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SYSTEMATIC REVIEW

Induction of labor at full-term in pregnant women with uncomplicated singleton pregnancy: A systematic review and meta-analysis of randomized trials

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Abstract

Introduction: The lowest incidence of perinatal morbidity and mortality occurs around 39-40 weeks. Therefore, some have advocated induction of uncomplicated singleton gestations once they reach full-term. The aim of the study was to evaluate the risk of cesarean delivery, and any maternal and perinatal effects of a policy of induction of labor in women with full-term uncomplicated singleton gestations.

Material and methods: We performed an electronic search from inception of each database to August 2018. All results were then limited to randomized trial. No restrictions for language or geographic location were applied. Inclusion criteria were randomized clinical trials of asymptomatic women with uncomplicated, singleton gestations at full-term (ie, between 39^{+0} and 40^{+6} weeks) who were randomized to either planned induction of labor or control (ie, expectant management). Only trials on asymptomatic singleton gestations without premature rupture of membranes or any other indications for induction evaluating the effectiveness of planned induction of labor in full-term singleton gestations were included. The primary outcome was the incidence of cesarean delivery.

Results: Seven randomized clinical trials, including 7598 participants were analyzed. Three studies enrolled only women with favorable cervix, defined as a Bishop score of ≥5 in nulliparous women or ≥4 in multiparous women. One trial included only women aged 35 years or older. Women randomized to the planned induction of labor, received scheduled induction usually at 39^{+0} to 39^{+6} weeks of gestation, whereas women in the control group received expectant management usually until 41-42 weeks of gestation, or earlier if medically indicated. Methods of induction usually included cervical ripening, with either misoprostol or Foley catheter, in conjunction with or followed by oxytocin for women with unfavorable cervix, and oxytocin and artificial rupture of membranes for those with favorable cervix. Five trials also used artificial rupture of membranes as a method for induction. Uncomplicated full-term singleton gestations that were randomized to receive induction of labor had similar incidence of cesarean delivery compared with controls (18.6% vs 21.4%;

Abbreviations: CI, confidence interval; I^2, Higgins *I*-squared; MSAF, meconium-stained amniotic fluid; RCT, randomized controlled trial; RR, relative risk.

relative risk 0.96, 95% CI 0.78-1.19). Regarding neonatal outcomes, induction of labor at full-term was associated with a significantly lower rate of meconium-stained amniotic fluid (4.0% vs 13.5%; relative risk 0.32, 95% CI 0.18-0.57), and lower mean birthweight (mean difference −98.96 g, 95% CI −126.29 to −71.63) compared with the control group. There were no between-group differences in other adverse neonatal outcomes.

Conclusions: Induction of labor at about 39 weeks is not associated with increased risk of cesarean delivery.

KEYWORDS

cesarean delivery, induction of labor, operative delivery, oxytocin, prostaglandin, vaginal delivery

1 | INTRODUCTION

Several studies have shown that the lowest incidence of perinatal morbidity and mortality occurs at around 39 weeks of gestation.[1,2] Perinatal mortality starts to increase with late-term and post-term pregnancies.[3]

Therefore, some authors have advocated induction of labor of even uncomplicated singleton pregnancies once they reach full-term (39^{+0}-40^{+6} weeks).[4-8] Opponents of such a policy have remarked that induction has often been associated with an increased risk of cesarean delivery.[9-12] Randomized controlled trials of pregnancies with indications for induction have shown that induction is not associated with an increased risk of cesarean, and is instead associated with maternal and perinatal benefits.[13-15]

The aim of this study was to evaluate the risk of cesarean delivery and any maternal and perinatal effects of a policy for induction of labor in women with full-term uncomplicated singleton gestations.

Key message

Induction of labor at full-term is not associated with increased risk of cesarean delivery.

2 | MATERIAL AND METHODS

2.1 | Search strategy

We performed electronic research in Scopus, ClinicalTrials.gov, MEDLINE, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials with the use of the following key words: "induction," "cesarean section," "expectant management," and "pregnancy" from inception of each database to August 2018. All results were then limited to "clinical trial." No restrictions for language or geographic location were applied.

