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.

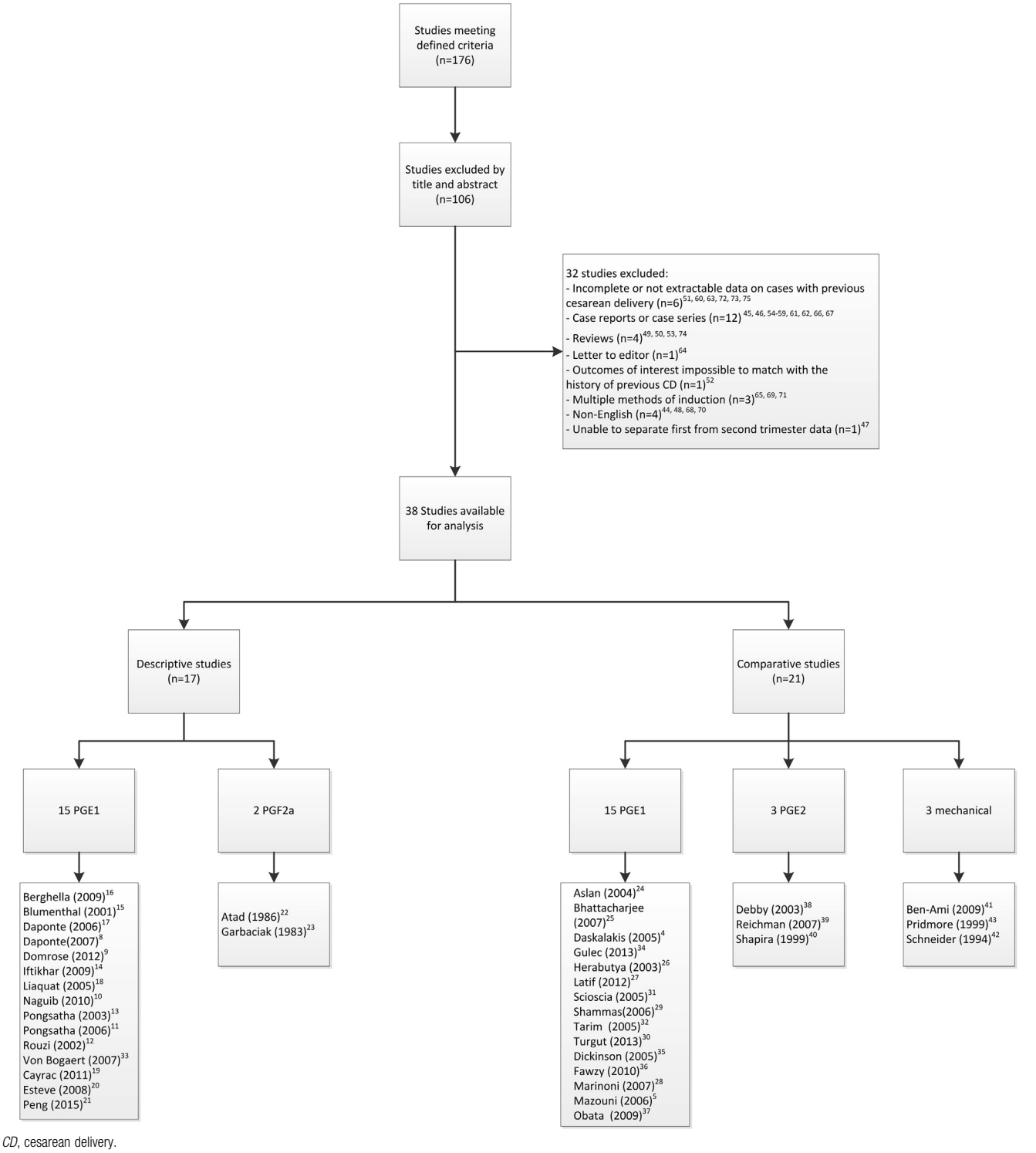
Primary and secondary outcomes

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

FIGURE 1
Flow chart indicating study selection process



CD, cesarean delivery.

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Manager v5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) via the inverse variance method in a random effects analysis.[77] In the absence of heterogeneity across studies, the random effects model will match a fixed effects analysis. In the presence of heterogeneity across studies, this method produces wider CI, and so is more conservative in its

TABLE 1
Characteristics of descriptive studies

Study (year)	Country	Duration	Total no. of subjects	Method of induction of labor	Outcomes
Berghella et al[16] (2009)	United States	1998 through 2004	17	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Blumenthal and Medina[15] (2001)	United States	1997 through 2000	10	PGE1	Vaginal delivery rate, uterine rupture, endometritis, blood transfusion
Daponte et al[17] (2006)	South Africa	1997 through 2000	85	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Daponte et al[8] (2007)	South Africa	3 y	21	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception
Domröse et al[9] (2012)	Germany	2005 through 2009	100	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Iftikhar and Burney[14] (2009)	Pakistan	2007 through 2009	50	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception
Liaquat et al[18] (2006)	Pakistan	2003 through 2005	5	PGE1	Vaginal delivery rate, uterine rupture
Naguib et al[10] (2010)	Egypt	January 2008 through August 2008	50	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Pongsatha and Tongsong[13] (2003)	Thailand	Not reported	21	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception
Pongsatha and Tongsong[11] (2006)	Thailand	2003 through 2005	17	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Rouzi[12] (2003)	Saudi Arabia	1998 through 2002	10	PGE1	Vaginal delivery rate, uterine rupture
van Bogaert[33] (2008)	South Africa	9 mo (year unspecified)	18	PGE1	Uterine rupture
Cayrac et al[19] (2011)	France	2000 through 2008	67	PGE1, mifepristone, laminaria	Vaginal delivery rate, uterine rupture, endometritis, blood transfusion
Esteve et al[20] (2008)	Spain	2003 through 2007	17	PGE1, mifepristone	Vaginal delivery rate, uterine rupture
Peng et al[21] (2015)	China	2006 through 2013	33	PGE1, mifepristone	Vaginal delivery rate, uterine rupture
Atad et al[22] (1986)	Israel	Not reported	13	PGF2α	Vaginal delivery rate, uterine rupture, blood transfusion
Garbaciak and Benzie[23] (1983)	Canada	1972 through 1979	38	PGF2α, hypertonic saline, laminaria	Vaginal delivery rate, uterine rupture, endometritis, retained products of conception

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TABLE 2
Characteristics of comparative studies

