National Institute for Health and Care Excellence

Draft for consultation

Inducing labour

[C] Induction of labour for prevention of prolonged pregnancy

NICE guideline number CG70 (update)

Evidence review underpinning recommendations 1.1.1, 1.1.2,1.1.5, 1.2.2 to 1.2.4, 1.2.7, 1.2.8 and research recommendations in the NICE guideline

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Draft for consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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ISBN:

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Induction of labour for prevention of prolonged pregnancy

Review question

At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Introduction

There are a number of options available for women if spontaneous labour does not occur at the end of their pregnancy: to wait until labour begins naturally, to induce labour, or to consider a caesarean birth. There is a balance of risks and benefits of each option, and there is evidence that a prolonged pregnancy may lead to adverse outcome for the baby.

The aim of this review is to determine the gestational age at which induction of labour should be offered in uncomplicated pregnancies to optimise outcomes for the woman and baby.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	**Inclusion:** • Women with pregnancies that pass 37 completed weeks, uncomplicated pregnancies (as defined by studies). **Exclusion:** • Women who have any co-existing medical conditions or obstetric complications. • Women who are due to have a planned caesarean birth. • Studies predominantly in women with diabetes, women with multiple pregnancy, women with spontaneous rupture of membrane.
Intervention	Induction of labour (using any methods broadly in line with those recommended in this guideline) at the following gestational age brackets: • 37+0 to 37+6 (hereafter referred to as "37 weeks") • 38+0 to 38+6 (hereafter referred to as "38 weeks") • 39+0 to 39+6 (hereafter referred to as "39 weeks") • 40+0 to 40+6 (hereafter referred to as "40 weeks") • 41+0 to 41+6 (hereafter referred to as "41 weeks") • 42+0 to 42+6 (hereafter referred to as "42 weeks") • 43+0 or later (hereafter referred to as "43 weeks")
Comparison	Any study that compares 2 or more induction timing strategies, including expectant management to a specified timepoint at which induction then occurs (for example, induction at 40 weeks versus 42 weeks or induction at 39 weeks versus expectant management until 41 weeks).
Outcome	**Critical** • Maternal mortality/morbidity (death or uterine rupture) • Maternal quality of life • Perinatal mortality (stillbirth or neonatal death) **Important** • Mode of birth (instrumental versus unassisted vaginal versus caesarean) • Maternal satisfaction/experience of care • Neonatal unit admission • Neonatal morbidity (MAS/HIE)

HIE: hypoxic ischemic encephalopathy; MAS: meconium aspiration syndrome.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines. Please see the methods chapter for further details. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Fifteen randomised controlled trials (RCTs) were included in this review. Most studies compared induction versus expectant management, where a maximum gestational age was specified for induction, for example, expectant management to 42 weeks and then induction

for women who had not yet gone into spontaneous labour or had to be induced earlier for medical reasons.

One included study (Wennerholm 2019) was powered for a much larger sample, but was terminated early for ethical reasons due to a significantly higher perinatal death rate in the expectant management (delayed induction) group.

None of the included studies reported usable data on maternal quality of life, and only one examined maternal satisfaction/experience of care (Grobman 2018).

Three studies reported "spontaneous vaginal delivery" under mode of birth outcomes (Herabutya 1992, Keulen 2019, Nielsen 2005), and have been included here as "unassisted vaginal birth" based on the description and definitions within the original publication.

Comparisons were grouped according to gestational age at planned induction. See Table 2.

Table 2: Grouping of comparisons

Comparison	Studies	Outcomes reported
Comparison 1: 39 versus 40-42 weeks	• Grobman 2018	• Maternal death/uterine rupture • Perinatal death • Caesarean • Instrumental/operative vaginal • Maternal experience of birth • NICU admission • MAS & HIE
Comparison 2: 39 versus 42 weeks	• Nielsen 2005	• Caesarean • Instrumental/operative vaginal • Unassisted vaginal • NICU admission
Comparison 3: 39-40 versus 41 weeks	• Cole 1975	• Perinatal death • Caesarean • Instrumental/operative vaginal • Unassisted vaginal
Comparison 4: 40 versus 42 weeks	• Baev 2017 • Egarter 1989 • Leijon 1979 • Ohel 1996	• Perinatal death • Caesarean • Instrumental/operative vaginal • NICU admission
Comparison 5: 41 versus 42 weeks	• Gelisen 2005 • Heimstad 2007 • Keulen 2019 • Wennerholm 2019	• Maternal death/uterine rupture • Perinatal death • Caesarean • Instrumental/operative vaginal • Unassisted vaginal • NICU admission • MAS & HIE
Comparison 6: 41-42 versus 44 weeks	• Chanrachakul 2003 • Herabutya 1992	• Perinatal death • Caesarean • Instrumental/operative vaginal • Unassisted vaginal • NICU admission
Comparison 7: 42 versus 43 weeks	• Augensen 1987 • Bergsjo 1989	• Perinatal death • Caesarean • Instrumental/operative vaginal

Comparison	Studies	Outcomes reported
		• Unassisted vaginal • NICU admission • MAS

HIE: hypoxic ischemic encephalopathy; MAS: meconium aspiration syndrome; NICU: neonatal intensive care unit

The included studies are summarised in Table 3.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 3.

Table 3: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Induction method
Augensen 1987 RCT Norway	N=409 randomised Age NR	41+4 to 42+3 weeks "42 weeks" induction N=214	42+3 to 43+3 weeks "43 weeks" induction N=195	• Perinatal death • NICU admission • Caesarean (elective /emergency) • Instrumental birth • Unassisted vaginal	Amniotomy & oxytocin
Baev 2017 RCT Russia	N=156 randomised N=149 analysed Mean age: 28 years	40 weeks induction N=74 analysed	42 weeks induction N=75 analysed	• NICU admission • Caesarean • Instrumental birth • Vaginal delivery (including instrumental)	Mifespristone
Bergsjo 1989 RCT China (authors in Norway)	N=188 Age range: 21-36 years	294 days "42 weeks" induction N=94	"43 weeks" induction N=94	• Perinatal death • Caesarean • Instrumental birth • Vagina unassisted • Aspiration pneumonia	Membrane sweep and oxytocin
Chanrachakul 2003 RCT Thailand	N=249 randomised Mean age: 27 years	41+3 weeks (290 days) induction N=124	44 weeks (308 days) induction N=125	• Caesarean • Vaginal delivery (unclear if instrumental/ unassisted) • NICU admission	ARM and oxytocin
Cole 1975 RCT	N=237 randomised	39-40 weeks induction N=111	41 weeks induction N=117	• Perinatal death • Caesarean	Amniotomy and oxytocin

Study	Population	Intervention	Comparison	Outcomes	Induction method
UK	Age: 18-30 years if primigravida; 18-35 years with 1/2/3 parity if uncomplicated			• Instrumental birth • Vaginal unassisted/ spontaneous	
Egarter 1989 RCT Austria	N=345 randomised Age: NR	40 weeks (280 days) induction N=157	42 weeks (294 days) induction N=156	• Perinatal death • Caesarean • Instrumental birth	Dinoprostone (PGE_2)
Gelisen 2005 RCT Turkey	N=600 Age: 24-26 years	41 weeks induction N=300	42 weeks induction N=300	• Perinatal death • Caesarean • Vaginal delivery (unclear if instrumental) • NICU admission • MAS	Misoprostol/ Oxytocin/ Foley
Grobman 2018 (ARRIVE trial) RCT USA	N=6106 randomised N=6103 analysed Age: median 23-24 [IQR 20-28] years	39+0 to 39+4 weeks "39 weeks" induction N=3059 analysed	40+5 to 42+2 weeks "40 to 42 weeks" induction N=3037 analysed	• Maternal death/ uterine rupture • Perinatal death • Caesarean • Instrumental/ operative birth • Maternal experience • NICU admission • HIE • MAS	Any
Heimstad 2007 RCT Norway	N=508 Age: NR	41+2 weeks (289 days) "41 weeks" Induction N=254	300 days "42 weeks" Induction N=254	• Perinatal death • Caesarean • Operative vaginal birth • NICU admission • Meconium in airway	Amniotomy and oxytocin or misoprostol
Herabutya 1992 RCT Thailand	N=108 randomised Mean age: 27 years	294 days "42 weeks" induction N=57	"44 weeks" induction N=51	• Perinatal death • Caesarean • Instrumental birth • Spontaneous delivery • SCBU admission	Dinoprostone (PGE_2)
Keulen 2019 (INDEX trial) RCT The Netherlands	N=1815 randomised N=1801 analysed Age: 18-34 years (80-85%)	41+0 to 41+1 weeks "41 weeks" induction N=900	42+0 weeks "42 weeks" induction N=901	• Maternal death/ uterine rupture • Perinatal death (Stillbirth and neonatal death postpartum) • Caesarean • Vaginal operative	PGE_1, dinoprosotone (PGE_2), Foley catheter, Cooks catheter, amniotomy and oxytocin

Study	Population	Intervention	Comparison	Outcomes	Induction method
				• Vaginal spontaneous • NICU admission • MAS	
Leijon 1979 RCT Sweden	N=112 randomised N=80 analysed Mean age: 24.5 years (SD 4.0 years)	40 weeks induction N=41	42 weeks induction N=39	• Instrumental (vacuum) birth	Amniotomy and oxytocin
Nielsen 2005 RCT USA	N=226 randomised Mean age: 24.5 years	39+0 to 39+6 weeks "39 weeks" Induction N=116	41 weeks induction N=110	• Caesarean • Operative vaginal • Vaginal unassisted (spontaneous labour) • NICU admission	Amniotomy and oxytocin
Ohel 1996 RCT Israel	N=200 randomised Mean age: 28 years	40+4 weeks "40 weeks" induction N=96 randomised N=70 analysed	42 weeks induction N=104	• Caesarean	Dinoprostone (PGE_2)
Wennerholm 2019 (SWEPIS trial) RCT Sweden	N=2762 randomised Mean age:31 years *NOTE: Power calculation based on N=5019 per group; 10038 total*	41 weeks induction N=1383 randomised N=1381 analysed	42 weeks induction N=1379 *NOTE: Study terminated early due to high perinatal death in this group*	• Maternal death/ uterine rupture • Perinatal death • Caesarean • Instrumental birth/ assisted vaginal • Vaginal unassisted • NICU admission • MAS • HIE (grades 1-3)	PGE_1, dinoprostone (PGE_2), Foley catheter, Cooks catheter, amniotomy and oxytocin

ARM: artificial rupture of membranes; HIE: Hypoxic-ischemic encephalopathy; IQR: inter-quartile range; MAS: meconium aspiration syndrome; N: number; NICU: neonatal intensive care unit; NR: not reported; $PGE_{1/2}$: prostaglandin E_1/E_2; RCT: *randomised controlled trial; SCBU: special care baby unit; SD: standard deviation*

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles (GRADE tables) in appendix F.

Economic evidence

Included studies

Two economic studies were identified from a search of the published literature which were relevant to this question (Caughey 2009, Hersh 2019).

Caughey 2009 developed a decision analytic cost-utility model to evaluate expectant management compared to induction of labour at 39 weeks, 40 weeks and 41 weeks respectively.

A more recent study (Hersh 2019) also modelled the cost-utility of expectant management versus induction of labour at 39 weeks.

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Economic model

No economic modelling was undertaken for this review because the clinical evidence, especially with regard to perinatal deaths, was considered to make the cost-effectiveness of recommendations on timing self-evident.

Evidence statements

Comparison 1: 39 weeks versus 40-42 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- High quality evidence from 1 RCT (N=6096) showed no clinically important difference between groups

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- Low quality evidence from 1 RCT (N=6096) showed no clinically important difference between groups

Important outcomes

Mode of birth

- Caesarean birth: Low quality evidence from 1 RCT (N=6096) showed a clinically important difference in favour of earlier induction: lower incidence in the 39 week induction group compared to 40-42 week induction group.
- Instrumental/operative vaginal birth: Low quality evidence from 1 RCT (N=6096) showed no clinically important difference between groups, though it neared statistical significance in favour of earlier induction.

- Unassisted/spontaneous vaginal birth: No evidence was available for this outcome.

Maternal satisfaction/experience of care

- 6-96 hours post-delivery: Moderate quality evidence from 1 RCT (N=5808) showed no clinically important difference in feelings of perceived control in childbirth.
- 4-8 weeks post-delivery: Moderate quality evidence from 1 RCT (N=5360) showed no clinically important difference in feelings of perceived control in childbirth.

Neonatal unit admission

- Low quality evidence from 1 RCT (N=6096) showed no clinically important difference between groups, though it neared statistical significance

Neonatal morbidity (meconium aspiration syndrome [MAS]/ hypoxic ischaemic encephalopathy [HIE])

- Meconium aspiration syndrome: Moderate quality evidence from 1 RCT (N=6096) showed no clinically important difference between groups
- Hypoxic-ischemic encephalopathy: Low quality evidence from 1 RCT (N=6096) showed no clinically important difference between groups

Comparison 2: 39 weeks versus 42 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- No evidence was available for this outcome

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- No evidence was available for this outcome

Important outcomes

Mode of birth

- Caesarean birth: Very low quality evidence from 1 RCT (N=226) showed no clinically important difference between groups
- Instrumental/operative vaginal birth: Very low quality evidence from 1 RCT (N=226) showed no clinically important difference between groups
- Unassisted/spontaneous vaginal birth: Moderate quality evidence from 1 RCT (N=226) showed no clinically important difference between groups

Maternal satisfaction/experience of care

- No evidence was available for this outcome.

Neonatal unit admission

- Very low quality evidence from 1 RCT (N=226) showed no clinically important difference between groups

Neonatal morbidity (MAS/HIE)

- Meconium aspiration syndrome: No evidence was available for this outcome
- Hypoxic-ischemic encephalopathy: No evidence was available for this outcome

Comparison 3: 39-40 weeks versus 41 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- No evidence was available for this outcome.

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- Low quality evidence from 1 RCT (N=228) showed no clinically important difference between groups

Important outcomes

Mode of birth

- Caesarean birth: Very low quality evidence from 1 RCT (N=228) showed no clinically important difference between groups
- Instrumental/operative vaginal birth: Very low quality evidence from 1 RCT (N=228) showed no clinically important difference between groups
- Unassisted/spontaneous vaginal birth: Very low quality evidence from 1 RCT (N=228) showed no clinically important difference between groups.

Maternal satisfaction/experience of care

- No evidence was available for this outcome.

Neonatal unit admission

- No evidence was available for this outcome.

Neonatal morbidity (MAS/HIE)

- Meconium aspiration syndrome: No evidence was available for this outcome.
- Hypoxic-ischemic encephalopathy: No evidence was available for this outcome.

Comparison 4: 40 weeks versus 42 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- No evidence was available for this outcome.

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- Low quality evidence from 1 RCT (N=313) showed no clinically important difference between groups

Important outcomes

Mode of birth

- Caesarean birth: Very low quality evidence from 3 RCTs (N=636) showed no clinically important difference between groups
- Instrumental/operative vaginal birth: Very low quality evidence from 3 RCTs (N=636) showed no clinically important difference between groups
- Unassisted/spontaneous vaginal birth: No evidence was available for this outcome.

Maternal satisfaction/experience of care

- No evidence was available for this outcome.

Neonatal unit admission

- Very low quality evidence from 1 RCT (N=149) showed no clinically important difference between groups

Neonatal morbidity (MAS/HIE)

- Meconium aspiration syndrome: No evidence was available for this outcome
- Hypoxic-ischemic encephalopathy: No evidence was available for this outcome

Comparison 5: 41 weeks versus 42 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- High quality evidence from 2 RCTs (N=4561) showed no clinically important difference between groups

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- High quality evidence from 4 RCTs (N=5669) showed a clinically important difference in favour of earlier induction: lower incidence in the 41 week induction group compared to 42 week induction group.

Important outcomes

Mode of birth

- Caesarean birth: Low quality evidence from 4 RCTs (N=5670) showed no clinically important difference between groups
- Instrumental/operative vaginal birth: Very low quality evidence from 3 RCTs (N=5069) showed no clinically important difference between groups
- Unassisted/spontaneous vaginal birth: Moderate quality evidence from 2 RCTs (N=4561) showed no clinically important difference between groups

Maternal satisfaction/experience of care

- No evidence was available for this outcome.

Neonatal unit admission

- Very low quality evidence from 4 RCTs (N=5661) showed a clinically important difference in favour of earlier induction: lower incidence in the 41 week induction group compared to 42 week induction group.

Neonatal morbidity (MAS/HIE)

- Meconium aspiration syndrome: Moderate quality evidence from 4 RCTs (N=5664) showed no clinically important difference between groups
- Hypoxic-ischemic encephalopathy (grade 1-3): Low quality evidence from 1 RCT (N=2755) showed no clinically important difference between groups

Comparison 6: 41-42 weeks versus 44 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- No evidence was available for this outcome.

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- Low quality evidence from 1 RCT (N=108) showed no clinically important difference between groups

Important outcomes

Mode of birth

- Caesarean birth: Very low quality evidence from 2 RCTs (N=357) showed no clinically important difference between groups
- Instrumental/operative vaginal birth: Very low quality evidence from 1 RCT (N=108) showed no clinically important difference between groups
- Unassisted/spontaneous vaginal birth: Very low quality evidence from 1 RCT (N=108) showed no clinically important difference between groups

Maternal satisfaction/experience of care

- No evidence was available for this outcome.

Neonatal unit admission

- Very low quality evidence from 1 RCT (N=357) showed no clinically important difference between groups

Neonatal morbidity (MAS/HIE)

- Meconium aspiration syndrome: No evidence was available for this outcome.
- Hypoxic-ischemic encephalopathy: No evidence was available for this outcome.

Comparison 7: 42 weeks versus 43 weeks

Critical outcomes

Maternal mortality/morbidity (death/uterine rupture)

- No evidence was available for this outcome.

Maternal quality of life

- No evidence was available for this outcome.

Perinatal mortality (stillbirth and neonatal stratified)

- Low quality evidence from 2 RCTs (N=597) showed no clinically important difference between groups

Important outcomes

Mode of birth

- Caesarean birth: Low quality evidence from 2 RCTs (N=597) showed a clinically important difference in favour of earlier induction: lower incidence in the 42 week induction group compared to 43 weeks induction group.
- Instrumental/operative vaginal birth: Very low quality evidence from 2 RCTs (N=597) showed no clinically important difference between groups
- Unassisted/spontaneous vaginal birth: Very low quality evidence from 2 RCTs (N=597) showed no clinically important difference between groups

Maternal satisfaction/experience of care

- No evidence was available for this outcome.

Neonatal unit admission

- Very low quality evidence from 1 RCT (N=399) showed no clinically important difference between groups

Neonatal morbidity (MAS/HIE)

- Meconium aspiration syndrome: Low quality evidence from 1 RCT (N=188) showed no clinically important difference between groups
- Hypoxic-ischemic encephalopathy: No evidence was available for this outcome.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

As the aim of this review was to determine the gestational age at which induction of labour should be offered to improve outcomes for women and babies, maternal mortality or serious morbidity (uterine rupture) and perinatal mortality (stillbirth or neonatal death) were deemed critical outcomes. Additionally, maternal quality of life was assessed as a critical outcome, although no evidence was available for this.

Mode of birth (for example, unassisted vaginal birth, assisted/instrumental vaginal birth, or caesarean birth) was chosen as an important outcome as this could impact maternal and neonatal recovery. NICU admission and neonatal morbidity (specifically meconium aspiration syndrome and hypoxic ischaemic encephalopathy) were also important outcomes as these have potentially long term implications for the baby, and additional costs for treatment.

Maternal satisfaction/experience of care was also chosen as an important outcome as induction of labour can have a large impact of a woman's experience of birth but there was only study that reported this outcome.

The quality of the evidence

The quality of the evidence for the chosen outcomes was assessed with GRADE and was rated as very low to high. Evidence was typically downgraded for risk of bias and imprecision. Risk of bias often arose as it was not possible to blind participants or personnel to their allocation. However, for mortality outcomes the evidence was not downgraded as it was deemed unlikely to bias the results. Evidence was downgraded for imprecision due to wide confidence intervals or small sample size.

The committee specifically discussed the quality of the evidence from the SWEPIS study (Wennerholm 2019). The strengths of this study include its large size and relevance to this question. However, the fact that the study was terminated early and never reached the sample size intended to power its primary endpoint was a limitation. The committee discussed the fact that as such a study was initiated and was terminated on the grounds of perinatal mortality differences, it is unlikely that future research into this specific question will be conducted. Taking this into consideration the committee considered what recommendations could and should be made on the basis of this study, and agreed that the results should be considered with the results of the other studies reviewed.

The committee discussed that this review looked specifically at studies that compared different timings of induction and not necessarily the entire body of evidence that could inform a full discussion of the risks at each week (for example non-comparative cohort or cross-sectional studies that report adverse event incidence at each week).

Benefits and harms

The committee reviewed the evidence presented for the timing of induction in uncomplicated singleton pregnancies. They noted that for many outcomes there were very few significant differences between comparisons, but agreed that this may be due to trials often being underpowered for rare outcomes such as maternal and perinatal mortality or serious morbidity. The committee discussed the evidence for the perinatal complications of meconium aspiration syndrome and hypoxic ischaemic encephalopathy and noted the low event rate reported by the studies included in the analyses. This low rate was reassuring, but meant that the committee had to use NICU admission and perinatal mortality as the main outcomes to determine effects of earlier or later induction on the baby, as these outcomes were more widely reported and often powered as a primary outcome in included studies.

The committee agreed that discussions about different modes of birth should be held with a woman early in the pregnancy, to prepare her for the birth, and so create feeling of control wherever possible. The committee discussed that in their experience, planned caesarean is discussed but that women also needed to be informed about induction of labour and how this could impact on their plans for birth. However, the committee also noted that more women with low risk pregnancies are requesting induction, and it would be useful to have evidence on the optimal timing of induction to aid these discussions.

The committee agreed that after the initial discussions in early pregnancy it was important to revisit the woman's decision and preferences for mode of birth (induction of labour, expectant, management or caesarean birth) later in the pregnancy to incorporate the woman's current clinical status and any new risk factors (for example any pregnancy complications). The committee discussed the current scheduling of antenatal appointments, which usually includes a "birth chat" between 34 and 38 weeks, therefore the committee agreed that, as had been stated in the previous recommendations, this discussion should

take place by week 38 in order to revisit preferences and decisions about planned place and mode of birth.

The main aim of induction of labour is to lead to the safe delivery of the baby, and so the committee felt it was important to discuss the risks of a prolonged pregnancy with the woman. Comparison of induction at 39 weeks versus 40 to 42 weeks and 42 weeks versus 43 weeks, showed that earlier induction reduced the risk of caesarean birth. The evidence also showed that, when comparing induction at 41 weeks to delaying induction to 42 weeks, there was a reduced likelihood of perinatal mortality and NICU admission. The committee also noted a possible increase in the need for assisted vaginal birth (for example instrumental delivery using forceps or ventouse) with induction at 40 to 42 weeks compared to induction at 39 weeks. Although this difference was not deemed clinically important, it did near statistical significance, based on low quality evidence (downgraded for risk of bias as it was not possible to blind participants/personnel and imprecision due to wide confidence intervals) from one large trial (Grobman 2018). The committee discussed that it was very difficult, based on the evidence, to recommend an absolute gestational age at which risk suddenly increased, but that the evidence indicated there seemed to be increased risk from 41 weeks and this increase in risk was a continuum, with risks increasing as the length of the post-term pregnancy increased.

When discussing the evidence for the significantly increased perinatal mortality and NICU admission when delaying induction by one week (from 41 to 42 weeks), the committee noted that this difference was predominantly driven by the largest study included in the analysis (SWEPIS; Wennerholm 2019). Despite not being powered for these outcomes, SWEPIS was stopped early for ethical reasons because of the significantly greater rate of perinatal mortality in the delayed induction (42 weeks) group. However, other smaller studies within the same comparison found no significant difference for this outcome, and most of the studies had no cases of perinatal death in the earlier induction (41 weeks) group. Most (n=10/11) deaths that did occur were in the delayed induction (42 weeks) group, with most deaths occurring in the week while waiting for the delayed induction (41+1 to 41+6 weeks). The committee commented that despite the non-significant difference in the other 3 studies, the fact that a study (SWEPIS) was halted for this reason in itself was significant. The SWEPIS study was larger than the other three studies combined for this comparison and the committee considered how much the precise timing of induction strategies should therefore be guided by the SWEPIS study. In this study induction in the 41 weeks group could have taken place between 41+0 and 41+2 weeks, whereas induction in the 42 weeks group took place between 42+0 and 42+1 weeks. On more detailed review of the deaths that occurred the committee noted that they seemed to occur at 41+2 or 41+3 days. On this basis the committee agreed to recommend induction at 41+0 weeks or as soon as possible afterwards. They agreed that this outlined an appropriate target, but without being specific to a single day, as this could cause undue concern to women if induction didn't happen on that exact day, or be overly prescriptive to healthcare providers.

The committee noted a possible harm from these recommendations might be that discussing the risks of prolonged pregnancy (beyond 41+0 weeks) with women might make them feel forced into an unwanted medical intervention (induction or caesarean), and while the committee agreed that the risk of perinatal mortality, NICU admission, and caesarean birth increases over time with a prolonged pregnancy, the absolute risk remains low.

The committee then discussed higher risk groups, who had otherwise uncomplicated singleton pregnancies. The committee were aware from their knowledge and experience that women from the Black, Asian and minority ethnic family background, women with BMI of 30 kg/m^2 or more, women aged 35 years or more, and women who had assisted conception were at a higher risk of adverse events in a pregnancy that was prolonged beyond term. They were also aware that this difference had been reported in wider literature, such as the Mothers and Babies Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) reports. The committee noted that there was a lack of direct evidence

available from this review, therefore they based the recommendation on women with otherwise uncomplicated singleton pregnancies who are at a higher risk of complications associated with continued pregnancy on their knowledge and experience.

