ANALYSIS

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Effects of misoprostol in the first and second trimester of pregnancy termination in women with prior uterine scar: a meta-analysis

Shirin Niroomanesh[1], Salmeh Dadgar[2]✉, Somayeh Moindarbari[3]

Introduction: **Medical abortion is the termination of pregnancy using pharmaceutical agents. Prostaglandin agents are the most common drugs used to achieve medical termination in women in the first and second trimester of pregnancy. Misoprostol is an available and low cost drug and a prostaglandin E1 analogue that is useful in women requiring induction of abortion. The current meta-analysis reviewed the safety of misoprostol for induced-abortion in first and second trimester of pregnancy in subjects with a previous cesarean section delivery to detect the complications related to this agent.** ***Materials and Methods:*** **This meta-analysis investigation recruited studies evaluating the efficacy of Misoprostol in termination of first and/or second trimester pregnancy in subjects with prior cesarean section. A systematic article review in English language manuscripts was performed by searching different databases. The primary outcome in terms of efficacy of misoprostol was the proportion of failure rate of pregnancy termination (primary measure) as well as time to complete pregnancy termination (secondary measure).** ***Results:*** **Twenty-two articles encompassed the inclusion criteria and were included in the meta-analysis. In total, these studies included 1838 participants with a previous uterine scar due to cesarean section delivery, who underwent medical-induced abortion by misoprostol. The sample size of these studies ranged from 10 to 279 cases. Based on the results, failure rate was reported in all studies and was 12.24% (225/1838). Uterine rupture was not reported in two investigations and its cumulative rate was 1.57% (28/1778). Need for blood transfusion was reported in all, except two studies, and the rate was 1.91% (31/1621).** ***Conclusion:*** **Induction of labor in the first and second trimesters with misoprostol could lead to reduction of repeat cesarean without increasing the risk of uterine rupture as a safe method by low failure rate.**

INTRODUCTION

Despite occurrence of most abortions in the first trimester, there is still a necessity for second trimester abortion because of delayed diagnosis of fetal anomalies, logistic and financial challenges in obtaining abortion services, and failure to recognize an undesired pregnancy in the first trimester, all of which are related to the continuing need for late abortions (1). Ten to fifteen percent of all induced abortions in the world are related to second trimester abortions. They are the cause of two-thirds of all important complications due to abortions (2). The management of pregnancy termination by induced abortion is a prevalent obstetric and gynecologic operation, however, it is invasive and in some cases a risky procedure (3). Medical abortion is the termination of pregnancy using pharmaceutical agents, which are able to reduce complications and allow access to abortion opportunities provided by both specially trained clinicians and other health care providers, who might or not have training in surgical methods of abortions (4).Spontaneous labor in patients with a previous cesarean delivery rarely leads to problems, yet induction of labor has risks of uterine rupture and dehiscence (5).

Prostaglandin agents are the most common drugs for achieving the medical termination in women in the first and second trimester of pregnancy (6). Misoprostol is an available and low cost drug and a prostaglandin E1 analogue, which is potentially beneficial for women requiring induction of labor or abortion (7). The safety profile of misoprostol as abortifacient or labor-inducing agent in women with a prior cesarean delivery is yet to be established (8, 9). In this study, the researchers evaluated the safety of misoprostol for induced-abortion in the first and second trimester of pregnancy in subjects with a previous cesarean section delivery in a meta-analysis to detect the complications related to this agent.

MATERIALS AND METHODS

Definition of Studies

This meta-analysis investigation recruited studies evaluating the efficacy of Misoprostol in termination of first and/or second trimester pregnancy in subjects with prior cesarean section. A systematic article review in

[1]Perinatologist, Maternal, Fetal and Neonatal Research Center, Moheb Yas Women General Hospital, Tehran University of Medical Sciences, Tehran, Iran; [2]Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Emam reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [3]Assistant, professor, Department of Obstetrics and Gynecology, Neonatal and Maternal Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

✉*Corresponding author:* Salmeh Dadgar, Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Emam reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, Email: dadgars@mums.ac.ir

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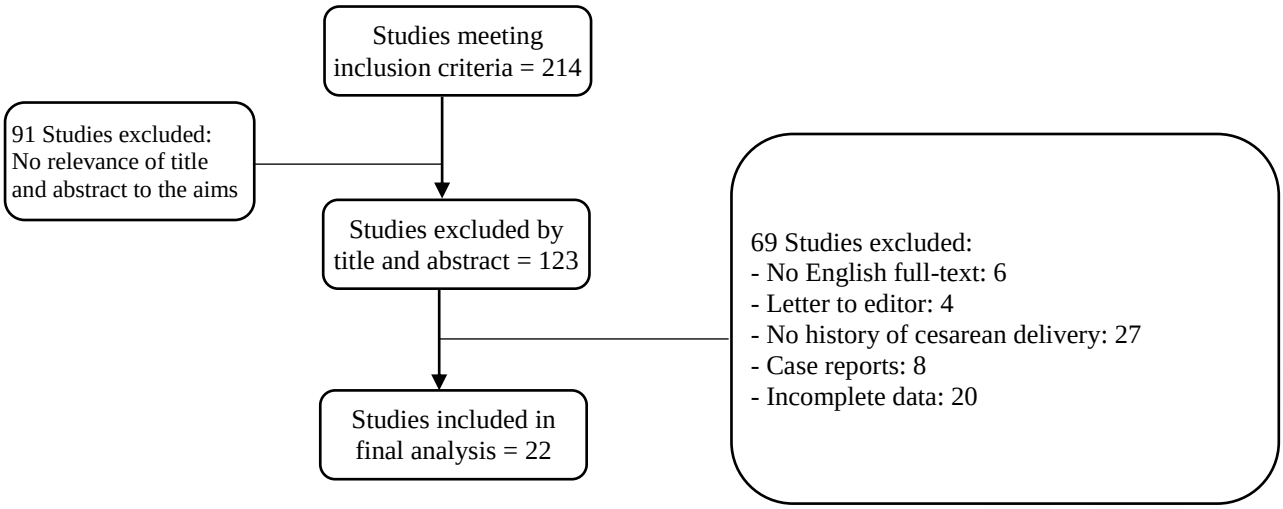

Figure 1 Schematic of literature search results for included studies

English language manuscripts was performed by searching different databases, including Google scholar, PubMed, EMBASE, CINHAL, ISI Web of Science, Scopus, Cochrane Library, and Database of Abstracts of Reviews of Effectiveness (DARE). Search keywords included "first trimester", "pregnancy termination", "misoprostol", "misotrol", "second trimester", "caesarean", "cesarean", "induced abortion", "post-cesarean abortion", "complication", "adverse effect", "Prostaglandin analogues" and the combination of these terms. Articles were included without limitation in the time of publication up to December 2018.