Study (year)	Country	Duration	Design	Total no. of subjects	Method of induction of labor	Outcomes
Aslan et al[24] (2004)	Turkey	1999 through 2002	Retrospective cohort	91	PGE1	Vaginal delivery rate, uterine rupture
Bhattacharjee et al[25] (2007)	India	2003 through 2006	Retrospective cohort	160	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion, endometritis, retained products of conception
Daskalakis et al[4] (2005)	Greece	1997 through 2002	Retrospective cohort	324	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception, endometritis
Güleç et al[34] (2013)	Turkey	2007 through 2010	Retrospective cohort	279	PGE1	Vaginal delivery rate, uterine rupture
Herabutya et al[26] (2003)	Thailand	1996 through 2002	Prospective cohort	584	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception
Latif et al[27] (2012)	Egypt	2010 through 2012	Prospective cohort	210	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception, blood transfusion
Marinoni et al[28] (2007)	Italy	1998 through 2005	Retrospective cohort	429	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Scioscia et al[31] (2007)	Italy	2000 through 2005	Retrospective cohort	423	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Shammas and Momani[29] (2006)	Jordan	2000 through 2004	Prospective cohort	520	PGE1	Vaginal delivery rate, uterine rupture, retained products of conception, blood transfusion
Tarim et al[32] (2005)	Turkey	1998 through 2004	Prospective cohort	57	PGE1	Vaginal delivery, uterine rupture
Turgut et al[30] (2013)	Turkey	2009 through 2012	Retrospective cohort	219	PGE1	Vaginal delivery rate, uterine rupture, blood transfusion
Dickinson[35] (2005)	Australia	1997 through 2004	Retrospective cohort	720	PGE1, Foley	Vaginal delivery rate, blood transfusion, retained products of conception
Fawzy and Abdel-Hady[36] (2010)	Egypt	2006 through 2009	Prospective cohort	138	PGE1, Foley	Vaginal delivery rate, uterine rupture, blood transfusion, retained products of conception
Mazouni et al[5] (2006)	France	2000 through 2004	Retrospective cohort	252	PGE1, mifepristone, PGE2	Vaginal delivery rate, uterine rupture, retained products of conception, blood transfusion
Obata-Yasuoka et al[37] (2009)	Japan	1999 through 2006	Retrospective cohort	195	PGE1, laminaria	Vaginal delivery rate, uterine rupture, blood transfusion
Debby et al[38] (2003)	Israel	1987 through 2000	Retrospective cohort	261	PGE2	Vaginal delivery rate, uterine rupture, retained products of conception
Reichman et al[39] (2007)	Israel	1999 through 2004	Retrospective cohort	375	PGE2	Vaginal delivery rate, uterine rupture, blood transfusion
Shapira et al[40] (1999)	Israel	1992 through 1997	Retrospective cohort	282	PGE2	Vaginal delivery rate, uterine rupture, blood transfusion
Ben-Ami et al[41] (2009)	Israel	2002 through 2008	Retrospective cohort	636	Laminaria, dilation and evacuation	Vaginal delivery rate, uterine rupture, blood transfusion, retained products of conception

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TABLE 2
Characteristics of comparative studies *(continued)*

Study (year)	Country	Duration	Design	Total no. of subjects	Method of induction of labor	Outcomes
Pridmore and Chambers[43] (1999)	South Australia	1992 through 1998	Retrospective and prospective cohort	1869	Laminaria, dilation and evacuation, PGE1	Vaginal delivery rate, uterine rupture
Schneider et al[42] (1994)	Israel	1978 through 1993	Retrospective cohort	1064	Laminaria, dilation and evacuation	Vaginal delivery rate, uterine rupture, blood transfusion

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TABLE 3
Efficacy and safety of PGE1 and PGF2α in patients with previous cesarean delivery in second trimester based on descriptive studies

Outcomes	PGE1	PGF2α
Vaginal delivery, % (range)	96.8 (75–100)	100
No. of studies	13[8-12,14-21]	2[22,23]
No. of subjects	473	51
Delivery <24 h, % (range)	76.3 (84–100)	100
No. of studies	3[9,12,14]	1[22]
No. of subjects	160	13
Uterine rupture, % (range)	0.8 (0.0–5.9)	0
No. of studies	15[8-21,33]	2[22,23]
No. of subjects	512	51
Blood transfusion, % (range)	1.4 (0.0–5.9)	0 (–)
No. of studies	7[8,10,11,15-17,19]	1[22]
No. of subjects	346	13
Retained placenta, % (range)	10.8 (8.0–25.0)	31.6 (–)
No. of studies	3[13,14,17]	1[23]
No. of subjects	83	38
Endometritis, % (range)	3.9 (3.0–10.0)	5.3 (–)
No. of studies	2[15,19]	1[23]
No. of subjects	77	38

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estimates of the risk difference and RR. Between-study heterogeneity was assessed based on the I^2 measure, and substantial heterogeneity was considered to be an I^2 >50%.

Assessment of risk of bias

Each study was evaluated for potential bias based on 6 measures. These included representativeness of the population, ascertainment of the exposure, assessment of the outcomes, blinding of the investigators to the exposure, incomplete outcome data (loss to follow-up), and control for confounders. Each of these 6 measures were rated on a 3-level color scale with green denoting that the criterion was met, red denoting that the criterion was not met, and orange denoting an uncertain status. For the 6 criteria, studies received a red rating if the study were conducted in a way that could introduce bias or decrease generalizability. For example, single-center studies received a red rating for being representative of the population, because it is possible that patients at a single institution are more similar to each other and not necessarily representative of all patients in the population. Studies received a rating of green for a bias criterion if there was little or no concern that the study methods introduced bias. For example, for the criterion of incomplete outcome data, studies received a green rating when none of the outcome data were missing for the primary outcome of vaginal delivery.

Results

Study selection and characteristics

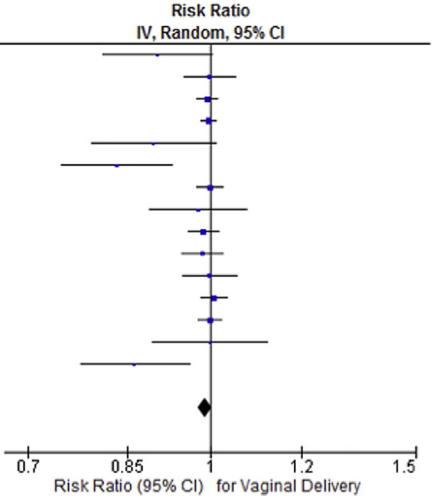
In all, 38 observational studies met the inclusion criteria. There were no randomized controlled trials. Seventeen

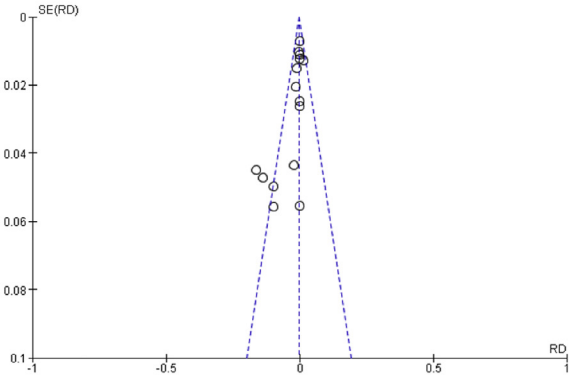
FIGURE 2
Metaanalysis, forest, and funnel plots of comparative studies using prostaglandin E1