2.2 | Study selection and risk of bias

Inclusion criteria were randomized clinical trials of asymptomatic pregnant women with uncomplicated singleton gestations at full-term (ie, between 39^{+0} and 40^{+6} weeks) who were randomized to either planned elective induction of labor or control (ie, expectant management).

Only trials on asymptomatic singleton gestations without premature rupture of membranes or any other indications for induction evaluating the effectiveness of planned "elective" induction of labor in full-term singleton gestations were included. Exclusion criteria included quasi-randomized trials and trials in women with premature rupture of membranes, or with indication for induction (ie, intrauterine growth restriction, diabetes, gestational hypertension/preeclampsia, oligohydramnios, fetal macrosomia).

Inclusion criteria included different methods of induction, including amniotomy, balloon, oxytocin, and prostaglandins. Trials using methods of induction that are not currently considered the standard of care, such as laminaria tent, were excluded from the meta-analysis.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[16] Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42018094876).

The risk of bias in each included study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[17] Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.

2.3 | Outcomes

All analyses were performed using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials.

The primary outcome was the incidence of cesarean delivery. Secondary outcomes were incidences of spontaneous vaginal

delivery, operative vaginal delivery (either forceps or vacuum), chorioamnionitis, mean postpartum blood loss, and neonatal outcomes including meconium-stained amniotic fluid (MSAF), Apgar score <7 at 5 min, birthweight, admission to neonatal intensive care unit, and perinatal death.

We planned to assess the primary outcome in subgroup analyses of women with favorable cervix (defined as a Bishop score of ≥5 in nulliparous women or ≥4 in multiparous women), with unfavorable cervix, of nulliparous women only, of women with a previous cesarean section, and of trials published after 2010.

2.4 | Data analysis

The data analysis was completed using Review Manager 5.3 (The Nordic Cochrane Centre 2014, Copenhagen, Denmark).

The summary measures were reported as summary relative risk (RR) or as summary mean difference with 95% confidence intervals (95% CI) using the random effects model of Der Simonian and Laird. *I*-squared (Higgins I^2) >0% was used to identify heterogeneity and a *P* value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Study selection and study characteristics

We initially identified 18 trials evaluating the effectiveness of induction of labor in women with full-term pregnancies.[4-8,13-15,18-27] Eleven studies were excluded.[13-15,18,25] Seven randomized clinical trials, including 7598 participants, which met the inclusion criteria for this meta-analysis, were analyzed.[4-8,26,27] Figure 1 shows the flow diagram (PRISMA template) of information through the different phases of the review. Two authors provided unpublished data from their trials.[7,8]

The overall risk of bias was judged as low. Most studies had a low risk of bias in selective reporting and incomplete outcome data according to the Cochrane Collaboration tool. No study was double blind because this was deemed difficult methodologically given the intervention (Figure 2). Statistical heterogeneity within the trials ranged from low to high with no inconsistency (I^2 = 0%) for some of the secondary outcomes, and I^2 = 38% for the primary outcome.

The characteristics of the 7 included trials are summarized in Table 1. Of the 7598 women, 3807 (50%) were randomized to the induction group, and 3791 (50%) to control. All studies enrolled only uncomplicated full-term vertex singleton gestations. Three studies enrolled only women with a favorable cervix, defined as a Bishop score of ≥5 in nulliparous women or ≥4 in multiparous women. Walker et al included only women aged ≥35 years. Women randomized in the planned induction of labor, received scheduled induction usually at 39^{+0} to 39^{+6} weeks of gestation, whereas women in the control group received expectant management usually until 41-42 weeks of gestation, or earlier if medically indicated.[25,26] Methods of induction usually included cervical ripening, with either misoprostol or Foley catheter, in conjunction with or followed by oxytocin for women with unfavorable cervix (Bishop score <5), and Oxytocin alone for those with favorable cervix (Bishop score ≥5). Five trials also used artificial rupture of membranes as method for induction.