Eligibility criteria

Investigations were included for review if data were available regarding efficacy and safety of misoprostol in induced abortion of patients with at least one previous cesarean delivery presented in the first and/or second trimester. This study did not include case reports or case series with less than five cases, abstracts, and poster presentations. The study included observational and interventional studies.

Assessment of methodological quality

Quality assessment of the included studies was assessed by two independent authors, according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross sectional studies and CONSORT for clinical trials. A third reviewer settled discordance. The items used to assess each study were as follows: 1) the study capability to appropriately respond to the study question; 2) well defined sampling strategy (for both the subjects and setting); 3) adequate sample size; 4) checking for selection bias; 5) properly outcome measurement; 6) properly outcome analysis; 7) reporting the results with Confidence Interval (CI); and 8) justifying the conclusion according to the results. According to the appraiser agreement, a response of "yes" revealed low risk of bias and was coded as "1" and "no" revealed high risk of bias and coded as "0". If an item was coded as unclear, it indicated an unclear or unknown risk of bias. A score of zero to eight was assigned to each study. The studies attained six or more scores rated as high quality while four to five was considered as moderate quality.

Data collection process

Information regarding the type of study, country of origin, year the study was extracted, gestational age, dose of Misoprostol and the route and protocol used, mode of delivery, duration of pregnancy termination or hospitalization, need for transfusion, bleeding, rupture of uterine, and failure rate of induced abortion were recorded. Failure rate was defined as women who did not abort or deliver within 24 hr (partial failure of procedure) were evacuated surgically (up to 15 weeks of gestation) and received additional doses of misoprostol, where gestational ages were longer than 15 weeks.

Primary and secondary outcomes

The primary outcome in terms of efficacy of misoprostol was the proportion of failure rate of pregnancy termination (primary measure) as well as time to complete pregnancy termination (secondary measure). We checked secondary outcome by the risk of uterine rupture (primary measure) and bleeding or need for blood transfusion (secondary measures).

Data synthesis

Summary measures reported in comparative studies included the risk difference and Risk Ratio (RR) with 95% Confidence Intervals (CI). Risk differences and RR were computed in Comprehensive Meta-Analysis V2.0 (Biostat, New Jersey, USA) via the inverse variance method in a random effects analysis. In the absence of heterogeneity across studies, the random effects model matched the fixed effects analysis. In the presence of heterogeneity across studies, this method produces wider CI, and so is more conservative in its estimates of the risk difference and RR. Between-study heterogeneity was assessed based on the I2 measure, and substantial heterogeneity was considered to be an I2 >50%.

RESULTS

Search Results

Overall, 214 articles were initially identified, of which 91 were excluded after screening the title and abstract, as not being relevant to the aims of the meta-analysis. The texts of the remaining 123 manuscripts were fully reviewed as mentioned previously and finally 22 articles were included in the study. Gray studies were not found and no additional articles were added after the reference review. Finally, 22 articles encompassed the inclusion criteria and were included in the meta-analysis. The search process and literature selection are demonstrated in the PRISMA flow diagram (Figure 1).

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Table 1 Characteristics of included studies

Study (year)	Trimester	Duration Design	Num. of subjects	Dose of misoprostol	Route	Outcomes	
Bhattacharjee et al. (8)	Second	2003-2006 Observational study	80	200-400μg	Intravaginal or sublingually	Blood loss	12.5%
						Blood transfusion	6.25%
						Uterine rupture	17.5%
						Induction–abortion interval (hrs)	16.4 (10-21)
						Failure rate	27%
Mobusher(19)	Second	2008-2011 Observational study	100	400μg	Intravaginal	Blood loss	2%
						Blood transfusion	2%
						Uterine rupture	0
						Induction–abortion interval (hrs)	20 (11-31)
						Failure rate	0
Daskalakis et al. (15)	Second	1997-2002 Observational study	108	1600μg	Oral and Intravaginal	Blood loss	1.85%
						Blood transfusion	1.85%
						Uterine rupture	0
						Induction–abortion interval (hrs)	19 (11-31)
						Failure rate	1.85%
Daponte et al. (23)	First and Second	2007 Case series	21 First (9) Second (12)	800μg	Intravaginal	Blood loss	0
						Blood transfusion	1.85%
						Uterine rupture	0
						Induction–abortion interval (hrs)	14.15 (4-16.5)
						Failure rate	14.29%6 6.6% in first 25% in second
Daptone et al. (24)	Second	2006 Case series	85	600μg and 400μg	Intravaginal	Blood loss	0
						Blood transfusion	0
						Uterine rupture	0
						Induction–abortion interval (hrs)	16.32 (10-36)
						Failure rate	0
Turgut et al. (30)	Second	2009-2012 Retrospective study	56	100-4400μg	Intravaginal	Blood loss	8.92%
						Blood transfusion	8.92%
						Uterine rupture	5.35%
						Induction–abortion interval (hrs)	N/A
						Failure rate	23.2%
Naguib et al. (20)	Second	2008 Prospective study	50	200-1800μg	Intravaginal	Blood loss	2%
						Blood transfusion	2%
						Uterine rupture	10%
						Induction–abortion interval (hrs)	21.90 (10.16–48.41)
						Failure rate	20%
Küçükgöz Güleç et al. (26)	Second	2007-2010 Retrospective cohort	279	400-2400μg	Intravaginal	Blood loss	1.1%
						Blood transfusion	0.35%

