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Review article

Perinatal and maternal outcomes according to timing of induction of labour: A systematic review and meta-analysis

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ABSTRACT

The risk of adverse perinatal and maternal outcomes increases with gestational age, and although induction of labour may reduce these risks, the optimal timing of induction remains unknown. We carried out a systematic review and meta-analysis, to determine the gestational age at which induction should be offered.

We searched Cochrane Central Register of Controlled Trials, Medline, and Embase databases from inception to July 2022, to identify randomised trials comparing induction of labour at or beyond 37′ weeks gestation with expectant management or delayed induction, and according to the gestational age at planned induction. We undertook random effects meta-analysis and pooled estimates as odds ratios with 95% confidence intervals. We assessed risk of bias of studies using the Cochrane Risk of Bias tool 2.0.

We included 44 trials (23,960 women and 22,191 offspring) from 1,839 citations in our meta-analysis. The odds of perinatal death (odds ratio 0.42, 95% confidence interval 0.22 to 0.81; 26 studies, 20,154 offspring), stillbirth (0.40, 0.16 to 0.98; 25 studies, 19,412 offspring), admission to neonatal intensive care unit (0.86, 0.78 to 0.96; 23 studies, 18,846 offspring), and caesarean section (0.90, 0.83 to 0.98; 40 studies, 23,616 women) were reduced in the induction of labour group compared to expectant management or delayed induction. The odds of admission to neonatal intensive care unit (0.82, 0.70 to 0.96; 6 studies, 9,316 offspring) were lower with induction of labour at 41 weeks compared to induction at or after 42 weeks' gestation, and the odds of caesarean section were reduced with labour induction at 39 weeks' compared to induction at or after 40 weeks' (0.83, 0.74 to 0.93; 8 studies, 7,677 women). There were no significant differences in pregnancy outcomes by method of induction of labour.

Induction of labour compared to expectant management or delayed induction reduces the risk of adverse pregnancy outcomes, and the optimal timing may depend on the specific outcome of interest.

Introduction

Despite advances in antenatal and intrapartum care, progress in reducing the global rate of stillbirths has been slow, with only a 35% decrease in the last two decades.[1]Current interventions to prevent stillbirths include routinely offering induction of labour to women from 41 weeks' gestation onwards.[2–6]However, a third of stillbirths happen at term (≥37 weeks'), and the risk of perinatal mortality increases with advancing gestation at term.[7–8]Individual studies have also reported increasing risk of adverse maternal outcomes in pregnancies from 39 weeks' gestation through to 41 weeks' gestation.[8].

There is insufficient (Table 1) evidence on the timing of induction of labour to optimise maternal and neonatal outcomes.[9]Existing systematic reviews of randomised trials on induction of labour failed to assess what the best window of timing for induction of labour is to achieve improved maternal and perinatal outcomes. Most trials included

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Table 1
Effect of induction of labour by week of planned induction on perinatal and maternal outcomes.