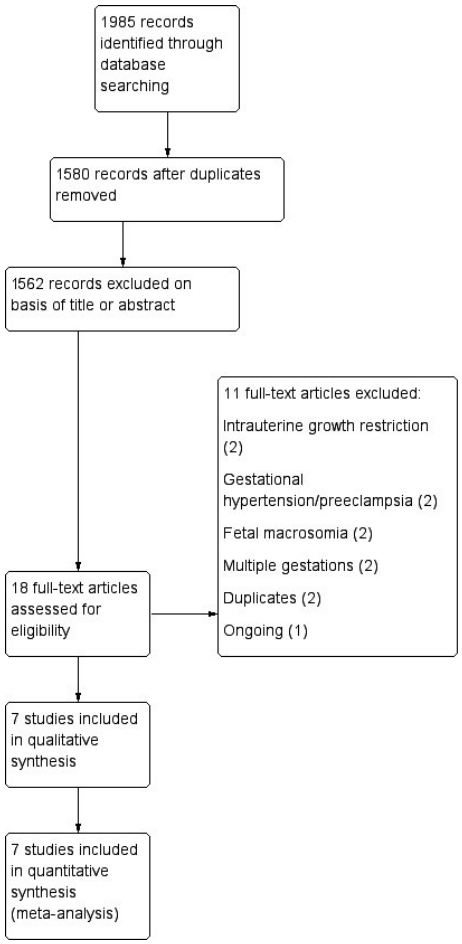

FIGURE 1 Flow diagram of studies identified in the systematic review

3.2 | Synthesis of results

Uncomplicated full-term singleton gestations who received induction of labor had similar incidence of cesarean delivery compared with controls (18.6% vs 21.4%; RR 0.96, 95% CI 0.78-1.19) (Figure 3). Regarding neonatal outcomes, induction was associated with a significantly lower rate of MSAF (4.0% vs 13.5%; RR 0.32, 95% CI 0.18-0.57) (Figure 4), and significantly lower mean birthweight (mean difference −98.96 g, 95% CI −126.29 to −71.63) compared with the control group. There were no differences in other adverse neonatal outcomes (Table 2).

Table 3 shows the results for primary outcome in the subgroup analyses. We found no differences in the rate of cesarean delivery in women with favorable or unfavorable cervix and nulliparous women, and in trials published after 2010 (Table 3). No study stratified data by previous cesarean section.

