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Review Article

Timing induction of labour at 41 or 42 weeks? A closer look at time frames of comparison: A review

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ABSTRACT

Background: Postterm pregnancy is associated with increased perinatal risk. The WHO defines postterm pregnancy as a pregnancy at or beyond 42 weeks + 0 days, though currently labour is induced at 41 weeks in many settings. Guidelines on timing of labour induction are frequently based on the Cochrane systematic review 'Induction of labour for improving birth outcomes for women at or beyond term' in which is concluded that a policy of induction of labour is associated with fewer adverse perinatal outcome and fewer Caesarean sections. However, the included trials differed regarding the timing of induction, ranging from 39 to beyond 42 weeks while the upper limit of expectant management exceeded a gestational age of 42 weeks in most studies. Objective: to evaluate perinatal mortality, meconium aspiration syndrome and Caesarean section rate of trials comparing a policy of elective induction of labour and expectant management according to timeframes of comparison with a focus on studies within the 41–42 weeks' timeframe. Design: Review. Methods: The systematic review of Cochrane was used as a starting point for assessing relevant trials and a search was performed for additional recent trials. We evaluated incidence and causes of perinatal mortality, incidence of meconium aspiration syndrome and Caesarean section according to three time frames of comparison. We pooled estimates and heterogeneity was tested. The quality of the included trials was assessed using the Quality Assessment Tool for Quantative Studies (EPHPP). Findings: In total 22 trials were included which had all different timeframes of comparison. Only one trial compared induction of labour at 41 weeks + 0–2 days with induction at 42 weeks + 0 days, three other trials compared induction of labour at 41 weeks + 0–6 days with induction at 42 weeks + 0–6 days. In 18 trials the comparison was outside the 41–42 weeks' timeframe: in six trials induction was planned ≤ 40 weeks and in another 12 trials expectant management was beyond 43 weeks. The incidence of potentially gestational age associated perinatal mortality between 41 and 42 weeks was 0/2.444 [0%] (induction) versus 4/2.452 [0.16%] (expectant management), NNT 613; 95%CI 613 – infinite. Two trials in the timeframe of comparison 41–42 weeks were available for evaluation of meconium aspiration syndrome (6/554 (induction) versus 14/554 (expectant management), RR 0.44; 95%CI 0.17–1.16). Three trials in the timeframe 41–42 weeks could be evaluated for Caesarean section, with different inclusion criteria regarding Bishop score. There was no significant difference in the Caesarean section rate 93/629 (induction) versus 106/629 (expectant management), RR 0.88; 95%CI 0.68–1.13. Conclusion: Evidence is lacking for the recommendation to induce labour at 41 weeks instead of 42 weeks for the improvement of perinatal outcome. More studies comparing both timeframes with an adequate sample size are needed to establish the optimal timing of induction of labour in late-term pregnancies.

Introduction

Postterm pregnancy is associated with an increased risk on adverse perinatal outcomes. Although WHO's definition (1998) of postterm pregnancy concerns a gestational age of 42 weeks + 0 days and beyond, late term pregnancy (≥ 41 weeks + 0 days) is considered more and more as the same high risk condition as postterm pregnancy. The presumed increased risk of foetal death is probably an important factor in decision making whether or not to induce labour beyond 41 weeks. The systematic review of Cochrane 'Induction of labour for improving birth outcomes for women at or beyond term' concluded that induction of labour improved perinatal outcome. IOL at or beyond 41 weeks + 0 days was associated with a decreased risk on perinatal mortality and neonatal morbidity caused by meconium aspiration syndrome (MAS) and a lower rate of Caesarean sections (CS). However, the gestational age at start of induction in the included trials varied, with the majority

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of the trials starting IOL beyond 41 weeks + 0 days. Furthermore, the accepted upper limit of gestational age in the expectant management (EM) groups varied as well with most trials exceeding 42 weeks + 0 days (with some up to 44 weeks). The heterogeneity of the included studies hampers a clear interpretation of the results.

Several guidelines on the management of late term and postterm pregnancies were published (Guidance, 2008; American College of and Gynecologists, 2014; American College of et al., 2014), based on data from systematic reviews, especially the Cochrane review of Gülmezoglu et al. (2012). Recently, an updated version of the Cochrane review was published by Middleton et al. (2018). Although the Cochrane review concluded that induction at or beyond 41 weeks improves neonatal and maternal outcomes, the preferred timing for IOL remains indistinct. The conclusion of the Cochrane review is incorporated in various guidelines as a recommendation for induction at or during week 41, resulting in a shift from IOL at 42 weeks to earlier induction starting at 41 weeks (American College of and Gynecologists, 2014; NICE, 2008). However, most studies included in the Cochrane review compared IOL with a policy of EM that goes far beyond 42 weeks. EM beyond 42 weeks is no longer regular policy in current obstetrics which questions the status of the evidence for induction at labour at 41 weeks for improving birth outcomes. Therefore we evaluated existing data with 41 and 42 weeks as relevant time frame of comparison.

Objective

To evaluate perinatal mortality, meconium aspiration syndrome and Caesarean section rate of trials comparing a policy of IOL and EM according to timeframes of comparison with a focus on studies in the 41–42 weeks' timeframe.

Methods

The Cochrane systematic review of Gülmezoglu and the recently updated version of Middleton et al "Induction of labour for improving birth outcomes for women at or beyond term" included the relevant trials we used as a starting point. In our search we checked for more recent trials which were not included in the Cochrane review. Search terms in DARE and NHS Evidence included "labor OR labour AND induction OR postterm pregnancy", and in MEDLINE "labor AND induction AND prolonged pregnancy AND randomized controlled trial". We used the inclusion criteria similar to the critera used in the Cochrane systematic review: randomised controlled trials conducted in women at or beyond term comparing a policy of labour induction with a policy of awaiting spontaneous onset of labour.