		Induction		Expectant			
Outcome/ category	**No. of studies**	**Events**	**Total**	**Events**	**Total**	**Odds ratio [95% CI]**	**I^2 (%)**
Perinatal outcomes							
Induction ≤ 38 weeks vs ≥ 39 weeks							
Perinatal death	3	1	319	2	307	0.68 [0.11, 4.32]	0%
Stillbirth	3	1	319	0	307	3.06 [0.12, 76.95]	N/A
Neonatal death	3	0	319	2	307	0.32 [0.03, 3.09]	0%
NICU admission	2	10	229	7	217	0.96 [0.12, 7.73]	49%
Induction 39 weeks vs ≥ 40 weeks							
Perinatal death	4	2	3566	5	3560	0.51 [0.13, 2.09]	0%
Stillbirth	4	1	3566	3	3560	0.52 [0.09, 3.02]	0%
Neonatal death	4	1	3566	2	3560	0.50 [0.04, 5.48]	N/A
Apgar score < 7 in 5 min	3	11	500	12	503	0.94 [0.41, 2.17]	N/A
NICU admission	6	377	3674	414	3651	0.89 [0.77, 1.03]	0%
Induction 40 weeks vs ≥ 41 weeks							
Perinatal death	2	0	256	1	255	0.30 [0.01, 7.51]	N/A
Stillbirth	2	0	256	1	255	0.30 [0.01, 7.51]	N/A
Apgar score < 7 in 5 min	3	12	202	10	202	1.03 [0.42, 2.52]	0%
NICU admission	3	10	202	16	202	0.66 [0.21, 2.00]	36%
Induction 41 weeks vs ≥ 42 weeks							
Perinatal death	8	3	4983	14	4974	0.38 [0.13, 1.12]	0%
Stillbirth	5	1	4310	10	4307	0.25 [0.06, 1.03]	0%
Neonatal death	5	0	4310	2	4307	0.33 [0.03, 3.20]	0%
Apgar score < 7 in 5 min	6	54	4659	66	4657	0.82 [0.57, 1.19]	0%
NICU admission	6	325	4659	386	4657	0.82 [0.70, 0.96]	0%
Induction 42 weeks vs ≥ 43 weeks							
Perinatal death	4	1	377	3	350	0.41 [0.06, 2.83]	0%
Neonatal death	4	1	377	2	350	0.41 [0.06, 2.83]	0%
NICU admission	2	13	271	19	246	0.01 [0.28, 1.36]	4%
Maternal outcomes							
Induction ≤ 38 weeks vs ≥ 39 weeks							
Caesarean delivery	3	50	290	43	276	1.12 [0.71, 1.76]	0%
Operative vaginal delivery	2	23	111	20	109	1.16 [0.59, 2.28]	0%
Induction 39 weeks vs ≥ 40 weeks							
Caesarean delivery	8	702	3845	810	3832	0.83 [0.74, 0.93]	0%
Operative vaginal delivery	5	384	3670	400	3657	1.07 [0.80, 1.42]	44%
Postpartum haemorrhage	3	242	3443	233	3430	1.06 [0.87, 1.28]	0%
Induction 40 weeks vs ≥ 41 weeks							
Caesarean delivery	5	52	496	40	484	1.25 [0.65, 2.39]	37%
Operative vaginal delivery	5	32	438	28	436	1.24 [0.71, 2.16]	0%

(*continued on next page*)

in the Cochrane review started induction of labour beyond 41 weeks' gestation, with variable treatment in the expectant management group.[10]Analysis in the NICE guideline review on prevention of prolonged pregnancy were restricted to full-text articles only, thereby potentially introducing publication bias in the findings.[11].

We therefore undertook a systematic review to determine the optimal gestational age thresholds beyond 37 weeks' gestation at which induction of labour should be offered in uncomplicated pregnancies to optimise outcomes for the woman and baby.

Methods

We followed current recommendations in the conduct and reporting of systematic reviews and complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (appendix 1).

Search strategy and study selection

Our review is based on a prospectively designed protocol and is registered on the OSF registry (https://doi.org/10.17605/OSF.IO/N7AWP). We searched Cochrane Central Register of Controlled Trials (CENTRAL), Medline, and Embase from inception to July 2022 to identify randomised trials (including pseudo-randomised and cluster randomised trials) of induction of labour in women at or beyond term. We supplemented the searches with manual searches of reference lists of included studies. No language restrictions were applied (appendix 2).

Two reviewers (BJ and EH) independently selected studies using a two-stage process. The first stage involved title and abstract screening, followed by assessment of full texts of selected studies in detail to determine eligibility. Disagreements were resolved through consensus, or by arbitration with a third reviewer (JA).

Multiple publications from the same trial were included if they reported different outcome data, otherwise we selected the most recent and complete version in cases of duplicate publication. We included randomised trials that evaluated induction of labour in pregnant women at or beyond term gestation, compared to expectant management or delayed induction at a later point. The following perinatal and maternal outcomes were assessed: perinatal death, stillbirth, neonatal death, Apgar score < 7 at 5 min, admission to neonatal intensive care unit (NICU), maternal death, caesarean section, operative vaginal delivery, postpartum haemorrhage and breastfeeding status at discharge. We used definitions provided by the investigators for all outcomes. We excluded animal studies, non-experimental studies, and cross-over trials.