The committee considered the post-hoc analyses presented from available data within the review, which compared induction at 41 weeks with induction at 42 weeks (see appendix M). For perinatal death, this included analyses for women aged below and above 35 years (Wennerholm 2019) and for women with a BMI above and below 30 kg/m^2 (Wennerholm 2019, Gelisen 2005). In general, these analyses showed that the results of earlier induction compared with later induction were broadly consistent with the overall population of women, and that earlier induction was preferable. Results from specific subgroups showed no difference between induction at 41 weeks and induction at 42 weeks, with the exception of BMI<30 kg/m^2, however the committee considered that these subgroups were often not powered to assess differences as a result of the timing of induction. Another included study (Grobman 2018) had examined pre-specified subgroups (BAME, BMI and age) but reported a non-statistically significant difference for caesarean birth, and did not report the absolute or relative difference by group.

The committee agreed that it was important that women with these additional risk factors are therefore given the opportunity to have an earlier induction than that recommended for the general population, and that decisions to induce should take into consideration the woman's preference, previous obstetric history and local resources. The committee agreed that these decisions should be taken on a case by case basis, with individualised care, making the woman aware of the risk factors that applied to her, although her pregnancy was otherwise uncomplicated. The committee did not have sufficient evidence to recommend a particular gestational age at which to consider early induction, but agreed that it should be considered earlier than the 41+0 week (although no earlier than term, in other words 37+0 weeks). The committee decided that considering induction at 39+0 weeks for women in these groups would likely reduce risks of prolonged pregnancy without over-burdening NHS resources, or increasing risks to babies due to earlier birth. The committee noted that offering induction earlier might impact on women's choice of place of birth, as women having an induction would be more likely to give birth in an obstetric unit. Some women may choose not to have this earlier induction so they could plan to give birth in a birth centre or at home, and the committee agreed that if this was the choice the woman made it should be respected.

The committee discussed what should be the approach if a woman declined induction, and decided to continue with the pregnancy. The previous guideline (2008) recommended increased monitoring to twice per week beyond 42+0 weeks, though the committee discussed the false sense of security this may offer as they were not aware of any evidence that increased monitoring improves outcomes in a prolonged pregnancy. To avoid false assurances, the committee discussed the importance of informing the women that risks with prolonged pregnancy were increased and would not necessarily be ameliorated with twice weekly monitoring. The committee discussed situations where women have questioned why a potential issue was not picked up with increased monitoring, and how having this additional information in a recommendation would be helpful. Without any additional evidence to support any other monitoring strategy, the committee agreed to leave the monitoring strategy from the previous guideline with the added warnings that it may not rule out or prevent adverse effects and can only provide a snapshot as to the status of the baby at the time of monitoring. Based on their knowledge and experience, the committee added recommendations that women should be given an opportunity to revisit their decision at least once a week, or to change their mind, and to seek advice if they had concerns about their babies.

The committee agreed that the ranges of weeks used in the included studies had made it difficult to determine if there was a more precise defined gestational age at which the risk of prolonged pregnancy increased. The committee agreed that this information was probably available in the studies, but just not reported, and so made a research recommendation to

conduct an individual patient data meta-analysis to identify the most common timing of fetal death, which in turn would provide clearer guidance on the optimal timing of induction of labour.

As the committee had identified the lack of evidence for the optimal gestational age at which to offer induction for higher risk groups they made a research recommendation to identify this.

Cost effectiveness and resource use

The previous NICE guideline recommended induction should be offered between 41+0 and 42+0 weeks, so recommending it be offered at 41+0 weeks or as soon as possible afterwards represents a substantial change of practice. This is likely to mean that a larger number of women undergo induction than previously as some women who would have given birth spontaneously by 42+0 weeks will now be induced. The committee also accepted that the increased monitoring recommended in women who have chosen not to be induced may apply to more women, and for a longer period of time in those giving birth after 42 weeks. However, the committee did not think the increased monitoring costs would amount to a significant resource impact as only 11,300 births (1.9%) in England occurred after 42+0 weeks between April 2019 and March 2020 (ONS 2021). It is also possible that the recommendation to give women who decline induction of labour the opportunity to revisit their options could have some impact on both the numbers of women having induction of labour and the amount of monitoring that would be required. However, the committee believed that this would not have a big resource impact as it would only apply to a small proportion of pregnant women.

However, a published US study (Caughey 2009) suggested that induction of labour at 41 weeks was cost-effective relative to expectant management with a high probability at a cost-effectiveness threshold of £20,000 per QALY. Whilst, the committee acknowledged that costs from the US are often not generalisable to an NHS setting they still considered that this offered some supporting cost-effectiveness evidence for their recommendation.

The committee also considered that the findings of meta-analysis undertaken as part of this evidence review, driven by the SWEPIS study in particular, and agreed that this was more important in establishing the probable cost-effectiveness of induction of labour at 41+0 weeks. In particular, they considered that the absolute reduction in perinatal deaths was likely to represent a cost-effective use of NHS resources given the QALY gains this would generate. According to the National Schedule of Reference Costs 2018/19 (https://www.england.nhs.uk/national-cost-collection/), a vaginal birth with induction of labour costs approximately £600 more than a vaginal birth without induction ('Normal Delivery, with Epidural or Induction, with CC Score 0' costs £2,500 and 'Normal Delivery with CC Score 0' costs £1,916). The net incremental costs of induction of labour at 41 weeks are likely to be less than £600 as a result of reduced antenatal monitoring in the period after 41 weeks and as a result of lower NICU admission. There was no suggestion in the meta-analysis undertaken for this review that induction of labour at 41+0 weeks would lead to increased costs from instrumental vaginal birth or caesarean birth when compared to induction of labour at 42 + 0 weeks, as the point estimates for instrumental vaginal birth and caesarean birth both favoured induction of labour at 41+0 weeks.

The published study from the United States (Caughey 2009) suggested that induction of labour prior to 41 weeks could also be cost-effective although with a lower level of certainty. However, another US study (Hersh 2019) reported an incremental cost-effectiveness ratio (ICER) of $88,000 per QALY for induction of labour at 39 weeks relative to expectant management until 41 weeks, which would not be considered cost-effective at a threshold of £30,000 per QALY if denominated in British currency. Taken together with the clinical evidence presented in this review, the committee considered that there was not sufficient

economic evidence to support a recommendation for induction of labour earlier than 41+0 weeks.

Other factors the committee took into account

The committee were aware of qualitative literature that suggests that induction of labour can be a challenging experience for many women and many women have reported that they did not have adequate information about the benefits, risks and alternatives to make informed decisions. The committee therefore emphasised that women should be fully informed in order to have realistic expectations about the timing and induction process, allowing for true informed consent. This should include that induction itself would impact on the birthing process and experience, as it is a medical intervention with its own risks, including the possibility of failure (and need for caesarean), a possibility that the risk of assisted vaginal birth (instrumental delivery) and associated obstetric anal sphincter injury (OASI) may be increased, as well as reduced options regarding place of birth due to additional monitoring during the induction process. The committee therefore updated the existing recommendations in the guideline on information and decision-making to clarify these points.

When making their recommendations, the committee discussed the terminology surrounding assisted vaginal birth, and how often it is interpreted by non-clinicians as meaning assistance from a midwife or other professional. Consequently, they added additional terms to the recommendation, to make clear that an assisted vaginal birth included the use of instruments such as forceps or ventouse.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1, 1.1.2, 1.1 5, 1.2.2 to 1.2.4, 1.2.7, 1.2.8 and research recommendations in the NICE guideline.

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Appendices

Appendix A Review protocols

Review protocol for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Table 4: Review protocol

Field	Content
Actual review question	At what gestational age should induction of labour be offered if spontaneous labour does not ensue?
Type of review question	Intervention
Objective of the review	To determine the gestational age at which induction of labour should be offered in uncomplicated pregnancies to optimise outcomes for the woman and baby.
Population	Inclusion: • Women with pregnancies that pass 37 completed weeks), uncomplicated pregnancies (as defined by studies). Exclusion: • Women who have any co-existing medical conditions or obstetric complications. • Women who are due to have a planned caesarean birth. • Studies predominantly in women with diabetes, women with multiple pregnancy, women with spontaneous rupture of membrane.
Interventions	Induction of labour (using any methods broadly in line with those recommended in this guideline) at following gestational age brackets: • 37+0 to 37+6 • 38+0 to 38+6 • 39+0 to 39+6 • 40+0 to 40+6 • 41+0 to 41+6

Field	Content
	• 42+0 to 42+6 • 43+0 or later
Comparison	Including any study that compares 2 or more induction timing strategies, including expectant management (for example induction at 40 weeks vs 42 weeks or induction at 39 weeks vs expectant management until 41 weeks). Studies that compare induction of labour against expectant management with insufficient information to determine the timing of eventual induction in the expectant management arm will not be included.
Outcomes and prioritisation	**Critical outcomes:** Outcomes for women: • Maternal mortality/morbidity (death/uterine rupture) • Maternal quality of life Outcomes for babies: • Perinatal mortality – critical (stillbirth and neonatal stratified) **Important outcomes:** Outcomes for women: • Mode of birth (instrumental vs unassisted vaginal vs Caesarean) • Maternal satisfaction/experience of care Outcomes for babies: • Neonatal unit admission • Neonatal morbidity (meconium aspiration/HIE)
Study design	Randomised controlled trials only, conference abstracts will not be included If identified, systematic reviews of RCTs will be used to check for relevant primary studies for inclusion. If a high quality systematic review is identified that matches the full PICO criteria sufficiently, the systematic review itself will be used as the basis for this review. If it is insufficiently recent (published >1 year from date of this protocol), if more recent primary studies are published, these will be incorporated into the analysis in that review.
Other exclusion criteria	Not in English

Field	Content
Proposed stratified, sensitivity/sub-group analysis	When heterogeneity is encountered, evidence may be subgrouped by: • Age of mother (<35 vs >/= 35) • Previous Caesarean birth vs not • Obesity vs not • IVF/ICSI vs not
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. This information will be uploaded into EPPI and made available in the appendix of the evidence report. Data extraction fields will include as a minimum study location, setting, dates, source of funding, duration of follow-up, inclusion/exclusion criteria, sample size, age of participants, details of precise induction timing strategy, actual timing of birth and any outcomes matching the protocol.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • Cochrane RoB tool for RCTs and quasi-RCTs • ROBIS for systematic reviews if included in their entirety The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled.

Field	Content
	The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Data management: If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADE' will be used to assess the quality of evidence for each outcome. EPPI will be used for bibliographies/citations, study sifting, data extraction and quality assessment/critical appraisal Minimally important differences: Any statistically significant difference will be used as the minimally important difference guide for the following outcomes: • Maternal death • Perinatal death For all other outcomes, GRADE default values will be used of 0.8 and 1.25 for relative risk of dichotomous outcomes; 0.5 times SD of the control group for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Information sources – databases and dates	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Searches will be restricted by: • Language: English • Studies: Human • Study type: Systematic reviews and RCTs Other searches: • Inclusion lists of systematic reviews • The full search strategies for MEDLINE database will be published in the final review.
Identify if an update	No
Author contacts	Developer: National Guideline Alliance nga-enquiries@rcog.org.uk

Field	Content
Review team members	From the National Guideline Alliance: Louise Geneen, systematic reviewer James Gilbert, senior systematic reviewer Paul Jacklin, economist Tim Reeves, information scientist
Search strategy – for one database	For details please see appendix B.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. Consider exploring publication bias for review questions where it may be more common, such as pharmacological questions, certain disease areas, etc. Describe any steps taken to mitigate against publication bias, such as examining trial registries.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	CRD42020193333

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB(IS): risk of bias (in systematic reviews); SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 25/03/2020

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	LABOR, INDUCED/
21	(labo?r adj5 induc$).ti,ab.
22	CERVICAL RIPENING/
23	(cervi$ adj3 ripen$).ti,ab.
24	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
25	((bishop$ or cerv$) adj3 scor$).ti,ab.
26	or/20-25
27	CONSERVATIVE TREATMENT/
28	(conservative$ adj3 (manag$ or treat$ or policy or policies)).ti,ab.
29	(expect$ adj3 manag$).ti,ab.
30	WATCHFUL WAITING/
31	(watchful$ adj3 wait$).ti,ab.
32	(no treat$ or non treat$).ti,ab.
33	(no interven$ or non interven$).ti,ab.
34	(no induc$ or non induc$).ti,ab.
35	(spontaneous$ adj5 (labo?r or deliver$ or onset or follow$ up)).ti,ab.
36	((f?etal or f?otus$) adj5 (test$ or monitor$)).ti,ab.
37	or/27-36
38	PREGNANCY, PROLONGED/
39	((prolonged or protracted or postmature or post-mature or postterm or post-term or postdate? or post-date?) adj5 pregnanc$).ti,ab.
40	full term.ti,ab.
41	or/38-40
42	37$ week?.ti,ab.
43	38$ week?.ti,ab.
44	39$ week?.ti,ab.
45	40$ week?.ti,ab.
46	41$ week?.ti,ab.
47	42$ week?.ti,ab.
48	43$ week?.ti,ab.
49	44$ week?.ti,ab.
50	45$ week?.ti,ab.
51	or/42-50
52	(37$ week? adj5 (38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.

#	Searches
53	(38$ week? adj5 (37$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
54	(39$ week? adj5 (37$ week? or 38$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
55	(40$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
56	(41$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
57	(42$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
58	(43$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 44$ week? or 45$ week?)).ti,ab.
59	(44$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 45$ week?)).ti,ab.
60	(45$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week?)).ti,ab.
61	or/52-60
62	(compar$ adj10 gestation$ adj3 week?).ti,ab.
63	(compar$ adj10 GW?).ti,ab.
64	or/62-63
65	26 and 37 and 41
66	26 and 37 and 51
67	26 and 61
68	26 and 64
69	or/65-68
70	limit 69 to english language
71	LETTER/
72	EDITORIAL/
73	NEWS/
74	exp HISTORICAL ARTICLE/
75	ANECDOTES AS TOPIC/
76	COMMENT/
77	CASE REPORT/
78	(letter or comment*).ti.
79	or/71-78
80	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
81	79 not 80
82	ANIMALS/ not HUMANS/
83	exp ANIMALS, LABORATORY/
84	exp ANIMAL EXPERIMENTATION/
85	exp MODELS, ANIMAL/
86	exp RODENTIA/
87	(rat or rats or mouse or mice).ti.
88	or/81-87
89	70 not 88
90	10 and 89
91	19 and 89
92	or/90-91

Databases: Embase; and Embase Classic

Date of last search: 25/03/2020

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.

#	Searches
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	LABOR INDUCTION/
23	(labo?r adj5 induc$).ti,ab.
24	UTERINE CERVIX RIPENING/
25	(cervi$ adj3 ripen$).ti,ab.
26	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
27	((bishop$ or cerv$) adj3 scor$).ti,ab.
28	or/22-27
29	CONSERVATIVE TREATMENT/
30	(conservative$ adj3 (manag$ or treat$ or policy or policies)).ti,ab.
31	(expect$ adj3 manag$).ti,ab.
32	WATCHFUL WAITING/
33	(watchful$ adj3 wait$).ti,ab.
34	(no treat$ or non treat$).ti,ab.
35	(no interven$ or non interven$).ti,ab.
36	(no induc$ or non induc$).ti,ab.
37	(spontaneous$ adj5 (labo?r or deliver$ or onset or follow$ up)).ti,ab.
38	((f?etal or f?otus$) adj5 (test$ or monitor$)).ti,ab.
39	or/29-38
40	PROLONGED PREGNANCY/
41	((prolonged or protracted or postmature or post-mature or postterm or post-term or postdate? or post-date?) adj5 pregnanc$).ti,ab.
42	full term.ti,ab.
43	or/40-42
44	37$ week?.ti,ab.
45	38$ week?.ti,ab.
46	39$ week?.ti,ab.
47	40$ week?.ti,ab.
48	41$ week?.ti,ab.
49	42$ week?.ti,ab.
50	43$ week?.ti,ab.
51	44$ week?.ti,ab.
52	45$ week?.ti,ab.
53	or/44-52
54	(37$ week? adj5 (38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
55	(38$ week? adj5 (37$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
56	(39$ week? adj5 (37$ week? or 38$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
57	(40$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
58	(41$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
59	(42$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
60	(43$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 44$ week? or 45$ week?)).ti,ab.
61	(44$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 45$ week?)).ti,ab.
62	(45$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week?)).ti,ab.
63	or/54-62
64	(compar$ adj10 gestation$ adj3 week?).ti,ab.
65	(compar$ adj10 GW?).ti,ab.
66	or/64-65
67	28 and 39 and 43
68	28 and 39 and 53
69	28 and 63
70	28 and 66
71	or/67-70
72	limit 71 to english language
73	letter.pt. or LETTER/
74	note.pt.
75	editorial.pt.
76	CASE REPORT/ or CASE STUDY/
77	(letter or comment*).ti.

#	Searches
78	or/73-77
79	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
80	78 not 79
81	ANIMAL/ not HUMAN/
82	NONHUMAN/
83	exp ANIMAL EXPERIMENT/
84	exp EXPERIMENTAL ANIMAL/
85	ANIMAL MODEL/
86	exp RODENT/
87	(rat or rats or mouse or mice).ti.
88	or/80-87
89	72 not 88
90	11 and 89
91	21 and 89
92	90 or 91

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews

Date of last search: 25/03/2020

#	Searches
#1	[mh ^"LABOR, INDUCED"]
#2	((labor or labour) near/5 induc*):ti,ab
#3	[mh ^"CERVICAL RIPENING"]
#4	(cervi* near/3 ripen*):ti,ab
#5	((unfavorabl* or unfavourabl* or un-favorabl* or un-favourabl* or unripe* or un-ripe*) near/3 cervi*):ti,ab
#6	((bishop* or cerv*) near/3 scor*):ti,ab
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	[mh ^"CONSERVATIVE TREATMENT"]
#9	(conservative* near/3 (manag* or treat* or policy or policies)):ti,ab
#10	(expect* near/3 manag*):ti,ab
#11	[mh ^"WATCHFUL WAITING"]
#12	(watchful* near/3 wait*):ti,ab
#13	("no treat*" or "non treat*"):ti,ab
#14	("no interven*" or "non interven*"):ti,ab
#15	("no induc*" or "non induc*"):ti,ab
#16	(spontaneous* near/5 (labor or labour or deliver* or onset or "follow* up")):ti,ab
#17	((fetal or foetal or fetus*or foetus) near/5 (test* or monitor*)):ti,ab
#18	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	[mh ^"PREGNANCY, PROLONGED"]
#20	((prolonged or protracted or postmature or post-mature or postterm or post-term or postdate* or post-date*) near/5 pregnanc*):ti,ab
#21	"full term":ti,ab
#22	#19 or #20 or #21
#23	"37* week*":ti,ab
#24	"38* week*":ti,ab
#25	"39* week*":ti,ab
#26	"40* week*":ti,ab
#27	"41* week*":ti,ab
#28	"42* week*":ti,ab
#29	"43* week*":ti,ab
#30	"44* week*":ti,ab
#31	"45* week*":ti,ab
#32	#23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33	("37* week*" near/5 ("38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#34	("38* week*" near/5 ("37* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#35	("39* week*" near/5 ("37* week*" or "38* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#36	("40* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#37	("41* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#38	("42* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#39	("43* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "44* week*" or "45* week*")):ti,ab

#	Searches
#40	("44* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "45* week*")):ti,ab
#41	("45* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*")):ti,ab
#42	#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
#43	(compar* near/10 gestation* near/3 week*):ti,ab
#44	(compar* near/10 GW*):ti,ab
#45	#43 or #44
#46	#7 and #18 and #22
#47	#7 and #18 and #32
#48	#7 and #42
#49	#7 and #45
#50	#46 or #47 or #48 or #49

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 07/04/2020

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	LABOR, INDUCED/
23	(labo?r adj5 induc$).ti,ab.
24	CERVICAL RIPENING/
25	(cervi$ adj3 ripen$).ti,ab.
26	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
27	((bishop$ or cerv$) adj3 scor$).ti,ab.
28	or/22-27
29	CONSERVATIVE TREATMENT/
30	(conservative$ adj3 (manag$ or treat$ or policy or policies)).ti,ab.
31	(expect$ adj3 manag$).ti,ab.
32	WATCHFUL WAITING/
33	(watchful$ adj3 wait$).ti,ab.
34	(no treat$ or non treat$).ti,ab.
35	(no interven$ or non interven$).ti,ab.
36	(no induc$ or non induc$).ti,ab.
37	(spontaneous$ adj5 (labo?r or deliver$ or onset or follow$ up)).ti,ab.
38	((f?etal or f?otus$) adj5 (test$ or monitor$)).ti,ab.
39	or/29-38
40	PREGNANCY, PROLONGED/
41	((prolonged or protracted or postmature or post-mature or postterm or post-term or postdate? or post-date?) adj5 pregnanc$).ti,ab.
42	full term.ti,ab.
43	or/40-42
44	37$ week?.ti,ab.

#	Searches
45	38$ week?.ti,ab.
46	39$ week?.ti,ab.
47	40$ week?.ti,ab.
48	41$ week?.ti,ab.
49	42$ week?.ti,ab.
50	43$ week?.ti,ab.
51	44$ week?.ti,ab.
52	45$ week?.ti,ab.
53	or/44-52
54	(37$ week? adj5 (38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
55	(38$ week? adj5 (37$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
56	(39$ week? adj5 (37$ week? or 38$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
57	(40$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
58	(41$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
59	(42$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
60	(43$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 44$ week? or 45$ week?)).ti,ab.
61	(44$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 45$ week?)).ti,ab.
62	(45$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week?)).ti,ab.
63	or/54-62
64	(compar$ adj10 gestation$ adj3 week?).ti,ab.
65	(compar$ adj10 GW?).ti,ab.
66	or/64-65
67	28 and 39 and 43
68	28 and 39 and 53
69	28 and 63
70	28 and 66
71	or/67-70
72	limit 71 to english language
73	LETTER/
74	EDITORIAL/
75	NEWS/
76	exp HISTORICAL ARTICLE/
77	ANECDOTES AS TOPIC/
78	COMMENT/
79	CASE REPORT/
80	(letter or comment*).ti.
81	or/73-80
82	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
83	81 not 82
84	ANIMALS/ not HUMANS/
85	exp ANIMALS, LABORATORY/
86	exp ANIMAL EXPERIMENTATION/
87	exp MODELS, ANIMAL/
88	exp RODENTIA/
89	(rat or rats or mouse or mice).ti.
90	or/83-89
91	72 not 90
92	21 and 91

Databases: Embase; and Embase Classic

Date of last search: 07/04/2020

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.

