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Patrick ROZENBERG [1], M.D., Marie-Victoire SÉNAT [2], M.D., Ph.D., Philippe DERUELLE [3], M.D., Ph.D., Norbert WINER [4], M.D., Ph.D., Emmanuel SIMON [5], M.D., Ph.D., Yves VILLE [6], M.D., Gilles KAYEM [7], M.D., Ph.D., Raphael PORCHER [8], Ph.D., Élodie PERRODEAU [8], MSc., Raoul DESBRIÈRE [9], M.D., Isabelle BOUTRON [8], M.D., Ph.D., for the Groupe de Recherche en Obstétrique et Gynécologie (GROG).

[1] Department of Obstetrics and Gynecology, Hôpital Poissy-Saint Germain, Versailles-Saint Quentin University, research unit EA 7285.
patrick.rozenberg@ght-yvelinesnord.fr

[2] Department of Obstetrics and Gynecology, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre.
marie-victoire.senat@aphp.fr

[3] Department of Obstetrics and Gynecology, Hôpital Jeanne de Flandre, Lille.
philippe.deruelle@chru-strasbourg.fr

[4] Department of Obstetrics and Gynecology, Hôpital Mère-Enfant, Nantes.
norbert.winer@chu-nantes.fr

[5] Department of Obstetrics and Gynecology, Hôpital Bretonneau, Tours.
emmanuel.simon@chu-dijon.fr

[6] Department of Obstetrics and Gynecology, Hôpital Necker, AP-HP, Paris.
ville.yves@gmail.com

[7] Department of Obstetrics and Gynecology, Hôpital Armand-Trousseau, AP-HP, Paris.
gilles.kayem@aphp.fr

[8] Centre of Research Epidemiology and Statistics, INSERM U1153, Université de Paris, Paris ; Centre of Clinical Epidemiology, Hôpital Hôtel-Dieu, AP-HP, Paris.

raphael.porcher@aphp.fr elodie.perrodeau@aphp.fr isabelle.boutron@aphp.fr

[9] Department of Obstetrics and Gynecology, Hôpital Saint Joseph, Marseille

raoul.desbriere@orange.fr

Conflicts of interest

The authors report no conflict of interest.

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Trial Registration: ClinicalTrials.gov Identifier: NCT01916044.

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corresponding author:

Pr Patrick Rozenberg

Service d'Obstétrique et Gynécologie, Centre Hospitalier Poissy-Saint Germain

10 rue du champ Gaillard, 78300 Poissy, France

phone: + 33 1 39 27 52 57; Fax : + 33 1 39 27 44 79

E-mail: patrick.rozenberg@ght-yvelinesnord.fr

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1) Condensation:

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

2) Short Title:

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

3) AJOG at a Glance:

A. Why was this study conducted?

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

B. What are the key findings?

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

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

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

Abstract

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

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

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

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

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

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

Trial Registration: ClinicalTrials.gov Identifier: NCT01916044.

K**ey words**: vaginal birth after cesarean; uterine rupture; lower uterine segment thickness; ultrasound; cesarean delivery.

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

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

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

Materials and Methods

Study design

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

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

Participants

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

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

Randomization and masking

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

- The study group, with a proposed mode of delivery determined by ultrasound measurement of the LUSt thickness.
- The control group, with a proposed mode of delivery decided according to the usual management at the center, without an ultrasound measurement of the LUS.

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

Procedures

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

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

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

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

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

- if the LUS thickness >3.5 mm, she was considered at low risk of uterine rupture and was encouraged to choose a planned vaginal delivery;
- if this measurement ≤3.5 mm, she was considered at risk for uterine rupture and was encouraged to choose a planned repeat cesarean delivery.

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

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

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

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

Outcomes

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

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

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

Statistical analysis

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

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

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

Role of the funding source

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

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

Results

Patient characteristics

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

Interventions

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

- 1351 (94.1%) women with a thickness >3.5 mm: trial of labor was recommended to 1326/1347 (98.4%) (4 missing data), and 1286/1348 (95.4%) (3 missing data) finally agreed.
- 84 (5.9%) women with a thickness ≤3.5 mm: a planned cesarean delivery was proposed to 58/83 (69.9%) (1 with missing data), and 53/83 (63.9%) (1 missing data) finally agreed to this recommendation.

Primary outcome

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

Secondary outcomes

Maternal outcomes

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

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

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

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

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

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

Fetal and neonatal outcomes

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

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

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

Comment:

Principal Findings

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

Results in the Context of What is Known

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

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

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

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

Clinical and Research Implications

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

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

Strengths and Limitations

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

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

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

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

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

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

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

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

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

Contributors

Patrick Rozenberg and Isabelle Boutron contributed to the study design and methodology. Marie-Victoire Sénat, Philippe Deruelle, Norbert Winer, Emmanuel Simon, Yves Ville, Gilles Kayem, and Raoul Desbrière were responsible for the oversight of the study at their respective hospitals and contributed to the recruitment of participants.
Raphael Porcher and Élodie Perrodeau were responsible for data analysis.
Patrick Rozenberg and Isabelle Boutron wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content and gave final approval.

Declaration of interests

We declare no competing interests.

Data sharing

The study dataset, including anonymised individual participant data and a data dictionary defining each field in the dataset, will be available to appropriate academic parties for qualified researchers upon request from the principal investigator, PR. Data availability is in accordance with the hospital ethics committee approval, and subject to submission of a suitable and clinically important study protocol, provided with a signed data access agreement. The study protocol will be made available if necessary for the proposed study. All data will be made available upon publication of this manuscript and be shared via email.

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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/m²	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)

Q_1: first quartile; Q_3: third quartile

IUFD: intrauterine fetal death

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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Table 3. Primary outcome analysis.

	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)

Table 4. Comparison of the proportion of each secondary criterion between the study 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

583 **Table 5. Descriptive analysis of secondary outcomes**

	Study group (n=1472) no. (%)	Control group (n=1476) 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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585 **Figure 1: Enrolment, randomisation, and follow-up of the study participants.**

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