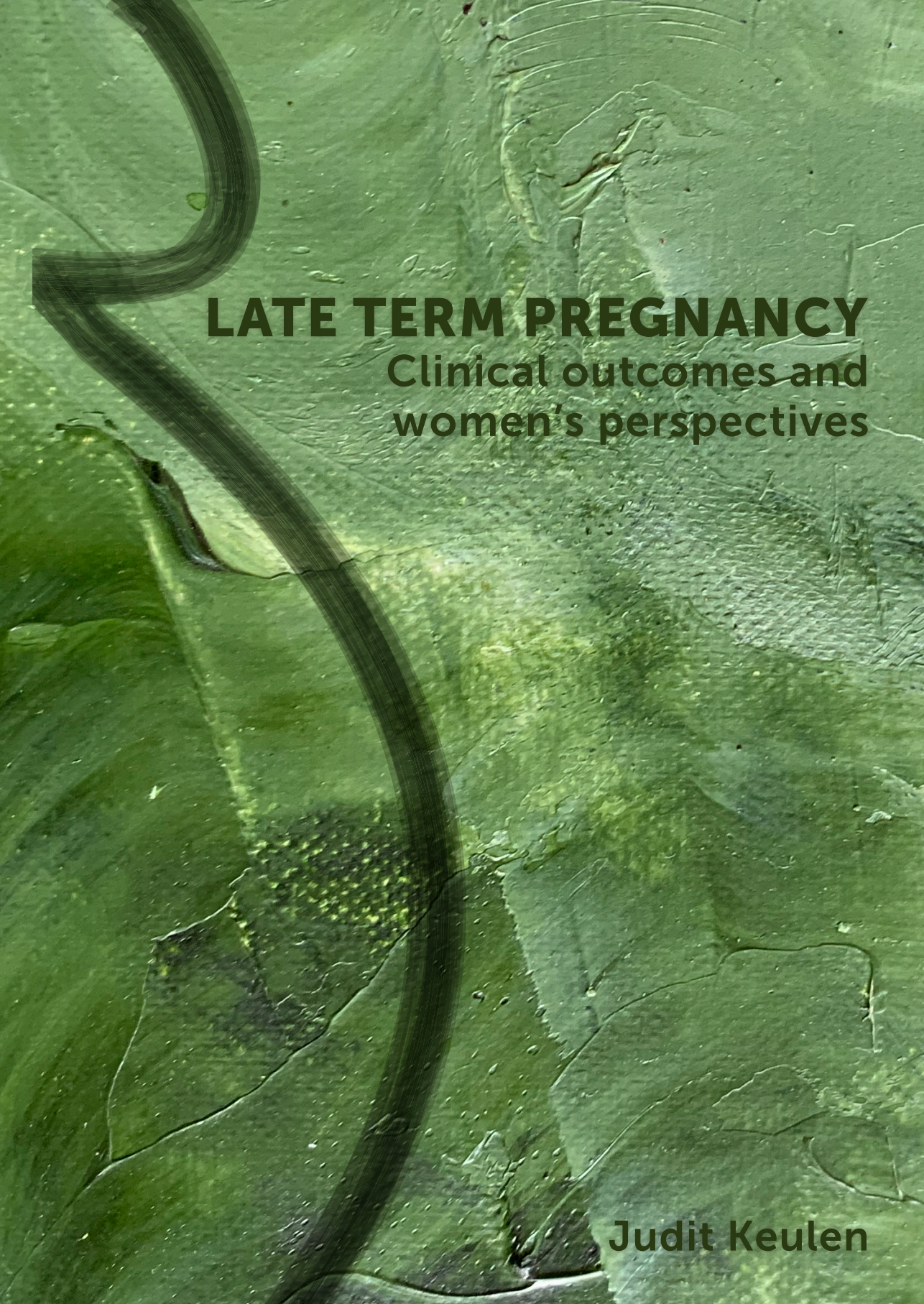

LATE TERM PREGNANCY

Clinical outcomes and women's perspectives

Judit Keulen

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COLOFON

LATE TERM PREGNANCY
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INDEX

CHAPTER 1

GENERAL INTRODUCTION

Adverse perinatal outcome is strongly related to gestational age and mainly to preterm labour. However, pregnancies beyond term have also been associated with less favourable outcomes compared to term pregnancies. This is of clinical importance since the number of women delivering at these gestational ages are considerable compared to the preterm period.

Duration of human pregnancy has since long been subject of interest. The biological variability in the duration of pregnancy was already described by Aristoteles (384-322 BC) in The History of Animals: *"Now all other animals bring the time of pregnancy to an end in a uniform way ... in the case of mankind alone of all animals the times are diverse, for pregnancy may be of 7 months' duration or of 8 months or of 9 and still more commonly of 10 (lunar) months, whilst some women go even into the eleventh month."*

In contemporary obstetrics, the estimated date of delivery (EDD) is still set at 280 days or 40 weeks. To calculate the EDD, the menstrual cycle has been used previously. Nowadays, in most high income countries, the EDD is based on measurements of fetal length during first trimester ultrasound, because of more accurate dating [1, 2]. The use of ultrasound to determine the EDD is associated with a reduction in pregnancies beyond 42 weeks [3, 4]. Furthermore, a trend in reduction in pregnancies beyond 42 weeks is observed due to more inductions of labour between 41 and 42 weeks after recommendations in guidelines to offer elective induction from 41 weeks onwards [5-10]. These recommendations originate from meta-analysis in which was concluded that pregnancies beyond 41 weeks were already at higher risk of perinatal mortality [10]. With advancing gestational age placental biochemistry changes leading to e.g. DNA/RNA oxidation which mediates placental ageing and gradual declining of placental function [11]. The length of gestational age may also be influenced by fetal abnormalities and maternal factors, like genetic predisposition or obesity [12]. The onset of labour is a complex biochemical, mechanical and endocrinological process in which the fetus, mother and placenta interact. The exact mechanism of labour onset is still unknown, as is predicting when labour will start.

If fetal or maternal condition are considered to be a risk factor for adverse outcome, or to prevent an increased risk of adverse outcome, women will be offered induction of labour. Since this is a medical intervention informed consent is required.

As any medical intervention, induction of labour carries risks associated with the intervention as such. Side effects of induced labour could be uterine rupture, uterine

hyper stimulation, postpartum haemorrhage or the experience of more painful contractions [5, 13-15]. Little is known so far on possible late effects of synthetic oxytocin [16, 17]. Furthermore, there are procedural consequences of labour induction such as hospital admission with intravenous drip and monitoring of the fetal and maternal condition.

In the decision to induce labour it is important to weigh possible side-effects of the intervention against the risks of continuing pregnancy. To detect whether perinatal risks are increasing after a certain gestational age, many randomised controlled trials have been executed comparing induction of labour with a policy of expectant management, also in low-risk pregnancies. The risk on both stillbirth and neonatal mortality increases gradually after 41 weeks. The first trial comparing induction with expectant management of women with a low-risk prolonged pregnancy was already published in 1969 [18]. In the trials that followed, many different timeframes were compared. In these trials induction groups varied between 37 and 42 weeks, and expectant management lasted until 41 up to 44 weeks, while in some trials the expectant management group did not even have an upper limit in time. In 2012, the Cochrane collaboration published a systematic review and meta-analysis of trials on induction of labour compared to a policy of expectant management in low-risk women at or beyond 37 weeks. The meta-analysis showed that induction of labour at or beyond 41 weeks was associated with fewer perinatal deaths and a lower caesarean section rate [10]. The absolute risk of perinatal mortality, however, was low and the optimal timing of induction of labour to improve perinatal outcomes was still unclear. Additionally, comparison of elective induction at 41 weeks with a policy of expectant management until 42 weeks was not performed in the review. Further investigation of the timing of induction was recommended in this systematic review, as well as further exploration of risk profiles of women and their values and preferences.

Several trials have been performed in The Netherlands to compare induction of labour with expectant management in high-risk pregnancies, and no differences in caesarean section rate were found [19-21]. Two recently published trials with medium- or low-risk women showed a similar or decreased rate of caesarean section after elective induction, which is in line with the Cochrane systematic review [22, 23]. In some cohort studies evaluating late-term pregnancies, the incidence of caesarean section has been shown higher in the induction of labour groups [24-27].

In the Netherlands uncomplicated pregnancy is still considered low-risk until 42 weeks, after which induction of labour is indicated according to the Dutch nationwide

obstetric indication list [28]. Nevertheless, whether elective induction should start earlier has been debated for many years, and revealed the need for more studies with adequate sample size. A study comparing earlier elective induction (at 41 weeks) with the regular policy (induction at 42 weeks) was also prioritised by the Dutch Organisation for Obstetricians and Gynaecologists (NVOG) and the Royal Dutch Organisation for Midwives (KNOV) in 2011. The need for research became even more urgent after publication of the updated Cochrane review on Induction of labour for improving birth outcomes for women at or beyond term in 2012 [10, 29].

This was the starting point of the INDEX-study in which the key question is whether —for low-risk women— there is a difference in adverse perinatal outcomes, adverse maternal outcomes and mode of delivery between induction at 41 weeks and expectant management until 42 weeks. Following the recommendation of the Cochrane review, women's perspectives on these two management strategies were also included in the study.

Outcomes important for decision-making in medicine, should comprise also the perspective of whom it concerns. In the WHO recommendation on Intrapartum Care for a Positive Childbirth Experience, a positive childbirth experience is described as "a significant end point for all women undergoing labour". The WHO defines a positive childbirth experience as "one that fulfils or exceeds a woman's prior personal and sociocultural beliefs and expectations, including giving birth to a healthy baby in a clinically and psychologically safe environment" [30]. This means —besides good clinical outcomes— outcome measures that matter most to patients, and engaging women into policy making regarding their own pregnancy [31]. The shared decision making model is preferred to engage women in deciding upon treatment or interventions, when several options are reasonable [32]. Although there is a variety of different models of shared decision making, some components are rather consistent in most models [33]. The shared decision process model of Stiggelbout et al. consists of four steps: 1) the professional informs the woman that a decision needs to be made and that woman's opinion is important in this; 2) pros and cons of all options are explained; 3) discussion of woman's preferences with support of her deliberation; 4) the professional and woman discuss the woman's wish to make the decision, they make or defer the decision, and discuss follow-up [34].

Shared decision making could improve healthcare experience [35-38]. Therefore, it is important for caregivers involved in counselling women approaching late term pregnancy, to know the variety of women's experience of a policy of elective induction

of labour or expectant management and —in addition to that— why women prefer either management strategy.

Several qualitative studies have been performed on birth experience after induction of labour. A systematic review including qualitative studies, with mostly studies on elective induction of labour for prolonged pregnancy, concluded that induction of labour is a challenging experience for women [39]. Women have indicated that they were insufficiently involved in the decision-making process in which other options than elective induction were hardly discussed. Late-term pregnancy and induction studies have described and explored women's needs and report on women's feelings about late-term induction [40, 41]. Women described that the hope of spontaneous labour had to be given up, they felt that induction was a recommendation of the caregiver and they were not able to decline induction. The induction process was experienced as a protocolled set of steps where the woman was expected to fit in.

Childbirth experience is influenced by several factors such as the level of women's anxiety; more anxious women generally report a more negative birth experience [42, 43]. Medical interventions such as induction of labour and caesarean section may have a negative effect on childbirth experiences [44]. Women's experiences in late-term pregnancy after a policy of induction or expectant management is sparsely compared. One study found that women with electively induced labour had better experiences, but this study mainly focused on the duration and the experienced pain of labour [45]. Women's personal preference is an important factor in the decision making process. Some women will have a preference for elective induction, but other women prefer not to intervene in the natural course of pregnancy. The proportion of women preferring induction in a next pregnancy differs between studies [41, 45, 46]. Which policy women prefer when reaching 41 weeks of pregnancy and to understand the most important reasons for their preference has not been explored yet.

Therefore, when a woman reaches a gestational age of 41 weeks and the management strategy has to be chosen, many issues need to be considered. First, the woman has to know whether she is at risk for adverse perinatal outcomes and/or adverse maternal outcomes and she has to know the magnitude of these risks. Secondly, the consequences of the different management strategies for the mother have to be discussed. The weighing of the risks, benefits, personal values and wishes are all important factors for women to make an informed choice between induction of labour and expectant management, since in the Netherlands the decision making power lies with her [32].

This thesis will focus on the risks and benefits of elective induction of labour at 41 weeks in low-risk pregnancy compared to expectant management until 42 weeks, with perinatal mortality and morbidity as primary outcomes of interest. Because perinatal mortality is a rare outcome in obstetric research, a composite of adverse perinatal outcomes is used as in many other studies examining low-risk pregnancies. Furthermore, maternal and delivery outcomes will be assessed. In this thesis we will only address uncomplicated pregnancies of healthy women with no pre-birth detected fetal risks. In addition and to enable a better understanding of women's values and wishes, this thesis will also focus on the experiences and preferences of women allocated to a policy of induction of labour or expectant management and the influence of anxiety and actual onset of labour on women's birth experience.

SETTING

In the current **INDEX** project multiple studies were performed around the comparison of a policy of **IND**uction of labour at 41 weeks with **EX**pectant management until 42 weeks in low-risk pregnancies. Over 6000 women from 168 different centres (midwifery care practices and hospitals) were included so far.

The project included a review on the timing of induction of labour at 41 or 42 weeks, studies on the identification of relevant subgroups at increased risk of adverse perinatal outcome and risk factors, an RCT, an IPD-MA resulting from an international research cooperation, a prospective cohort study alongside the trial, questionnaires on the 41-42 weeks dilemma, a cost-effectiveness study, and more studies to come. The INDEX team is a multidisciplinary research group of professionals dedicated to obstetrics who work in all care levels or the related professional training and research.

This thesis is the second of three PhD-theses as output from the INDEX project.

AIM AND OUTLINE

This thesis aims to compare a policy of induction of labour at 41 weeks with expectant management until 42 weeks in different research settings in order to:

- assess clinical outcomes
- define relevant subgroups which benefit (or not) from elective induction
- assess women's perspectives

Chapter 2 describes the identification of the existing literature by reviewing the reviews on the comparison of induction of labour at 41 weeks versus expectant management until 42 weeks.

Chapter 3 reports the results of perinatal and maternal outcomes comparing induction of labour at 41 weeks with expectant management until 42 weeks in a randomised controlled trial.

Chapter 4 reports the results of an individual patient data analysis and meta analysis of randomised controlled trials comparing induction of labour at 41 weeks with expectant management until 42 weeks, and the identification of possible relevant subgroups at risk are described.

Chapter 5 describes and discusses women's preferences regarding the management strategy in late-term pregnancy and the origin of their preferences.

Chapter 6 evaluates women's experiences and preferences after induction of labour or expectant management.

Chapter 7 contains the general discussion and future perspectives of this thesis.

Chapter 8 summarises this thesis.

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CHAPTER 2

TIMING INDUCTION OF LABOUR AT 41 OR 42 WEEKS? A CLOSER LOOK AT TIME FRAMES OF COMPARISON: A REVIEW

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Midwifery 2018, 66: 111-118

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 Quantitative 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 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 [1-3], 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 [4]. 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 [2, 5]. 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 criteria 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 [6]. 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 to 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 additionally 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. [7-9]. We excluded one RCT [10], 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 (Figure 1). Timing of induction and the upper limit of expectant management varies within the groups.

In six RCTs IOL was performed between 39-40 weeks and compared to EM until 41 or 42 weeks [11-16].

Four RCTs focused on IOL at 41 weeks +0-6 days versus EM at 42 weeks +0-6 days [7, 17-20]. Only one trial compared IOL at 41 weeks with expectant management until 42 weeks [17]. 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 [8, 21-26]. In six RCTs IOL was performed at or beyond 42 weeks [27-32].

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.

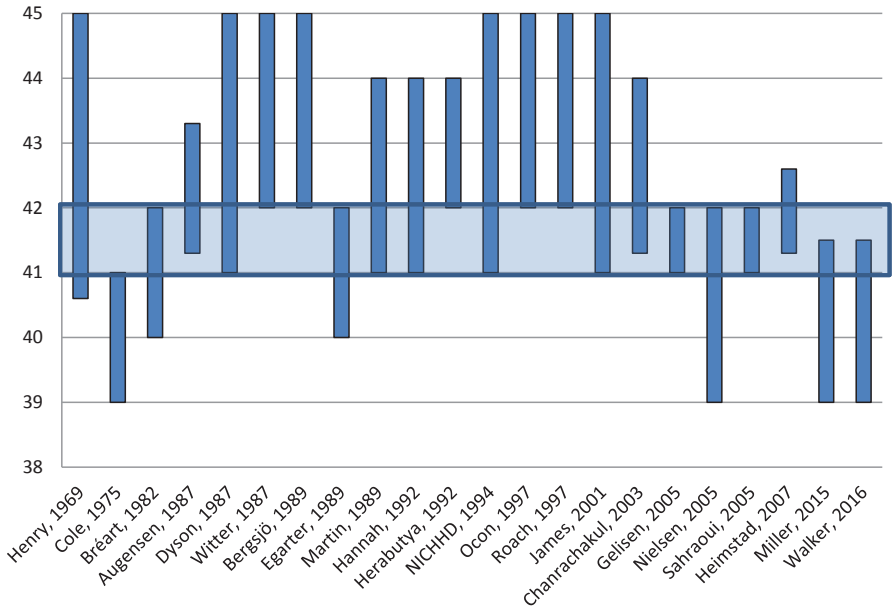

FIGURE 1. Timeframes of comparison of included studies

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 Assessment (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)	Fetal 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)	Fetal 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 encephalopathy (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)

TABLE 1 (continued)

Study (year)	Quality Assessment (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 at 41 weeks +0-6 days versus EM at 42 weeks +0-6 days											
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)
James (2001)	Moderate	No	74		41	No upper limit	-	-	-	1/37 (IOL) 2/37 (EM)	2/37 (IOL) 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) 2/175 (EM)	39/174 (IOL) 32/175 (EM)

TABLE 1 (continued)

Study (year)	Quality Assessment (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 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) 1/97 (EM)	30/103 (IOL) 27/97 (EM)
IOL > 42 weeks versus EM > 44 weeks											
Bergsjö (1989)	Weak	No	188		>42	No upper limit	1/94 (IOL) 2/94 (EM)	1: (IOL) severe malformations (>42 weeks) 2: (EM) malformations (>42 weeks) 3: (EM) pneumonia (>42 weeks)	1: No 2: No 3: Unclear	4/94 (IOL) 8/94 (EM)	27/94 (IOL) 39/94 (EM)
Herabutya (1992)	Weak	No	108	>42	>42	44	0/57 (IOL) 1/51 (EM)	Congenital anomaly (43 weeks)	No	Not reported	27/57 (IOL) 24/51 (EM)

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.

