Maternal and perinatal outcomes after elective labor induction at 39 weeks in uncomplicated singleton pregnancies: a meta-analysis

Alexandros Sotiriadis[1], Stamatios Petousis[2], Basky Thilaganathan[3,4], Francesc Figueras[5,6], Wellington P Martins[7], Anthony O Odibo[8], Konstantinos Dinas[1], Jon Hyett[9]

[1]Second Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Third Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; [3]Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, London, UK; [4]Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK; [5]BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine, Hospital Clínic and Hospital Sant Joan de Deu, Institut Clínic de Ginecologia, Obstetricia i Neonatologia Fetal i+D Fetal Medicine Research Center, Barcelona, Spain; [6]Center for Biomedical Research on Rare Diseases (CIBER-ER), Madrid, Spain; [7]SEMEAR Fertilidade, Reproductive Medicine and Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Brazil; [8]Department of Obstetrics and Gynecology, Morsani College of Medicine, University of South Florida, Tampa, FL, USA; [9]RPA Women and Babies, Royal Prince Alfred Hospital; and Obstetrics, Gynecology and Neonatology, University of Sydney, Sydney, New South Wales, Australia

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Correspondence to: Dr A. Sotiriadis, Second Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, 92 Tsimiski Street, 54622 Thessaloniki, Greece (e-mail: asotir@gmail.com)

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ABSTRACT

Objective: The rate of maternal and perinatal complications increases after 39 weeks in both unselected and complicated pregnancies. The aim of this study was to synthesize quantitatively the evidence on the effect of elective induction of labor at term on the risk of Cesarean section, and maternal and perinatal outcome.

Methods: We searched PubMed, US Registry of Clinical Trials, SCOPUS and CENTRAL databases from inception to August 2018. We additionally searched the references of retrieved articles. Eligible studies were randomized controlled trials including singleton uncomplicated pregnancies, in which participants were randomized between 39+0 and 39+6 gestational weeks to either labor induction or expectant management.

The risk of bias of individual studies was assessed using the Cochrane Risk of Bias Tool. The overall quality of evidence was assessed per GRADE guideline. Primary outcomes included Cesarean section, maternal death and admission to the neonatal intensive care unit (NICU). Secondary outcomes included operative delivery, grade 3/4 perineal laceration, postpartum hemorrhage, maternal infection, hypertensive disease of pregnancy, maternal thrombotic events, length of maternal hospital stay, neonatal death, need for neonatal respiratory support, cerebral palsy, length of stay in NICU and length of neonatal hospital stay. Pooled risk ratios (RRs) were calculated using random-effects models.

Results: The meta-analysis included 5 studies (7261 cases). Labor induction was associated with decreased risk for Cesarean section (moderate quality of evidence; RR 0.86; 95% CI, 0.78–0.94; I^2=0.1%), maternal hypertension (moderate quality of evidence; RR 0.65; 95% CI, 0.57–0.75; I^2=0) and neonatal respiratory support (moderate quality of evidence; RR 0.73; 95% CI, 0.58–0.95; I^2=0%). No significant effects were found for the other outcomes with available data. The main limitation of our analysis was that the majority of data were derived from a single large study. A second limitation arises from the open-label design of the studies, which may theoretically affect the preparedness of the attending clinician to resort to Cesarean section.

Conclusions: Elective induction of labor in uncomplicated singleton pregnancies from 39 weeks' gestation is not associated with maternal or perinatal complications and may reduce the risk of Cesarean section, hypertensive disease of pregnancy and need for neonatal respiratory support.

INTRODUCTION

Population studies have shown that the prevalence of maternal and fetal complications increases with advancing pregnancy beyond 39 weeks of gestation[1-3]. This pattern appears to be similar both for unselected populations and groups with risk factors, and there is evidence that elective birth from 39 weeks minimizes maternal and fetal risk[4], except for specific groups like growth-restricted[5] and macrosomic[6] fetuses, morbidly obese women[7], women older than 44 years[8], cholestasis of pregnancy[9] and multiple pregnancy[10], who may benefit from even earlier scheduled birth.

In this context, induction of labor at 39 weeks has been proposed as a means to ensure optimal maternal and neonatal outcomes. The arguments against such a policy would focus on the theoretical concerns about logistics, cost, and the consequences of failed induction[11]. However, there are both retrospective[12,13] and prospective[14,15] data showing that induction at 39 weeks may in fact decrease the rate of complications, including cesarean section[15], while there are still no cost-effectiveness analyses of this policy. Finally, an additional factor, which is commonly overlooked, is women's preferences and perceptions about induction[16,17].

As the largest to date RCT on the issue has been just published[15], we performed a meta-analysis of randomized trials aiming to assess the impact of elective labor induction at 39 weeks in uncomplicated singleton pregnancies on core maternal and fetal outcomes.

