Cervical ripening agents in the second trimester of pregnancy in women with a scarred uterus: a systematic review and metaanalysis of observational studies

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OBJECTIVE: The aim of this systematic review and metaanalysis was to determine the efficacy and safety of cervical ripening agents in the second trimester of pregnancy in patients with previous cesarean delivery.

STUDY DESIGN: Data sources were PubMed, EMBASE, CINAHL, LILACS, Google Scholar, and clinicaltrials.gov (1983 through 2015). Eligibility criteria were cohort or cross-sectional studies that reported on efficacy and safety of cervical ripening agents in patients with previous cesarean delivery. Efficacy was determined based on the proportion of patients achieving vaginal delivery and vaginal delivery within 24 hours following administration of a cervical ripening agent. Safety was assessed by the risk of uterine rupture and complications such as retained placental products, blood transfusion requirement, and endometritis, when available, as secondary outcomes. Of the 176 studies identified, 38 met the inclusion criteria. Of these, 17 studies were descriptive and 21 studies compared the efficacy and safety of cervical ripening agents between patients with previous cesarean and those with no previous cesarean. From included studies, we abstracted data on cervical ripening agents and estimated the pooled risk differences and risk ratios with 95% confidence intervals. To account for between-study heterogeneity, we estimated risk ratios based on underlying random effects analyses. Publication bias was assessed via funnel plots and across-study heterogeneity was assessed based on the I^2 measure.

RESULTS: The most commonly used agent was PGE1. In descriptive studies, PGE1 was associated with a vaginal delivery rate of 96.8%, of which 76.3% occurred within 24 hours, uterine rupture in 0.8%, retained placenta in 10.8%, and endometritis in 3.9% in patients with ≥1 cesarean. In comparative studies, the use of PGE1, PGE2, and mechanical methods (laminaria and dilation and curettage) were equally efficacious in achieving vaginal delivery between patients with and without prior cesarean (risk ratio, 0.99, and 95% confidence interval, 0.98—1.00; risk ratio, 1.00, and 95% confidence interval, 0.98—1.02; and risk ratio, 1.00, and 95% confidence interval, 0.98—1.01; respectively). In patients with history of ≥1 cesarean the use of PGE1 was associated with higher risk of uterine rupture (risk ratio, 6.57; 95% confidence interval, 2.21—19.52) and retained placenta (risk ratio, 1.21; 95% confidence interval, 1.03—1.43) compared to women without a prior cesarean. However, the risk of uterine rupture among women with history of only 1 cesarean (0.47%) was not statistically significant (risk ratio, 2.36; 95% confidence interval, 0.39—14.32), whereas among those with history of ≥2 cesareans (2.5%) was increased as compared to those with no previous cesarean (0.08%) (risk ratio, 17.55; 95% confidence interval, 3.00—102.8). Funnel plots did not demonstrate any clear evidence of publication bias. Across-study heterogeneity ranged from 0-81%.

CONCLUSION: This systematic review and metaanalysis provides evidence that PGE1, PGE2, and mechanical methods are efficacious for achieving vaginal delivery in women with previous cesarean delivery. The use of prostaglandin PGE1 in the second trimester was not associated with significantly increased risk for uterine rupture among women with only 1 cesarean; however, this risk was substantially increased among women with ≥2 cesareans although the absolute risk appeared to be relatively small.

Key words: cesarean delivery, balloon, dilation and evacuation, dinoprostone, Foley catheter, laminaria, misoprostol, prostaglandin E1, prostaglandin E2, prostaglandin F2a, pregnancy termination, prostaglandins, second trimester, uterine rupture, uterine scar

Introduction

The indications for delivery in the second trimester of pregnancy can be the result of obstetrical complications necessitating delivery or pregnancy termination of prenatally diagnosed anomalous fetuses.[1] In such cases, there may be a need for cervical ripening methods. It is noteworthy that 7% of all pregnancy terminations are performed at 14-20 weeks and 1.3% at or >21 weeks' gestation.[2] Given that a third of all pregnancies are delivered by cesarean in the United States,[3] the number of patients with a prior cesarean delivery (CD) who require a cervical ripening agent in the second trimester of pregnancy is expected to increase.

Different methods of cervical ripening have been used in the second trimester of pregnancy in patients with existing uterine scar including mechanical methods (ie, laminaria or cervical dilators) or medical methods (ie, synthetic prostaglandins).[4-6] The purpose of these methods is to achieve an expeditious delivery without significant morbidity. However, one rare but

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well-described serious complication of cervical ripening methods is uterine rupture.[7] Thus, the clinician has to balance the benefit of achieving vaginal delivery in an expeditious manner vs the risk of uterine rupture or any other maternal complications. The efficacy and safety of cervical ripening agents has been extensively studied in the third trimester and in women without a history of CD but much less is known regarding the efficacy vs risks in using these agents in the second trimester in patients with a prior CD.