We systematically evaluated the quality of the trials using the 'Quality assessment tool for quantitative studies' of EPHPP, additional to the GRADE evaluation performed in the Cochrane review (Armijo-Olivo et al., 2010). The EPHPP tool evaluates six items (selection bias, study design, confounders, blinding, data collection method) that can be scored as strong (no 'weak' rating), moderate (one 'weak' rating) or weak (two or more 'weak' ratings). The quality score was independently assessed by two authors (JK and EDM or JK and AB) and results were compared to set a final score. We evaluated the applicability of the studies for the 41–42 weeks comparison.

We pooled data (unweighted) of the studies within the same timeframe to summarise risk ratios (RR) and 95% confidence intervals (CI) and tested heterogeneity (Comprehensive Meta Analysis V3).

RCTs with alternate allocation and trials which were only available as conference report were excluded because it is not possible to assess the quality of these trials due to missing or incomplete information. We evaluated the timeframe of comparison, incidence of perinatal mortality, MAS and CS with a focus on the 41–42 weeks' timeframe. For perinatal mortality we also identified and evaluated the reported cause of death and the gestational age at time of perinatal death. For MAS we additionaly compared the incidence of neonatal intensive care unit (NICU) admission, because MAS requires neonatal intensive care treatment. For CS we evaluated whether the induction policy in both study arms was comparable.

Results

30 RCTs were included in the recently updated Cochrane systematic review of Middleton et al, we found no additional trials. The 22 studies included in the previous version of Gülmezoglu, were all included in the review of Middleton. Of four trials only conference reports were available, it was not possible to obtain more detailed information regarding these RCTs and the abstracts provided limited and/or incomplete information on the aspects subject to evaluation, and were therefore excluded. (Chakravarti, 2000; Suikkari et al., 1983; Kortekaas et al., 2014; Cohn, 1992 #989)}. We excluded one RCT (Brane et al., 2014), because the objective of this trial was to evaluate the timing of augmentation in the latent phase of labour, which is not similar to labour induction in the absence of contractions. 22 RCTs remained for evaluation (Table 1).

Identification of timeframes of comparison

To identify the incidence of perinatal mortality, MAS and Caesarean section in certain weeks, we categorized the studies in three timeframes of comparison in which the RCTs were performed: IOL ≤ 40 weeks versus EM ≤ 42 weeks, IOL at 41 weeks + 0–6 days versus EM at 42 weeks + 0–6 days, and IOL ≥ 41 weeks versus EM ≥ 43 weeks (Fig. 1). Timing of induction and the upper limit of expectant management varies within the groups.

In six RCTs IOL was performed between 39 and 40 weeks and compared to EM until 41 or 42 weeks (Breart et al., 1982; Cole et al., 1975; Egarter et al., 1989; Nielsen et al., 2005; Miller et al., 2015; Walker et al., 2016).

Four RCTs focused on IOL at 41 weeks + 0–6 days versus EM at 42 weeks + 0–6 days (Chakravarti 2000; Gelisen et al., 2005; Hannah et al., 1992; Heimstad et al., 2008; Sahraoui et al., 2005). Only one trial compared IOL at 41 weeks with expectant management until 42 weeks (Gelisen et al., 2005). We included the RCT of Hannah et al. in this timeframe, although the inclusion time was broader (up to 44 weeks), the majority of the inclusions (IOL 91%, EM 92%) took place in the 41–42 weeks' timeframe.

12 RCTs compared IOL ≥ 41 weeks with EM > 43 weeks. In six RCTs IOL was started at or beyond 41 weeks, but EM was beyond 42 weeks or had no upper limit (Chanrachakul and Herabutya, 2003; Dyson et al., 1987; Henry, 1969; James et al., 2001; Martin et al., 1989; 1994; Suikkari et al., 1983). In six RCTs IOL was performed at or beyond 42 weeks: (Augensen et al., 1987; Ocon, 1997; Roach and Rogers, 1997; Witter and Weitz, 1987; Bergsjo et al., 1989; Herabutya et al., 1992).

Perinatal mortality

In the Cochrane review IOL at or beyond 41 weeks was associated with lower perinatal mortality (RR 0.33; 95%CI 0.14–0.78). Fourteen cases of perinatal mortality occurred in the 22 included RCTs, one in the induction group and thirteen in the expectant management group (Table 1). For perinatal mortality is was possible to obtain the exact gestational age at time of the event, therefore we could assess the cases of perinatal mortality between 41 weeks + 0 days and 42 weeks + 0 days. Nine of the perinatal deaths occurred in RCTs outside the 41 to 42 weeks' time frame. Five perinatal deaths occurred within the 41–42 weeks' time frame, of which one was unlikely to be associated with advancing gestational age.

Perinatal mortality before 41 weeks

Two perinatal deaths occurred before 41 weeks. Cole et al. (1975) reported one perinatal death between 39 and 41 weeks, due to a congenital heart condition. Egarter et al. (1989) reported one intrauterine foetal death at 40 weeks + 3 days of gestation as a result of a cord constriction.

Table 1
Overview of included trials according to gestational age (GA) at intended timing of induction and upper limit of expectant management.

