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

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KEYWORDS: Cesarean; hypertensive disease of pregnancy; induction; labor; meta-analysis

ABSTRACT

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

Methods *PubMed, US Registry of Clinical Trials, SCOPUS and CENTRAL databases were searched from inception to August 2018. Additionally, the references of retrieved articles were searched. Eligible studies were randomized controlled trials of singleton uncomplicated pregnancies in which participants were randomized between 39 + 0 and 39 + 6 gestational weeks to either induction of labor 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 according to the 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 five studies (7261 cases). Induction of labor was associated with a 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);* $I^2 = 0\%$*). Neonates born after induction weighed, on average, 81 g (95% CI, 63–100 g) less than those born after expectant management. No significant effects were found for the other outcomes with the available data. The main limitation of our analysis was that the majority of data were derived from a single large study. A second limitation arose from the open-label design of the studies, which may theoretically have affected the readiness of the attending clinician to resort to Cesarean section.*

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

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INTRODUCTION

Population studies have shown that the prevalence of maternal and fetal complications increases with advancing pregnancy beyond 39 weeks' gestation[1–3]. This pattern appears to be similar for both 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], women with cholestasis of pregnancy[9] and women with a multiple pregnancy[10], who may benefit from even earlier scheduled delivery.

In this context, induction of labor at 39 weeks has been proposed as a means of ensuring optimal maternal and neonatal outcomes. The arguments against such a policy relate to theoretical concerns about logistics, cost and the consequences of failed induction[11]. However, there are both retrospective and prospective data showing that induction at 39 weeks may in fact decrease the rate of complications[12–15], including Cesarean section[15], while no cost-effectiveness analysis of this policy is available to date. An additional factor, which is commonly overlooked, is women's preference and perception about induction of labor[16,17].

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

METHODS

This meta-analysis was structured and reported following a predefined protocol, according to the PRISMA guidelines, and is registered with PROSPERO (CRD42018106768).

Eligibility criteria

Only RCTs comparing elective induction of labor with expectant management in low-risk singleton pregnancy at term were considered eligible for inclusion. Studies reporting on high-risk pregnancies, multiple pregnancies, medically indicated inductions (e.g. for pre-eclampsia, growth restriction, macrosomia, preterm rupture of membranes), post-term pregnancy or trial of labor after Cesarean section 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 have led to selection bias.

Study participants were pregnant women with a singleton, low-risk pregnancy between 39 + 0 and 39 + 6 weeks' gestation. Interventions evaluated were induction of labor (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 that underwent induction of labor for post-term (as defined in primary studies) pregnancy in the expectant arm were treated as expectant management cases.

Outcome measures

Primary outcomes included Cesarean section, admission of the neonate to the neonatal intensive care unit (NICU) and maternal death, defined as death of the woman during pregnancy and puerperium.

Secondary outcomes included: operative delivery (forceps or ventouse), significant (Grade-3/4) perineal laceration, postpartum hemorrhage (as defined in the primary studies), maternal infection (including postpartum endometritis), maternal hypertension, maternal thrombotic events, length of maternal hospital stay, neonatal death, need for neonatal respiratory support, neonatal cerebral palsy, length of neonatal stay in NICU, length of neonatal hospital stay and birth weight.

Information sources and search

PubMed, SCOPUS, the US Registry of Clinical Trials (www.clinicaltrials.com) and Cochrane CENTRAL were searched from inception to August 2018 for RCTs comparing induction of labor between 39 + 0 and 39 + 6 weeks with expectant management. Combinations of the terms 'induction', 'expectant' and 'randomize*' were used for the electronic searches (Table S1). Wide terms were used deliberately to avoid missing potentially eligible trials. In addition to database searches, the references of retrieved articles and of studies included in previous systematic reviews on the topic were perused. Only studies in European languages were considered.

Study selection and data extraction

Search results were screened by two of the authors (S.P., A.S.) and the full text of all relevant studies was reviewed. The same two authors independently assessed the eligibility of all the potential studies identified from the search. Data were extracted using a prespecified form. Any disagreement was resolved through discussion or, if required, through consultation with a third author (K.D.).