METHODS

This meta-analysis was structured and reported following a pre-defined protocol, according to the PRISMA guideline and is registered with PROSPERO CRD42018106768)..

Eligibility criteria

Only randomized controlled trials comparing induction of labor vs. expectant management in low-risk pregnant women at term were considered eligible. Studies reporting on high-risk pregnancies, multiple pregnancies, medically indicated inductions (e.g. for preeclampsia, growth restriction or macrosomia, preterm rupture of membranes), post-term pregnancy, or trial of labor after cesarean (TOLAC) were not considered eligible. Studies describing only women with a favorable or unfavorable Bishop score were also excluded, as recruitment of women based on their likelihood of successful induction would lead to selection bias.

Types of participants: pregnant women with a singleton, low-risk pregnancy between 39+0 and 39+6 gestational weeks.

Types of interventions: Labor induction (any method, as defined by authors), between 39+0 and 39+6 weeks, vs. expectant management, i.e. anticipation of spontaneous onset of labor. Cases with labor induction for post-term (as defined in primary studies) pregnancy in the expectant arm were analyzed as expectant arm cases.

Outcome measures

The primary outcomes included

1. Cesarean section
2. Admission of the neonate to the neonatal intensive care unit (NICU)
3. Maternal death, defined as death of the woman during pregnancy and puerperium

The secondary outcomes included

1. Operative delivery (forceps or ventouse)
2. Significant (grade 3/4) perineal laceration
3. Postpartum hemorrhage (as defined in the primary studies)
4. Maternal infection (including postpartum endometritis)
5. Maternal hypertension
6. Maternal thrombotic events
7. Length of maternal hospital stay
8. Neonatal death
9. Need for respiratory support (neonate)
10. Cerebral palsy (neonate)
11. Length of stay in NICU (neonate)
12. Length of hospital stay (neonate)
13. Birth weight

Information sources and search

We searched PubMed, SCOPUS, the US registry of clinical trials (www.clinicaltrials.com) and Cochrane CENTRAL from inception to August 2018 for randomized controlled trials comparing induction between 39+0 and 39+6 weeks vs. expectant management. We used combinations of the terms “induction”, “expectant” and “randomize*” for the electronic searches (Table S1). We deliberately used wide terms to avoid missing potentially eligible trials. We complemented the searches by perusing the references of retrieved articles and the studies included in previous systematic reviews on the topic. We considered studies in European languages.

Study selection and data extraction

Search results were screened by two of the authors (SP and AS) and the full text of all relevant studies was reviewed. These two authors independently assessed for inclusion all the potential studies identified from the search strategy. Data were extracted using a pre-specified form. We resolved any disagreement through discussion or, if required, we consulted a third author (KD).

The variables for which data were sought (in addition to pregnancy outcomes and inclusion/exclusion criteria) included country/countries where the studies were conducted, mean gestational age at randomization, mean maternal age, attrition rate and method of induction.

In case of missing and unclear data, we contacted the authors of the primary studies for additional information.

Risk of bias of individual studies

The risk of bias in individual studies was assessed using the Cochrane Risk of Bias 2.0 tool[18]. This tool assesses potential bias in five domains: randomization process; deviations from intended intervention; missing outcome data; measurement of the outcome; selection of the reported result. For each domain, the judgment of bias may indicate either high or low risk of bias, of the presence of some concerns. According to the instructions of the tool, we allocated an overall low risk of bias for a given result when the risk of bias was low for all domains for this result; some concerns when there were some concerns in at least one domain for this result; high risk of bias when there was high risk in at least one domain or some concerns for multiple domains in a way that substantially lowered confidence in the result[18].

Quality of evidence

We assessed the overall quality of the evidence for the primary and secondary outomes as per GRADE guideline[19, 20], using the GRADEpro GD tool. Briefly, GRADE is a system for rating the quality of evidence in systematic reviews and guidelines using a scoring system across five fields, i.e. risk of bias, inconsistency, indirectness, imprecision and publication bias. GRADE specifies four categories for the quality of a body of evidence. This reflects the degree of confidence of how close our estimate of the effect lies to the true effect. High quality levels means that we are very confident that the true effect lies close to the estimate of the effect calculated by the meta-analysis. The level of confidence decreases with decreasing quality (high → moderate → low → very low) and ver low quality means that the true effect is likely to be substantially different from that estimated in the review[20].

Summary measures and synthesis of the results

For dichotomous data, we calculated the summary risk ratios (RRs) with 95% confidence intervals. We calculated the mean difference (MD) for continuous outcomes, if they were measured in the same way between trials. We used random effects models (DerSimonian and Laird) for data synthesis.

For each outcome, we also calculated the number needed to treat (NNT), based on our pooled effect sizes. NNT defined by the inverse of the absolute value of the risk difference, and it shows the number of patients who need to be treated with one intervention rather than its comparator to have one more event of interest (eg, success).