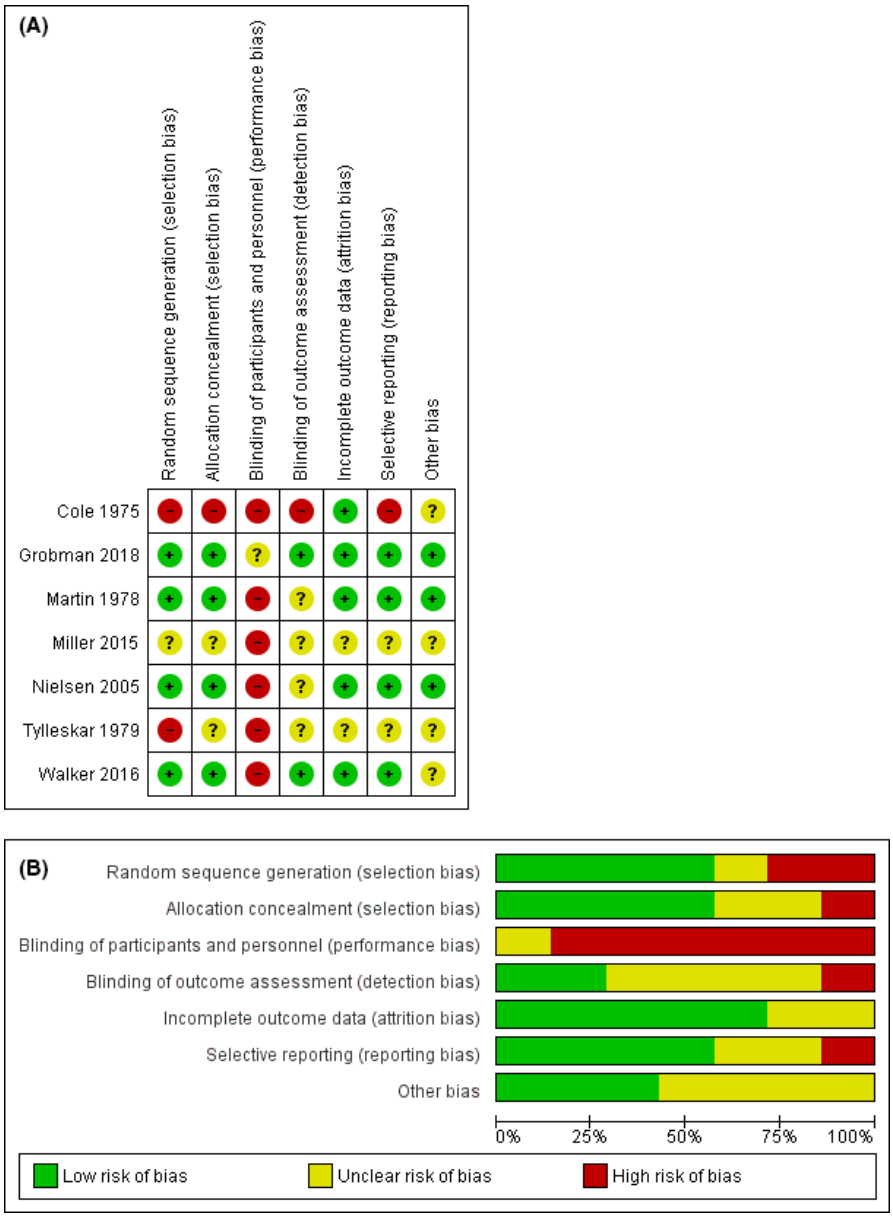

FIGURE 2 Assessment of risk of bias. A, Summary of risk of bias for each trial; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. B, Risk of bias graph about each risk of bias item presented as percentages across all included studies [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This meta-analysis of pooled data of the 7 randomized controlled trials (RCTs) evaluating full-term uncomplicated vertex singleton gestations showed that scheduled induction of labor at about 39 weeks is not associated with an increased risk of cesarean delivery compared with controls expectantly managed at least until ≥41 weeks. Furthermore, induction of labor was associated with a significantly lower rate of MSAF. MSAF is associated with an increased risk of adverse fetal outcomes including meconium aspiration syndrome, cerebral palsy, seizure, and pulmonary disease.[28-32] Meconium aspiration syndrome occurs in 5% of the cases of MSAF and >4% of infants with meconium aspiration syndrome die, accounting for 2% of perinatal deaths.[31,32]

Although induction was associated with lower birthweight, a mean difference of about 100 g at full-term is probably not clinically significant, and we found no differences in adverse neonatal outcomes, including Apgar score <7 at 5 min, and admission to neonatal intensive care unit between intervention and control groups. There were 3 fewer perinatal deaths in the induction vs control group (Table 2), which equates to about one fewer perinatal deaths every 1000 births if a woman is induced at 39 weeks vs expectant management, but this difference was not significant, and our study was not powered for this outcome.

Other meta-analyses have addressed induction of labor and cesarean delivery.[33-38] Two reviews[33,34] included women with indications for induction, such as intrauterine growth restriction,

TABLE 1 Characteristics of the included studies

	Cole 1975[4]	Martin 1978[5]	Tyllerskar 1979[6]	Nielsen 2005[7]	Miller 2015[8]	Walker 2016[26]	Grobman 2018[27]
Location	United Kingdom	United Kingdom	Sweden	USA	USA	United Kingdom	USA
Sample size, n (induction/control)	228 (111/117)	184 (92/92)	84 (43/41)	226 (116/110)	162 (82/80)	618(304/314)	6096 (3059/3037)
Inclusion criteria	Singleton, uncomplicated	Singleton, uncomplicated	Singleton, uncomplicated, favorable cervix	Singleton, uncomplicated, favorable cervix	Singleton, uncomplicated, nulliparous, unfavorable cervix	Singleton, uncomplicated, nulliparous, favorable cervix	Singleton, uncomplicated, nulliparous, unfavorable and favorable cervix
Range gestational age at randomization (weeks^{days})	39^{+0}-40^{+6}	38^{+0}-38^{+6}	40^{+0}-40^{+6}	38^{+0}-38^{+6}	38^{+0}-38^{+6}	36^{+0}-39^{+6}	38^{+0}-38^{+6}
Range gestational age at induction in the intervention group (weeks^{days})	39^{+0}-40^{+6}	38^{+0}-38^{+6}	40^{+0}-40^{+6}	39^{+0}-39^{+6}	39^{+0}-39^{+6}	39^{+0}-39^{+6}	39^{+0}-39^{+4}
Induction method	AROM, oxytocin	AROM, oxytocin	AROM, oxytocin	AROM, oxytocin	Misoprostol followed by Foley and oxytocin, or Foley and oxytocin	AROM, oxytocin, prostaglandin	Misoprostol, Foley, oxytocin
Control group	Expectant management and possible induction at 41 wk	Expectant management and possible induction at 42 wk	Expectant management	Expectant management and possible induction at 42 wk	Expectant management	Expectant management and possible induction between 41 and 42 wk	Expectant management and possible induction between 41 and 42 wk
Study primary outcomes	Meconium staining	Serum bilirubin levels, meconium staining	Not reported	Cesarean delivery	Cesarean delivery	Cesarean delivery	Adverse perinatal events

