. Absolute standardized differences of baseline characteristics between the two groups (conservative management or cesarean-hysterectomy) before and after propensity score weighting.



IPTW, inverse probability of treatment weighting with the propensity score creates a sample in which treatment assignment is independent of baseline characteristics. Weights are assigned to women, calculated as the inverse of their probability of receiving treatment estimated by the propensity score [28-29].

Absolute standardized difference is a measure of effect size between two groups which is independent of sample size. It is the absolute value of the mean difference divided by the pooled standard deviation.

Triangle shapes are variables included in the propensity score and round shapes are variables not included in the propensity score

BMI, body mass index; PPH, postpartum hemorrhage; IVF, in vitro fertilization; PPROM, preterm premature rupture of membranes; PAS, placenta accreta spectrum