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						Uterine rupture	1.1%
						Induction–abortion interval (hrs)	33.4 (22.7-294.6)
						Failure rate	8.6%
Cuellar Torriente et al. (14)	Second	2010-2013 Retrospective study	268	1400µg	Oral and intravaginal	Blood loss	0
						Blood transfusion	0
						Uterine rupture	0
						Induction–abortion interval (hrs)	9 (7-15)
						Failure rate	2.2%
Bhandekar et al. (11)	Second	2017 Prospective study	30	400-2000µg	Oral	Blood loss	0
						Blood transfusion	0
						Uterine rupture	N/A
						Induction–abortion interval (hrs)	21.6 (12-28)
						Failure rate	26.7%
			30		Intravaginal	Blood loss	0
						Blood transfusion	0
						Uterine rupture	N/A
						Induction–abortion interval (hrs)	18.5 (12-28)
						Failure rate	6.7%
Fawzy and Abdel-Hady(16)	Second	2006-2009 Retrospective study	31	200-1200µg	Intravaginal	Blood loss	6.5%
						Blood transfusion	6.5%
						Uterine rupture	3.2%
						Induction–abortion interval (hrs)	16.9 (10.1-23.7)
						Failure rate	25.8%
Pongsatha and Tongsong(27)	Second	2003 Case series	21	400-2400µg	Oral and intravaginal	Blood loss	4.7%
						Blood transfusion	4.7%
						Uterine rupture	0
						Induction–abortion interval (hrs)	16.6 (8.23–37.17)
						Failure rate	23.8%
Rouzi (29)	Second	1998-2002 Case series	10	200-1200µg	Intravaginal	Blood loss	0
						Blood transfusion	0
						Uterine rupture	0
						Induction–abortion interval (hrs)	13.1
						Failure rate	0
Herabutya et al. (17)	Second	1996-2002 prospective cohort	56	1200µg	Intravaginal	Blood loss	5.4%
						Blood transfusion	1.7%
						Uterine rupture	0
						Induction–abortion interval (hrs)	15.1 (11.37-24.25)
						Failure rate	37.5%
Dickinson(25)	Second	1997-2004 Retrospective cohort	101	1200-1800µg	Oral and intravaginal	Blood loss	7.9%
						Blood transfusion	4%
						Uterine rupture	0
						Induction–abortion interval (hrs)	14.5 (11.4 – 21.4)

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						Failure rate	0
Tarim et al. (21)	Second	1998-2004 Retrospective study	12	1200µg	Oral	Blood loss	N/A
						Blood transfusion	N/A
						Uterine rupture	0
						Induction–abortion interval (hrs)	12.33 (3.55-21.05)
						Failure rate	0
Latif et al. (18)	Second	2010-2012 prospective controlled trial	80	900µg	Intravaginal	Blood loss	6.25%
						Blood transfusion	2.5%
						Uterine rupture	1.25%
						Induction–abortion interval (hrs)	N/A
						Failure rate	21.25%
Pongsatha and Tongsong(28)	Second	2003-2005 Case series	70	400-2400µg	Intravaginal	Blood loss	0
						Blood transfusion	0
						Uterine rupture	0
						Induction–abortion interval (hrs)	25.9 (4.0-142.7)
						Failure rate	0
Chamsi et al.(12)	First	2016-2017 prospective cohort study	205	400-2400µg	Oral and intravaginal	Blood loss	17.07%
						Blood transfusion	N/A
						Uterine rupture	0
						Induction–abortion interval (hrs)	N/A
						Failure rate	32.2%
Berghella et al. (22)	Second	2009 Case series	17	100-800µg	Intravaginal	Blood loss	6.66%
						Blood transfusion	6.66%
						Uterine rupture	6.66%
						Induction–abortion interval (hrs)	N/A
						Failure rate	6.66%
Ayati et al. (10)	First	2013 Prospective clinical trial	40	800µg	Intravaginal	Blood loss	2.5%
						Blood transfusion	2.5%
						Uterine rupture	0
						Induction–abortion interval (hrs)	22.51 (4-48)
						Failure rate	20%
Ayati et al. (10)	First	2013 Prospective clinical trial	40	800µg	Rectal	Blood loss	2.5%
						Blood transfusion	2.5%
						Uterine rupture	0
						Induction–abortion interval (hrs)	28.38 (5-120)
						Failure rate	20%
Choy-Hee and Raynor(13)	Second	1996-1998 Retrospective cohort	48	50-300µg	Intravaginal	Blood loss	2.5%
						Blood transfusion	2.5%
						Uterine rupture	0
						Induction–abortion interval (hrs)	N/A
						Failure rate	8%

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Table 2 Methodological quality of the studies included in meta-analysis

Study	Year	Appropriately study design according to study question	Well-defined sampling strategy	Adequate sample size	Checking for selection bias	Properly outcome measurement	Properly outcome analysis	Reporting the results with CI*	Justifying the conclusion and the results
Choy-Hee and Raynor (13)	2001	+	+	+	?	+	-	-	+
Pongsatha and Tongsong (27)	2003	+	+	?	?	+	+	+	+
Rouzi (29)	2003	+	?	-	?	-	+	-	+
Herabutya et al. (17)	2003	+	+	?	+	+	+	+	+
Daskalakis et al. (15)	2005	+	+	+	?	+	+	+	+
Dickinson (25)	2005	+	-	-	+	+	+	+	+
Tarim et al. (21)	2005	+	?	?	?	+	+	+	+
Daptone et al. (24)	2006	-	?	?	-	+	+	+	+
Pongsatha and Tongsong (28)	2006	-	?	?	-	+	+	+	+
Bhattacharjee et al. (8)	2007	+	+	+	?	+	-	-	+
Daponte et al. (23)	2007	+	+	?	?	+	+	+	+
Berghella et al. (22)	2009	+	?	-	?	-	+	-	+
Naguib et al. (20)	2010	+	+	?	+	+	+	+	+
Fawzy and Abdel-Hady (16)	2010	+	+	+	?	+	+	+	+
Latif et al. (18)	2012	+	-	-	+	+	+	+	+
Mobusher (19)	2013	+	?	?	?	+	+	+	+
Turgut et al. (30)	2013	-	?	?	-	+	+	+	+
Küçükgöz Güleç et al. (26)	2013	+	-	-	+	+	+	+	+
Ayati et al. (10)	2013	+	?	?	?	+	+	+	+
Cuellar Torriente et al. (14)	2017	-	?	?	-	+	+	+	+
Bhandekar et al. (11)	2018	+	?	?	?	+	+	+	+
Chamsi et al.(12)	2018	-	?	?	-	+	+	+	+

+ is referred to positive comment in each item quality, - is referred to negative comment in each item quality, ? is related to those items which cannot be judge well by expert opinion.