Study quality assessment and data extraction

We used the Cochrane Risk of Bias tool 2.0,[12]to assess the risk of bias and methodological quality of each individual study across the five domains of randomisation process, deviations from intended intervention, incomplete outcome data, outcome measurement, and selective reporting. An overall low risk of bias was given to trials with a low risk of bias in all domains, moderate risk of bias to trials with concern of bias in one domain, and a high risk of bias to trials with a high risk of bias in at least one domain or concerns of bias in multiple domains.[12] Two reviewers (BJ and EH) independently carried out quality assessment and extracted data in duplicates using a pre-designed and piloted data extraction form. We extracted data on study characteristics such as study period, country, participant inclusion and exclusion criteria, number of recruited participants, and timing and method of induction of labour.

Statistical analysis

We compared the odds of adverse maternal and perinatal complications in pregnant women in the following groups: overall induction versus expectant management or delayed induction, and according to the gestational age at planned induction ($\leq$38 weeks' versus induction at $\geq$ 39 weeks'; induction at 39 weeks' versus induction at $\geq$ 40 weeks'; induction at 40 weeks' versus induction at $\geq$ 41 weeks'; induction at 41 weeks versus induction at $\geq$ 42 weeks'; and induction at 42 weeks versus induction at $\geq$ 43 weeks'). We reported the results obtained after pooling individual study estimates using random effects meta-analysis and summarised the findings as odds ratio (OR) with 95% confidence intervals. Heterogeneity was assessed using I2 statistic.

We undertook subgroup analysis by induction method (mechanical, pharmacological, mechanical plus pharmacological, membrane sweeping, and mixed methods). Studies where the method differed depending on the cervical ripeness of the participant, or where a combination of mechanical, pharmacological and membrane stripping was used were allocated to the mixed methods group. We assessed publication bias and the effect of small studies using funnel plots and Begg's and Egger's tests on outcomes with at least ten trials. All analysis were done using Review Manager 5.4.1.[13].

Results

From 1,839 citations identified, we selected 138 articles for detailed full text assessment, and 44 studies were included in our meta-analysis (Fig. 1).

Characteristics of the included studies

Most of the included trials (32/44, 73%)[14–45]compared induction of labour at a planned gestational age with expectant management and induction at a later gestational age. Twelve trials (12/44, 27%)[46–57] did not report the timing of induction in the expectant management group if labour did not spontaneously initiate. The timing of induction in the induction group ranged from 37 weeks to 42 weeks.

Of the 44 included studies, ten (23%) were from the United States,

Table 1 (*continued*)

			Induction		Expectant		
Induction 41 weeks vs ≥ 42 weeks							
Caesarean delivery	9	802	5284	863	5282	0.92 [0.82, 1.02]	0%
Operative vaginal delivery	4	673	4357	701	4353	0.95 [0.84, 1.07]	0%
Postpartum haemorrhage	4	254	2659	253	2659	1.00 [0.84, 1.21]	0%
Induction 42 weeks vs ≥ 43 weeks							
Caesarean delivery	4	70	377	84	350	0.70 [0.47, 1.03]	0%
Operative vaginal delivery	4	57	377	55	350	0.97 [0.64, 1.46]	0%

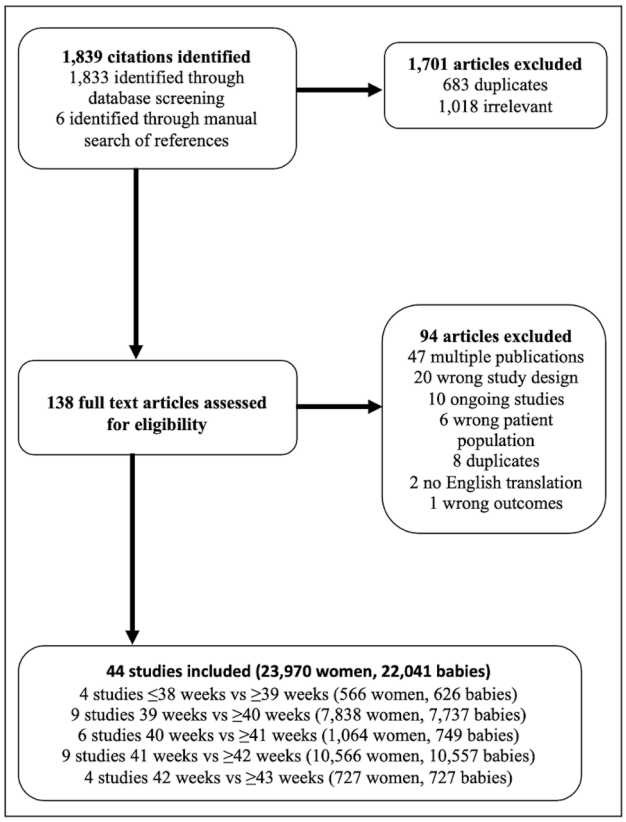

Fig. 1. Study selection process of the systematic review.