The variables for which data were sought (in addition to pregnancy outcomes and inclusion/exclusion criteria) included country in which the study was conducted, mean gestational age at randomization, mean maternal age, attrition rate and method of induction. In case of missing or unclear data, the authors of the primary studies were contacted for additional information.

Risk of bias of individual studies

The risk of bias in individual studies was assessed using the Cochrane Risk of Bias Tool 2.0[18]. This tool assesses potential bias in five domains: randomization process;

deviation from intended intervention; missing outcome data; measurement of the outcome; and selection of the reported result. For each domain, the judgment of bias may indicate either high or low risk, or presence of some concerns. According to the instructions for the tool, an overall 'low risk of bias' was allocated 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; and '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

The overall quality of evidence for the primary and secondary outomes was assessed 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, namely, 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 level 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 very 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 results

For dichotomous data, summary risk ratios (RRs) with 95% CIs were calculated. Mean difference was calculated for continuous outcomes, if they were measured in the same way between trials. Random-effects models (DerSimonian and Laird) were used for data synthesis.

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

Between-study 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.

Statistical analysis was carried out using Stata 14.0 software (StataCorp., College Station, TX, USA).

Subgroup 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 perform exploratory analyses using formal statistical tests if asymmetry was suggested. However, only five studies were included in this review, and thus, the evaluation of publication bias was suboptimal.

RESULTS

Study selection

The electronic search and complementary hand-searching of references yielded 811 titles. After removal of duplicates ($n = 62$) and exclusion of studies based on title/abstract, we assessed 32 studies in full text (Figure 1). Twenty-seven

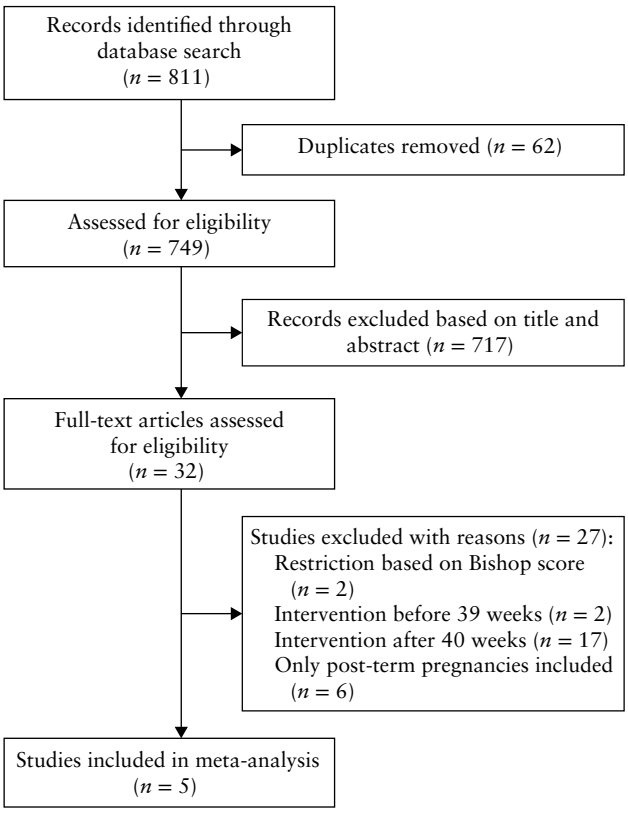

Figure 1 Flowchart showing selection and inclusion in meta-analysis of randomized controlled trials reporting on induction of labor *vs* expectant management in low-risk singleton pregnancy at term.

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[23] Bishop scores, which made them susceptible to selection bias. Eventually, five studies[14,15,24–26] were included in the analysis, which involved 7261 cases, 3629 allocated to elective induction and 3632 to expectant management. A single study[15] represented 84% of all participants.

