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HAL Authorization

1 **Evaluation of the usefulness of ultrasound measurement of the lower uterine segment**
2 **before delivery of women with a prior cesarean: a randomized trial**

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34 **Conflicts of interest**

35 The authors report no conflict of interest.

36

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41 analysis, data interpretation, or writing of the report.

42

43 **Trial Registration:** ClinicalTrials.gov Identifier: NCT01916044.

44

45 The abstract of this paper was selected for oral presentation at the **Society for Maternal-Fetal**

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48

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55

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58

59 **1) Condensation:**

60 Ultrasound measurements of lower uterine segment thickness did not decrease adverse maternal
61 and perinatal outcomes compared with standard management among pregnant women with a
62 previous cesarean delivery.

63

64 **2) Short Title:**

65 Ultrasound measurements of lower uterine segment thickness and previous cesarean delivery.

66

67 **3) AJOG at a Glance:**

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

69 It is currently unclear if choice of mode of delivery based on the ultrasound measurement of the
70 lower uterine segment thickness is useful in reducing maternal-fetal mortality and morbidity
71 among pregnant women with a previous cesarean delivery.

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

73 In this randomized clinical trial that included 2948 women at 36⁺⁰ to 38⁺⁶ weeks of gestation with
74 1 prior low transverse cesarean delivery and no contraindication to trial of labor, choice of mode
75 of delivery based on the ultrasound measurement of the lower uterine segment thickness did not
76 significantly reduce maternal-fetal mortality and morbidity compared with usual management.

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

78 Among pregnant women with a previous cesarean delivery, ultrasound measurements of lower
79 uterine segment thickness cannot be recommended in routine practice.

80

81

82

83 **Abstract**

84 **Background:** The main reason to avoid trial of labor after cesarean delivery is the possibility of
85 uterine rupture. Identifying women at risk is thus an important aim, for it would enable women at
86 low risk to proceed with a secure planned vaginal birth.

87 **Objective:** To evaluate the impact of proposing mode of delivery based on the ultrasound
88 measurement of the lower uterine segment thickness on a composite outcome of maternal-fetal
89 mortality and morbidity, compared with usual management, among pregnant women with a
90 previous cesarean delivery.

91 **Study Design:** This multicenter, randomized, controlled, parallel-group, unmasked trial was
92 conducted at 8 referral university hospitals with a neonatal intensive care unit and enrolled 2948
93 women at 36⁺⁰ to 38⁺⁶ weeks of gestation with 1 prior low transverse cesarean delivery and no
94 contraindication to trial of labor were enrolled. Women in the study group had their lower uterine
95 segment thickness measured by ultrasound. Those with measurements >3.5 mm were encouraged
96 to choose a planned vaginal delivery and those with measurements ≤3.5 mm were encouraged to
97 choose a planned repeat cesarean delivery. This measurement was not taken in the control group:
98 their mode of delivery was decided according to standard management. The primary outcome
99 was a composite criterion comprising maternal mortality, uterine rupture, uterine dehiscence,
100 hysterectomy, thromboembolic disease, transfusion, endometritis, perinatal death, or neonatal
101 encephalopathy. Prespecified secondary outcomes were repeat cesarean deliveries, elective or
102 after trial of labor.

103 **Results:** The study group included 1472 women, and the control group 1476. These groups were
104 similar at baseline. The primary outcome occurred in 3.4% of the study group and 4.3% of the
105 control group (relative risk, 0.78; 95% confidence interval, 0.54–1.13; risk difference, -1.0%;
106 95% confidence interval -2.4 to 0.5). The uterine rupture rate in the study group was 0.4% and in
107 the control group 0.9% (relative risk, 0.43; 95% confidence interval, 0.15–1.19). The planned
108 cesarean rate was 16.4% in the study group and 13.7% in the control group (relative risk, 1.21;

109 95% confidence interval, 1.00–1.47) and the rates of cesarean during labor respectively 25.1%
110 and 25.0% (relative risk, 1.01; 95% confidence interval, 0.89–1.14).

111 **Conclusions:** Ultrasound measurements of lower uterine segment thickness did not result in a
112 statistically significant lower frequency of maternal and perinatal adverse outcomes than standard
113 management. However, because this study was underpowered, further research should be
114 encouraged.

115

116 **Trial Registration:** ClinicalTrials.gov Identifier: NCT01916044.

117

118 **Key words:** vaginal birth after cesarean; uterine rupture; lower uterine segment thickness;
119 ultrasound; cesarean delivery.

120

121

122 The cesarean delivery rate has dramatically increased in many countries over the past three
123 decades, reaching 31.9% in the United States and 26.9% in Western Europe.^{1,2} The most
124 common indication for cesarean delivery is a history of a previous one; these account for more
125 than one third of these procedures annually.³ Among the medical and nonmedical factors
126 contributing to the decline of vaginal birth after cesarean delivery,⁴ one frequently cited as a
127 reason to avoid trial of labor is the possibility of uterine rupture, which can lead to perinatal
128 asphyxia or death and severe maternal complications.⁵⁻⁹ There are also, however, serious
129 concerns about the long-term risks associated with cesarean deliveries, particularly placenta
130 previa and placenta accreta in later pregnancies. They are responsible for substantial maternal
131 and neonatal mortality and morbidity, and their risks increase with each subsequent cesarean
132 delivery.¹⁰⁻¹³

