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REVIEW

REPRODUCTIVE, FEMALE AND CHILD HEALTH

Timing of induction of labour in the prevention of prolonged pregnancy: Systematic review with meta-analysis

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Abstract

Objective: To update the systematic review which informed the National Institute for Health and Care Excellence guideline "Inducing Labour" (NG207), including additional data and analyses, and comparison with a recent individual patient data analysis of 41- versus 42-week induction.

Search Strategy: Multiple database search (including Cochrane Central Register of Controlled Trials, MEDLINE, and Embase) from inception to 10th September 2021 for randomised controlled trials (RCTs) comparing different induction timing in uncomplicated singleton pregnancies.

Data Collection and Analysis: One reviewer screened, extracted, analysed, and assessed the quality/certainty of the evidence (using ROB1 and GRADE), with second reviewer verification.

Main Results: Five week-to-week comparisons, and one overall comparison (induction vs. delayed induction, 20 RCTs, $n = 15\,725$ pregnant women) for assessment of predefined subgroups. Most data were for 41 versus 42 weeks and 39 versus 41 weeks: 10 times as many participants as the other week-to-week comparisons. There was evidence of an effect at 41 versus 42 weeks (five RCTs, $n = 5819$) in favour of 41-week induction: fewer perinatal deaths and neonatal intensive care unit admissions (low-to-moderate certainty of the evidence); there was no evidence of an effect in either direction for the remaining outcomes (very-low to moderate certainty). There was no evidence of an effect for outcomes

reported for: 40 versus 42 weeks (three RCTs, $n = 668$, very-low to low certainty); 39 versus 42 weeks (three RCTs, $n = 1103$, very-low to moderate certainty); 39 versus 41 weeks (four RCTs, $n = 7101$, very-low to low certainty); and 41/42 versus 43/44 weeks (four RCTs, $n = 954$, very-low to low certainty).
Conclusion: The evidence supports offering induction at 41 + 0 weeks compared to 42 + 0 weeks to reduce adverse perinatal and obstetric outcomes.

KEYWORDS
conservative treatment, expectant management, gestational age, labour induced, labour obstetric, pregnancy

INTRODUCTION

Prolonged pregnancy, defined as pregnancy beyond 42 weeks, is associated with increased risk of perinatal complications: higher incidence of perinatal death (stillbirth or neonatal death),[1] and the need for either instrumental or caesarean birth.[2,3] There are several options available for women if spontaneous labour does not begin at full term (40 + 0 weeks): wait until labour begins naturally (expectant management [EM]), induce labour, or choose a caesarean birth.

Induction of labour (IOL) can have a significant impact on birth experiences and the planned place of birth. Research has highlighted women's poor experiences of the induction process, including long delays, increased need for pain relief, and lack of information, autonomy, and support.[4–8] Women undergoing induction may also have a longer in-patient stay, with an additional cost to the National Health Service (NHS) of £600 per birth, compared to labours that start spontaneously.[9,10] It is, therefore, essential that any offer of medical intervention for prolonged pregnancy is evidence-based and has been shown to reduce the risk of adverse perinatal outcomes when compared to EM.

The National Institute for Health and Care Excellence (NICE) recently published an update to the guideline "Inducing Labour."[11] The previous (2008) guideline recommended that: "*[1.2.1.2] women… should usually be offered [IOL] between 41+0 and 42+0 weeks to avoid the risks of prolonged pregnancy.… timing should take into account the woman's preferences and local circumstances.*"[12] The 2021 guideline[11] updated the recommendation to "*[1.2.4] discuss with women that [IOL] from 41+0 weeks may reduce these risks, but that they will also need to consider the impact of induction on their birth experience when making their decision.*" The committee also made a recommendation for research to identify the optimal timing of induction in certain groups of women who may be at higher risk of stillbirth: women over 35 years, higher body mass index (BMI), using artificial reproductive technology (ART) and women from black, Asian, and minority ethnic backgrounds.[11]

The objective of this systematic review (SR) is to update the evidence from which these recommendations were made, focusing on safety outcomes for the mother and baby, with subgrouping by the groups identified by NICE as potentially at higher risk.

Practioners points

1. Evidence supports offering induction at 41 + 0 weeks compared to 42 + 0 weeks to reduce adverse perinatal outcomes in uncomplicated singleton pregnancies.
2. Other week-to-week comparisons require more data for all outcomes.
3. More data is needed for all week-to-week comparisons for women at potentially higher risk for adverse outcomes: black, Asian, and minority ethnic groups, higher body mass index (30+), older (35+ years), and women who conceived using artificial reproductive technology.

METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020193333), and the review was carried out in accordance with the Cochrane guidelines for Rapid Reviews[13] and PRISMA.[14]

This is an update of the SR produced for NICE guideline (NG207),[11] focusing on objectively measured outcomes only. We did not examine the maternal quality of life or satisfaction with their management, as these were heterogeneously reported by contributing trials, and could not be meta-analysed in the original review. The protocol also stated a composite primary outcome of maternal mortality and morbidity (uterine rupture). Due to the zero event rate in the original review, we have not assessed uterine rupture, and have focused on maternal mortality only.