#	Searches
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	LABOR INDUCTION/
19	(labo?r adj5 induc$).ti,ab.
20	UTERINE CERVIX RIPENING/
21	(cervi$ adj3 ripen$).ti,ab.
22	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
23	((bishop$ or cerv$) adj3 scor$).ti,ab.
24	or/18-23
25	CONSERVATIVE TREATMENT/
26	(conservative$ adj3 (manag$ or treat$ or policy or policies)).ti,ab.
27	(expect$ adj3 manag$).ti,ab.
28	WATCHFUL WAITING/
29	(watchful$ adj3 wait$).ti,ab.
30	(no treat$ or non treat$).ti,ab.
31	(no interven$ or non interven$).ti,ab.
32	(no induc$ or non induc$).ti,ab.
33	(spontaneous$ adj5 (labo?r or deliver$ or onset or follow$ up)).ti,ab.
34	((f?etal or f?otus$) adj5 (test$ or monitor$)).ti,ab.
35	or/25-34
36	PROLONGED PREGNANCY/
37	((prolonged or protracted or postmature or post-mature or postterm or post-term or postdate? or post-date?) adj5 pregnanc$).ti,ab.
38	full term.ti,ab.
39	or/36-38
40	37$ week?.ti,ab.
41	38$ week?.ti,ab.
42	39$ week?.ti,ab.
43	40$ week?.ti,ab.
44	41$ week?.ti,ab.
45	42$ week?.ti,ab.
46	43$ week?.ti,ab.
47	44$ week?.ti,ab.
48	45$ week?.ti,ab.
49	or/40-48
50	(37$ week? adj5 (38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
51	(38$ week? adj5 (37$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
52	(39$ week? adj5 (37$ week? or 38$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
53	(40$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
54	(41$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 42$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
55	(42$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 43$ week? or 44$ week? or 45$ week?)).ti,ab.
56	(43$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 44$ week? or 45$ week?)).ti,ab.
57	(44$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 45$ week?)).ti,ab.
58	(45$ week? adj5 (37$ week? or 38$ week? or 39$ week? or 40$ week? or 41$ week? or 42$ week? or 43$ week? or 44$ week?)).ti,ab.
59	or/50-58
60	(compar$ adj10 gestation$ adj3 week?).ti,ab.
61	(compar$ adj10 GW?).ti,ab.
62	or/60-61
63	24 and 35 and 39
64	24 and 35 and 49
65	24 and 59
66	24 and 62
67	or/63-66
68	limit 67 to english language
69	letter.pt. or LETTER/

#	Searches
70	note.pt.
71	editorial.pt.
72	CASE REPORT/ or CASE STUDY/
73	(letter or comment*).ti.
74	or/69-73
75	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
76	74 not 75
77	ANIMAL/ not HUMAN/
78	NONHUMAN/
79	exp ANIMAL EXPERIMENT/
80	exp EXPERIMENTAL ANIMAL/
81	ANIMAL MODEL/
82	exp RODENT/
83	(rat or rats or mouse or mice).ti.
84	or/76-83
85	68 not 84
86	17 and 85

Database: Cochrane Central Register of Controlled Trials

Date of last search: 07/04/2020

#	Searches
#1	MeSH descriptor: [Economics] this term only
#2	MeSH descriptor: [Value of Life] this term only
#3	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#4	MeSH descriptor: [Economics, Hospital] explode all trees
#5	MeSH descriptor: [Economics, Medical] explode all trees
#6	MeSH descriptor: [Resource Allocation] explode all trees
#7	MeSH descriptor: [Economics, Nursing] this term only
#8	MeSH descriptor: [Economics, Pharmaceutical] this term only
#9	MeSH descriptor: [Fees and Charges] explode all trees
#10	MeSH descriptor: [Budgets] explode all trees
#11	budget*:ti,ab
#12	cost*:ti,ab
#13	(economic* or pharmaco?economic*):ti,ab
#14	(price* or pricing*):ti,ab
#15	(financ* or fee or fees or expenditure* or saving*):ti,ab
#16	(value near/2 (money or monetary)):ti,ab
#17	resourc* allocat*:ti,ab
#18	(fund or funds or funding* or funded):ti,ab
#19	(ration or rations or rationing* or rationed) .ti,ab.
#20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	[mh ^"LABOR, INDUCED"]
#22	((labor or labour) near/5 induc*):ti,ab
#23	[mh ^"CERVICAL RIPENING"]
#24	(cervi* near/3 ripen*):ti,ab
#25	((unfavorabl* or unfavourabl* or un-favorabl* or un-favourabl* or unripe* or un-ripe*) near/3 cervi*):ti,ab
#26	((bishop* or cerv*) near/3 scor*):ti,ab
#27	#21 or #22 or #23 or #24 or #25 or #26
#28	[mh ^"CONSERVATIVE TREATMENT"]
#29	(conservative* near/3 (manag* or treat* or policy or policies)):ti,ab
#30	(expect* near/3 manag*):ti,ab
#31	[mh ^"WATCHFUL WAITING"]
#32	(watchful* near/3 wait*):ti,ab
#33	("no treat*" or "non treat*"):ti,ab
#34	("no interven*" or "non interven*"):ti,ab
#35	("no induc*" or "non induc*"):ti,ab
#36	(spontaneous* near/5 (labor or labour or deliver* or onset or "follow* up")):ti,ab
#37	((fetal or foetal or fetus*or foetus) near/5 (test* or monitor*)):ti,ab
#38	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
#39	[mh ^"PREGNANCY, PROLONGED"]
#40	((prolonged or protracted or postmature or post-mature or postterm or post-term or postdate* or post-date*) near/5 pregnanc*):ti,ab
#41	"full term":ti,ab
#42	#39 or #40 or #41
#43	"37* week*":ti,ab
#44	"38* week*":ti,ab
#45	"39* week*":ti,ab

#	Searches
#46	"40* week*":ti,ab
#47	"41* week*":ti,ab
#48	"42* week*":ti,ab
#49	"43* week*":ti,ab
#50	"44* week*":ti,ab
#51	"45* week*":ti,ab
#52	#43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51
#53	("37* week*" near/5 ("38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#54	("38* week*" near/5 ("37* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#55	("39* week*" near/5 ("37* week*" or "38* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#56	("40* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#57	("41* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "42* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#58	("42* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "43* week*" or "44* week*" or "45* week*")):ti,ab
#59	("43* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "44* week*" or "45* week*")):ti,ab
#60	("44* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "45* week*")):ti,ab
#61	("45* week*" near/5 ("37* week*" or "38* week*" or "39* week*" or "40* week*" or "41* week*" or "42* week*" or "43* week*" or "44* week*")):ti,ab
#62	#53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61
#63	(compar* near/10 gestation* near/3 week*):ti,ab
#64	(compar* near/10 GW*):ti,ab
#65	#63 or #64
#66	#27 and #38 and #42
#67	#27 and #38 and #52
#68	#27 and #62
#69	#27 and #65
#70	#66 or #67 or #68 or #69
#71	#20 and #70

Databases: NHS Economic Evaluation Database

Date of last search: 07/04/2020

#	Searches
1	MeSH DESCRIPTOR LABOR, INDUCED IN NHSEED
2	(((labor or labour) adj5 induc*)) IN NHSEED
3	MeSH DESCRIPTOR CERVICAL RIPENING IN NHSEED
4	((cervi* adj3 ripen*)) IN NHSEED
5	(((unfavorabl* or unfavourabl* or un-favorabl* or unfavourabl* or unripe* or un-ripe*) adj3 cervi*)) IN NHSEED
6	(((bishop* or cerv*) adj3 scor*)) IN NHSEED
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6

Databases: Health Technology Assessment

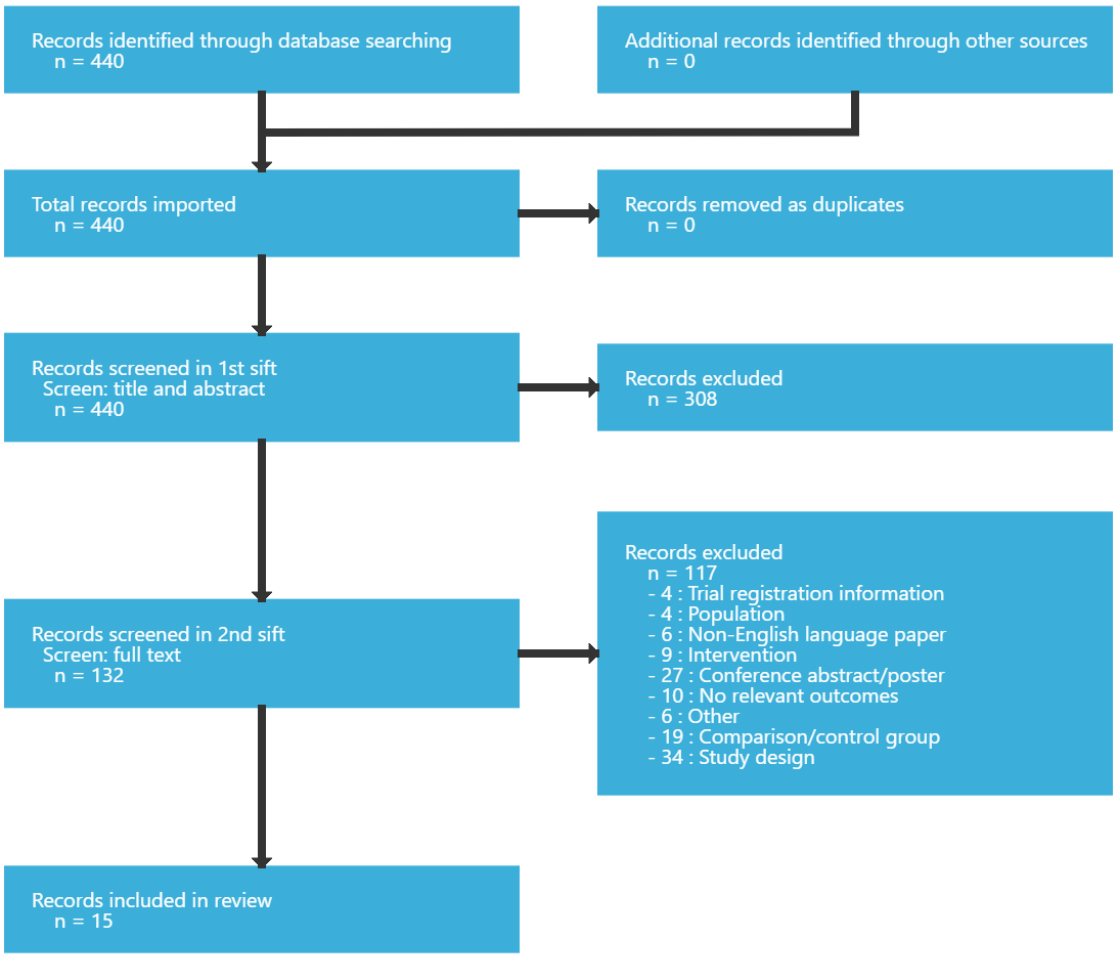
Date of last search: 07/04/2020

#	Searches
1	MeSH DESCRIPTOR LABOR, INDUCED IN HTA
2	(((labor or labour) adj5 induc*)) IN HTA
3	MeSH DESCRIPTOR CERVICAL RIPENING IN HTA
4	((cervi* adj3 ripen*)) IN HTA
5	(((unfavorabl* or unfavourabl* or un-favorabl* or unfavourabl* or unripe* or un-ripe*) adj3 cervi*)) IN HTA
6	(((bishop* or cerv*) adj3 scor*)) IN HTA
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6

Appendix C Clinical evidence study selection

Clinical evidence study selection for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Table 5: Evidence tables – Augensen 1987

Augensen 1987	
Bibliographic Reference	Augensen, K.; Bergsjo, P.; Eikeland, T.; Askvik, K.; Carlsen, J.; Randomised comparison of early versus late induction of labour in post-term pregnancy; British medical journal (Clinical research ed.); 1987; vol. 294 (no. 6581); 1192-5
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Bergen, Norway
Study setting	Dept of Obstetrics and Gynaecology
Study dates	1 Jan 1982 - June 1985
Sources of funding	Not reported
Duration of follow-up	None
Inclusion criteria	• Healthy women, normal pregnancy • single fetus, cephalic presentation • gestational age 290-297 days from LMP • undelivered by 42 weeks
Exclusion criteria	• use of contraceptive pill 2 month before LMP • unclear dating • hypertension of growth retardation • other medical conditions • obstetric problems • birth started spontaneously
Sample size	N=409 randomised group 1 ("42 weeks induction" 41+4 to 42+3 weeks) n=214 group 2 ("one week post-referral induction" 42+3 to 43+3 weeks) n=195
Baseline characteristics	Nulliparous: group 1 n=137 (46%); group 2 n=82 (42%) Bishop score <6: group 1 n=77 (36%); group 2 n=69 (35%) BMI/weight: NR Ethnicity: NR IVF: NR
Intervention(s)	group 1 ("42 weeks induction" 41+4 to 42+3 weeks) group 2 ("one week post-referral induction if undelivered" 42+3 to 43+3 weeks) Women referred by doctor if undelivered at 42 weeks. Those assigned to group 2 (postponement of induction) were suibmitted to cardiotocographic non-stress tests on the day of referral (day zero) and again on day 3 or 4 if still undelivered. If birth had not occurred by day 7 labour was induced. In

Augensen 1987	
	cases of failed induction in group 1 further management was as for group 2. For mothers who were still undelivered after the attempted induction on day 7 management was left to clinical judgment. Labour was induced with 5 IU oxytocin in 500 ml 5% glucose given by intravenous drip infusion, dose rates being increased stepwise according to response. In exceptional cases amniotomy was performed at the start of induction but otherwise only once labour was established. If labour was not clearly established after six to eight hours of infusion induction was considered unsuccessful. A cardiotocographic recording was obtained before disconnection from the drip in these cases.
Timing of birth (as reported by study)	1. Group 1 (42 weeks) 2. Group 2 (43 weeks) Actual timing of birth 1. 294.8 days (SD 2.9) 2. 297.6 days (SD 3.7) Passed 300 days (43 weeks) 1. N=13/214 2. N=40/195 Spontaneous labour 1. N=38/214 (18%) 2. N=135/195 (69%)
Study arms	
42 weeks (N = 214)	
43 weeks (N = 195)	
Outcomes	

	42 weeks	**43 weeks**
	N = 214	N = 195
Perinatal death *Polarity: Not set*		
No of events	n = 0 ; % = 0	n = 0 ; % = 0
NICU admission *Polarity: Not set*		
No of events	n = 12	n = 15
C-section (elective) *Polarity: Not set*		
No of events	n = 0	n = 5
C-section (emergency) *Polarity: Not set*		
No of events	n = 14	n = 15
Instrumental birth *Polarity: Not set*		
No of events	n = 22	n = 19
Unassisted vaginal birth *Polarity: Not set*		
No of events	n = 177	n = 155
No of events	n = 177	n = 155

Augensen 1987		
Risk of bias assessment		
Section	**Question**	**Answer**
Selection bias	Random sequence generation	Low risk of bias *(List of random numbers)*
	Allocation concealment	Low risk of bias *(random number list was inaccessible to participating physicians)*
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline - No block randomisation)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 6: Evidence tables – Baev 2017

Baev 2017	
Bibliographic Reference	Baev, Oleg R.; Rumyantseva, Valentina P.; Tysyachnyu, Oleg V.; Kozlova, Olga A.; Sukhikh, Gennady T.; Outcomes of mifepristone usage for cervical ripening and induction of labour in full-term pregnancy. Randomized controlled trial; European journal of obstetrics, gynecology, and reproductive biology; 2017; vol. 217; 144-149
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Moscow, Russia
Study setting	Department of Obstetrics Research Centre
Study dates	January 2014-2015
Sources of funding	None stated
Duration of follow-up	Not applicable
Inclusion criteria	Age between 18 and 45 years; singleton live pregnancies; cephalic presentation, at least 40 + 4 weeks gestation; unripe uterine cervix at the moment of enrolment (Bishop score less than 8), intact membranes, no contraindication for vaginal delivery and no contraindication for labour induction with mifepristone, prostaglandin or oxytocin, informed written consent before participation in the study.
Exclusion criteria	Myoma/uterine anomaly, parity greater than 3, severe hypertension/ preeclampsia, prior caesarean deliveries, diabetes, impaired renal, adrenal, or hepatic function, fetal malformations, breech presentation, estimated fetal weight (>4500 or <2500 g), any concerns about the well-being of the fetus, any medical indication for scheduled caesarean delivery

Baev 2017	
Sample size	N= 156, 40+4 weeks n = 76 (74 analysed), 42 weeks n= 78 (75 analysed)
Baseline characteristics	40+4 weeks 1. age - mean 28.72, SD 4.89 years 2. nulliparous - n = 63/74, 85.14% 3. GA at enrollment - mean 285.35 , SD 0.93 days 4. BMI - mean 27.08, SD 4.03 5. IVF - NR 6. Ethnicity - NR 42 weeks 1. age - mean 28.07, SD 4.27 years 2. nulliparous - n = 58/75, 77.33% 3. GA at enrollment - mean 285.47, SD 1.3 days 4. BMI - mean 27.03, SD 3.38 5. IVF – NR 6. Ethnicity - NR
Intervention(s)	Induction at 40 weeks: Women randomized to induction of labour received one tablet mifepristone 200 mg per os at the moment of enrolment. Then the patients were reviewed for Bishop score after 24 h. Any progression of associated conditions was also noted. If the Bishop score was still less than 8, women received second dose of mifepristone 200 mg and were reviewed for Bishop score again after 24 h. If after 72 h from the first dose of mifepristone the Bishop score had not changed, the induction attempt was categorized as failed. If after second dose of mifepristone Bishop score was 6–7, women received an initial dose of 0,5 mg of dinoprostone followed by a further 0,5 mg of dinoprostone after 6 h. Dinoprostone used in gel form and was inserted into the cervical canal in accordance to manufacturer recommendations. Before each dose of mifepristone or dinoprostone fetal wellbeing was evaluated by clinical examination and cardiotocography. If at any of examinations the Bishop score was 8 or greater, the participant was transferred to the labour ward for artificial rupture of membranes (ARM) and continued monitoring. Induction at 42 weeks: Women in the expectant management group were scheduled for routine appointments, except examination for Bishop score after 24 and 48 h. All of them were evaluated for maternal and fetal wellbeing, including cardiotocography. The vast majority of women of this group entered the labour spontaneously no later than 42 weeks of gestation. The remaining were induced in labour by dinoprostone. If at 42 weeks of gestation women were still undelivered with unripe cervix expectant management was categorized as failed.
Timing of birth (as reported by study)	40+4 weeks 1. GA at delivery - mean 288.07, SD 2.36 days 2. failed induction/expectant - n 4/74 (5.41%) 42 weeks 1. GA at delivery - mean 289.21, SD 2.14 days 2. failed induction/expectant - n 2/75 (2.67%)
Study arms	
40+4 weeks (N = 74)	
42 weeks (N = 75)	
Outcomes	

	40+4 weeks	**42 weeks**
	N = 74	N = 75
NICU admission		

Baev 2017		
Polarity: Not set		
No of events	n = 4 ; % = 5.41	n = 3 ; % = 4
C-section *Polarity: Not set*		
No of events	n = 25 ; % = 33.78	n = 19 ; % = 25.33
Instrumental birth *Polarity: Not set*		
No of events	n = 2 ; % = 2.7	n = 0 ; % = 0
Vaginal delivery Including instrumental *Polarity: Not set*		
No of events	n = 49 ; % = 66.22	n = 56 ; % = 74.67

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(computer generated list of random numbers in permuted blocks)*
	Allocation concealment	Low risk of bias *(concealed in sequentially numbered, opaque, sealed enveloped)*
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias *(ITT analysis)*
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 7: Evidence tables – Bergsjo 1989

Bergsjo 1989	
Bibliographic Reference	Bergsjo, P.; Huang, G. D.; Yu, S. Q.; Gao, Z. Z.; Bakketeig, L. S.; Comparison of induced versus non-induced labor in post-term pregnancy. A randomized prospective study; Acta obstetricia et gynecologica Scandinavica; 1989; vol. 68 (no. 8); 683-7
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Wuhan, China (study group based in Norway)

Bergsjo 1989	
Study setting	Hospital obstetric department
Study dates	July 1982 to 1984
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	Voluntary participation, including pregnant women of all parities who were not in labour and had intact membranes upon examination at or following 42 completed weeks (294 days). Normal menstrual cycle (28 +/- 4 days) and accurate recall of LMP, and normal pregnancies without significant risk factors.
Exclusion criteria	Not reported
Sample size	N = 188
Baseline characteristics	42 weeks 1. Age - mean 26.2 years 2. Nulliparity - 6/94 3. Bishop score - NR 4. BMI/weight - NR 5. Ethnicity - NR 6. IVF - NR 43 weeks 1. Age - 27.8 years 2. Nulliparity - 12/94 3. Bishop score - NR 4. BMI/weight - NR 5. Ethnicity - NR 6. IVF - NR
Intervention(s)	Labour was induced by stripping of the membranes, followed by oxytocin infusion (5 IU in 500 ml 5% glucose and Ringer). Infusion rate was regulated according to response. The membranes were ruptured artificially if the cervix was dilated 3 cm or more. If less, the infusion was continued as long as there was some progress of labour. Following clinical examination and upon giving informed consent the patients were allocated to one of two groups, according to a list of random numbers. Women in group I underwent labour induction, whereas those in group 2 had no special intervention for one week unless complications arose. At and after 43 completed weeks, labour was induced according to clinical judgement. Due to poor transportation facilities, all women in group 2 stayed in the hospital while waiting, which ensured close daily clinical surveillance. Fetal movement test, atropine test, ultrasound and urinary estriol excretion tests were also employed.
Timing of birth (as reported by study)	42 weeks 1. GA at birth - range 294-309 days 2. Number induced - 77/86 3. Spontaneous labour - 8/94 43 weeks 1. GA at birth - range 294-309 days 2. Number induced - 34 (for fetal distress)/86 3. Spontaneous labour - 60/94

Bergsjo 1989

Study arms

42 weeks (N = 94)

43 weeks (N = 94)

Outcomes

	42 weeks	43 weeks
	N = 94	N = 94
Perinatal death *Polarity: Not set*		
No of events	n = 1	n = 2
C-section *Polarity: Not set*		
No of events	n = 27	n = 39
Instrumental birth *Polarity: Not set*		
No of events	n = 21	n = 25
Vaginal unassisted birth *Polarity: Not set*		
No of events	n = 46	n = 30
Aspiration pneumonia *Polarity: Not set*		
No of events	n = 4	n = 8

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(list of random numbers)*
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 8: Evidence tables – Chanrachakul 2003

Chanrachakul 2003	
Bibliographic Reference	Chanrachakul, Boonsri; Herabutya, Yongyoth; Postterm with favorable cervix: is induction necessary?; European journal of obstetrics, gynecology, and reproductive biology; 2003; vol. 106 (no. 2); 154-7
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Thailand
Study setting	Dept of Obstetrics and Gynaecology, Ramathibodi Hospital
Study dates	October 1998 - May 2000
Sources of funding	Ramathibodi Hospital Research Grant no. 2/2542
Duration of follow-up	Not applicable
Inclusion criteria	Pregnant women, GA 280-287 days confirmed by routine ultrasound at 18-22 weeks. Low risk pregnancy. Informed consent given. Bishop score>/=6
Exclusion criteria	Any medical or obstetric complication.
Sample size	N = 249 randomised
Baseline characteristics	41+3 weeks 1. Age - mean 27.1, SD 4.5 years 2. Nulliparous - 84/124 3. Bishop score - mean 6.9, SD 0.8 4. GA at enrolment mean 290.5, SD 1.3 days 5. BMI/weight - NR 6. Ethnicity - NR 7. IVF - NR 44 weeks 1. Age - mean 26.7, SD 5.3 years 2. Nulliparous - 87/125 3. Bishop score - mean 6.8, SD 0.9 4. GA at enrolment mean 290.4, SD 1.4 days 5. BMI/weight - NR 6. Ethnicity - NR 7. IVF - NR
Intervention(s)	Induction at 41+3 weeks (290 days): sent for induction on day of randomisation. Amnitotomy performed and oxytocin started if inadequate uterine contraction after 2 hours. Oxytocin started at 1-2mU/min and increased at 30mins intervals to 40mU.min. Expectant to 44 weeks (308 days): evaluated once a week with a nonstress test (NST) and ultrasonographic estimation of amniotic fluid index (AFI), and twice weekly after 43 weeks. Spontaneous labour was awaited, induction performed if (1) NST nonreactive, (2) AFI <5cm, (3) medical or obstetric complication, (4) reached 308 completed days (44 completed weeks). FHR and uterine contraction recorded by midwife every 30mins in 1st stage, and 15mins in 2nd stage of labour. Continuous FHR monitoring if abnormalities detected. Failed induction defined as inability to achieve active phase despite adequate oxytocin for at least 6hrs. Decision for c-section made by obstetrician in charge of labour ward.