133 Identifying women at real risk for uterine rupture is thus an important aim in obstetric
134 care, for it would enable women at low risk to proceed with a secure planned vaginal birth,
135 whereas women at high risk could plan a cesarean delivery. Several authors have evaluated the
136 interest of ultrasound for predicting the risk of a cesarean scar defect by measuring the thickness
137 of the lower uterine segment (LUS) in women with a history of cesarean birth. Their results are
138 concordant: the thinner the LUS on ultrasound, the higher the likelihood of a uterine defect.¹⁴⁻²³
139 The most recent meta-analysis concluded that the thickness of this segment should be used as an
140 additional tool to help make an informed decision about a trial of labor after cesarean delivery
141 (TOLAC).²⁴

142 The LUSTrial (Lower Uterine Segment Trial) aimed to evaluate the impact of proposing
143 mode of delivery based on the ultrasound measurement of the LUS thickness on a composite
144 outcome of maternal-fetal mortality and morbidity, compared with usual management, among
145 pregnant women with a previous cesarean delivery.

146

147 **Materials and Methods**

148 **Study design**

149 We conducted a multicenter, randomized, controlled, parallel-group, unmasked trial at eight
150 hospitals, all referral university hospitals with a neonatal intensive care unit. The Ethics
151 Committee of Poissy Saint-Germain Hospital (Comité de Protection des Personnes, Saint-
152 Germain en Laye, France) approved the study protocol for all centers before participant
153 enrollment. All participants provided written informed consent before randomization. An
154 independent data monitoring committee, whose members had access to unblinded data related to
155 key trial outcomes and reviewed trial safety and progress. The committee also reviewed a
156 planned interim analysis halfway through the trial and recommended that it continue. The trial is
157 registered at ClinicalTrials.gov (NCT01916044).

158 The authors vouch for the accuracy and completeness of the data and for the fidelity of
159 the trial to the protocol.

160

161 **Participants**

162 Women were potentially eligible for inclusion if they were 18 years or older, at 36 weeks 0 days
163 to 38 weeks 6 days of gestation with a live singleton fetus in vertex presentation and had
164 previously had one low transverse cesarean birth. They were ineligible if they had two or more
165 previous cesareans, an indication for a repeat cesarean delivery, a classic cesarean scar, a
166 multiple pregnancy, placenta previa, or if they requested an elective repeat cesarean delivery.

167 Eligible women were informed of the risks of both planned vaginal and cesarean
168 deliveries. They were also informed that ultrasound measurement of the thickness of the
169 LUSLUS can be used to assess the risk of uterine rupture, but that the value of this examination
170 was controversial.

171

172 **Randomization and masking**

173 After verification of the inclusion and exclusion criteria, eligible consenting women were
174 randomly assigned by the physician-investigator in a 1:1 ratio to one of the two following
175 groups:

176 - The study group, with a proposed mode of delivery determined by ultrasound measurement of
177 the LUS thickness.

178 - The control group, with a proposed mode of delivery decided according to the usual
179 management at the center, without an ultrasound measurement of the **LUS**.

180 An independent, centralized, computer-generated randomization sequence (CleanWeb,
181 Télémedecine Technologies, Boulogne, France) was used for this allocation, based on a
182 randomization list established by the study statistician, according to a permuted block method
183 stratified by center.

184

185 **Procedures**

186 Each center selected one expert sonographer to be responsible for all ultrasound measurements of
187 the LUS thickness for women randomized to the study group. Each expert sonographer was a
188 maternal-fetal medicine specialist with at least 5 years of experience. The sonographers received
189 uniform training and certification by the principal investigator who had previously published this
190 method to ensure that the same measurement technique was used in each participating center.²¹

191 This measurement was performed transabdominally by a standardized technique between
192 36 weeks 0 days to 38 weeks 6 days of gestation, with the bladder moderately filled. This
193 examination of the LUS in the sagittal plane looked for the thinnest area of the upper third of this
194 segment. The image was then frozen, and the measurements were taken with the cursor placed at
195 the bladder/urine and amniotic fluid/decidua interfaces. The LUS was at an angle of 0 to 30° with
196 the horizontal plane and was then enlarged such that any movement of the cursor induced a
197 measurement variation of only ± 0.1 mm. Three successive measurements were taken, and the
198 lowest value was recorded. All centers performed ultrasounds with General Electric Voluson E8

199 ultrasound machines with a 2–5 MHz convex transabdominal transducer or a 4.0–8.5 MHz 4D
200 convex volumetric transabdominal transducer or Voluson E10 ultrasound machines with a 1.5–6.0
201 MHz convex transabdominal transducer or a 1–7 MHz 4D convex volumetric transabdominal
202 transducer (GE Medical System Europe, Vélizy, France).

203 Validation of 10 ultrasound images was required before these sonographers started the
204 study. As this was a pragmatic trial, the quality of the images was not verified later.

205 After this ultrasound assessment, the obstetrician and the woman discussed the decision
206 about planned mode of delivery. The LUS thickness was used as a tool to help her make an
207 informed decision. She received the following information:

208 - if the LUS thickness >3.5 mm, she was considered at low risk of uterine rupture and was
209 encouraged to choose a planned vaginal delivery;

210 - if this measurement ≤ 3.5 mm, she was considered at risk for uterine rupture and was
211 encouraged to choose a planned repeat cesarean delivery.