Between-studies heterogeneity was assessed using the I^2 statistic, which is the ratio of between-study variance over the sum of the within- and between-study variances and describes the percentage of the true effect variation that is due to heterogeneity rather than chance (range, 0–100%). A simplistic grouping would assign descriptions of low, moderate and high heterogeneity to I^2 values of 25, 50 and 75%, respectively [21].

The unit of analysis was the mother for maternal outcomes and the fetus/neonate for perinatal outcomes. The initial number of cases was the same for maternal and fetal outcomes, as only singleton pregnancies with live fetuses at randomization were included.

We carried out statistical analyses using Stata 14.0 software (StataCorp College Station, TX).

Subroup and sensitivity analyses

We planned to perform a sensitivity analysis of studies at low risk of bias and a meta-regression for maternal age and method of induction .

Publication bias

We planned *a priori* to investigate reporting biases (such as publication bias) using funnel plots, if there were 10 or more studies in the meta-analysis. We planned to assess funnel plot asymmetry visually, and will perform exploratory analyses using formal statistical tests if asymmetry was suggested. However, only five studies were included in this review, and the evaluation of publication bias was suboptimal.

RESULTS

Study selection

The flowchart of searches and study selection in shown in Figure 1. Electronic searches and complementary hand-searching retrieved 811 titles. After removal of duplicates (N=62) and exclusion of studies based on title/abstract, we downloaded 32 cases in full text. Twenty-seven of them were excluded with reasons (Table S2). Two of these studies would be otherwise eligible, but were excluded because their participants were exclusively women with favorable[22] or unfavorable Bishop scores[23], which made them susceptible to selection bias. Eventually, five studies[14,15, 24-26] (7261 cases; 3629 allocated in induction, 3632 allocated in exectant management) were included in the analysis. A single study[15] represented approximately 83% of all participants.

Study characteristics

The characteristics of studies are shown in Table 1. The largest study was performed in the US[15], three came from the UK[14,24,26] and one from Japan[25]. Four studies only included nulliparous women and one study[26] included both nuliparous women and parous women with a faborable obstetric history. The methods of induction varied both across and within studies, involving amniotomy, laminariae, oxytocin and prostaglandins.

Risks of bias within studies

The assessment of risk per Cochrane Risk of Bias Tool v.2 is shown in Table 2. None of the studies was overall judged as being at a low risk of bias. All studies had unavoidably open-label design, which might have affected the rate of succesful induction and thereby a string of outcomes, starting with mode of delivery. There were some concerns for bias in two of the studies[14,15] and the rest three studies were judged as being at high risk of bias[24-26]. A common limitation of the other three studies[24-26] is that they provided insufficient information about the randomization methods, allocation concealment and handling of the results.

Results of individual studies

The results of the individual studies are presented in Table S3. All five studies reported on the rate of cearean section; three studies[14,15,25] presented information about NICU admision and one[15] about maternal death. There was no information about thrombotic maternal complications, length of hospital stay, cerebral palsy, length of NICU stay and hospital stay for the neonate.

Synthesis of the results

Primary outcomes

Five studies[14,15,24-26] reported on cesarean section (6096 participants, 1471 women submitted to cesarean section).Elective induction was associated with reduced risk of cesarean section (RR 0.86, 95%CI 0.78-0.94, I^2=0.1%) (Figure 2). The number of elective inductions needed to prevent one cesarean section was 32.

Only one study[15] examined maternal death. There were no deaths among the 6096 participants.

Three studies[14,15,25] reported on NICU admission (6849 cases, 767 admissions to NICU). There was no significant difference between induction and expectant management (RR 0.90, 95%CI 0.79-1.03, I^2=0%) (Figure 3).

Secondary outcomes

There was no difference between the two groups in the rates of operative delivery (5 studies[14,15,24,26], 7261 participants, 854 operative deliveries; RR 1.11, 95%CI 0.88-1.41, $I^{2=}$65.5%); grade 3-4 perineal laceration (2 studies[14,15], 6794 women, 199 women with grade 3-4 perineal laceration; RR 1.18, 95%CI 0.89-1.50, I^2=0%); postpartum hemorrhage (2 studies[14,15], 6714 women, 464 with postpartum hemorrhage; RR 1.06, 95%CI 0.90-1.25, I^2=0%) and postpartum maternal infection (2 studies[14,15], 6714 women, 137 with postpartum infection; RR 0.84 95%CI 0.58-1.22, I^2=9.8%). Two studies[14,15] reported on hypertensive disease of pregnancy (6715 women, 741 with hypertensive disease of pregnancy). Elective induction at 39 weeks was associated with a significant decrease in the risk of hypertension (RR 0.65, 95%CI 0.57-0.75, I^2=0%, NNT=21) (Figure S1).