Study characteristics

In total, these studies included 1838 participants with a previous uterine scar due to cesarean section delivery, who underwent medical-induced abortion by misoprostol. The sample size of these studies ranged from 10 to 279 cases. Eligible studies were published between 2001 and 2018 and were carried out in India, Greece, Iran, South Africa, Turkey, Egypt, Pakistan, Thailand, Saudi Arabia, Australia, and United States. Type of studies and the demographics and characteristics of the included studies is demonstrated in Table 1.

Risk of bias assessment

The methodological quality of the included studies is shown in Table 2.

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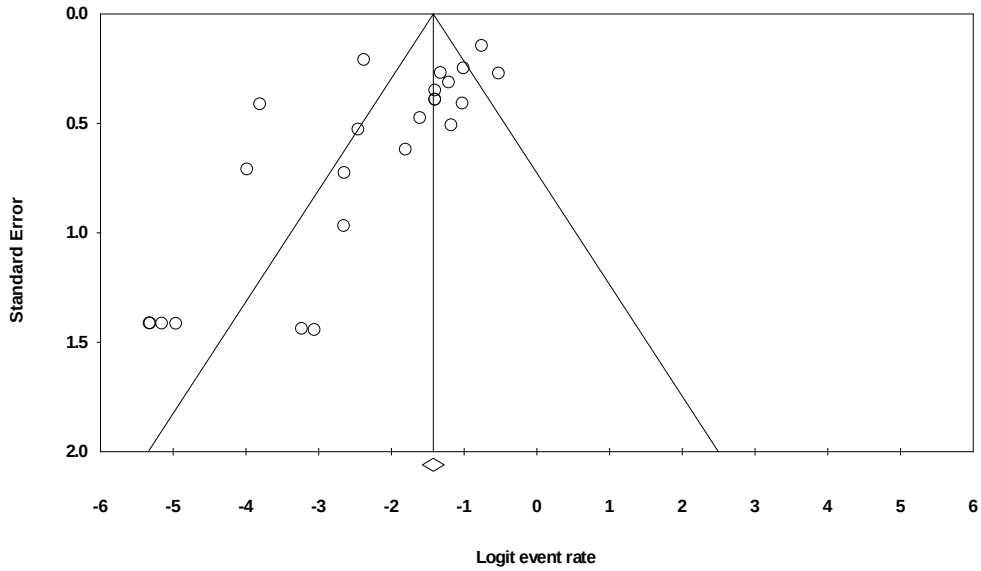


Study name	Statistics for each study						Weight (Fixed)		Residual (Fixed)			Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight	Relative weight	Std Residual	Std Residual	Std Residual	
Bhattacharjee et al.	0.2700	0.1842	0.3773	-3.9495	0.0001	22 / 80	9.09		1.79			
Mobusher	0.0050	0.0003	0.0742	-3.7407	0.0002	0 / 100	0.29		-2.74			
Daskalakis et al.	0.0185	0.0046	0.0710	-5.5613	0.0000	2 / 108	1.13		-3.59			
Daponte et al.	0.1429	0.0468	0.3614	-2.8730	0.0041	3 / 21	1.48		-0.59			
Daptone et al.	0.0058	0.0004	0.0861	-3.6251	0.0003	0 / 85	0.29		-2.62			
Turgut et al.	0.2320	0.1397	0.3597	-3.7812	0.0002	13 / 56	5.75		0.74			
Naguib et al.	0.2000	0.1111	0.3333	-3.9210	0.0001	10 / 50	4.61		0.11			
Kucukgoz Gulec et al.	0.0860	0.0583	0.1251	-11.0682	0.0000	24 / 279	12.64		-4.71			
Cuellar Torriente et al.	0.0220	0.0098	0.0484	-9.1117	0.0000	6 / 268	3.32		-5.79			
Bhandekar et al.1	0.2670	0.1396	0.4499	-2.4471	0.0144	8 / 30	3.38		1.02			
Bhandekar et al.2	0.0670	0.0169	0.2310	-3.6067	0.0003	2 / 30	1.08		-1.67			
Fawzy and Abdel-Hady	0.1690	0.0736	0.3422	-3.3233	0.0009	5 / 31	2.51		-0.36			
Pongsatha and Tongsong	0.2380	0.1027	0.4602	-2.2710	0.0231	5 / 21	2.20		0.51			
Rouzi	0.0455	0.0028	0.4483	-2.1033	0.0354	0 / 10	0.28		-1.12			
Herabutya et al.	0.3750	0.2589	0.5075	-1.8506	0.0642	21 / 56	7.57		3.44			
Dickinson	0.0049	0.0003	0.0735	-3.7478	0.0002	0 / 101	0.29		-2.75			
Tarim et al.	0.0385	0.0024	0.4032	-2.2319	0.0256	0 / 12	0.28		-1.25			
Latif et al.	0.2125	0.1364	0.3156	-4.7929	0.0000	17 / 80	7.72		0.44			
Pongsatha and Tongsong2	0.0070	0.0004	0.1027	-3.4870	0.0005	0 / 70	0.29		-2.49			
Chamsi et al.	0.3220	0.2616	0.3890	-4.9813	0.0000	66 / 205	25.80		5.28			
Berghella et al.	0.0666	0.0105	0.3244	-2.7141	0.0066	1 / 17	0.61		-1.25			
Ayati et al. 1	0.2000	0.1033	0.3517	-3.5071	0.0005	8 / 40	3.69		0.10			
Ayati et al. 2	0.2000	0.1033	0.3517	-3.5071	0.0005	8 / 40	3.69		0.10			
Choy-Hee and Raynor	0.0800	0.0297	0.1979	-4.5906	0.0000	4 / 48	2.04		-1.93			
	0.1940	0.1718	0.2183	-18.7590	0.0000							