212 The 3.5-mm threshold value was chosen based on previously published results.²¹

213
214 Women in the control group did not have an ultrasound measurement of the LUS
215 thickness. Mode of delivery was decided according to the center's standard management and the
216 woman's preference. The risk of contamination was limited in the control group because this
217 examination was performed by only one referent sonographer-investigator, aware of the
218 randomization arm.

219 For all included women, the final decision was specified in the medical file by the
220 attending physician and in the study electronic file by a research midwife.

221 Obstetric providers managing the labor of women who underwent ultrasound
222 measurement were aware of the value of the LUS measurement and therefore were not blinded to
223 group assignment.

224

225 **Outcomes**

226 The primary outcome measure applied the maternal and perinatal outcomes and definitions used
227 by Landon et al. to compare outcomes after trial of labor or elective cesarean delivery in women
228 with a previous cesarean birth.⁶ It was a composite criterion of maternal mortality, uterine
229 rupture, uterine dehiscence, hysterectomy, thromboembolic disease, transfusion, endometritis,
230 antepartum stillbirth, intrapartum stillbirth, neonatal death, and neonatal hypoxic-ischemic
231 encephalopathy.

232 Prespecified secondary outcomes were each element of the composite principal criterion;
233 repeat cesarean deliveries, elective or after trial of labor, separately; and third- and fourth-degree
234 perineal lacerations.

235 Maternal and neonatal data were collected from women's inclusion until their discharge.
236 To ensure accurate diagnoses, all cases identified with uterine rupture or dehiscence or neonatal
237 encephalopathy were reviewed and, if necessary, reclassified by an independent blinded
238 adjudication committee, from reports that deleted all information about their randomization
239 group.

240

241 **Statistical analysis**

242 The sample size calculation was based on the data from Landon et al.,⁶ which reported a 6.41%
243 rate for the composite principal criterion in the trial of labor group and 4.07% in the elective
244 repeat cesarean group.⁶ On the assumption that measuring the LUS thickness would reduce fetal
245 and maternal mortality and morbidity to levels similar to those of women with elective cesarean
246 deliveries, each group required 1423 women for a power of 80% with a two-sided 5%
247 significance level. Because an intermediate analysis was planned at mid-trial with O'Brien–
248 Fleming boundaries, the tests for the primary outcome at the final analysis used a 4.67%
249 significance level. The planned sample size was increased to 1471 per arm, to take the interim
250 analysis and potential loss to follow-up into account.

251 The primary analysis applied the intention-to-treat principle, i.e., all randomized women
252 were analyzed in the group to which they had been allocated, regardless of protocol deviations.
253 Missing outcome data were handled by multiple imputation by chained equations; 20 datasets
254 with complete data were generated and analyzed separately, and the resulting estimates pooled.
255 Log-binomial models adjusted for parity (randomization stratification variable) were used to
256 estimate relative risks. To account for clustering by center, we fit models with generalized
257 estimating equations (GEE) with an exchangeable correlation matrix and derived risk difference
258 estimates from them. For the primary outcome, sensitivity analyses used complete cases only and
259 did not impute missing data or adjust for parity or center clustering.

260 The trial was open-label, but the data analysts were blinded to allocated treatment group,
261 until the entire analysis was completed. Analyses were performed with R v 3.4.4. (The R
262 Foundation for Statistical Computing, Vienna, Austria).

263

264 **Role of the funding source**

265 This study was funded by a research grant from the French Ministry of Health (*PHRC*
266 *R 12139*) and sponsored by the Département de la Recherche Clinique et du Développement de
267 l'Assistance Publique–Hôpitaux de Paris. The study sponsor did not participate in the study
268 design, data analysis, data interpretation, or writing of the report.

269 All authors confirm that they had full access to all the data in the study and accept
270 responsibility for submitting the article for publication.

271

272 **Results**

273

274 **Patient characteristics**

275 From August 2013 to February 2018, 2948 women underwent randomization: 1472 were
276 assigned to the study group, and 1476 to the control group (Fig. 1). These groups were similar at
277 baseline (Table 1). Timing of and indications for the previous cesarean delivery in each group are
278 reported in Table 2. Twenty-five women in the study group and 17 in the control group were lost
279 to follow-up or withdrew consent.

280

281 **Interventions**

282 In the study group, LUS thickness was measured by ultrasound in 1435 (97.5%) women. It
283 identified:

284 - 1351 (94.1%) women with a thickness >3.5 mm: trial of labor was recommended to
285 1326/1347 (98.4%) (4 missing data), and 1286/1348 (95.4%) (3 missing data) finally agreed.

286 - 84 (5.9%) women with a thickness ≤ 3.5 mm: a planned cesarean delivery was proposed to
287 58/83 (69.9%) (1 with missing data), and 53/83 (63.9%) (1 missing data) finally agreed to this
288 recommendation.

289

290 **Primary outcome**

291 After imputation of missing data and adjustment for center and parity, the primary
292 composite outcome occurred in 3.4% of the study group and 4.3% of the control group (relative
293 risk [RR], 0.78; 95% confidence interval [CI], 0.54–1.13). This finding remained unchanged in
294 both sensitivity analyses (Table 3).

295

296 **Secondary outcomes**

297 **Maternal outcomes**

298 No maternal deaths occurred during the study period. After imputation of missing data and
299 adjustment for center and parity, the uterine rupture rate in the study group was 0.4% and in the
300 control group 0.9% (RR, 0.43; 95% CI, 0.15–1.19) (Table 4). The 5 and 13 uterine ruptures in
301 the study and control groups, respectively, were repaired by suture and no woman underwent a
302 hysterectomy.