Study characteristics

Characteristics of the included studies are shown in Table 1. The largest study was performed in the USA[15], three in the UK[14,24,26] and one in Japan[25]. Three studies included only nulliparous women and two[24,26] included both nulliparous and parous women with a favorable obstetric history. The methods of labor induction varied both across and within studies, involving amniotomy, laminarias, oxytocin and prostaglandins.

Risks of bias within studies

Assessment of risk of bias according to the Cochrane Risk of Bias Tool v.2 is shown in Table 2. None of the studies was judged as having an overall low risk of bias. All studies had unavoidably open-label design, which might have affected the rate of successful induction and thereby a string of outcomes, starting with the mode of delivery. There were some concerns for bias in two of the studies[14,15], and the other three[24–26] were judged as being at high risk of bias. A common limitation of the latter three studies[24–26] was 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 Cesarean section, three studies[14,15,25] presented information about NICU admission 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 results

All included studies[14,15,24–26] reported on Cesarean section (7261 participants; 1471 women underwent Cesarean section). Elective induction of labor was associated with a reduced risk for Cesarean section (RR 0.86 (95% CI, 0.78–0.94); $I^2 = 0.1\%$) (Figure 2, Table 3). The number of elective inductions needed to prevent one Cesarean section was 32.

Only one study[15] examined maternal death, and no death occurred 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 of labor and expectant management with respect to risk of NICU admission (RR 0.90 (95% CI, 0.79–1.03); $I^2 = 0\%$) (Figure 3, Table 3).

Regarding secondary outcomes, there was no difference between the two groups in the rates of operative delivery (five 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 (two studies[14,15], 6714 women, 199 with Grade-3/4 perineal laceration; RR 1.18 (95% CI, 0.89–1.50); $I^2 = 0\%$), postpartum hemorrhage (two 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 (two studies[14,15], 6714 women, 137 with postpartum infection; RR 0.84 (95% CI, 0.58–1.22); $I^2 = 9.8\%$) (Table 3). Two studies[14,15] reported on hypertensive disease of pregnancy (6714 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 (four studies[14,15,24,26], 7126 neonates; six cases of neonatal death; RR 0.57 (95% CI, 0.12–2.71); $I^2 = 0\%$). Induction of labor was associated with a significant reduction in the need for neonatal respiratory support (two 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 of labor had significantly lower mean birth weight than those in the expectant management group (three studies[14,15,26], 6942 neonates; pooled mean difference −81 g (95% CI, −100 to −63 g); $I^2 = 0\%$).

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

Overall quality of 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 perineal laceration, postpartum hemorrhage 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 high risk, or with some concerns, 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 too 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.

Table 1 Characteristics of included studies (PICOS) reporting on induction of labor *vs* expectant management in low-risk singleton pregnancy at term