Perinatal mortality between 41-42 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 [18]. 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 grams) 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 congenital 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.

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

Timeframe	Reported causes of perinatal mortality		
	Potentially gestational age associated	**Congenital malformations**	**Unlikely gestational age associated**
Before 41 weeks		Congenital heart condition Cole (1975)	Fetal cord contriction (40w3d) Egarter (1989)
41-42 weeks	• Fetal death, cause unknown (41w5d) Gelisen (2005) • Stillbirth, cause unknown (42w0d) Sahraoui (2005) • Fetal distress during labour, MAS, SGA (42w0d) Hannah (1992) • Stillbirth, hypoxic ischemic encephalopathy (41w5d) Hannah (1992)		True knot umbilical cord (42w0d) Heimstad (2007)
After 42 weeks	• Fetal distress during labour, urgent CS, MAS, persistent fetal circulation (43w4d) Dyson (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 (1989)	Severe malformations (GA unknown) Bergsjo (1989) Malformations (GA unknown) Bergsjo (1989) Congenital anomaly (GA unknown) Herabutya (1992)	

CS: caesarean section
GA: gestational age
MAS: meconium aspiration syndrome

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 41-42 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 cervix who needed IOL received only oxytocin. Because of the different management strategies in both arms, these data are incomparable for the outcome Caesarean section [33].

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 41-42 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 (1989), Herabutya (1982), 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: 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).

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 weeks	0/796	2/785 (0.3%)					Bréart, Cole, Egarter, Nielsen
41-42 weeks	0/2330	5/2335 (0.2%)					Chakravarti, Gelisen, Hannah, Heimstad, Sahraoui
After 42 weeks	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 weeks	-	-	-				-
41-42 weeks	6/554 (1.1%)	14/554 (2.5%)	0.44 (0.17-1.16)	0.9	1	0.0%	Gelisen, Heimstad
After 42 weeks	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 weeks	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 weeks	93/629 (14.8%)	106/629 (16.9%)	0.88 (0.68-1.13)	0.1	2	0.0%	Gelisen, Heimstad, Sahraoui
After 42 weeks	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

IOL: induction of labour
EM: expectant management
MAS: meconium aspiration syndrome
CS: caesarean section

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 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 [12, 23]. 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, 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 [20]. 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., 2012). 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 authors 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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CHAPTER 3

INDUCTION OF LABOUR AT 41 WEEKS VERSUS EXPECTANT MANAGEMENT UNTIL 42 WEEKS (INDEX): MULTICENTRE, RANDOMISED NON-INFERIORITY TRIAL

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ABSTRACT

Objective To compare induction of labour at 41 weeks with expectant management until 42 weeks in low risk women.

Design Open label, randomised controlled non-inferiority trial.

Setting 123 primary care midwifery practices and 45 hospitals (secondary care) in the Netherlands, 2012-16.

Participants 1801 low risk women with an uncomplicated singleton pregnancy: randomised to induction (n=900) or to expectant management until 42 weeks (n=901).

Interventions Induction at 41 weeks or expectant management until 42 weeks with induction if necessary.

Primary outcome measures

Primary outcome was a composite of perinatal mortality and neonatal morbidity (Apgar score <7 at five minutes, arterial pH <7.05, meconium aspiration syndrome, plexus brachialis injury, intracranial haemorrhage, and admission to a neonatal intensive care unit (NICU). Secondary outcomes included maternal outcomes and mode of delivery. The null hypothesis that expectant management is inferior to induction was tested with a non-inferiority margin of 2%.

Results Median gestational age at delivery was 41.0 weeks (interquartile range 41.0 weeks to 41.1 weeks) for the induction group and 41.2 weeks (41.0 weeks to 41.5 weeks) for the expectant management group. The primary outcome was analysed for both the intention-to-treat population and the per protocol population. In the induction group, 15/900 (1.7%) women had an adverse perinatal outcome versus 28/901 (3.1%) in the expectant management group (absolute risk difference –1.4%, 95% confidence interval (CI) –2.9% to 0.0%, P=0.22 for non-inferiority). 11 (1.2%) infants in the induction group and 23 (2.6%) in the expectant management group had an Apgar score <7 at five minutes (relative risk (RR) 0.48, CI 0.23 to 0.98). No infants in the induction group and three (0.3%) in the expectant management

group had an Apgar score <4 at five minutes. One foetal death (0.1%) occurred in the induction group and two (0.2%) in the expectant management group. No neonatal deaths occurred. 3 (0.3%) neonates in the induction group versus 8 (0.9%) in the expectant management group were admitted to an NICU (RR 0.38, CI 0.10 to 1.41). No significant difference was found in composite adverse maternal outcomes (induction n=122 (13.6%) *v* expectant management n=102 (11.3%)) or in caesarean section rate (both groups n=97 (10.8%)).

Conclusions This study could not show non-inferiority of expectant management compared with induction of labour in women with uncomplicated pregnancies at 41 weeks; instead a significant difference of 1.4% was found for risk of adverse perinatal outcomes in favour of induction, although the chances of a good perinatal outcome were high with both strategies and the incidence of perinatal mortality, Apgar score <4 at five minutes, and NICU admission was low.

Trial registration

Netherlands Trial Register NTR3431.

What is already known on this topic

A policy of labour induction at or beyond term compared with expectant management is associated with fewer perinatal deaths and fewer caesarean sections; but more operative vaginal births (Cochrane review)

Aggregated results of trials need to be interpreted with caution because of trials heterogeneity caused by different outcome measures, protocols, and time frames of comparison

Evidence is lacking for the recommendation to induce labour at 41 weeks instead of 42 weeks for the improvement of perinatal outcome

What this study adds

Induction of labour at 41 weeks resulted in less overall adverse perinatal outcome than a policy of expectant management until 42 weeks, although the absolute risk of severe adverse outcome (perinatal mortality, NICU admission, Apgar score <4 at five minutes) was low in both groups

INTRODUCTION

Post-term pregnancy, defined as a pregnancy extended to or beyond 42 weeks, or 294 days or more, is associated with increased perinatal morbidity and mortality [1-10] The World Health Organization and various guidelines throughout the world therefore recommend induction of labour after 42 weeks [10-15]. Although the overall probability of favourable perinatal outcomes between 40 and 42 weeks is good in high resource settings, the risk of adverse perinatal outcome increases gradually after 40 weeks [16-19].

Several studies concluded that induction of labour from 41 weeks onwards improves perinatal outcomes, and this has been confirmed in a meta-analysis [16, 17, 19, 20]. These results need to be interpreted with caution, however, because of heterogeneity between trials as a result of different outcome measures, protocols, and time frames of comparison because several trials compared induction beyond 41 weeks or starting induction at 42 weeks with a policy of expectant management far beyond 42 weeks [21].

The obstetric management of women with a pregnancy exceeding 41 weeks varies considerably between and within countries. Although induction at 41 weeks has now

become an accepted policy in many countries, in some others no consensus exists on the timing of induction in late term pregnancy. In Sweden and the Netherlands, for example, expectant management until 42 weeks is considered standard of care in women with an uncomplicated pregnancy [15, 22]. In Norway, induction is started no later than 42 weeks, and in Denmark delivery takes place before 42 weeks. Guidelines from the Royal College of Obstetricians and Gynaecologists/National Institute for Health and Care Excellence recommend that women should be offered induction between 41 and 42 weeks [23].

We compared two strategies: induction of labour at 41.0 or 41.1 weeks and expectant management until 42.0 weeks with subsequent induction if necessary. We anticipated that a policy of expectant management at 42 weeks, being the simpler strategy, would be acceptable for a low risk population if it did not lead to a substantially higher proportion of women with adverse perinatal outcomes compared with induction at 41 weeks.

METHODS

Study design

Because induction of labour at 41 weeks as well as expectant management until 42 weeks are practised in the Netherlands, our study was designed to investigate non-inferiority of expectant management. We conducted a multicentre, open label, randomised controlled non-inferiority trial to investigate the effect of INDuction of labour at 41 weeks with a policy of EXpectant management until 42 weeks (INDEX trial) on adverse perinatal outcomes. Women were recruited at 123 primary care midwifery practices and 45 hospitals (secondary care) equally distributed across the Netherlands. Twenty six of these 45 hospitals actively recruited participants, and 19 supported the study by inducing labour in women who had been recruited in a primary care setting and were allocated to induction. In the Netherlands obstetric care is provided by primary care (midwives) for low risk women and secondary care (clinical midwives, residents, and obstetricians) for women with an increased risk of adverse maternal or perinatal outcome, or both. Low risk women in primary care can give birth at home or in an outpatient setting (birth centre or hospital), whereas women in secondary care give birth in hospital. For most low risk women, independent primary care midwives provide obstetric care. If risk factors are present during pregnancy, labour, or the postpartum period, women are referred to secondary care (obstetrician or gynaecologist). Secondary care may also be provided by clinical midwives or trainee

obstetricians under the responsibility of an obstetrician [24-30].

Our protocol has been published previously [31]. The study was performed within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology in cooperation with the Midwifery Research Network Netherlands.

Participants

Women were eligible for the study if they had a low risk, uncomplicated singleton pregnancy with the child in a stable cephalic position at a certain gestational age of 40.5 weeks to 41.0 weeks and no contraindications to expectant management until 42 weeks. Gestational age had to be determined by ultrasonography before a gestational age of 16 weeks. Exclusion criteria for the study were age younger than 18 years, ruptured membranes or in labour, or both, non-reassuring foetal status (e.g., no foetal movements, or abnormal foetal heart rate and/or expected intrauterine growth restriction), known foetal abnormalities (including abnormal karyotype) that could influence perinatal outcome, contraindications to induction (including previous caesarean section), or contraindications to expectant management (e.g., pregnancy induced hypertension).

Randomisation and masking

Eligible women were informed about the study at the 40-week antenatal check. At their next visit (40.5 weeks to 41.0 weeks) the women were counselled by the community midwife, secondary obstetric caregiver, or research-nurse or research-midwife of the participating centres collaborating in the Dutch Obstetric Research Consortium. After written informed consent had been obtained, the study participants underwent digital vaginal examination to determine the Bishop score which is used to assess the ripeness of the cervix before planning of induction of labour. It rates position, consistency, and dilation of the cervix and engagement of the foetal head (station) in a single score. Sweeping of the membranes was optional. Participants were randomly allocated by a web-based program (ALEA) using randomly permuted block sizes of 4 and 2, stratified by centre to induction of labour at 41.0 or 41.1 weeks or to expectant management with subsequent induction if necessary, at 42.0 weeks. Owing to the nature of the intervention it was not possible to blind the women or caregivers to treatment allocation.

Procedures

Women allocated to induction were scheduled for the procedure at 41.0 or 41.1 weeks. All women were primed or induced, or both according to local protocols. Women

with a Bishop score of less than 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.

Women in primary and secondary care who were allocated to expectant management awaited spontaneous onset of labour until 42.0 weeks 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 42.0 weeks in secondary care, following a similar induction protocol to the intervention group.

In both groups, labour was induced if the maternal or foetal condition was no longer reassuring—for example, reduced foetal 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.

The caregivers systematically collected information on perinatal and maternal condition, as well as protocol deviations and the reasons for these. Every case report form was checked on completion and inconsistency. Trained staff entered data in an online digital case report form (Oracle Clinical, version 4.6.6.4.1). Anonymised source documents were collected at the midwifery practice or hospital to check adverse perinatal and maternal outcomes. Serious adverse events were reported on a case by case basis to an independent Data Safety and Monitoring Board and to the Dutch national internet portal for the submission, review, and disclosure of medical-scientific research with participants (www.toetsingonline.nl).

Outcomes

The primary outcome was a composite of perinatal mortality and neonatal morbidity. Perinatal mortality was defined as foetal death, intrapartum death, and neonatal death until 28 days. Neonatal morbidity was defined as having an Apgar score <7 at five minutes and/or an arterial umbilical cord pH <7.05 and/or meconium aspiration syndrome and/or plexus brachialis injury and/or intracranial haemorrhage and/or or being admitted to a neonatal intensive care unit (NICU). Though a neonate could suffer from more than one adverse event, it is counted as one composite adverse perinatal outcome (neonatal level).

We defined meconium aspiration syndrome as respiratory distress after birth in the presence of meconium stained amniotic fluid. NICU admissions were reviewed to reveal final diagnosis and presence of congenital anomalies.

The cut-off for Apgar score <7 at five minutes was based on the committee opinion of the American College of Obstetricians and Gynecologists and American Academy of Pediatrics (ACOG/AAP), 2006. October 2015, after trial registration and during inclusion for this study, the ACOG/AAP committee released an update, which stated that the inappropriate use of the Apgar score in outcome studies had led to an erroneous definition of asphyxia [32]. Although it is incorrect to use Apgar score alone to diagnose birth asphyxia, an Apgar score <4 at five minutes 'can be considered as a non-specific sign of illness'. Because of this mid-trial change of cut-off value, we also planned an additional analysis of the primary outcome including Apgar scores <4 instead of <7 at five minutes.

Secondary perinatal outcomes consisted of maternal outcomes: instrumental delivery (instrumental vaginal delivery, caesarean section), pain treatment (epidural, remifentanil, pethidine), postpartum haemorrhage, and severe perineal injury (third- or fourth-degree perineal tear (obstetrical anal sphincter injuries (OASIS)). Other neonatal outcomes included admission to medium care, congenital abnormality, hypoglycaemia, neonatal infection or sepsis, and small for gestational age (<10th centile) or large for gestational age (>90th centile). We also added a composite of adverse maternal outcome and other delivery outcomes.

The composite adverse maternal outcome included postpartum haemorrhage (≥1000 mL), manual removal of the placenta, third- or fourth-degree perineal tear (obstetrical anal sphincter injuries), and admission to an intensive care unit (ICU). Other delivery outcomes concerned onset of labour, pain treatment during labour, use of tocolytics, maternal intrapartum infection, meconium stained amniotic fluid, gestational age at delivery, mode of delivery, episiotomy, total postpartum blood loss, and blood transfusion. Though a woman could experience more than one adverse event, it is counted as one composite adverse maternal outcome.

For both the perinatal and the maternal composite outcomes, we also compared the individual components.

Statistical analysis

Before the start of the trial, we formed an expert panel, consisting of midwives,

gynaecologists, and paediatricians, and methodologists to conceive the design, content, and execution of the trial. Using data on adverse perinatal outcomes in the Netherlands from the Perined registry (www.perined.nl/), we expected an incidence of 3% for the primary composite adverse perinatal outcome with both strategies. The panel made a reasoned choice about the acceptable difference in adverse perinatal outcome and feasibility of the trial. As a result, the non-inferiority margin (Δ) was defined as a 2% risk difference in incidence of the composite outcome favouring induction to justify a possible change in management strategy of pregnancies reaching a gestational age of 41.0 weeks.

With a one-sided α of 0.05, the study could achieve a power (β) of more than 0.80 if 900 women were recruited in each trial arm (1800 women in total). Non-inferiority would be concluded if the lower limit of the 95% confidence interval of the risk difference excluded a 2% higher proportion of women with an adverse perinatal outcome in the group allocated to expectant management. We established a Data Safety Monitoring Board to review the accumulating data of the trial. Interim analyses were conducted on safety after 517 and 1088 women had been recruited.

The statistician who performed the analyses was blinded to the allocation of the participants and performed the analysis according to a predefined analysis plan. The analysis of the primary outcome was done for both the intention-to-treat groups and the per protocol groups. For the per protocol analysis, we selected all randomised women with start of cervical ripening or spontaneous onset of labour at 41.0 weeks or more. Subsequently we defined the per protocol induction group as women allocated to induction who received induction before 41.2 weeks or who had a spontaneous onset of labour before induction could be started (<41.2 weeks). The per protocol expectant management group included women allocated to expectant management with spontaneous onset of labour until 42.0 weeks, women with a medical reason for induction before 42.0 weeks during expectant management, and women with induction at 42.0 weeks or more.

For all outcomes we estimated relative risks (RR) or median or mean differences, with 95% confidence intervals (CI). As appropriate, we investigated significance using χ^2 test, Fisher's exact test, *t* test, or Mann-Whitney U test statistics. We plotted Kaplan-Meier curves for the time between randomisation and birth. The log-rank test statistic was used to evaluate the difference in time to birth. Birth centiles were determined using national reference data for the Netherlands on birthweight, ethnicity, parity, and gestational age by week and day. Analyses were performed using SAS software for Windows, version 9.4 (SAS Institute, Cary, NC).

Patient and public involvement

No patients were asked for input in the creation of this article. Patient representatives will be asked to join a multidisciplinary working group consisting of (representatives of) obstetric caregivers (primary and secondary care) and neonatologists to create a new nationwide guideline addressing the management of late term pregnancy. Patients will also be involved in writing patient information brochures and a patient decision aid on this topic.

RESULTS

Between 14 May 2012 and 17 March 2016, 6088 eligible women were invited to participate in the INDEX trial, of whom 4273 declined owing to a maternal preference for induction of labour or expectant management, or refusal to let randomisation determine the management strategy. After randomisation but before analysis, one woman (induction group) withdrew her consent, and 13 women did not to meet the eligibility criteria (n=6 induction and n=7 expectant management). Of the remaining 1801 participants, 900 were randomly allocated to the induction group and 901 to the expectant management group (Figure 1). Baseline characteristics were comparable between the groups, except for nulliparity: induction 50.8% (457/900) and expectant management 56.7% (511/901) (Table 1).

In the induction group, 28.9% (260/900) of the women had a spontaneous onset of labour before the planned induction, and 71.1% (640/900) underwent induction (42.2% (382/900) underwent cervical ripening) (Figure 2). In the induction group, 4.8% (43/900) of the women were not induced at 41.0 weeks–41.1 weeks but at 41.2 weeks or later.