303 The uterine dehiscence rates were also similar: 1.0% in the study group and 1.2% in the
304 control group (RR, 0.86; 95% CI, 0.43–1.72) (Table 4). None of the 31 women with uterine
305 dehiscence needed a hysterectomy (Table 5).

306 Two hysterectomies occurred in each group (Table 5), three caused by an intractable
307 hemorrhage due to uterine atony unresponsive to prostaglandins and the fourth due to an
308 accidental extension of the uterine incision after cesarean delivery when trial of labor failed.

309 The study and control groups did not differ significantly for rates of thromboembolic
310 disease, transfusion, or endometritis. Overall maternal morbidity was 2.9% in the study group
311 and 3.8% in the control group (RR, 0.78; 95% CI, 0.53–1.16) (Table 3).

312 The elective cesarean rates were 16.4% in the study group and 13.7% in the control group
313 (RR, 1.21; 95% CI, 1.00–1.47), and the rates of cesarean delivery during labor were similar:
314 respectively, 25.1% vs 25.0% (RR, 1.01; 95% CI, 0.89–1.14). No differences were observed in
315 the rates of severe perineal lacerations (Tables 4 and 5).

316 Finally, in the study group, the mean LUS thickness among the 5 women with uterine
317 rupture was 4.6 mm (standard deviation: 1.2). None had a thickness less than or equal to 3.5 mm.
318 Among the other women of this group, the mean LUS thickness was 5.4 mm (standard deviation:
319 2.4). The mean difference was equal to -0.8 (95% CI: -2.9 to 1.3; $P = .45$).

320

321 **Fetal and neonatal outcomes**

322 After imputation of missing data and adjustment for center and parity, the rate of antepartum
323 stillbirths in the study group was 0.2% and in the control group, 0.1% (RR, 1.65; 95% CI, 0.25–

324 10.8) (Table 4). The five antepartum stillbirths were diagnosed at a routine visit or at admission
325 for uterine contractions (Table 5), and none was associated with uterine rupture. No intrapartum
326 stillbirth occurred. The only neonatal death (control group) occurred after elective cesarean birth
327 before labor for severe fetal heart rate abnormalities diagnosed during a routine visit. No uterine
328 rupture was observed.

329 The rates of neonatal encephalopathy were similar in the study and control groups: 0.2%
330 vs 0.5%, respectively (RR, 0.48; 95% CI, 0.12–1.87) (Table 3). None of the 10 cases of neonatal
331 encephalopathy occurred after uterine rupture (Table 5).

332

333 **Comment:**

334 **Principal Findings**

335 In this randomized trial, we found no statistically significant difference in the frequency of the
336 primary outcome between women with a previous cesarean delivery randomly assigned to
337 ultrasound measurement of the LUS thickness and women assigned to standard management.

338

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

340 In a landmark observational study, Rozenberg et al. showed that the risk of a defective
341 scar was directly related to the degree of thinning of the LUS on ultrasound between 36 and 38
342 weeks of gestation.²¹ Since this publication, numerous other observational studies have also
343 assessed this relation,^{15-20, 25-30} and three meta-analyses have concluded that the thickness on
344 ultrasound of the LUS is a strong predictor of a uterine scar defect in women with a prior
345 cesarean delivery.^{24,31,32} In a multicenter prospective study, Jastrow et al. included this
346 measurement in the decision about mode of delivery. Among 1849 women with a previous
347 cesarean delivery, 984 had a trial of labor and there were no symptomatic uterine ruptures.³³

348 In accordance with the method initially reported by Rozenberg et al.,²¹ we included the
349 bladder wall in the measurement of the LUS and note that this method of LUS ultrasound
350 measurement yields an excellent negative predictive value for the risk of a uterine defect (99.3%)
351 with the 3.5 mm cutoff. In a prospective cohort study including 236 women with a previous
352 cesarean delivery, Bujold et al. measured the full thickness and the myometrial thickness only
353 between 35 and 38 weeks of gestation. Only the full LUS thickness was associated with the risk
354 of complete uterine rupture.²³ Finally, Gizzo et al. measured transabdominally the total LUS and
355 myometrial thickness only in all patients before undergoing a CD and reported that measuring
356 the myometrial layer was more technically challenging. This finding raises the question of
357 reproducibility of this myometrial layer measurement alone.²⁰

358 Transvaginal sonography was not used to measure the LUS thickness in our study. In
359 cesareans in France, the hysterotomy is usually performed above the vesico-uterine pouch, thus
360 too distant from the transvaginal transducer to produce an adequate image of the thinnest area of
361 the upper third of the LUS. Six studies have specifically evaluated the predictive value of
362 transvaginal sonographic examination of the LUS in pregnant women with previous cesarean
363 deliveries. However, the methodology of these studies precludes any reliable conclusion. Three
364 studies compared the antepartum LUS thickness measurements only with direct intraoperative
365 observation at the elective repeated CD^{15,29,34} and therefore did not allow the performance of the
366 LUS examination to be tested after TOLAC. This leads to a substantial overestimation of the
367 potential risks of uterine rupture. Furthermore, in the studies by Qureshi et al.²⁶ and Montanari et
368 al.,³⁵ which respectively included 43 and 61 pregnant women with a previous cesarean, only 26
369 and 8 had a TOLAC. Finally, the study by Asakura et al. included 186 women with a previous
370 cesarean, 125 of whom had a TOLAC but none a uterine rupture.²⁷ Finally, as clarified in the
371 most recent meta-analysis, the only ultrasound methodology that has been validated to correlate
372 with uterine rupture in previous studies is the transabdominal measurement of the full LUS
373 thickness.²⁴