Regarding neonatal outcomes, there was no difference between the two groups in the risk of neonatal death (4 studies, 7126 neonates, 6 cases of neonatal death; RR 0.57, 95% 0.12-2.71, I^2=0%). Labor induction was associated with a significant reduction in the need for neonatal respiratory support (2 studies[14,15], 6714 neonates, 250 needed support; RR 0.73 95%CI 0.58-0.95, I^2=0%) (Figure S2). Neonates born after induction had significantly lower mean birth weight than those in the expectant group (3 studies[14,15,26], 6942 neonates; pooled MD -81 g, 95%CI -100 g to -63 g, I^2=0%).

Subgroup and sensitivity analyses

There was insufficient published data to perform the prespecified subgroup and sensitivity analyses.

Overall quality of the evidence

The overall quality of the evidence (Table 3) was moderate for cesarean section, maternal hypertension and need for neonatal respiratory support; low for NICU admission, grade 3-4 perinatal lacerations and postpartum maternal infection, and very low for operative vaginal delivery and neonatal death. All outcomes were downgraded by one level for bias, as all evidence was derived exclusively from studies at concern or at high risk of bias. Several outcomes were further downgraded by one level for imprecision, as the 95%CIs of their pooled effect sizes included the unit; neonatal death was downgraded by two levels, as the number of events (n=6) was quite small to reach any robust conclusion. Operative delivery was also downgraded by one level because of inconsistency, as the corresponding studies indicated heterogeneous direction of effect.

DISCUSSION

Summary of evidence

Our synthesis of evidence from randomized controlled trials showed that, compared to expectant management, elective induction of labor at 39 weeks in uncomplicated singleton pregnancies is associated with reduced risk of cesarean section (RR 0.86, moderate quality of evidence), reduced risk of maternal hypertension (RR 0.65, moderate quality of evidence) and reduced need for neonatal respiratory support (RR 0.73, moderate quality of evidence). There is no indication that elective induction from 39 weeks is associated with an adverse effect on maternal or neonatal outcomes.

Interpretation of the results

The rationale supporting elective induction at 39 weeks is that population data demonstrate an increase in the rate of perinatal and maternal complications in both unselected and complicated pregnancies after 38-39 weeks[1-3]. The major counterarguments against such a policy have been the concerns for failed induction and the concomitant risk for maternal and neonatal complications, mostly arising from retrospective studies[27, 28].

Our results do not support these concerns. Elective induction at 39 weeks may, in fact, result in a relative reduction of the rate of caesarean sections, from approximately 22% in expectant management to approximately 19% with induction (NNT 32). This does not appear to happen at the expense of an increase in the rate of operative deliveries. A possible explanation is that 39 weeks is the optimal time for induction. Women who continue their pregnancy beyond 39 weeks become progressively less likely to succeed after induction[29]. This may reflect increasing rates of failure to progress in labour (as the foetus becomes larger there is a higher risk of cephalopelvic disproportion) and increasing risks of fetal distress due to a simultaneous decrease in placental reserve[30]. In our analysis, the mean birthweight of neonates in the induction group was approximately 80 g lower than those in the expectant management group, although it is not clear if this difference affected the chance of successful induction.

We found that labour induction at 39 weeks can decrease the risk of hypertensive disease of pregnancy, from approximately 13% with expectant management to approximately 9% (NNT 21). We hypothesize that the beneficial effect of induction at

39 weeks is mostly mediated though the prevention of hypertensive complications that would manifest later, should pregnancy continue[31, 32].

A third potentially beneficial effect of induction was the reduced need for respiratory support of the neonate, from approximately 4% with expectant management to approximately 3% when performing induction of labor at 39 weeks (NNT 83). A retrospective study of 5000 non-anomalous term fetuses found that the presence of meconium increases the risk for respiratory distress by 3.3 times and caesarean section by 4.2 times[33] and it is likely that the improvement in respiratory outcomes may be related to a reduction in meconium exposure before birth.

Strengths and limitations

Our strict selection methodology ensures that our results describe a well-defined population of singleton uncomplicated pregnancies between 39+0 and 39+6 weeks. In this context, we excluded two otherwise eligible studies, one of them only including women with favorable[22] and one including only women with unfavorable cervix [23], as both of them would be at theoretical risk of selection bias. Our focus on singleton uncomplicated pregnancies at 39 weeks differentiates our meta-analysis from previous systematic reviews[34-37], which analyzed term pregnancies (i.e. ≥37 weeks) as a group[34-37], included all indications for induction in their main analyses[34-37], or only assessed the impact of induction on cesarean section rate[34]. Moreover, none of the previous meta-analyses included the data from the ARRIVE trial[15], which contributes by more than 80% of the total sample for our target population.