Study selection

We included randomised controlled trials (RCTs), including cluster RCTs, quasi RCTs, and SRs of RCTs that assessed women with uncomplicated, singleton pregnancies that pass 37 + 0 weeks (as defined by studies).

Only studies using methods of induction approved for use in the United Kingdom (UK) were included, and at a specified week or period (from 37 + 0 onwards) compared to delayed induction at a later point. High quality SRs[3] have compared IOL to EM, however, we specified that the comparator could only be EM if the study provided sufficient information to determine the timing of eventual induction in the EM arm.

Outcomes

Our primary outcomes were maternal mortality and perinatal mortality (stillbirth and neonatal mortality to 28 days). Secondary outcomes included: mode of birth (unassisted vaginal, instrumental, and caesarean), neonatal unit admission, and neonatal morbidity (meconium aspiration syndrome [MAS] and hypoxic-ischaemic encephalopathy [HIE]). We excluded studies that did not report any of our prespecified outcomes.

Searches

One author (Tim Reeves) searched electronic databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase, and MEDLINE) from database inception to 25th March 2020, updated on 10th September 2021, using a predefined search strategy (see Supporting Information: Appendix S1).

Searches were restricted to the English language, SRs, and RCTs. We did not search for ongoing trials, conference abstracts, or other grey literature. One reviewer (Louise J. Geneen) hand-searched the reference lists of included studies and relevant SRs to identify further studies.

Data collection and analysis

We used Endnote software for initial screening (title and abstract) and full-text assessment. One reviewer (Louise J. Geneen) screened all titles and abstracts, and full-text publications and a second reviewer (James Gilbert) verified the reason for exclusion.

Data extraction and risk of bias (ROB) assessment were performed by a single author (Louise J. Geneen) with verification by a second author (James Gilbert). Disagreements were resolved through discussion. Information was collected from the studies selected for inclusion using a standardised data collection form (Supporting Information: Appendix S5). We also double-checked our ROB assessment (using Cochrane ROB1 for RCTs[15]) and extracted data against published SRs.[3,16–18] We have presented a ROB graph and a ROB summary figure (Supporting Information: Appendix S2) with detailed reasons for assessment.

We did not seek missing data from trial authors as this is an SR using rapid review methods.[13] Where possible, we analysed data on an intention-to-treat (ITT) basis, which reflects best practice, and how planning for the timing of induction is implemented.

Data synthesis

We grouped comparisons according to the gestational age at the allocated timing of induction: for example, induction at 41 weeks (41 + 0–6 weeks) versus 42 weeks (42 + 0–6 weeks), and an overall combined analysis of all RCTs comparing induction versus delayed induction for subgroup analyses. Where the allocated period for induction did not fall within a single week, we assigned the trial to the period most closely associated, and footnoted all analyses to state the true period. This was only necessary for two trials (ARRIVE[19]: the delayed induction group allocated to 40 + 5 to 42 + 2 weeks, assigned here to "41 weeks"; and Tan[20]: induction 39 + 0 to 40 + 3 weeks, assigned to "39 weeks").

We used RevMan5[21] to calculate risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes (except where we have used Peto odds ratio [POR] for low event rates, or risk difference [RD] where there were zero cases in both arms) using pairwise meta-analysis. We used a random-effects model (Mantel–Haenszel method) due to the heterogeneous nature of the studies.

We examined heterogeneity using the I^2 and τ^2 statistics, and where it was deemed to be high, we planned to investigate through subgroup and sensitivity analyses.

Subgroups were pre-specified as BMI (above and below 30), maternal age (under 30, under 35, and over 35 years), and geographical location (Europe, Asia, North America, and the Middle East) due to limited data on ethnicity. We were unable to subgroup by use of fertility treatment due to the lack of reporting of outcomes by fertility status, and the low number of studies reporting fertility status of the included women.

Sensitivity analyses were performed for the BMI subgroup analysis due to a baseline imbalance in BMI in one trial. No sensitivity analyses were performed for the week-to-week comparisons due to the small number of trials.

A single reviewer (Louise J. Geneen) assessed the certainty of the evidence using GRADEpro[22] with verification of all judgements (and footnoted rationale) by a second reviewer (James Gilbert). Disagreements were resolved through discussion.

RESULTS

After the removal of duplicates, we screened 509 references based on title and abstract: excluding 351 references (Figure 1). We screened 158 full-text articles and excluded 123 (Supporting Information: Table S1): of which 28 publications were systematic or narrative reviews, which were hand-searched for additional relevant studies.