374 We used the 3.5 mm cutoff point from the Rozenberg study because we considered it to
375 have the lowest risk of bias when we designed our randomized trial,²¹ as it was the largest series
376 including 642 pregnant women with a previous cesarean, 517 of whom underwent a TOLAC,
377 and, importantly, caregivers were blinded to the LUS measurement. However, the recent meta-
378 analysis of Swift et al. including 28 studies showed that, when measuring the full LUS thickness
379 by transabdominal ultrasound, a LUS thickness >3.65 mm provides reassurance that the
380 likelihood of uterine rupture is lower.²⁴ A future analysis of our data may provide useful
381 information to determine whether a better cutoff point than 3.5 mm could identify the women at
382 the highest risk of uterine rupture.

383

384 **Clinical and Research Implications**

385 This trial presented important challenges. Evaluating a complex intervention is much
386 more difficult than evaluating the effectiveness of a drug, especially when this complex
387 intervention is only one tool among several to help make an informed decision about TOLAC.

388 Furthermore, because of the lower-than-expected incidence of the primary composite
389 outcome, our study was underpowered. We hypothesized an absolute decrease in primary
390 composite outcome rate of 2.34% but found an absolute difference of only 0.9%. Our sample size
391 was insufficient to demonstrate such small differences. We conducted this trial at eight referral
392 university hospitals with a neonatal intensive care unit and immediate availability of an
393 obstetrician, anesthesiologist, and neonatologist. These factors probably help to explain the low
394 incidence of the primary composite outcome. Additional research is thus required before any
395 formal conclusions, especially since our results, despite their lack of statistical significance,
396 continue to point in the same direction as the evidence before this study.

397

398 **Strengths and Limitations**

399 This trial has several strengths. Using the keywords pregnancy, lower uterine segment,
400 cesarean, ultrasound, and uterine rupture, we performed an electronic search of PubMed for
401 relevant articles published from January 1980 through December 2020. After this search, we
402 conclude that this is the first randomized controlled trial evaluating the effectiveness of
403 ultrasound measurement of the LUS in reducing fetal and maternal morbidity and mortality at
404 delivery among women with a prior cesarean birth. It was large, analyzed by the intent-to-treat
405 principle, and pragmatic, reflecting real life.

406 Limitations of the trial should be noted. As previously stated, our study was
407 underpowered. Because masking was not feasible, ascertainment bias is possible. However, all
408 cases of uterine rupture, uterine dehiscence, and neonatal encephalopathy were reviewed, and, if
409 necessary, reclassified by a blinded adjudication committee. Furthermore, a potential

410 performance bias associated with the management of labor by obstetric providers aware of the
411 value of the LUS measurement was possible. However, the similar rates of cesarean deliveries
412 during labor indicate that this potential performance bias is unlikely.

413 Our primary outcome is a composite outcome of various entities of very disparate
414 significance. However, the true question raised by the introduction of ultrasound measurement of
415 LUS thickness into clinical practice for a woman with a previous CD is not simply if the
416 ultrasound examination predicts the risk of uterine rupture but whether this examination can help
417 reduce the risks of maternal-fetal mortality and morbidity associated with the uterine defect by
418 better selection of candidates for TOLAC. Uterine rupture is only a surrogate marker. Therefore,
419 like Landon et al. in their study,⁶ we have considered that the most interesting endpoint to assess
420 the utility of ultrasound measurement of LUS thickness was a composite outcome of maternal-
421 fetal mortality and morbidity.

422 Another weakness of our study was the absence of data about patients before their
423 enrollment. Therefore, we do not know how many women did not meet the inclusion criteria, the
424 reasons for their ineligibility, or how many eligible women declined to participate.

425 As this was a pragmatic trial, the quality of the images was not verified later. Therefore,
426 we do not know how many cases were technically inadequate. However, consistent with our
427 "real-life" approach, no woman was excluded after randomization due to poor visualization of the
428 lower uterine segment.

429 Finally, the generalizability of our results should be interpreted with caution, for all
430 centers were referral university hospitals with a neonatal intensive care unit.

431
432 In summary, we found that ultrasound measurements of LUS thickness did not result in a
433 statistically significantly lower frequency of maternal and perinatal adverse outcomes than
434 standard management. However, our study was underpowered. Accordingly, while we think that

435 ultrasound measurements of LUS thickness cannot be recommended in routine practice, we hope
436 that our results encourage further research.

437

438

439 **Contributors**

440 Patrick Rozenberg and Isabelle Boutron contributed to the study design and methodology.

441 Marie-Victoire Sénat, Philippe Deruelle, Norbert Winer, Emmanuel Simon, Yves Ville, Gilles

442 Kayem, and Raoul Desbrière were responsible for the oversight of the study at their respective

443 hospitals and contributed to the recruitment of participants.

444 Raphael Porcher and Élodie Perrodeau were responsible for data analysis.

445 Patrick Rozenberg and Isabelle Boutron wrote the first draft of the manuscript. All authors

446 contributed to critical revision of the manuscript for important intellectual content and gave final

447 approval.