The main limitation of our analysis was that most of the data was derived from a single large study[15], which, depending on the outcome ranged from 29% to 97%. A second limitation arises from the unavoidably open-label/unblinded design of all included studies, which might affect the preparedness of the attending clinician to resort to cesarean section. Although this is mostly a theoretical concern, and it is not possible to safely predict its direction of effect, we downgraded all outcomes by one degree for bias. There were no data for many of our pre-defined outcomes, and not sufficient data to perform subgroup and sensitivity analyses. The methods of induction differed across and within studies, preventing us from exploring the potential impact of different methods on the observed results; previous pooled results indicate that cervical ripening before induction of contractions increases the likelihood of success[34]. Moreover, there was no information amenable to quantitative synthesis from the included studies to gauge the impact of systematic induction on women´s

satisfaction and experience, although data from the largest included study[15] indicate similar scores of perceived control during childbirth in the two groups. Finally, the small number of included studies did not allow a formal evaluation of publication bias; however, this is likely to be low, judging from the dispersion of the estimates even in smaller studies.

Generalizability and applicability

Almost all data come from studies of nulliparous women having an uncomplicated singleton pregnancy between 39+0 and 39+6 weeks. Therefore, our results are applicable to such women, and their generalization to the entire population is uncertain.

Although the US Society for Maternal and Fetal Medicine issued an instant statement proposing that it is reasonable to offer elective IOL to low-risk, nulliparous women at or beyond 39 weeks [38], there are still significant unresolved issues. Thus, there are no data on how such a policy would affect the logistics and cost of maternity care. Also, the current studies do not provide information about the long-term neurodevelopmental impact of induction at 39 weeks. This is an important consideration given the retrospective observational data showing that the nadir of special education need is reached for children born at 40-41 weeks[39,40]. In this context, the most likely subgroup to be benefited from an induction policy might be nulliparous women with risk factors for hypertensive, other medical or fetal complications in pregnancy.

Conclusions

There is moderate quality evidence that elective induction of labor in uncomplicated singleton pregnancies from 39 weeks may be associated with reduced risk of cesarean section, maternal hypertension and need for respiratory support in the neonate. Unresolved issues, should systematic induction be adopted, involve logistics, cost, the preferences of women and possibly the long-term neurodevelopmental outcome of the offspring.

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Legends for figures

Figure 1. Flowchart of study selection of randomized controlled trials for meta-analysis.

Figure 2. Relative risks for cesarean section in selective labor induction at 39 weeks and expectant management.

Figure 3. Relative risks for admission to the neonatal intensive care unit (NICU) in selective labor induction at 39 weeks and expectant management.

Supplemental Figure S1. Relative risks for hypertensive disorders of pregnancy in selective labor induction at 39 weeks and expectant management

Supplemental Figure S2. Relative risks for neonatal respiratory support in selective labor induction at 39 weeks and expectant management

Figure 1. PRISMA flowchart of study collection.