Chanrachakul 2003	
Timing of birth (as reported by study)	41+3 weeks - GA at birth NR, number induced = 123/124 44 weeks - GA at birth 95% delivered within one week, 100% by day 9 (299 days), none induced
Study arms	
41+3 weeks (N = 124)	
44 weeks (N = 125)	

Outcomes

	41+3 weeks	44 weeks
	N = 124	N = 125
C-section *Polarity: Not set*		
No of events	n = 33	n = 27
Vaginal delivery Unclear if instrumental *Polarity: Not set*		
No of events	n = 91	n = 98
NICU admission *Polarity: Not set*		
No of events	n = 1	n = 0

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(computer generated numbers)*
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 9: Evidence tables – Cole 1975

Cole 1975	
Bibliographic Reference	Cole, R. A.; Howie, P. W.; Macnaughton, M. C.; Elective induction of labour. A randomised prospective trial; Lancet (London, England); 1975; vol. 1 (no. 7910); 767-70
Study details	

Cole 1975	
Study type	Randomised controlled trial (RCT)
Study location	Glasgow, UK
Study setting	Royal Maternity Hospital, Glasgow
Study dates	Not reported
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	Primigravidae aged 18-30 years or women of 1, 2, or 3 parity aged 18-35 years who had had normal pregnancies without any previous obstetric abnormality. Other criteria were: certainty of the date of the last menstrual period, a regular menstrual cycle, and an early examination which had shown the uterine size to be consistent with the period of amenorrhoea.
Exclusion criteria	Not reported
Sample size	N=237
Baseline characteristics	39-40 weeks 1. Age - mean 23.9, SD 3.2 years 2. Primigavida - 52/111 3. BMI/weight - NR 4. Ethnicity - NR 5. IVF - NR 41 weeks 1. Age - mean 24.3, SD 3.7 years 2. Primigavida - 53/117 3. BMI/weight - NR 4. Ethnicity - NR 5. IVF - NR
Intervention(s)	Induction 39-40 weeks: labour induced between 39 and 40 weeks. Induction 41 weeks (control): left to await the onset of spontaneous labour. In the control group, induction was performed at 41 weeks if labour had not occurred by that time, although if some obstetric complication supervened before then, induction was carried out as necessary. The method of induction of labour was forewater amniotomy followed immediately by oxytocin at increasing doses using the Cardiff pump. An experienced midwife assessed uterine activity by abdominal palpation, and, when satisfactory contractions were achieved, the oxytocin dose was stabilised and continued until 1 hour after delivery of the placenta.
Timing of birth (as reported by study)	39-40 weeks 1. GA at birth - all between 39 and 40 weeks 2. Number induced - 100/111 (11 had spontaneous labour) 41 weeks 1. GA at birth - from term date -10 days to +13 days Number induced - 32/117 as reached 41 weeks, 22/117 due to obstetric complications <41 weeks

Cole 1975			
Study arms			
39-40 weeks (N = 111)			
41 weeks (N = 117)			
Outcomes			
		39-40 weeks	**41 weeks**
		N = 111	N = 117
Perinatal death *Polarity: Not set*			
No of events		n = 0	n = 1
C-section *Polarity: Not set*			
No of events		n = 5	n = 9
Instrumental birth *Polarity: Not set*			
No of events		n = 34	n = 26
Vaginal unassisted/spontaneous *Polarity: Not set*			
No of events		n = 72	n = 82
Risk of bias assessment			
Section	**Question**	**Answer**	
Selection bias	Random sequence generation	Unclear risk of bias	
	Allocation concealment	Unclear risk of bias	
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*	
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*	
Attrition bias	Incomplete outcome data	Low risk of bias	
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*	
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*	
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported	
	Directness	Directly applicable	

Table 10: Evidence tables – Egarter 1989

Egarter 1989	
Bibliographic Reference	Egarter, C.; Kofler, E.; Fitz, R.; Husslein, P.; Is induction of labor indicated in prolonged pregnancy? Results of a prospective randomised trial; Gynecologic and obstetric investigation; 1989; vol. 27 (no. 1); 6-9
Study details	
Study type	Randomised controlled trial (RCT)

Egarter 1989	
Study location	Vienna, Austria
Study setting	Hospital
Study dates	Not reported
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	Healthy pregnant women with singleton pregnancies in cephalic presentation reaching their estimated date of confinement. Length of pregnancy had to be established by early ultrasound; membranes had to be intact and the cervix favourable for induction (modified Bishop score of more than 4)
Exclusion criteria	Any pregnancy carrying fetal or maternal risk factors based on history, gynecological/obstetrical investigation, cardiotocogram and routine lab.
Sample size	Randomised N=345
Baseline characteristics	40 weeks - nulliparity - n=99 42 weeks - nulliparity - n=88 BMI/weight - NR, Ethnicity - NR, IVF - NR
Intervention(s)	In group A, labour was induced by means of vaginal application of 3-mg PGEi-containing vaginal tablets (Prostin E2 Vaginal Tablets, Upjohn Ltd., Crawley, Sussex) with a repeat dose of another 3 mg at 6 h if labour did not start or contractions were judged to be inadequate. If the patient had still not given birth at 24 h, but the cervix was at least 3 cm dilated, she received another treatment course. In case the cervical score did not improve to 3 cm dilatation, no further induction attempt was performed. In group B the spontaneous onset of labour was awaited until the completion of 42 weeks of amenorrhea. Cardiotocographic evaluation of fetal well-being was performed at 2- to 3-day intervals. Amniotomy was only performed when the cervical dilatation exceeded 5 cm; at this time an electrode was placed on the fetal head for internal cardiographie monitoring routinely. The infusion of oxytocin was added only to support labour once it had been fully established.
Timing of birth (as reported by study)	40 weeks - number induced - 80-96% success 42 weeks - n = 7 (undelivered after the 294 days)
Study arms	
40 weeks (N = 157) 280 days	
42 weeks (N = 156) 294 days	
Outcomes	

	40 weeks	**42 weeks**
	N = 157	N = 156
Perinatal death *Polarity: Not set*		
No of events	n = 0	n = 1
C-section *Polarity: Not set*		
No of events	n = 2	n = 3
Instrumental birth		

Egarter 1989		
Polarity: Not set		
No of events	n = 4	n = 3

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Unclear risk of bias
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 11: Evidence tables – Gelisen 2005

Gelisen 2005	
Bibliographic Reference	Gelisen, O.; Caliskan, E.; Dilbaz, S.; Dilbaz, B.; Ozdas, E.; Haberal, A.; Induction of labor with three different techniques at 41 weeks of gestation or spontaneous follow-up until 42 weeks in women with definitely unfavorable cervical scores; European Journal of Obstetrics and Gynecology and Reproductive Biology; 2005; vol. 120 (no. 2); 164-169
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Hospital
Study dates	Not reported
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	(1) singleton live pregnancy with vertex presentation and intact membranes, (2) gestational age 287 +/- 1 days (41 completed weeks of gestation confirmed by first-trimester ultrasound), (3) Bishop score [8] of <5 (assigned by E.O.), (4) absence of spontaneous uterine contractions (i.e., fewer than four spontaneous contractions per

Gelisen 2005	
	hour), (5) estimated fetal body weight < 4500 g, (6) a reactive nonstress test (NST), and (7) amniotic fluid index >=5 cm
Exclusion criteria	Known hypersensitivity to the use of prostaglandins, previous caesarean delivery or other uterine surgery, noncephalic presentation, body mass index (BMI) >= 30 before conception, parity >=5, any previous attempt at induction of labour during the current pregnancy, and low-lying placenta. In our institution, labour is induced at 40 weeks of pregnancy in women with known diabetes mellitus, so that no patients with diabetes were included in the study
Sample size	N = 600
Baseline characteristics	Age, mean 24-26 years 41 weeks 1. Nulliparity - 144/300 2. Bishop score - Mean 1.5-1.8, SD 1 3. BMI - Mean 27-29, SD 3-5 42 weeks 1. Nulliparity - 135/300 2. Bishop score - Mean 1.5, SD 1 3. BMI - Mean 25.6, SD 5
Intervention(s)	Expectant (42 weeks): Spontaneous follow-up (follow-up group, N = 300) involved nonstress testing and amniotic fluid measurement twice weekly and biophysical scoring on a single occasion 3–5 days after randomization. If patients did not give birth until the 294th day (42 completed weeks) of gestation (n = 73) induction of labour was attempted with 50 mg vaginal misoprostol every 6 h. If misoprostol failed to induce labour within 24 h caesarean delivery was performed. Induction (41 weeks, 287 days): Misoprostol/Foley/Oxytocin as induction method. Membrane sweeping was routinely performed before misoprostol induction (n = 93/100), oxytocin induction (n = 88/100), or Foley catheter insertion (n = 92/100), and before labour induction in the follow-up group (n = 73/73). Early amniotomy was performed in all patients when the cervix was dilated to >=3 cm.
Timing of birth (as reported by study)	41 weeks - timing of birth - mean 287 days 42 weeks - timing of birth - mean 290 days, SD 3.2, 34/300 induced due to obstetric complications and 73/300 induced as undelivered at 42 complete weeks (294 days)
Study arms	
41 weeks (N = 300)	
42 weeks (N = 300)	
Outcomes	

	41 weeks	42 weeks
	N = 300	N = 300
Perinatal death *Polarity: Not set*		
No of events	n = 0	n = 1
C-section *Polarity: Not set*		
No of events	n = 58	n = 66
Vaginal delivery Unclear if any instrumental *Polarity: Not set*		
No of events	n = 242	n = 234

Gelisen 2005		
NICU admission *Polarity: Not set*		
No of events	n = 13	n = 15
MAS *Polarity: Not set*		
No of events	n = 5	n = 12

Risk of bias assessment		
Section	**Question**	**Answer**
Selection bias	Random sequence generation	Unclear risk of bias
	Allocation concealment	Low risk of bias *(sealed opaque envelope)*
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 12: Evidence tables – Grobman 2018

Grobman 2018	
Bibliographic Reference	Grobman, W. A.; Rice, M. M.; Reddy, U. M.; Tita, A. T. N.; Silver, R. M.; Mallett, G.; Hill, K.; Thom, E. A.; El-Sayed, Y. Y.; Perez-Delboy, A.; Rouse, D. J.; Saade, G. R.; Boggess, K. A.; Chauhan, S. P.; Iams, J. D.; Chien, E. K.; Casey, B. M.; Gibbs, R. S.; Srinivas, S. K.; Swamy, G. K.; Simhan, H. N.; MacOnes, G. A.; Labor induction versus expectant management in low-risk nulliparous women; New England Journal of Medicine; 2018; vol. 379 (no. 6); 513-523
Study details	
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Multiple hospitals participating in the Maternal–Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development
Study dates	March 2014 to August 2017
Sources of funding	Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; ARRIVE ClinicalTrials.gov number, NCT01990612
Duration of follow-up	Not applicable

Grobman 2018	
Inclusion criteria	Nulliparous - no previous pregnancy beyond 20 weeks 0 days; Singleton gestation. Twin gestation reduced to singleton, either spontaneously or therapeutically, is not eligible unless the reduction occurred before 14 weeks 0 days project gestational age. Gestational age at randomization between 38 weeks 0 days and 38 weeks 6 days inclusive based on clinical information and evaluation of the earliest ultrasound as described below
Exclusion criteria	• Projected gestational age at date of first ultrasound is > 20 weeks 6 days • Plan for induction of labour prior to 40 weeks 5 days • Plan for caesarean delivery or contraindication to labour • Breech presentation • Signs of labour (regular painful contractions with cervical change) • Fetal demise or known major fetal anomaly • Heparin or low-molecular weight heparin use during the current pregnancy • Placenta previa, accreta, vasa previa • Active vaginal bleeding greater than bloody show • Ruptured membranes • Cerclage in current pregnancy • Known oligohydramnios, defined as amniotic fluid index < 5 cm or maximal vertical pocket < 2 cm • Fetal growth restriction, defined as EFW < 10th percentile • Known HIV positivity because of modified delivery plan • Major maternal medical illness associated with increased risk for adverse pregnancy outcome (e.g. any diabetes mellitus, lupus, any hypertensive disorder, cardiac disease, renal insufficiency) • Refusal of blood products • Participation in another interventional study that influences management of labour at delivery or perinatal morbidity or mortality • Delivery planned elsewhere at a non-Network site
Study arms	
39+0 to 39+4 (N = 3062)	
40+5 to 42+2 (N = 3044)	

Outcomes

	39+0 to 39+4	**40+5 to 42+2**
	N = 3059	N = 3037
Maternal death/uterine rupture *Polarity: Not set*		
No of events	n = 0	n = 0
Perinatal death *Polarity: Not set*		
No of events	n = 2	n = 3
C-section *Polarity: Not set*		
No of events	n = 569	n = 674
Instrumental (operative vaginal) birth *Polarity: Not set*		
No of events	n = 222	n = 258
NICU admission *Polarity: Not set*		
No of events	n = 358	n = 394
HIE		

Grobman 2018		
Polarity: Not set		
No of events	n = 14	n = 20
MAS *Polarity: Not set*		
No of events	n = 17	n = 26
Maternal satisfaction Labor Agentry Scale (29 to 203) *Polarity: Higher values are better*		
6-96 hours post delivery p<0.001		
Sample Size	n = 2932	n = 2876
MedianIQR	168 (148 to 183)	164 (143 to 181)
4-8 weeks post delivery p=0.01		
Sample Size	n = 2710	n = 2650
MedianIQR	176 (157 to 189)	174 (154 to 188)

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias
	Allocation concealment	Low risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Low risk of bias *(protocol available on clinicaltrials.gov)*
Other sources of bias	Any other sources of bias	Low risk of bias
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 13: Evidence tables – Heimstad 2007

Heimstad 2007	
Bibliographic Reference	Heimstad, R.; Skogvoll, E.; Mattsson, L. A.; Johansen, O. J.; Eik-Nes, S. H.; Salvesen, K. A.; Induction of labor or serial antenatal fetal monitoring in postterm pregnancy: A randomized controlled trial; Obstetrics and Gynecology; 2007; vol. 109 (no. 3); 609-617
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Norway
Study setting	St.Olavs Hospital, Trondheim University Hospital
Study dates	September 2002 to July 2004

Heimstad 2007	
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	Women with singleton pregnancies who had had their routine ultrasound scan and delivery at St. Olavs Hospital and who spoke fluent Norwegian. The study was confined to pregnancies with a cephalic presentation with no history of prelabour rupture of membranes
Exclusion criteria	Not reported
Sample size	N = 508
Baseline characteristics	41 weeks 1. Nulliparity - 110/254 2. Bishop score - NR 3. BMI - mean 24.7, SD 4.2 4. IVF - NR 5. Ethnicity - caucasian - 98% 42 weeks 1. Nulliparity - 124/254 2. Bishop score - NR 3. BMI - mean 24.7, SD 4.3 4. IVF - NR 5. Ethnicity - caucasian - 98%
Intervention(s)	Induction: immediate induction of labour (booked the following day), women were seen at 289+/-2 days. Delayed intervention (300 days): For women assigned to continued antenatal assessment, induction of labour was arranged if the cardiotocogram recordings were abnormal, the estimated fetal weight was less than 2 standard deviations, or oligohydramnios was found (amniotic fluid index less than 5 cm or single deepest pocket less than 2 cm). If these investigations were reassuring, they were reassessed every third day until spontaneous delivery occurred or until labour was induced on day 300. Women who had a favourable cervix (Bishop score 6 or more) were induced by amniotomy followed by oxytocin (Syntocinon, Novartis, EastHanover, NJ) infusion. Women with an unfavourable cervix (Bishop score less than 6) had cervical priming using misoprostol (prostaglandin E1 analog, Cytotec, Searle, Chicago, IL, 50 mcg pessary encased in a gelatin capsule) at 6-hour intervals in the posterior fornix. A maximum of four doses was given in a 24-hour period, and cervical priming was continued for a maximum of 2 days. Once the cervix was favourable, amniotomy and oxytocin infusion were used. Women with a uterine scar were induced with 0.5 mg dinoprostone (prostaglandin E2, Minprostin endocervical gel, Pfizer, New York, NY) given intracervically every 12 hours.
Timing of birth (as reported by study)	41 weeks 1. GA at birth - mean 289 days, SD 0.7 2. Number induced 215/254

Heimstad 2007

	42 weeks 1. GA at birth - mean 289 days, SD 0.9 2. Number induced - 19/254 at day 300, 59/254 for medical reasons

Study arms

41 weeks (N = 254)

42 weeks (N = 254)

Outcomes

	41 weeks	42 weeks
	N = 254	N = 254
Perinatal death *Polarity: Not set*		
No of events	n = 0	n = 0
C-section *Polarity: Not set*		
No of events	n = 28	n = 33
Operative vaginal birth *Polarity: Not set*		
No of events	n = 32	n = 27
NICU admission *Polarity: Not set*		
No of events	n = 14	n = 18
Meconium in airway *Polarity: Not set*		
No of events	n = 7	n = 5

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(computerised randomisation)*
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	High risk of bias *(Comparable at baseline, but used block randomisation in unblinded trial (blocks of 16, no stratification))*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 14: Evidence tables – Herabutya 1992

Herabutya 1992	
Bibliographic Reference	Herabutya, Y.; Prasertsawat, P. O.; Tongyai, T.; Isarangura Na Ayudthya, N.; Prolonged pregnancy: the management dilemma; International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics; 1992; vol. 37 (no. 4); 253-8
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Thailand
Study setting	Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital
Study dates	July 1987 to January 1991
Sources of funding	This study was supported by Ramathibodi Hospital Research Fund Grant 1988
Duration of follow-up	Not applicable
Inclusion criteria	(1) a normal last menstrual period where the date of onset was certain and the cycles were regular and monthly; (2) no history of recent oral contraception usage, amenorrhea, irregular menstruations for at least 3 months; (3) booked for confinement before 20 weeks and with a uterine size consistent with menstrual dates throughout. Only low-risk patients whose pregnancies extended beyond 294 complete days were included in this study.
Exclusion criteria	Bishop score more than 6 (favourable cervix)
Sample size	N = 108
Baseline characteristics	42 weeks 1. Age - mean 27.4, SD 4.1 2. Nulliparous - n = 51/57 3. Bishop score - NR 4. BMI/weight - NR 5. Ethnicity - NR 6. IVF - NR 44 weeks 1. Age - mean 27.1, SD 4.3 2. Nulliparous - n = 41/51 3. Bishop score - NR 4. BMI/weight - NR 5. Ethnicity - NR 6. IVF - NR
Intervention(s)	Induction group: After confirmation of the cervical score by one of the authors, patients randomized to the induction group underwent immediate cervical ripening with prostaglandin gel administered on an outpatient basis. The prostaglandin gel was prepared using six tablets of prostaglandin E2 (Prostarmon E, May and Baker), 0.5 mg each, were crushed to powder in a sterile container and mixed with 5 ml of hydro-ethyl cellulose (K-Y Jelly, Johnson and Johnson). The prostaglandin E2 (PGE,) gel was applied intracervically. These patients were allowed to be ambulatory under routine nursing observation.

Herabutya 1992	
	Monitoring group: antepartum fetal testing group underwent a nonstress test (NST) once weekly, and then 2/week from 43 weeks gestation. Patients in the antepartum testing group underwent induction of labour only if there were (1) abnormalities on antepartum fetal testing such as a nonreactive nonstress test, or variable decelerations on nonstress testing, (2) the Bishop score become more than 6, (3) on reaching 44 completed weeks of gestation.
Timing of birth (as reported by study)	GA at birth not reported for either arm, 21/51 induced in the 44 weeks arm
Study arms	
42 weeks (N = 57)	
44 weeks (N = 51)	

Outcomes

	42 weeks	**44 weeks**
	N = 57	N = 51
Perinatal death *Polarity: Not set*		
No of events	n = 0	n = 1
C-section *Polarity: Not set*		
No of events	n = 27	n = 24
Instrumental birth *Polarity: Not set*		
No of events	n = 11	n = 9
Spontaneous/unassisted delivery Reported as spontaneous delivery *Polarity: Not set*		
No of events	n = 19	n = 18
SCBU admission *Polarity: Not set*		
No of events	n = 1	n = 4

Risk of bias assessment

Section	**Question**	**Answer**
Selection bias	Random sequence generation	Unclear risk of bias
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*

Herabutya 1992		
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 15: Evidence tables – Keulen 2019

Keulen 2019	
Bibliographic Reference	Keulen, J. K. J.; Bruinsma, A.; Kortekaas, J. C.; Van Dillen, J.; Bossuyt, P. M. M.; Oudijk, M. A.; Duijnhoven, R. G.; Van Kaam, A. H.; Vandenbussche, F. P. H. A.; Van Der Post, J. A. M.; Mol, B. W.; De Miranda, E.; Induction of labour at 41 weeks versus expectant management until 42 weeks (INDEX): Multicentre, randomised non-inferiority trial; Obstetrical and Gynecological Survey; 2019; vol. 74 (no. 7); 381-383
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Amsterdam
Study setting	123 primary care midwifery practises and 45 hospitals in The Netherlands
Study dates	May 2012 to March 2016
Sources of funding	This study was supported by a grant from the Netherlands Organisation for Health Research and Development ZonMw (grant No 171202008)
Duration of follow-up	Not applicable
Inclusion criteria	Low risk, uncomplicated singleton pregnancy with the child in a stable cephalic position at a certain gestational age of 40 weeks+5 days to 41 weeks+0 days and no contraindications to expectant management until 42 weeks.
Exclusion criteria	Age of 16 weeks. Exclusion criteria for the study were age younger than 18 years, ruptured membranes or in labour, or both, non-reassuring fetal status (eg, no fetal movements, or abnormal fetal heart rate and/or expected intrauterine growth restriction), known fetal abnormalities (including abnormal karyotype) that could influence perinatal outcome, contraindications to induction (including previous caesarean section), or contraindications to expectant management (eg, pregnancy induced hypertension).
Study setting	123 primary care midwifery practises and 45 hospitals in The Netherlands
Study dates	May 2012 to March 2016
Sources of funding	This study was supported by a grant from the Netherlands Organisation for Health Research and Development ZonMw (grant No 171202008)
Duration of follow-up	Not applicable
Inclusion criteria	Low risk, uncomplicated singleton pregnancy with the child in a stable cephalic position at a certain gestational age of 40 weeks+5 days to 41 weeks+0 days and no contraindications to expectant management until 42 weeks.
Exclusion criteria	Age of 16 weeks. Exclusion criteria for the study were age younger than 18 years, ruptured membranes or in labour, or both, non-reassuring fetal status (eg, no fetal movements, or abnormal fetal heart rate and/or expected intrauterine growth restriction), known fetal abnormalities (including abnormal karyotype) that could influence perinatal outcome, contraindications to induction (including previous

Keulen 2019	
	caesarean section), or contraindications to expectant management (eg, pregnancy induced hypertension).
Sample size	Randomised N=1815; analysed N= 1801
Baseline characteristics	41 weeks 1. Age - mean 30.6, SD 4.8 years 2. Nulliparous - 457/900 3. Bishop score <6 at study entry - 670/900, missing 112 4. BMI <25 - 62% 5. BMI 25-30 - 25.6% 6. BMI >/=30 - 9.9% 7. IVF - NR 8. Ethnicity - White - 86.6% 9. Ethnicity - Other - 13.4% 42 weeks 1. Age - mean 30.2, SD 4.6 years 2. Nulliparous - 511/901 3. Bishop score <6 at study entry - 659/901, missing 125 4. BMI <25 - 60.2% 5. BMI 25-30 - 25.4% 6. BMI >/=30 - 13.0% 7. IVF - NR 8. Ethnicity - White - 85.1% 9. Ethnicity - Other - 14.9%
Intervention(s)	41 weeks: Women allocated to induction were scheduled for the procedure at 41 weeks+0 days-41 weeks+1 day. All women were primed or induced, or both according to local protocols. Women with a Bishop score < 6 received cervical priming with prostaglandin E1 (misoprostol, oral or vaginal), prostaglandin E2 (dinoprostone), Foley catheter or double balloon catheter, or a combination of these until amniotomy could be performed. Amniotomy was followed by intravenous oxytocin if required. 42 weeks: expectant management awaited spontaneous onset of labour until 42 weeks+0 days in their initial care setting, with monitoring according to local protocol. Monitoring typically involved a combination of cardiotocography, and sonographic assessment of amniotic fluid in secondary care at 41- 42 weeks. Women in the expectant management group with ongoing pregnancies were scheduled for induction at 42 weeks+0 days in secondary care, following a similar induction protocol to the intervention group. In both groups, labour was induced if the maternal or fetal condition was no longer reassuring—for example, reduced fetal movements, non-optimal cardiotocography findings, or oligohydramnios. Labour was also induced if prelabour rupture of membranes had occurred more than 24 hours previously or meconium stained amniotic fluid was present
Timing of birth (as reported by study)	41 weeks 1. GA at birth - median 287 days (IQR 287-288) 2. Number induced - 640/900 per protocol, 43/900 induced later than 41+2 weeks 42 weeks 1. GA at birth - median 289 days (IQR 287-292)

Keulen 2019

2. Number induced - 237/901 induced, 85/901 for post-term, 65/901 for medical reasons

Study arms

41 weeks (N = 900)

42 weeks (N = 901)

Outcomes

	41 weeks	42 weeks
	N = 900	N = 901
Maternal death/uterine rupture *Polarity: Not set*		
No of events	n = 0	n = 0
Perinatal death Stillbirth and neonatal death postpartum *Polarity: Not set*		
No of events	n = 1	n = 2
C-section *Polarity: Not set*		
No of events	n = 97	n = 97
Vaginal operative birth *Polarity: Not set*		
No of events	n = 93	n = 108
Spontaneous/unassisted delivery Reported as vaginal spontaneous birth *Polarity: Not set*		
No of events	n = 710	n = 696
MAS *Polarity: Not set*		
No of events	n = 0	n = 2

	41 weeks	42 weeks
	N = 899	N = 899
NICU admission *Polarity: Not set*		
No of events	n = 3	n = 8

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(web-based programme using randomly permuted block sizes of 4 and 2, stratified by centre)*
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*

Keulen 2019		
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Low risk of bias *(protocol checked)*
Other sources of bias	Any other sources of bias	High risk of bias *(Comparable at baseline except for distribution of nulliparous women, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 16: Evidence tables – Leijon 1979

Leijon 1979	
Bibliographic Reference	Leijon, I.; Finnstrom, O.; Hedenskog, S.; Ryden, G.; Tylleskar, J.; Spontaneous labour and elective induction--a prospective randomized study. Behavioural assessment and neurological examination in the newborn period; Acta paediatrica Scandinavica; 1979; vol. 68 (no. 4); 553-60
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Linkoping & Motala, Sweden
Study setting	Departments of Paediatrics and Obstetrics and Gynaecology, University Hospital, Linkoping and the Women's Clinic, Central Hospital, Motala
Study dates	Not reported
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	1. Maternal age between 18 and 30 years for primiparae and 18 to 35 for multiparae. 2. The last menstrual period normal and known. Regular menstrual periods before the actual pregnancy. Women using hormonal contraceptives should have had at least three normal periods after completed medication. 3. Previous pregnancies and deliveries normal with birth weights between 3 000 and 4000 grams. 4. Normal symphysis-fundus distance and weight gain according to gravidogram. 5. The present pregnancy normal and the foetus in vertex presentation. 6. Normal pelvic outlet according to clinical examination.
Exclusion criteria	If a pelvic score of at least 5 points for primiparae and at least 4 points for multiparae was found, the patient was invited to participate in the study
Sample size	N=112 randomised, N=80 analysed
Baseline characteristics	Age - mean 24.5, SD 4.0 years

Leijon 1979	
	Intervention 1. Nulliparity - 18/41 2. Bishop score - NR 3. BMI/weight - NR 4. Ethnicity - NR 5. IVF - NR Delayed intervention 1. Nulliparity - 18/39 2. Bishop score - NR 3. BMI/weight - NR 4. Ethnicity - NR 5. IVF - NR
Intervention(s)	In group I deliveries were induced and in group 2 deliveries were allowed to start spontaneously. Group 1: The date of planned delivery was decided to +/-2 days from the date of expected delivery (40 weeks). On the morning of the day of planned delivery, amniotomy was performed through an amnioscope and a catheter for registration of intraamniotic pressure was inserted. A scalp electrode was applied on the foetal head for registration of foetal heart frequency. Group 2: if pregnancy was prolonged more than 14 days from the date of estimated delivery (42 weeks), the delivery was induced according to the routine clinical indications in the departments. These patients belonged to the original group.
Timing of birth (as reported by study)	Intervention 1. GA at birth - mean 280, SD 1 days 2. Number induced - not reported Delayed intervention 1. GA at birth - mean 285, SD 4 days 2. Number induced - 3 for prolonged pregnancy
Study arms	
40 weeks (N = 41)	
42 weeks (N = 39)	

Outcomes

	40 weeks	42 weeks
	N = 41	N = 39
Instrumental (vacuum) birth *Polarity: Not set*		
No of events	n = 1	n = 2