Study	*Grobman (2018)*[15]	*Walker (2016)*[14]	*Amano (1999)*[25]	*Martin (1978)*[24]	*Cole (1975)*[26]
Patients (*n*)	6096	618	135	184	228
Inclusion criteria	Low-risk nulliparous women, live singleton fetus in vertex presentation, no contraindication to vaginal delivery, no planned Cesarean delivery, certain gestational age	Nulliparous women, ≥ 35 years of age on their expected due date, with singleton live fetus in cephalic presentation	Uncomplicated nullipara at 38+6 wks	Obstetrically normal past and/or present pregnancies, booking of index pregnancy no later than 18th week, menstrual cycle did not exceed 36 days, no pregnancy for at least 3 months before last menstrual period, size of uterus at booking corresponded to period of amenorrhea	Primigravidae aged 18–30 years or women of parity 1, 2, or 3 aged 18–35 years who had had normal pregnancy without any previous obstetric abnormality; certain gestational age
Exclusion criteria	Women in labor or with premature rupture of membranes, vaginal bleeding at 38+0 to 38+6 wks	Fetal congenital abnormality, contraindication to labor, vaginal delivery or expectant management, history of myomectomy, certain gestational age	No information	No information	No information
Outcomes	Cesarean delivery, perinatal death, need for respiratory support within 72 h 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 neonatal intermediate or intensive care unit, length of hospitalization Hypertensive disorders of pregnancy, indication for Cesarean delivery, operative vaginal delivery, indication for operative vaginal delivery, uterine incisional extensions during Cesarean delivery, chorioamnionitis, 3/4-degree perineal laceration, postpartum hemorrhage, postpartum infection, venous thromboembolism, number of hours in labor and delivery unit, length of postpartum hospital stay, NICU admission, maternal death	Cesarean delivery, method of delivery other than Cesarean section, onset of labor, intrapartum complications, postpartum complications (e.g. systemic infection or need for blood transfusion) Live birth or stillbirth, birth weight, NICU admission, birth trauma, and two composite outcomes for serious neonatal complications (direct trauma and hypoxia) Maternal expectations and experience of childbirth	Normal spontaneous delivery, vacuum extraction, forceps, Cesarean section, incidence of pathological FHR, resuscitation in labor, 1-min Apgar score, umbilical artery pH, NICU admission, meconium-stained amniotic fluid, maternal blood loss	Vaginal delivery, forceps delivery, Cesarean section, length of labor, unexplained postpartum pyrexia, demand for analgesia, meconium staining for amniotic fluid, 1-min and 5-min Apgar scores, stillbirth, neonatal jaundice	Vaginal delivery, forceps delivery, Cesarean section, length of labor, dose of pethidine, number of epidurals, blood loss after vaginal delivery, perinatal loss, meconium staining in labor, first stage fetal heart irregularity, Apgar score, birth weight, unsuspected SGA, transient respiratory distress, neonatal jaundice
Intervention	Induction of labor at 39+0 to 39+4 wks; no specific induction protocol mandated	Local policies for induction of labor	Laminaria tents ± oral administration ± rupture of membranes ± oxytocin or PGF-2, under direct CTG monitoring. Epidural or balanced anesthesia used	Amniotomy ± intravenous oxytocin	Amniotomy followed immediately by oxytocin at increasing doses using Cardiff pump
Low-risk definition	Absence of any condition considered to be maternal or fetal indication for delivery before 40+5 wks	N/A	N/A	N/A	N/A
Induction	Induction of labor at 39+0 to 39+4 wks	Induction of labor between 39+0 and 39+6 completed wks	Induction of labor at 39 completed wks	Induction of labor at 39 wks	Induction of labor between 39 and 40 wks
Expectant management	Elective delivery after 40+5 and no later than 42+2 wks	Await spontaneous onset of labor until 42 wks unless induction required earlier for medical reasons	Await spontaneous onset of labor until 42 completed wks	Await spontaneous onset of labor until 42 wks, unless induction required earlier for medical reasons	Await spontaneous onset of labor until 41 wks unless induction required earlier for medical reasons

CTG, cardiotocography; FHR, fetal heart rate; N/A, not applicable; NICU, neonatal intensive care unit; PGF-2, prostaglandin F-2 alpha; SGA, small-for-gestational-age; wks, weeks.

Table 2 Risk of bias of studies included in meta-analysis, according to Cochrane Collaboration Risk of Bias Tool 2.0[18]

Domain/ signaling question	*Grobman (2018)*[15]	*Walker (2016)*[14]	*Amano (1999)*[25]	*Martin (1978)*[24]	*Cole (1975)*[26]
Bias arising from 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 judgment	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?	—	—	—	—	—
2.5. Were any participants analyzed 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 analyzing participants in the wrong group?	N	PN	PN	PY	PN
Risk of bias judgment	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.: Were 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.: Was there evidence that results were robust to the presence of missing outcome data?	Y	Y	PY	PY	PY
Risk of bias judgment	Low	Low	Some concerns	Some concerns	Low
Bias in measurement of 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 judgment	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Bias in selection of reported result					
Were 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 judgment	Low	Low	Some concerns	Some concerns	Some concerns
Overall bias					
Risk of bias judgment	Some concerns	Some concerns	High	High	High

N, no; NI, no information; PN, probably no; PY, probably yes; Y, yes.