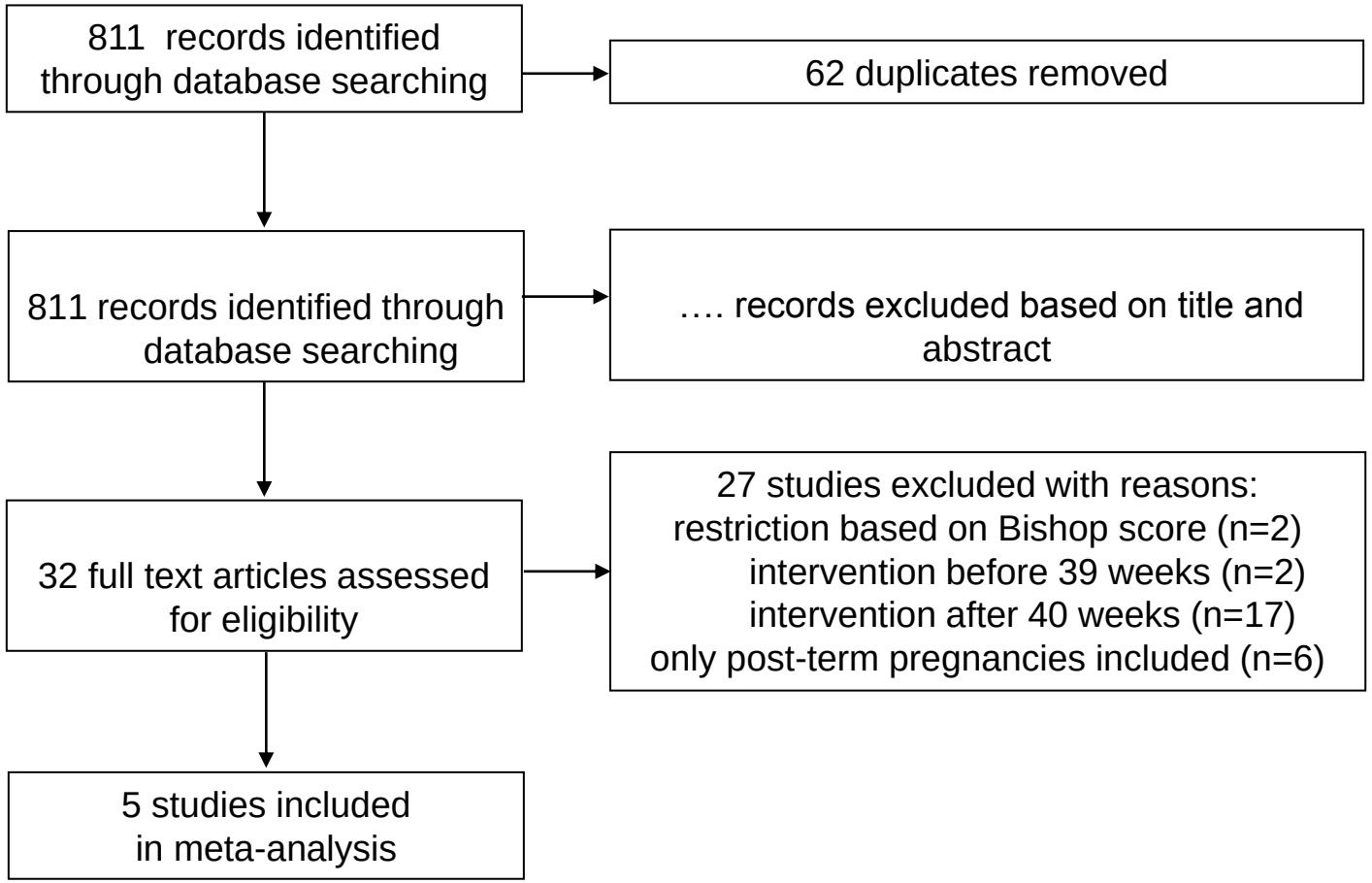


Figure 2. Relative risks for cesarean section in selective labor induction at 39 weeks and expectant management.

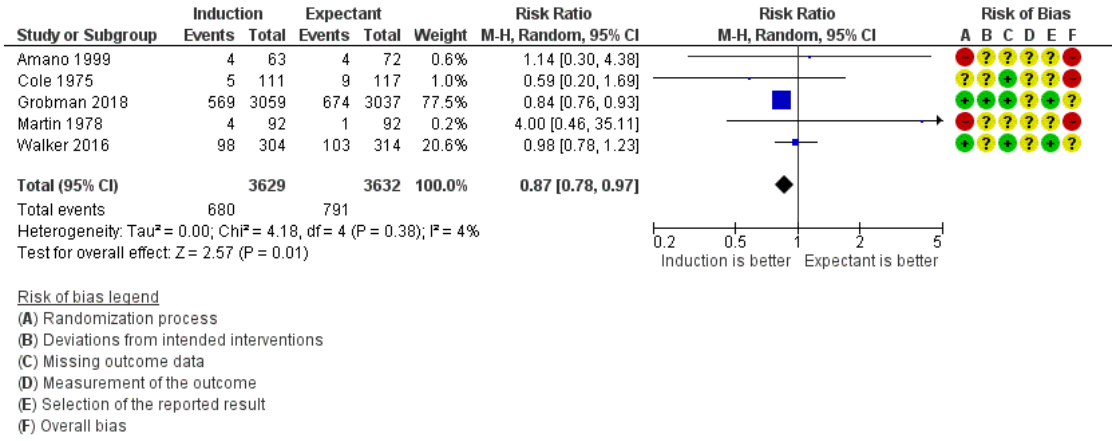
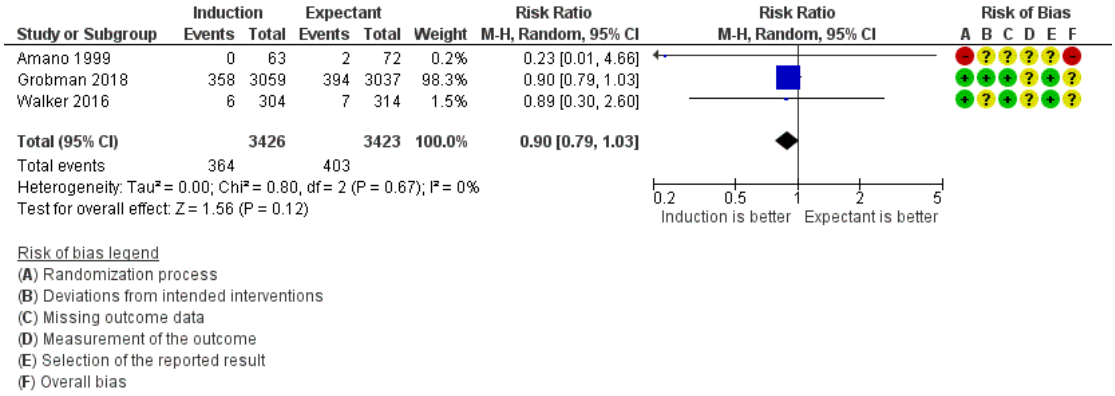


Figure 3. Relative risks for admission to the neonatal intensive care unit (NICU) in selective labor induction at 39 weeks and expectant management.