In the expectant management group, 73.7% (664/901) of the women had a spontaneous onset of labour and 26.3% (237/901) were induced (14.7% (132/901) underwent cervical ripening). In the expectant management group, 35.9% (85/237) underwent induction at 42 weeks for post-term pregnancy, and 27.4% (65/237) underwent induction before 42 weeks due to medical reasons (e.g., foetal condition in 15.6% (37/237), maternal condition in 9.7% (23/237)), whereas 36.7% (87/237) in the expectant management group underwent induction on request. The median gestational age at time of delivery was 287 days (interquartile range 287-288 days) corresponding with 41.0 weeks (interquartile range 41.0 weeks to 41.1 weeks) for the induction group and 289 days (interquartile range 287-292 days), corresponding with 41.2 weeks (41.0 weeks to 41.5 weeks) in the expectant management group (Table 2). In both groups three quarters of

the women had a Bishop score <6 at study entry. Figure 3 shows the time to delivery for both groups.

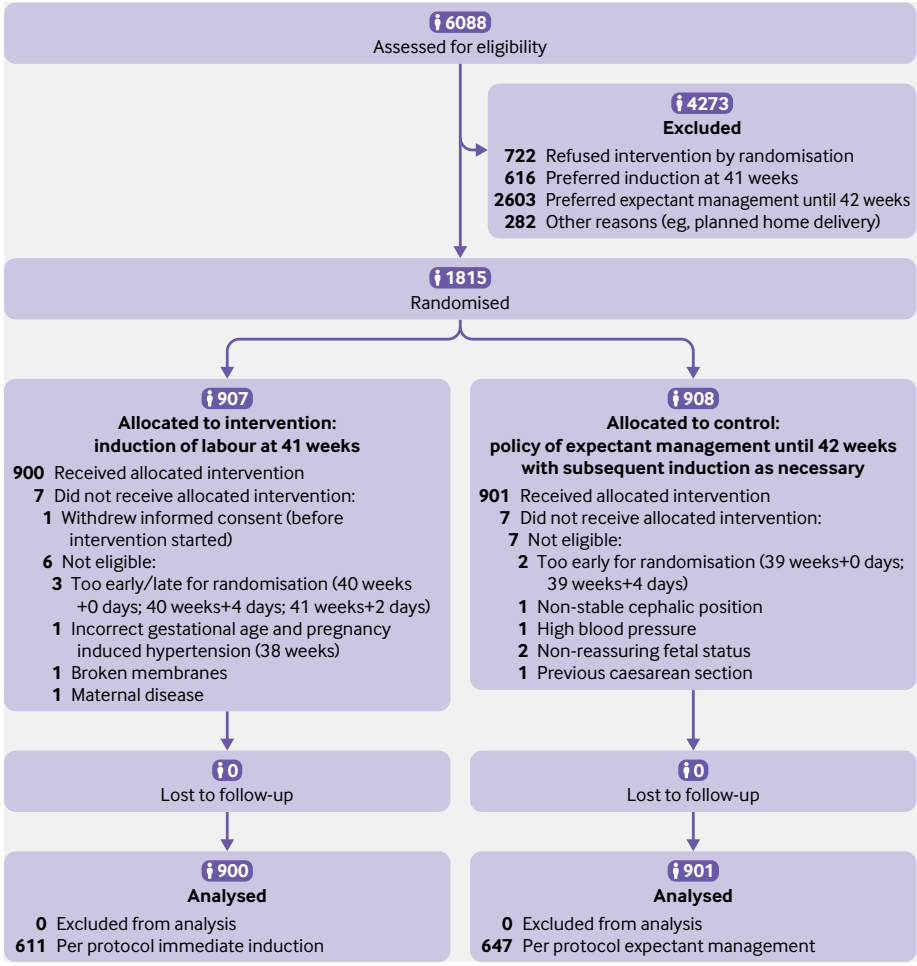

FIGURE 1. Flow of women through study

TABLE 1. Baseline characteristics of study participants by intervention group. Values are numbers (percentages) unless stated otherwise

Characteristics	Induction of labour (n=900)	Expectant management (n=901)
Mean (SD) maternal age (years)	30.6 (4.8)	30.2 (4.6)
18-34	728 (80.9)	758 (84.2)
35-39	148 (16.4)	132 (14.7)
≥40	24 (2.7)	11 (1.2)
Ethnicity		
White	779 (86.6)	767 (85.1)
Other	121 (13.4)	134 (14.9)
Body mass index at start of pregnancy		
<18.5	26 (2.9)	19 (2.1)
18.5-<25	532 (59.1)	523 (58.1)
25-<30	230 (25.6)	229 (25.4)
≥30	89 (9.9)	117 (13.0)
Missing	23 (2.6)	13 (1.4)
Highest level of education		
Primary school	7 (0.8)	4 (0.4)
Secondary school	37 (4.1)	15 (1.7)
Lower/medium professional education	358 (39.8)	350 (38.8)
Higher professional education/university	286 (31.8)	322 (35.7)
Other/unknown	212 (23.4)	210 (23.3)
Social economic status		
Low	219 (24.3)	251 (27.9)
Medium	401 (44.6)	365 (40.5)
High	225 (25.0)	233 (25.9)
Unknown	55 (6.1)	52 (5.8)
Parity		
Nulliparous	457 (50.8)	511 (56.7)
Multiparous	443 (49.2)	390 (43.3)
Previous post-term pregnancy (≥294 days)*	51/443 (11.5)	34/390 (8.7)
Level of care at recruitment		
Primary	851 (94.6)	850 (94.3)
Secondary	49 (5.4)	51 (5.7)
Bishop score at study entry		
Nulliparous women		
≥6	47/457 (10.3)	71/511 (13.9)
<6	360/457 (78.8)	365/511 (71.4)
Missing	50/457 (10.9)	75/511 (14.7)
Multiparous women		
≥6	71/443 (16.0)	46/390 (11.8)
<6	310/443 (70.0)	294/390 (75.4)
Missing	62/443 (14.0)	50/390 (12.8)
Membrane sweeping before randomisation	286/900 (31.8)	343/901 (38.1)

**Numerator: multiparous women.*

In the per protocol induction group, 15.1% (92/611) of the women had spontaneous onset of labour before the planned induction. Of these women, 11.1% (67/611) had a spontaneous onset of labour at 41.0 weeks and 4.1% (25/611) at 41.1 weeks. In the per protocol induction group, 84.9% (519/611) of the women were induced: 62.5% (382/611) at 41.0 weeks and 22.4% (137/611) at 41.1 weeks. In the per protocol expectant management group, 80.9% (524/647) of the women had a spontaneous onset of labour at 41.0 weeks or later and 19.0% (123/647) were induced: 5.4% (35/647)

because of concerns about foetal condition at 41.0 weeks or later, 3.4% (22/647) because of maternal condition 41.0 weeks or later, 0.6% (4/647) because of rupture of the membranes more than 24 hours previously at 41.0 weeks or later, and 9.6% (62/647) because of post-term pregnancy (≥42.0 weeks).

Primary outcome

Table 3 presents the perinatal outcomes in the intention-to-treat analysis. Fifteen women in the induction group (1.7%) and 28 in the expectant management group (3.1%) had a composite adverse perinatal outcome (absolute risk difference –1.4%, 95% CI –2.9% to 0.0%; number needed to treat (NNT) 69, CI 35 to 3059). The P value for non-inferiority was 0.22, indicating that we could not exclude that expectant management leads to 2% or more adverse perinatal outcomes compared with induction. All neonates in the expectant management group with a composite adverse perinatal outcome were born in secondary care. In these cases, women either had labour started in secondary care or were transferred during labour from primary to secondary care.

The per protocol analysis showed a 1.6% risk of an adverse perinatal outcome (10/611) in the induction group compared with 2.9% (19/647) in the expectant management group (risk difference –1.3%, 95% CI –3.0% to 0.4%, P=0.21 for non-inferiority; see supplementary appendix).

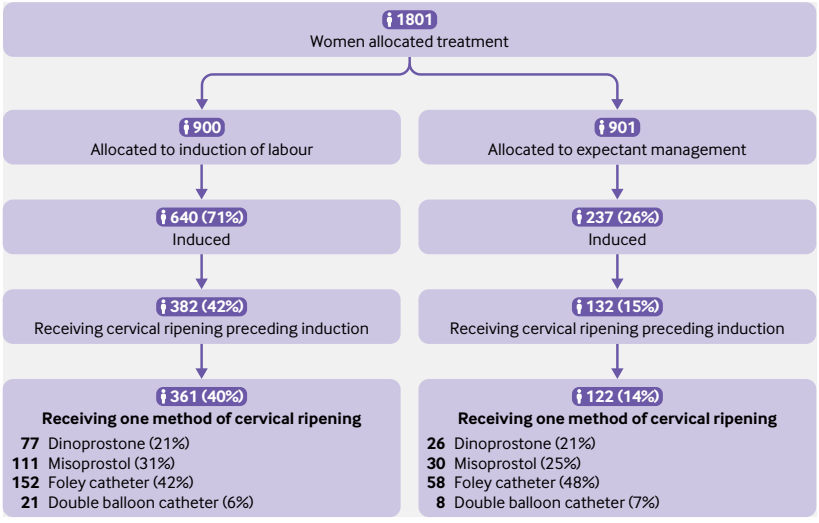

FIGURE 2. Cervical ripening during study

TABLE 2. Delivery outcomes in intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Outcomes	Induction of labour (n=900)	Expectant management (n=901)	Relative risk (95% CI)	*P value*
Median (interquartile range) gestational age delivery (days)	287 (287-288)	289 (287-292)	−2.1 (−2.3 to −1.9) *	<0.001†
Mean (SD) time from randomisation to delivery (days)	2.1 (1.6)	4.2 (3.0)	−2.2 (−2.5 to −2.0) *	<0.001†
Level of care at onset of labour:				
Primary	255 (28.3)	619 (68.7)	NC	-
Secondary	645 (71.7)	282 (31.3)	NC	-
Onset of labour:				
Spontaneous (reference)	260 (28.9)	664 (73.7)	1.00	-
Induction	640 (71.1)	237 (26.3)	2.70 (2.41 to 3.04)	<0.001
Mode of induction:	n=640	n=237		
Cervical ripening (catheter/prostaglandins)	382 (59.7)	132 (55.7)	1.07 (0.94 to 1.22)	0.30
Amniotomy without oxytocin	87 (13.6)	34 (14.8)	0.95 (0.66 to 1.37)	0.77
Amniotomy with oxytocin	156 (24.4)	59 (24.9)	0.98 (0.76 to 1.27)	0.87
Indication for induction:				
Randomisation	634 (99.1)	0 (0.0)	NC	-
Post-term pregnancy	0 (0.0)	85 (35.9)	NC	-
Foetal condition	5 (0.8)	37 (15.6)	NC	-
Maternal condition	0 (0.0)	23 (9.7)	NC	-
Elective or maternal request	1 (0.2)	87 (36.7)	NC	-
Membranes ruptured >24 h	0 (0.0)	4 (1.7)	NC	-
Other	0 (0.0)	1 (0.4)	NC	-
Use of oxytocin	533 (59.2)	355 (39.4)	1.50 (1.36 to 1.66)	<0.001
Use of tocolytics	28 (3.1)	16 (1.8)	1.75 (0.95 to 3.22)	0.07
Maternal intrapartum infection:	n=900	n=901		
Fever during labour (≥38°C)	50 (5.6)	46 (5.1)	1.09 (0.74 to 1.61)	0.67
Use of antibiotics	48 (5.3)	35 (3.9)	1.37 (0.90 to 2.10)	0.14
Meconium stained amniotic fluid	147 (16.3)	205 (22.8)	0.72 (0.59 to 0.87)	0.001
Level of care at time of birth:				
Primary	129 (14.3)	309 (34.3)	NC	-
Secondary	771 (85.7)	592 (65.7)	NC	-
Mode of delivery:				
Spontaneous vaginal	710 (78.9)	696 (77.2)	1.02 (0.97 to 1.07)	0.40
Operative vaginal	93 (10.3)	108 (12.0)	0.86 (0.66 to 1.12)	0.27
(Secondary) caesarean section	97 (10.8)	97 (10.8)	1.00 (0.77 to 1.31)	0.99
Indication successful operative vaginal delivery:	n=93	n=108		
Failure to progress at second stage	39 (41.9)	49 (45.4)	0.92 (0.67 to 1.27)	0.63
Suspected foetal distress	43 (46.2)	37 (34.3)	1.35 (0.96 to 1.90)	0.08
Suspected foetal distress and failure to progress	10 (10.8)	22 (20.4)	0.53 (0.26 to 1.06)	0.07
Maternal complication or other	1 (1.1)	0 (0.0)	NA	-
Indication for secondary caesarean section:	n=97	n=97		
Failure to progress at first stage	29 (29.9)	21 (21.6)	1.38 (0.85 to 2.25)	0.19
Failure to progress at second stage	12 (12.4)	18 (18.6)	0.67 (0.34 to 1.31)	0.24
Failed operative vaginal delivery	6 (6.2)	12 (12.4)	0.50 (0.20 to 1.28)	0.22‡
Suspected foetal distress	24 (24.7)	21 (21.6)	1.14 (0.68 to 1.91)	0.61
Suspected foetal distress and failure to progress at first stage	7 (7.2)	8 (8.3)	0.75 (0.17 to 3.26)	1.00‡
Suspected foetal distress and failure to progress at second stage	4 (4.1)	3 (3.1)	1.00 (0.26 to 3.88)	1.00‡
Maternal complication or other	15 (15.5)	14 (14.4)	0.93 (0.48 to 1.83)	0.84

NC: not calculable NA: not applicable.

**Mean (95% CI) difference between groups.*

†Mann-Whitney U test.

‡Fisher's exact test.

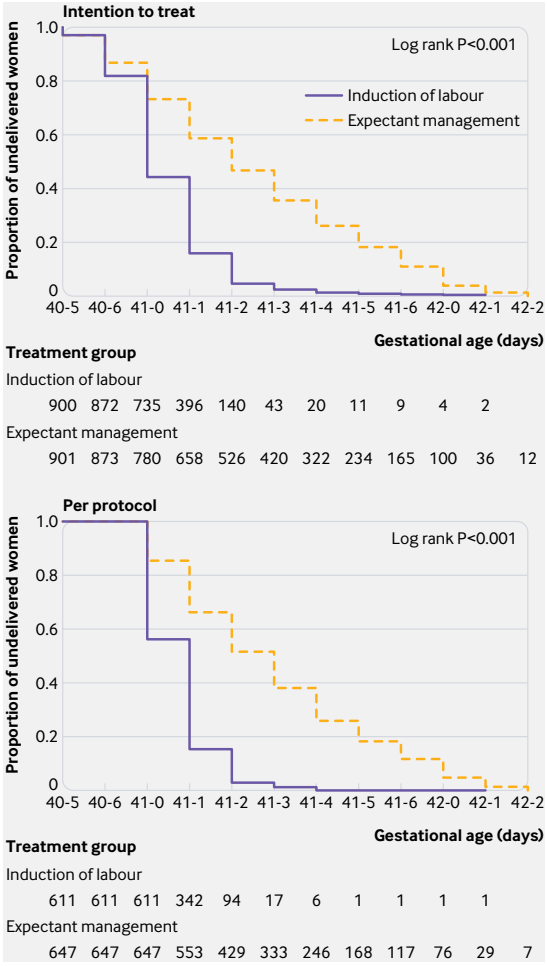

FIGURE 3. Time to delivery

Additional analysis of the composite primary outcome including Apgar score <4 at five minutes instead of <7 resulted in 0.4% (4/900) adverse perinatal outcomes in the induction group and 1.3% (12/901) in the expectant management group (absolute risk difference −0.9%, −1.9% to 0.2%; NNT 113, 57 to 4624, P=0.02 for non-inferiority).

The additional per protocol analysis of the composite primary outcome including Apgar score <4 at five minutes showed a 0.5% risk (3/611) of an adverse perinatal outcome in the induction group versus 1.2% (8/647) in the expectant management group (risk difference −0.7%, −2.0% to 0.5%, P=0.02 for non-inferiority; see supplementary appendix).

TABLE 3. Perinatal outcomes in intention-to-treat groups

Outcomes	Induction of labour (n=900)	Expectant management (n=901)	Relative risk (95% CI)	*P value*
Composite adverse perinatal outcome*	15 (1.7)	28 (3.1)	0.54 (0.29 to 1.00)	0.045†
with 5 min Apgar score <4 instead of <7	4 (0.4)	12 (1.3)	0.33 (0.11 to 1.03)	0.06†
including arterial pH <7.05	27 (3.0)	37 (4.1)	0.72 (0.44 to 1.20)	0.16†
Stillbirth	1 (0.1)	2 (0.2)	0.50 (0.05 to 5.51)	1.00†
Neonatal death post-partum	0 (0.0)	0 (0.0)	NA	-
Apgar score 5 mins post-partum¤				
<7	11 (1.2)	23 (2.6)	0.48 (0.23 to 0.98)	0.038
<4	0 (0.0)	3 (0.3)	NA	-
Neonate admitted to:				
NICU	3/899 (0.3)	8/899 (0.9)	0.38 (0.10 to 1.41)	0.23†
Medium care	59 (6.6)	60 (6.7)	0.98 (0.69 to 1.39)	0.90
Meconium aspiration syndrome‡	0 (0.0)	2 (0.2)	NA	-
Plexus brachialis injury	0 (0.0)	0 (0.0)	NA	-
Intracranial haemorrhage§	0 (0.0)	0 (0.0)	NA	-
Umbilical cord pH (arterial)				
<7.05	16 (1.8)	12 (1.3)	1.06 (0.51 to 2.20)	0.88
Missing	557 (62.0)	629 (70.0)	NA	-
Congenital abnormality	16 (1.8)	19 (2.1)	0.84 (0.44 to 1.63)	0.61
Hypoglycaemia¶	3 (0.3)	6 (0.7)	0.50 (0.13 to 2.00)	0.51†
Neonatal infection/sepsis**	37 (4.1)	37 (4.1)	1.00 (0.64 to 1.56)	1.00
Female	453 (50.3)	463 (51.4)	0.98 (0.89 to 1.07)	0.65
Mean (SD) birthweight (g)	3685 (417.4)	3741 (430.0)	−56.6 (−95.8 to −17.4) ††	0.005
Small for gestational age				
<2.3rd centile	13 (1.4)	11 (1.2)	1.18 (0.53 to 2.62)	0.68
<10th centile	61 (6.8)	62 (6.9)	0.99 (0.70 to 1.39)	0.93
Large for gestational age				
>90th centile	86 (9.6)	99 (11.0)	0.87 (0.66 to 1.14)	0.32
>97th centile	15 (1.7)	27 (3.0)	0.56 (0.30 to 1.04)	0.07

NA: not applicable; NICU: neonatal intensive care unit.