A

Study or Subgroup	Prior Cesarean Delivery Events	Total	No Prior Cesarean Delivery Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Aslan 2003	37	41	50	50	1.4%	0.90 [0.81, 1.00]
Bhattacharjee 2007	78	80	78	80	5.2%	1.00 [0.95, 1.05]
Daskalakis 2005	107	108	215	216	13.4%	1.00 [0.98, 1.02]
Dickinson 2005	101	101	618	619	16.0%	1.00 [0.98, 1.01]
Fawsy 2009	28	31	107	107	1.1%	0.89 [0.79, 1.01]
Gulec 2013	69	86	186	193	1.4%	0.83 [0.75, 0.93]
Herabutya 2003	56	56	528	528	11.7%	1.00 [0.98, 1.02]
Latif 2012	71	80	118	130	1.7%	0.98 [0.89, 1.08]
Marioni 2006	66	67	361	362	9.7%	0.99 [0.96, 1.02]
Mazouni 2006	49	50	201	202	6.8%	0.98 [0.95, 1.03]
Obata 2009	26	26	167	167	4.8%	1.00 [0.95, 1.05]
Scioscia 2005	64	64	340	345	11.4%	1.01 [0.98, 1.03]
Shammas 2006	63	63	457	457	12.7%	1.00 [0.98, 1.02]
Tarim 2004	12	12	45	45	1.3%	1.00 [0.89, 1.12]
Turgut 2013	48	56	162	163	1.4%	0.86 [0.77, 0.96]
Total (95% CI)		**921**		**3664**	**100.0%**	**0.99 [0.98, 1.00]**
Total events	875		3633			

Heterogeneity: Tau² = 0.00; Chi² = 25.48, df = 14 (P = 0.03); I² = 45%
Test for overall effect: Z = 1.48 (P = 0.14)

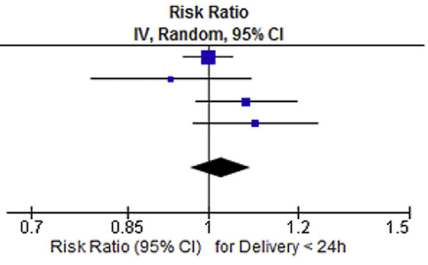




B

Study or Subgroup	Prior Cesarean Delivery Events	Total	No Prior Cesarean Delivery Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bhattacharjee 2007	78	80	78	80	47.8%	1.00 [0.95, 1.05]
Daskalakis 2005	71	108	153	216	11.5%	0.93 [0.79, 1.09]
Dickinson 2005	83	101	471	619	23.4%	1.08 [0.98, 1.19]
Shammas 2006	52	63	343	457	17.2%	1.10 [0.97, 1.25]
Total (95% CI)		**352**		**1372**	**100.0%**	**1.03 [0.97, 1.09]**
Total events	284		1045			

Heterogeneity: Tau² = 0.00; Chi² = 4.54, df = 3 (P = 0.21); I² = 34%
Test for overall effect: Z = 0.85 (P = 0.40)



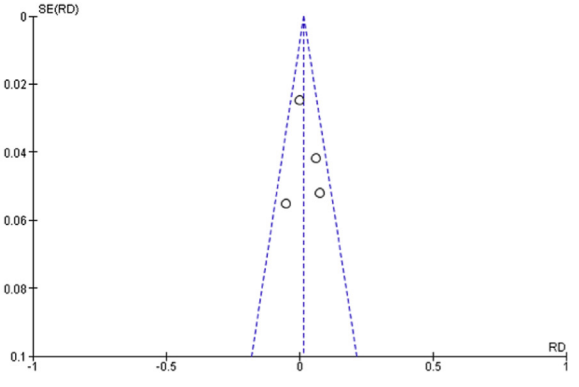


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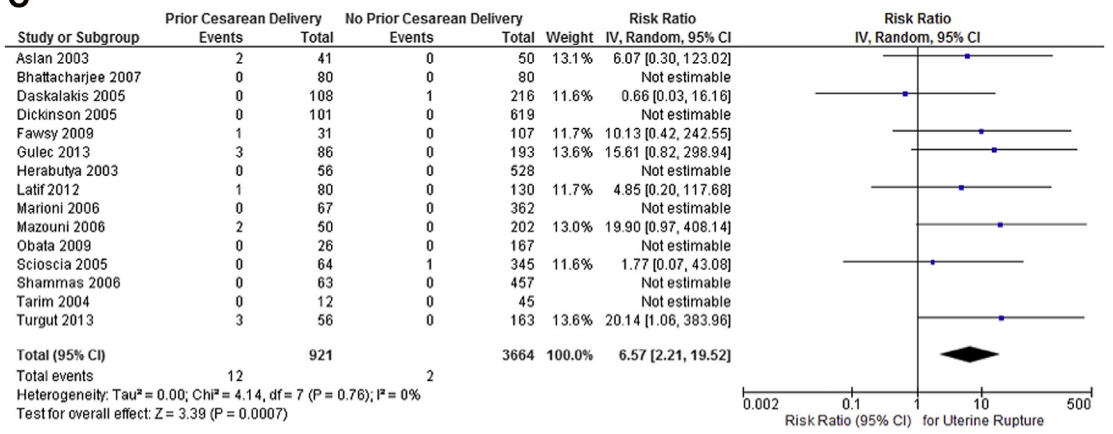
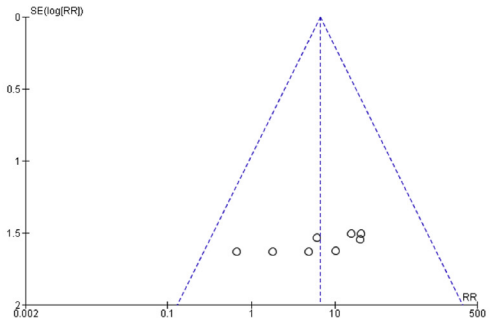
FIGURE 2
(Continued)

C





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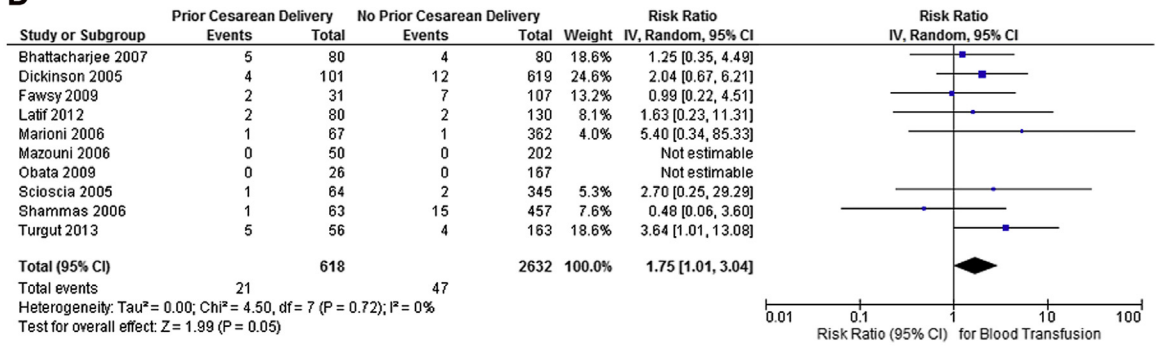