Study (year)	Quality Asessement (EPHPP)	Estimated day of delivery by ultra-sound <22 weeks	Number of inclusions	GA at time of inclusion (in weeks)	GA age at intended start IOL (in weeks)	Excepted upper limit GA EM (in weeks)	Perinatal death n/N	Cause of death (with Gestational Age)	Association with GA	MAS	Caesarean Section
IOL ≤ 40 weeks versus EM ≤ 42 weeks											
Bréart (1982)		No	716	37-39	40	42	Not reported	-	-	Not reported	19/481 (IOL) 16/235 (EM)
Cole (1975)	Moderate	No	228		39-40	41	0/111 (IOL) 1/117 (EM)	Congenital heart condition (GA not reported)	No	Not reported	5/111 (IOL) 9/117 (EM)
Egarter (1989)	Weak	**Yes**	345	40	40	42	0/180 (IOL) 1/165 (EM)	Foetal cord constriction (40w3d)	No	Not reported	2/180 (IOL) 3/165 (EM)
Miller (2015)	Moderate	Yes	161	38w0-6d	39	41-42	-	-	-	Not reported	25/85 (IOL) 14/79 (EM)
Nielsen (2005)	Moderate	No	226	38-39	39-40	42	-	-	-	Not reported	8/116 (IOL) 8/110 (EM)
Walker (2016)	Moderate	Yes	619	36w0d-39w6d	39	41w0d-42w0d	-	-	-	Not reported	98/304 (IOL) 103/314 (EM)
IOL at 41 weeks +0-6 days versus EM at 42 weeks +0-6 days											
Gelisen (2005)	Weak	Yes	600	41	41	42	0/300 (IOL) 1/300 (EM)	Foetal death (41w5d)	Yes	4/300 (IOL) 12/300 (EM)	58/300 (IOL) 66/300 (EM)
Hannah (1992)	Moderate	No	3407		41-44	44 (91% at 42 wks)	0/1701 (IOL) 2/1706 (EM)	1:Stillbirth; hypoxic ischemic encephalo-pathy (41w5d) 2:Acute fetal distress during labor, MAS, SGA (42w0d)	1: Yes 2: Yes (missed SGA)	Not reported	360/1701 (IOL) 418/1706 (EM) *Prostaglandin for cervical ripening only in IOL group*
Heimstad (2007)	Moderate	Yes at 18 weeks	508	41.2 (±2)	41w3d (±2d)	42w6d	0/254 (IOL) 1/254 (EM)	Neonatal death after fetal distress during labor due to true knot in umbilical cord, emergency CS (42w0d)	No	2/254 (IOL) 2/254 (EM)	28/254 (IOL) 33/254 (EM)
Sahraoui (2005)	Weak	Yes <20 weeks	150		41-41w6d	42	0/75 (IOL) 1/75 (EM)	Stillbirth (42w0d)	Yes	Not reported (meconium stained liquid reported)	7/75 (IOL) 7/75 (EM)
IOL ≥ 41 weeks versus EM ≥ 44 weeks											
Chanrachakul (2003)	Moderate	Yes at 18-22 weeks	249	41w3d	41w3d-42	44	-	-	-	Not reported	33/124 (IOL) 27/125 (EM)
Dyson (1987)	Moderate	No	302	>41	>41	No upper limit	0/152 (IOL) 1/150 (EM)	Neonatal death following fetal distress during labor, urgent CS, MAS, persistent fetal circulation (43w4d)	Yes	0/152 (IOL) 6/150 (EM)	22/152 (IOL) 41/150 (EM)
Henry (1969)	Weak	No	112		40w6d-43w1d	No upper limit	0/55 (IOL) 2/57 (EM)	1: Stillbirth after abnormal GTT, GA unknown 2: Neonatal death (MAS) after delayed birth due to refused induction (GA unknown)	1: Unclear 2: Yes	Not reported	0/55 (IOL) 1/57 (EM)

(*continued on next page*)

Table 1 (*continued*)

Study (year)	Quality Asesement (EPHPP)	Estimated day of delivery by ultra-sound <22 weeks	Number of inclusions	GA at time of inclusion (in weeks)	GA age at intended start IOL (in weeks)	Excepted upper limit GA EM (in weeks)	Perinatal death n/N	Cause of death (with Gestational Age)	Association with GA	MAS	Caesarean Section
James (2001)	Moderate	No	74		41	No upper limit	-	-	-	1/37 (IOL)	2/37 (IOL)
										2/37 (EM)	4/37 (EM)
Martin (1989)	Weak	No	22	41.2-43.3	≥ 41w2d	44	-	-	-	Not reported	2/12 (IOL)
											1/10 (EM)
NICHHD (1994)	Moderate	No	440	41-43	41-43	44	-	-	-	1/174 (IOL)	39/174 (IOL)
										2/175 (EM)	32/175 (EM)
IOL at 42 weeks versus EM ≥ 43 weeks											
Augensen (1987)	Weak	No	409	41w3d-42w3d	42	43w2d	-	-	-	Not reported	14/214 (IOL)
											20/195 (EM)
Ocon (1997)	Weak	Yes (1st trimester)	113	42	42w1d	No upper limit	-	-	-	Not reported	10/57 (IOL)
											3/56 (EM)
Roach (1997)	Weak	No	201	41 (± 2d)	42 (±2d)	No upper limit	-	-	-	Not reported	16/96 (IOL)
											18/105 (EM)
Witter (1987)	Moderate		200		42	No upper limit	-	-	-	2/103 (IOL)	30/103 (IOL)
										1/97 (EM)	27/97 (EM)
IOL > 42 weeks versus EM > 44 weeks											
Bergsjö (1989)	Weak	No	188		>42	No upper limit	1/94 (IOL)	1: (IOL) severe malformations (>42 weeks)	1: No	4/94 (IOL)	27/94 (IOL)
							2/94 (EM)	2: (EM) malformations (>42 weeks)	2: No	8/94 (EM)	39/94 (EM)
								3: (EM) pneumonia (>42 weeks)	3: Unclear		
Herabutya (1992)	Weak	No	108	>42	>42	44	0/57 (IOL)	Congenital anomaly (43 weeks)	No	Not reported	27/57 (IOL)
							1/51 (EM)				24/51 (EM)