448

449 **Declaration of interests**

450 We declare no competing interests.

451

452 **Data sharing**

453 The study dataset, including anonymised individual participant data and a data dictionary

454 defining each field in the dataset, will be available to appropriate academic parties for qualified

455 researchers upon request from the principal investigator, PR. Data availability is in accordance

456 with the hospital ethics committee approval, and subject to submission of a suitable and clinically

457 important study protocol, provided with a signed data access agreement. The study protocol will

458 be made available if necessary for the proposed study. All data will be made available upon

459 publication of this manuscript and be shared via email.

460

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473

474 **References**

- 475 1. ACOG Practice Bulletin No. 205: Vaginal Birth After Cesarean Delivery. *Obstet Gynecol.*
476 2019;133:e110-e127.
- 477 2. Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in
478 caesarean sections. *Lancet.* 2018;392:1341-1348.
- 479 3. Guise JM, Denman MA, Emeis C, et al. Vaginal birth after cesarean: new insights on maternal
480 and neonatal outcomes. *Obstet Gynecol.* 2010;115:1267-78.
- 481 4. American College of Obstetricians and Gynecologists (College); Society for Maternal-Fetal
482 Medicine, Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary
483 cesarean delivery. *Am J Obstet Gynecol.* 2014;210:179-93.
- 484 5. National Institutes of Health Consensus Development Conference Panel. National Institutes of
485 Health Consensus Development conference statement: vaginal birth after cesarean: new insights
486 March 8-10, 2010. *Obstet Gynecol.* 2010;115:1279-95.
- 487 6. Landon MB, Hauth JC, Leveno KJ, et al. National Institute of Child Health and Human
488 Development Maternal-Fetal Medicine Units Network. Maternal and perinatal outcomes
489 associated with a trial of labor after prior cesarean delivery. *N Engl J Med.* 2004;351:2581-9.
- 490 7. Crowther CA, Dodd JM, Hiller JE, et al. Birth After Cesarean Study Group. Planned vaginal
491 birth or elective repeat caesarean: patient preference restricted cohort with nested randomised
492 trial. *PLoS Med.*2012;9:e1001192.
- 493 8. Young CB, Liu S, Muraca GM, et al.; Canadian Perinatal Surveillance System. Mode of
494 delivery after a previous cesarean birth and associated maternal and neonatal morbidity. *CMAJ.*
495 2018;190:E556-E564.
- 496 9. Fitzpatrick KE, Kurinczuk JJ, Bhattacharya S, et al.. Planned mode of delivery after previous
497 cesarean section and short-term maternal and perinatal outcomes: A population-based record
498 linkage cohort study in Scotland. *PLoS Med.*2019;16:e1002913.

- 499 10. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat
500 cesarean deliveries: National Institute of Child Health and Human Development maternal-fetal
501 medicine units network. *Obstet Gynecol* 2006;107:1226-32.
- 502 11. Marshall NE, Fu R, Guise JM. Impact of multiple cesarean deliveries on maternal morbidity:
503 a systematic review. *AmJ Obstet Gynecol* 2011;205:262.e1-8.
- 504 12. Smith GC, Pell JP, Dobbie R. Cesarean section and risk of unexplained stillbirth in
505 subsequent pregnancy. *Lancet* 2003;362:1779-84.
- 506 13. Solheim KN, Esakoff TF, Little SE, et al. The effect of cesarean delivery rates on the future
507 incidence of placenta previa, placenta accreta, and maternal mortality. *J Matern Fetal Neonatal*
508 *Med* 2011;24:1341-6.
- 509 14. Michaels WH, Thompson HO, Boutt A, et al. Ultrasound diagnosis of defects in the scarred
510 lower uterine segment during pregnancy. *Obstet Gynecol.* 1988;71:112-20.
- 511 15. Gotoh H, Masuzaki H, Yoshida A, et al. Predicting incomplete uterine rupture with vaginal
512 sonography during the late second trimester in women with prior cesarean. *Obstet*
513 *Gynecol.* 2000;95:596-600.
- 514 16. Tanik A, Ustun C, Cil E, et al. Sonographic evaluation of the wall thickness of the lower
515 uterine segment in patients with previous cesarean section. *J Clin Ultrasound.* 1996;24:355-7.
- 516 17. Suzuki S, Sawa R, Yoneyama Y, et al. Preoperative diagnosis of dehiscence of the lower
517 uterine segment in patients with a single previous Caesarean section. *Aust N Z J Obstet*
518 *Gynaecol.* 2000;40:402-4.
- 519 18. Cheung VYT, Constantinescu OC, Ahluwalia BS. Sonographic evaluation of the lower
520 uterine segment in patients with previous cesarean delivery. *J Ultrasound Med.* 2004;23:1441-
521 1447.
- 522 19. Sen S, Malik S, Salhan S. Ultrasonographic evaluation of lower uterine segment thickness in
523 patients of previous cesarean section. *Int J Gynaecol Obstet.* 2004;87:215-219.