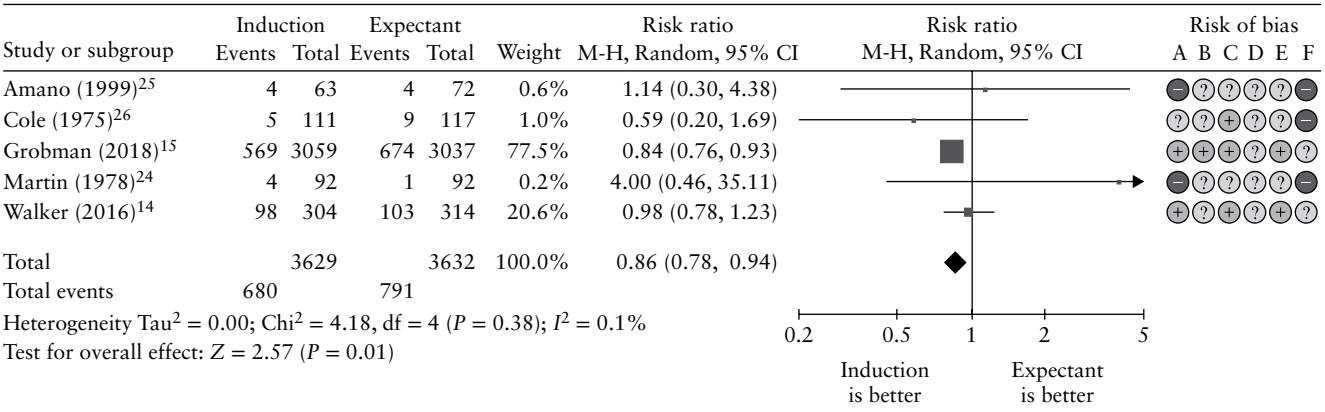

Figure 2 Forest plot showing relative risk for Cesarean section in low-risk singleton pregnancies undergoing elective induction of labor at 39 weeks *vs* those managed expectantly. Risk of bias (low (⊕), high (⊖) or unclear (?)): A, randomization process; B, deviation from intended interventions; C, missing outcome data; D, measurement of outcome; E, selection of reported result; F, overall bias. Only first author of each study is given. M-H, Mantel–Haenszel.

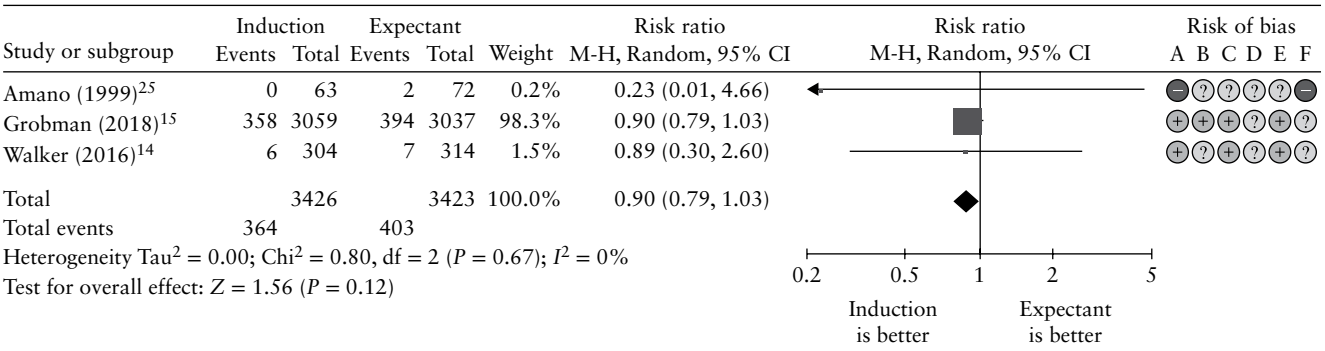

Figure 3 Forest plot showing relative risk for admission to neonatal intensive care unit in low-risk singleton pregnancies undergoing elective induction of labor at 39 weeks *vs* those managed expectantly. Risk of bias (low (⊕), high (⊖) or unclear (?)): A, randomization process; B, deviation from intended interventions; C, missing outcome data; D, measurement of outcome; E, selection of reported result; F, overall bias. Only first author of each study is given. M-H, Mantel–Haenszel.