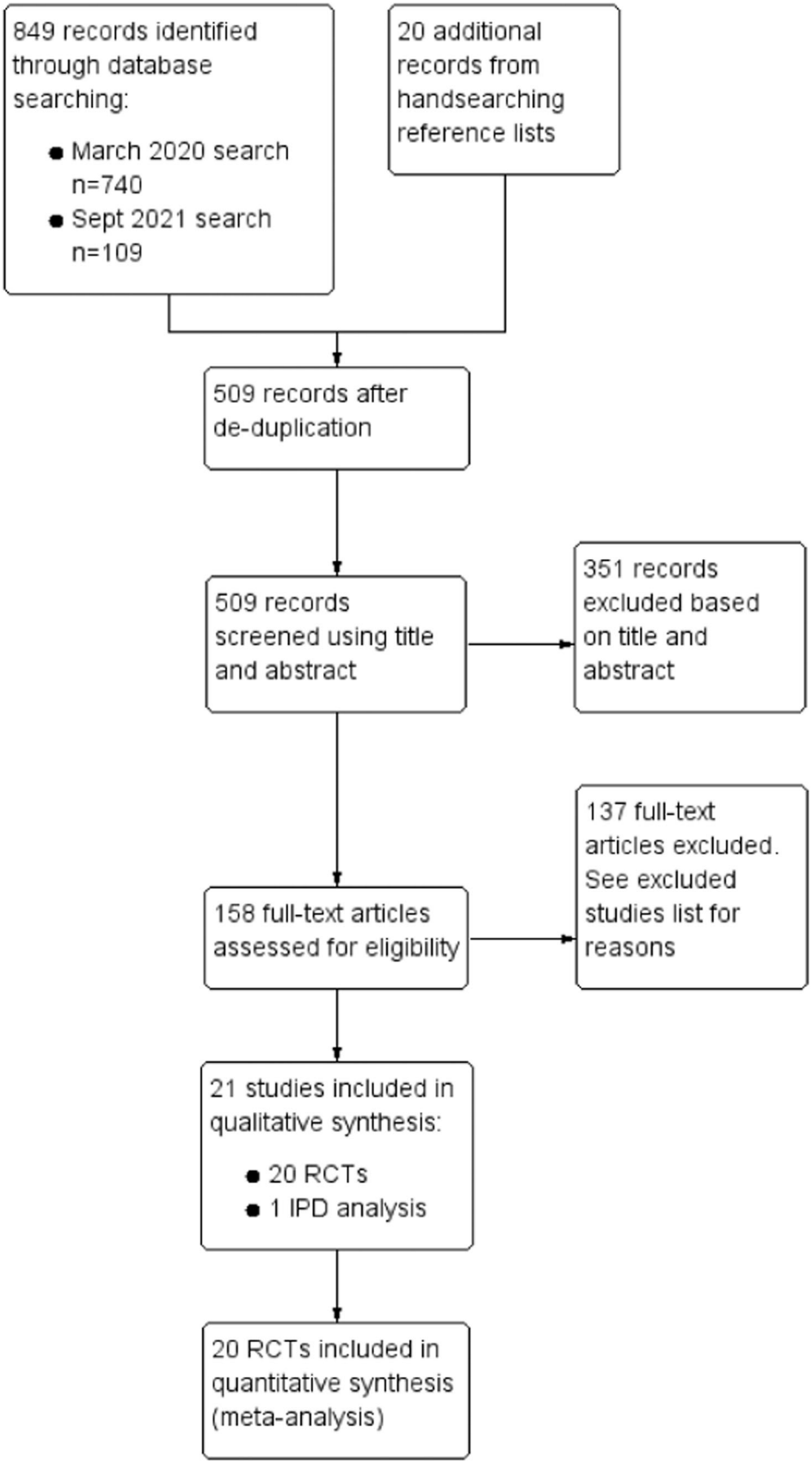

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. IPD, individual patient data; RCT, randomised controlled trials.

We included 20 RCTs and one individual patient data (IPD) analysis in the narrative synthesis, and 20 RCTs in the quantitative analysis. Three studies[23–25] excluded for non-English language in the NICE guideline SR were re-included for these analyses, using data extracted from published Cochrane reviews.[3,17,18]

The IPD analysis of 41 versus 42 weeks[26] was compared to the results of our aggregate data meta-analysis. The IPD SR compared IOL at 41 + 0–2 weeks to 42 + 0–1 weeks, obtaining individual data from two RCTs also included in our analyses (INDEX[27] and SWEPIS[28]). We have presented our results beside theirs (Table 2): their IPD results, our aggregate analysis of the same two studies, and our aggregate analysis of all studies available for the same comparison.

Study characteristics

Twenty RCTs totalling 15 725 participants fulfilled our predefined criteria[19,20,23–25,27–41] and were included in this review. This includes an additional five RCTs ($n = 1807$[20,23–25,34]) compared to the NICE guideline.[11] Most studies compared induction to EM, where a maximum gestational age was specified for induction.