[17,20,27,32,34,37,39,53–55]four (9%) from the UK,[19,44–45,57] three each from India,[30–31,50]Norway,[23,41–42]Sweden, [16,43,48]and Thailand,[29,33,35]two each from Canada,[36,51] China,[38,52]Iran,[25,46]Malaysia,[14,47]Netherlands,[15,24]and Turkey,[22,26]and one each from Austria,[40]Canary Islands,[49] Finland,[56]Nigeria,[21]Russia,[18]and Tunisia.[28]Studies were published between 1969 and 2021. Thirty-eight studies reported on perinatal outcomes (11,139 offspring in the induced group vs 11,052 offspring in the expectant management group) and forty-three studies reported on maternal outcomes (12,069 women in the induced group vs 11,901 women in the expectant management group).

Four studies used mechanical induction as the method of induction, [15,29,46,53]nine studies used pharmacological agents such as oxytocin and prostaglandin.[17,34,36,44,49,40–41]Both mechanical and pharmacological methods were used in 13 studies, [14,16,20,23,28,35,42–43,45,50,54–55,57]while membrane stripping was used in 9 studies,[21–22,24–25,37,32–33]and 9 studies used mixed methods for induction[18–19,26–27,30,38,47–48,56](appendix 3).

Quality assessment

Most of the included trials had an overall high (48%, 21/44) or moderate (34%, 15/44) risk of bias. Twenty-one studies (48%, 21/44) had a low risk of bias for the randomisation process, 32% (14/44) for the effect of assignment to the intervention, 77% (34/44) for the effect of adhering to the intervention, 82% (36/44) for missing outcome data, and 48% (21/44) for selection of the reported data. Risk of bias for measurement of the outcome was low in all 44 trials (Fig. 2, appendix 4).

Effect of induction of labour versus expectant management or delayed induction on perinatal and maternal outcomes

The odds of perinatal death (odds ratio 0.42, 95% confidence interval 0.22 to 0.81, $I^2 = 0\%$; 26 studies, 20,154 offspring), stillbirth (0.40, 0.16 to 0.98, $I^2 = 0\%$; 25 studies, 19,412 offspring), admission to NICU (0.86, 0.78 to 0.96, $I^2 = 0\%$; 23 studies, 18,846 offspring), and caesarean section (0.90, 0.83 to 0.98, $I^2 = 10\%$; 40 studies, 23,616 women) were reduced in the induction of labour group. The summary estimate for induction of labour showed a trend towards reduction in neonatal death (0.37, 0.14 to 1.00), and Apgar score < 7 at 5 min (0.78, 0.58 to 1.05) that were not statistically significant. Meta-analysis of the studies showed no difference between the groups for operative vaginal delivery, postpartum haemorrhage, and breastfeeding status at discharge (Fig. 3, appendix 5). No maternal deaths were recorded in any of the six studies reporting this outcome.