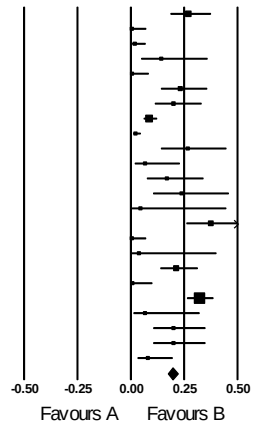
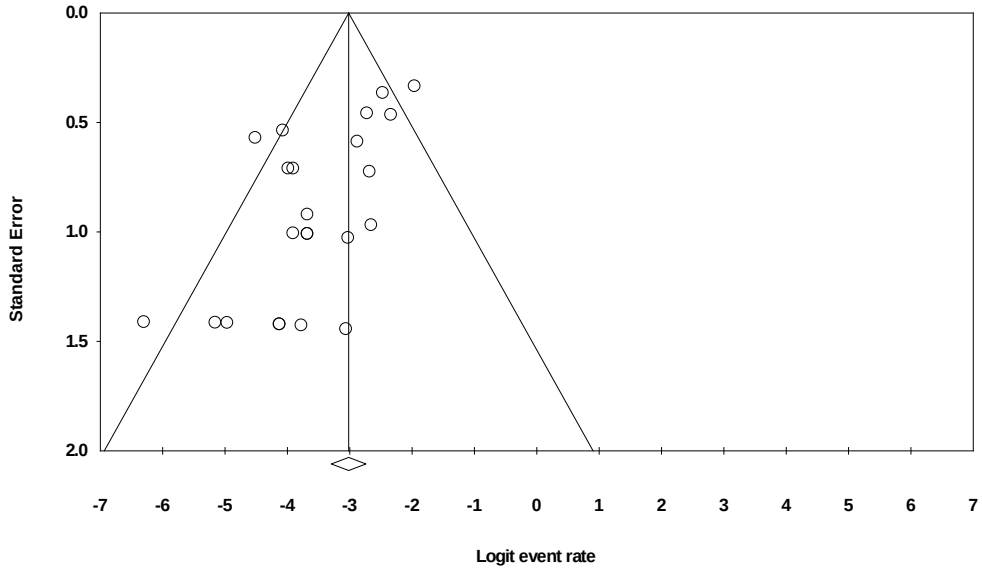


Figure 2 Meta-analysis, forest, and funnel plots of studies according to failure rate in patients with prior cesarean deliveries. *I^2= 83.60, Heterogeneity Tau^2= 0, P<0.001, Z= -18.75.*



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Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight	Relative weight	Std Residual	Std Residual	Std Residual
Bhattacharjee et al.	0.1250	0.0686	0.2170	-5.7561	0.0000	10 / 80	17.50		3.49		
Mobusher	0.0200	0.0050	0.0764	-5.4485	0.0000	2 / 100	3.92		-1.25		
Daskalakis et al.	0.0185	0.0046	0.0710	-5.5613	0.0000	2 / 108	3.92		-1.36		
Daponte et al.	0.0227	0.0014	0.2774	-2.6292	0.0086	0 / 21	0.98		-0.52		
Daptone et al.	0.0058	0.0004	0.0861	-3.6251	0.0003	0 / 85	0.99		-1.51		
Turgut et al.	0.0892	0.0376	0.1971	-4.9559	0.0000	5 / 56	9.10		1.55		
Naguib et al.	0.0200	0.0028	0.1288	-3.8527	0.0001	1 / 50	1.96		-0.87		
Kucukgoz Gulec et al.	0.0110	0.0036	0.0331	-7.8378	0.0000	3 / 279	6.07		-2.66		
Cuellar Torriente et al.	0.0019	0.0001	0.0290	-4.4407	0.0000	0 / 268	1.00		-2.32		
Bhandekar et al.1	0.0161	0.0010	0.2114	-2.8833	0.0039	0 / 30	0.98		-0.77		
Bhandekar et al.2	0.0161	0.0010	0.2114	-2.8833	0.0039	0 / 30	0.98		-0.77		
Fawzy and Abdel-Hady	0.0650	0.0164	0.2247	-3.6596	0.0003	2 / 31	3.77		0.49		
Pongsatha and Tongsong	0.0470	0.0065	0.2712	-2.9187	0.0035	1 / 21	1.88		0.01		
Rouzi	0.0455	0.0028	0.4483	-2.1033	0.0354	0 / 10	0.95		-0.02		
Herabutya et al.	0.0540	0.0176	0.1539	-4.8428	0.0000	3 / 56	5.72		0.27		
Dickinson	0.0790	0.0400	0.1502	-6.6579	0.0000	8 / 101	14.70		1.65		
Latif et al.	0.0625	0.0263	0.1415	-5.8631	0.0000	5 / 80	9.37		0.70		
Pongsatha and Tongsong2	0.0070	0.0004	0.1027	-3.4870	0.0005	0 / 70	0.99		-1.37		
Chamsi et al.	0.0170	0.0060	0.0475	-7.5098	0.0000	3 / 205	6.85		-1.99		
Berghella et al.	0.0666	0.0105	0.3244	-2.7141	0.0066	1 / 17	2.11		0.39		
Ayati et al. 1	0.0250	0.0035	0.1573	-3.6175	0.0003	1 / 40	1.95		-0.64		
Ayati et al. 2	0.0250	0.0035	0.1573	-3.6175	0.0003	1 / 40	1.95		-0.64		
Choy-Hee and Raynor	0.0250	0.0042	0.1357	-3.9627	0.0001	1 / 48	2.34		-0.71		
	0.0466	0.0358	0.0606	-21.3364	0.0000						

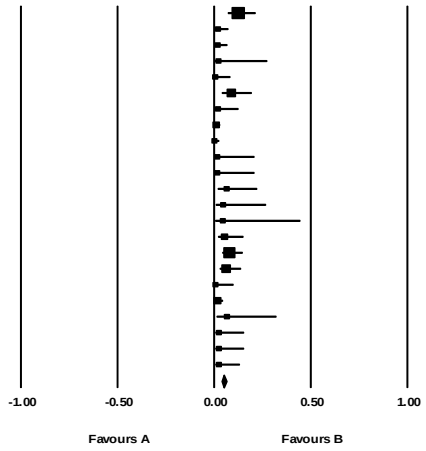
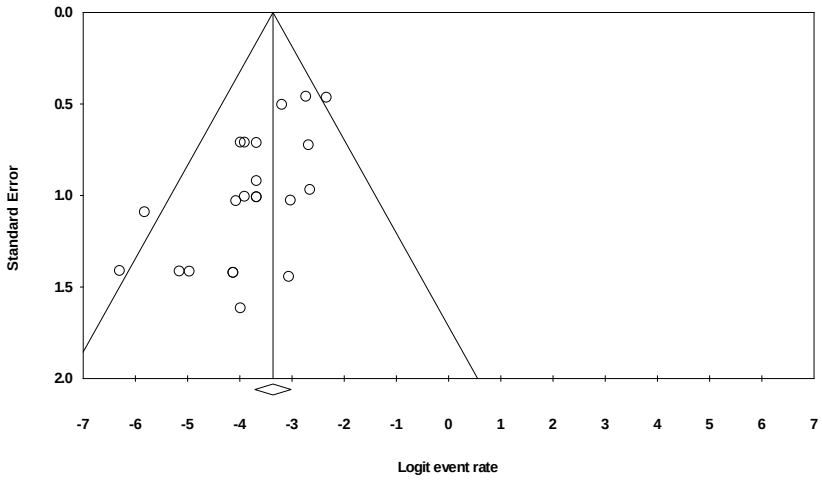