DISCUSSION

Summary of evidence

Our synthesis of evidence from RCTs showed that, compared with expectant management, elective induction of labor at 39 weeks' gestation in uncomplicated singleton pregnancies is associated with a 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 of labor from 39 weeks is associated with an adverse effect on maternal or neonatal outcomes.

Interpretation of results

The rationale supporting elective induction of labor 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 in the rate of Cesarean section, from approximately 22% with 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 have a successful induction[29]. This may reflect increasing rates of failure to progress in labor (as the fetus 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 birth weight of neonates in the induction group was approximately 80 g lower than that of those in the expectant management group, although it is not clear if this difference affected the chance of successful induction.

We found that induction of labor at 39 weeks can decrease the risk of hypertensive disease of

Table 3 Summary of findings in five randomized controlled trials that compared induction of labor at 39 + 0 to 39 + 6 weeks with expectant management in low-risk singleton pregnancy

	*Anticipated absolute effect**					
Outcome	*Risk with expectant management (%)*	*Risk with labor induction at 39 weeks (% (95% CI))*	*NNT (95% CI)*	*Risk ratio (95% CI)*	*Number of participants (studies)*	*Quality of evidence (GRADE)†*
Cesarean section	21.8	18.7 (17.0–20.5)	32 (21–77)	0.86 (0.78–0.94)	7261 (5)	⊕⊕⊕○ Moderate‡
NICU admission	11.8	10.6 (9.3–12.1)	—	0.90 (0.79–1.03)	6849 (3)	⊕⊕○○ Low‡§
Operative delivery	11.6	11.9 (10.9–13.0)	—	1.11 (0.88–1.41)	7261 (5)	⊕○○○ Very low‡§¶
Grade-3/4 perineal laceration	2.7	3.2 (2.4–4.1)	—	1.18 (0.89–1.50)	6714 (2)	⊕⊕○○ Low‡§
Postpartum hemorrhage	6.8	7.2 (6.1–8.5)	—	1.06 (0.90–1.25)	6714 (2)	⊕⊕○○ Low‡§
Postpartum maternal infection	2.2	1.9 (1.3–2.7)	—	0.84 (0.58–1.22)	6714 (2)	⊕⊕○○ Low‡§
Maternal hypertension	13.4	8.7 (7.6–10.0)	21 (17–29)	0.65 (0.57–0.75)	6714 (2)	⊕⊕⊕○ Moderate‡
Neonatal death	0.1	0.1 (0.0–0.3)	—	0.57 (0.12–2.71)	7126 (4)	⊕○○○ Very low‡§#
Neonatal respiratory support	4.3	3.1 (2.5–4.1)	83 (56–500)	0.73 (0.58–0.95)	6714 (2)	⊕⊕⊕○ Moderate‡

*Risk in intervention group (and 95% CI) based on assumed risk in comparison group and relative effect of intervention (and its 95% CI). †GRADE Working Group grades of evidence: high certainty, we are very confident that true effect lies close to that of estimate of effect; moderate certainty, we are moderately confident in effect estimate – true effect is likely to be close to estimate of effect, but there is a possibility that it is substantially different; low certainty, our confidence in effect estimate is limited – true effect may be substantially different from estimate of effect; very low certainty, we have very little confidence in effect estimate – true effect is likely to be substantially different from estimate of effect. ‡Data are derived exclusively from studies at concern for bias or at high risk of bias. §95% CI for pooled effect sizes includes the unit. ¶Different direction of effect across studies. #Very small number of events. NICU, neonatal intensive care unit; NNT, number needed to treat (calculated only when significant difference was observed).

pregnancy, from approximately 13% with expectant management to approximately 9% (NNT = 21). We hypothesize that the beneficial effect of induction at 39 weeks is mediated mainly through 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 Cesarean section by 4.2 times[33], and it is likely that the improvement in respiratory outcomes is related to a reduction in meconium exposure before birth (RR 0.23 (95% CI, 0.06–0.98) for the studies included in this meta-analysis; not a prespecified outcome).