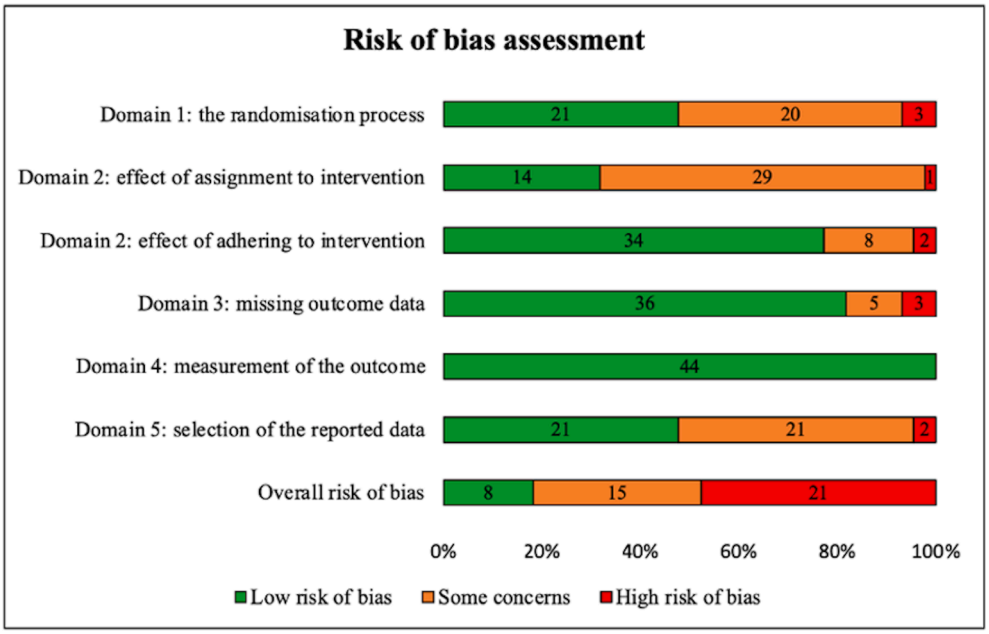

Fig. 2. Risk of bias assessment of included studies using the Risk of Bias tool 2.0.

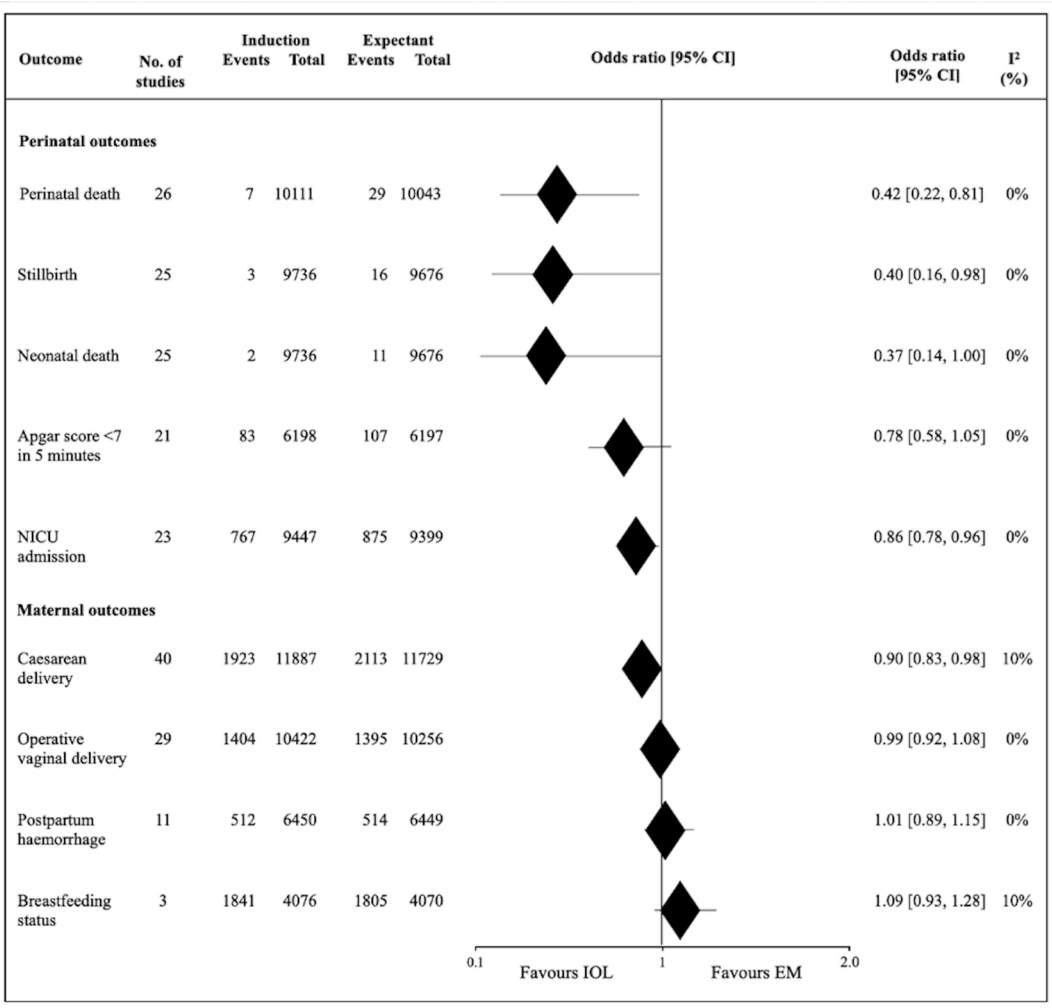

Fig. 3. Effect of induction of labour versus expectant management or delayed induction on perinatal and maternal outcomes IOL = induction of labour; EM = expectant management; NICU = neonatal intensive care unit.