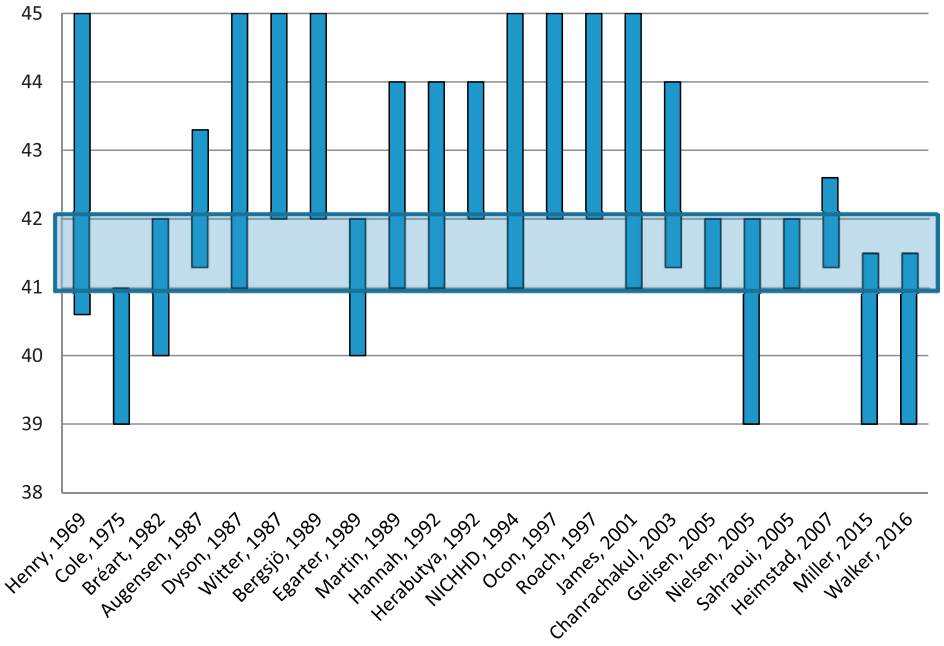

Fig. 1. Overiew of trials included in Cochrane.

Perinatal mortality between 41 and 42 weeks

Five perinatal deaths occurred in the 41–42 weeks' time frame. Only Gelisen et al. (2005) compared IOL at 41 weeks ($n = 300$) with IOL at 42 weeks ($n = 300$), in this RCT one foetal death occurred in the EM group at a gestational age of 41 weeks + 5 days. Sahraoui et al. (2005) compared IOL in week 41 ($n = 75$, inclusion between 41 weeks + 0–6 days,) with induction at or beyond 42 weeks ($n = 75$). One foetal death was detected at 42 weeks + 0 days in the EM group with foetal monitoring every other day after randomisation. In the RCT of Hannah et al. (1992) two perinatal deaths were reported, both in the EM group ($n = 1706$). Inclusion for this RCT ranged from 41 weeks + 0 days until 44 weeks, and expectant management was allowed until 44 weeks with non-stress test three times per week and foetal kick count every day. Gestational age was not routinely determined by early ultrasound (Hannah et al., 1992). The first case was a foetal death confirmed at 41 weeks + 5 days and diagnosed as hypoxic ischemic encephalopathy. The second case concerned an intrapartum death of a small for gestational age baby (2600 gs) with MAS born at 42 weeks + 0 days following emergency CS because of acute foetal distress during labour. The fifth death in the 41–42 weeks' timeframe was unlikely to be associated with the timing of delivery. Perinatal death at 42 weeks + 0 days followed after birth asphyxia secondary to a true knot of the umbilical cord. The authors pointed out that this perinatal death "*would probably not have been avoided with induction a few days earlier*". The incidence of potentially gestational age associated perinatal mortality between 41 and 42 weeks was 0/2.330 (IOL) 4/2.335 [0.17%] (EM), NNT 584; 95% CI (584 – infinite).

Perinatal mortality after 42 weeks

Seven cases of perinatal mortality occurred in RCTs on IOL after 42 weeks of gestation. Three of these cases were due to congentital anomalies.

Bergsjo et al. (1989) reported three cases, one in the induction group (severe malformations) and two in the monitoring group (pneumonia, malformations). Dyson et al. (1987) reported one perinatal death in the monitoring group, which concerned a delivery at 43 weeks + 4 days of gestation. Herabutya et al. (1992) reported one neonatal death at 43 weeks of gestation due to congenital anomaly. In the study of Henry (1969) two perinatal deaths were reported. In this study from 1969, the time before routine early ultrasound, the window of inclusion ranged from 40 weeks + 6 days to > 43 weeks with no upper limit for expectant management, the gestational age at time of birth or perinatal death was not specified. The first concerned a foetal death following abnormal glucose tolerance test and the second was a perinatal death after meconium aspiration in a woman with a positive amnioscopy (detection of meconium stained amniotic fluid) who refused induction of labour.

The identified causes of perinatal mortality are shown in Table 2.

Meconium aspiration syndrome (MAS)

The incidence of MAS was reported in eight individual RCTs. However, MAS definitions varied among the RCTs or were unclear. The RCT of Sahraoui et al. (2005; IOL between 41 weeks + 0–6 days versus IOL at 42 weeks) was included in the systematic review of Middleton et al.. Though Sahraoui reported the incidence of meconium stained amniotic fluid, and not the incidence of MAS (IOL 19/75, EM 33/75).

MAS before 41 weeks

No MAS was reported in these trials.