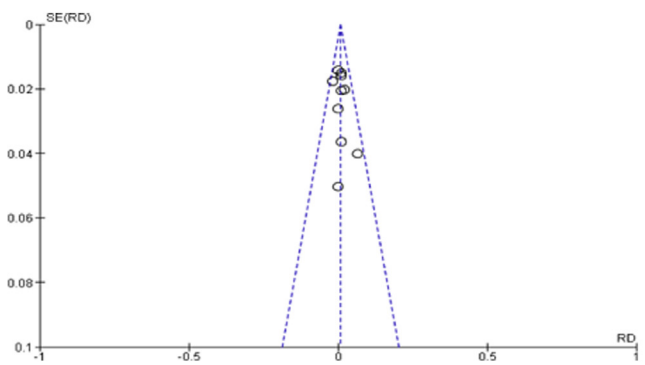

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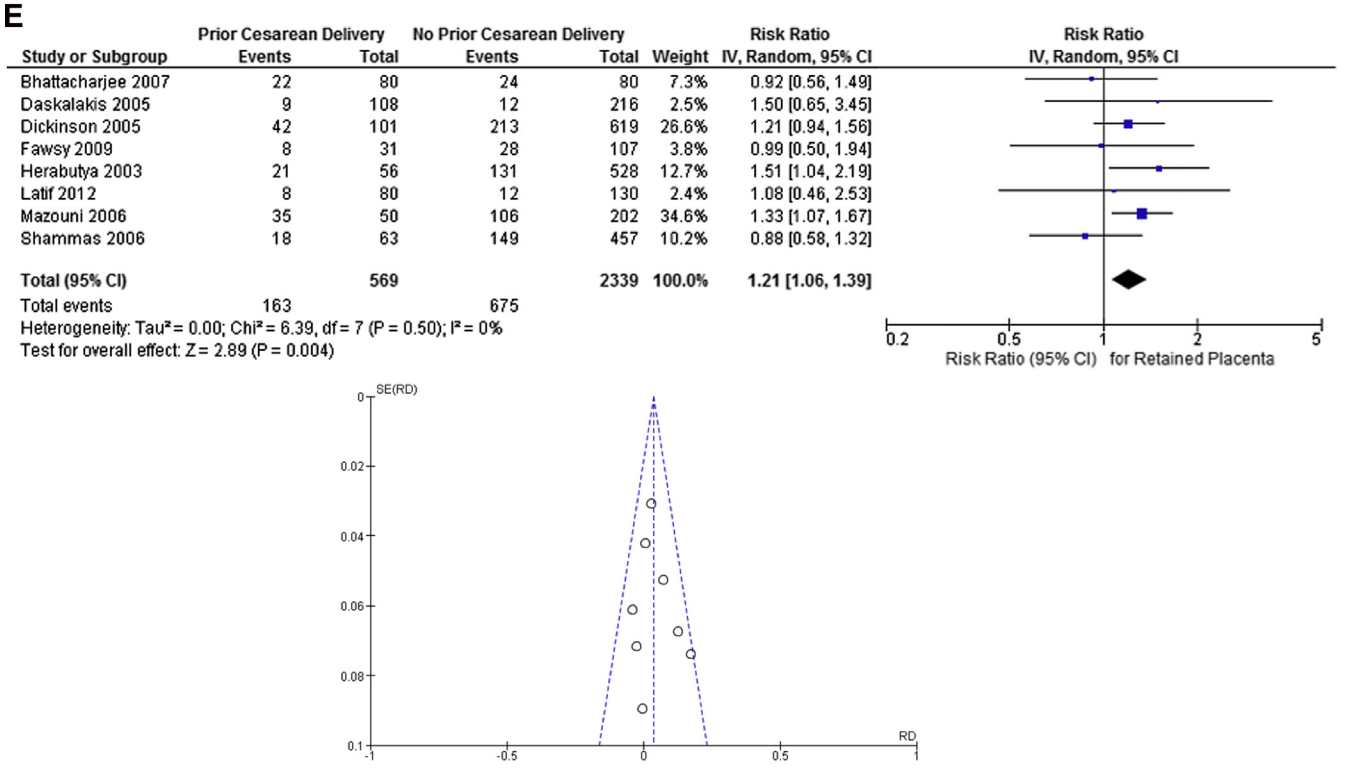
FIGURE 2
(Continued)

E



Comparison of efficacy (**2A, 2B**) and safety (**2C, 2D, 2E**) of prostaglandin E1 in patients with history of one or more cesarean compared to no history of uterine scar.

CI, confidence interval; *RD*, risk difference; *RR*, risk ratio.

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studies were descriptive without a comparison group (563 patients)[8-23,33] and 21 studies compared the efficacy and safety of cervical ripening agents between patients with previous CD and those with no uterine scar (8419 patients).[4,5,24-32,34-43] The individual characteristics of the descriptive and comparative studies are outlined in Tables 1 and 2.

Results of individual studies

The most commonly used agent in both descriptive and comparative studies was PGE1; it was used in 15 descriptive[8-21,33] and in 15 comparative[4,5,24-32,34-37] studies. Descriptive studies contained information only for PGE1, PGE1 in combination with other agents, and PGF2α. Based on the descriptive studies, PGE1 was associated with vaginal delivery rate of 96.8% (13 studies, 473 patients) with 76.3% of the patients delivering in <24 hours (3 studies, 160 patients), uterine rupture 0.8% (15 studies, 512 patients), blood transfusion 1.4% (7 studies, 346 patients), retained placenta 10.8% (3 studies, 83 patients), and endometritis 3.9% (2 studies, 77 patients). There were only 2 descriptive studies on PGF2α, which included 51 women with previous CD.[22,23] The use of PGF2α was associated with 100% vaginal delivery rates and no cases of uterine rupture (Table 3).

Synthesis of findings

In the comparative studies, the safety and efficacy of induction of labor methods were compared between patients with previous CD and patients with no uterine scar. The comparative studies contained information only for PGE1, PGE2, and mechanical methods. The use of PGE1, PGE2, and mechanical methods were equally efficacious in achieving vaginal delivery, as well as delivery within 24 hours, between patients with and without prior CD (RR, 0.99, and 95% CI, 0.98−1.00; RR, 1.00, and 95% CI, 0.98−1.02; and RR, 1.00, and 95% CI, 0.98−1.01; respectively). However, patients with ≥1 prior CD that used PGE1 had higher risk of uterine rupture (RR, 6.57; 95% CI, 2.21−19.52), retained placenta (RR, 1.21; 95% CI, 1.03−1.43), and blood transfusion (RR, 1.75; 95% CI, 1.01−3.04) compared to women without a prior CD (Figure 2 and Table 4). We also analyzed the risk of uterine rupture based on the number of previous CD when PGE1 was used. We found that the risk of uterine rupture among women with only 1 CD (0.47%) was not statistically significant (RR, 2.36; 95% CI, 0.39−14.32), whereas among

TABLE 4
Comparison of safety and efficacy of ripening agents in patients with history of cesarean compared to no history of uterine scar