Supplemental Figure S1. Relative risks for hypertensive disorders of pregnancy in selective labor induction at 39 weeks and expectant management

Supplemental Figure S2. Relative risks for neonatal respiratory support in selective labor induction at 39 weeks and expectant management

Table 1. Characteristics of the included studies (PICOS)

Study	No of patients	Inclusion criteria	Exclusion criteria	Outcomes	Intervention	Low-risk definition	T1	T2
Grobman 2018	6,096	Low-risk nulliparous women; live singleton fetus in vertex presentation; no contraindication to vaginal delivery, no planned cesarean delivery; certain gestational age.	Women in labor or with premature rupture of membranes or vaginal bleeding at 38+0 to 38+6	Cesarean delivery; perinatal death; need for respiratory support within 72 hours after birth; Apgar score; hypoxic–ischemic encephalopathy; seizure; infection; meconium aspiration syndrome; birth trauma; intracranial or subgaleal hemorrhage; hypotension requiring vasopressor support. Birth weight, duration of respiratory support, cephalohematoma, shoulder dystocia, transfusion of blood products,hyperbilirubinemia requiring phototherapy or exchange transfusion, hypoglycemia requiring intravenous therapy, admission to the neonatal intermediate or intensive care unit, and length of hospitalization. Hypertensive disorders of pregnancy, indication for cesarean delivery, operative vaginal delivery, indication for operative vaginal delivery, uterine incisional extensions during cesarean	Iinduction of labor at 39+0 to 39+4. No specific induction protocol mandated	Absence of any condition considered to be a maternal or fetal indication for delivery before 40 weeks 5 days	Undergo induction of labor at 39+0 to 39+4	Elective delivery before 40+5 and no later than 42+2

				delivery, chorioamnionitis, 3- or 4-degree perineal laceration, postpartum hemorrhage, postpartum infection, venous thromboembolism, number of hours in the labor and delivery unit, length of postpartum hospital stay, admission to the intensive care unit, and maternal death.				
Walker 2016	618	Nulliparous women, 35 years of age or older on their expected due date, with a singleton live fetus in a cephalic presentation.	Fetal congenital abnormality; contraindication to labor, vaginal delivery or expectant management History of myomectomy, certain gestational age	Cesarean delivery. Method of delivery other than cesarean section, onset of labor, intrapartum complications, postpartum complications (e.g., systemic infection or the need for a blood transfusion). Live birth or stillbirth, birth weight, admission to a neonatal intensive care unit, birth trauma, and two composite outcomes for serious neonatal complications (direct trauma and hypoxia). Maternal expectations and experience of childbirth	Local policies for induction of labor.	N/A	Induction of labor between 39^{+0} and 39^{+6} completed weeks	Await the spontaneous onset of labour until 42 weeks unless induction was required earlier for medical reasons.
Amano 1999	135	Uncomplicated nullipara in 38^{+6}	No information	Normal spontaneous delivery, vacuum extraction,forceps, cesarean section, incidence of pathological FHR, resuscitation in labor Apgar score in 1^{st} minute, Umbilical artery pH, NICU	Laminaria tents ± oral administration± rupture of membranes± oxytocin or PGF2, under direct CTG monitorin	N/A	Induction of labor at 39 completed weeks	Spontaneous onset of labor was awaited until 42 completed weeks

				admission, meconium-stained amniotic fluid, maternal blood loss	g. Epidural or balanced anesthesia used.			
Martin 1978	184	Past and/or present pregnancies were obstetrically normal, booking in the index pregnancy no later than the 18th week, menstrual cycle did not exceed <36 days, no pregnancy for at least three months before the last menstrual period, size of the uterus at booking corresponded to the period of amenorrhoea	N/A	Vaginal delivery, forceps delivery, caesarean section, length of labor, unexplained postpartum pyrexia, demand for analgesia, meconium staining for amniotic fluid, Apgar score at 1st and 5th minute, stillbirth, neonatal jaundice	Amniotomy ± intravenous oxytocin.	N/A	Induction of labor at at 39 weeks	Wait for spontaneous onset of labour until 42 weeks, unless induction was required earlier for medical reasons.
Cole 1975	228	Primigravidae aged 18-30 years or women of 1, 2, or 3 parity aged 18-35 years who had had normal pregnancies without any previous obstetric abnormality. Certain	N/A	Vaginal delivery, forceps delivery, caesarean section, length of labor, dose of pethidine, number of epidurals, blood loss after vaginal delivery, perinatal loss, meconium staining in labour, first stage fetal heart irregularity, Apgar score, birth weight, unsuspected SGA, transient respiratory distress, neonatal	Amniotomy followed immediately by oxytocin at increasing doses using the Cardiff pump.	N/A	Induction of labour between 39 and 40 weeks	Await the spontaneous onset of labour until 41 weeks unless induction was required earlier for medical reasons.

		gestation al age.		jaundice				

Table 2: Risk of bias table, as per Cochrane Collaboration Risk of Bias Tool II.