Strengths and limitations

Our strict selection methodology ensured that our results describe a well-defined population of singleton uncomplicated pregnancies between 39 + 0 and 39 + 6 weeks' gestation. In this context, we excluded two otherwise eligible studies, one of them including only women with favorable[22] and one including only women with unfavorable[23] cervix score, 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' gestation) as a group[34–37], included all indications for induction in their main analyses[34–37] or assessed only the impact of induction on the rate of Cesarean section[34]. Moreover, none of the previous meta-analyses included data from the ARRIVE trial[15], which contributed more than 80% of the total sample of our target population.

The main limitation of our analysis was that most of the data were derived from a single large study[15], which, depending on the outcome, contributed from 29% to 97% of the data. A second limitation arose 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 of bias. There were no data for many of our predefined outcomes, and insufficient 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 indicate similar scores of perceived control during childbirth in the two groups[15]. 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 the data in our study were derived from studies of nulliparous women having an uncomplicated singleton pregnancy between 39 + 0 and 39 + 6 weeks. Therefore, our results are applicable only to such women, and their generalization to the entire population is uncertain.

Although the Society for Maternal and Fetal Medicine issued a response to the ARRIVE study[15] proposing that it is reasonable to offer elective induction of labor 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 included studies do not provide information on 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 educational need is reached for children born at 40–41 weeks[39,40]. In this context, the most likely subgroup to benefit from an induction policy might be nulliparous women with risk factors for hypertensive or other medical or fetal complications of pregnancy.

Conclusions

There is moderate-quality evidence that elective induction of labor in uncomplicated singleton pregnancy at 39 weeks' gestation 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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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 PubMed searches, 10 August 2018

Table S2 Excluded studies and reason for exclusion

Table S3 Results of individual studies

Figure S1 Forest plot showing relative risk for hypertensive disorders of pregnancy in women with low-risk singleton pregnancy undergoing elective labor induction at 39 weeks *vs* expectant management.

Figure S2 Forest plot showing relative risk for need for neonatal respiratory support in low-risk singleton pregnancies undergoing elective labor induction at 39 weeks *vs* those managed expectantly.

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Resultados maternos y perinatales después de la inducción electiva del parto a las 39 semanas en embarazos con feto único sin complicaciones: un metaanálisis

RESUMEN

Objetivo La tasa de complicaciones maternas y perinatales aumenta después de las 39 semanas de gestación, tanto en los embarazos no seleccionados como en los complicados. El objetivo de este estudio fue sintetizar cuantitativamente la evidencia disponible sobre el efecto de la inducción electiva del parto a las 39 semanas sobre el riesgo de cesárea y sobre los resultados maternos y perinatales.

Métodos Se realizaron búsquedas en las bases de datos PubMed, Registro Estadounidense de Ensayos Clínicos, SCOPUS y CENTRAL, desde su inicio hasta agosto de 2018. Además, se realizaron búsquedas en las referencias de los artículos recuperados. Los estudios elegibles fueron ensayos controlados aleatorizados de embarazos con feto único sin complicaciones en los que las participantes fueron asignadas al azar entre las 39+0 y 39+6 semanas de gestación a la inducción del parto o al tratamiento expectante. El riesgo de sesgo de los estudios individuales se evaluó mediante la Herramienta Cochrane de Riesgo de Sesgo. La calidad general de la evidencia se evaluó de acuerdo con las directrices de GRADE. Los resultados principales incluyeron cesárea, muerte materna e ingreso a la unidad de cuidados intensivos neonatales (UCIN). Los resultados secundarios incluyeron parto quirúrgico, laceración perineal de grado 3/4, hemorragia puerperal, infección materna, enfermedades hipertensivas del embarazo, episodios trombóticos maternos, duración de la estancia materna en el hospital, muerte neonatal, necesidad de ayuda respiratoria al neonato, parálisis cerebral, duración de la estancia en la UCIN y duración de la estancia en el hospital del neonato. Se calcularon los cocientes de riesgo (CR) combinados mediante un modelo de efectos aleatorios.