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Unclear risk of bias

Leijon 1979		
	Allocation concealment	Unclear risk of bias
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias
Other sources of bias	Any other sources of bias	Low risk of bias
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 17: Evidence tables – Nielsen 2005

Nielsen 2005	
Bibliographic Reference	Nielsen, P. E.; Howard, B. C.; Hill, C. C.; Larson, P. L.; Holland, R. H. B.; Smith, P. N.; Comparison of elective induction of labor with favorable Bishop scores versus expectant management: A randomized clinical trial; Journal of Maternal-Fetal and Neonatal Medicine; 2005; vol. 18 (no. 1); 59-64
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Washington, USA
Study setting	Madigan Army Medical Center, a regional tertiary care teaching center for the United States Armed Forces
Study dates	September 1999 to December 2002
Sources of funding	Not reported
Duration of follow-up	None
Inclusion criteria	Cephalic presentation, singleton gestation, maternal age of greater than 17 years, candidate for vaginal delivery and a semi-favourable cervical Bishop score defined as a score of 5 or greater in nulliparous or 4 or greater in multiparous patients, pregnancy dating criteria were required establishing the patient to be 39 weeks gestation or greater at the time of elective induction
Exclusion criteria	Not reported
Sample size	N = 226
Baseline characteristics	39 weeks 1. Age - mean 24.5, SD 4.3 years 2. Nulliparous - 45/116 3. Bishop score at randomisation - mean 6.5, SD 1.7 4. Weight (lbs) - mean 180.7, SD 31.7 5. Height (inches) - mean 64.8, SD 2.8 6. IVF - NR

Nielsen 2005	
	7. Ethnicity - White - 78% 8. Ethnicity - Black - 8% 9. Ethnicity - Hispanic - 0% 10. Ethnicity - Asian - 6% 11. Ethnicity - other - 8% 42 weeks 1. Age - mean 24.5, SD 4.7 years 2. Nulliparous - 58/110 3. Bishop score at randomisation - mean 6.3, SD 1.4 4. Weight (lbs) - mean 182.6, SD 28.6 5. Height (inches) - mean 65.0, SD 2.6 6. IVF - NR 7. Ethnicity - White - 85% 8. Ethnicity - Black - 8% 9. Ethnicity - Hispanic - 1% 10. Ethnicity - Asian - 5% 11. Ethnicity - other - 1%
Intervention(s)	Induction at 39 weeks: induction (IND) were scheduled within 1 week of randomization, but not prior to 39 weeks gestation (39+0 to 39+6 weeks). The method of induction included amniotomy, oxytocin or both. No prostaglandin cervical ripening agents or mechanical dilators were used. Expectant management (induction at 41 weeks): Patients expectantly managed (EM) were scheduled for weekly follow-up appointments until 41 weeks gestation. Antepartum fetal testing (nonstress testing with amniotic fluid evaluation) was initiated twice weekly for all EM patients who reached 41 weeks gestation and all patients who reached 42 weeks gestation were induced. For induction or augmentation of labour, oxytocin was started at a rate 4 mIU/ min and increased 4 mIU/min every 15–30 min until an adequate contraction pattern was established
Timing of birth (as reported by study)	Induction at 39 weeks 1. GA at birth - mean 3.7, SD 2.8 days 2. Number induced - 93/116 Induction at 42 weeks 1. GA at birth - mean 8.3, SD 5.6 days 2. Number induced - 10/110 (for medical reasons)
Study arms	
39 weeks (N = 116)	
42 weeks (N = 110)	
Outcomes	

	39 weeks	**42 weeks**
	N = 116	N = 110
C-section *Polarity: Not set*		
No of events	n = 8	n = 8
Operative vaginal birth *Polarity: Not set*		
No of events	n = 8	n = 9
Spontaneous/unassisted delivery Reported as SVD *Polarity: Not set*		

Nielsen 2005		
No of events	n = 100	n = 93
NICU admission *Polarity: Not set*		
No of events	n = 0	n = 0

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(computer generated list)*
	Allocation concealment	Low risk of bias *(sequentially numbered, opaque, sealed envelopes)*
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Unclear risk of bias *(No protocol available to assess reporting of outcomes)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 18: - Evidence tables – Ohel 1996

Ohel 1996	
Bibliographic Reference	Ohel, G.; Rahav, D.; Rothbart, H.; Ruach, M.; Randomised trial of outpatient induction of labor with vaginal PGE2 at 40-41 weeks of gestation versus expectant management; Archives of gynecology and obstetrics; 1996; vol. 258 (no. 3); 109-12
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Israel
Study setting	Department of Obstetrics and Gynecology, Poriya Hospital, Tiberias
Study dates	Not reported
Sources of funding	Not reported
Duration of follow-up	Not applicable
Inclusion criteria	Uncomplicated, singleton pregnancies (gestational age had always been verified by early sonography)

Ohel 1996	
Exclusion criteria	Not reported
Sample size	N=200
Baseline characteristics	40 weeks 1. Age - mean 28.9, SD 4.0 years 2. Nulliparous - NR 3. Bishop score - mean 4.1, SD 1.6 4. BMI/weight - NR 5. Ethnicity - NR 6. IVF - NR 42 weeks 1. Age - mean 28.2, SD 5.3 years 2. Nulliparous - NR 3. Bishop score - mean 4.6, SD 1.6 4. BMI/weight - NR 5. Ethnicity - NR 6. IVF - NR
Intervention(s)	Induction 40 weeks: Patients in the induction group had sonographic assessment of amniotic fluid volume, and a non stress (CTG) test. If the latter was normal, a 3 mg vaginal tablet of PGE 2 was inserted into the posterior vaginal fornix. Patients were then send home and told to return for repeat testing and a further dose of PGE2 within 3 to 4 days. Expectant management (42 weeks): The expectant group were seen twice a week and then had an inpatient induction of labour if they passed 42 completed weeks of gestation
Timing of birth (as reported by study)	40 weeks 1. GA at birth - mean 40.2, SD 0.5 weeks 2. Days from randomisation to birth - mean 1.6 3. Number induced - NR 42 weeks 1. GA at birth - mean 40.9, SD 0.7 weeks 2. Days from randomisation to birth - mean 5.2 3. Number induced - NR
Study arms	
40 weeks (N = 96)	
42 weeks (N = 104)	
Outcomes	

	40 weeks	**42 weeks**
	N = 70	N = 104
C-section *Polarity: Not set*		
No of events	n = 4	n = 6

Ohel 1996		
Risk of bias assessment		
Section	**Question**	**Answer**
Selection bias	Random sequence generation	High risk of bias *(allocated according to odd/even registration numbers)*
	Allocation concealment	High risk of bias *(allocated according to odd/even registration numbers)*
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias *(exclusions in induction group explained, as the women withdrew (no wish to be induced))*
Reporting bias	Selective reporting	Unclear risk of bias
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Table 19: Evidence tables – Wennerholm 2019

Wennerholm 2019	
Bibliographic Reference	Wennerholm, U. B.; Saltvedt, S.; Wessberg, A.; Alkmark, M.; Bergh, C.; Wendel, S. B.; Fadl, H.; Jonsson, M.; Ladfors, L.; Sengpiel, V.; Wesstrom, J.; Wennergren, G.; Wikstrom, A. K.; Elden, H.; Stephansson, O.; Hagberg, H.; Induction of labour at 41 weeks versus expectant management and induction of labour at 42 weeks (SWEdish Post-term Induction Study, SWEPIS): Multicentre, open label, randomised, superiority trial; The BMJ; 2019; vol. 367; l6131
Study details	
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Fourteen hospitals with antenatal clinics linked to the register
Study dates	May 2016 to October 2018
Sources of funding	This study was supported by the Swedish state under the agreement between the Swedish government and the county councils
Duration of follow-up	Not applicable

Wennerholm 2019	
Inclusion criteria	Aged 18 or more, understood oral and written information, and had a singleton pregnancy with a fetus in cephalic presentation at 40 weeks+6 days to 41 weeks+1 day according to ultrasound based dating in the first or early second trimester or for pregnancies after assisted reproduction according to the day of oocyte retrieval.
Exclusion criteria	Previous caesarean delivery or other uterine surgery, pregestational and insulin dependent gestational diabetes, hypertensive disorder of pregnancy, known oligohydramnios (amniotic fluid index <50 mm or deepest vertical pocket <20 mm) or small for gestational age fetus (estimated fetal weight ≤2 standard deviations according to the sex and gestational age specific Swedish reference), diagnosed fetal malformation, contraindication to vaginal delivery, and any other maternal condition affecting the progress of the pregnancy to 42 weeks
Sample size	N = 2762 Power calculation based on n=5019 per group, but study terminated early due to high perinatal death rate in expectant management group “On 2 October 2018 the Data and Safety Monitoring Board strongly recommended the SWEPIS steering committee to stop the study owing to a statistically significant higher perinatal mortality in the expectant management group. Although perinatal mortality was a secondary outcome, it was not considered ethical to continue the study”
Baseline characteristics	41 weeks 1. Age - mean 31.2, SD 4.7 years 2. Age >/= 35 - 21.9% 3. Nulliparous - 762/1381 4. Bishop score - not reported 5. BMI at first antenatal visit - mean 24.9, SD 4.7 6. BMI >/=30 - 12.3% 7. Assisted IVF/ICSI - 4.9% 8. Subfertility - 12.8% 9. Ethnicity - NR 42 weeks 1. Age - mean 31.1, SD 4.5 years 2. Age >/= 35 - 20.2% 3. Nulliparous - 753/1379 4. Bishop score - not reported 5. BMI at first antenatal visit - mean 25.1, SD 4.9 6. BMI >/=30 - 14.5% 7. Assisted IVF/ICSI - 3.8% 8. Subfertility - 12.2% 9. Ethnicity - NR
Intervention(s)	In the induction group, labour was induced within 24 hours of randomisation (ie, same or next day) but not earlier than 41 weeks+0 days. In the expectant management group, labour was induced at 42 weeks+0 days to 42 weeks+1 day. Induction of labour was carried out in the same way in both groups. At admission, the women were examined for blood pressure, proteinuria, fetal presentation by abdominal palpation, cervical status, and fetal wellbeing by cardiotocography. Amniotomy was performed if the fetal head was well engaged and the cervix was ripe (Bishop score ≥6 for primiparous women and ≥5 for multiparous women), followed by oxytocin infusion after 1-2 hours without spontaneous regular contractions. If the fetal head was not engaged or the cervix was less ripe, any of the following methods was used according to local routines: mechanical dilation with a Foley-like catheter, prostaglandin E1 (misoprostol, oral or vaginal), or prostaglandin E2 (dinoprostone, vaginal).

Wennerholm 2019

Timing of birth (as reported by study)	41 weeks 1. GA at birth - mean 288.8, SD 1.3 days 2. Number induced - 1181/1381 42 weeks 1. GA at birth - mean 291.7, SD 2.7 days 2. Number induced - 457/1379

Study arms

41 weeks (N = 1381)

42 weeks (N = 1379)

Outcomes

	41 weeks	42 weeks
	N = 1381	N = 1379
Maternal death/uterine rupture *Polarity: Not set*		
No of events	n = 0	n = 0
Perinatal death *Polarity: Not set*		
No of events	n = 0	n = 6
Instrumental birth (assisted vaginal) *Polarity: Not set*		
No of events	n = 88	n = 91
Vaginal unassisted birth *Polarity: Not set*		
No of events	n = 1150	n = 1140

	41 weeks	42 weeks
	N = 1382	N = 1379
C-section *Polarity: Not set*		
No of events	n = 143	n = 148

	41 weeks	42 weeks
	N = 1381	N = 1374
NICU admission *Polarity: Not set*		
No of events	n = 55	n = 82
MAS *Polarity: Not set*		
No of events	n = 2	n = 3
HIE (grades 1-3) *Polarity: Not set*		
No of events	n = 2	n = 3

Risk of bias assessment

Section	Question	Answer
Selection bias	Random sequence generation	Low risk of bias *(central randomisation by dynamic allocation to minimise imbalance)*

Wennerholm 2019		
	Allocation concealment	Low risk of bias *(access to randomisation used separate log-in to the pregnancy register)*
Performance bias	Blinding of participants and personnel	High risk of bias *(Unable to blind participants or personnel)*
Detection bias	Blinding of outcome assessment	Low risk of bias *(Unable to blind outcomes, but unlikely to bias results due to objective nature)*
Attrition bias	Incomplete outcome data	Low risk of bias
Reporting bias	Selective reporting	Low risk of bias *(protocol checked)*
Other sources of bias	Any other sources of bias	Low risk of bias *(Comparable at baseline, No block randomisation in unblinded trial)*
Overall risk of bias and directness	Risk of bias variation across outcomes	No subjective outcomes reported
	Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 4: 40 versus 42 weeks

Important outcomes

Figure 2: Mode of birth: Caesarean

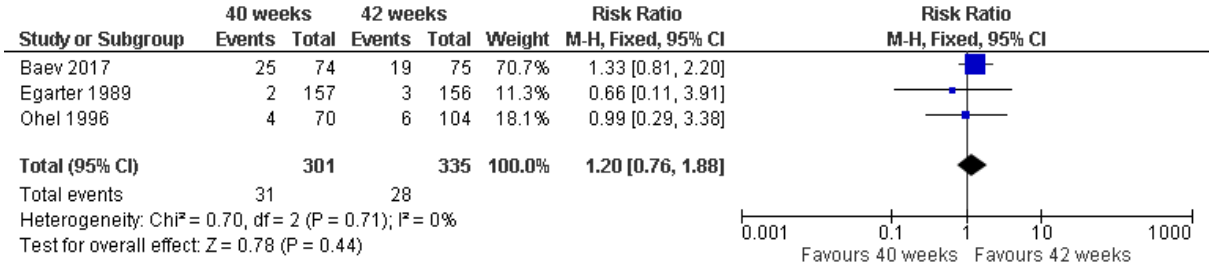
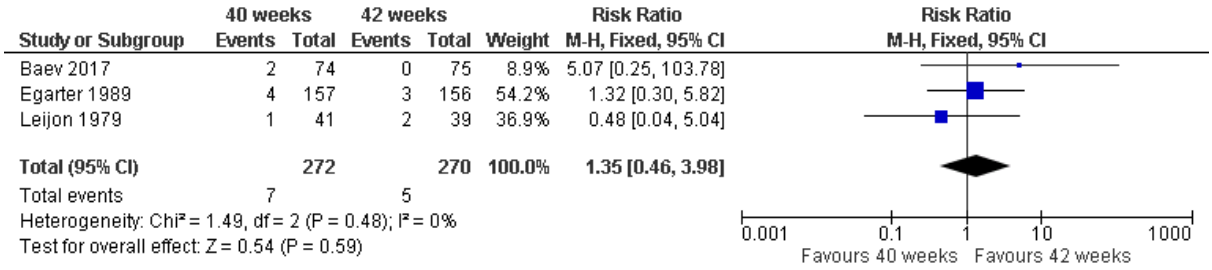


Figure 3: Mode of birth: Instrumental/operative vaginal



Comparison 5: 41 versus 42 weeks

Critical outcomes

Figure 4: Maternal death/uterine rupture

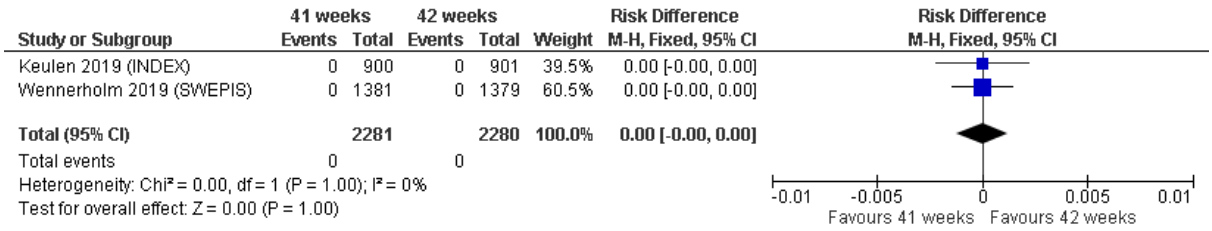
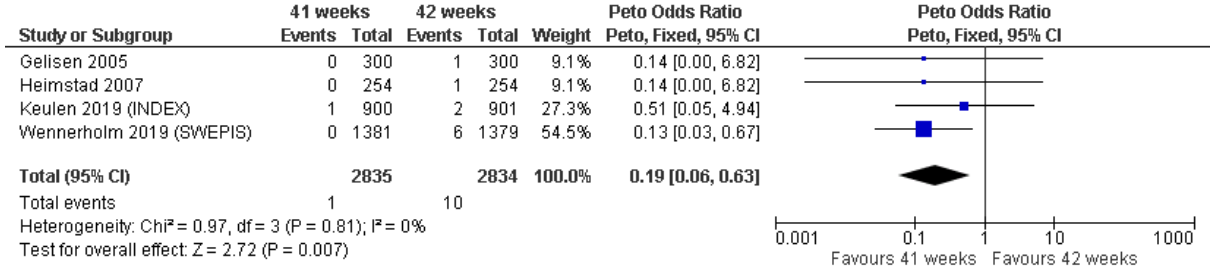


Figure 5: Perinatal death



*Wennerholm 2019 terminated early due to significantly higher perinatal mortality in delayed induction group

Important outcomes

Figure 6: Mode of birth: Caesarean

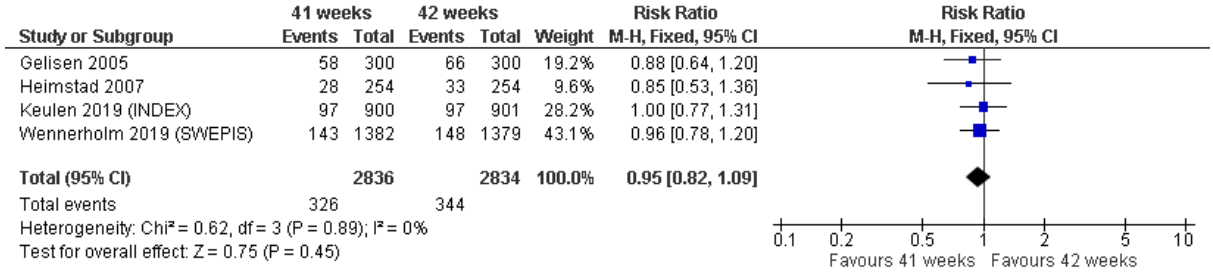


Figure 7: Mode of birth: Instrumental/operative vaginal

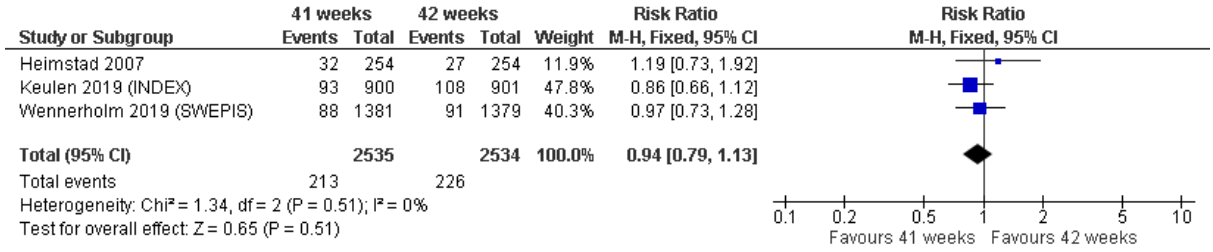


Figure 8: Mode of birth: Unassisted/spontaneous vaginal

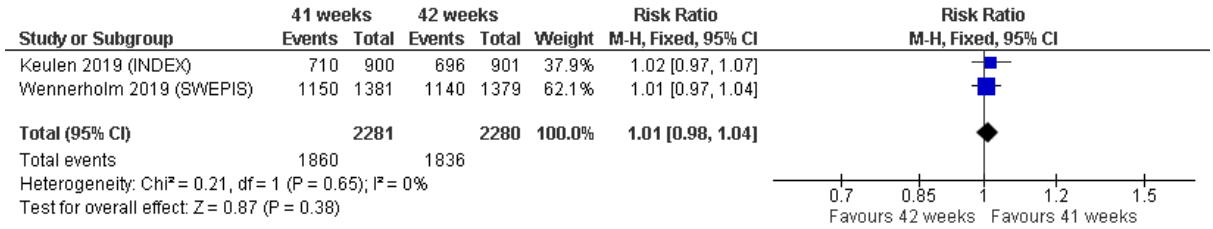


Figure 9: NICU admission

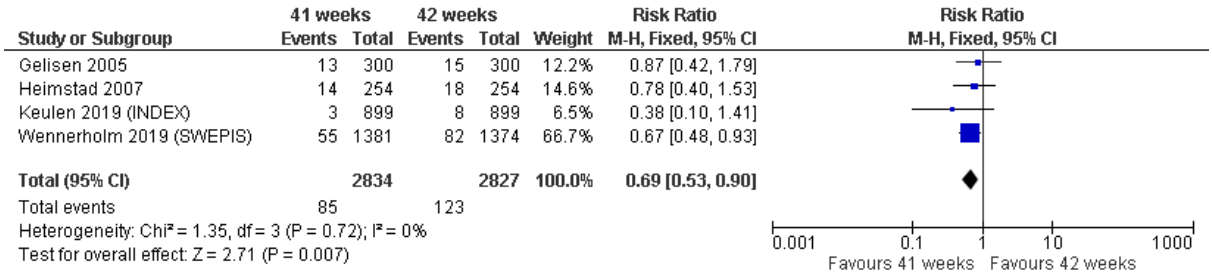
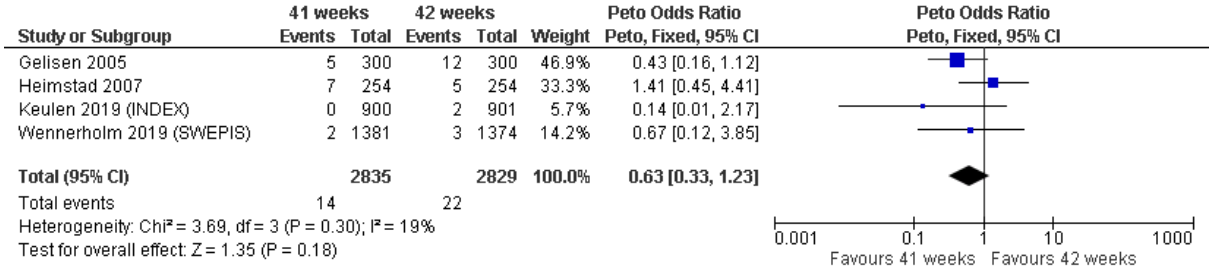


Figure 10: Meconium aspiration syndrome



Comparison 6: 41-42 versus 44 weeks

Important outcomes

Figure 11: Mode of birth: Caesarean

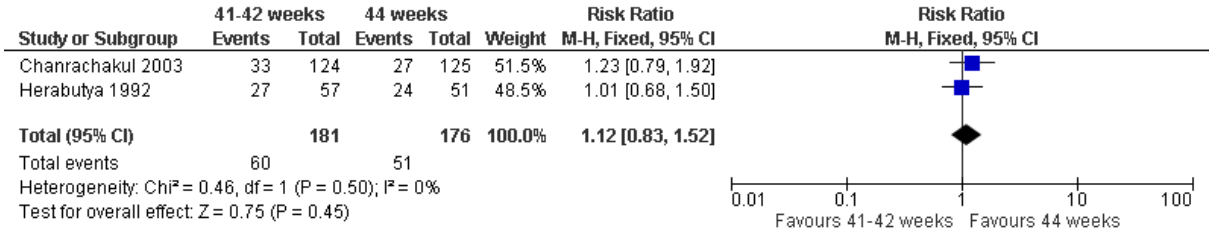
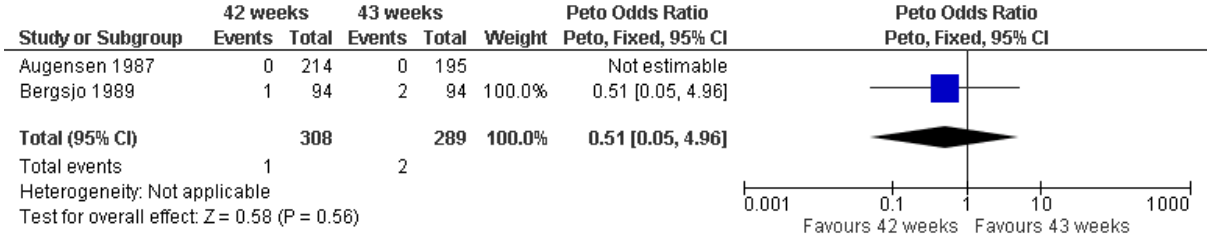