Included trials were published between 1975 and 2021. Funding was reported by seven RCTs[19,20,27,28,30,34,38]: all from universities and public funding bodies (non-pharmaceutical). Trials varied in size from 80[31] to 6103[19] participants. One included study (SWEPIS[25]) was powered for a much larger sample but was terminated early for ethical reasons due to a significantly higher perinatal death rate in the delayed induction group.

Study location, ethnicity, maternal age, and BMI descriptors are discussed as subgroups (Supporting Information: Appendix S4).

Power calculations were reported by nine RCTs[19,20,27–29,32,34,36,38]: five based on a "successful induction" (difference in caesarean birth,[32,34,38] vaginal delivery,[20] or spontaneous labour within 48 h[36]), and four based on a difference in adverse perinatal outcomes.[19,27–29]

Comparisons

Comparisons were grouped according to gestational age at planned induction. We also combined all 20 RCTs in an overall *induction versus delayed induction* analysis to examine our prespecified subgroups. The intervention and comparator groups are described in detail in Supporting Information: Table S2a–e.

Outcomes

Our primary outcome of maternal mortality was reported in four trials,[19,27,28,34] reporting zero cases. Perinatal mortality was reported in 12 trials.[19,23,27–30,34,35,37,39–41] All predefined outcomes are shown in Table 1. Three studies reported "spontaneous vaginal delivery" under mode of birth outcomes,[27,30,32] and have been included in this review as "unassisted vaginal birth (VB)" based on the description and definitions in the original publications. Most studies reported neonatal unit admission as neonatal intensive care unit (NICU) admission, and three reported differently: special care baby unit[30]; neonatal unit[20]; and NICU or intermediate care unit.[19] All have been combined as NICU admission for analysis.

ROB included studies

See Supporting Information: Appendix S2 for an overview of ROB by study and by ROB domain.

None of the studies were able to blind to group allocation so were assessed as having high ROB as this may have affected clinical decision-making (except for maternal and perinatal mortality). There was unclear ROB in multiple domains for multiple studies due to a lack of information in reporting, including the randomisation process and lack of trial registration/published protocols. Most studies reported data as ITT, and some studies reported baseline imbalance in some participant characteristics (high ROB for other biases).

The combined data for *induction versus delayed induction* suggest there was minor publication bias where we could assess it (at least 10 studies: caesarean, instrumental vaginal, and NICU admission). The likelihood is that some data from smaller, older, studies are missing (Supporting Information: Appendix S3), though not to the extent to downgrade the certainty of the evidence. This is also seen in the funnel plots for subgroups (same distribution of data, Supporting Information: Appendix S4).

Effects of intervention

Certainty of the evidence was assessed as very-low to moderate using GRADE for randomised studies. Downgrading was due to ROB and large imprecision (small sample size and wide CIs). In the induction versus delayed induction pooled analysis, we also downgraded for indirectness. See Table 1 (overview of results) and appendices for more information: Forest plots (Supporting Information: Appendix S3) and GRADE tables (Supporting Information: Table S3a–f).

Comparison: 41 vesus 42 weeks

Data were available for all prespecified outcomes (Table 1, Supporting Information: Appendix S3 and Table S3a).

Perinatal death was significantly lower with earlier induction (five RCTs, $n = 5819$; Peto odds ratio [POR]: 0.19 [95% CI: 0.06, 0.58], moderate certainty). No maternal deaths were reported (two RCTs, $n = 4561$, low certainty).

TABLE 1 Overview of results

	Overall: Induction versus delayed induction: (20 RCTs)	41 versus 42 weeks: (5 RCTs)	40 versus 42 weeks: (4 RCTs)	39 versus 42 weeks: (3 RCTs)	39 versus 41 weeks: (4 RCTs)	41/42 versus 43/44 weeks: (4 RCTs)
Maternal death	4 RCTs, $n = 11\,275$ ⊕○○○	2 RCTs, $n = 4561$ ⊕⊕○○	–	–	2 RCTs, $n = 6714$ ⊕⊕○○	–
Perinatal death	12 RCTs, $n = 13\,811$** ⊕⊕⊕○	5 RCTs, $n = 5819$** ⊕⊕⊕○	1 RCT, $n = 345$ ⊕⊕○○	–	3 RCTs, $n = 6942$ ⊕⊕○○	3 RCTs, $n = 705$ ⊕⊕○○
Caesarean	19 RCTs, $n = 15\,645$* ⊕⊕○○	5 RCTs, $n = 5819$ ⊕⊕⊕○	3 RCTs, $n = 668$ ⊕○○○	3 RCTs, $n = 1103$ ⊕○○○	4 RCTs, $n = 7101$ ⊕⊕○○	4 RCTs, $n = 954$ ⊕⊕○○
Instrumental/ operative vaginal	15 RCTs, $n = 14\,391$ ⊕⊕○○	3 RCTs, $n = 5069$ ⊕⊕○○	3 RCTs, $n = 574$ ⊕○○○	2 RCTs, $n = 942$ ⊕○○○	4 RCTs, $n = 7101$ ⊕○○○	3 RCTs, $n = 705$ ⊕○○○
Unassisted vaginal	8 RCTs, $n = 5879$ ⊕⊕○○	2 RCTs, $n = 4561$ ⊕⊕⊕○	–	1 RCT, $n = 226$ ⊕⊕⊕○	2 RCTs, $n = 387$ ⊕⊕⊕○	3 RCTs, $n = 705$ ⊕○○○
NICU admission	13 RCTs, $n = 13\,836$** ⊕○○○	4 RCTs, $n = 5661$** ⊕⊕○○	1 RCT, $n = 149$ ⊕○○○	2 RCTs, $n = 387$ ⊕○○○	3 RCTs, $n = 6873$ ⊕⊕○○	3 RCTs, $n = 766$ ⊕○○○
HIE	3 RCTs, $n = 9469$ ⊕○○○	1 RCT, $n = 2755$ ⊕○○○	–	–	2 RCTs, $n = 6714$ ⊕○○○	–
MAS	6 RCTs, $n = 11\,945$** ⊕○○○	4 RCTs, $n = 5661$ ⊕○○○	–	–	1 RCT, $n = 6096$ ⊕⊕○○	1 RCT, $n = 188$ ⊕○○○