Figure 3 Meta-analysis, forest, and funnel plots of studies according to blood loss in patients with prior cesarean deliveries. *I^2= 47.65, Heterogeneity Tau^2= 0, P<0.001, Z= -21.33.*



Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight	Relative weight	Residual	Variance	Std Err	Std Residual	Std Residual	Std Residual
Bhattacharjee et al.	0.0620	0.0260	0.1409	-5.8596	0.0000	5 / 80	12.31		0.72	0.27	0.52	1.38		
Mobusher	0.0200	0.0050	0.0764	-5.4485	0.0000	2 / 100	6.32		-0.45	0.57	0.75	-0.60		
Daskalakis et al.	0.0185	0.0046	0.0710	-5.5613	0.0000	2 / 108	6.32		-0.53	0.57	0.75	-0.71		
Daponte et al.	0.0185	0.0008	0.3106	-2.4523	0.0142	0 / 21	1.41		-0.53	2.68	1.64	-0.33		
Daptone et al.	0.0058	0.0004	0.0861	-3.6251	0.0003	0 / 85	1.82		-1.70	2.07	1.44	-1.18		
Turgut et al.	0.0892	0.0376	0.1971	-4.9559	0.0000	5 / 56	12.12		1.11	0.28	0.53	2.11		
Naguib et al.	0.0200	0.0028	0.1288	-3.8527	0.0001	1 / 50	3.43		-0.45	1.08	1.04	-0.44		
Kucukgoz Gulec et al.	0.0030	0.0004	0.0251	-5.3039	0.0000	1 / 279	2.96		-2.37	1.26	1.12	-2.11		
Cuellar Torriente et al.	0.0019	0.0001	0.0290	-4.4407	0.0000	0 / 268	1.82		-2.85	2.06	1.44	-1.98		
Bhandekar et al.1	0.0161	0.0010	0.2114	-2.8833	0.0039	0 / 30	1.80		-0.67	2.09	1.45	-0.47		
Bhandekar et al.2	0.0161	0.0010	0.2114	-2.8833	0.0039	0 / 30	1.80		-0.67	2.09	1.45	-0.47		
Fawzy and Abdel-Hady	0.0650	0.0164	0.2247	-3.6596	0.0003	2 / 31	6.11		0.77	0.59	0.77	1.01		
Pongsatha and Tongsong	0.0470	0.0065	0.2712	-2.9187	0.0035	1 / 21	3.30		0.43	1.12	1.06	0.40		
Rouzi	0.0455	0.0028	0.4483	-2.1033	0.0354	0 / 10	1.75		0.39	2.15	1.47	0.27		
Herabutya et al.	0.0170	0.0023	0.1160	-3.9250	0.0001	1 / 56	3.29		-0.62	1.13	1.06	-0.58		
Dickinson	0.0400	0.0152	0.1013	-6.2587	0.0000	4 / 101	10.82		0.26	0.32	0.56	0.46		
Latif et al.	0.0250	0.0063	0.0945	-5.1159	0.0000	2 / 80	6.29		-0.23	0.57	0.76	-0.30		
Pongsatha and Tongsong2	0.0070	0.0004	0.1027	-3.4870	0.0005	0 / 70	1.82		-1.51	2.07	1.44	-1.05		
Berghella et al.	0.0666	0.0105	0.3244	-2.7141	0.0066	1 / 17	3.67		0.80	1.00	1.00	0.80		
Ayati et al. 1	0.0250	0.0035	0.1573	-3.6175	0.0003	1 / 40	3.41		-0.23	1.08	1.04	-0.22		
Ayati et al. 2	0.0250	0.0035	0.1573	-3.6175	0.0003	1 / 40	3.41		-0.23	1.08	1.04	-0.22		
Choy-Hee and Raynor	0.0250	0.0042	0.1357	-3.9627	0.0001	1 / 48	4.03		-0.23	0.91	0.96	-0.24		
	0.0311	0.0214	0.0450	-17.5633	0.0000									

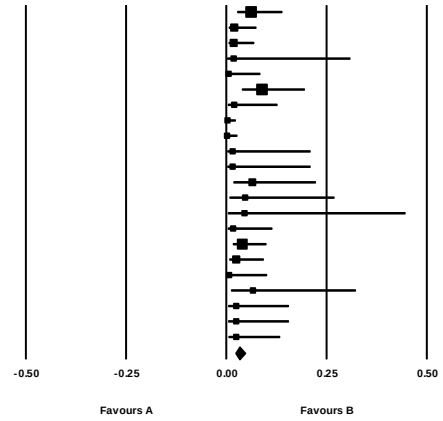


Figure 4 Meta-analysis, forest, and funnel plots of studies according to need to blood transfusion in patients with prior cesarean deliveries. *I^2= 11.91, Heterogeneity Tau^2= 0, P<0.001, Z= -19.04.*