- 524 20. Gizzo S, Zambon A, Saccardi C, et al. Effective anatomical and functional status of the lower
525 uterine segment at term: estimating the risk of uterine dehiscence by ultrasound. *Fertil Steril.*
526 2013;99:496-501.
- 527 21. Rozenberg P, Goffinet F, Phillippe HJ, et al. Ultrasonographic measurement of lower uterine
528 segment to assess risk of defects of scarred uterus. *Lancet.*1996;347:281-4.
- 529 22. Cheung VYT. Sonographic measurement of the lower uterine segment thickness in women
530 with previous caesarean section. *J Obstet Gynaecol Can.* 2005;27:674-681.
- 531 23. Bujold E, Jastrow N, Simoneau J, et al. Prediction of complete uterine rupture by
532 sonographic evaluation of the lower uterine segment. *Am J Obstet Gynecol.* 2009;201:e1-e6.
- 533 24. Swift BE, Shah PS, Farine D. Sonographic lower uterine segment thickness after prior
534 cesarean section to predict uterine rupture: A systematic review and meta-analysis. *Acta Obstet*
535 *Gynecol Scand.* 2019;98:830-41.
- 536 25. Fukuda M, Shimizu T, Ihara Y, et al. Ultrasound examination of caesarean section scars
537 during pregnancy. *Arch Gynecol Obstet.* 1991;248:129-38
- 538 26. Qureshi B, Inafuku K, Oshima K, et al. Ultrasonographic evaluation of lower uterine segment
539 to predict the integrity and quality of cesarean scar during pregnancy: a prospective study.
540 *Tohoku J Exp Med.* 1997;183:55-65.
- 541 27. Asakura H, Nakai A, Ishikawa G, et al. Prediction of uterine dehiscence by measuring lower
542 uterine segment thickness prior to the onset of labor: evaluation by transvaginal ultrasonography.
543 *J Nippon Med Sch.* 2000;67:352-6.
- 544 28. Kushtagi P, Garepalli S. Sonographic assessment of lower uterine segment at term in women
545 with previous cesarean delivery. *Arch Gynecol Obstet.* 2011;283:455-9.
- 546 29. Sanlorenzo O, Farina A, Pula G, et al. Sonographic evaluation of the lower uterine segment
547 thickness in women with a single previous Cesarean section. *Minerva Ginecol.* 2013;65:551-5.

548 30. Uharček P, Brešťanský A, Ravinger J, et al. Sonographic assessment of lower uterine
549 segment thickness at term in women with previous cesarean delivery. Arch Gynecol
550 Obstet. 2015;292:609-12.

551 31. Jastrow N, Chaillet N, Roberge S, et al. Sonographic lower uterine segment thickness and
552 risk of uterine scar defect: a systematic review. J Obstet Gynaecol Can. 2010;32:321-7.

553 32. Kok N, Wiersma IC, Opmeer BC, et al. Sonographic measurement of lower uterine segment
554 thickness to predict uterine rupture during a trial of labor in women with previous Cesarean
555 section: a meta-analysis. Ultrasound Obstet Gynecol. 2013;2013:132-9.

556 33. Jastrow N, Demers S, Chaillet N, et al. Lower uterine segment thickness to prevent uterine
557 rupture and adverse perinatal outcomes: a multicenter prospective study. Am J Obstet Gynecol.
558 2016;215:604.e1-604.e6.

559 34. Indraccolo U, Scutiero G, Matteo M, Masticci AL, Barone I, Greco P. Correlations between
560 sonographically measured and actual incision site thickness of lower uterine segment after
561 repeated caesarean section. Minerva Ginecol. 2015;67:225-9.

562 35. Montanari L, Alfei A, Drovanti A, Lepadatu C, Lorenzi D, Facchini D, Iervasi MT, Sampaolo
563 P. Valutazione ecografica transvaginale dello spessore del segmento uterino inferiore in tagli
564 cesarei pregressi [Transvaginal ultrasonic evaluation of the thickness of the section of the uterine
565 wall in previous cesarean sections]. Minerva Ginecol. 1999;51:107-12.

566

567 **Table 1. Women's characteristics at randomisation.**

	Study group (N=1472)	Control group (N=1476)
Maternal age, median [Q ₁ -Q ₃], years	32.5 [29.4-35.7]	32.4 [29.2-35.4]
Missing data	0	0
Body Mass Index, median [Q ₁ -Q ₃], kg/m ²	24.2 [21.6-28.1]	24.2 [21.2-28.4]
Missing data	8 (0.5)	11 (0.7)
Mother's country of birth		
France	769 (55.6)	782 (56.8)
Other country in Europe	48 (3.5)	52 (3.8)
North Africa	315 (22.8)	261 (19.0)
Sub-Saharan Africa	135 (9.8)	171 (12.4)
Other	117 (8.2)	110 (7.9)
Missing data	88 (6.0)	100 (6.8)
Gestational age, median [Q ₁ -Q ₃], week	37.0 [36.4-37.6]	36.9 [36.4-37.4]
Missing data	0	0
Smoking during pregnancy, no. (%)	150 (10.3)	160 (11.0)
Missing data	19 (1.3)	18 (1.2)
Parity, no. (%)		
1	1176 (80.8)	1178 (80.7)
≥ 2	280 (19.2)	281 (19.3)
Missing data	16 (1.1)	17 (1.2)
Previous IUFD, no. (%)	17 (1.2)	25 (1.7)
Missing data	2 (0.1)	2 (0.1)