	PGE1					PGE2					Mechanical methods				
		Frequency, %[a]					Frequency, %[a]					Frequency, %[a]			
	No. of studies	Previous CD	No CD	RR (95% CI)	RD (95% CI)	No. of studies	Previous CD	No CD	RR (95% CI)	RD (95% CI)	No. of studies	Previous CD	No CD	RR (95% CI)	RD (95% CI)
Efficacy															
Vaginal delivery	15[4,5,24-32,34-37]	95.0	99.2	0.99 (0.98–1.00)	−0.01 (−0.03 to 0.00)	3[38-40]	100.0	99.9	1.00 (0.98–1.02)	0.00 (−0.02 to 0.02)	3[41-43]	98.6	99.9	1.00 (0.98–1.01)	−0.00 (−0.02 to 0.01)
Delivery <24 h	4[4,25,29,35]	80.7	76.2	1.03 (0.97–1.09)	0.02 (−0.03 to 0.07)	—	—		—		2[41,42]	100	100	1.00 (0.99–1.01)	0.00 (−0.01 to 0.01)
Safety															
Uterine rupture	15[4,5,24-32,34-37]	1.3	0.05	6.57 (2.21–19.52)	0.00 (−0.00 to 0.01)	3[38-40]	0	0	N/A	0.00 (−0.02 to 0.02)	3[41-43]	1.4	0.1	19.25 (3.97–93.38)	0.00 (−0.01 to 0.02)
Blood transfusion	10[5,25,27-31,35-37]	3.4	1.8	1.75 (1.01–3.04)	0.01 (−0.01 to 0.02)	2[39,40]	2.9	1.3	2.43 (0.62–9.56)	0.02 (−0.02 to 0.05)	2[41,42]	0	0.8	0.74 (0.10–5.65)	−0.01 (−0.02 to 0.01)
Retained placenta	5[5,27,29,35,44]	31.0	32.3	1.21 (1.03–1.43)	0.05 (−0.02 to 0.12)	1[38]	0.0	0.4	2.42 (0.10–58.07)	−0.00 (−0.05 to 0.04)	1[41]	0	0	N/A	0.00 (−0.02 to 0.02)
Endometritis	2[4,2]	3.7	3.4	1.05 (0.41–2.70)	0.00 (−0.03 to 0.04)	—	—	—	—	—	—	—	—	—	—

CD, cesarean delivery; *CI*, confidence interval; *N/A*, not applicable; *RD*, risk difference; *RR*, risk ratio.

[a] Unweighted and reflect overall risk of outcome measure among women with previous CD and women without previous CD in studies listed. RR and RD columns are weighted analyses; weights are provided in each figure.

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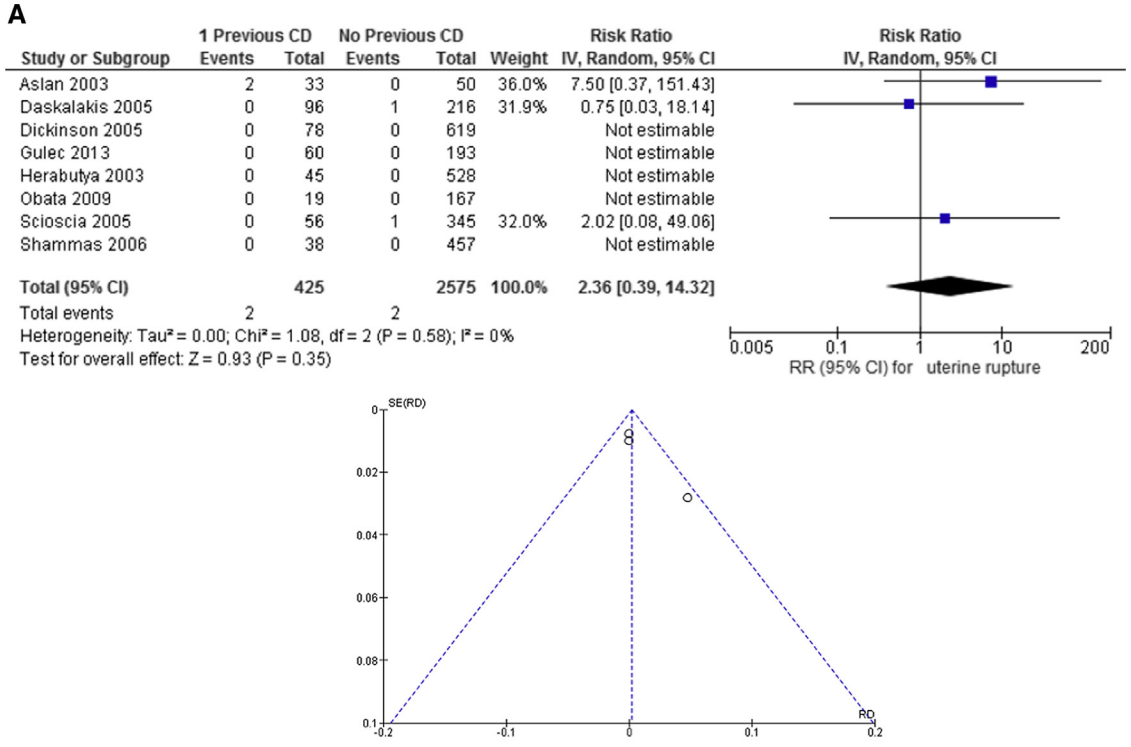
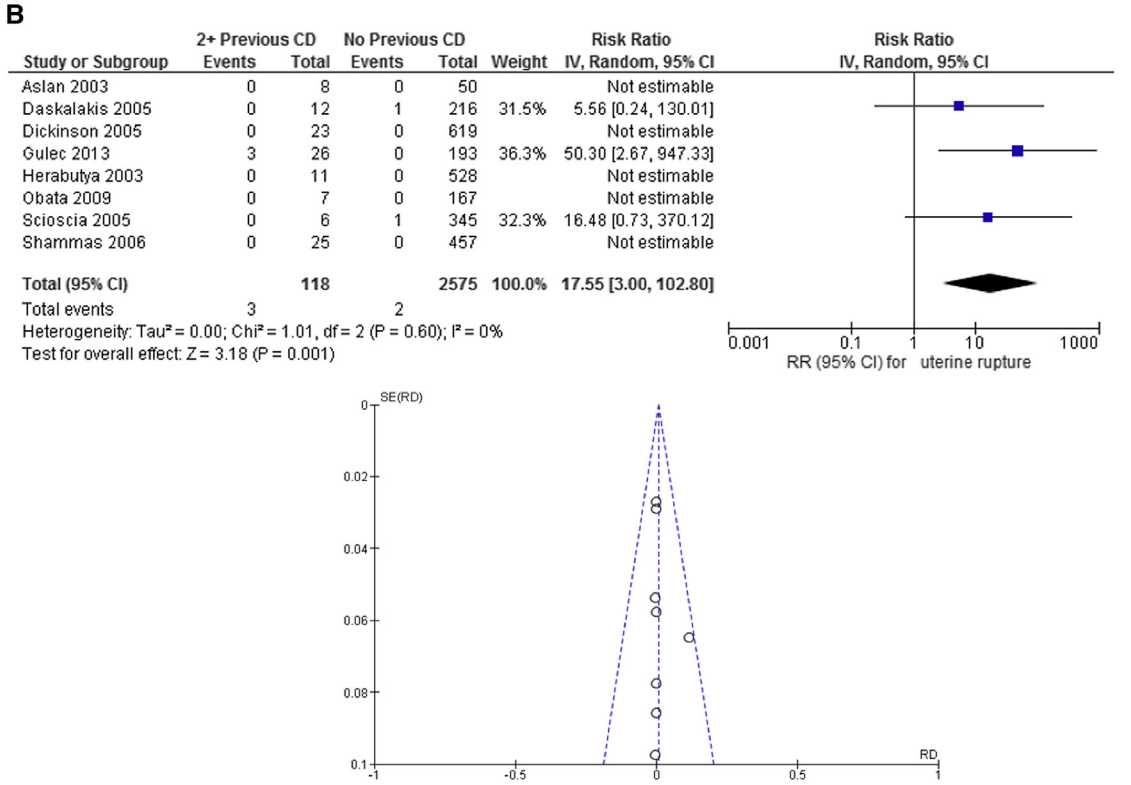
FIGURE 3
Metaanalysis, forest, and funnel plots of comparative studies according to the number of prior cesarean deliveries

A



B



Comparison of safety of prostaglandin E1 in patients with history of **A**, only 1 or **B**, ≥2 cesarean deliveries (CD) compared to no history of uterine scar.