MAS between 41 and 42 weeks

The only RCT which compared IOL at 41 weeks + 0–2 days weeks with EM until 42 weeks and reported on MAS was Gelisen et al. (2005). MAS occurred less frequently after IOL compared to EM (4/300 versus 12/300; RR 0.25; 95% CI: 0.06–0.93). Because MAS was not clearly defined in the study protocol and the incidence was substantially higher comparing to most other trials, we compared NICU admission in both groups as MAS requires neonatal intensive care treatment. There was no difference in NICU admission in both groups: IOL 13/300 versus EM 15/300 (RR 0.87; CI 0.39–1.89). Heimstad et al. (2007) compared IOL at 41 weeks and 2 days with EM until 42 weeks and 6 days, they found no difference in MAS: 2/254 (IOL), 2/254 (EM). It was not possible to differentiate the number of MAS before and after 42 weeks in this trial. Pooling of the results of these two trials showed no significant difference in MAS (6/554 versus 14/554; RR 0.44; 95%CI: 0.17–1.16). (Table 3)

MAS after 42 weeks

MAS was also reported in the trials of Bergsjo, Dyson, James, NICHHD and Witter et al. These trials had all expectant management policies that exceeded a gestational age of 42 weeks, which is outside our time frame of comparison (Bergsjo et al., 1989; Dyson et al., 1987; James et al., 2001; 'NICHHD', 1994;Witter and Weitz, 1987) (8/560 versus 19/553; RR 0.50; 95%CI: 0.22–1.17). (Table 3)

Caesarean section

Different inclusion criteria regarding Bishop score, timing of inclusion, upper limit of allowed gestational age in the EM group and different protocols for methods of induction were used, which complicated the comparison of groups. We excluded the trial of Hannah et al. (1992) because of incomparable study arms. In this trial only women in the induction group were treated with prostaglandins in case of an unfavourable cervix. Women in the EM group with an unfavourable cevix who needed IOL received only oxytocin. Because of the different management strategies in both arms, these data are incomparable for the outcome Caesarean section (Wennerholm et al., 2009).

Caesarean section before 41 weeks

The RCTs of Bréart, Cole, Egarter, Miller, Nielsen and Walker et al. IOL were performed before a gestational age of 41 weeks (Table 3), no significant difference in the risk of CS was found (157/1277 versus 153/1020; RR 0.94; 95%CI: 0.70–1.28).

Caesarean section between 41 and 42 weeks

Gelisen et al. (2005) compared three types of IOL at 41 weeks with IOL at 42 weeks in women with unfavourable cervical scores (Bishop score < 5). There was no significant difference in CS between IOL and EM (58/300 versus 66/300, RR 0.88; 95%CI 0.63–1.22). Sahraoui et al. (2005) included women with a Bishop score < 4 and compared IOL at 41 weeks + 0–6 days with IOL at 42 weeks. They found no difference in CS (IOL: 7/75; EM: 7/75). In the RCT of Heimstad et al. (2007) women with a prior Caesarean Section were included. IOL at 41weeks + 2 days was compared with EM until 42 weeks + 6 days, no significant difference was found (28/254 versus 33/254). Pooling these three trials showed no significant difference between IOL and EM (93/629 versus 106/629; RR 0.88; 95%CI 0.68–1.13).

Caesarean section after 42 weeks

RCTs of Chanrachakul et al. (2003), Dyson et al. (1987), Henry (1969), James et al. (2001), Martin et al. (1989), NICHHD (1994), Augensen et al. (1987), Bergsjo et al. (1989), Herabutya (1992), Ocon (1997), Roach (1997) and Witter et al.(1987) were beyond 42 weeks (Table 3). There was no significant difference in the incidence of CS (222/1175 versus 237/1152; RR 0.92; 95%CI: 0.74–1.15).

Quality assessment

We evaluate the quality of the included trials with the EPHPP Quality Asssessment Tool, which gives an overall methodological rating of strong, moderate or weak in eight sections:

Table 2
Reported causes of perinatal mortality in the included trials.

	Reported causes of perinatal mortality		
Timeframe	Potentially gestational age associated	Congenital malformations	Unlikely gestational age associated
Before 41 weeks		Congenital heart condition Cole et al. (1975)	Foetal cord contriction (40w3d) (Egarter et al., 1989)
41–42 weeks	Foetal death, cause unknown (41w5d) Gelisen et al. (2005) Stillbirth, cause unknown (42w0d) Sahraoui et al. (2005) Fetal distress during labor, MAS, SGA (42w0d) Hannah et al. (1992) Stillbirth, hypoxic ischemic encephalopathy (41w5d) Hannah et al. (1992)		True knot umbilical cord (42w0d) (Heimstad et al., 2007)
After 42 weeks	Fetal distress during labor, urgent CS, MAS, persistent fetal circulation (43w4d) (Dyson et al., 1987) Stillbirth after abnormal GTT (GA unknown) (Henry, 1969) Neonatal death (MAS) after delayed birth due to refused induction (GA unknown) (Henry, 1969) Pneumonia (GA unknown) Bergsjo et al. (1989)	Severe malformations (GA unknown) (Bergsjo et al., 1989) Malformations (GA unknown) (Bergsjo et al., 1989) Congenital anomaly (GA unknown) (Herabutya et al., 1992)	

Table 3
Risks on perinatal mortality, MAS and CS in the different timeframes with heterogeneity testing.