We undertook a systematic review and metaanalysis to evaluate the efficacy and safety of different cervical ripening agents in the second trimester of pregnancy in patients with previous CD.

Materials and Methods

Identification of studies

This metaanalysis included studies addressing safety and efficacy of cervical ripening methods in the second trimester in patients with ≥1 previous CD. A systematic review of English-language articles was performed using PubMed, EMBASE, CINAHL, LILACS, Google Scholar, and clinicaltrials.gov and by identifying studies cited in the references of published articles. Search terms included "cesarean," "second trimester, pregnancy termination," "misoprostol," "dilation and evacuation," "dinoprostone," "PGE2 analogues," "Foley catheter," "balloon," "laminaria," "hypertonic saline," "mifepristone," "PG analogues," "PGF2α," "synthetic dilators," "oxytocin," "hysterotomy," and combinations of these. Articles were included from January 1983 through May 2015.

Eligibility criteria

Studies were included for review if data were available regarding efficacy and safety of cervical ripening methods in patients with previous CD. Case reports and case series with <5 cases were excluded. Abstracts and poster presentations were included for review only if they included the aforementioned relevant information. We included both descriptive studies and studies comparing efficacy and safety of different ripening agents between patients with previous CD and those with no uterine scar.

Study selection

Two authors (M.A. and J.A.L.) were involved in identifying the eligible manuscripts; 176 were initially identified, of which 106 were excluded, after screening the title and abstract, as not being relevant to the aims of the metaanalysis. The texts of the remaining 70 manuscripts were fully reviewed,[4,5,8-75] from which case reports or case series with <5 patients (n = 12),[45,46,54-59,61,62,66,67] reviews (n = 4),[49,50,53,74] and a letter to the editor (n = 1)[64] were further excluded. We also excluded non-English-language articles (n = 4)[44,48,68,70] because it has been shown that exclusion of such articles has little effect on summary treatment estimates.[76] Additionally, studies where the outcomes of interest was impossible to match with the history of CD (n = 1)[52] or studies with no information or incomplete or not extractable information on cases with previous CD or studies which included small number of cases with previous CD were excluded (n = 6).[51,60,63,72,73,75] Articles where the patients within the study group had received multiple ripening methods were excluded on the basis that conclusions could not be drawn for each ripening method separately (n = 3)[65,69,71] (Figure 1). Also 1 study, which did not separate first- from second-trimester cases, was excluded, as we could not isolate the second-trimester termination cases.[47] This selection process resulted in 38 studies that fit our inclusion criteria, all of which were reviewed by 1 author (M.A.).[4,5,8-43] In cases of uncertainty regarding inclusion or exclusion, 2 other authors were consulted (C.V.A. and A.M.V.).

Data collection process

Information regarding the type of study; country of origin; year the study was conducted; ripening agent used; gestational age; dose of ripening agent and the protocol used; mode of delivery; duration of delivery; and complications such as uterine rupture, blood transfusion requirement, endometritis, retained placental tissue, and analgesia were collected. When the range of gestational age was not clearly specified, we allocated the studies to second-trimester group according to mean or median gestational age (<28 weeks for second trimester). When prostaglandins were used as ripening agent (with or without oxytocin), this was defined as the main agent. The only exception was when 1 dose of prostaglandin was given prior to dilation and evacuation.[43] These studies were classified under mechanical methods because mechanics was the final main method of termination.

Primary and secondary outcomes

The primary outcome in terms of efficacy of ripening agents was the proportion of patients achieving vaginal delivery (primary measure) as well as vaginal delivery within 24 hours (secondary measure). Safety was assessed as a secondary outcome by the risk of uterine rupture (primary measure) and complications such as retained placental products, blood transfusion requirement, and endometritis, if available (secondary measures). In determining uterine rupture, we grouped true uterine rupture and silent uterine rupture (or dehiscence) together, since silent rupture can be considered as a "near miss." In addition, it was not always possible to separate out the patients with uterine rupture from those with silent uterine rupture (dehiscence) because the authors did not always distinguish between these 2 conditions. The risk of uterine rupture was assessed overall for patients with ≥1 CD and also in the subgroups with only 1 and ≥2 prior CD if the data were available.

Data synthesis

From descriptive studies we collected descriptive statistics regarding the rate of the outcome in women with a previous CD. Summary measures reported in comparative studies included the risk difference and risk ratio (RR) with 95% confidence intervals (CI) comparing the risk of the outcome in the group with a previous CD to the risk in the group without a previous CD. Risk differences and RR were computed in Review