**Composite outcome defined as perinatal mortality (foetal death, intrapartum death, and neonatal death until 28 days) or perinatal morbidity (a 5-minute Apgar score <7, and/or meconium aspiration syndrome, and/or plexus brachialis injury, and/or intracranial haemorrhage, and/or NICU admission). In the IOL group all livebirths with a CAPO had either a 5-minute Apgar score <7 or a NICU admission. In the EM group livebirths with a CAPO: two neonates had MAS, 5-minute Apgar score <7 and NICU admission; three neonates were admitted to NICU, and also had a 5-minute Apgar score <7; three neonates were admitted to NICU, but had no 5-minute Apgar score <7; 18 neonates had a 5-minute Apgar score <7, but no NICU admission.*

†Fisher's exact test.

¤Apgar score of live births.

‡Defined as respiratory distress after birth in presence of meconium stained amniotic fluid.

§Defined as clinical signs of intracranial haemorrhage.

¶Defined as glucose concentration <1.9 mmol/L and need for intravenous glucose.

***Defined as clinical suspected findings or proved positive blood culture result.*

††Mean (95% confidence interval) difference between groups.

Three perinatal deaths (stillbirths) occurred: one in the induction group and two in the expectant management group. There were no neonatal deaths. The stillbirth in the induction group was in a 30 year old multiparous woman who was randomised at 40 weeks+5 days and scheduled for induction at 41 weeks+1 day. She had reduced foetal movements at 40 weeks+6 days, and foetal death was diagnosed at consultation. She

delivered a neonate weighing 3595 g (20th to 50th centiles). Investigations, including a post-mortem examination, did not explain the stillbirth. In the expectant management group, stillbirth was diagnosed in a 36-year-old nulliparous woman at 41 weeks+3 days, when she was admitted to hospital in labour. She delivered a neonate weighing 2945 g (5th to 10th centiles). Investigations, including placental examination, did not explain the stillbirth, and the parents declined a post-mortem examination. The second stillbirth in the expectant management group was diagnosed in a 32-year-old multiparous woman at 41 weeks+4 days during a regular consultation in secondary care for impending post-term pregnancy. She delivered a neonate weighing 3715 g (20th to 50th centiles). No post-mortem examination was performed, but the placenta showed signs of chorioamnionitis.

The main contributor to the composite adverse outcome was an Apgar score <7 at five minutes: 1.2% (11/900) of neonates in the induction group and 2.6% (23/901) in the expectant management group (RR 0.48, CI 0.23 to 0.98). Three of these neonates, all in the expectant management group, had an Apgar score <4 at five minutes. The first neonate was born at 41.6 weeks after spontaneous onset of labour and an operative vaginal delivery (vacuum), because of foetal distress and failure to progress in second stage. The diagnosis was meconium aspiration syndrome, and the neonate was admitted to the NICU (Table 4). Sepsis after spontaneous onset of labour at 40.6 weeks and rupture of membranes of more than 24 hours was diagnosed in the second neonate. The third neonate, weighing 4320 g, was born after cervical ripening that started at 41.6 weeks and failure to progress of second stage followed by a caesarean section at 42.2 weeks. The diagnosis in this neonate was airway obstruction caused by vernix caseosa. Both these neonates were admitted to a medium care unit for observation. All three neonates recovered without complications. Admission to an NICU was reported in 0.3% (3/899) of neonates in the induction group versus 0.9% (8/899) in the expectant management group (RR 0.38, CI 0.10 to 1.41). Of the 11 children admitted to the NICU, six (three in each group) had a diagnosis of severe congenital disorder. Meconium aspiration syndrome was diagnosed twice, but only in the expectant management group, and both neonates recovered fully. No plexus brachialis lesions and no intracranial haemorrhage were diagnosed in the study population. In two admissions because of a (suspected) infection, one neonate had group B streptococcus and the other had a negative culture result. One neonate was admitted because of a pneumothorax.

Arterial pH measurements were not recorded systematically and therefore could not be included in the analysis. Imputing was not possible owing to many missing data (62.0% induction *v* 70.0% expectant management). However, when we analysed data

including the available pH measurements, the composite adverse perinatal outcome was 27/900 (3.0%) in the induction group versus 37/901 (4.1%) in the expectant management group (risk difference –1.11%, CI –2.84% to 0.63%, P=0.16 for non-inferiority). For the per protocol analysis, the composite adverse perinatal outcome including the available pH measurement was 3.1% (19/611) in the induction group versus 4.0% (26/647) in the expectant management group (risk difference –0.91%, –2.98 to 0.01%, P=0.15 for non-inferiority).

When stratifying by parity, we observed 2.4% (11/457) nulliparous women with a composite adverse perinatal outcome in the induction group and 4.1% (21/511) in the expectant management group (RR 0.59, CI 0.29 to 1.20). In multiparous women the incidence of adverse perinatal outcome was lower in both groups compared with nulliparous women: 0.9% (4/443) in the induction group and 1.8% (7/390) in the expectant management group (RR 0.50, CI 0.15 to 1.71). In logistic regression analysis, no interaction was found between parity and induction or expectant management.

TABLE 4. Admission to neonatal intensive care unit (NICU) by intervention

Allocation	NICU admission: diagnosis	Congenital anomaly	Gestational age at birth
Induction	Long QT syndrome	Yes	40.6 weeks
Induction	Mild mitral valve insufficiency, persistent ductus arteriosus	Yes	41.0 weeks
Induction	Interstitial lung disorder	Yes	41.1 weeks
Expectant management	Diaphragm herniation, atrial septal defect, ventricular septal defect	Yes	40.6 weeks
Expectant management	Muscular ventricular septal defect	Yes	41.5 weeks
Expectant management	Vocal cord paresis, dysmorphic features	Yes	41.5 weeks
Expectant management	Infection (suspected, but culture was sterile)	No	41.2 weeks
Expectant management	Infection, Group B Streptococcus positive	No	41.3 weeks
Expectant management	Pneumothorax	No	41.4 weeks
Expectant management	Meconium aspiration syndrome	No	41.2 weeks
Expectant management	Meconium aspiration syndrome	No	41.6 weeks

Secondary outcomes

Table 3 shows the secondary perinatal outcomes in the intention-to-treat groups. No difference was found in medium care admissions, 6.6% (59/899) in the induction group versus 6.7% (60/899) in the expectant management group. Small for gestational age (<10th centile), according to Dutch birthweight centiles, was similar between the groups: 6.8% (61/900) in the induction group versus 6.9% (62/901) in the expectant management group. Overall, 9.6% (86/900) of infants in the induction group were large for gestation age (>90th centile) versus 11.0% (99/901) in the expectant management group. The incidence of congenital abnormalities was similar between groups: 1.8% in the induction group (16/900) versus 2.1% in the expectant management group (19/901).

Table 2 summarises the characteristics of labour and mode of delivery. Oxytocin was given significantly more often in the induction group than in the expectant management group (59.2% (533/900) and 39.4% (355/901) (RR 1.50, CI 1.36 to 1.66)). Meconium stained amniotic fluid occurred significantly less often in the induction group compared with expectant management group (16.3% (147/900) and 22.8% (205/901) (RR 0.72, CI 0.59 to 0.87). Ninety-seven women in each group (10.8%) had a caesarean section (RR 1.00, CI 0.77 to 1.31), mainly for non-progressive labour at the first stage of labour (Table 2).

Table 5 shows the results of adverse maternal outcomes in the intention-to-treat groups. The composite adverse maternal outcome occurred in 13.6% (122/900) of the women in the induction group versus 11.3% (102/901) in the expectant management group (RR 1.20, CI 0.94 to 1.53). Postpartum haemorrhage ≥1000 mL was the main contributor to the composite adverse maternal outcome and occurred in 9.1% (82/900) of women in the induction group versus 8.0% (72/901) in the expectant management group (RR 1.14, CI 0.84 to 1.54). Manual removal of the placenta occurred in 5.1% (41/803) in the induction group versus 4.1% (33/804) in the expectant management group (RR 1.24, CI 0.79 to 1.95). Obstetrical anal sphincter injuries were diagnosed in 3.5% (28/803) of women in the induction group versus 3.9% (31/804) in the expectant management group (RR 0.90, CI 0.55 to 1.49). Three mothers (0.3%) in the induction group and two (0.2%) in the expectant management group were admitted to an ICU post-partum (RR 1.50, CI 0.25 to 8.97), all after postpartum haemorrhage. Blood loss in these women was 3000 mL, 5100 mL, and 7000 mL in the induction group and 3390 mL and 5000 mL in the expectant management group. No maternal deaths occurred. During labour, 29.4% (265/900) of the women in the induction group received epidural anaesthesia compared with 25.6% (231/901) in the expectant management group (RR 1.15, CI 0.99 to 1.33).

TABLE 5. Adverse maternal outcomes in intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Adverse outcomes	Induction of labour (n=900)	Expectant management (n=901)	Relative risk (95% CI)	*P value*
Composite adverse maternal outcome*	122 (13.6)	102 (11.3)	1.20 (0.94 to 1.53)	0.15
Maternal death	0 (0.0)	0 (0.0)	NA	-
Postpartum blood loss				
<1000 mL (reference)	818 (90.9)	829 (92.0)	1.00	-
≥1000 mL	82 (9.1)	72 (8.0)	1.14 (0.84 to 1.54)	0.40
1000-1499 mL	34 (3.8)	35 (3.9)	0.97 (0.61 to 1.54)	0.91
1500-1999 mL	21 (2.3)	14 (1.6)	1.50 (0.77 to 2.93)	0.23
≥2000 mL	27 (3.0)	23 (2.6)	1.18 (0.68 to 2.04)	0.56
Median (interquartile range) postpartum blood loss (mL)	300 (200-500)	300 (250-500)	-	0.18†
Transfusion (packed cells or plasma)	23 (2.6)	17 (1.9)	1.35 (0.73 to 2.52)	0.34
Manual removal placenta	41/803 (5.1)	33/804 (4.1)	1.24 (0.79 to 1.95)	0.34
Perineal tear	n=803	n=804		
Episiotomy (without tear)	234 (29.3)	246 (30.6)	0.95 (0.82 to 1.11)	0.52
Obstetrical anal sphincter injuries	28 (3.5)	31 (3.9)	0.90 (0.55 to 1.49)	0.69
Third degree tear	15 (1.9)	19 (2.4)	0.79 (0.40 to 1.54)	0.49
Fourth degree tear	8 (1.0)	7 (0.9)	1.14 (0.41 to 3.14)	0.80‡
Episiotomy and third-degree tear	4 (0.5)	2 (0.3)	2.00 (0.37 to 10.90)	0.45‡
Episiotomy and fourth degree tear	1 (0.1)	3 (0.4)	0.33 (0.03 to 3.20)	0.62‡
Maternal admission (highest level of care)				
Intensive care	3 (0.3)	2 (0.2)	1.50 (0.25 to 8.97)	0.66‡
Medium care	5 (0.6)	5 (0. 6)	1.00 (0.29 to 3.45)	1.00‡
Ward	271 (30.1)	277 (30.7)	0.98 (0.85 to 1.13)	0.77
Indications for maternal admission				
Thromboembolic complications	0 (0.0)	0 (0.0)	NA	-
Hypertensive disorders§	5 (0.6)	14 (1.6)	0.36 (0.13 to 0.99)	0.06‡
Postpartum blood loss	49 (5.5)	52 (5.8)	1.06 (0.72 to 1.54)	0.78
Post-caesarean section	97 (10.8)	97 (10.8)	1.00 (0.77 to 1.31)	0.99
Pain treatment during labour	420 (46.7)	386 (42.8)	1.09 (0.98 to 1.20)	0.10
Remifentanil	128 (14.2)	129 (14.3)	0.99 (0.79 to 1.25)	0.95
Pethidine/promethazine/other opiates	60 (6.7)	51 (5.7)	1.18 (0.82 to 1.69)	0.38
Epidural anaesthesia	265 (29.4)	231 (25.6)	1.15 (0.99 to 1.33)	0.07
Other	1 (0.1)	5 (0.6)	0.20 (0.02 to 1.71)	0.22‡

NA: not applicable.

**Defined as postpartum haemorrhage ≥1000 mL, and/or manual removal of placenta, and/or third- or fourth-degree tears (obstetrical anal sphincter injuries), and/or intensive care admission, and/or maternal death. Denominator for perineal tear are vaginal deliveries only.*

†Mann-Whitney U test

‡Fisher's exact test.

§Including pre-eclampsia, and HELLP syndrome.

DISCUSSION

This randomised controlled trial compared the effect of induction of labour at 41 weeks with expectant management until 42 weeks with subsequent induction if necessary, on perinatal and maternal outcomes in women with an uncomplicated pregnancy. A policy of induction resulted in a median reduction in gestational age at delivery of two

days. We found a 1.4% difference in composite adverse perinatal outcome favouring induction, although the absolute risk of severe adverse perinatal outcome (perinatal mortality, Apgar score <4 at five minutes, admission to a neonatal intensive care unit (NICU) without severe congenital anomalies) was low in both groups.

Most of our primary composite outcomes can be attributed solely to the component Apgar score <7 at five minutes 73.3% (11/15) in the induction group *v* 64.3% (18/28) in the expectant management group), which means that these neonates did not have any other adverse outcome besides the Apgar score being <7 at five minutes. We performed a post hoc analysis of the composite outcome including Apgar scores <4 instead of <7 at five minutes owing to the American College of Obstetricians and Gynecologists/ American Academy of Pediatrics (ACOG/AAP) mid-trial change in recommended cut-off value for Apgar score at five minutes indicating a non-specific sign of illness. A considerably lower incidence of adverse perinatal outcome was found in both groups (0.4% induction and 1.3% expectant management), with an absolute risk difference of −0.9% (CI −1.9% to 0.2%) favouring induction, showing non-inferiority of expectant management with respect to the predefined margin of 2% (P=0.02 for non-inferiority).

Comparison with other studies

The incidence of perinatal death in our study was one after induction with two after expectant management. The corresponding risk ratio for perinatal death (RR 0.50, CI 0.05 to 5.51) is comparable with that of the four studies (n=998) starting induction at 41 weeks (n=501) versus expectant management with varying upper limits of gestational age (n=497) included in a Cochrane systematic review (RR 0.33, CI 0.03 to 3.17) [19, 21, 33].

Congenital anomaly accounted for a substantial part of the NICU admissions in our trial, although it was an exclusion criterion at study entry. It is unknown if the outcome for these children would have been better if they had been born earlier, although it is unlikely (Table 4). For these reasons we also analysed the primary composite outcome using an Apgar score <4 at five minutes and NICU admission without severe congenital anomalies. With these adapted adverse outcomes (perinatal mortality, Apgar score <4 instead of <7 at five minutes, and NICU admission without severe congenital anomalies), the absolute risk on the composite adverse perinatal outcome was substantially lower in both groups, with a still significant difference in favour of induction (0.1% (1/897)) versus expectant management (1.0% (9/898)): absolute risk difference −0.9%, CI −1.6% to 0.2%; P=0.01 for non-inferiority; P=0.02 for Fisher's exact test; and NNT of 112 (CI 63 to 491)).

Since in our trial all women in the 41-week induction group received obstetrician led intrapartum secondary care whereas in the expectant management group until 42 weeks 68.7% of the women received midwifery led primary care at start of labour and 34.3% at time of birth, it could be suggested that our study is prone to performance bias (different care) and measurement bias (different assessment of neonates). Several studies, however, showed that Apgar scoring does not differ significantly between midwives and obstetricians [34-36] Furthermore, in our trial all neonates in the expectant management group with an adverse outcome were born in secondary care—the women had started labour in secondary care or were referred from primary to secondary care during labour. Various studies have shown that it is safe for low risk women in the Netherlands to deliver in midwifery led care, and the level of care does not seem to influence delivery outcome for these women [24-28]. Although this study could be considered as a comparison between obstetrician led care with labour induction and midwife led care with a policy of expectant management, we cannot adjudicate whether the difference in the composite adverse perinatal outcome is due to the level of care (performance bias) or to a possible difference in Apgar scoring (measurement bias). We do not, however, expect bias to be a major factor.

In our study, meconium aspiration syndrome occurred in two neonates in the expectant management group. In a randomised controlled trial with a comparable time frame, Gelisen et al reported meconium aspiration syndrome in 16/600 neonates of whom 12/300 were in the expectant management group. We found a 10- and 20-times lower rate of meconium aspiration syndrome (0.0% and 0.2% versus 1.3% and 4%) in the induction and expectant management groups compared with the study by Gelisen et al. Since these authors did not specify meconium aspiration syndrome, the difference in magnitude could be attributed to a difference in definition. Despite this, Gelisen et al found no difference in NICU admissions (4.3% induction *v* 5.0% expectant management), which is expected to be associated with meconium aspiration syndrome. We found a lower rate of NICU admissions compared with the Cochrane systematic review on induction of labour at more than 41 weeks: 0.3% induction and 0.9% expectant management (INDEX trial) *v* 11% induction and 12% expectant management (systematic review). The systematic review lacked details on NICU admission, such as diagnosis, potential association with gestational age, or presence of congenital anomalies, which hampers a clear comparison [16, 33].