AROM, artificial rupture of membranes.

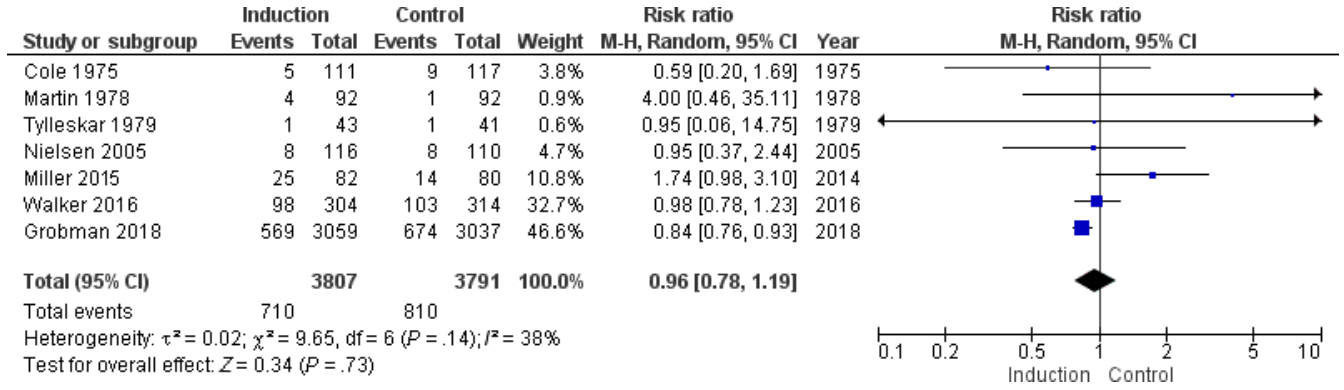

FIGURE 3 Forest plot for the risk of cesarean delivery [Color figure can be viewed at wileyonlinelibrary.com]

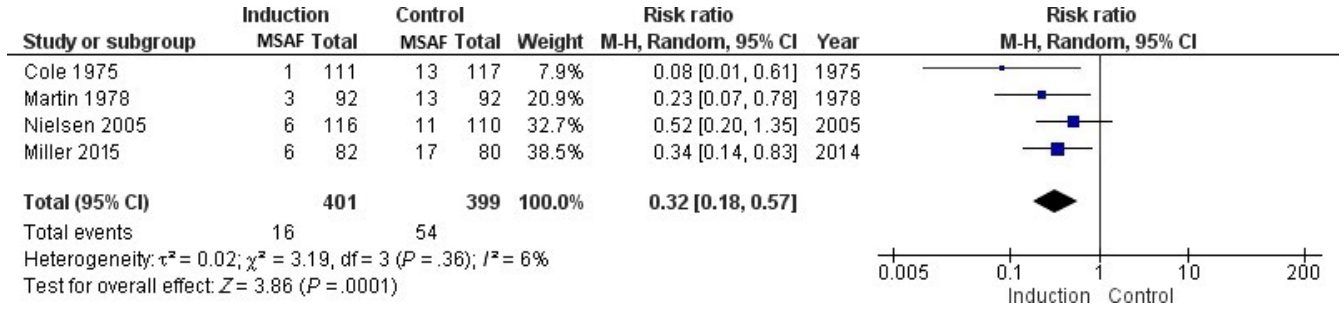

FIGURE 4 Forest plot for the risk of meconium-stained amniotic fluid [Color figure can be viewed at wileyonlinelibrary.com]