Figure 12: NICU admission

Comparison 7: 42 versus 43 weeks

Critical outcomes

Figure 13: Perinatal death



Important outcomes

Figure 14: Mode of birth: Caesarean

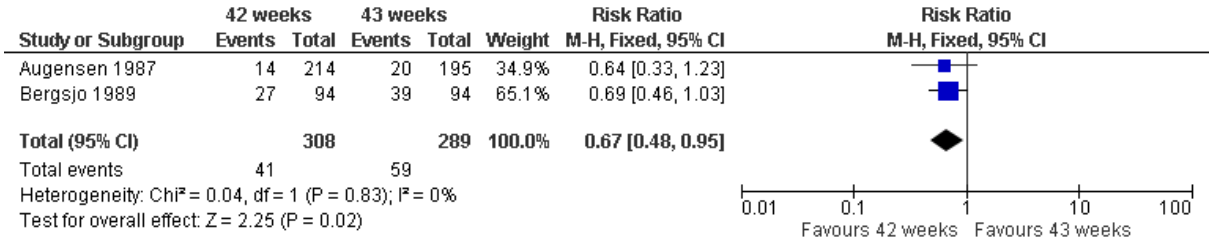


Figure 15: Mode of birth: Instrumental/operative vaginal

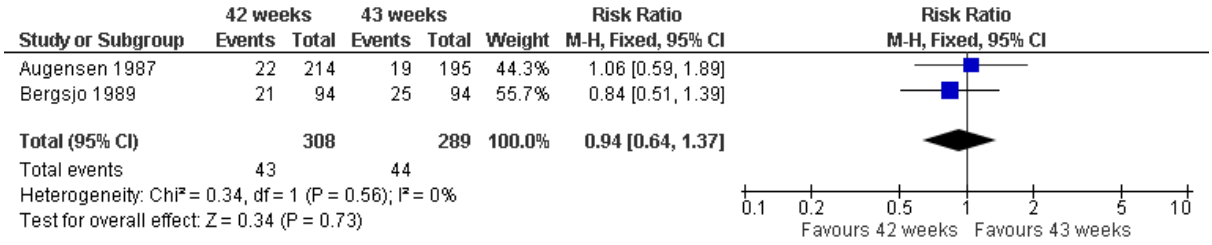
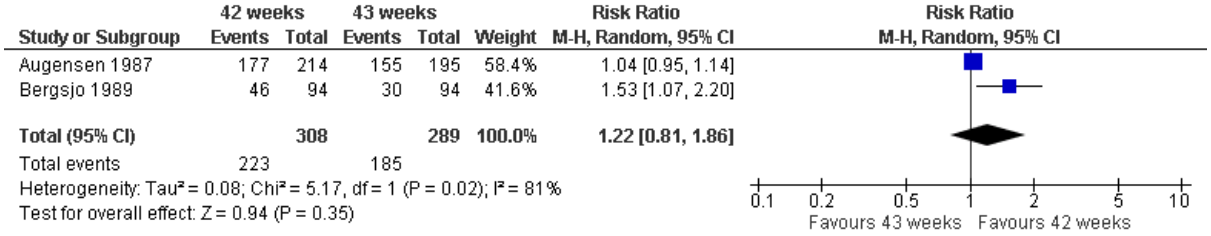


Figure 16: Mode of birth: Unassisted/spontaneous vaginal



Appendix F GRADE tables

GRADE tables for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Table 20: Comparison 1: 39 versus 40-42 weeks

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	39 weeks	40-42 weeks	Relative (95% CI)	Absolute	Quality	Importance
Maternal mortality/morbidity: death/uterine rupture												
1 (Grobman 2018)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	0/3059 (0%)	0/3037 (0%)	RD 0.00 (0 to 0)	0 more per 1000 (from 0 more to 0 more)[3]	HIGH	CRITICAL
Perinatal mortality												
1 (Grobman 2018)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/3059 (0.07%)	3/3037 (0.1%)	POR 0.67 (0.12 to 3.84)[5]	0 fewer per 1000 (from 1 fewer to 3 more)	LOW	CRITICAL
Mode of birth: Caesarean												
1 (Grobman 2018)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	569/3059 (18.6%)	674/3037 (22.2%)	RR 0.84 (0.76 to 0.93)	36 fewer per 1000 (from 16 fewer to 53 fewer)	LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
1 (Grobman 2018)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	222/3059 (7.3%)	258/3037 (8.5%)	RR 0.85 (0.72 to 1.01)	13 fewer per 1000 (from 24 fewer to 1 more)	LOW	IMPORTANT
Maternal satisfaction (experience of birth) (follow-up 6-96 hours post-delivery; measured with: Labor Agentry Scale; range of scores: 29-203; Better indicated by higher values)												
1 (Grobman 2018)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	N=2932	N=2876	-	Median 4 higher, p<0.001	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**39 weeks**	**40-42 weeks**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
							Median 168 IQR [148-183]	Median 164 IQR [143-181]				
Maternal satisfaction (experience of birth) (follow-up 4-8 weeks; measured with: Labor Agentry Scale; range of scores: 29-203; Better indicated by higher values)												
1 (Grobman 2018)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	N=2710 Median 176 IQR [157-189]	N=2650 Median 174 IQR [154-188]	-	Median 2 higher, p=0.01	MODERATE	IMPORTANT
NICU admission												
1 (Grobman 2018)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[7]	none	358/3059 (11.7%)	394/3037 (13%)	RR 0.9 (0.79 to 1.03)	13 fewer per 1000 (from 27 fewer to 4 more)	LOW	IMPORTANT
Neonatal morbidity - MAS												
1 (Grobman 2018)	randomised trials	no serious risk of bias[8]	no serious inconsistency	no serious indirectness	serious[7]	none	17/3059 (0.56%)	26/3037 (0.86%)	POR 0.65 (0.36 to 1.19)[5]	3 fewer per 1000 (from 5 fewer to 2 more)	MODERATE	IMPORTANT
Neonatal morbidity - HIE												
1 (Grobman 2018)	randomised trials	no serious risk of bias[8]	no serious inconsistency	no serious indirectness	very serious[4]	none	14/3059 (0.46%)	20/3037 (0.66%)	POR 0.70 (0.35 to 1.37)5	2 fewer per 1000 (from 4 fewer to 2 more)	LOW	IMPORTANT

[1] High ROB in one domain (unable to blind participants and personnel), but deemed unlikely to affect outcome (death)
[2] Sample size >500
[3] absolute effect calculated from risk difference as zero cases in both groups
[4] 95%CI crosses two MID boundaries (0.8 to 1.25)
[5] Peto OR due to low events (<1% per arm)
[6] High ROB in one domain (unable to blind participants or personnel)
[7] 95%CI crosses one MID boundary (0.8 to 1.25)
[8] High ROB in one domain (unable to blind participants or personnel), but deemed unlikely to affect outcome (neonatal morbidity)

Table 21: Comparison 2: 39 versus 42 weeks

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	39 weeks	42 weeks	Relative (95% CI)	Absolute		
Mode of birth: Caesarean												
1 (Nielsen 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/116 (6.9%)	8/110 (7.3%)	RR 0.95 (0.37 to 2.44)	4 fewer per 1000 (from 46 fewer to 105 more)	VERY LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
1 (Nielsen 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/116 (6.9%)	9/110 (8.2%)	RR 0.84 (0.34 to 2.11)	13 fewer per 1000 (from 54 fewer to 91 more)	VERY LOW	IMPORTANT
Mode of birth: Unassisted/spontaneous vaginal												
1 (Nielsen 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/116 (86.2%)	93/110 (84.5%)	RR 1.02 (0.92 to 1.14)	17 more per 1000 (from 68 fewer to 118 more)	MODERATE	IMPORTANT
NICU admission												
1 (Nielsen 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/116 (0%)	0/110 (0%)	RD 0.00 (-0.02 to 0.02)	0 more per 1000 (from 20 fewer to 20 more)[4]	VERY LOW	IMPORTANT

[1] *High ROB in one domain (unable to blind participants and personnel)*
[2] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[3] *Sample size <300*
[4] *absolute effect calculated from risk difference as zero cases in both groups*

Table 22: Comparison 3: 39-40 versus 41 weeks

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	39-40 weeks	41 weeks	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality												
1 (Cole 1975)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/111 (0%)	1/117 (0.85%)	POR 0.14 (0.00 to 7.19)[3]	7 fewer per 1000 (from 9 fewer to 50 more)	LOW	CRITICAL
Mode of birth: Caesarean												
1 (Cole 1975)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/111 (4.5%)	9/117 (7.7%)	RR 0.59 (0.2 to 1.69)	32 fewer per 1000 (from 62 fewer to 53 more)	VERY LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
1 (Cole 1975)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	34/111 (30.6%)	26/117 (22.2%)	RR 1.38 (0.89 to 2.14)	84 more per 1000 (from 24 fewer to 253 more)	VERY LOW	IMPORTANT
Mode of birth: Unassisted/spontaneous vaginal												
1 (Cole 1975)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	72/111 (64.9%)	82/117 (70.1%)	RR 0.93 (0.77 to 1.11)	49 fewer per 1000 (from 161 fewer to 77 more)	VERY LOW	IMPORTANT

[1] High ROB in one domain (unable to blind participants and personnel) and unclear randomisation (sequence generation and allocation concealment), deemed unlikely to affect some outcomes (death), likely to affect others
[2] 95%CI crosses two MID boundaries (0.8 to 1.25)
[3] Peto OR due to low events (<1% in both arms)
[4] 95%CI crosses one MID boundary (0.8 to 1.25)

Table 23: Comparison 4: 40 versus 42 weeks

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40 weeks	42 weeks	Relative (95% CI)	Absolute		
Perinatal mortality												
1 (Egarter 1989)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/157 (0%)	1/156 (0.64%)	POR 0.13 (0.00 to 6.78)[3]	6 fewer per 1000 (from 6 fewer to 35 more)	LOW	CRITICAL
Mode of birth: Caesarean												
3 (Baev 2017, Egarter 1989, Ohel 1996)	randomised trials	very serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[2]	none	31/301 (10.3%)	28/335 (8.4%)	RR 1.2 (0.76 to 1.88)	17 more per 1000 (from 20 fewer to 74 more)	VERY LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
3 (Baev 2017, Egarter 1989, Leijon 1979)	randomised trials	very serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[2]	none	7/272 (2.6%)	5/270 (1.9%)	RR 1.35 (0.46 to 3.98)	6 more per 1000 (from 10 fewer to 55 more)	VERY LOW	IMPORTANT
NICU admission												
1 (Baev 2017)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/74 (5.4%)	3/75 (4%)	RR 1.35 (0.31 to 5.83)	14 more per 1000 (from 28 fewer to 193 more)	VERY LOW	IMPORTANT

[1] *High ROB in one domain (unable to blind participants and personnel) and unclear in multiple domains, though deemed unlikely to affect outcome (death)*
[2] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[3] *Peto OR due to low event rate (<1% per arm)*
[4] *High ROB in at least one domain in all studies (unable to blind patients and personnel) and unclear or high ROB in other domains in each study*
[5] *i2=0%*
[6] *High ROB in one domain (unable to blind participants and personnel), unclear in one other domain (selective reporting)*

Table 24: Comparison 5: 41 versus 42 weeks

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	41 weeks	42 weeks	Relative (95% CI)	Absolute		
Maternal death/uterine rupture												
2 (Keulen 2019, Wennerholm 2019)	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision[3]	none	0/2281 (0%)	0/2280 (0%)	RD 0.00 (0 to 0)	0 more per 1000 (from 0 more to 0 more)[4]	HIGH	CRITICAL
Perinatal death												
4 (Gelisen 2005, Heimstad 2007, Keulen 2019, Wennerholm 2019)	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	1/2835 (0.04 %)	10/2834 (0.35%)	POR 0.19 (0.06 to 0.63)[5]	3 fewer per 1000 (from 1 fewer to 3 fewer)	HIGH	CRITICAL
Mode of birth: Caesarean												
4 (Gelisen 2005, Heimstad 2007, Keulen 2019, Wennerholm 2019)	randomised trials	very serious[6]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	326/2836 (11.5 %)	344/2834 (12.1%)	RR 0.95 (0.82 to 1.09)	6 fewer per 1000 (from 22 fewer to 11 more)	LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
3 (Heimstad 2007, Keulen 2019, Wennerholm 2019)	randomised trials	very serious[6]	no serious inconsistency[2]	no serious indirectness	serious[7]	none	213/2535 (8.4%)	226/2534 (8.9%)	RR 0.94 (0.79 to 1.13)	5 fewer per 1000 (from 19 fewer to 12 more)	VERY LOW	IMPORTANT
Mode of birth: Unassisted/spontaneous vaginal												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**41 weeks**	**42 weeks**	**Relative (95% CI)**	**Absolute**		
2 (Keulen 2019, Wennerholm 2019)	randomised trials	serious[8]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	1860/2281 (81.5%)	1836/2280 (80.5%)	RR 1.01 (0.98 to 1.04)	8 more per 1000 (from 16 fewer to 32 more)	MODERATE	IMPORTANT
NICU admission												
4 (Gelisen 2005, Heimstad 2007, Keulen 2019, Wennerholm 2019)	randomised trials	very serious[9]	no serious inconsistency[2]	no serious indirectness	serious[7]	none	85/2834 (3%)	123/2827 (4.4%)	RR 0.69 (0.53 to 0.9)	13 fewer per 1000 (from 4 fewer to 20 fewer)	VERY LOW	IMPORTANT
Neonatal morbidity: MAS												
4 (Gelisen 2005, Heimstad 2007, Keulen 2019, Wennerholm 2019)	randomised trials	no serious risk of bias[10]	no serious inconsistency[11]	no serious indirectness	serious[7]	none	14/2835 (0.49%)	22/2829 (0.78%)	POR 0.63 (0.33 to 1.23)[5]	3 fewer per 1000 (from 5 fewer to 2 more)	MODERATE	IMPORTANT
Neonatal morbidity: HIE (grade 1-3)												
1 (Wennerholm 2019)	randomised trials	no serious risk of bias[10]	no serious inconsistency	no serious indirectness	very serious[12]	none	2/1381 (0.14%)	3/1374 (0.22%)	POR 0.67 (0.12 to 3.85)[5]	1 fewer per 1000 (from 2 fewer to 6 more)	LOW	IMPORTANT

[1] *High ROB in one domain in all studies (unable to blind participants and personnel) and high or unclear ROB in one or more other domains, but deemed unlikely to affect outcome (death)*
[2] *i2=0%*
[3] *Sample size >500*
[4] *Absolute effect calculated from risk difference as zero cases in both groups*
[5] *Peto OR due to low event rate (<1% per arm)*
[6] *High ROB in one domain in all studies (unable to blind participants or personnel) and high or unclear ROB in one or more other domains per study*
[7] *95%CI crosses one MID boundary (0.8 to 1.25)*

[8] *High ROB in one domain in all studies (unable to blind participants and personnel) and high or unclear in one other domain*
[9] *High ROB in one domain in all studies (unable to blind participants and personnel) and high or unclear ROB in one or more other domains*
[10] *High ROB in one domain (unable to blind participants and personnel), but deemed unlikely to affect this outcome (neonatal morbidity)*
[11] *i2=19% (POR)*
[12] *95%CI crosses two MID boundaries (0.8 to 1.25)*

Table 25: Comparison 6: 41-42 versus 44 weeks

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**41-42 weeks**	**44 weeks**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Perinatal death												
1 (Herabutya 1992)	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/57 (0%)	1/51 (2%)	POR 0.12 (0.00 to 6.10)[3]	17 fewer per 1000 (from 20 fewer to 89 more)	LOW	CRITICAL
Mode of birth: Caesarean												
2 (Chanrachakul 2003, Herabutya 1992)	randomised trials	very serious[4]	no serious inconsistency[5]	no serious indirectness	serious[6]	none	60/181 (33.1%)	51/176 (29%)	RR 1.12 (0.83 to 1.52)	35 more per 1000 (from 49 fewer to 151 more)	VERY LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
1 (Herabutya 1992)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/57 (19.3%)	9/51 (17.6%)	RR 1.09 (0.49 to 2.42)	16 more per 1000 (from 90 fewer to 251 more)	VERY LOW	IMPORTANT
Mode of birth: Unassisted/spontaneous vaginal												
1 (Herabutya 1992)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/57 (33.3%)	18/51 (35.3%)	RR 0.94 (0.56 to 1.59)	21 fewer per 1000 (from 155 fewer to 208 more)	VERY LOW	IMPORTANT
NICU admission												
2 (Chanrachakul 2003, Herabutya 1992)	randomised trials	very serious[4]	no serious inconsistency[8]	no serious indirectness	very serious[2]	none	2/181 (1.1%)	4/176 (2.3%)	RR 0.52 (0.12 to 2.34)	11 fewer per 1000 (from 20 fewer to 30 more)	VERY LOW	IMPORTANT

[1] *High ROB in one domain (unable to blind participants and personnel) and unclear in multiple domains, but deemed unlikely to affect outcome (death)*
[2] *95%CI crosses two MID boundaries (0.8 to 1.25)*

[3] *Peto OR due to low event rate*
[4] *High ROB in one domain in each study (unable to blind participants and personnel) and unclear across multiple domains in each study*
[5] *i2=0%*
[6] *95%CI crosses one MID boundary (0.8 to 1.25)*
[7] *High ROB in one domain (unable to blind participants or personnel) and unclear in multiple domains*
[8] *i2=43%*

Table 26: Comparison 7: 42 v 43 weeks

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**42 weeks**	**43 weeks**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Perinatal death												
2 (Augensen 1987, Bergsjo 1989)	randomised trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	1/308 (0.32%)	2/289 (0.69%)	POR 0.51 (0.05 to 4.96)[4]	3 fewer per 1000 (from 7 fewer to 26 more)	LOW	CRITICAL
Mode of birth: Caesarean												
2 (Augensen 1987, Bergsjo 1989)	randomised trials	serious[5]	no serious inconsistency[2]	no serious indirectness	serious[6]	none	41/308 (13.3%)	59/289 (20.4%)	RR 0.67 (0.48 to 0.95)	67 fewer per 1000 (from 10 fewer to 106 fewer)	LOW	IMPORTANT
Mode of birth: Instrumental/operative vaginal												
2 (Augensen 1987, Bergsjo 1989)	randomised trials	serious[5]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	43/308 (14%)	44/289 (15.2%)	RR 0.94 (0.64 to 1.37)	9 fewer per 1000 (from 55 fewer to 56 more)	VERY LOW	IMPORTANT
Unassisted/spontaneous vaginal												
2 (Augensen 1987, Bergsjo 1989)	randomised trials	serious[5]	very serious[7]	no serious indirectness	serious[6]	none	223/308 (72.4%)	185/289 (64%)	RR 1.22 (0.81 to 1.86)[7]	141 more per 1000 (from 122 fewer to 551 more)	VERY LOW	IMPORTANT
NICU admission												
1 (Augensen 1987)	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/214 (5.6%)	15/195 (7.7%)	RR 0.73 (0.35 to 1.52)	21 fewer per 1000 (from 50 fewer to 40 more)	VERY LOW	IMPORTANT
Neonatal morbidity: MAS (aspiration pneumonia)												

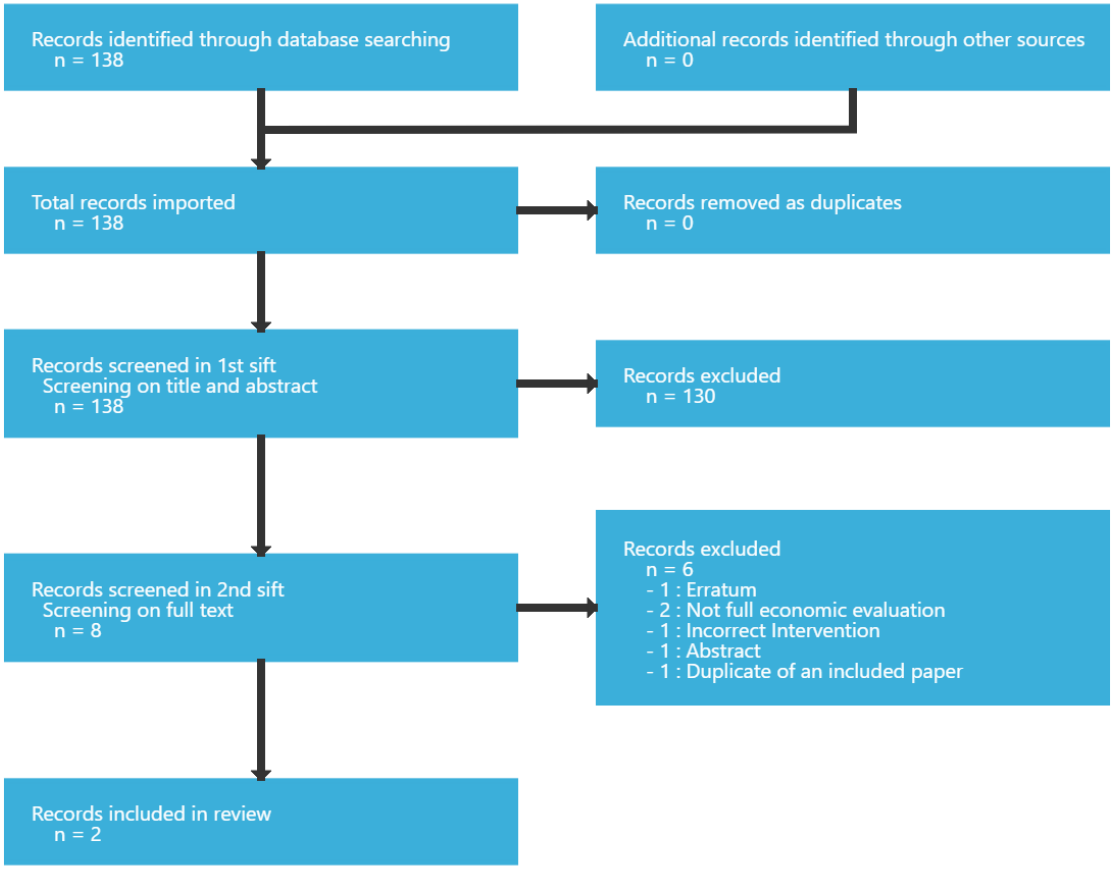
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**42 weeks**	**43 weeks**	**Relative (95% CI)**	**Absolute**		
1 (Bergsjo 1989)	randomised trials	no serious risk of bias[9]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/94 (4.3%)	8/94 (8.5%)	RR 0.5 (0.16 to 1.6)	43 fewer per 1000 (from 71 fewer to 51 more)	LOW	IMPORTANT

[1] *High ROB in one domain in each study (unable to blind participants and personnel) and unclear in at least one other domain per study, but deemed unlikely to affect outcome (death)*
[2] *i2=0%*
[3] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[4] *Peto OR due to low event rate (<1% in both arms)*
[5] *High ROB in one domain in each study (unable to blind participants and personnel) and unclear in at least one other domain per study*
[6] *95%CI crossed one MID boundary (0.8 to 1.25)*
[7] *i2=81% (random effects model)*
[8] *High ROB in one domain (unable to blind participants or personnel) and unclear in one domain (selective reporting)*
[9] *High ROB in one domain (unable to blind participants and personnel) and unclear in multiple domain, but deemed unlikely to affect outcome (neonatal morbidity)*

Appendix G Economic evidence study selection

Study selection for: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Figure 17: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Table 27: Economic evidence tables for induction of labour if spontaneous labour does not ensue

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Caughey et al. 2009 **Country:** United States **Type of economic analysis:** CUA **Source of funding:** The report was sponsored by the Agency for Healthcare Research and Quality The authors state that they do not have any affiliations or financial involves that conflict with the material presented in the report.	**Intervention in detail:** IoL at 39 weeks IoL at 40 weeks IoL at 41 weeks **Comparator in detail:** . EM of labour – this was usually for an additional week with IoL at the end of that period although the model that considered IoL at 39 weeks was compared to EM till 40 weeks and EM till 41 weeks	**Population characteristics:** Nulliparous women with low risk, singleton, cephalic gestations **Modelling approach:** Decision analytic model using TreeAgePro 2007 software (TreeAge Software, Inc, Williamstown, MA) **Source of base-line and effectiveness data:** A mixture of published literature and the US Birth Cohort 2003 **Source of cost data:** Published literature **Source of QoL data:** Published literature and assumption	**<u>IoL 41 weeks v EM until 42 weeks</u>** **Mean cost per patient** • EM: $9,770 • IoL: $10,139 • Difference: $368 **Mean QALYs per patient:** • EM: 56.876 QALYs • IoL: 56.910 QALYs • Difference: 0.033 QALYs **ICER:** $10,789 per QALY **Subgroup analysis:** Not conducted. **Deterministic sensitivity analysis:** Sensitivity analysis was undertaken on the caesarean birth rate and the ICER was $26,450 when a 22% higher caesarean birth rate with IoL	**Perspective:** Societal **Currency:** USD ($) **Cost year:** 2007 **Time horizon:** Lifetime for QALYs **Discounting:** 3% for QALYs but no discounting of costs which occur around the time of the intervention. **Applicability:** The study was deemed to be only

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			was assumed (the "worst case" for IoL) Additional sensitivity/threshold analyses were undertaken and the authors report that "the model was slightly more sensitive to changes in cost inputs" **Probabilistic sensitivity analysis:** PSA suggested there was an approximate 80% probability that IoL was cost-effective at a cost-effectiveness threshold of $25,000 per QALY (≈£20,000 per QALY). **<u>IoL 40 weeks v EM until 41 weeks</u>** **Mean cost per patient** • EM: $9,760 • IoL: $10,030 • Difference: $269 **Mean QALYs per patient:** • EM: 56.889 QALYs • IoL: 56.916 QALYs • Difference: 0.027 QALYs **ICER:** $9,932 per QALY **Subgroup analysis:**	*partially applicable* to the UK because it was based on fairly dated US costs **Limitations:** The study is quite dated and model probabilities are therefore not based on a systematic review of the most recent evidence. The method to identify unit costs from the published literature is not described. NICU admission is not included as an outcome even though it is reported in studies and included in the systematic review undertaken for this guideline. Therefore, this study is considered to have potentially serious limitations. **Other comments:** It is stated that the analysis takes a societal perspective

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			Not conducted. **Deterministic sensitivity analysis:** Sensitivity analysis was undertaken on the caesarean birth rate and the ICER was $28,267 when a 22% higher caesarean birth rate with IoL was assumed (the "worst case" for IoL) Additional sensitivity/threshold analyses were undertaken and the authors report that "the model was slightly more sensitive to changes in cost inputs" **Probabilistic sensitivity analysis:** PSA suggested there was just over a 50% probability that IoL was cost-effective at a cost-effectiveness threshold of $25,000 per QALY (≈£20,000 per QALY). **<u>IoL 39 weeks v EM until 40 v EM until 41 weeks</u>** **Mean cost per patient** • EM_{41}: $8,915 • EM_{40}: $9,253 • IoL: $9,568 • Difference EM_{40} v EM_{41}: $338 • Difference IoL v EM_{40}: $316	but the only costs reported relate to healthcare utilisation.