	IOL	EM	RR (with 95%CI)	Heterogeneity			RCT
			(random effects)	Q-value	Df (Q)	I-squared	
Perinatal mortality	1/4301	13/4272 (0.3%)	0.32 (0.12–0.83)	0.3	9	0.0%	
Before 41 wks	0/796	2/785 (0.3%)					Bréart, Cole, Egarter, Nielsen
41–42 wks	0/2330	5/2335 (0.2%)					Chakravarti, Gelisen, Hannah, Heimstad, Sahraoui
After 42 wks	1/1175 (0.1%)	6/1152 (0.5%)	0.33 (0.08–1.42)	0.2	3	0.0%	Augensen, Bergsjo, Chanrachakul, Dyson, Henry, Herabutya, James, Martin, NICCHD, Ocon, Roach, Suikkari, Witter
MAS	14/1230 (0.1%)	33/1217 (0.3%)	0.47 (0.25–0.90)	3.9	6	0.0%	
Before 41 wks	–	–	–				–
41–42 wks	6/554 (1.1%)	14/554 (2.5%)	0.44 (0.17–1.16)	0.9	1	0.0%	Gelisen, Heimstad
After 42 wks	8/560 (1.4%)	19/553 (3.4%)	0.50 (0.22–1.17)	3.0	4	0.0%	Bergsjo, Dyson, James, Martin, Witter
CS	472/3081 (15.3%)	496/2801 (17.7%)	0.92 (0.81–1.06)	25.2	20	20.6%	
Before 41 wks	157/1277 (12.3%)	153/1020 (15.0%)	0.94 (0.70–1.28)	6.9	5	27.5%	Bréart, Cole, Egarter, Miller, Nielsen, Walker
41–42 wks	93/629 (14.8%)	106/629 (16.9%)	0.88 (0.68–1.13)	0.1	2	0.0%	Gelisen, Heimstad, Sahraoui
After 42 wks	222/1175 (18.9%)	237/1152 (20.6%)	0.92 (0.74–1.15)	17.8	11	38.2%	Augensen, Bergsjo, Chanrachakul, Dyson, Henry, Herabutya, James, Martin, NICCHD, Ocon, Roach, Witter

1. selection bias; 2. study design; 3. confounders; 4. blinding; 5. data collection methods; 6. withdrawals and dropouts; 7. intervention integrity; 8. analysis. Scoring was adapted for the section 'blinding' because it is not possible to blind women or caregivers for the intervention, therefore we excluded this item from the quality rating. No trials were scored as 'strong', 11 trials as 'moderate' and 11 trials as' week' (Table 1). Some components of the rating were not or not clearly described in most trials (blinding of the outcomes assessors, data collection tools, withdrawals and drop outs) which has add to the low performance of most trials. The criteria for reporting of RCTs have been tightened the last years, which can explain the non reporting in older trials.

Heterogeneity

We pooled data (unweighted) of the studies within the same timeframe to summarise risk ratios (RR) and 95% confidence intervals (CI) and tested heterogeneity. We tested heterogeneity of the pooled (unweighted) results, calculated the random effects, and the Q-value, degrees of freedom and I-square. The included studies were heterogeneous regarding their objectives, setting, time frames of comparison and study population (women with different risk profiles like nulliparous only or not, women with, low Bishop score or all Bishop scores, women with previous CS or not), but the combined relative risks of the outcomes under study did not show statistical heterogeneity, since I-square was not greater than 30% (Table 3).

Discussion

The objective of this review was to evaluate perinatal mortality, MAS and Caesarean section rate of trials comparing a policy of IOL and EM according to timeframe of comparison with a focus on studies comparing IOL at 41 weeks + 0–6 days with EM at 42 weeks + 0–6 days in order to identify the incidence of perinatal mortality, MAS and Caesarean section between 41 and 42 weeks. We assessed the evidence favouring induction of labour at 41 weeks for the improvement of birth outcome instead of 42 weeks, the international borderline between late-term and postterm pregnancy. The largest systematic review on this subject, the Cochrane review (Middleton et al., 2018) concluded that IOL at or beyond 41 weeks improved birth outcomes compared to a policy of expectant management. Most studies in this review had an expectant management policy that went far beyond 42 weeks (which exceeds the international borderline of 42 weeks). Among them also rather old studies in which the standard of care could not be compared with today's (Henry, 1969; Cole et al., 1975). We identified only one RCT which compared IOL at 41weeks with EM until 42 weeks. Four other RCT applied a policy

of induction at 41 weeks + 0–6 days, with EM at 42 weeks + 0–6 days. All other trials had different timeframes of IOL as well as EM.

Perinatal mortality

In the systematic reviews on labour induction at or beyond term RCTs with different timeframes, different inclusion criteria and different protocols were combined. The Cochrane review concluded that perinatal mortality was significantly lower when labour was induced. However, most deaths (9 out of 14) did not occur in the 41–42 weeks' time frame. It was not possible to combine RCTs for the comparison of IOL at 41 and 42 weeks because there was only one RCT with this comparison. The nearest estimate for the incidence of perinatal death comes from RCTs with confirmed perinatal deaths between 41 and 42 weeks. The incidence of perinatal mortality in this time frame was low. These RCTs have different policies regarding eligibility, planned timing of induction and accepted upper limit of gestational age in the control groups.

MAS

MAS was registered in seven RCTs, of which four had an upper limit for gestational age of 44 weeks or beyond in the EM group. As meconium passage will increase in pregnancies with advanced gestational age, the incidence of MAS was increased in studies comparing management strategies beyond 42 weeks. Only one RCT compared IOL at 41 weeks + 0 days with IOL at 42 weeks + 0 days, with a higher incidence of MAS in the EM group (Gelisen et al., 2005: 4/300 vs. 12/300; RR 0.33, 95%CI: 0.09–1.10). However, the definition of MAS in this trial was not clear and there was no difference in NICU admittance (12/300 vs. 15/300). We tried to obtain the individual patient data from this trial for a closer look at the discrepancy between the incidence of MAS and the incidence of NICU admittance but unfortunately, the original study database as well as individual patient data are not available anymore. One trial (published in French) in the Cochrane review was misinterpreted regarding to MAS: the rate of meconium stained amniotic fluid was used for the rate of MAS (Sahraoui et al., 2005). Another problem is the lack of consistency regarding the definition of MAS in the various RCTs, which complicates the interpretation of the actual risk.