Previous PPH, no. (%)	85 (5·8)	84 (5·7)
Missing data	4 (0·3)	4 (0·3)
Chronic hypertension, no. (%)	31 (7·8)	33 (8·2)
Missing data	0	0
Diabetes mellitus, no. (%)	28 (7·0)	18 (4·5)
Missing data	0	0
Preeclampsia, no. (%)	11 (0·7)	20 (1·4)
Missing data	3 (0·2)	7 (0·5)
Estimated fetal weight, median [Q ₁ -Q ₃], g	3075 [2760-3437]	3021 [2734-3400]
Missing data	435 (29·6)	451 (30·6)
Suspected macrosomia, no. (%)	105 (7·2)	110 (7·5)
Missing data	4 (0·3)	8 (0·5)

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569 Q₁: first quartile; Q₃: third quartile

570 IUFD: intrauterine fetal death

571 PPH: postpartum haemorrhage

572 **Table 2:** Timing of and indications for the previous CD in the study and control groups

	Study group n (%)	Control group n (%)	P-value
Planned elective CD	178 (12.1)	195 (13.2)	0.37
CD during labor	1160 (78.8)	1142 (77.4)	
Arrest of labor during the first stage	263 (22.7)	285 (25.0)	0.04
Arrest of labor during the second stage	83 (7.2)	72 (6.3)	
Nonreassuring fetal heart rate	539 (46.5)	473 (41.4)	
Failed induction	275 (23.7)	312 (27.3)	
Missing Data	134 (9.1)	139 (9.4)	

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575 **Table 3. Primary outcome analysis.**

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	Study group	Control group	Risk Difference (95% CI)	Relative Risk (95% CI)
With imputed data	3.4%	4.3%	-1.0% (-2.4 to 0.5)	0.78 (0.54-1.13)
Complete cases without imputation of missing data	48/1467 (3.3%)	63/1468 (4.3%)	-1.2% (-2.6 to 0.2)	0.73 (0.50-1.07)
Crude analysis without adjustment for centre or parity	3.4%	4.3%	-1.0% (-2.4 to 0.5)	0.78 (0.54-1.13)

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579 **Table 4. Comparison of the proportion of each secondary criterion between the study**
 580 **groups.** Comparisons are adjusted for centre and parity.

	Study group, %	Control group %	Risk difference (95% CI)	Relative risk (95% CI)	p
Maternal morbidity	2.9	3.8	-0.8% (-2.1 to 0.5)	0.78 (0.53-1.16)	0.21
Uterine rupture	0.4	0.9	-0.5% (-1.1 to 0.1)	0.43 (0.15-1.19)	0.09
Uterine dehiscence	1.0	1.2	-0.2% (-0.9 to 0.6)	0.86 (0.43-1.72)	0.66
Hysterectomy	0.2	0.1	+0.0% (-0.3 to 0.3)	1.16 (0.18-7.62)	0.87
Thromboembolic disease	0.3	0.2	+0.1% (-0.3 to 0.5)	1.41 (0.28-7.25)	0.68
Transfusion	1.4	2.1	-0.7% (-1.7 to 0.2)	0.68 (0.39-1.16)	0.15
Endometritis	0.09	0.07	+0.0% (-0.2 to 0.2)	1.16 (0.14-9.50)	0.89
Fetal mortality	0.2	0.1	+0.1% (-0.2 to 0.4)	1.65 (0.25-10.8)	0.59
Neonatal mortality	0.0	0.07	—	—	—
Neonatal encephalopathy	0.2	0.5	-0.2% (-0.7 to 0.2)	0.48 (0.12-1.87)	0.28
Elective caesarean delivery	16.4	13.7	+2.6% (0.0 to 5.1)	1.21 (1.00-1.47)	0.052
Non-elective caesarean delivery	25.1	25.0	+0.2% (-2.9 to 3.3)	1.01 (0.89-1.14)	0.90
Third- and fourth-degree perineal lacerations	2.1	1.8	+0.2% (-0.8 to 1.3)	1.13 (0.65-1.98)	0.65

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Table 5. Descriptive analysis of secondary outcomes

	Study group (n=1472)	Control group (n=1476)
	no. (%)	no. (%)
Maternal morbidity	42 (2.9)	55 (3.7)
Missing data	5 (0.3)	7 (0.5)
Uterine rupture	5 (0.3)	13 (0.9)
Missing data	5 (0.3)	6 (0.4)
Uterine dehiscence	14 (1.0)	17 (1.2)
Missing data	5 (0.3)	6 (0.4)
Hysterectomy	2 (0.1)	2 (0.1)
Missing data	5 (0.3)	6 (0.4)
Thromboembolic disease	4 (0.3)	3 (0.2)
Missing data	5 (0.3)	7 (0.5)
Transfusion	20 (1.4)	31 (2.1)
Missing data	5 (0.3)	6 (0.4)
Endometritis	1 (0.1)	1 (0.1)
Missing data	5 (0.3)	7 (0.5)
Fetal mortality	3 (0.2)	2 (0.1)
Missing data	4 (0.3)	5 (0.3)
Neonatal mortality	0 (0.0)	1 (0.1)
Missing data	5 (0.3)	5 (0.3)
Neonatal encephalopathy	3 (0.2)	7 (0.5)
Missing data	7 (0.5)	9 (0.6)
Elective CD	240 (16.3)	202 (13.7)
Missing data	4 (0.3)	5 (0.3)
Non-elective CD	368 (25.1)	367 (24.9)
Missing data	4 (0.3)	5 (0.3)
3rd and 4th degree perineal tears	29 (2.1)	25 (1.8)
Missing data	108 (7.3)	100 (6.8)

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Figure 1: Enrolment, randomisation, and follow-up of the study participants.