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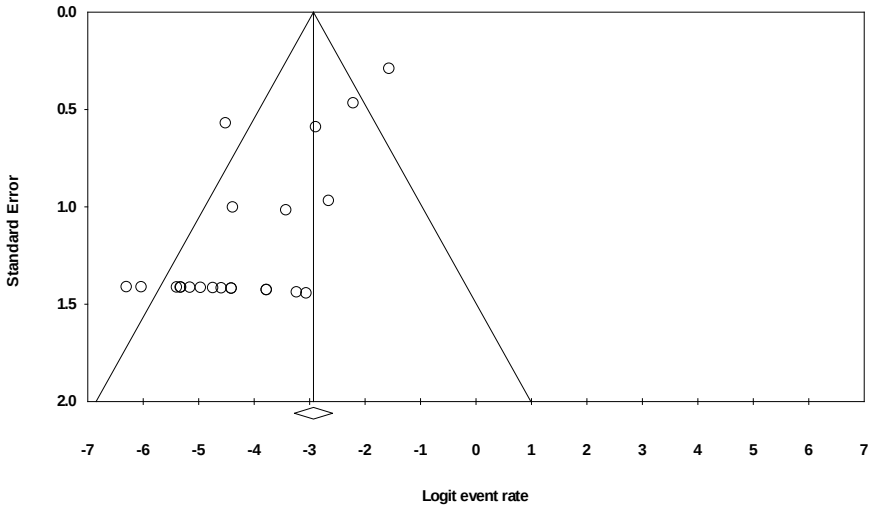
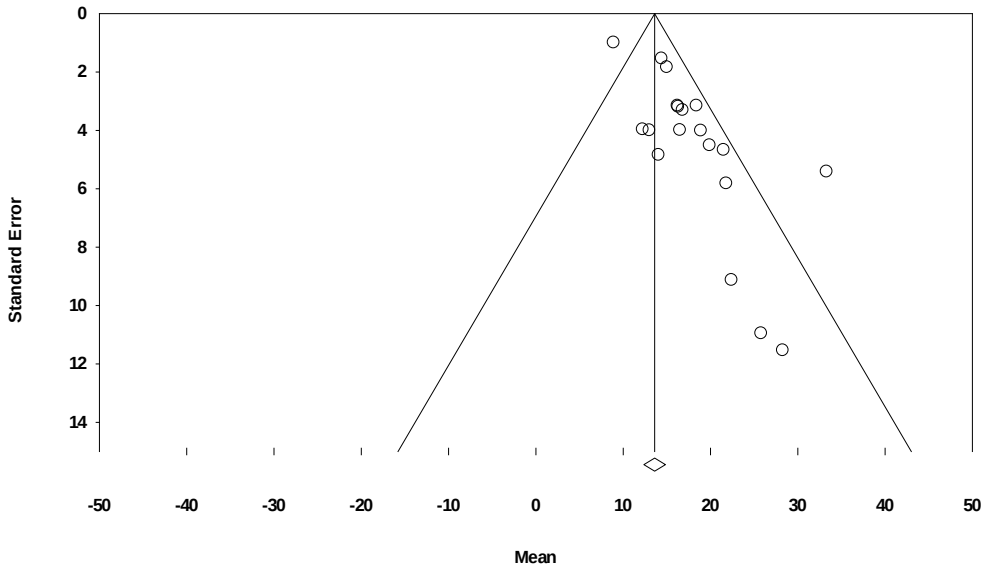


Study name	Statistics for each study						Event rate and 95% CI	Weight (Fixed)					
	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total		Relative weight	Relative weight	Std Residual	Std Residual	Std Residual	P-Val
Bhattacharjee et al.	0.1750	0.1065	0.2741	-5.2698	0.0000	14 / 80		35.73		5.85			0.00
Mobusher	0.0050	0.0003	0.0742	-3.7407	0.0002	0 / 100		1.54		-1.69			0.09
Daskalakis et al.	0.0046	0.0003	0.0690	-3.7954	0.0001	0 / 108		1.54		-1.74			0.08
Daponte et al.	0.0227	0.0014	0.2774	-2.6292	0.0086	0 / 21		1.51		-0.59			0.56
Daptone et al.	0.0058	0.0004	0.0861	-3.6251	0.0003	0 / 85		1.54		-1.57			0.12
Turgut et al.	0.0535	0.0173	0.1533	-4.8382	0.0000	3 / 56		8.77		0.10			0.92
Naguib et al.	0.1000	0.0422	0.2187	-4.6610	0.0000	5 / 50		13.92		1.68			0.09
Kucukgoz Gulec et al.	0.0110	0.0036	0.0331	-7.8378	0.0000	3 / 279		9.39		-2.87			0.00
Cuellar Torriente et al.	0.0019	0.0001	0.0290	-4.4407	0.0000	0 / 268		1.54		-2.39			0.02
Fawzy and Abdel-Hady	0.0320	0.0045	0.1963	-3.3411	0.0008	1 / 31		2.97		-0.48			0.63
Pongsatha and Tongsong	0.0227	0.0014	0.2774	-2.6292	0.0086	0 / 21		1.51		-0.59			0.56
Rouzi	0.0455	0.0028	0.4483	-2.1033	0.0354	0 / 10		1.48		-0.08			0.94
Herabutya et al.	0.0088	0.0005	0.1253	-3.3281	0.0009	0 / 56		1.53		-1.28			0.20
Dickinson	0.0049	0.0003	0.0735	-3.7478	0.0002	0 / 101		1.54		-1.69			0.09
Tarim et al.	0.0385	0.0024	0.4032	-2.2319	0.0256	0 / 12		1.49		-0.20			0.84
Latif et al.	0.0125	0.0018	0.0834	-4.3421	0.0000	1 / 80		3.06		-1.45			0.15
Pongsatha and Tongsong2	0.0070	0.0004	0.1027	-3.4870	0.0005	0 / 70		1.54		-1.43			0.15
Chamsi et al.	0.0024	0.0002	0.0376	-4.2506	0.0000	0 / 205		1.54		-2.20			0.03
Berghella et al.	0.0666	0.0105	0.3244	-2.7141	0.0066	1 / 17		3.27		0.30			0.76
Ayati et al. 1	0.0122	0.0008	0.1672	-3.0883	0.0020	0 / 40		1.53		-1.04			0.30
Ayati et al. 2	0.0122	0.0008	0.1672	-3.0883	0.0020	0 / 40		1.53		-1.04			0.30
Choy-Hee and Raynor	0.0102	0.0006	0.1432	-3.2183	0.0013	0 / 48		1.53		-1.17			0.24
	0.0507	0.0364	0.0701	-16.6592	0.0000								

Figure 5 Meta-analysis, forest, and funnel plots of studies according to uterine rupture in patients with prior cesarean deliveries. *I^2= 66.90, Heterogeneity Tau^2= 0, P<0.001, Z= -16.65.*