Note: ⊕○○○, very low certainty; ⊕⊕○○, low certainty; ⊕⊕⊕○, moderate certainty; and ⊕⊕⊕⊕, high certainty.

Abbreviations: HIE, hypoxic-ischaemic encephalopathy; MAS, meconium aspiration syndrome; NICU, neonatal intensive care unit; RCT, randomised controlled trial.

*Favours earlier induction, $p = 0.06$.

**Favours earlier induction, $p < 0.05$.

There was evidence of an effect showing a lower incidence of NICU admission with 41 weeks of induction compared to 42 weeks (four RCTs, $n = 5661$, RR: 0.69 [95% CI: 0.53, 0.91], low certainty). There was no evidence of an effect on the remaining outcomes (moderate certainty: caesarean, unassisted VB; low certainty: instrumental VB; and very-low certainty: HIE, MAS).

Other week-to-week comparisons

There was no evidence of an effect for any of the reported outcomes for 40 versus 42 weeks, 39 versus 42 weeks, 39 versus 41 weeks, and 41/42 versus 43/44 weeks: see Table 1, Supporting Information: Appendix S3 and Table S3b-e.

IPD comparison (41 vs. 42 weeks)

We compared the IPD analyses of SWEPIS and INDEX to our aggregate analyses of the same two studies and to the aggregate analyses of the data available from all five RCTs comparing 41 versus 42 weeks (three RCTs[23,29,41] in addition to INDEX[27] and SWEPIS[28]) (Table 2).

Nearly 80% of participants came from just two RCTs (SWEPIS and INDEX), thereby driving the similarity of the IPD results compared to our aggregate analyses of all five RCTs. However, the additional data available for perinatal mortality, caesarean, NICU admission, and MAS resulted in tighter CIs, signifying homogeneity of the results and therefore increasing confidence that it represents a true estimate of the effect. In contrast, additional data for instrumental VB led to wider CIs (greater error), reducing the certainty that this reflects the true estimate of the effect.

Comparison: Induction versus delayed induction (all 20 RCTs)

All 20 RCTs were combined into a single comparison, primarily to assess publication bias and our prespecified subgroups, though results for the meta-analyses without subgrouping are described here. Data were available for all prespecified outcomes (Supporting Information: Appendix S3 and Table S3f).

Perinatal death was significantly lower with earlier induction (12 RCTs, $n = 13\,811$; POR: 0.27 [95% CI: 0.12, 0.61], moderate certainty). Zero cases of maternal death were reported (four RCTs, $n = 11\,275$, very-low certainty).

There was some evidence ($p = 0.06$) of a lower incidence of caesarean births with earlier induction (19 RCTs, $n = 15\,645$; RR: 0.92 [95% CI: 0.84, 1.01]; low certainty). There was evidence of an effect showing lower incidence of NICU admission (13 RCTs, $n = 13\,836$, RR: 0.86 [95% CI: 0.76, 0.96], very-low certainty) and fewer diagnoses of MAS (6 RCTs, $n = 11\,945$, RR: 0.63 [95% CI: 0.41, 0.97], very-low certainty) with earlier induction. There was no evidence of an effect for the remaining outcomes (low certainty: instrumental VB, unassisted VB; very-low certainty: HIE).