CI, confidence interval; *RD*, risk difference; *RR*, risk ratio.

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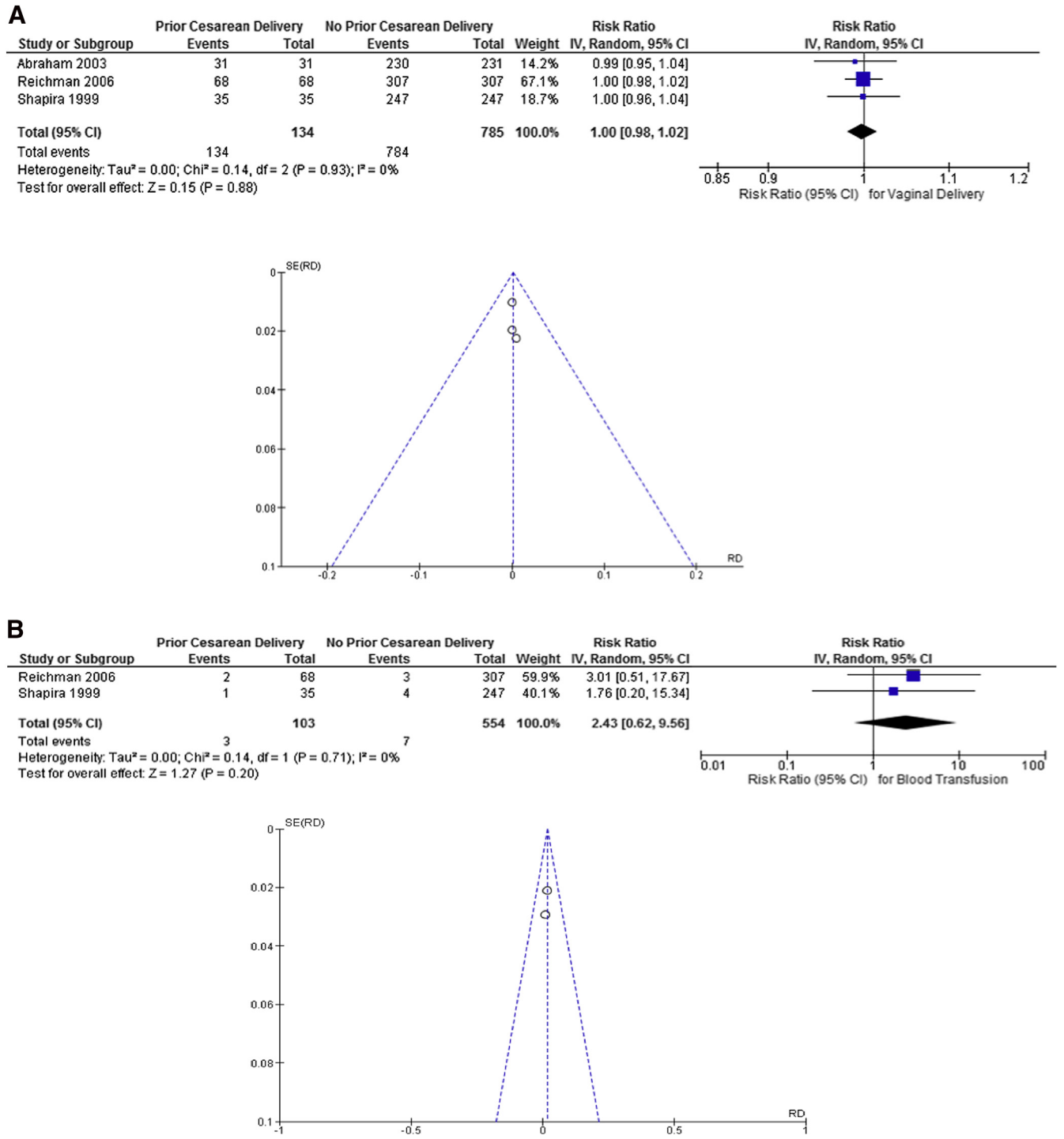
FIGURE 4
Metaanalysis, forest, and funnel plots of comparative studies using prostaglandin E2



Comparison of **A**, efficacy and **B**, safety of prostaglandin E2 in patients with history of cesarean delivery compared to no history of uterine scar.

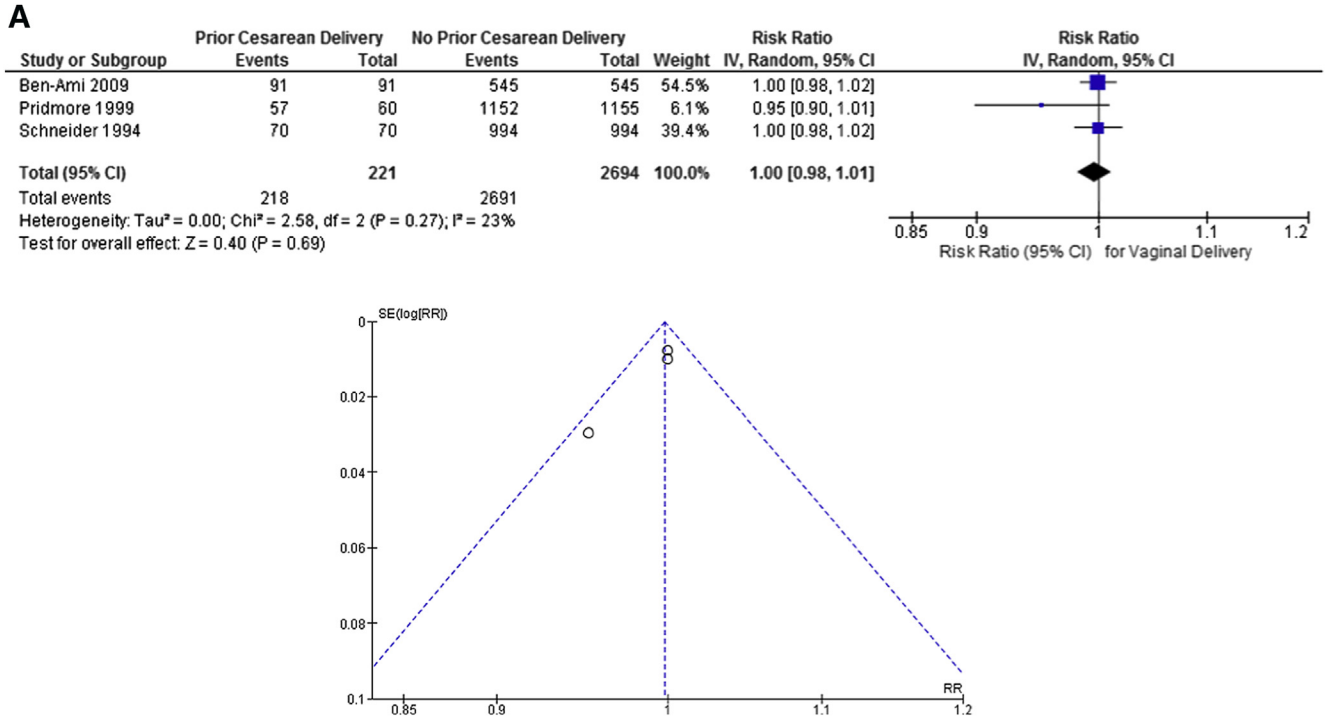
CI, confidence interval; *RD*, risk difference.