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			Mean QALYs per patient: • EM_{41}: 56.877 QALYs • EM_{40}: 56.903 QALYs • IoL: 56.920 QALYs • Difference EM_{40} v EM_{41}: 0.026 QALYs • Difference IoL v EM_{40}: 0.017 QALYs **ICER:** EM_{40} v EM_{41}: $13,900 per QALY IoL v EM_{40}: $20,222 per QALY **Subgroup analysis:** Not conducted. **Deterministic sensitivity analysis:** Sensitivity analysis was undertaken on the caesarean birth rate and the ICER of IoL was $71,945 per QALY and $25,931 per QALY respectively when compared to EM until 40 weeks and EM until 41 weeks respectively when a 22% higher caesarean birth rate with IoL was assumed (the “worst case” for IoL). Additional sensitivity/threshold analyses were undertaken on model probabilities and costs.	

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			Probabilistic sensitivity analysis: PSA suggested there was just under a 50% probability that IoL was cost-effective at a cost-effectiveness threshold of $25,000 per QALY (≈£20,000 per QALY) relative to EM until 40 weeks.	
Author & year: Hersh et al. 2019 **Country:** United States **Type of economic analysis:** CUA **Source of funding:** None stated Authors report no conflicts of interest.	**Intervention in detail:** IoL at 39 weeks **Comparator in detail:** EM of labour until 41 weeks, followed by IoL if they had not gone into labour or given birth by then.	**Population characteristics:** Nulliparous women with low risk, **Modelling approach:** Decision analytic model using TreeAge Pro software (2018 version; TreeAge Software, Inc, Williamstown,MA) **Source of base-line and effectiveness data:** Model inputs were estimated from published literature. **Source of cost data:** The unit cost of clinic and triage visits was estimated from previously published cost-effectiveness analyses, with use of those resources derived from the ARRIVE trial.	**Mean cost per patient*** • EM: $10,832 • IoL: $12,106 • Difference: $1,274 *Derived from results for hypothetical cohort of 1.6 million women **Mean QALYs per patient*** • EM: 57.012 QALYs • IoL: 57.026 QALYs • Difference: 0.014 QALYs *Derived from results for hypothetical cohort of 1.6 million women **ICER:** $87,692 per QALY **Subgroup analysis:**	**Perspective:** Societal **Currency:** USD ($) **Cost year:** 2018 **Time horizon:** Lifetime for QALYs **Discounting:** 3% for QALYs but no discounting of costs which occur around the time of the intervention. **Applicability:**

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		Costs of vaginal and caesarean birth were estimated from a previously published economic evaluation. The costs of IoL were obtained using birth registry and discharge data using a 2007-2011 cohort of singleton, non-anomalous births. **Source of QoL data:** Published literature and assumption	Not conducted **Deterministic sensitivity analysis:** One-way sensitivity analysis was performed for all model probabilities, costs and utilities. The authors report that, using a cost-effectiveness threshold of $100,000 per QALY, cost-effectiveness was sensitive to the cost of induction. The authors report that a Tornado analysis suggested that the rate of caesarean birth, hypertensive disorders of pregnancy and stillbirth were all important in determining the model result. **Probabilistic sensitivity analysis:** PSA suggested that IoL had a 65% probability of being cost-effective at a cost-effectiveness threshold of $100,000 per QALY. .	The study was deemed to be only partially applicable to the UK because it was based on US costs **Limitations:** The method to identify unit costs from the published literature is not described. NICU admission is not included as an outcome even though it is reported in studies and included in the systematic review undertaken for this guideline. Therefore, this study is considered to have potentially serious limitations. **Other comments:** It is stated that the analysis takes a societal perspective but the only costs reported relate to healthcare utilisation.

CUA = Cost-utility analysis; EM = Expectant management; IoL = Induction of labour; PSA = Probabilistic sensitivity analysis

Appendix I Health economic evidence profiles

Health economic evidence profiles for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Table 28: Economic evidence profile for induction of labour if spontaneous labour does not ensue

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Caughey 2009 Induction of labour at 41 weeks versus expectant management of labour until 42 weeks	Potentially serious limitations[1,2,3]	Partially applicable[4]	Study employed a decision-analytic model with a lifetime time horizon for benefits A cost-effectiveness threshold of $100,000 per QALY is used to assess cost-effectiveness but it was possible to estimate the probability cost-effective at a threshold of $25,000 per QALY (≈£24,000 per QALY[5]) from a cost-effectiveness acceptability curve.	£353[5]	0.033 QALYs	£10,377 per QALY[5] gained	One-way sensitivity analysis was undertaken on all model probabilities and costs. This produced an ICER of £25,392 per QALY[5] when a 22% caesarean birth rate was assumed. Probabilistic sensitivity analysis suggested there was an approximate 80% chance that induction of labour was cost-effective at a threshold of £24,000 per QALY[5]
Caughey 2009 Induction of labour at 40 weeks versus expectant management of labour until 41 weeks	Potentially serious limitations[1,2,3]	Partially applicable[4]	Study employed a decision-analytic model with a lifetime time horizon for benefits	£258[5]	0.027 QALYs	£9,535 per QALY gained[5]	One-way sensitivity analysis was undertaken on all model probabilities and costs. This produced an ICER of £27,136 per QALY[5] when a 22% caesarean birth rate was assumed. Probabilistic sensitivity analysis suggested there was just over a 50% chance that induction of labour was cost-

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
							effective at a threshold of £24,000 per QALY
Caughey 2009 Induction of labour at 39 weeks versus expectant management of labour until 40 weeks	Potentially serious limitations[1,2,3]	Partially applicable[4]	Study employed a decision-analytic model with a lifetime time horizon for benefits	£303[5]	0.0017 QALYs	£19,413 per QALY[5]	One-way sensitivity analysis was undertaken on all model probabilities and costs. This produced an ICER of £69,067 per QALY[5] when a 22% caesarean birth rate was assumed. A probabilistic sensitivity analysis suggested there was just under a 50% probability that induction of labour was cost-effective at £24,000 per QALY
Caughey 2009 Expectant management of labour until 40 weeks versus expectant management of labour until 41 weeks	Potentially serious limitations[1,2,3]	Partially applicable[4]	Study employed a decision-analytic model with a lifetime time horizon for benefits	£324[5]	0.026 QALYs	£13,344 per QALY[5]	One-way sensitivity analysis was undertaken on the caesarean birth rate. This produced an ICER of £24,894 per QALY[5] when a 22% caesarean birth rate was assumed.
Caughey 2009 Induction of labour at 39 weeks versus expectant management of labour until 41 weeks	Potentially serious limitations[1,2,3]	Partially applicable[4]	Study employed a decision-analytic model with a lifetime time horizon for benefits	£628[3,5]	0.042 QALYs[6]	£14,948 per QALY[5,6]	The study did not explicitly address an incremental comparison of these alternatives.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Hersh 2019 IoL at 39 weeks versus expectant management of labour until 41 weeks	Potentially serious limitations[1,3]	Partially applicable[4]	Study employed a decision-analytic model with a lifetime time horizon for benefits A cost-effectiveness threshold of $100,000 per QALY is used to assess cost-effectiveness	£1,006[7]	0.014 QALYs	£84,184 per QALY[7]	One-way sensitivity analysis was undertaken for all model probabilities, utilities and costs. The cost of induction of labour, stillbirth, rates of caesarean birth, hypertensive disorders of pregnancy and stillbirth are identified as important determinants of cost-effectiveness. Probabilistic sensitivity analysis suggested there was a 65% chance that induction of labour was cost-effective using a threshold of $100,000 per QALY

[1] The study does not include NICU admission which would cause cost-effectiveness of earlier induction to be underestimated if that resulted in a lower rate of NICU admissions
[2] The study is dated and will not capture more recent data on effectiveness in its model inputs
[3]. The process of identifying unit costs from published literature is not described.
[4] The study was based on US healthcare and costs and practice are unlikely to be generalisable to the NHS.
[5] US costs from a 2007 price year were updated for inflation to 2019/20 using an inflator of 1.24 derived from the hospital & community health services (HCHS) index and NHS Cost Inflation Index (NHSCII). Prices were converted from Pounds Sterling using an exchange rate of £1 = $1.29 based on the average exchange rate for the year until 31 March 2021 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/977861/avergae_for_the_year_to_31_March_2021.csv/preview)
[6] This incremental analysis was calculated based on data available in the study, but was not presented in the study itself.
[7] US costs from a 2018 price year were updated for inflation to 2019/20 using an inflator of 1.02 derived from the hospital & community health services (HCHS) index and NHS Cost Inflation Index (NHSCII). Prices were converted from Pounds Sterling using an exchange rate of £1 = $1.29 based on the average exchange rate for the year until 31 March 2021 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/977861/avergae_for_the_year_to_31_March_2021.csv/preview)

Appendix J – Health economic analysis

Health economic analysis for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

No health economic analysis was carried out for this review question.

Appendix K – Excluded studies

Excluded studies for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Clinical studies

Table 29: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
(2019) SMFM Statement on Elective Induction of Labor in Low-Risk Nulliparous Women at Term: the ARRIVE Trial. American Journal of Obstetrics and Gynecology 221(1): B2-B4	- Study design Narrative overview of ARRIVE trial, data cannot be extracted. Original RCT assessed for inclusion: Grobman 2018
Actrn (2019) Screening and Induction of Labour: oUTcomes for mothers and babies. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12619000388112	- Trial registration information
Amano, K., Saito, K., Shoda, T. et al. (1999) Elective induction of labor at 39 weeks of gestation: a prospective randomized trial. The journal of obstetrics and gynaecology research 25(1): 33-7	- Comparison/control group Expectant management group followed to 42 weeks, but no mention of induction or clinical management if undelivered at 42 weeks (no clear intention to induce)
Ayala, Nina K.; Lewkowitz, Adam K.; Rouse, Dwight J. (2020) Delivery at 39 Weeks of Gestation: The Time Has Come. Obstetrics and gynecology	- Study design Narrative review of literature
Baev, O.; Rumyantseva, V.; Tysyachnyu, O. (2018) Randomized trial of labour preinduction with mifepristone versus expectant management. International Journal of Gynecology and Obstetrics 143(supplement3): 277	- Conference abstract/poster
Bailit, Jennifer L., Grobman, William, Zhao, Yuan et al. (2015) Nonmedically indicated induction vs expectant treatment in term nulliparous women. American journal of obstetrics and gynecology 212(1): 103.e1-7	- Study design Retrospective study (chart review/ audit)
Bapoo, S., Shukla, M., Abbasi, N. et al. (2018) Induction of labour in low-risk pregnancies before 40 weeks of gestation: A systematic review and meta-analysis. Obstetrics and Gynecology 131(supplement1): 176s	- Conference abstract/poster
Bashir, K.; Navid, S.; Awan, A. S. (2017) A comparison of 24 hours expectant management versus induction of labour in pre-labour rupture of membranes at term. Medical Forum Monthly 28(5): 7-10	- Population Women had ruptured membranes; referred to trial "within 8 hours of onset of leaking"
Battarbee, A. N. (2019) 46: Maternal and neonatal outcomes associated with early amniotomy in term nulliparous labor induction. American Journal of Obstetrics and Gynecology 220(1supplement): 37	- Conference abstract/poster
Benito Reyes, V., Hurtado Mendoza, R., Rodriguez Rodriguez, F. et al. (2010) Elective	- Non-English language paper Article in Spanish

Study	Reason for exclusion
termination versus expectant management in prolonged pregnancy: a prospective study of 200 pregnant women. Progresos de obstetricia y ginecologia 53(11): 446-453	
Boulvain, M., Senat, M. V., Rozenberg, P. et al. (2012) Induction of labor or expectant management for large-for-dates fetuses: A randomized controlled trial. American Journal of Obstetrics and Gynecology 206(1suppl1): 2	- Conference abstract/poster
Brane, Elena; Olsson, Ann; Andolf, Ellika (2014) A randomized controlled trial on early induction compared to expectant management of nulliparous women with prolonged latent phases. Acta obstetricia et gynecologica Scandinavica 93(10): 1042-9	- Comparison/control group No intention to induce in expectant management (control) group unless requested by woman or indicated clinically
Breart, G., Goujard, J., Maillard, F. et al. (1982) [Comparison of 2 obstetrical attitudes vis-a-vis inducing labor at term. Randomized study]. Comparaison de deux attitudes obstetricales vis-a-vis du declenchement artificiel du travail a terme. Essai randomise. 11(1): 107-12	- Non-English language paper Article in French
Briscoe, D., Nguyen, H., Mencer, M. et al. (2005) Management of pregnancy beyond 40 weeks' gestation. American Family Physician 71(10): 1935-1941	- Study design Narrative overview of literature
Bruinsma, A., Keulen, J., Kortekaas, J. et al. (2017) Induction of labor at 41 weeks or expectant management until 42 weeks-preliminary results of the INDEX trial. American Journal of Obstetrics and Gynecology 216(1supplement1): S27-S28	- Conference abstract/poster
Bruinsma, A., Keulen, J., Kortekaas, J. et al. (2017) Induction of labour at 41 weeks or expectant management until 42 weeks in obstetrical low risk women (the INDEX trial). BJOG: An International Journal of Obstetrics and Gynaecology 124(supplement2): 15	- Conference abstract/poster
Burgos, Jorge, Rodriguez, Leire, Otero, Borja et al. (2012) Induction at 41 weeks increases the risk of caesarean section in a hospital with a low rate of caesarean sections. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 25(9): 1716-8	- Study design Retrospective cohort study
Cardozo, L.; Fysh, J.; Pearce, J. M. (1986) Prolonged pregnancy: the management debate. British medical journal (Clinical research ed.) 293(6554): 1059-63	- Comparison/control group Conservative (control) group monitored until 40+16 (42+2) weeks; they could then "request or decline induction of labour after 42 weeks"
Carmichael, Suzan L. and Snowden, Jonathan M. (2019) The ARRIVE Trial: Interpretation from an Epidemiologic Perspective. Journal of midwifery & women's health 64(5): 657-663	- Study design Epidemiological impact of ARRIVE trial (original RCT paper assessed for inclusion: Grobman 2018)
Caughey, Aaron B., Sundaram, Vandana, Kaimal, Anjali J. et al. (2009) Maternal and neonatal outcomes of elective induction of	- Study design

Study	Reason for exclusion
labor. Evidence report/technology assessment: 1-257	Systematic review. References checked for inclusion
Caughey, Aaron B., Sundaram, Vandana, Kaimal, Anjali J. et al. (2009) Systematic review: elective induction of labor versus expectant management of pregnancy. Annals of internal medicine 151(4): 252-63	- Study design Systematic review. References checked for inclusion
Chakravarti, S. and Goenka, B. (2000) Conservative policy of induction of labor in uncomplicated postdated pregnancies. XVI FIGO world congress of obstetrics & gynecology; 2000 sept 3-8; washington dc, USA book3: 62	- Conference abstract/poster
Chen, D. C., Yuan, S. S. F., Su, H. Y. et al. (2005) Urinary cyclic guanosine 3',5'-monophosphate and cyclic adenosine 3',5'-monophosphate changes in spontaneous and induced onset active labor. Acta Obstetricia et Gynecologica Scandinavica 84(11): 1081	- No relevant outcomes - Comparison/control group Timing of birth data unavailable for expectant management group
Coates, Dominiek, Makris, Angela, Catling, Christine et al. (2020) A systematic scoping review of clinical indications for induction of labour. PloS one 15(1): e0228196	- Study design Systematic review. References checked for inclusion
Cohain, J. S. (2015) To what extent do English language RCT meta-analysis justify induction of low-risk pregnancy for postdates?. Journal de gynecologie, obstetrique et biologie de la reproduction 44(5): 393-7	- Study design Narrative overview of literature
Cohn, M and Rogers, M (1992) Post maturity; a randomised study in a Hong Kong population. Proceedings of the 26th British Congress of Obstetrics and Gynaecology; 1992 July 7-10; Manchester, UK 306	- Conference abstract/poster
Costantine, M. M. (2020) 461: Resource utilization in low-risk pregnant women after 39 weeks by body mass index. American Journal of Obstetrics and Gynecology 222(1supplement): S302-S303	- Conference abstract/poster
Crowley, P. (2000) Interventions for preventing or improving the outcome of delivery at or beyond term. The Cochrane database of systematic reviews: cd000170	- Other SR. Superceded by Gulmezoglu 2012 Cochrane review
Daskalakis, George, Zacharakis, Dimitrios, Simou, Maria et al. (2014) Induction of labor versus expectant management for pregnancies beyond 41 weeks. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 27(2): 173-6	- Study design Retrospective study
de Miranda, E., van der Bom, J. G., Bonsel, G. J. et al. (2006) Membrane sweeping and prevention of post-term pregnancy in low-risk pregnancies: a randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 113(4): 402-8	- No relevant outcomes

Study	Reason for exclusion
Dekker, Rebecca L. (2016) Labour induction for late-term or post-term pregnancy. Women and birth : journal of the Australian College of Midwives 29(4): 394-8	- Study design Narrative overview of literature, discussing Hannah 1992 "post-term trial"
Dogl, M.; Heimstad, R.; Vanky, E. (2012) Cervical ripening- Bishop score, cervical length and hormonal status in post-term pregnancies. Acta Obstetricia et Gynecologica Scandinavica 91(suppl159): 75	- Conference abstract/poster
Dyson, D. C.; Miller, P. D.; Armstrong, M. A. (1987) Management of prolonged pregnancy: induction of labor versus antepartum fetal testing. American journal of obstetrics and gynecology 156(4): 928-34	- Comparison/control group No intention to induce in monitoring (control) group unless clinically indicated; increased monitoring after 42 weeks
Edwards, M. S. (1996) Mifepristone: cervical ripening and induction of labor. Clinical obstetrics and gynecology 39(2): 469-73	- Study design Narrative overview of the literature
El-Sayed, Y. Y. (2019) 23: Factors associated with adverse outcomes in nulliparas at 39 weeks with induction or expectant management. American Journal of Obstetrics and Gynecology 220(1supplement): 20	- Conference abstract/poster
el-Torkey, M. and Grant, J. M. (1992) Sweeping of the membranes is an effective method of induction of labour in prolonged pregnancy: a report of a randomized trial. British journal of obstetrics and gynaecology 99(6): 455-8	- Intervention Assesses method of induction, not timing
Goeree, R.; Hannah, M.; Hewson, S. (1995) Cost-effectiveness of induction of labour versus serial antenatal monitoring in the Canadian Multicentre Postterm Pregnancy Trial. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 152(9): 1445-50	- No relevant outcomes Focus on cost-effectiveness. Relevant clinical data could not be extracted
Gonen, O., Rosen, D. J., Dolfin, Z. et al. (1997) Induction of labor versus expectant management in macrosomia: a randomized study. Obstetrics and gynecology 89(6): 913-7	- Population Induction timing in women with suspected macrosomia (obstetric complication)
Grobman, W. (2018) A randomized trial of elective induction of labor at 39 weeks compared with expectant management of low-risk nulliparous women. American Journal of Obstetrics and Gynecology 218(1supplement1): 601	- Conference abstract/poster
Grobman, W. A. (2019) 2: Resource utilization among low-risk nulliparas randomized to elective induction at 39 weeks or expectant management. American Journal of Obstetrics and Gynecology 220(1supplement): S2-S3	- Conference abstract/poster
Grobman, W. A., Sandoval, G., Reddy, U. M. et al. (2020) Health resource utilization of labor induction versus expectant management. American Journal of Obstetrics and Gynecology	- No relevant outcomes Secondary analysis of ARRIVE trial (Grobman 2018); no additional relevant data provided

Study	Reason for exclusion
Gulmezoglu, A. M.; Crowther, C. A.; Middleton, P. (2009) Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database of Systematic Reviews: cd004945	- Other SR superceded by 2012 update
Gulmezoglu, A. Metin, Crowther, Caroline A., Middleton, Philippa et al. (2012) Induction of labour for improving birth outcomes for women at or beyond term. The Cochrane database of systematic reviews: cd004945	- Study design Systematic review. References checked for inclusion. Provides no additional data
Hannah, M. E., Hannah, W. J., Hellmann, J. et al. (1992) Induction of labor as compared with serial antenatal monitoring in post- term pregnancy: A randomized controlled trial. New England Journal of Medicine 326(24): 1587-1592	- Comparison/control group IF expectant management (control) group were undelivered by 44 weeks, they were treated immediately through either induction of labour or caesarean. Unclear whether through woman's choice, clinical need, or protocol at this point
Hannah, M. E., Huh, C., Hewson, S. A. et al. (1996) Postterm pregnancy: putting the merits of a policy of induction of labor into perspective. Birth (Berkeley, Calif.) 23(1): 13-9	- No relevant outcomes Post-hoc analysis of Hannah 1992
Heden, L., Ingemarsson, I., Ahlstrom, H. et al. (1991) Induction of labor vs conservative management in prolonged pregnancy: controlled study. International journal of feto-maternal medicine 4(4): 148-152	- Comparison/control group No intention to induce in expectancy (control) group, unless clinically indicated; treated with usual care for that department/ hospital
Heimstad, R., Romundstad, P. R., Hyett, J. et al. (2007) Women's experiences and attitudes towards expectant management and induction of labor for post-term pregnancy. Acta Obstetricia et Gynecologica Scandinavica 86(8): 950-956	- No relevant outcomes Same trial as Heimstad 2007. Cannot use SF-36 data as they were collected at recruitment at 41 weeks (pre-induction), cannot use attitudes/experiences data as they were pooled across induction and serial monitoring (control) groups
Heimstad, R., Skogvoli, E., Mattsson, L. et al. (2008) Induction of labour or serial antenatal fetal monitoring in post-term pregnancy. A randomised controlled trial. 36th nordic congress of obstetrics and gynecology; 2008 june 14-17; reykjavik, iceland: 84	- Conference abstract/poster
Henry, G. R. (1969) A controlled trial of surgical induction of labour and amnioscopy in the management of prolonged pregnancy. The Journal of obstetrics and gynaecology of the British Commonwealth 76(9): 795-8	- Comparison/control group No intention to induce in amnioscopy only (control) group, though 12 were surgically induced due to accidental rupture of membranes
Hjertberg, R., Hammarstrom, M., Moberger, B. et al. (1996) Premature rupture of the membranes (PROM) at term in nulliparous women with a ripe cervix. A randomized trial of 12 or 24 hours of expectant management. Acta obstetricia et gynecologica Scandinavica 75(1): 48-53	- Intervention Examines management after PROM
Hussain, Arwa Abbas, Yakoob, Mohammad Yawar, Imdad, Aamer et al. (2011) Elective induction for pregnancies at or beyond 41 weeks of gestation and its impact on stillbirths: a systematic review with meta-analysis. BMC public health 11suppl3: 5	- Study design Systematic review. References checked for inclusion

Study	Reason for exclusion
Iqbal, S. (2004) Management of prolonged pregnancy. JCPSP, journal of the college of physicians and surgeons, pakistan 14(5): 274-277	- Study design Quasi-RCT - Comparison/control group Expectant management (control) group managed until 43 weeks (301 days), unclear how they were managed from 43 weeks (no clear intention to induce unless clinically indicated).
Isrctn (2017) The Finnish randomised controlled multicentre trial on optimal timing of labor induction in nulliparous women with post-term pregnancy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN83219789	- Trial registration information
James, C., George, S. S., Gaunekar, N. et al. (2001) Management of prolonged pregnancy: a randomized trial of induction of labour and antepartum foetal monitoring. The National medical journal of India 14(5): 270-3	- Comparison/control group No usable timing of birth data for expectant management (control) group
Katz, Z., Yemini, M., Lancet, M. et al. (1983) Non-aggressive management of post-date pregnancies. European journal of obstetrics, gynecology, and reproductive biology 15(2): 71-9	- Comparison/control group No intention to induce (no upper limit) in non-induction group
Keulen, Judit K. J., Bruinsma, Aafke, Kortekaas, Joep C. et al. (2018) Timing induction of labour at 41 or 42 weeks? A closer look at time frames of comparison: A review. Midwifery 66: 111-118	- Study design Systematic review. References checked for inclusion. Provides no additional data
Kortekaas, J. C., Bruinsma, A., Keulen, J. K. et al. (2014) Effects of induction of labour versus expectant management in women with impending post-term pregnancies: the 41 week - 42 week dilemma. BMC pregnancy and childbirth 14: 350	- Study design Study protocol of INDEX trial
Kortekaas, J., Bruinsma, A., Keulen, J. et al. (2018) Induction of labour at 41 weeks versus expectant management until 42 weeks (index-trial). International Journal of Gynecology and Obstetrics 143(supplement3): 256	- Conference abstract/poster
Ladfors, L., Mattsson, L. A., Eriksson, M. et al. (1996) A randomised trial of two expectant managements of prelabour rupture of the membranes at 34 to 42 weeks. British journal of obstetrics and gynaecology 103(8): 755-62	- Population Women already had PROM; induced within 2 hours or 72 hours of PROM occurring
Leijon, I., Finnstrom, O., Hedenskog, S. et al. (1980) Spontaneous labor and elective induction--a prospective randomized study. II. Bilirubin levels in the neonatal period. Acta obstetricia et gynecologica Scandinavica 59(2): 103-6	- No relevant outcomes Same study as Leijon 1979 and Tylleskar 1979; no additional relevant outcomes
Liu, Jing, Song, Guang, Meng, Tao et al. (2018) Membrane sweeping added to formal induction method to increase the spontaneous vaginal delivery: a meta-analysis. Archives of gynecology and obstetrics 297(3): 623-630	- Intervention Does not compare different timing of induction