TABLE 2 Comparison with IPD analysis[23] for 41 versus 42 weeks

	Aggregate MA (this SR): All data (5 RCTs) for 41 versus 42 weeks; *n* = 5819	**IPD (2 RCTs: SWEPIS and INDEX); *n* = 4561**	**Aggregate MA (this SR): 2 RCTs used in the IPD only (SWEPIS and INDEX); *n* = 4561**	**Notes/comments (additional data: 5 RCTs, compared to the IPD of 2 RCTs)**
Maternal death	2 RCTs, $n = 4561$: Zero cases reported; $i^2 = 0\%$; $\tau^2 = 0$	IPD, $n = 4561$: Zero cases reported	2 RCTs, $n = 4561$: Zero cases reported; $i^2 = 0\%$; $\tau^2 = 0$	Same data. No group difference
Perinatal mortality	5 RCTs, $n = 5819$: POR: 0.19 (0.06, 0.58), $p = 0.004$; $i^2 = 0\%$	IPD, $n = 4561$ POR: 0.21 (0.06, 0.78), $p = 0.019$; $i^2 = 0\%$	2 RCTs, $n = 4561$: POR: 0.21 (0.06, 0.78), $p = 0.02$; $i^2 = 0\%$; $\tau^2 = 0$	Additional data: *Tighter 95% CI* *All analyses significantly favour 41 weeks**
Caesarean	5 RCTs, $n = 5819$: RR: 0.95 (0.82, 1.09), $p = 0.44$; $i^2 = 0\%$; $\tau^2 = 0$	IPD, $n = 4561$ RR: 0.98 (0.83, 1.16), $p = 0.81$; $i^2 = 0\%$	2 RCTs, $n = 4561$ RR: 0.98 (0.83, 1.16), $p = 0.819$; $i^2 = 0\%$; $\tau^2 = 0$	Additional data: *Tighter 95% CI* All analyses cross line of no effect
Instrumental/ operative VB	3 RCTs, $n = 5069$: RR: 0.94 (0.79, 1.13), $p = 0.51$; $i^2 = 0\%$; $\tau^2 = 0$	IPD, $n = 4561$ RR: 0.91 (0.75, 1.10), $p = 0.33$; $i^2 = 0\%$	2 RCTs, $n = 4561$ RR: 0.91 (0.75, 1.10), $p = 0.33$; $i^2 = 0\%$; $\tau^2 = 0$	Additional data: *Wider 95% CI* All analyses cross line of no effect
Unassisted VB	2 RCTs, $n = 4561$: RR: 1.01 (0.98, 1.04), $p = 0.41$; $i^2 = 0\%$; $\tau^2 = 0$	IPD, $n = 4561$ RR: 1.01 (0.98, 1.04), $p = 0.41$; $i^2 = 0\%$	2 RCTs, $n = 4561$: RR: 1.01 (0.98, 1.04), $p = 0.41$; $i^2 = 0\%$; $\tau^2 = 0$	Same data. No group difference
NICU admission[a]	4 RCTs, $n = 5661$: RR: 0.69 (0.53, 0.91), $p = 0.008$; $i^2 = 0\%$; $\tau^2 = 0$	IPD, $n = 4553$ aRR: 0.72 (0.54, 0.96), $p = 0.024$; $i^2 = 0\%$	2 RCTs, $n = 4553$ RR: 0.64 (0.47, 0.89), $p = 0.008$; $i^2 = 0\%$; $\tau^2 = 0$	Additional data: *Tighter 95% CI* *All analyses significantly favour 41 weeks**
HIE	Grade 1–3: 1 RCT, $n = 2755$: POR: 0.67 (0.12, 3.85), $p = 0.65$	Grade 2–3: IPD not estimable	Grade 1–3: 1 RCT, $n = 2755$: POR: 0.67 (0.12, 3.85), $p = 0.65$	IPD effect estimate unavailable
MAS	4 RCTs, $n = 5661$: POR: 0.67 (0.33, 1.34), $p = 0.38$; $i^2 = 2\%$; $\tau^2 = 0.01$	IPD, $n = 4553$ POR: 0.42 (0.10, 1.86), $p = 0.25$; $i^2 = 0\%$	2 RCTs, $n = 4553$ POR: 0.49 (0.10, 2.27), $p = 0.36$; $i^2 = 0\%$; $\tau^2 = 0$	Additional data: *Tighter 95% CI* All analyses cross line of no effect

Note: Perinatal mortality: stillbirth and <28-day neonatal death.

Aggregate MA data used a random effect model (for RR) and a fixed effect model (for POR).

Abbreviations: 95% CI, 95% confidence interval; aRR, adjusted for RCTs as part of the IPD methodology; HIE, hypoxic-ischaemic encephalopathy; IPD, individual patient data; MA, meta-analysis, MAS, meconium aspiration syndrome; NICU, neonatal intensive care unit; POR, Peto odds ratio; RCT, randomised controlled trial; RR, risk ratio; SR, systematic review; VB, vaginal birth; i^2, i^2 statistic assessing heterogeneity (of two or more studies); τ^2, τ^2 statistic assessing heterogeneity (of two or more studies) using a random-effects model.

[a]NICU data provided by the IPD defined NICU admission as excluding those babies admitted for routine surveillance; our data could not correct this.

*Favours 41-week induction ($p < 0.05$).