Andrikopoulou. Second-trimester cervical ripening agents in patients with previous cesarean delivery. Am J Obstet Gynecol 2016.

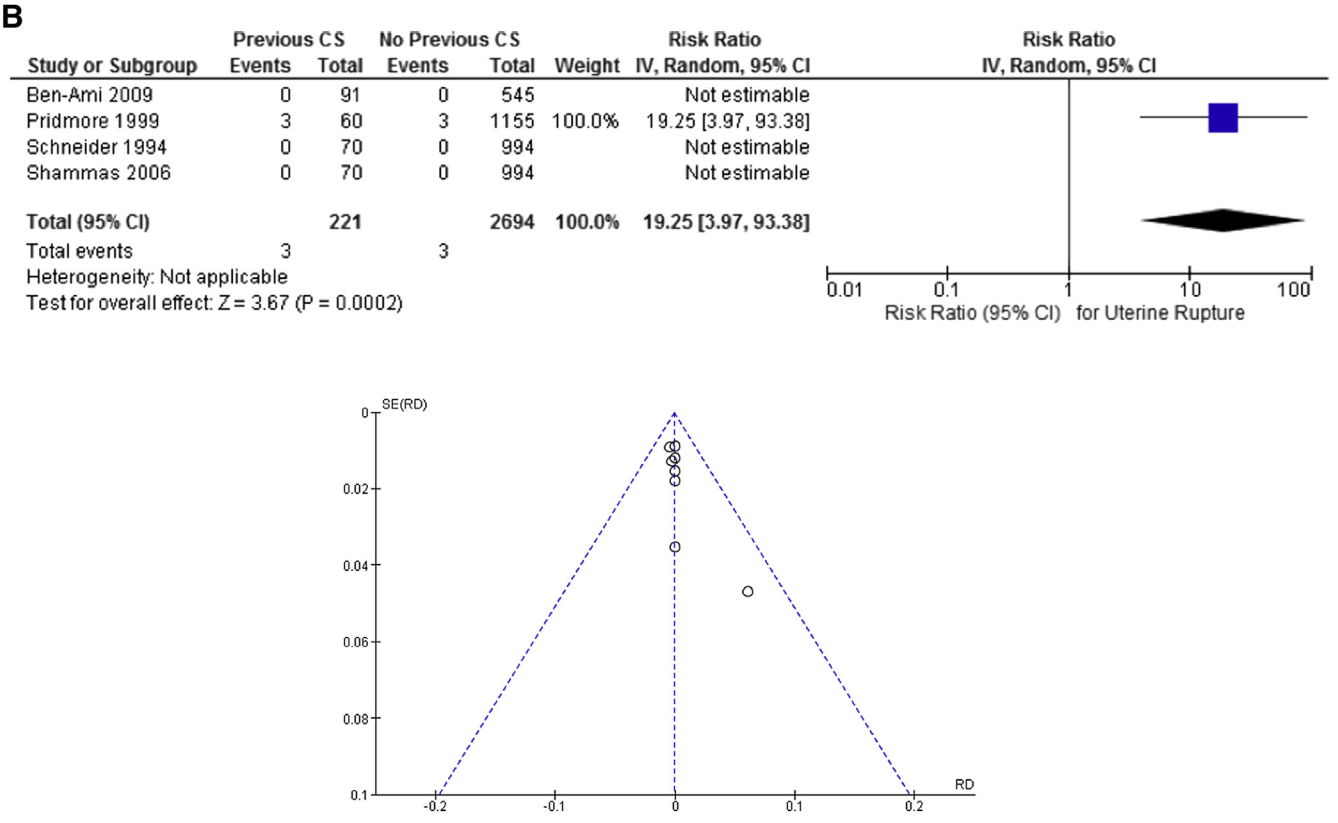
those with ≥2 CD (2.5%), it was significantly increased as compared to those with no previous CD (0.08%) (RR, 17.55; 95% CI, 3−102.8) (Figure 3). This separate analysis for women with only 1 vs ≥2 previous CD could not be reliably performed for the other cervical ripening agent due to small number of studies.

FIGURE 5
Metaanalysis, forest and funnel plots of comparative studies using mechanical methods

A



B



Comparison of **A**, efficacy and **B**, safety of mechanical methods in patients with history of cesarean delivery (CS) compared to no history of uterine scar.

CI, confidence interval; *RD*, risk difference; *RR*, risk ratio.

Andrikopoulou. Second-trimester cervical ripening agents in patients with previous cesarean delivery. Am J Obstet Gynecol 2016.

FIGURE 6
Risk of bias across studies

Andrikopoulou. Second-trimester cervical ripening agents in patients with previous cesarean delivery. Am J Obstet Gynecol 2016. *(continued)*

The use of PGE2 or laminaria with dilation and evacuation was examined in a smaller number of studies. There were 3 retrospective cohort studies on PGE2 in second trimester, which included a total of 134 women with a uterine scar[38-40] and 3 retrospective studies on laminaria and dilation and evacuation with 221 women with previous CD[41-43] (Table 4). There were no documented cases of uterine rupture among those using PGE2. The risk for blood transfusion with PGE2 was similar between women with and without a prior CD (Figure 4). Among mechanical methods (dilation and evacuation) there was a significantly increased risk of uterine rupture in patients with ≥1 CD as compared to those with no previous CD (1.4% vs 0.11%; RR, 19.25; 95% CI, 3.97–93.38) (Figure 5).

Assessment of risk of bias across studies

A tabulation of every study based on bias characteristics is shown in Figure 6. Of the 38 studies included, 34 studies were based on a single institution, 1 study was conducted in 2 hospitals, 1 study was based on 1 hospital and some private clinics, and 1 study included patients from many hospitals from different cities. In 1 study the number of hospitals included was not clearly stated.[33] Nineteen studies were reported to contain any bias in the ascertainment of the exposure or the outcome, and none of the studies had a blinding of the investigators to either the exposure or the outcome. Two of the 38 studies were reported as incomplete case ascertainment. With the exception of 1 study that reported adjustment for confounding factors, and 2 with probable adjustment for confounders, none of the other studies reported any adjustment for confounders. The exclusion criterion was mentioned in 15 of the 38 studies.