hypertensive complications, or gestation ≥41 weeks. Both showed not only no increase in cesarean delivery, but a significant decrease in the incidence of cesarean delivery. Saccone and Berghella[35] showed that induction of labor at full-term in women with uncomplicated singleton pregnancies was not associated with increased risk of cesarean delivery. However, they included only trials published before 2014, and therefore fewer trials and fewer participants. Sotiriadis et al recently published a meta-analysis on the effect of induction of labor at 39 weeks compared with expectant management on the risk of cesarean delivery, and on maternal death and neonatal intensive care admission.[36] This meta-analysis, including 5 studies (n = 7261), is concordant with our findings from 7 studies (n = 7598) showing that planned induction of labor in uncomplicated singleton pregnancy at 39 weeks of gestation may reduce the need for cesarean delivery, as well as the risk of hypertensive disease of pregnancy and the need for neonatal respiratory support.[36] Notably the meta-analysis by Sotiriadis et al excluded 3 RCTs[6-8] each of which included women only with a favorable or unfavorable cervix. For example the Miller et al study[8] only included women with Bishop score ≤5 whereas Tyllerskar et al[6] and Nielsen et al[7] only included women with a favorable cervical examination. The addition of these 3 studies[6-8] causes the cesarean delivery rate to be non-significant in this study.

Limitations of our study are inherent to the limitations of the included RCTs. Only 2 of the included RCTs had cesarean delivery as primary outcome. No long-term outcomes were reported in any of the trials. The vast majority of the included participants came from one large RCT, which therefore drives the results.

Induction of labor can be used to intervene in a pregnancy when the risks of continuing the pregnancy outweigh those of intervention. However, induction was once widely believed to increased the risk of cesarean delivery.[12,38] Several studies also showed higher rates of cesarean delivery in women who underwent induction of labor compared with those who underwent spontaneous labor.[38] However, at any given point in a pregnancy, the decision is not between induction of labor and spontaneous labor, but between induction and expectant management, which yields a pregnancy of greater gestational age and which may not lead to spontaneous labor.[39]

Recently, the ARRIVE trial concluded that induction of labor at 39 weeks of gestation in low-risk nulliparous women did not result in a significantly lower frequency of adverse perinatal outcome, but did result in lower frequency of cesarean delivery.[27] The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine released a statement in response to the results of the ARRIVE trial.[40] Given the benefit in terms of decreased risk of cesarean delivery, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine determined that it is reasonable for obstetric care providers to offer an induction of labor at 39 weeks in well-dated low-risk singleton pregnancies.

This meta-analysis, including data from the ARRIVE trial, showed that induction of labor in asymptomatic and uncomplicated singleton