Subgroup analyses of induction versus delayed induction

Subgroup analyses were based on the pooling of all 20 RCTs for induction vs delayed induction. We did not GRADE for subgroup analyses (Supporting Information: Appendix S4).

Body mass index

Women with BMI < 30[27–29,36,41] had greater benefit from earlier induction (perinatal death: four RCTs, $n = 5108$; NICU admission: five RCTs, $n = 5810$), whereas the higher BMI categories did not show evidence of an effect for the same outcomes.[19,20,28,32,34] This is reflected in the IPD analysis as both SWEPIS and INDEX were also categorised as BMI < 30. There was also a benefit (reduced caesarean: three RCTs, $n = 6940$) for mixed BMI (crossing 30) when we excluded one study[20] with BMI baseline imbalance. Only one RCT[28] reported BMI > 30.

Maternal age

There was evidence of an effect for age <30 years[19,31,32,39,41] in favour of earlier induction (caesarean: four RCTs, $n = 7150$; MAS: two RCTs, $n = 6696$) whereas the groups of older women[30,33,34,36–38] did not show an effect for the same outcomes, likely due to the much smaller sample sizes. There was evidence of an effect in the mixed age group (above and below 35 years[20,27,28]) for NICU admission (three RCTs, $n = 4712$). No other age group showed evidence of an effect.

Ethnicity/global location

European studies[24,27–29,31,34–36,39,40] have shown evidence of an effect in favour of earlier induction (perinatal death: seven RCTs, $n = 6669$; NICU admission: six RCTs, $n = 6237$). Both outcomes were driven by the largest trial (SWEPIS). None of the reported outcomes showed evidence of an effect in the Asian,[20,30,37,38] North American,[19,25,32] and North Africa/Middle Eastern[23,33,41] studies. There were no large studies similar in size to ARRIVE, INDEX, or SWEPIS, from Asia or North Africa/Middle East, with most studies nearer 10% of the sample size.

DISCUSSION

Main findings

We identified five RCTs and one IPD analysis not previously included in the 2021 NICE guideline review which have been incorporated into this meta-analysis and narrative review. The additional data supported and refined all the week-to-week analyses, and resulted in a more effective comparison with the IPD analyses at 41 versus 42 weeks.

Most data available were for 39 versus 41 weeks (nearly 90% of participants from ARRIVE) and 41 versus 42 weeks (nearly 80% of the data from INDEX and SWEPIS, which the IPD used). Both comparisons included about 10 times as many participants as the other week-to-week comparisons, due to the size of these three trials.

The 41 versus 42 weeks comparison showed evidence of an effect in favour of 41 weeks for perinatal death and NICU admission. This was reflected in the reported outcomes in the IPD analysis (41 vs. 42 weeks) of INDEX and SWEPIS (which also only found evidence of an effect for perinatal death and NICU admission), likely due to the aggregate analysis being driven by these two large trials. However, the additional data tightened the spread of the result, suggesting we can also have confidence in the results of our aggregate analysis. It should be noted that while SWEPIS drove the results due to the larger sample size, the study was terminated early due to the high perinatal mortality rate in the delayed induction (42 weeks) group, and so did not reach the required sample size specified in their power calculation.

The other week-to-week comparisons showed no evidence of an effect on any outcomes, though this may be due to the much smaller sample sizes.

Strengths and limitations

We have endeavoured to minimise bias within our review. We attempted to identify all relevant RCTs by performing a comprehensive, systematic search of multiple electronic databases. However, we did not include grey literature, such as conference proceedings, and did not search trial registries for ongoing studies or unpublished data. We registered the SR protocol on PROSPERO and prespecified all outcomes before analysis. However, we did not include subjective outcomes of maternal quality of life and satisfaction with treatment due to the heterogeneous reporting between trials, and the wish to focus on maternal and perinatal safety, and mode of birth.

A strength of this update is the inclusion of four RCTs that were previously excluded for lack of availability, or non-English language, using data extracted by Cochrane reviews[3,17] that had obtained the translation, and one newly published RCT[20]: expanding the data pool for analysis. We also assessed publication bias for the outcomes with sufficient data (Supporting Information: Appendix S2), showing possible publication bias from smaller, older trials, though we did not downgrade our assessment of the evidence for this, as it was not significant enough to have affected the result.

As this is an SR using rapid review methods, we did not undertake duplicate screening, data extraction, or analysis. However, a second reviewer (James Gilbert) verified all screening decisions made by the lead reviewer (Louise J.

Geneen), and checked and verified the data extraction and GRADE assessment, as described by the Cochrane Interim Guidelines for Rapid Reviews.[13]

Interpretation and context

Individual primary studies and aggregate analyses of published data have not been sufficiently powered to assess subgroup differences in perinatal outcomes. However, the IPD[26] noted significant benefit from induction at 41 + 0–2 weeks for women with BMI < 30 (also seen in our aggregate analysis for perinatal death and NICU admission), nulliparous women, women age ≥35 years, and baby boys, for their primary composite outcome of severe adverse perinatal outcome (mortality or severe neonatal morbidity including HIE, MAS, and mechanical ventilation).