We did not find differences in caesarean section or operative vaginal delivery rates, which is consistent with other large studies on induction of labour [37, 38]. In the only study that compared the same timeframes as our study, the risk ratio for caesarean

section was comparable for both groups, although the absolute risk was twice as high compared with that of our study. This could be due to other inclusion criteria (Gelisen et al, Bishop score <5) or differences in policy during labour, as reflected by differences in national overall caesarean rates in Turkey (53% *v* 16% in the Netherlands) [35, 39] The Cochrane systematic review concluded that induction at or beyond 41 weeks is associated with lower caesarean section rates. The largest contribution to this outcome was from a randomised controlled trial in which women in the control group were induced only with oxytocin according to study protocol, whereas prostaglandin use was allowed in women with low Bishop scores in the induction group [16] Two other systematic reviews including the same trial concluded that the difference in caesarean section rate is possibly due to the influence of this study with incomparable study arms [17, 20, 40]. Population based cohort studies showed conflicting results on the effect of induction on caesarean section rates [41-43]. In the recently published ARRIVE (A Randomized Trial of Induction Versus Expectant Management) trial, low risk nulliparous women were randomised in the 39th week of pregnancy to be induced at 39.0 weeks to 39.4 weeks or to expectant management until 41 weeks. No statistically significant difference was found in perinatal outcome (RR 0.80, CI 0.64 to 1.00), although fewer caesarean sections took place in the induction group (18.6% *v* 22.2%; RR 0.84, CI 0.76 to 0.93). Our study comprised more white women (86% *v* 44%), with a higher median age (30 *v* 24 years) and a lower percentage of body mass index ≥30 (12% *v* 53%), whereas 46% of the participants in our study were multiparous women and ARRIVE included only nulliparous woman. Caesarean section rates in our nulliparous low risk women were comparable between the groups: 18.6% in the induction group and 18.0% in the expectant group. This could be due to the differences in gestational age, baseline characteristics, indication for induction of labour, or indication for a caesarean section (suspected foetal distress or failure to progress) [44].

Our trial had some notable results besides those for the main outcomes. Around 85% of participating women were of white ethnicity. The risk of perinatal mortality beyond term has been shown to be higher in women of South Asian, African, and Mediterranean origin compared with white women [45]. In our study, we were not able to assess the effect of induction in women of non-white ethnicity owing to the low number of women of other ethnic origin. Also, we were unable to assess the effect of age on adverse perinatal outcome because of the low number of participating older mothers (>35 years).

As in other studies on pregnancies at or beyond 41 weeks, most women in our study had an unfavourable cervix, with a Bishop score of <6 at randomisation. Although

induction was planned one or two days after randomisation, 28.9% of the women in the induction group had a spontaneous onset of labour before induction started, compared with 73.7% in the expectant management group. Despite women with suspected or established intrauterine growth restriction being ineligible for inclusion in the study, the birthweight for 7% of the children was less than the 10th Dutch centile (61/900 induction and 62/901 expectant management), confirming the difficulty in diagnosing growth restricted babies at term. In the induction group, 2/61 infants had a birthweight less than the 10th centile and an adverse perinatal outcome: one neonate, weighing 3100 g (<10th centile), had an Apgar score of 6 at five minutes after operative vaginal delivery by forceps because of foetal distress. The other neonate, weighing 2595 g (<2.3rd centile), had an Apgar score of 6 at five minutes after caesarean section because of foetal distress, with an umbilical cord pH of 6.87, possibly due to hypotension of the mother after epidural analgesia for pain relief or multiple entanglement of the umbilical cord. In the expectant management group, 3/62 infants weighed less than the 10th centile at birth and had an adverse perinatal outcome: one (birthweight 2945 g) was a stillbirth, one (2980 g) was admitted to the NICU because of a pneumothorax, and one (3040 g) had an Apgar score of 6 at five minutes that was attributed to pethidine use in the mother.

Strengths and limitations of this study

A major strength of our study is that it concerns a nationwide multicentre randomised controlled trial of a well-defined obstetrical population at low risk; the largest trial to date to compare induction of labour at 41 weeks with expectant management until 42 weeks [46]. No cases were lost to follow-up.

In the Netherlands, expectant management until 42 weeks is the standard of care in the low risk obstetrical population at 41-42 weeks according to the Dutch Obstetrical Indication List, although there is wide variation in practice because of women and caregiver preferences, which complicated inclusion [15]. Not all eligible women were invited, and not all women who were asked participated, because of a preference for induction or expectant management. Despite this selective participation, our trial offers the best possible representation of pregnant women reaching 41.0 weeks in the Netherlands.

We are aware of some potential limitations of our trial. We chose to use a composite adverse perinatal outcome instead of a single outcome like perinatal mortality. We considered any major adverse perinatal outcome in an otherwise uncomplicated pregnancy as undesirable. It is debatable if all the included adverse perinatal outcomes

in our composite outcome measure are relevant to identify real severe adverse perinatal outcome with an effect on an infant's short term or long-term health status. However, if we included an Apgar score of <4 instead of <7 at five minutes, according to the ACOG/AAP criteria, and excluded severe congenital abnormalities, induction of labour resulted in a statistically significant risk reduction of 0.9%, although with a substantially lower incidence of the composite adverse outcome in both groups.

We chose the non-inferiority design because we did not expect the Dutch standard policy of expectant management in our low risk obstetrical population to be inferior to a policy of induction of labour but acceptable or preferable if leading to comparable outcomes [47]. It is good practice to use a per protocol analysis in non-inferiority trials, as an intention-to-treat analysis carries a risk of falsely rejecting the null hypothesis of inferiority. Because we did not reject the null hypothesis and do not conclude non-inferiority, we presented the intention-to-treat analyses first, since such analyses are more common in reports of clinical trials. We also reported the per protocol outcome of the primary outcome (see supplementary appendix for the other per protocol analyses).

We did not stratify randomisation by parity, because we expected a balanced allocation in both groups owing to the large study population. However, it did result in an imbalance between groups: 50.8% of nulliparous women in the induction group compared with 56.7% in the expectant management group. After stratifying by parity in an additional analysis, we observed similar results. A higher incidence of the composite adverse perinatal outcome was seen in the nulliparity group in both the induction group (nulliparous 2.4% *v* multiparous 0.9%) and the expectant management group (nulliparous 4.1% *v* multiparous 1.8%), which is in concordance with other studies [48]. Furthermore, we saw no interaction between parity and induction of labour or expectant management in logistic regression analysis.

The measurement of arterial pH is not possible in primary care, and pH measurement is no standard policy for uncomplicated birth in most hospitals in the Netherlands. Because of the high number of missing pH measurements (60-70%) and the impossibility to impute, we could not include umbilical artery pH in the composite outcome, which could have led to selection bias. Including the available data on umbilical arterial pH in the analyses, however, did not alter the results.

The results of our study can be interpreted in different ways, which might have implications for standard practice. If the composite outcome is interpreted

straightforwardly, there is a small benefit of induction at 41 weeks that could justify standard induction at 41 weeks. It could be argued, however, that a change of policy to earlier induction, concerning roughly one fifth of all women with a singleton pregnancy, is too rigorous in light of the relatively low incidence of perinatal mortality, gestational age associated NICU admission, and Apgar score <4 at five minutes as indicator for encephalopathy. This could justify expectant management if women want to avoid induction. On both sides of the spectrum, caregivers are challenged to provide neutral, evidence-based counselling of low risk women in late term pregnancy on the pros and cons of induction. In a recent report by Walsh et al, women felt they were not offered a real choice when it came to management of their prolonged pregnancy, and this is confirmed by other studies; induction of labour is often presented as an inevitable next step to women, without information provided on alternative management strategies [49-51].

CONCLUSIONS AND POLICY IMPLICATIONS

Our large trial compared induction of labour at 41 weeks with expectant management until 42 weeks and subsequent induction if necessary. Substantial larger trials are needed to evaluate differences in rare outcomes, such as perinatal mortality and NICU admission. A systematic review or individual participant meta-analysis on the comparison between 41 weeks and 42 weeks could then be performed including findings from those studies as well as those of our own study. Future research could also focus on long term adverse perinatal outcome of both strategies, although this requires long term follow-up of children [46]. In addition, a more tailored approach will need identification of women who could maintain pregnancy until 42 weeks or are at increased risk of adverse perinatal outcomes (e.g., relational model).

The incidence of late term pregnancy varies between countries because of different management strategies [52]. Women need to be counselled on the desired policy in late term pregnancy. In this trial, induction of labour at 41 weeks resulted in less overall adverse perinatal outcome than a policy of expectant management until 42 weeks, although the absolute risk of severe adverse outcome (perinatal mortality, NICU admission, Apgar score <4 at five minutes) was low in both groups. As with every intervention in the natural birth process, the decision to induce labour must be made with caution, as the expected benefits should outweigh possible adverse effects for both mother and child [53]. The results of our study should be used to inform women approaching a gestational age of 41 weeks, so they can weigh the respective

outcomes and decide whether to be induced at 41 weeks or to continue pregnancy until 42 weeks.

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Contributors

JKJK, AB, and JCK are joint first authors and contributed equally to the study. EdM and BWM initiated this study. EdM and JP supervised this study. JKJK, AB, and JCK wrote the first and subsequent drafts of the paper. RD conducted the statistical analyses and takes responsibility for the integrity of the data and accuracy of the data analyses. PB advised on statistical issues and interpretation of the results. AK is the neonatologist who reviewed all anonymised NICU admissions on case level with JCK and EdM. All authors have approved the final version of this manuscript submitted for publication. JKJK, AB, JCK, JD, JP, and EdM are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author) and declare: BWM is supported by a National Health and Medical Research Council practitioner fellowship (GNT1082548) and reports consultancy for ObsEva, Merck, and Guerbet; no support from any other organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

This trial was approved by the ethics committee of the Academic Medical Centre, Amsterdam (No NL38455.018.11). The board of directors of each of the participating centres approved local execution of the study.

Data sharing

The full dataset is available from the corresponding author at e.demiranda@amc.uva.nl on reasonable request.

Transparency

The corresponding author (EdM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, no important aspects of the study have been omitted, and any discrepancies from the study as planned have been explained.

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APPENDIX

Per-protocol population

Perinatal outcomes

	Induction of labour (n=611)	Expectant management (n=647)	Relative risk (95% CI)	*P value*
Composite adverse perinatal outcome*	10 (1.6%)	19 (2.9%)	0.56 (0.26 to 1.19)	0.13†
with Apgar score 5' <4 instead of <7	3 (0.5%)	8 (1.2%)	0.40 (0.11 to 1.49)	0.23†
including arterial pH <7.05	19 (3.1%)	26 (4.0%)	0.40 (0.11 to 1.49)	0.15†
Stillbirth	1 (0.2%)	2 (0.3%)	0.53 (0.05 to 5.82)	1.00†
Neonatal death, post-partum	0 (0.0%)	0 (0.0%)	n/a	-
Apgar score 5 min. post-partum¤				
<7	7 (1.1%)	16 (2.5%)	0.46 (0.19 to 1.12)	0.08
<4	0 (0.0%)	1 (0.2%)	n/a	-
Admission neonate to				
intensive care (NICU)	2 (0.3%)	6 (0.9%)	0.35 (0.07 to 1.74)	0.51†
medium care	39 (6.4%)	48 (7.4%)	0.86 (0.57 to 1.29)	0.45
Meconium aspiration syndrome‡	0 (0.0%)	2 (0.2%)	n/a	-
Plexus brachialis injury	0 (0.0%)	0 (0.0%)	n/a	-
Intracranial haemorrhage	0 (0.0%)	0 (0.0%)	n/a	-
Umbilical cord pH (arterial)				
pH <7.05	11 (1.8%)	10 (1.6%)	1.12 (0.49 to 2.58)	0.79
missing	366 (59.9%)	447 (69.6%)	n/c	-
Congenital abnormality	11 (1.8%)	12 (1.9%)	0.97 (0.42 to 2.18)	0.94
Hypoglycaemia§	1 (0.2%)	5 (0.8%)	0.21 (0.02 to 1.81)	0.22†
Neonatal infection / sepsis	23 (3.8%)	29 (4.5%)	0.84 (0.49 to 1.44)	0.52
Sex, female	305 (49.9%)	337 (52.1%)	0.96 (0.86 to 1.07)	0.44
Birth weight (g; mean, sd)	3,697 (414.4)	3,747 (433.5)	-50.2 (-97.2 to -3.2) **	0.04
Small of gestational age				
<2.3rd percentile	11 (1.8%)	8 (1.2%)	1.46 (0.59 to 3.60)	0.42
<10th percentile	40 (6.6%)	46 (7.1%)	0.92 (0.61 to 1.39)	0.69
Large for gestational age				
>90th percentile	54 (8.8%)	74 (11.4%)	0.77 (0.55 to 1.08)	0.13
>97.7th percentile	12 (2.0%)	22 (3.4%)	0.58 (0.29 to 1.16)	0.12

Perinatal outcomes (per-protocol). Data are n (%) or mean (standard deviation). Confidence intervals are 95%. NICU: Neonatal Intensive Care Unit * Composite outcome defined as: perinatal mortality, and/or a 5-minute Apgar-score below 7, and/or meconium aspiration syndrome, and/or plexus brachialis injury, and/or intracranial haemorrhage, and/or NICU admission. ¤ Apgar score of the live births. † Fisher's exact test. ‡ Defined as respiratory distress after birth in presence of meconium stained amniotic fluid). § Defined as glucose concentration <1.9 mmol/L and need for intravenous glucose. ¶ Defined as clinical suspected findings, or proved positive culture. ** Mean difference between groups with 95% confidence interval.

Delivery outcomes

	Induction of labour (n=611)	Expectant management (n=647)	Relative risk (95% CI)	*P value*
Gestational age at delivery (days; median, IQR)	288 (287 - 288)	290 (288 - 292)	-2.3 (-2.5 to -2.1) *	<0.001 †
Time randomisation to delivery (days; mean, sd)	2.2 (1.5)	4.5 (2.9)	-2.2 (-2.5 to -2.0) *	<0.001 †
Level of care at onset of labour				
Primary care	96 (15.7%)	474 (73.3%)	n/c	-
Secondary care	515 (84.3%)	173 (26.7%)	n/c	-
Onset of labour				
Spontaneous (reference)	92 (15.1%)	524 (81.0%)	1.00	-
Induction	519 (84.9%)	123 (19.0%)	4.47 (3.80 to 5.26)	<0.001
Mode of induction				
cervical ripening (catheter /prostaglandins)	304 / 519 (58.6%)	71 / 123 (57.7%)	1.01 (0.86 to 1.20)	0.86
amniotomy, without oxytocin	72 / 519 (13.9%)	12 / 123 (9.8%)	1.42 (0.80 to 2.54)	0.23
amniotomy, with oxytocin	135 / 519 (26.0%)	33 / 123 (26.8%)	0.97 (0.70 to 1.34)	0.85
Indication for induction				
randomisation	519 / 519 (100%)	0 / 123 (0.0%)	n/c	-
post-term pregnancy	0 / 519 (0.0%)	62 / 123 (50.4%)	n/c	-
foetal condition	0 / 519 (0.0%)	35 / 123 (28.5%)	n/c	-
maternal condition	0 / 519 (0.0%)	22 / 123 (17.9%)	n/c	-
elective / maternal wish	0 / 519 (0.0%)	0 / 123 (0.0%)	n/c	-
>24 h of ruptured membranes	0 / 519 (0.0%)	4 / 123 (3.3%)	n/c	-
other	0 / 519 (0.0%)	0 / 123 (0.0%)	n/c	-
Use of oxytocin	402 (65.8%)	255 (39.4%)	1.69 (1.49 to 1.87)	<0.001
Use of tocolytics	20 (3.3%)	13 (2.0%)	1.63 (0.82 to 3.25)	0.17
Maternal intrapartum infection				
fever during labour (≥38 °C)	33 (5.4%)	35 (5.4%)	0.99 (0.63 to 1.59)	0.99
use of antibiotics	34 (5.6%)	22 (3.4%)	1.64 (0.97 to 2.77)	0.07
Meconium stained amniotic fluid	82 (13.4%)	163 (25.2%)	0.53 (0.42 to 0.68)	0.001
Level of care at time of birth				
Primary care	44 (7.2%)	221 (34.2%)	n/c	-
Secondary care	567 (92.8%)	426 (65.8%)	n/c	-
Mode of delivery				
spontaneous vaginal delivery	484 (79.2%)	493 (76.2%)	1.04 (0.98 to 1.10)	0.20
operative vaginal delivery	56 (9.2%)	80 (12.4%)	0.74 (0.54 to 1.02)	0.07
(secondary) caesarean section	71 (11.6%)	74 (11.4%)	1.02 (0.75 to 1.38)	0.92
Indication successful operative vaginal delivery				
failure to progress at second stage	27 / 56 (48.2%)	37 / 80 (46.3%)	1.04 (0.73 to 1.49)	0.82
suspected foetal distress	24 / 56 (42.9%)	29 / 80 (36.3%)	1.18 (0.78 to 1.80)	0.43
suspected foetal distress and failure to progress	5 / 56 (8.9%)	14 / 80 (17.5%)	0.51 (0.19 to 1.34)	0.21‡
maternal complication or other	0 / 56 (0.0%)	0 / 80 (0.0%)	n/a	-
Indication secondary caesarean section				
failure to progress at first stage	27 / 71 (38.0%)	16 / 74 (21.6%)	1.76 (1.04 to 2.98)	0.04
failure to progress at second stage	8 / 71 (11.3%)	12 / 74 (16.2%)	0.69 (0.30 to 1.60)	0.39
failed OVD	3 / 71 (4.2%)	9 / 74 (12.2%)	0.35 (0.10 to 1.23)	0.13‡
suspected foetal distress	14 / 71 (19.7%)	18 / 74 (24.3%)	0.81 (0.44 to 1.50)	0.51
suspected foetal distress and failure to progress at first stage	3 / 71 (4.2%)	7 / 74 (9.5%)	0.45 (0.12 to 1.66)	0.33‡
suspected foetal distress and failure to progress at second stage	3 / 71 (4.2%)	3 / 74 (4.1%)	0.96 (0.22 to 4.99)	1.00‡
maternal complication or other	13 / 71 (18.3%)	9 / 74 (12.2%)	1.51 (0.69 to 3.30)	0.31

Delivery outcomes (per-protocol). Data are n (%), mean and standard deviation, or median (IQR). OVD: Operative Vaginal Delivery. * Mean difference between groups with 95% confidence interval. †Mann-Whitney U test. ‡Fisher's exact test.