TABLE 2 Primary and secondary outcomes

	Cole 1975[4]	Martin 1978[5]	Tyllerskar 1979[6]	Nielsen 2005[7]	Miller 2015[8]	Walker 2016[26]	Grobman 2018[27]	Total	I^2	RR (95% CI)
Cesarean delivery	5/111 (4.5%) vs 9/117 (7.7%)	4/92 (4.3%) vs 1/92 (1.1%)	1/43 (2.3%) vs 1/41 (2.4%)	8/116 (6.7%) vs 8/110 (7.8%)	25/82 (30.5%) vs 14/80 (17.5%)	98/304 (32%) vs 103/314 (33%)	569/3059 (18.6%) vs 674/3037 (22.2%)	710/3807 (18.6%) vs 810/3791 (21.4%)	38%	0.96 (0.78-1.19)
Spontaneous vaginal delivery	72/111 (64.7%) vs 82/117 (70.1%)	Not reported	41/43 (95.3%) vs 38/41 (92.7%)	100/116 (86.2%) vs 93/110 (84.5%)	54/82 (65.9%) vs 66/80 (82.5%)	115/304 (38%) vs 104/314 (33%)	2268/3059 (74.1%) vs 2105/3037 (69.3%)	2650/3715 (71.3%) vs 2488/3699 (67.3%)	60%	1.01 (0.94-1.09)
Operative vaginal delivery	34/111 (30.6%) vs 26/117 (22.2%)	Not reported	1/43 (2.3%) vs 2/41 (4.9%)	8/116 (6.9%) vs 9/110 (8.2%)	3/82 (3.7%) vs 0/80	Not reported	222/3059 (7.3%) vs 258/3037 (8.5%)	268/3411 (7.8%) vs 295/3385 (8.7%)	30%	0.97 (0.72-1.30)
Chorioamnionitis	Not reported	Not reported	Not reported	7/116 (6.0%) vs 6/110 (5.5%)	12/82 (14.6%) vs 9/80 (11.3%)	1/304 (0.3%) vs 1/314 (0.3%)	407/3059 (13.3%) vs 429/3037 (14.1%)	427/3561 (12%) vs 445/3541 (12.6%)	0%	0.94 (0.83-1.07)
Blood loss (mL)	185 ± 139 vs 233 ± 150	Not reported	Not reported	303 ± 182 vs 312 ± 192	754 ± 180 vs 900 ± 190	Not reported	Not reported	—	85%	−65.79 (−123.21 to 4.64)
Meconium-stained amniotic fluid	1/111 (0.9%) vs 13/117 (11.1%)	3/92 (3.3%) vs 13/92 (14.1%)	Not reported	6/116 (5.2%) vs 11/110 (10%)	6/82 (7.3%) vs 17/80 (21.3%)	Not reported	Not reported	16/401 (4.0%) vs 54/399 (13.5%)	32%	**0.32 (0.18-0.57)**
Apgar <7 at 5 min	Not reported	Not reported	Not reported	0/116 vs 0/110	0/82 vs 1/80	11/304 (3.6%) vs 12/314 (3.8%)	Not reported	11/502 (2.2%) vs 13/504 (2.6%)	0%	0.89 (0.41-1.93)
Birthweight (g)	3250 ± 380 vs 3390 ± 440	Not reported	3638 ± 453 vs 3720 ± 499	3459 ± 347 vs 3604 ± 438	3401 vs 3513	3352 ± 425 vs 3428 ± 466	3300 vs 3380	—	100%	**−98.96 (−126.29 to −71.63)**
NICU	Not reported	Not reported	Not reported	0/116 vs 0/110	5/82 (6.1%) vs 5/80 (6.3%)	6/304 (2%) vs 7/314 (2.2%)	4/3059 (0.1%) vs 8/3037 (0.3%)	15/3561 (0.4%) vs 20/3431 (0.6%)	0%	0.83 (0.43-1.43)
Perinatal death	0/111 vs 1/117 (0.9%)	0/92 vs 1/92 (1.1%)	Not reported	0/116 vs 0/110	0/82 vs 0/80	0/304 (0%) vs 0/314 (0%)	2/3059 (0.1%) vs 3/3037 (0.1%)	2/3764 (0.05%) vs 5/3750 (0.1%)	0%	0.51 (0.13-2.08)

Data are presented as n for induction vs n for control (as either number with percentage or as mean ± SD). Data in bold type: statistically significant.
CI, confidence interval; NICU, neonatal intensive care unit; RR, relative risk.

TABLE 3 Incidence of cesarean delivery in subgroup analyses

Population	Outcome	Included studies	Total	I^2	RR (95% CI)
Favorable cervix	Cesarean delivery	Tyllerskar 1979[6]Nielsen 2005[7]Walker 2016[26]	107/463 (23.1%) vs 112/465 (24.1%)	0%	0.98 (0.79-1.22)
Unfavorable cervix	Cesarean delivery	Miller 2015[8]	25/82 (30.5%) vs 14/80 (17.5%)	Not applicable	1.74 (0.98-3.10)
Nulliparous women	Cesarean delivery	Tyllerskar 1979[6]Miller 2015[8]Grobman 2018[27]	595/3184 (18.7%) vs 689/3158 (21.8%)	67%	1.12 (0.60-2.07)
Prior cesarean delivery	Cesarean delivery	—	—	—	—
Trials published after 2010	Cesarean delivery	Miller 2015[8]Walker 2016[26]Grobman 2018[27]	692/3445 (20.1%) vs 791/3431 (23.0%)	72%	0.99 (0.76-1.29)

CI, confidence interval; RR, relative risk.

gestations at full-term (39^0-40^6 weeks) is not associated with an increased risk of cesarean delivery, but is in fact associated with a significantly lower risk of MSAF.

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CONFLICTS OF INTEREST

None.

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