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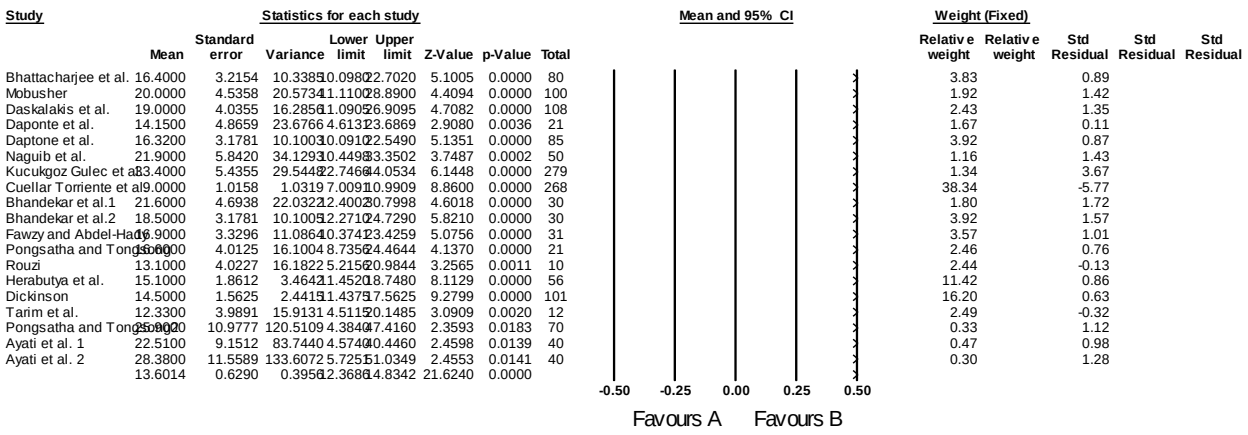

Figure 6 Meta-analysis, forest, and funnel plots of studies according to induction-abortion time (hours) in patients with prior cesarean deliveries. *I^2= 65.93, Heterogeneity Tau^2= 0, P<0.001, Z= 21.62.*

Results of individual studies

Most studies were comparative (8, 10-21) and others were case series and had a descriptive design (22-30). Based on the results, failure rate was reported in all studies and was 12.24% (225/1838). Uterine rupture was not reported in two investigations and its cumulative rate was 1.57% (28/1778). Need for blood transfusion was reported in all, except two studies, and the rate was 1.91% (31/1621). Blood loss was reported in all but one study and its rate was 2.73% (50/1826). The mean induction–abortion interval was not reported in five studies and the mean total was 13.60 (12.36 to 14.83) hours in 1432 patients. The range of administered doses of misoprostol in included studies was between 400 and 2400µg. The route of administration was mainly intravaginal (14/22), oral and intravaginal (5/22), sublingual or intravaginal in one and rectal or intravaginal in another study.

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 for misoprostol. The success rate of induced abortion was higher with the misoprostol method. The current study showed that the failure rate in all studies was low and the induction in patients with previous cesarean section delivery was efficient. The analysis of the failure rate and forest plot is shown in Figure 2 (I^2= 83.60, Heterogeneity Tau2= 0, P<0.001, Z= -18.75) and is significantly representative in all studies. In safety components, the researchers analyzed the risk of blood loss in studies and showed that its risk was significantly low (2.73%) in patients with previous cesarean delivery (I^2= 47.65, Heterogeneity Tau^2= 0, P<0.001, Z= -21.33, Figure 3). Another safety component was the need for blood transfusion, which had a low risk (1.91%) and it is shown in Figure 4 (I^2= 11.91, Heterogeneity Tau^2= 0, P<0.001, Z= -19.04). Uterine rupture in patients with previous cesarean delivery was low (1.57%), which is demonstrated in Figure 5 (I^2= 66.90, Heterogeneity Tau^2= 0, P<0.001, Z= -16.65). The mean of induction-abortion time in all studies is presented in Figure 6 (I^2= 65.93, Heterogeneity Tau^2= 0, P<0.001, Z= 21.62).

DISCUSSION

Misoprostol is being used extensively in the obstetric fields as an agent for induction of labor termination of pregnancy in the second and third trimesters of pregnancy (31). Despite of association of increased risk of some complications such as uterine rupture by use of misoprostol, the percent of complications in this study was lower in large-scale populations of included studies in patients with at least one previous cesarean delivery. Relative risk of uterine rupture was 0.05 (CI: 0.03 to 0.07) in this study. The risk of blood transfusion was reported 0.03 (CI: 0.02 to 0.04), blood loss 0.04 (CI: 0.03 to 0.06) and failure rate 0.19 (CI: 0.17 to 0.21). Our study focused on misoprostol as a non-expensive agent and available for medical abortion. We also emphasized on population of previous cesarean section in first or second trimester induced abortion that the large number of patients in this narrow field, allows this meta-analysis to improve the conclusions. The main indications for pregnancy termination included in utero fetal demise, chromosomal anomalies, structural fetal defects, hemoglobinopathy, Preterm Premature Rupture of Membranes (PPROM), fetal infection, and severe maternal disease.

Medical abortion was started in the late 1980s, becoming more widely used in the late nineties with the mifepristone and misoprostol being the most used. It came as an alternative for the dilation and curettage, which caused more complications, resulting in 50000 to 100000 maternal deaths every year (32). Misoprostol has been used for termination of pregnancy in different ways, vaginal, oral, and the combination of the two routes in the first and second trimester (33). Abortion-related morbidity and mortality increase significantly as pregnancy advances with a sharp rise in the rate of severe complications in induced abortion after 14 weeks of pregnancy (34). According to high rate of cesarean section delivery (35), considering induction of labor in the first and second trimesters in women with a uterine has become a common challenge in obstetrics (36).

Although there are some case reports of complications related to use of misoprostol in the first or second trimester for labor induction (37-41), in this meta-analysis the researchers showed that the risk of complications using misoprostol in different routes is non-significant and seems safe. Overall, limited data are available regarding misoprostol safety in women with previous multiple cesarean deliveries and available evidence is mainly dependent on individual practice and/or underpowered retrospective studies. Furthermore, there are inconsistencies about the optimum regimen of misoprostol, and the optimum dose is yet to be established. There was no previous meta-analysis on misoprostol use in the first and second trimester, and the efficacy and safety profile in induction of labor in women with previous cesarean scar was largely unknown. The most important concern in this

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drug is uterine rupture that can be life threatening. The current study demonstrated that its rate is low and is not significant in the large-scale.

CONCLUSION

In conclusion, induction of labor in the first and second trimesters with misoprostol could lead to reduction of repeat cesarean without increasing the risk of uterine rupture as a safe method by low failure rate. Favorable outcomes were gained with misoprostol for the second and first trimester induced abortion management in a woman with previous cesarean deliveries.

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Article Keywords
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Conflict of interests
There was no financial source for this study. There was no conflict of interest.

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