Caesarean section

IOL was associated with a lower rate of CS in the Cochrane systematic review, though the pooling of results for CS is questionable because of the heterogeneity of the included RCTs regarding the a priori risk on CS. Different inclusion criteria regarding Bishop score, timing of IOL, upper limit of allowed gestational age in the EM group and different protocols for methods of induction were used, which complicated the interpretation of the results. Furthermore, one large study (Hannah et al., 1992; 36% of all women included in the Cochrane review) with incomparable treatment strategies in both study arms was included for analysis (Wennerholm et al., 2009). This RCT only used prostaglandins for cervical ripening in the induction arm, women in the expectant management arm were only induced with oxytocin. There is sufficient evidence that prostaglandins will increase the success rate of labour induction in case of an unfavourable cervix (Jozwiak et al., 2011). In the 41–42 weeks' time frame there was no significant difference in the rate of CS.

Heterogeneity of included RCTs

We found a high level of heterogeneity in population, setting, protocols, and incidences of the study outcomes. However, comparison of the relative risks for both study arms did not show statistical heterogeneity. This shows that the direction of the RR for the evaluated outcomes is consistent despite the heterogeneity of population or setting.

Quality assessment

Quality scoring of the included trials was moderate to low. However, a low scoring does not directly imply that the study itself is indeed of low quality. Some of the essential information that is needed for the EPHPP quality assessment (blinding outcome assessors, data collection methods, withdrawals-drop outs) is missing in most trials. All trials were published more than ten years ago and criteria for trial reporting have been tightened the last years. If the required information was not provided in the paper this item had to be scored 'weak'. However, if this was known at time of submission, the autors could have provide the necessary information. That quality rating of RCTs appears to be difficult is also shown in other quality assessment tools. Though the interrater agreement was high in our study, the GRADE scoring of 22 RCTs in the recent Cochrane review showed only 2 full agreements compared to the rating performed in 2012 by other authors of the same RCTs. The many items which could not be scored because of missing information could be the reason for this. In future studies this problem will hopefully be solved because of the current strict criteria for trial reporting.

Conclusion

The debate regarding management of late term pregnancy in some high income countries focuses on whether induction of labour should be planned already at 41 weeks or can be postponed to 42 weeks. Evidence is lacking for the recommendation to induce labour at 41 weeks instead of 42 weeks. More and adequately powered studies are needed on the comparison of a policy of labour induction at 41 weeks to a policy of induction at 42 weeks to establish the optimal timing of induction of labour in late-term pregnancy.

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References

American College of, Obstetricians, and Gynecologists, 2014. Practice bulletin no. 146: management of late-term and postterm pregnancies. Obstet. Gynecol. 124, 390–396.
Armijo-Olivo, S., Stiles, C.R., Hagen, N.A., Biondi, P.D., Cummings, G.C., 2010. Assessment of study quality for systematic reviews: acomparison of the cochrane collaboration risk of bias tool and the effective public health practice project quality assessment tool: methodological research. J. Eval. Clin. Pract. 18, 12–18.
Augensen, K., Bergsjo, P., Eikeland, T., Askvik, K., Carlsen, J., 1987. Randomised comparison of early versus late induction of labour in post-term pregnancy. Br. Med. J. (Clin. Res. Ed.) 294, 1192–1195.
Bergsjo, P., Huang, G.D., Yu, S.Q., Gao, Z.Z., Bakketeig, L.S., 1989. Comparison of induced versus non-induced labor in post-term pregnancy. A randomized prospective study. Acta Obstet. Gynecol. Scand. 68, 683–687.
Brane, E., Olsson, A., Andolf, E., 2014. A randomized controlled trial on early induction compared to expectant management of nulliparous women with prolonged latent phases. Acta Obstet. Gynecol. Scand. 93, 1042–1049.
Breart, G., Goujard, J., Maillard, F., Chavigny, C., Sureau, S., Rumeaurouquette, C., 1982. A randomized trial on induction of labor. Dev. Pharmacol. Therap. 4, 218–219.
Chakravarti, S., Goenka, B. 2000. Conservative policy of induction of labor in uncomplicated postdated pregnancies. XVI FIGO World Congress of Obstetrics … Gynecology; Sept 3–8; Washington DC, USA (Book 3). 2000: page 62.
Chanrachakul, B., Herabutya, Y., 2003. Postterm with favorable cervix: is induction necessary? Eur. J. Obstet. Gynecol. Reprod. Biol. 106, 154–157.
Cole, R.A., Howie, P.W., Macnaughton, M.C., 1975. Elective induction of labour. A randomised prospective trial. Lancet 1, 767–770.
Cohn, M., Rogers, M. 1992. Post maturity; a randomised study in a Hong Kong population. Proceedings of the 26th British Congress of Obstetrics and Gynaecology; July 7-10; Manchester, UK. 1992:306.
Dyson, D.C., Miller, P.D., Armstrong, M.A., 1987. Management of prolonged pregnancy: induction of labor versus antepartum fetal testing. Am. J. Obstet. Gynecol. 156, 928–934.
Egarter, C., Kofler, E., Fitz, R., Husslein, P., 1989. Is induction of labor indicated in prolonged pregnancy? Results of a prospective randomised trial. Gynecol. Obstet. Invest. 27, 6–9.
Gelisen, O., Caliskan, E., Dilbaz, S., Ozdas, E., Dilbaz, B., Ozdas, E., Haberal, A., 2005. 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. Eur. J. Obstet. Gynecol. Reprod. Biol. 120, 164–169.