Study	Reason for exclusion
Magann, E. F., Chauhan, S. P., McNamara, M. F. et al. (1999) Membrane sweeping versus dinoprostone vaginal insert in the management of pregnancies beyond 41 weeks with an unfavorable cervix. Journal of perinatology : official journal of the California Perinatal Association 19(2): 88-91	- Intervention Does not compare different timing of induction
Marrs, Caroline, La Rosa, Mauricio, Caughey, Aaron et al. (2019) Elective Induction at 39 Weeks of Gestation and the Implications of a Large, Multicenter, Randomized Controlled Trial. Obstetrics and gynecology 133(3): 445-450	- Study design Narrative review of literature and implications of ARRIVE trial
Martin, D. H., Thompson, W., Pinkerton, J. H. et al. (1978) A randomized controlled trial of selective planned delivery. British journal of obstetrics and gynaecology 85(2): 109-13	- Population Control group were excluded if they went beyond 42 weeks (induction not intended within study, data excluded if induction performed in control group)
Martin, J. N., Jr., Sessums, J. K., Howard, P. et al. (1989) Alternative approaches to the management of gravidas with prolonged-postterm-postdate pregnancies. Journal of the Mississippi State Medical Association 30(4): 105-11	- Comparison/control group Conservative/surveillance (control) group were managed until end or 43rd week then "scheduled for delivery and pregnancy terminated" by induction or caesarean (unclear which)
McKenzie, I.; Davis, D.; Ferguson, S. (2018) Induction of labour versus expectant management for well women and babies in pregnancies extending beyond 41 weeks: A systematic review and meta-analysis. Women and Birth 31(supplement1): 36	- Conference abstract/poster
McNellis, D., Medearis, A. L., Fowler, S. et al. (1994) A clinical trial of induction of labor versus expectant management in postterm pregnancy: The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. American Journal of Obstetrics and Gynecology 170(3): 716-723	- Other Duplicate (NICHHD 1994)
Medearis, A. L. (1990) Postterm pregnancy: active labor induction (PGE2 gel) not associated with improved outcomes compared to expectant management. A preliminary report. Proceedings of 10th annual meeting of society of perinatal obstetricians; 1990 jan 23-27; houston, texas, USA: 17	- Conference abstract/poster
Middleton, Philippa; Shepherd, Emily; Crowther, Caroline A. (2018) Induction of labour for improving birth outcomes for women at or beyond term. The Cochrane database of systematic reviews 5: cd004945	- Study design Systematic review. References checked for inclusion
Middleton, Philippa, Shepherd, Emily, Flenady, Vicki et al. (2017) Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). The Cochrane database of systematic reviews 1: cd005302	- Intervention Examines management/induction after PROM

Study	Reason for exclusion
Miller, N. R., Cypher, R. L., Foglia, L. M. et al. (2014) Elective induction of nulliparous labor at 39 weeks of gestation: A randomized clinical trial. Obstetrics and Gynecology 123(suppl1): 72s	- Conference abstract/poster
Miller, Nathaniel R., Cypher, Rebecca L., Foglia, Lisa M. et al. (2015) Elective Induction of Labor Compared With Expectant Management of Nulliparous Women at 39 Weeks of Gestation: A Randomized Controlled Trial. Obstetrics and gynecology 126(6): 1258-64	- Comparison/control group Expectant management (control) group were "...delivered for obstetric indications, but no later than 42 weeks of gestation" - unclear whether they would then be induced, undergo other intervention, or released from protocol
Miller and (2016) Elective induction of labor compared with expectant management of nulliparous women at 39 weeks of gestation: a randomized controlled trial: editorial comment. Obstetrical and gynecological survey. 71 (4) (pp 197-198), 2016. Date of publication: 2016.	- Study design Editorial comment on Miller 2015
Mishanina, Ekaterina, Rogozinska, Ewelina, Thatthi, Tej et al. (2014) Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 186(9): 665-73	- Study design Systematic review. References checked for inclusion
Mollart, Lyndall; Skinner, Virginia; Foureur, Maralyn (2016) A feasibility randomised controlled trial of acupressure to assist spontaneous labour for primigravid women experiencing a post-date pregnancy. Midwifery 36: 21-7	- Intervention Induction method used (acupressure) not advocated in this guideline
Moore, R. L., O'Connor, C., Byrne, F. et al. (2019) 793: Obstetric and neonatal outcomes in prolonged pregnancies at or beyond 42 weeks' gestation. American Journal of Obstetrics and Gynecology 220(1supplement): S518-S519	- Conference abstract/poster
Myers, E. R., Blumrick, R., Christian, A. L. et al. (2002) Management of prolonged pregnancy. Evidence report/technology assessment (Summary): 1-6	- Study design HTA report. References checked for inclusion
Nct (2006) Post Term Pregnancy - Induction of Labor or Monitoring of Pregnancy. https://clinicaltrials.gov/show/NCT00385229	- Trial registration information
NICHHD; McNellis; (1994) A clinical trial of induction of labor vs expectant management of postterm pregnancy. American journal of obstetrics and gynecology 170: 716-723	- Comparison/control group Expectant group monitored until 308 days (44 weeks), then released from protocol if undelivered, and "managed by the method appropriate to the clinical situation". Unclear if planned to induce or use operative/other intervention
Nielsen, T. M., Pedersen, M. V., Milidou, I. et al. (2019) Long-term cognition and behavior in children born at early term gestation: A systematic review. Acta Obstetricia et Gynecologica Scandinavica 98(10): 1227-1234	- No relevant outcomes

Study	Reason for exclusion
Ocon, L., Hurtado, R., Coteron, J. J. et al. (1997) Prolonged pregnancy: Procedure guidelines. Progresos en Obstetricia y Ginecologia 40(2): 101-106	- Non-English language paper Article in Spanish
Osmundson, S.; Ou-Yang, R.; Grobman, W. (2009) Labor outcomes among nulliparous women with an unfavorable cervix who are electively induced versus expectantly managed at term. American Journal of Obstetrics and Gynecology 201(6suppl1): 124	- Conference abstract/poster
Osmundson, S.; Ou-Yang, R.; Grobman, W. (2009) Labor outcomes among nulliparous women with a favorable cervix who are electively induced versus expectantly managed at term. American Journal of Obstetrics and Gynecology 201(6suppl1): 123	- Other Duplicate
Pearce, JM and Cardozo, C (1988) Prolonged pregnancy: the management debate. British Medical Journal 297(6650): 715	- No relevant outcomes Post-hoc analysis of Cardozo 1986
Quibel, T., Raynal, P., Bouyer, C. et al. (2020) Evolution of the cesarean delivery rate from 37 weeks of gestation among nulliparas or how to evaluate the external validity of a randomized North American trial about induction of labor. Gynecologie Obstetrique Fertilite et Senologie	- Non-English language paper Article in French
Rayburn, W. F., Gittens, L. N., Lucas, M. J. et al. (1999) Weekly administration of prostaglandin E2 gel compared with expectant management in women with previous cesareans. Obstetrics and Gynecology 94(2): 250-254	- Comparison/control group Expectant management (control) group had additional assessment at 40 and 41 weeks, but awaited spontaneous labour "unless intervention was indicated". No intention to induce at an upper limit
Rayburn, Lucas, Gittens et al. (1998) Attempted vaginal birth after cesarean section: a multicenter comparison of outpatient prostaglandin E(2) gel with expectant management. Primary care update for Ob/Gyns 5(4): 182-183	- Conference abstract/poster
Roach, V. J. and Rogers, M. S. (1997) Pregnancy outcome beyond 41 weeks gestation. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 59(1): 19-24	- Comparison/control group Expectant management (control) group had no upper limit for delivery; median delivery within same week as induced group (298.5 days vs 294 days)
Rozenberg, P. (2016) In case of fetal macrosomia, the best strategy is the induction of labor at 38 weeks of gestation. Journal de Gynecologie Obstetrique et Biologie de la Reproduction 45(9): 1037-1044	- Non-English language paper Article in French
Rydahl, Eva; Eriksen, Lena; Juhl, Mette (2019) Effects of induction of labor prior to post-term in low-risk pregnancies: a systematic review. JBI database of systematic reviews and implementation reports 17(2): 170-208	- Study design Systematic review. References checked for inclusion
Rydhstrom, H. and Ingemarsson, I. (1991) No benefit from conservative management in nulliparous women with premature rupture of the membranes (PROM) at term. A randomized	- Intervention Examines management after PROM

Study	Reason for exclusion
study. Acta obstetricia et gynecologica Scandinavica 70(78): 543-7	
Saccone, Gabriele and Berghella, Vincenzo (2015) Induction of labor at full term in uncomplicated singleton gestations: a systematic review and metaanalysis of randomized controlled trials. American journal of obstetrics and gynecology 213(5): 629-36	- Other SR. Superceded by 2019 update
Saccone, Gabriele, Della Corte, Luigi, Maruotti, Giuseppe M. et al. (2019) Induction of labor at full-term in pregnant women with uncomplicated singleton pregnancy: A systematic review and meta-analysis of randomized trials. Acta obstetricia et gynecologica Scandinavica 98(8): 958-966	- Study design Systematic review. References checked for inclusion. Provides no additional data
Sahraoui, W., Hajji, S., Bibi, M. et al. (2005) [Management of pregnancies beyond forty-one week's gestation with an unfavorable cervix]. Prise en charge obstetricale des grossesses prolongees au-dela de 41 semaines d'amenorrhee avec un score de Bishop defavorable. 34(5): 454-62	- Non-English language paper Article in French
Sanchez-Ramos, Luis, Olivier, Felicia, Delke, Isaac et al. (2003) Labor induction versus expectant management for postterm pregnancies: a systematic review with meta-analysis. Obstetrics and gynecology 101(6): 1312-8	- Study design Systematic overview of SRs. References checked for inclusion
Sande, H. A.; Tuveng, J.; Fonstelien, T. (1983) A prospective randomized study of induction of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 21(4): 333-6	- Comparison/control group No intention to induce in spontaneous birth (control) group; treated with usual care for that department/hospital
Silver, R. M. (2019) 794: Personalized counseling regarding induction of labor versus expectant management at 39 weeks. American Journal of Obstetrics and Gynecology 220(1supplement): 519	- Conference abstract/poster
Singh, Nilanchali, Tripathi, Reva, Mala, Yedla Manikya et al. (2014) Breast stimulation in low-risk primigravidas at term: does it aid in spontaneous onset of labour and vaginal delivery? A pilot study. BioMed research international 2014: 695037	- Intervention Induction method used (breast stimulation) not advocated in this guideline
Siozos, C. and Stanley, K. P. (2005) Prolonged pregnancy. Current Obstetrics and Gynaecology 15(2): 73-79	- Study design Narrative overview of the literature
Slctr (2014) A study to compare two methods of inducing labour in full term pregnancy. http://www.who.int/trialsearch/Trial2.aspx?TrialID=SLCTR/2014/001	- Trial registration information
Sotiriadis, A., Petousis, S., Thilaganathan, B. et al. (2019) Maternal and perinatal outcomes after elective induction of labor at 39 weeks in uncomplicated singleton pregnancy: a meta-analysis. Ultrasound in obstetrics & gynecology	- Study design Systematic review. References checked for inclusion. Provides no additional data

Study	Reason for exclusion
: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 53(1): 26-35	
Stock, Sarah J., Ferguson, Evelyn, Duffy, Andrew et al. (2012) Outcomes of elective induction of labour compared with expectant management: population based study. BMJ (Clinical research ed.) 344: e2838	- Study design Retrospective cohort (audit) study
Sue-A-Quan, A. K., Hannah, M. E., Cohen, M. M. et al. (1999) Effect of labour induction on rates of stillbirth and cesarean section in post-term pregnancies. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 160(8): 1145-9	- Study design Retrospective cohort (audit) study
Suikkari, AM, Jalkanen, M, Heiskala, H et al. (1983) Prolonged pregnancy: induction or observation. Acta Obstetricia et Gynecologica Scandinavica 62(s116): 58	- Conference abstract/poster
Tamsen, L.; Lyrenas, S.; Cnattingius, S. (1990) Premature rupture of the membranes--intervention or not. Gynecologic and obstetric investigation 29(2): 128-31	- Intervention Examines management after PROM
Tan, T. (2018) Induction of labour vs expectant management. International Journal of Gynecology and Obstetrics 143(supplement3): 126-127	- Conference abstract/poster
Tita, A. (2010) Timing of delivery and pregnancy outcomes among laboring nulliparous women. Reproductive Sciences 17(3suppl1): 207A-208A	- Conference abstract/poster
Tita, A. T. (2019) 128: Maternal and perinatal outcomes by gestational age with expectant management of full-term low -risk nulliparas. American Journal of Obstetrics and Gynecology 220(1supplement): S100-S101	- Conference abstract/poster
Tylleskar, J.; Finnstrom, O.; Leijon, I. (1979) Spontaneous labor and elective induction - a prospective randomized study. I. Effects on mother and fetus. Acta Obstetricia et Gynecologica Scandinavica 58(6): 513-518	- No relevant outcomes Same study as Leijon 1979. Also examined maternal experience of induction, but "no statistical differences between the groups were found" so data were presented as pooled results only (no additional data could be extracted)
Tylleskar, J., Finnstrom, O., Leijon, I. et al. (1979) Spontaneous labor and elective induction--a prospective randomized study. I. Effects on mother and fetus. Acta obstetricia et gynecologica Scandinavica 58(6): 513-8	- Other Duplicate
Walker, K. F., Bugg, G. J., Macpherson, M. et al. (2016) Randomized Trial of Labor Induction in Women 35 Years of Age or Older. New England journal of medicine 374(9): 813-822	- Comparison/control group Expectant management (control) group were offered induction at 41+0 to 42+0 weeks, but they could decline and continue with expectant monitoring and managed according to local clinical practice
Walker, K., Bugg, G., Macpherson, M. et al. (2015) The 35/39 trial: A multi-centre prospective randomised controlled trial of induction of labour versus expectant	- Conference abstract/poster

Study	Reason for exclusion
management for nulliparous women over 35 years of age. International Journal of Gynecology and Obstetrics 131(suppl5): e221	
Walker, Kate F., Bugg, George, Macpherson, Marion et al. (2012) Induction of labour versus expectant management for nulliparous women over 35 years of age: a multi-centre prospective, randomised controlled trial. BMC pregnancy and childbirth 12: 145	- Study design Protocol for 35/39 trial (Walker 2016)
Walker, Kate F. and Thornton, Jim G. (2018) Delivery at Term: When, How, and Why. Clinics in perinatology 45(2): 199-211	- Study design Systematic overview of SRs. References checked for inclusion
Wennerholm, U. B., Hagberg, H., Brorsson, B. et al. (2009) Induction of labor versus expectant management for post-date pregnancy: Is there sufficient evidence for a change in clinical practice?. Acta Obstetricia et Gynecologica Scandinavica 88(1): 6-17	- Study design Systematic overview of SRs. References checked for inclusion
Witter, F. R. and Weitz, C. M. (1987) A randomized trial of induction at 42 weeks gestation versus expectant management for postdates pregnancies. American journal of perinatology 4(3): 206-11	- Comparison/control group Expectant management (control) group had no upper limit for delivery (no intention to induce at certain point); mean delivery within same week as induced group (296.87 days vs 295.05 days)
Wood, S.; Cooper, S.; Ross, S. (2014) Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials in women with intact membranes. BJOG : an international journal of obstetrics and gynaecology 121(6): 674-685	- Study design Systematic review. References checked for inclusion. Provides no additional data

Economic studies:

Table 30: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Anonymous (2019) Erratum: Induction of labor at 39 weeks of gestation versus expectant management for low-risk nulliparous women: a cost-effectiveness analysis (American Journal of Obstetrics and Gynecology (2019) 220(6) (590.e1-590.e10), (S0002937819303588), (10.1016/j.ajog.2019.02.017)). American Journal of Obstetrics and Gynecology	- Erratum
Goeree, R.; Hannah, M.; Hewson, S. (1995) Cost-effectiveness of induction of labour versus serial antenatal monitoring in the Canadian Multicentre Postterm Pregnancy Trial. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 152(9): 1445-50	- Not full economic evaluation
Kaimal, Anjali J., Little, Sarah E., Odibo, Anthony O. et al. (2011) Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women. American journal of obstetrics and gynecology 204(2): 137.e1-9	- Duplicate of an included paper – economic model and analysis reported in Caughey 2009, an included study
Kaufman, Karen E.; Bailit, Jennifer L.; Grobman, William (2002) Elective induction: an analysis of economic and health consequences. American journal of obstetrics and gynecology 187(4): 858-63	- Not full economic evaluation
Rogers, R. G., Gardner, M. O., Tool, K. J. et al. (2000) Active management of labor: a cost analysis of a randomized controlled trial. Western Journal of Medicine 172(4): 240-243	- Incorrect Intervention
Wennerholm U-B, Flisberg A, Hagberg H, Ladfors L, Jivegård L, Svanberg T, Wessberg A, Bergh C (2012) [Induction of labour at 41 completed until 42 completed gestational weeks, update of mini-HTA VGR 2007].	- Abstract

Appendix L – Research recommendations

Research recommendations for review question: At what gestational age should induction of labour be offered if spontaneous labour does not ensue?

Research recommendation

At what gestational age should induction of labour be offered in the subgroups of women who may be more likely to experience adverse outcomes if pregnancy continues?

Why this is important

There is evidence to suggest the optimal gestational age to offer induction of labour in the general low risk population of pregnant women. However, there are subgroups of women in whom there may be a greater risk of adverse outcomes (for example stillbirth) in the later stages of pregnancy. Those groups include those from BAME backgrounds, with a BMI greater than 30 kg/m^2, age 35 years or more and those having had assisted conception. It is important to know if earlier induction can reduce these risks and if so what is the optimum time to induce in these specific populations.

Rationale for research recommendation

Table 31: Research recommendation rationale

Importance to 'patients' or the population	These subgroups of women may be at higher risk of critical adverse outcomes (for example stillbirth) if their pregnancy continues beyond certain timeframes, it is therefore very important that these risks be minimised.
Relevance to NICE guidance	NICE guidance currently suggests a timeframe of induction for the general low risk population, and for healthcare professionals to consider earlier induction in these subgroups but cannot currently does not have evidence for a more specific time.
Relevance to the NHS	Inducing at the optimum time for these groups of women could reduce adverse outcomes like stillbirth.
National priorities	High – reduction in neonatal mortality is a priority in Saving Babies' Lives and the NHS long-term plan.
Current evidence base	Only limited post-hoc subgroup analyses from existing trials
Equality considerations	Research could help address inequality in adverse outcomes in women from black, Asian and minority ethnic backgrounds

Modified PICO table

Table 32: Research recommendation modified PICO table

Population	Pregnant women from the following subgroups: • Women from BAME backgrounds • Women with a BMI of 30kg/m^2 or more • Women aged 35 years or more • Women who have had assisted conception

Intervention	Induction of labour (by methods as per the NICE recommendations) at: • 41+0 weeks • 40+0 weeks • 39+0 weeks • 38+0 weeks • 37+0 weeks
Comparator	Any of the timing strategies above compared with any other
Outcome	Maternal quality of life, maternal mortality/morbidity (death/uterine rupture), perinatal mortality, mode of birth, maternal satisfaction/experience of care, neonatal unit admission, neonatal morbidity (meconium aspiration syndrome or hypoxic ischemic encephalopathy)
Study design	Randomised controlled trial or non-randomised comparative cohort study with adjustment for confounding factors
Timeframe	Short term, focused on perinatal outcomes
Additional information	None

BAME: Black, Asian and minority ethnic

Research recommendation

Based on individual patient data (IPD) meta-analysis, what is the optimal timing of induction of labour?

Why this is important

The evidence in this report has been used to make a broad recommendation (to the nearest week) about the optimal timing of induction of labour in the low risk population of pregnant women. The precision in that timing recommendation is limited by the heterogeneity in the strategies used in the included studies and the limits of trial level meta-analysis. It is possible the recommendation could be more precise if an individual patient data meta-analysis or network meta-analysis on when fetal death actually occurred was conducted. This sort of analysis could either justify a precise timing or confirm whether a less precise window was appropriate. Either of these outcomes could reduce the likelihood of stillbirth and allow healthcare systems to tailor their service provision around a specific gestational age.

Rationale for research recommendation

Table 33: Research recommendation rationale

Importance to 'patients' or the population	This analysis could reduce the likelihood of stillbirth, a critical outcome for women.
Relevance to NICE guidance	This analysis could allow the timing of induction in the NICE recommendations to be made more precise or delineated
Relevance to the NHS	Beyond the benefit of reducing stillbirths, a further exploration of precise timings would allow NHS services to more efficiently plan birth and induction of labour strategies
National priorities	High – reduction in neonatal mortality is a priority in Saving Babies' Lives and the NHS long-term plan.

Current evidence base	There are a number of randomised controlled trials (included in this evidence report) from which IPD could be sought. Given the conclusion to the SWEPIS trial, it is unlikely that further large randomised controlled trials will be conducted in this area.
Equality considerations	While this analysis would inform the general recommendations, if information on subgroup data is available at an IPD level (e.g. ethnicity, age, assisted conception), it could also be used to refine recommendations on timing in those populations

IPD: individual patient data

Modified PICO table

Table 34: Research recommendation modified PICO table

Population	Women in studies where they have been randomised to different induction of labour timing strategies
Intervention	Time of induction both on an intention to treat level (in other words the strategy randomised to) and an as received level (in other words when induction was actually performed or when spontaneous labour began/fetal death occurred)
Comparator	To be led by the data available for the IPD network meta-analysis but likely used to compare induction windows around the 41+0 week period on a day-by-day basis. Earlier strategies may be of interest for the subgroups listed above that may warrant earlier induction
Outcome	Fetal death
Study design	IPD level network meta-analysis, no new primary evidence likely to be required though researchers may need to update this or equivalent systematic reviews to confirm no more recent primary data is available
Timeframe	Short term, focused on perinatal outcomes
Additional information	None

Appendix M – Post-hoc analyses

While these post-hoc analyses were not specifically described in the review protocol, the committee wished to further explore the relationships between BMI and age (as well as other subgroups, referenced in the discussion) and timing of induction. Few studies reported their population subgrouped by these categories but, where that was available, it is presented below.

Post-hoc analyses - comparison 5: 41 versus 42 weeks

Figure 18: Perinatal death - Subgroup by maternal age (35 years cut-off)

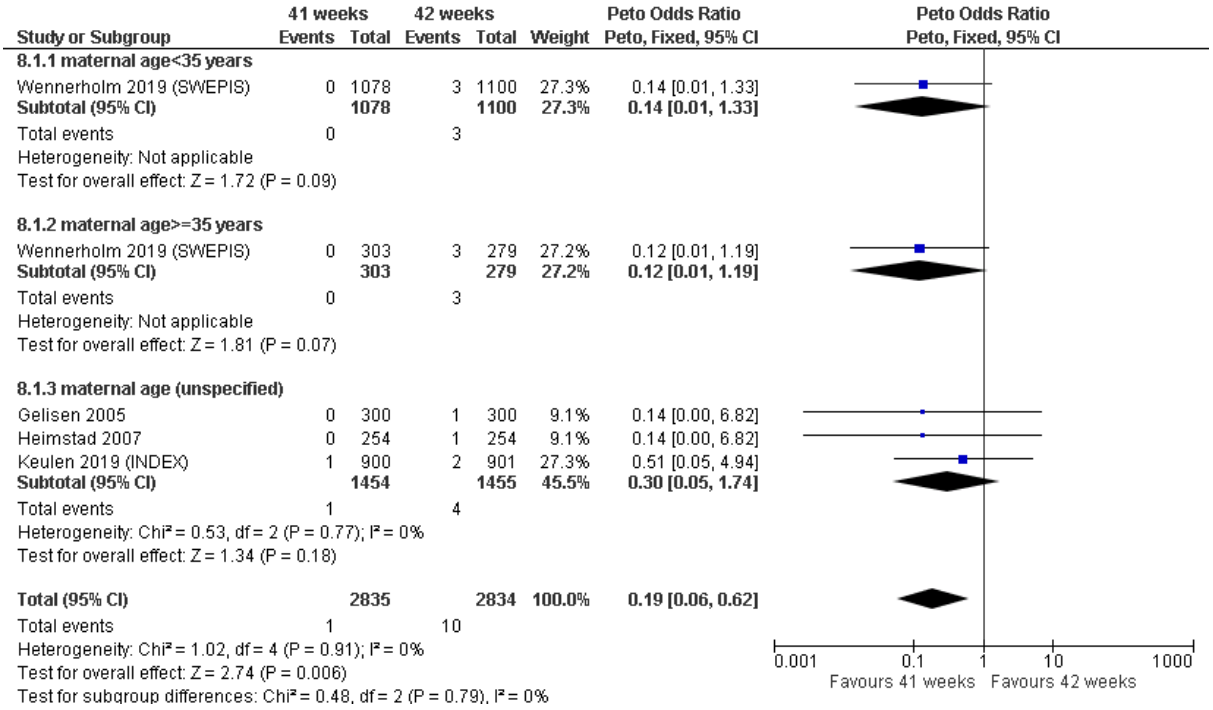


Figure 19: Perinatal death - subgroup by BMI (30 cut-off)