Resultados El metaanálisis incluyó cinco estudios (7261 casos). La inducción del parto se asoció con una disminución del riesgo de cesárea (calidad moderada de la evidencia; CR 0,86 (IC 95%: 0,78–0,94); I^2 = 0,1%), hipertensión materna (calidad moderada de las pruebas; CR 0,65 (IC 95%: 0,57–0,75); I^2 = 0%) y apoyo respiratorio neonatal (calidad moderada de las pruebas; CR 0,73 (IC 95%: 0,58–0,95); I^2 = 0%). Los neonatos nacidos después de la inducción pesaron, en promedio, 81 g (IC 95%: 63–100 g) menos que los nacidos después del tratamiento expectante. No se encontraron efectos significativos para los otros resultados con los datos disponibles. El limitante principal de nuestro análisis fue que la mayoría de los datos se derivaron de un único gran estudio. Una segunda limitación surgió del diseño abierto de los estudios, que teóricamente podría haber afectado a la predisposición del médico tratante para recurrir a la cesárea.

Conclusiones La inducción electiva del parto en embarazos no complicados con feto único a las 39 semanas de gestación no está asociada con complicaciones maternas o perinatales y puede reducir la necesidad de una cesárea, el riesgo de enfermedades hipertensivas del embarazo y la necesidad de ayuda respiratoria para el neonato.

无并发症的单胎妊娠在孕 39 周择期引产后孕产妇和围产期结局：meta 分析

目的：在未经选择的和有并发症的妊娠中，孕产妇和围产期并发症的发生率在孕 39 周后升高。本研究的目的是对孕 39 周择期引产对剖宫产风险以及孕产妇和围产期结局的影响的现有证据进行定量综合。

方法：检索 PubMed、US Registry of Clinical Trials、SCOPUS 和 CENTRAL 数据库，检索时间从建库至 2018 年 8 月。此外，追踪检索到的文献的参考文献。纳入标准为单胎无并发症妊娠的随机对照试验，孕妇随机分组，在孕 39^{+0}~39^{+6} 周时接受引产或期待治疗。采用 Cochrane 偏倚风险工具评估个别研究的偏倚风险。根据 GRADE 指南评估总的证据质量。主要结局包括剖宫产、孕产妇死亡、入住新生儿重症监护病房（neonatal intensive care unit，NICU）。次要结局包括手术分娩、3/4 度会阴裂伤、产后出血、孕产妇感染、妊娠期高血压疾病、孕产妇发生血栓事件、孕产妇住院时间、新生儿死亡、需要行新生儿呼吸支持、脑瘫、NICU 住院时间、新生儿住院时间。采用随机效应模型计算总的风险比。

结果：meta 分析纳入 5 项研究（7261 例孕产妇）。引产与剖宫产[证据质量中等；RR 0.86（95% CI，0.78~0.94）；I^2=0.1%]、孕产妇高血压[证据质量中等；RR 0.65（95% CI，0.57~0.75）；I^2=0%]、新生儿呼吸支持[证据质量中等；RR 0.73（95% CI，0.58~0.95）；I^2=0%]风险降低相关。引产后测量新生儿体重，平均为 81 g（95% CI，63~100 g），低于期待治疗后分娩的新生儿。根据现有数据，其他结局无明显差异。本研究的主要局限性是大部分数据来自单中心大规模研究。第二个局限性是研究的开放性设计，理论上可能影响主治医生是否愿意进行剖宫产手术。

结论：无并发症的单胎妊娠在孕 39 周时行择期引产与孕产妇或围产期并发症不相关，可能降低剖宫产率、妊娠期高血压疾病风险及新生儿呼吸支持需求。