(Adverse) maternal outcomes

	Induction of labour (n=611)	Expectant management (n=647)	Relative risk (95% CI)	*p-value*
Composite adverse maternal outcome*	84 (13.7%)	75 (11.6%)	1.19 (0.89 to 1.59)	0.25
Maternal death	0 (0.0%)	0 (0.0%)	n/a	-
Post-partum blood loss				
< 1000 mL (reference)	552 (90.3%)	592 (91.5%)	1.00	-
≥ 1000 mL	59 (9.7%)	55 (8.5%)	1.14 (0.80 to 1.61)	0.48
1000-1500 mL	23 (3.8%)	27 (4.2%)	0.92 (0.53 to 1.58)	0.76
>1500-2000 mL	15 (2.5%)	10 (1.6%)	1.59 (0.72 to 3.52)	0.25
> 2000 mL	21 (3.4%)	18 (2.8%)	1.24 (0.67 to 2.31)	0.49
Post-partum blood loss (mL; median, IQR)	300 (200 – 500)	300 (250 – 500)	-	0.18†
Transfusion (packed cells or plasma)	18 (2.9%)	13 (2.0%)	1.47 (0.72 to 2.97)	0.29
Manual removal placenta	29 (5.4%)	26 (4.5 %)	1.18 (0.71 to 1.98)	0.52
Perineal tear				
episiotomy (without tear)	150 / 540 (27.8%)	181 / 573 (31.6%)	0.88 (0.73 to 1.05)	0.17
OASIS	16 / 540 (3.0%)	21 / 573 (3.7%)	0.81 (0.43 to 1.53)	0.51
third degree tear	10 / 540 (1.9%)	14 / 573 (2.4%)	0.79 (0.40 to 1.55)	0.49
fourth degree tear	5 / 540 (0.9%)	5 / 573 (0.9%)	1.06 (0.31 to 3.64)	1.00‡
episiotomy and third-degree tear	0 / 540 (0.0%)	1 / 573 (0.2%)	-	-
episiotomy and fourth degree tear	1 / 540 (0.2%)	1 / 573 (0.2%)	1.06 (0.07 to 16.92)	1.00‡
Maternal admission (highest level of care)				
intensive care	3 (0.5%)	2 (0.3%)	1.59 (0.27 to 9.47)	0.61‡
medium care	4 (0.7%)	4 (0.6%)	1.06 (0.27 to 4.22)	1.00‡
ward	196 (32.1%)	209 (32.3%)	0.99 (0.85 to 1.17)	0.93
Indications for maternal admission				
Thromboembolic complications	0 (0.0%)	0 (0.0%)	n/a	-
Hypertensive disorders§	3 (0.5%)	13 (2.0%)	0.24 (0.07 to 0.85)	0.02‡
Post-partum blood loss	34 (5.6%)	40 (6.2%)	0.90 (0.58 to 1.40)	0.64
Post-caesarean	71 (11.6%)	74 (11.4%)	1.02 (0.75 to 1.38)	0.92
Pain treatment during labour	309 (50.6%)	278 (43.0%)	1.18 (1.05 to 1.33)	0.007
Remifentanil	93 (15.2%)	89 (13.8%)	1.11 (0.85 to 1.45)	0.46
Pethidine / promethazine / other opiates	47 (7.7%)	33 (5.1%)	1.51 (0.98 to 2.32)	0.06
Epidural / spinal	194 (31.4%)	173 (26.6%)	1.19 (1.00 to 1.41)	0.05
Others	1 (0.2%)	4 (0.6%)	0.26 (0.03 to 2.36)	0.38‡

(Adverse) maternal outcomes (per-protocol). *Defined as post-partum haemorrhage ≥ 1000 mL, and/or manual removal of placenta, and/or third- or fourth-degree tears (Obstetrical Anal Sphincter Injuries, OASIS), and/or intensive care admission, and/or maternal death. Denominator for perineal tear are vaginal deliveries only. †Mann Whitney U test. ‡Fisher's exact test. §Including (pre-)eclampsia, and HELLP syndrome.

CHAPTER 4

INDUCTION OF LABOUR AT 41 WEEKS OR EXPECTANT MANAGEMENT UNTIL 42 WEEKS: A SYSTEMATIC REVIEW AND AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS OF RANDOMISED TRIALS

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ABSTRACT

Background The risk of perinatal death and severe neonatal morbidity increases gradually after 41 weeks of pregnancy. Several randomised controlled trials (RCTs) have assessed if induction of labour (IOL) in uncomplicated pregnancies at 41 weeks will improve perinatal outcomes. We performed an individual participant data (IPD) meta-analysis (MA) on this subject.

Methods and findings

We searched PubMed, Excerpta Medica dataBASE (Embase), The Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and PsycINFO on February 21, 2020 for RCTs comparing IOL at 41 weeks with expectant management until 42 weeks in women with uncomplicated pregnancies. Individual participant data (IPD) were sought from eligible RCTs. Primary outcome was a composite of severe adverse perinatal outcomes: mortality and severe neonatal morbidity. Additional outcomes included neonatal admission, mode of delivery, perineal lacerations, and postpartum haemorrhage. Prespecified subgroup analyses were conducted for parity (nulliparous/multiparous), maternal age (<35/ ≥35 years), and body mass index (BMI) (<30/ ≥30). Aggregate data MA was performed to include data from RCTs for which IPD was not available.

From 89 full-text articles, we identified three eligible RCTs (n=5,161), two contributed with IPD (n=4,561). Baseline characteristics were similar between the groups regarding age, parity, BMI and higher level of education. IOL resulted overall in a decrease of severe adverse perinatal outcome (0.4% [10/2281] versus 1.0% [23/2280]; Relative Risk [RR] 0.43 [95% Confidence Interval [CI] 0.21 to 0.91], p-value 0.027, Risk Difference [RD] -57/10,000 [95%CI -106/10,000 to -8/10,000], I^2 0%). The number needed to treat (NNT) was 175 (95%CI 94 to 1,267). Perinatal deaths occurred in one (<0.1%) versus eight (0.4%) pregnancies (Peto odds ratio 0.21 [95%CI 0.06 to 0.78], p-value 0.019, RD -31/10,000, [95%CI -56/10,000 to -5/10,000], I^2 0%, NNT 326, [95%CI 177 to 2014]), admission to a neonatal care unit ≥4 days in 1.1% (24/2280) versus 2.0% (46/2273), (RR 0.52 [95%CI 0.32 to 0.85], p-value 0.009, RD -97/10,000 [-169/10,000 to -26/10,000], I^2 0%,

NNT 103 [95%CI 59 to 385]). There was no difference in the rate of cesarean delivery (10.5% versus 10.7%; RR 0.98, [95%CI 0.83 to 1.16], p-value 0.81) nor in other important perinatal, delivery and maternal outcomes. MA on aggregate data showed similar results.

Prespecified subgroup analyses for the primary outcome showed a significant difference in the treatment effect (p=0.01 for interaction) for parity, but not for maternal age or BMI. The risk of severe adverse perinatal outcome was decreased for nulliparous women in the IOL group (0.3% [4/1219] versus 1.6% [20/1264]; RR 0.20 [95%CI 0.07 to 0.60], p-value 0.004, RD -127/10,000, [95%CI -204/10,000 to -50/10,000], I^2 0%, NNT 79 [95%CI 49 to 201]) but not for multiparous women (0.6% [6/1219] versus 0.3% [3/1264]; RR 1.59 [0.15 to 17.30], p-value 0.35, RD 27/10,000, [95%CI -29/10,000 to 84/10,000], I^2 55%).

A limitation of this IPD-MA was the risk of overestimation of the effect on perinatal mortality due to early stopping of the largest included trial for safety reasons after the advice of the Data and Safety Monitoring Board. Furthermore, only two RCTs were eligible for the IPD-MA; thus, the possibility to assess severe adverse neonatal outcomes with few events was limited.

Conclusions In this study, we found that, overall, IOL at 41 weeks improved perinatal outcome compared with expectant management until 42 weeks without increasing the cesarean delivery rate. This benefit is shown only in nulliparous women, whereas for multiparous women, the incidence of mortality and morbidity was too low to demonstrate any effect. The magnitude of risk reduction of perinatal mortality remains uncertain. Women with pregnancies approaching 41 weeks should be informed on the risk differences according to parity so that they are able to make an informed choice for IOL at 41 weeks or expectant management until 42 weeks.

Study Registration

PROSPERO CRD42020163174

AUTHOR SUMMARY

Why was this study done?

- Timely induction of labour (IOL) aims to prevent adverse outcomes. In observational studies, although not usually in interventional studies, IOL has been associated with increased risks of emergency cesarean delivery, uterine hyperstimulation and uterine rupture.
- The risk of stillbirth and several other serious perinatal and maternal complications increases as the pregnancy continues beyond term.
- According to a recent meta-analysis (MA) on aggregate data from randomised controlled trials (RCTs), perinatal mortality was lower after IOL at or beyond term compared with a policy of expectant management. However, the upper limit of gestational age for expectant management was not taken into account in this MA.
- The aim of this individual participant data meta-analysis (IPD-MA) was to compare the effect of a management strategy of IOL at 41 weeks versus expectant management until 42 weeks on important perinatal and maternal outcomes of women with low-risk singleton pregnancies as well as to identify subgroups of women that could benefit from IOL at 41 weeks.

What did the researchers do and find?

- Three RCTs including a total of 5,161 women with low-risk singleton pregnancies comparing IOL at 41 gestational weeks with expectant management until 42 gestational weeks were identified.
- Data of two RCTs were available for inclusion in an IPD-MA with a total of 4,561 women.
- Overall, induction at 41 gestational weeks significantly reduced the composite outcome of perinatal mortality and severe neonatal morbidity, and perinatal mortality alone, without increasing the risk of cesarean delivery, operative vaginal delivery, perineal lacerations III and IV or postpartum haemorrhage. However, the magnitude of the risk of perinatal mortality remains uncertain.
- A prespecified subgroup analysis showed that the risk of composite severe adverse perinatal outcome in the IOL group was significantly decreased for nulliparous, but not for multiparous women.

What do these findings mean?

- Women with pregnancies approaching 41 gestational weeks should be informed of the benefits and risks of IOL at 41 weeks compared with expectant management until 42 weeks, with respect to risk differences for nulliparous and multiparous women.
- Women can then make an informed choice regarding induction of labour at 41 weeks or awaiting spontaneous onset of labour until 42 weeks.

INTRODUCTION

When to induce labour in overdue pregnancies has been under debate since many years. The risk of perinatal death and severe neonatal morbidity increases gradually after 41 weeks of pregnancy with a steeper increase after 42 weeks [1,2]. The proportion of women reaching 41 weeks varies in high income countries between 5% and 25% [3]. In 2018, 22% of women in Sweden reached 41 weeks and in the Netherlands the rate was 16% [4,5].

Two randomised controlled trials (RCTs) recently evaluated the risk of adverse perinatal outcome after a policy of induction of labour (IOL) at 41 weeks as compared with expectant management until 42 weeks [6,7]. The first RCT concerns a non-inferiority trial among low-risk women in the Netherlands (INDuction of labour at 41 weeks versus a policy of Expectant management until 42 weeks [INDEX]) comparing IOL at 41 weeks+0-1 days (41+0-1) with expectant management until 42 weeks+0 days (42+0), in which non-inferiority of expectant management was not proven [6]. The second RCT is a superiority trial from Sweden (SWEdish Post-term Induction Study [SWEPIS]) comparing induction at 41+0-2 with expectant management until 42+0-1 in low-risk women. It was stopped early because of safety reasons. The Data and Safety Monitoring Board recommended to stop the study owing to a higher perinatal mortality in the expectant management group (no perinatal mortality in the IOL group and six in the expectant management group). However, there was no significant difference in the primary outcome [7].

A Cochrane review from 2018 comparing birth outcomes after IOL or expectant management, concluded that a policy of IOL at or beyond term is associated with fewer adverse perinatal outcomes and fewer cesarean deliveries compared with expectant management though the absolute risk of perinatal death is small [8]. The conclusion is based on all included studies of the systematic review but a majority of the included

trials had expectant management groups that allows expectant management until far beyond 42 weeks, which could have influenced the overall outcomes. The authors suggested that women could be helped in deciding on IOL or expectant management by appropriate counselling (including information on absolute risks). Further exploration of risk profiles of women was recommended as well as individual participant data meta-analysis (IPD-MA), which could help elucidate the role of specific factors, such as parity, on outcomes of induction compared with expectant management. After results of the current study were already finalised, an update of this Cochrane review was published in which the main conclusion was similar as the previous version [9]. Although subgroup analysis was performed for parity, this was not done for the 41 to 42 weeks' comparison in this review. A recently published systematic review including two RCTs, two quasi-experimental trials and three retrospective cohort studies compared IOL at 41+1 to 41+6 weeks with expectant management until 42+0 to 42+6 weeks. IOL at 41+1 to 41+6 weeks was found to be associated with an increased risk of cesarean delivery and pH < 7.10, but it lacked power to estimate the risk of perinatal mortality [10]. However, the timeframe in this systematic review allows comparison beyond 41 weeks with expectant management until 43 weeks, which is not comparable with our timeframe. We chose an upper limit of 42 weeks because continuing pregnancy after 42 weeks is no longer regular policy since many years due to its association with increased perinatal mortality. This is reflected in many national and international guidelines [11-15]. Furthermore, non-experimental studies without clear randomisation procedure are prone for selection bias. Also, we aimed to evaluate outcomes of intended management strategies, not actual start of labour, because women have to decide on a management strategy before they know if and when they will go into spontaneous onset of labour. For this reasons we only included RCT's in our IPD-MA.

Sample sizes of RCTs are typically insufficient to estimate the risk for rare outcomes like perinatal mortality and severe morbidity. Exploring potential subgroup effects of maternal age, parity, body mass index (BMI) or fetal sex is therefore impossible in individual trials. IPD-MA increases power and has the advantage to allow investigation of interactions between intervention and participant characteristics in the total RCT population as well as in subgroups [16].

The objective of the PD-MA was to evaluate the effect of IOL at 41 weeks versus expectant management until 42 weeks on perinatal and maternal outcomes, with a focus on rare adverse perinatal outcomes. We also aimed to assess whether treatment effects differed in subgroups.

METHODS

The protocol for this IPD-MA was registered on PROSPERO (2020; CRD42020163174) and is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=163174. The IPD-MA is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-IPD guidelines, see S1 Text PRISMA checklist [17].

Data from the INDEX trial were pseudo anonymised. A code was generated for each participant and the key to the personal data is stored in the archives of the participating midwifery practices and hospitals. Data in the SWEPIS trial were not anonymised. All data in the merged database were fully anonymised. A collaboration group from the SWEPIS and INDEX project teams conducted the study.

Ethics statement

RCTs included in the IPD-MA had received country specific ethical approval for the study, and each participant gave informed written consent. Details can be found in the original manuscripts. Specific ancillary approval for the use of individual patient data for the purpose of this meta-analysis (MA) was given by the Medical Ethical Committee of Amsterdam UMC-AMC (Dnr W20_225#20.259, May 20, 2020) for reuse of data from the INDEX trial, and from the SWEPIS trial by the Swedish Ethical Review Authority (Dnr 285-14, amendment 2019-04094, August 5, 2019).

Specific objectives

The objectives of the IPD-MA were to apply IPD-MA methodology to assess the effect on perinatal and maternal outcomes, with a focus on rare adverse perinatal outcomes, after IOL at 41 weeks compared with expectant management until 42 weeks in women with low-risk singleton pregnancies and to identify possible subgroups that might benefit from IOL at 41 weeks. For this reason, the effect of the intervention was analysed for prespecified subgroups of participant characteristics: maternal age, parity and BMI. In addition, a post hoc analysis on fetal sex was carried out.

Eligibility criteria

RCTs were included if a strategy of IOL at 41+0-2 was compared with a strategy of expectant management with various regimes of fetal surveillance and induction at 42+0-1 in low-risk women with an uncomplicated singleton pregnancy. Perinatal mortality, neonatal and maternal morbidity had to be reported. Only RCTs were eligible. Cluster-randomised RCTs and quasi-random design studies were not considered.

Study identification: Information sources and search strategy

We performed a systematic literature search in PubMed, Excerpta Medica dataBASE (Embase), The Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and PsycINFO (EBSCOhost Research Databases). Our search was a continuation of a systematic literature search made in the context of a Health Technology Assessment (HTA) report in 2012 exploring the same research question but with a wider inclusion criterion than in this paper [18]. UBW, HH and CB authored this report. The searches comprised the time period from database inception to February 21, 2020. Reference lists of relevant articles were scrutinised for additional references. The detailed search strategy is presented in Supporting information (S2 Text). We searched Clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform databases for ongoing and unpublished RCTs. We used no limitation for publication year or language.

Study selection processes

Two HTA librarians carried out a first selection of eligible RCTs. Potential eligible RCTs were scrutinised independently by two teams (MA, HH, UBW and JKJK, JCK, EdM). Eligibility of RCTs was decided on at a consensus meeting.

Data collection process and data items

Corresponding authors of eligible RCTs were contacted and invited to participate and provide data to the IPD-MA.

Prespecified variables and outcomes were discussed and defined by the authors. Study-level and participant-level data were scrutinised on the proportion of missing variables and data. The definitions of variables and outcomes were compared and harmonised. If a definition did not correspond, a new definition was agreed upon. In case of neonatal complications e.g. meconium aspiration syndrome (MAS), intracranial bleeding and neonatal infection/sepsis we took advice from neonatologists and based the definition on the International Classification of Diseases 10th Revision (ICD-10) description [19].

IPD were collected on all randomised women. These included baseline data for descriptive purpose and analyses, date of randomisation, gestational age at randomisation, date of delivery and data on primary and secondary outcomes. Data were checked for extreme or missing values and consistency with published data. The IPD was collected by one of the statisticians (MM), who managed the data and merged all data into one anonymised IPD-MA dataset. The IPD-MA dataset was stored in a secure database accessible only by the two statisticians (MM and RGD).

IPD integrity

Sequence generation, data accuracy, data consistency and completeness, frequencies and possible baseline imbalances of all outcomes used in this IPD analysis were checked by statisticians and authors of the included RCTs.