		Grobman et al. 2018	Walker et al. 2016	Amano et al. 1999	Martin et al. 1978	Cole 1975
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Y	N	Y	Y
	1.2 Was the allocation sequence concealed until participants were recruited and assigned to intervention?	PY	PY	N	PY	NI
	1.3. Were there baseline imbalances that suggest a problem with the randomization process?	N	N	N	N	N
	Risk of bias judgement	Low	Low	High	Some concerns	Some concerns
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y	Y	Y	Y	Y
	2.2. Were carers and trial personnel aware of their assigned intervention during the trial?	Y	Y	Y	Y	Y
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from intended intervention beyond what would be expected in usual practice?	N	N	N	N	N
	2.4. If Y/PY/NI to 2.3: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	PN	PN	PN	PN	N
	2.5. Were any participants analysed in a group different from the one to which they were assigned?	Y	Y	Y	Y	NI
	2.6. If Y/PY/NI to 2.5. Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	N	PN	PN	PY	PN
	Risk of bias judgement	Low	Some concerns	Some concerns	Some concerns	Some concerns
Bias due to missing outcome data	3.1. Were outcome data available for all, or nearly all, participants randomized?	Y	Y	Y	Y	Y
	3.2. If Y/PY/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Y	Y	N	N	Y
	3.3. If Y/PY/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	Y	Y	PY	PY	PY
	Risk of bias judgement	Low	Low	Some concerns	Some concerns	Low
Bias in measurement of the outcome	4.1. Were outcome assessors aware of the intervention received by study participants?	Y	Y	Y	Y	Y
	4.2. If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	PN	PN	PN	PN	PN
	Risk of bias judgement	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Bias in selection of the reported result	Are the reported outcome data likely to have been selected, on the basis of the results, from… 5.1. …multiple outcome measurements (e.g scales, definitions, time points) within the outcome domain?	N	N	NI	NI	NI
	5.2. …multiple analysis of the data?	N	N	NI	NI	NI
	Risk of bias judgement	Low	Low	Some concerns	Some concerns	Some concerns
Overall bias	Risk of bias judgement	Some concerns	Some concerns	High	High	High

Table 3: Summary of findings:

Labor induction at 39 weeks in singleton uncomplicated pregnancies vs. to expectant management

Patient or population: reducing the rates of cesarean section
Setting:
Intervention: labor induction at 39w0d to 39w6d
Comparison: expectant management up to 41-42w

Outcomes	Anticipated absolute effects* (95% CI)		NNT	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with expectant management	Risk with labor induction at 39 weeks				
Cesarean section	**21.8%**	**18.7%** (17.0-20.5%)	**32** (21-77)	**RR 0.86** (0.78 to 0.94)	7,261 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]
NICU admission	**11.8%**	**10.6%** (9.3-12.1%)	**-**	**RR 0.90** (0.79 to 1.03)	6,849 (3 RCTs)	⊕⊕◯◯ LOW [a,b]
Operative delivery	**11.4%**	**11.8%** (9.4-14.7%)	**-**	**RR 1.03** (0.82 to 1.29)	7,126 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
Grade 3/4 perinatal lacerations	**2.7%**	**3.2%** (2.4-4.1%)	**-**	**RR 1.18** (0.89 to 1.50)	6,714 (2 RCTs)	⊕⊕◯◯ LOW [a,b]
Postpartum hemorrhage	**6.8%**	**7.2%** (6.1-8.5%)	**-**	**RR 1.06** (0.90 to 1.25)	6,714 (2 RCTs)	⊕⊕◯◯ LOW [a,b]
Postpartum maternal infection	**2.2%**	**1.9%** (1.3-2.7%)	**-**	**RR 0.84** (0.58 to 1.22)	6,714 (2 RCTs)	⊕⊕◯◯ LOW [a,b]
Maternal hypertension	**13.4%**	**8.7%** (7.6-10.0%)	**21** (17-29)	**RR 0.65** (0.57 to 0.75)	6,715 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]
Neonatal death	**0.1%**	**0.1%** (0.0-0.3%)	**-**	**RR 0.57** (0.12 to 2.71)	7,116 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,d]
Neonatal respiratory support	**4.3%**	**3.1%** (2.5-4.1%)	**83** (56-500)	**RR 0.73** (0.58 to 0.95)	6,714 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**
CI: Confidence interval; RR: Risk ratio; NNT = number needed to treat (calculated only when significant difference was observed)

Explanations

a. Data is exclusively derived from studies at concern for bias or at high risk of bias
b. The 95% CI for the pooled effect sizes include the unit
c. Different direction of effect across the studies
d. Very small number of events