Effect of induction of labour by week of planned induction on perinatal and maternal outcomes

The odds of admission to NICU (odds ratio 0.82, 95% confidence interval 0.70 to 0.96, $I^2 = 0\%$; 6 studies, 9,316 offspring) were lower with induction of labour at 41 weeks' gestation compared to induction at or after 42 weeks' gestation, while the odds of caesarean section were reduced with labour induction at 39 weeks compared to induction at or after 40 weeks' (OR O.83, 95% CI 0.74 to 0.93, $I^2 = 0\%$; 8 studies, 7,677 women). There were no statistically significant differences for any other outcomes with other week to week comparison of induction of labour (table 1, appendix 6).

Subgroup analysis and publication bias

Subgroup analysis by method of induction did not show significant differences between the groups and any of the reported maternal or perinatal outcomes (appendix 7). There was no evidence of small study effect (Egger-test of asymmetry) for any of the outcomes assessed using funnel plot asymmetry.

Discussion

We found that induction of labour compared to expectant management or delayed induction reduced the risk of perinatal death, stillbirth, NICU admissions, and caesarean section. There was also an overall trend towards reduction of neonatal death and abnormal Apgar score at 5 min. The intervention had less of an effect on maternal outcomes, with no evidence that induction of labour reduced the rates of operative vaginal delivery and postpartum haemorrhage or increased breastfeeding status at discharge. Compared with induction of labour at or after 42 weeks' gestation, induction at 41 weeks reduced the risk of admission to NICU, while the risk of caesarean section was reduced when labour was induced at 39 weeks compared to at or after 40 weeks' gestation. The method of induction had no effect on perinatal or maternal outcomes.

Strengths and limitations

Our review is the most up-to-date synthesis on the effect of induction of labour on maternal and perinatal outcomes. We considered all methods of induction used by individual trials in our meta-analysis, which is a representation of actual clinical practice in real-world settings. Our comprehensive review was conducted without language restrictions and with pre-specified subgroups to allow us to explore potential sources of heterogeneity. We also carried out robust quality assessment of the included studies. In addition to exploring the overall effect of induction of labour on maternal and perinatal outcomes, we also categorised trials based on the timing of induction in both the induction of labour and expectant management group (with induction at a later point) in order to generate comparisons between various gestational age of induction and pregnancy outcomes.

Our findings were limited by variations in the reported timing of

induction in the intervention group. Many trials reported a gestational age range rather than a single gestation week for labour induction, making it difficult to make a clear comparison between gestational age timings for induction of labour. We assumed an earlier gestational age at induction in such cases, and categorised trials based on this. Not all studies reported what the maximum gestation age before induction was initiated in the expectant management group, and this made it difficult to compare outcomes by gestation week of induction in those studies. There was paucity of data on maternal and perinatal outcomes within studies once groupings were made on timing of induction of labour, which made it difficult to comprehensively evaluate the optimal timing of induction. Small sample sizes available for each of these comparisons may have influenced the precision of our results. We did not consider perineal outcomes in the data analysis, which may be crucial for informed decision-making by both healthcare providers and expectant mothers regarding the timing and benefits of induction of labour. Our review included studies from as early as 1969, and it is likely that advances in medical care since then, including induction techniques and antenatal monitoring could impact the reported pregnancy outcomes. [50,57–58].