The IPD did not comment on ethnicity, likely due to the homogenous population in the SWEPIS (Sweden, ethnicity not reported) and INDEX (The Netherlands, 85% white) studies. The need to assess these subgroups is based on observational data (audit studies) and non-randomised trials that suggest a greater risk of stillbirth and obstetric complications in women over 35 years,[34,42] higher BMI,[43] black, Asian, and minority ethnic groups,[1,44] and those using ART.[45,46] Often these characteristics interact (older women are more likely to use ART, and have higher BMI), and therefore data may have significant confounding, highlighting the need to use randomised trials, ideally with stratification. Additionally, older women or those using fertility treatments are often excluded from trials as they are more likely to have complicated or multifetal pregnancies.[47–49]

CONCLUSION

The additional data included in this SR supports offering IOL at 41 + 0 weeks compared to 42 + 0 weeks in uncomplicated singleton pregnancies. The comparative analysis with the IPD analysis of SWEPIS and INDEX, with the additional data at 41 versus 42 weeks, tightened the CIs and increases the certainty of the evidence.

The remaining week-to-week comparisons require more data, as do all comparisons from under-represented groups that may be at greater risk of adverse outcomes from prolonged pregnancy.

We note that our recommendation to induce at a specific gestational age may not be applicable to women where accurate pregnancy dating is not possible.

Practical and research recommendations

It is important that IOL is considered an optional medical intervention and not a routine part of maternity care.[50,51] Women should be involved in shared decision-making,[52] which includes support for staff to have up-to-date knowledge of the evidence and confidence to provide a full risk and benefit overview.[53,54]

Offering induction to more women, rather than awaiting the spontaneous onset of labour, may increase pressure on facilities, with increased antenatal bed usage and greater need for additional skilled healthcare professionals (resources specific to IOL). However, health utilisation research has reported fewer antenatal visits and tests (less ongoing monitoring), fewer intrapartum interventions, and shorter postnatal stay with IOL, compared to EM.[3,55] Current pressures have already been exacerbated by the COVID-19 pandemic, which has affected resourcing and consequent maternal and perinatal outcomes,[56] and so re-evaluating ongoing resource management is essential to provide a high-quality experience for women and healthcare professionals alike.

Evidence regarding women's experience of IOL is currently limited and heterogeneous. Further research is required using validated scales for the assessment of satisfaction across multiple stages of the induction and birth process.[57] Difficulties in accurately assessing experience of IOL were noted by the SWEPIS study: there may be bias in favour of IOL due to the recruitment of women who were motivated towards it.[51]

Future trials should use randomisation with stratification by potential confounders (parity, maternal age, and BMI) to encourage equal distribution across the intervention groups, and increased recruitment of older women, those who conceived with ART, and black, Asian, and minority ethnic groups. This is especially important given the sparsity of randomised data, and the observational evidence of more adverse outcomes for these women. To date, no large trials or SRs assessing IOL timing have been able to subgroup by any of these categories as well as by induction group allocation, with sufficient power to detect a difference, which highlights the need for large RCTs in these under-represented groups.

AUTHOR CONTRIBUTIONS

Systematic reviewer and methodologist; developed and registered the protocol, screened all titles, full texts, and performed hand-searching, extracted and quality appraised the data (ROB and GRADE), undertook analyses, interpreted the data, and wrote the manuscript of the review: Louise J. Geneen. *Systematic reviewer; developed the protocol, verified full-text exclusions, verified extracted data, and risk of bias assessment*: James Gilbert. *Information specialist; developed the search strategy and performed all searches (including deduplication) and contributed to the development of the manuscript*: Tim Reeves. *Neonatologist; developed the protocol, interpreted the data, and contributed to the development of the manuscript*: Pramod Mainie. *Obstetrician; developed the protocol, interpreted the data, and contributed to the development of the manuscript*: Michael Maresh. *Midwife; developed the protocol, interpreted the data,*

and contributed to the development of the manuscript: Lisa Smith. *Obstetrician; developed the protocol, interpreted the data, and contributed to the development of the manuscript*: Pensee Wu. *Obstetrician; developed the protocol, interpreted the data, contributed to the development of the manuscript, and clinical lead for the review*: Maryam Parisaei. All authors contributed, read, and approved the review. All authors accept responsibility for the paper as published.

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CONFLICTS OF INTEREST

All authors were members of the National Institute for Health and Care Excellence Guideline Committee, or technical team, for "Inducing Labour (update)" NG207 (2019–2021). Michael Maresh has received an Honorarium from Novo Nordisk for chairing Data Monitoring Committee for EXPECT trial which was an randomised controlled trial comparing two insulins for pregnant women with type 1 diabetes (2018–2021).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

An ethics statement is not applicable because this study is based exclusively on published literature.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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