Study quality including risk of bias assessment

We used the risk of bias tool developed by Cochrane to assess the risk of bias for each study [20]. Risk of bias was assessed independently by some authors (MA, HH, UBW and JKJK, JCK, EdM) and disagreement was resolved by discussion. Each study was evaluated for adequacy of randomisation (selection bias), blinding for participants and personnel and statistician responsible for analysis (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (conflict of interest). Each risk of bias was rated as either low, unclear, moderate or high for the RCT.

Two individual teams (MA, UBW, HH and JKJK, JCK, EdM, respectively) evaluated external validity, internal validity (risk of bias-study limitations) and precision for each study.

Specification of outcomes and effect measures

The primary outcome 'severe adverse perinatal outcome' was a composite of perinatal mortality and severe neonatal morbidity. Perinatal mortality was defined as stillbirth, or neonatal mortality of live births with death between day 0 and 28 (deaths due to accidents were excluded). Severe neonatal morbidity was a composite of (1) 5 minute Apgar score <4 (as an Apgar score <4 at five minutes is associated with an increased risk on long-term adverse neonatal outcome [21]); (2) hypoxic-ischemic encephalopathy II-III (asphyxia/encephalopathy in need of therapeutic cooling); (3) intracranial haemorrhage (intracranial or intraventricular haemorrhage based on radiological findings with ultrasound of the brain, computed tomography or magnetic resonance imaging); (4) neonatal convulsions (seizures with electroencephalography [EEG]/amplitude-EEG confirmation, seizures without EEG/amplitude EEG confirmation and silent seizures [EEG/diagnosis]); (5) MAS (respiratory distress after birth in the presence of meconium stained amniotic fluid with need of mechanical ventilation); (6) mechanical ventilation within the first 72 hours (with laryngeal tube and ventilator machine) and/or (7) obstetric brachial plexus injury.

Secondary perinatal outcomes consisted of all individual components of the composite outcome separately including stillbirth and neonatal mortality. Additional secondary outcomes were: the composite outcome with 5 minute Apgar <7 instead

of Apgar <4, admission to neonatal care (medium care —excluding observation only for protocol— or intensive care unit), admission to neonatal care ≥ 4 days mimicking more intensified neonatal care for sick infants in need for longer treatment and/or more extensive observation (neonatal intensive care unit [NICU] admission as such could not be used as a variable due to different admission criteria in Sweden and the Netherlands), mean birthweight, small for gestational age (SGA) according to national birthweight curves (<10th percentile and <3rd percentile) [22,23], macrosomia (≥4500g), 5 minutes Apgar score <7, infection/sepsis (clinical suspected findings or proved positive blood culture and antibiotic treatment), meconium stained amniotic fluid, humerus fracture and congenital anomalies (any congenital anomalies after excluding minor congenital anomalies according to the European Surveillance of Congenital Anomalies [EUROCAT]) [24].

Secondary maternal outcomes included interval from randomisation to delivery, gestational age at time of delivery, onset of labour (spontaneous or IOL), oxytocin during labour (for IOL and/or augmentation), pain treatment during vaginal delivery (epidural anaesthesia/spinal anaesthesia/opiates), mode of delivery (spontaneous vaginal delivery, assisted vaginal delivery or cesarean delivery with indication for intervention), episiotomy, perineal lacerations III and IV, postpartum haemorrhage (>1000 ml and >2000 ml), fever during labour (≥ 38°C), antibiotics during labour (prophylaxis or therapy), manual removal of placenta (with or without haemorrhage >1000 ml), hypertensive disorders of pregnancy including eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, and a low platelet count), maternal deep vein thrombosis or pulmonary embolism, admission to intensive care unit and maternal death up to 42 days after delivery (deaths due to accidents excluded).

Outcomes were analysed as relative risks (RR) and risk differences (RD, expressed per 10,000 patients). For major outcomes the Number Needed to Treat (NNT), was provided as well.

Synthesis methods and data analysis

General baseline characteristics were presented as frequencies with percentages, means and standard deviations or medians with interquartile ranges (IQR).

Individual participant data meta-analysis

One-step MA was done for those outcomes where individual participant data could be used. For dichotomous outcomes, RR and RD were estimated using generalised linear models with a log- or identity-link and binomial distribution, respectively. A categorical

covariable coding for the study was used to permit for within-study associations. For all risk estimates a 95% confidence interval (CI) and p-value were calculated.

In case of a zero-event outcome in one arm of one or both trials, Peto odds ratios (ORs) were calculated using a two-step approach [25]. In case of zero events in both arms (double zero events) in all but one RCT, no risk estimates or inferential statistics were calculated because double zero events will add zero weight to the IPD-MA. Continuity correction for sparse events was not used.

For continuous outcomes the mean difference was estimated with 95%CI using a general linear model, also with a categorical covariable coding for study. Chi-Squared test was used for non-ordered categorical variables.

All randomised women with outcome data were included in the final analyses. Outcomes were analysed on an intention-to-treat (ITT) basis according to the treatment allocated by randomisation comparing IOL at 41+0-2 to expectant management until 42+0-1. Heterogeneity between trials was explored by calculating the I^2 and p-value estimates of variability. Values of $I^2 \geq 50\%$ were considered to indicate meaningful heterogeneity. Due to the low number of eligible RCTs, funnel plots for assessment of publication bias were not used. Application of meta-regression to explain heterogeneity was not possible for outcomes analysed by two-step analysis. Number needed to induce (NNT) for benefit with 95%CI was calculated as the inverse of the absolute risk reduction (ARR): 1/ARR.

In order to assess whether the effect of the intervention differed by prespecified subgroups, analyses were conducted for parity (nulliparous and multiparous), maternal age (<35 years and ≥35 years), and BMI (<30 and ≥30). In addition, a post-hoc subgroup analysis on fetal sex was performed. A test for multiplicative interaction between intervention and maternal characteristics was performed by means of an interaction term in the regression model to examine whether intervention effects differed between subgroups. An interaction with a p-value <0.05 was considered to indicate that the effect of intervention differed between subgroups. Subgroup analyses were only performed on the primary composite outcome and the selected secondary outcomes perinatal mortality and cesarean delivery. In case of significant interaction for any of these outcomes additional analysis was performed on all outcomes for this subgroup.

Meta-analysis on aggregate data

If IPD was not available, MA was performed on aggregate data from eligible trials. In this situation relative risks were calculated using a Mantel-Haenszel fixed effect model, or Peto ORs were calculated as appropriate.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, United States). Review Manager RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to conduct the MA on aggregate data.

RESULTS

Study selection and IPD obtained

The updated literature search resulted in 1,111 articles after removal of duplicates. Another 20 RCTs were added from the former HTA report from 2012 [18]. All articles were screened on title and abstract. We assessed 89 full-text articles, of which three RCTs published between 2005 and 2019 were eligible for IPD-MA (*n* = 5,161 participants), the Gelisen and colleagues trial, the INDEX trial and the SWEPIS trial (Figure 1) [6,7,26].

Eight RCTs were identified in the ongoing RCT search, of which one was relevant for our IPD-MA and is expected to run until September 2022 (ISRCTN 83219789, "The Finnish randomised controlled multicentre trial on optimal timing of labour induction in nulliparous women with post-term pregnancy"). Four RCTs were already published and three were not relevant for our research question due to deviating intervention, comparison group or gestational age.

The corresponding authors in each eligible RCT were contacted in order to participate in the IPD-MA. The corresponding author from the Gelisen and colleagues trial replied that they could not participate in the IPD-MA because the original database was not available anymore. We therefore conducted an MA on aggregate data available in all three RCTs for outcomes with similar definitions and relevance for this research question. In total, the three RCTs included 5,161 women, (n=600 from the Gelisen and colleagues trial, n=1,801 from the INDEX trial and n=2,760 from the SWEPIS trial); 2,581 women were assigned to IOL and 2,580 to expectant management. Two of three RCTs contributed data for the IPD-MA (the INDEX and SWEPIS RCTs). Hence, the IPD-MA included 4,561 women; 2,281 women were assigned to IOL and 2,280 to expectant management.

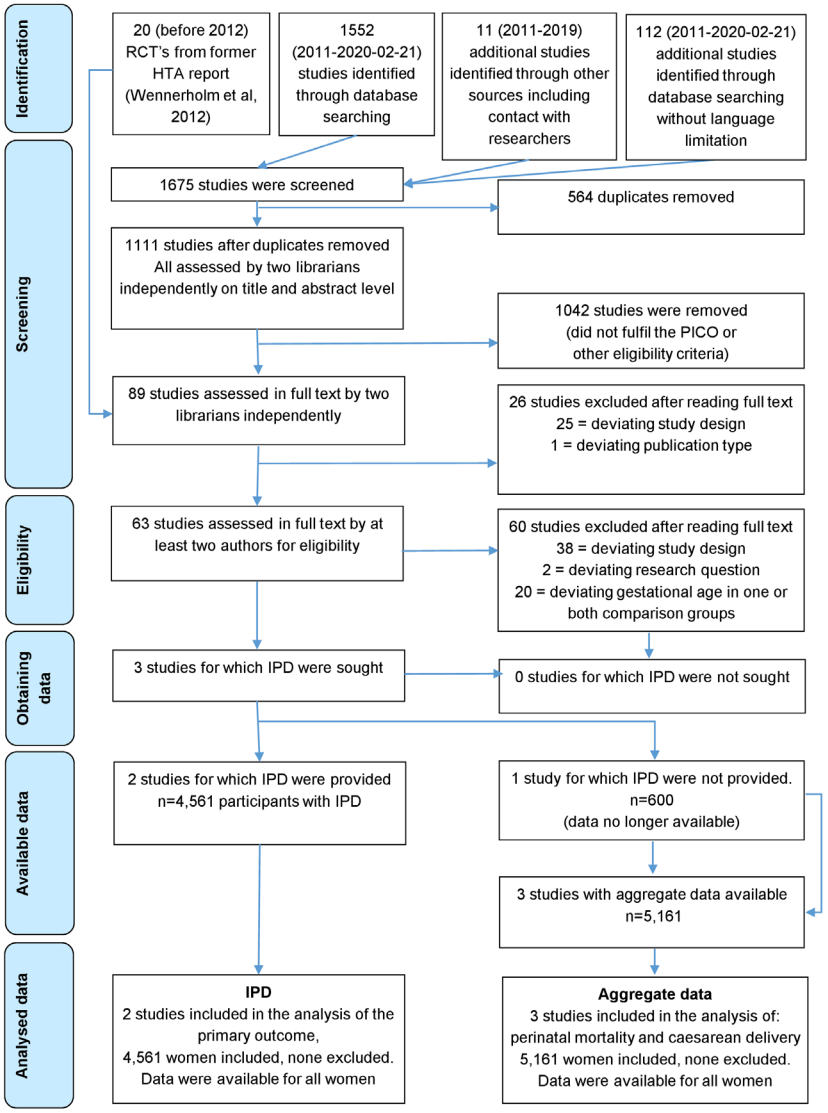

FIGURE 1. PRISMA IPD Flowchart of literature search

RCT: Randomised Controlled Trial
HTA: Health Technology Assessment
PICO: Patients Intervention Comparison Outcome
IPD: Individual Participant Data

Study characteristics

The characteristics of the included RCTs are shown in Table 1. All three trials included low-risk singleton pregnancies with fetus in cephalic position and had previous cesarean delivery or other major uterine surgery as an exclusion criterion. In the two

TABLE 1. Included RCTs in the aggregate meta-analysis and their characteristics

Author, Year of publication, Country	Gelisen et al. 2005 Turkey	Keulen et al. 2019 The INDEX trial The Netherlands	Wennerholm et al. 2019 The SWEPIS trial Sweden
Study design	Single-centre superiority RCT	Multi-centre, open label, randomised controlled non-inferiority RCT	Multi-centre, open label, randomised controlled superiority RCT
Participants	600 women with a Bishop score less than 5 (300 in IOL group and 300 in EM group)	1,801 women regardless of Bishop score (900 in the IOL group and 901 in the EM group)	2,760 women regardless of Bishop score (1,381 in the IOL group and 1,379 in the EM group). The RCT was planned to recruit 10 038 women, 5,019 in each arm. The RCT was stopped in advance due to safety reasons (6 perinatal deaths in EM group versus 0 in IOL group)
Intervention	IOL at 41+0-1 (three arms: 1) induction with 50µg vaginal misoprostol (n=100), 2) induction with transvaginal Foley balloon (n=100) and 3) induction with infusion of oxytocin (n=100)) compared with EM until 42+0. IOL method; 50µg vaginal misoprostol. Fetal surveillance in the EM group; a nonstress cardiotocography test and amniotic fluid measurement twice weekly. In addition, a biophysical scoring on a single occasion three to five days after randomisation	IOL at 41+0-1 compared with EM until 42+0. IOL method in both groups according to local protocol e.g. prostaglandin E1 (oral or vaginal), prostaglandin E2, Foley catheter or double balloon catheter, or a combination of them and/or amniotomy. Fetal surveillance in the EM group was performed according to local protocols and could include cardiotocography and/or an ultrasound assessment of amniotic fluid	IOL at 41+0-2 compared with EM until 42+0-1. IOL method in both groups according to local management e.g. prostaglandin E1 (oral or vaginal), prostaglandin E2, Foley catheter or double balloon catheter, or a combination of them and/or amniotomy. Fetal surveillance in the EM group was performed according to local protocols and typically included antenatal visits with auscultation of the fetal heart rate
Primary outcome	Cesarean delivery rate, length of hospital stay, and neonatal outcomes (i.e. rate of macrosomia, incidence of meconium stained amniotic fluid, arterial cord blood pH < 7.16 and rate of admission to NICU)	A composite of stillbirth, neonatal death until 28 days, Apgar<7 at five minutes and/or an arterial umbilical cord pH <7.05 and/or MAS and/or obstetric plexus brachialis injury and/or intracranial haemorrhage and/or NICU admission	A composite of stillbirth, neonatal death until 28 days, Apgar<7 at five minutes and/or an arterial umbilical cord pH<7.00 or metabolic acidosis (pH<7.05 and base deficit>12 mmol/L) and/or hypoxic ischaemic encephalopathy grades 1-3 and/or mechanical ventilation within 72 hours and/or intracranial haemorrhage, and/or convulsions and/or MAS and/or obstetric brachial plexus injury
Follow up	Until discharge from hospital	The neonates were followed until 28 days and the women 42 days postpartum regarding mortality. All other outcomes were followed until discharge from hospital	The neonates were followed until 28 days and the women 42 days postpartum regarding mortality. All other outcomes were followed until discharge from the hospital

INDEX: INDuction of labour at 41 weeks versus a policy of EXpectant management until 42 weeks
SWEPIS: SWEdish Post-term Induction Study
IOL: Induction of Labour
EM: Expectant Management
NICU: Neonatal Intensive Care Unit

trials included in the IPD-MA, fetal surveillance in the expectant management group was performed according to local protocol (Table 1).

In Table 2, the baseline characteristics of the population included in the IPD-MA are shown. Baseline characteristics were similar between the IOL and expectant management group. Heterogeneity between the two included RCTs was found for parity and educational level. In SWEPIS, 55.2% (762/1,381) of the IOL group were nulliparous versus 54.6% (753/1,379) in the expectant management group. In the INDEX trial 50.8% (457/900) in the IOL group were nulliparous compared to 56.7% (511/907) in the expectant management group (S1 Table). In SWEPIS 64.6 % (789/1,275) of women in the IOL group and 62.8% (780/1,242) in the expectant management group had education on university or similar level. In the INDEX trial the distribution was 31.8% (286/900) versus 35.7% (322/901) (S1 Table).

TABLE 2. Baseline characteristics of the population included in the individual patient data meta-analysis

Variable	Induction group (n=2,281)	Expectant management group (n=2,280)
Maternal age at randomisation (years)	**n=2,281**	**n=2,280**
Mean (standard deviation)	31.0 (4.8)	30.7 (4.6)
Age ≥35	479 (21.0)	431 (18.9)
Parity (includes stillbirths and live births)	**n=2,281**	**n=2,280**
Nulliparous	1,219 (53.4)	1,264 (55.4)
Multiparous	1,062 (46.6)	1,016 (44.6)
BMI at first antenatal visit	**n=2,152***	**n=2,153***
Mean (standard deviation)	24.8 (4.6)	25.1 (4.8)
BMI ≥30	246 (11.4)	301 (14.0)
Higher professional education/university	1,075/2,121 (50.7)*	1,102/2,143 (51.4)*

Values are numbers (percentages) unless stated otherwise

**information on all participants was not available*

IPD integrity

There were no important issues concerning outcome data identified in checking IPD in the two participating RCTs (S2 Table). A few secondary outcomes showed different proportions between the RCTs, e.g., admission to NICU and neonatal medium care, neonatal infection and use of antibiotics during labour. For NICU admission, the indications for admittance were not comparable in both RCTs resulting in an imbalance for NICU admission. Therefore, a new variable was defined for both studies: 'admission to neonatal care ≥ 4 days' as proxy for infants in need for longer treatment and more extensive monitoring. Regarding the imbalance of neonatal infection, the INDEX trial included suspected infection in their outcome, and it was not possible to distinguish the true infections from the suspected ones. A plausible explanation for the discrepancy

regarding maternal use of antibiotics during labour (significantly more in the SWEPIS trial) could be the difference in use of epidural anaesthesia which is associated with fever and different policies regarding prophylactic treatment for group B streptococcus.

Study quality including risk of bias assessment

Risk of bias within RCTs is presented in Table 3. The two RCTs included in the IPD-MA mostly had low risk of bias. In the Gelisen and colleagues trial the risk of selection-, detection- and reporting bias was unclear. In this RCT, published in 2004, sealed opaque envelopes were used for randomisation, the randomisation sequence process was not reported and the study protocol was not published, which is all according to the standards at the time. All three RCTs had some risk of performance bias due to lack of blinding of participants and clinical personnel. In addition, the Gelisen and colleagues trial did not report if the assessment was blinded or not. In the INDEX trial, the statisticians who performed the analyses were blinded but in the SWEPIS trial, they were not.