Comment

Principal findings

We found that PGE1 was the most commonly used agent and had great efficacy achieving vaginal delivery in 75-100% of the cases in both descriptive and comparative studies with approximately three fourths of patients delivering

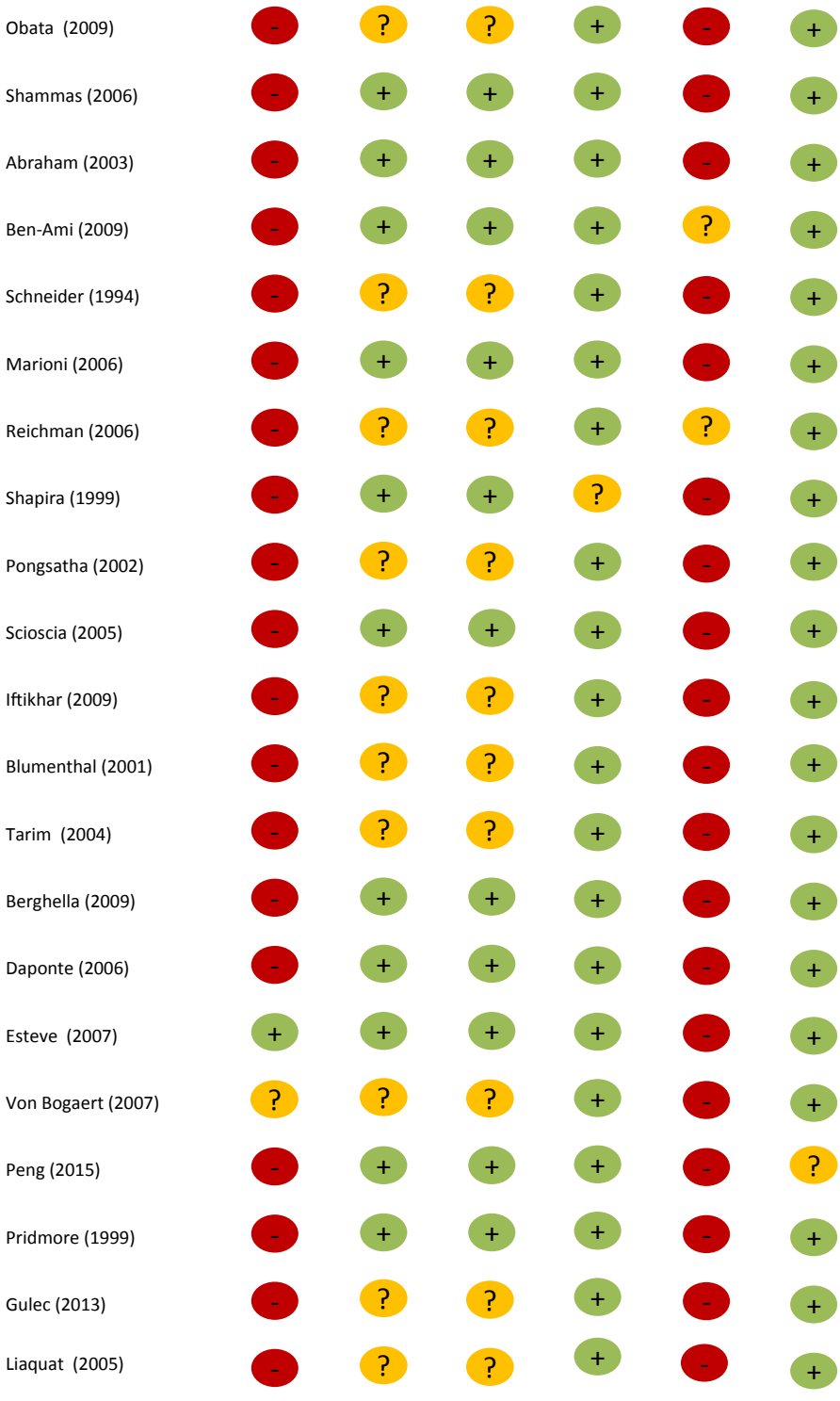
within 24 hours. Although PGE1 use was associated with increased risk of uterine rupture, this became significant only among women with ≥2 previous CD as compared to those with intact uterus; however, it should be noted that although the RR was increased by 17 times, the absolute risk was only 2.5%. The risk of blood transfusion was reported as 0-5.9%, endometritis 3.0-10.0%, and retained placental tissue 8.0-25.0%. The risk of retained placental tissue was also increased in cases with previous CD compared to women with no uterine scar among women who received PGE1. The results were similar for the risk for blood transfusion. The large number of studies using PGE1 for delivery in patients with prior CD and the combined number of subjects included in the metaanalysis enhances the strength of these conclusions.

The use of PGE2 was examined in a smaller number of studies. These studies showed the same efficacy of termination of pregnancy in second trimester in patients with previous CD compared to patients with no uterine scar. In terms of complications, no documented cases of uterine rupture were reported for this ripening agent.

In regards to PGF2α, it was also examined in only 2 descriptive studies. Its use was associated with 100% vaginal delivery rates and no cases of uterine rupture. However, it was interesting to note that for PGF2α the absolute risk of retained placental products was reported as high as 31.6%.

The majority of studies included in the metaanalysis examined the use of methods of induction in cases of indicated pregnancy termination in the setting of previous CD.[4,5,9-15,18-22,24-29,32,34-41] The chief indications for pregnancy termination included in utero fetal demise, chromosomal anomalies, structural fetal defects, hemoglobinopathy, preterm premature rupture of membranes, fetal infection, and severe maternal disease. However, some studies also included cases of elective termination for social reasons,[8,22,25,26,38,40,41] and in some studies

FIGURE 6
(Continued)



Assessment of bias in individual studies.

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the indications for termination were not clearly stated.[16,23,30,31,33,43]

Meaning of the findings—clinical implications

Given the high rate of CD in United States,[3] induction of labor in the second trimester in women with a uterine scar and unfavorable cervix has become a common challenge in obstetrics. Different methods of cervical ripening have been used, including synthetic prostaglandins (PGE1 and PGE2, PGF2α), and mechanical methods such as dilatation using laminaria, Foley catheter, Cook balloon, or double balloon devices.[78-80] However, most studies of labor induction have been focused on the third trimester of pregnancy in women without uterine scar.[81-90] Thus, the efficacy and safety profile of these methods of induction of labor in the second trimester in women with previous CD has remained largely unknown.

The primary concern in using cervical ripening agents in patients with previous CD is the potential risk of uterine rupture that can be life threatening. Some studies have concluded that induction of labor in the second trimester with prostaglandins can lead to reduction of repeat CD without increasing the risk of uterine rupture.[4,27] However, other studies have yielded contradictory results.[65,71] This review and metaanalysis provides evidence that the use of prostaglandin PGE1 in the second trimester is associated with great efficacy and it is relatively safe for women with only 1 previous CD. In women with $\geq$2 previous CD the risk of uterine rupture is significantly increased as compared to those without previous CD, but the absolute risk appears relatively small (2.5%).

Strengths and weaknesses

The strengths of the study include clinically important conclusions regarding the efficacy and safety of cervical ripening agents in cases of previous CD scar in induction of labor in the second trimester. We included studies in which we had to identify the cases with previous CD and additionally we performed a subanalysis on the risk of uterine rupture according to number of previous CD. Given that the literature on this topic is very limited, these conclusions can provide guidance for clinical decisions.

One of the weaknesses of this metaanalysis is that the type of agents, doses, and routes of administration varied widely among the studies given the lack of uniform protocols in different hospitals. Thus, in cases where >1 agent was used, the study was assigned to a group according to the main agent used. Another limitation is the nonuniform reporting of the number of previous CD (1 or >1) as well as the lack of information regarding the type of previous uterine scar especially in cases of uterine rupture. Additionally, we could not identify studies that compared the efficacy and safety of different cervical ripening agents when used in patients with previous CD.

Research implications

It is our belief that appropriately powered randomized controlled trials are needed to clearly demonstrate the efficacy and safety of these agents. Until then, the results of our metaanalysis may be used for patient counseling and to alert the physician of the efficacy and possible complications associated with the use of cervical ripening agents in the second trimester of pregnancy in patients with previous CD. Based on the available data it appears that PGE1 is highly efficacious, but its safety is restricted only in women with 1 previous CD. ■

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