Gulmezoglu, A.M., Crowther, C.A., Middleton, P., Heatley, E. 2012. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database Syst Rev. (6), CD004945.

Guidance, National Institute for Health and Clinical Excellence, 2008. Induction of Labour. National Institute for Health and Clinical Excellence, London.

Hannah, M.E., Hannah, W.J., Hellmann, J., Hewson, S., Milner, R., Willan, A., 1992. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. A randomized controlled trial. The Canadian multicenter post-term pregnancy trial group. N. Engl. J. Med. 326, 1587–1592.

Heimstad, R., Skogvoll, E., Mattsson, L.A., Johansen, O.J., Eik-Nes, S.H., Salvesen, K.A. 2007. Induction of labor or serial antenatal fetal monitoring in postterm pregnancy: a randomized controlled trial. Obstet Gynecol. 109 (3), 609–17.

Heimstad, R., Romundstad, P.R., Salvesen, K.A., 2008. Induction of labour for post-term pregnancy and risk estimates for intrauterine and perinatal death. Acta Obstet. Gynecol. Scand. 87, 247–249.

Henry, G.R., 1969. A controlled trial of surgical induction of labour and amnioscopy in the management of prolonged pregnancy. J. Obstet. Gynaecol. Br. Commonw. 76, 795–798.

Herabutya, Y., Prasertsawat, P.O., Tongyai, T., Isarangura Na Ayudthya, N., 1992. Prolonged pregnancy: the management dilemma. Int. J. Gynaecol. Obstet. 37, 253–258.

James, C., George, S.S., Gaunekar, N., Seshadri, L., 2001. Management of prolonged pregnancy: a randomized trial of induction of labour and antepartum foetal monitoring. Natl. Med. J. India 14, 270–273.

Kortekaas, J.C., Bruinsma, A., Keulen, J.K., van Dillen, J., Oudijk, M.A., Zwart, J.J., Bakker, J.J., de Bont, D., Nieuwenhuijze, M., Offerhaus, P.M., van Kaam, A.H., Vandenbussche, F., Mol, B.W., de Miranda, E., 2014. Effects of induction of labour versus expectant management in women with impending post-term pregnancies: the 41 week – 42 week dilemma. BMC Preg. Childbirth 14, 350.

Ocon, L., Hurtado, R, Coteron, J.J., Zubiria, A., Ramirez, O., Garcia, J.A., 1997. Gestacion prolongada: pautas de actuacion. Progresos de Obstetricia y Ginecologia 40, 101–106.

Martin Jr., J.N., Sessums, J.K., Howard, P., Martin, R.W., Morrison, J.C., 1989. Alternative approaches to the management of gravidas with prolonged-postterm-postdate pregnancies. J. Miss. State Med. Assoc. 30 (4), 105–111.

Middleton, P., Shepherd, E., Caroline, A., Crowther, CA., 2018. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database Syst. Rev. 5, CD004945.

Miller, N.R., Cypher, R.L., Foglia, L.M., Pates, J.A., Nielsen, P.E., 2015. Elective Induction of Labor Compared With Expectant Management of Nulliparous Women at 39 Weeks of Gestation: A Randomized Controlled Trial. Obstet. Gynecol. 126, 1258–1264.

NICE, 2008. Inducing labour. Clinical Guideline 70.. NICE, Manchester.

NICHHD, 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. Am. J. Obstet. Gynecol. 170, 716–723.

Nielsen, P.E., Howard, B.C., Hill, C.C., Larson, P.L., Holland, R.H., Smith, P.N., 2005. Comparison of elective induction of labor with favorable Bishop scores versus expectant management: a randomized clinical trial'. J. Matern. Fetal. Neonatal. Med. 18, 59–64.

Roach, V.J., Rogers, M.S., 1997. Pregnancy outcome beyond 41 weeks gestation. Int. J. Gynaecol. Obstet. 59, 19–24.

Sahraoui, W., Hajji, S., Bibi, M., Nouira, M., Essaidi, H., Khairi, H., 2005. [*Management of pregnancies beyond forty-one week's gestation with an unfavorable cervix*]. J. Gynecol. Obstet. Biol. Reprod. (Paris) 34, 454–462.

Suikkari, A.M., Jalkanen, M., Heiskala, H., Koskela, O., 1983. Prolonged pregnancy: induction or observation. Acta Obstet. et Gynecol. Scand. Supplement 116, 58.

Walker, K.F., Bugg, G.J., Macpherson, M., McCormick, C., Grace, N., Wildsmith, C., Bradshaw, L., Smith, G.C., Thornton, J.G., Trial, Group, 2016. Randomized trial of labor induction in women 35 years of age or older. N. Engl. J. Med. 374, 813–822.

Wennerholm, U.B., Hagberg, H., Brorsson, B., Bergh, C., 2009. Induction of labor versus expectant management for post-date pregnancy: is there sufficient evidence for a change in clinical practice? Acta Obstet. Gynecol. Scand. 88, 6–17.

Witter, F.R., Weitz, C.M., 1987. A randomized trial of induction at 42 weeks gestation versus expectant management for postdates pregnancies. Am. J. Perinatol. 4, 206–211.

Jozwiak, M., Oude Rengerink, K., Benthem, M., van Beek, E., Dijksterhuis, M.G., de Graaf, I.M., et al. 2011. Foley catheter versus vaginal prostaglandin E2 gel for induction of labour at term (PROBAAT trial): an openlabel, randomised controlled trial. Lancet. 378 (9809), 209–103.