Comparison to existing evidence

Findings in our review on the overall effect of induction of labour on maternal and perinatal outcomes, are similar to those from the last Cochrane update. [59]There is conflicting evidence on what the optimal timing for induction of labour should be to reduce adverse maternal and perinatal outcomes and to optimise pregnancy outcomes. Existing reviews of randomised trials have varied in the definition of the research question, with differences in the definition of the population, the intervention considered, the comparison group and even on the reported outcomes.[60–63]This adds to the complexity in making direct comparisons between existing evidence. While current guidelines[2,4] recommend the induction of labour at 41 weeks, we found no statistically significant reduction in adverse perinatal or maternal outcomes, except for an 18% reduction in NICU admission rate when induction of labour was performed at 41 weeks compared to at or after 42 weeks' gestation. However, these findings need to be interpreted in light of the limitations of the included studies, which had small event rates for perinatal mortality outcomes. Although not statistically significant, there were however strong and consistent effects in the reduction of perinatal death, stillbirth, and neonatal death, indicating potential benefit in the induction of labour group. Some studies have suggested that induction between 39 and 40 weeks does not improve maternal outcomes,[60]however we found a 17% reduction in the risk of caesarean section when labour was induced at 39 weeks compared to expectant management or later induction, which was largely driven by the ARRIVE trial[17].

Relevance for clinical practice and research

Our study confirms that induction of labour compared to expectant management or delayed induction reduces the risk of adverse perinatal and maternal outcomes. These findings can support shared decision-making between healthcare professionals and mothers, especially where there are concerns about the health of the mother or baby due to prolongation of pregnancy or in women with high-risk conditions.

Current guidelines recommend induction at 41 weeks' gestation [2,4]to reduce the risk of adverse maternal and perinatal outcomes, however we only found a reduction in the risk of NICU admission with labour induction at 41 weeks compared to at or after 42 weeks' gestation. This is particularly relevant in high-risk pregnancies, such as those with gestational diabetes or hypertension where the risk of NICU admission may already be higher.[64–65]Inducing labour in these women may reduce the risk of complications, the need for specialised medical care, and the associated healthcare costs of NICU admission. [66].

We found that induction of labour at 39 weeks reduced the risk of caesarean section, without an increase in risk of other maternal or perinatal. These findings suggest that the optimal timing for induction of may be dependent on the specific outcomes of interest. Maternal choice-based elective requests for induction of labour may be a valuable approach, with induction of labour at 39 weeks' potentially serving as a viable option for low-risk women to reduce the rate of caesarean section, and induction of labour at 41 weeks' considered for reducing the risk of NICU admission, especially in high-risk women. This approach emphasizes the significance of involving mothers in shared decision-making, enabling them to actively participate in determining the timing of induction based on their individual preferences and risk factors. We were unable to consider how these findings may vary by characteristics of the woman, such as age, ethnicity, BMI, and obstetric history.

Our subgroup analysis by method of induction did not show any significant differences between the groups and any of the reported outcomes. This is important because it offers flexibility to healthcare professionals on methods of induction of labour, allowing for personalisation of care based on the preference and characteristics of the woman. It also allows women to make informed decision about their care, with the knowledge that they have various options for the methods of induction of labour, without compromising the safety or outcomes of their pregnancy.

The precision of our findings was affected by the use of aggregated data. Future research should consider the use of individual participant data meta-analysis, where the raw participant data from the trials included here are obtained, harmonised and re-analysed based on both the time of planned induction, and the time induction of labour was actually performed. This will provide more precise information on the timing of induction of labour and the variation in intervention effects by important subgroups, which will refine recommendations for women in those groups. Additionally, although there is emerging research on women's experience of induction of labour, [67–68]including reports of an association between poor childbirth outcomes and labour induction, there remains a research gap in understanding the nuances of how women perceive the decision to undergo induction of labour, and how this experience impacts their physical and emotional well-being, satisfaction with childbirth, and postpartum recovery. Future studies should also explore the long-term effects of induction of labour on both maternal and child outcomes to better understand the implications beyond the immediate postpartum period. Addressing these research gap will inform clinical practice and lead to better support and care for pregnant women who may need induction of labour.

Conclusion

Induction of labour compared to expectant management or delayed induction reduces the risk of adverse pregnancy outcomes, however the optimal timing may depend on the specific outcome of interest. Clinical decision to induce labour in term pregnancies will need to take into account individual characteristics of the woman and her preferences, as well as the potential benefits and risks of induction versus expectant management.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

No data to share

Funding

None

Authors' contributions

BJ, EH performed the analysis and produced the first draft. JA revised the article and oversaw the statistical analyses. BJ, EH undertook the literature searches, study selection, and quality assessment. All authors provided input at all stages of the project and helped revise the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2023.07.021.

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