TABLE 3. Risk of bias within individual RCTs

Author	Gelisen et al.	INDEX trial	SWEPIS trial
Selection bias	Unclear	Low	Low
Performance bias	High*	Moderate*	High*
Detection bias	Unclear	Low	Low
Attrition bias	Low	Low	Low
Reporting bias	Unclear	Low	Low
Conflict of interest bias	Low	Low	Low

**The lack of blinding in all RCTs are due to the nature of intervention i.e. it is not possible to blind the participants and staff*

The Gelisen and colleagues trial had some or major problems regarding external validity, and precision. The sample size was too small for detection of severe adverse perinatal outcomes.

The INDEX trial had minor problems with external validity due to the low inclusion rate of eligible women (30%). The external validity was good to its own setting. Obstetric care in the Netherlands is divided into primary care (pregnancy and delivery of low-risk women supervised by a community midwife with delivery at home or in the hospital) and secondary care (pregnancy and delivery supervised by clinical midwives and obstetricians), which was reflected in the RCT. The RCT had no problems with precision for the primary outcome.

The SWEPIS trial had minor problems concerning external validity. There was a lower inclusion rate than expected (22% of eligible women), but compared to the background population there were only small deviations including a higher rate of women with

university education. In addition, the internal validity of the estimated risk for perinatal mortality can be affected by the early termination of the trial following advice from its Data and Safety Monitoring Board. The board recommended stopping for safety after an increased risk for perinatal mortality was observed at a planned interim analysis. Early termination of an RCT is associated with overestimating of the treatment effect, especially for events with low occurrence [27]. There were no or minor problems regarding study limitation for the other outcomes. Regarding precision, the study had lower power than planned for the composite outcome and perinatal mortality due to the early stopping.

Primary outcome

In this IPD-MA, there was a significant difference in the primary composite outcome, in favour of the IOL group with 0.4% (10/2,281) compared to the expectant management group with 1.0% (23/2,280); (RR 0.43 [95%CI 0.21 to 0.91], p-value 0.027, RD -57/10,000 [95%CI -106/10,000 to -8/10,000], I^2 0%) (Table 4). NNT was 175 (95%CI 94 to 1,267).

Perinatal secondary outcomes

In Table 4 the perinatal outcomes are presented. Perinatal mortality was significantly lower in the IOL group with 0.04% (1/2,281) versus 0.35% in the expectant management group (Peto OR 0.21 [95%CI 0.06 to 0.78], p-value 0.019, RD -31/10,000 [95%CI -56/10,000 to -5/10,000], I^2 0%). NNT was 326 (95%CI 177 to 2,014).

The only perinatal death in the IOL group was a stillbirth that occurred one day after randomisation but before IOL. In the expectant management group seven of the eight deaths were stillbirths and one baby died due to hypoxic ischemic encephalopathy. In post mortem examination of one of the stillbirths a non-lethal cardiovascular malformation was found, and two of the stillbirths were SGA (both between the 5th and 10th centiles). In the other six cases, no possible explanation was found.

Aggregate data MA on perinatal mortality of the three RCTs (n=5,161 infants) showed similar results (S1 Fig). Since both included RCTs in the IPD-MA had a primary outcome with Apgar <7 instead of Apgar <4 at five minutes we also calculated RR and RD for the primary outcome with Apgar <7. The primary outcome including Apgar <7 occurred in 1.5% (34/2,281) in the IOL group versus 2.3% (52/2,281) in the expectant management group (RR 0.65 [95%CI 0.43 to 1.00], p-value 0.051, RD -79/10,000 [95%CI -158/10,000 to 0], I^2 13%).

Admittance to neonatal care unit for four days or longer was significantly lower in the IOL group compared with the expectant management group (1.1% [24/2,280] versus

2.0% [46/2,273], p-value 0.009, RR 0.52 [95%CI 0.32 to 0.85], RD -97/10,000 [95%CI -169/10,000 to -26/10,000], I^2 0%). NNT was 103 (95%CI 59 to 385). There were fewer neonates with macrosomia (≥4,500g) than in the expectant management group (3.9% [92/2,281] versus 6.7% [155/2,280], RR 0.59 [95%CI 0.46 to 0.76], p-value <0.001, RD -278/10,000 [95%CI -409/10,000 to -147/10,000], I^2 0%). No significant differences were found in other perinatal secondary outcomes.

Delivery outcomes

Table 5 summarises the delivery outcomes for the IPD-MA. The median gestational age in the IOL group was 288 (IQR 287; 289) days and 291 (IQR 289;293) in the expectant management group, which corresponds with 41+1 versus 41+4 weeks, a difference of three days. In the IOL group, 79.8% (1,821/2,281) of the women were induced while the birth process started spontaneously in 19.9% (455/2,281 women). In the expectant management group, 30.4% (694/2,280) of the women were induced while labour started spontaneously in 69.5% (1,584/2,280). In the IOL group, 0.2% of the women (5/2,280) versus 0.1% (2/2,281) in the expectant management group had a scheduled cesarean delivery.

In addition aggregate data MA of the three RCTs (*n*=5.161 women) showed no difference in in the frequency of cesarean delivery (S2 Figure).

In the IOL group the presence of meconium stained amniotic fluid was lower than in the expectant management group (17.8% [380/2,281] versus 25.8%, [522/2,280] RR 0.69 [95%CI 0.61 to 0.77], p-value <0.001, RD -809/10,000 [95%CI -1058/10,000 to -560/10,000], I^2 0%). The rate of MAS in the IOL group was 0.1% (2/2280) and 0.2% (5/2,273) in the expectant management group, RR 0.42 (0.10 to 1.86), p-value 0.25, RD -13/10,000 (-36/10,000 to 10/10,000), I^2 0%. The use of oxytocin was higher in the IOL group compared to the expectant management group (63.1% [1,440/2,281] versus 47.2% [1,077/2,280], RR 1.33 [95%CI 1.26 to 1.40], p-value <0.001, RD 1,589/10,000 [95%CI 1,305/10,000 to 1,872/10,000], I^2 89%). The use of oxytocin was overall higher in SWEPIS, 65.7% versus 52.4% compared with the INDEX trial 26.6% versus 10.9% (S3 Table).

There were 10.5% (240/2,281) cesarean deliveries in the IOL group versus 10.7% (245/2,280) in the expectant management group (RR 0.98 [95%CI 0.83 to 1.16], p-value 0.81, RD -22/10,000 [95%CI -201/10,000 to 157/10,000], I^2 0%). Uterine hyperstimulation was not registered as such but there was no increase in cesarean delivery after IOL compared to expectant management and there was no difference between the groups with respect to the indication for cesarean delivery.

TABLE 4. Perinatal outcomes in the population included in the IPD-MA

Variable	Induction group (n=2,281)	Expectant management group (n=2,280)	Relative Risk or Peto Odds Ratio (95% Confidence Interval)	*P value*	Difference between groups Risk difference per 10,000 or Mean difference (95% Confidence Interval)	Heterogeneity	
						I^2 (%)	*P value*
Primary outcome	**n=2,281**	**n=2,280**					
Primary composite outcome*	10 (0.4%)	23 (1.0%)	0.43 (0.21; 0.91) †	0.027	-57 (-106; -8)	0	0.40
Subcomponents of primary composite outcome	**n=2,281**	**n=2,280**					
Perinatal mortality‡	1 (0.0)	8 (0.4)	0.21 (0.06; 0.78) #	0.019	-31 (-56; -5)	0	0.34
Stillbirth	1 (0.0)	7 (0.3)	0.22 (0.06; 0.89) #	0.034	-26 (-51; -2)	0	0.36
Subcomponents of primary composite outcome	**n=2,280**	**n=2,273**					
Neonatal mortality (live births with mortality < 28 days)	0 (0.0)	1 (0.0)	NE	NE	NE	NE	NE
Apgar score < 4 at 5 min. of live births	3 (0.1)	4 (0.2)	0.75 (0.17; 3.30) #	0.70	-4 (-27; 18)	74	0.05
Hypoxic ischemic encephalopathy (HIE) II-III	2 (0.1)	3 (0.1)	NE	NE	NE	NE	NE
Intracranial haemorrhage	1 (0.0)	2 (0.1)	NE	NE	NE	NE	NE
Neonatal convulsions	1 (0.0)	3 (0.1)	NE	NE	NE	NE	NE
Meconium aspiration syndrome	2 (0.1)	5 (0.2)	0.42 (0.10; 1.86) #	0.25	-13 (-36; 10)	0	1.00
Mechanical ventilation with tracheal intubation within first 72 hours	4 (0.2)	9 (0.4)	0.44 (0.14; 1.44) †	0.18	-22 (-53; 9)	0	0.51
Obstetric brachial plexus injury	4 (0.2)	1 (0.0)	NE	NE	NE	NE	NE
Additional secondary neonatal outcome	**n=2,280**	**n=2,273**					
Composite outcome with Apgar<7 at 5 minutes instead of <4	34 (1.5)	52 (2.3)	0.65 (0.43; 1.00) †	0.051	-79 (-158; -0)	13	0.28
Admittance to a neonatal care unit§	79 (3.5)	109 (4.8)	0.72 (0.54; 0.96) †	0.024	-133 (-249; -18)	0	0.38
Admission to a neonatal care unit ≥ 4 days	24 (1.1)	46 (1.9)	0.52 (0.32; 0.85) †	0.009	-97 (-163; -26)	0	0.35
Neonatal infection or sepsis¶	49 (2.1)	59 (2.6)	0.83 (0.57; 1.21)	0.33	-44 (-132; 44)	52	0.15
Apgar score < 7 at 5 min. of live births	29 (1.3)	39 (1.7)	0.74 (0.46; 1.19)	0.22	-44 (-115; 26)	66	0.09
Humerus fracture	0/2281 (0.0)	1/2,280 (0.0)	NE	NE	NE	NE	NE
Birth weight (g)	**n=2,281**	**n=2,280**					
Mean (standard deviation)	3,764 (417)	3,823 (439)		<0.001	-58.6 (-83.5; -33.8)		
Macrosomia (≥ 4500 g)	92 (3.9)	155 (6.7)	0.59 (0.46; 0.76) †	<0.001	-278 (-409; -147/)	0	0.97
Small for gestational age‖							
<3rd percentile	37 (1.6)	45 (2.0)	0.82 (0.54; 1.27)	0.38	-35 (-112; 42)	83	0.01
<10th percentile	169 (7.4)	188 (8.2)	0.90 (0.74; 1.10) †	0.29	-84 (-239; 72)	0	0.88
Congenital anomaly**	30 (1.3)	36 (1.6)	0.83 (0.52; 1.35) †	0.46	-26 (-96; 43)	0	0.96
Boy	1,228 (53.8)	1,194 (52.4)	1.03 (0.97; 1.09) †	0.31	146 (-143; 435)	0	0.87

Values are numbers (percentages) unless stated otherwise. Relative risk is adjusted for RCT. P-value correspond to the method used to calculate the relative risk/odds ratio. NE = Not estimated due to zero events in both arms in one or both trials

**Including perinatal mortality, Apgar<4 at five minutes, HIE II-III, intracranial haemorrhage, neonatal convulsions, meconium aspiration syndrome, obstetric brachial plexus injury, mechanical ventilation within 72 hours; †Adjusted relative risk; ‡Stillbirth and neonatal mortality (live births with mortality <28 days); #Peto odds ratio; §Neonates admitted only for routine observation excluded; ¶In the INDEX trial, neonates with suspected infection are included; ‖According to national gestational and sex specific references [22, 23]; **Minor birth anomalies according to EUROCAT excluded [24]*

TABLE 5. Delivery outcomes in the population included in the IPD-MA

Variable	Induction group (n=2,281)	Expectant management group (n=2,280)	Relative Risk (95% Confidence Interval)	*P value*	Difference between groups Risk difference per 10,000 or Mean difference (95% Confidence Interval)	Heterogeneity	
						I^2 (%)	*P value*
Gestational age at delivery (days)	**n=2,281**	**n=2,280**					
Median (interquartile range)	288 (287; 289)	291 (289; 293)		<0.001			
Time from randomisation to delivery (days)	**n=2,281**	**n=2,280**					
Mean (standard deviation)	1.88 (1.49)	4.47 (2.81)		<0.001	-2.59 (-2.72; -2.46)		
Onset of delivery	**n=2,281**	**n=2,280**					
Spontaneous	455 (19.9)	1584 (69.5)		<0.001			
Induction	1821 (79.8)	694 (30.4)					
Scheduled cesarean delivery	5 (0.2)	2 (0.1)					
Meconium stained amniotic fluid	380/2,138 (17.8)	525/2,028 (25.9)	0.68 (0.61; 0.77)	<0.001	-821 (-1070; -572)	0	0.52
Use of oxytocin*	1,440/2,281 (63.1)	1,077/2,280 (47.2)	1.33 (1.26; 1.40)	<0.001	1589 (1305; 1872)	89	0.002
Mode of delivery	**n=2,281**	**n=2,280**					
Spontaneous vaginal delivery	1860 (81.5)	1836 (80.5)	1.01 (0.98; 1.04)	0.41	101(-126; 328)	0	0.65
Cesarean delivery	240 (10.5)	245 (10.7)	0.98 (0.83; 1.16)	0.81	-22 (-201; 157)	0	0.83
Operative vaginal delivery	181 (7.9)	199 (8.7)	0.91 (0.75; 1.10)	0.33	-79 (-239; 81)	0	0.56
Indication for cesarean delivery	**n=240**	**n=245**					
Failure to progress ‡	120 (50.0)	122 (49.8)		0.34¶			
Suspected fetal distress	65 (27.0)	57 (23.3)					
Suspected fetal distress and failure to progress	17 (7.1)	21 (8.6)					
Failed operative vaginal delivery	13 (5.4)	24 (9.8)					
Other§	25 (10.4)	21 (8.6)					
Indication for operative vaginal delivery	**n=181**	**n=199**					
Failure to progress‖	89 (49.2)	98 (49.2)		0.24¶			
Fetal distress	76 (42.0)	71 (35.7)					
Fetal distress and failure to progress	15 (8.3)	29 (14.6)					
Maternal complication	1 (0.6)	1 (0.5)					

Values are numbers (percentages) unless stated otherwise. Relative risk is adjusted for trial

**Both induction and/or labour augmentation*

‡Including failed induction

§Including scheduled due to e.g. undetected breech or transverse presentation/maternal indication

¶Chi² test

‖Including maternal distress

Maternal secondary outcomes

The maternal outcomes are presented in Table 6. Use of pain treatment (epidural/spinal or opiates) was significantly higher in the IOL group compared to the expectant management group (50.5% [1,153/2,281] versus 46.4%, [1,058/2,280], RR 1.09 [95%CI 1.03 to 1.16], p-value 0.005, RD 414/10,000 [95%CI 125/10,000 to 703/10,000], I^2 0%). Opiates during delivery were only used in the INDEX trial.

The occurrence of hypertensive disorders of pregnancy was lower in the IOL than in the expectant management group (1.1% [26/2,281] versus 2.9% [66/2,280], RR 0.39 [95%CI 0.25 to 0.63], p-value <0.001, RD -176/10,000 [95%CI -257/10,000 to -94/10,000], I^2 0%, NNT 57 [95%CI 39 to 106]). There were no differences in severe morbidity, such as perineal lacerations III and IV, postpartum haemorrhage and rare events such as venous thromboembolism.

Subgroup analysis

The subgroup analysis on the primary composite outcome and cesarean delivery is presented in Figure 2 and in S5 Table. The prespecified analysis on the primary composite outcome showed a significant difference in the treatment effect according to parity (p=0.01 for interaction). The risk of adverse composite perinatal outcome in the IOL group versus the expectant management group was significantly decreased for nulliparous women (0.3% [4/1,219] versus 1.6% [20/1,264], RR 0.20 [95%CI 0.07 to 0.60], p-value 0.004, RD -127/10,000 [95%CI -204/10,000 to -50/10,000], I^2 0%, NNT 79 [49 to 201]), but not for multiparous women (0.6% [6/1,062] versus 0.3% [3/1,016], RR 1.93 [95%CI 0.48 to 7.72], p-value 0.35, RD 27 [95%CI -29/10,000 to 84/10,000], I^2 55%).

There was no significant difference in the treatment effect on the primary composite outcome according to maternal age (<35 years and ≥35 years) and BMI (<30 and ≥30) (p=0.45 and p=0.62, respectively, for interaction).

The post hoc subgroup analysis on fetal sex had a p-value for interaction of 0.1 on the primary composite outcome. In boys, the composite outcome in the IOL group versus the expectant management group occurred in 0.4% (5/1,228) versus 1.5% (18/1,194), (RR 0.28 [95%CI 0.10 to 0.75], p-value 0.01, RD -110/10,000 [95%CI -187/10,000 to -33/10,000], I^2 0%), and in girls in 0.5% (5/1053) versus 0.5% (5/1086), (RR 1.05 [95%CI 0.30 to 3.72], p-value 0.96, RD 2/10,000 [95%CI -56/10,000 to 59/10,000], I^2 0%).

TABLE 6. Maternal outcomes in the population included in the IPD-MA

Variable	Induction group (n=2,281)	Expectant management group (n=2,280)	Relative Risk (95% Confidence Interval)	*P value*	Risk difference per 10,000 (95% Confidence Interval)	Heterogeneity	
						I^2 (%)	*P value*
Pain treatment (Use of epidural/spinal/opiates)*	1,153 (50.5)	1,058 (46.4)	1.09 (1.03; 1.16)	0.005	414 (125; 703)	0	0.85
Use of epidural anaesthesia	998 (43.8)	906 (39.7)	1.10 (1.03; 1.17)	0.006	400 (122; 678)	0	0.50
Use of opiates	184 (8.1)	173 (7.6)	NE	NE	NE	NE	NE
Fever during labour	177 (7.8)	151 (6.6)	1.17 (0.95; 1.44)	0.14	114 (-96; 195)	0	0.66
Antibiotics during labour	296 (13.0)	297 (13.0)	0.99 (0.85; 1.15)	0.88	-6 (-197; 185)	62	0.11
Therapy	128 (5.6)	104 (4.6)	1.23 (0.96; 1.58)	0.11	105 (-22; 232)	0	0.62
Prophylaxis	168 (7.4)	193 (8.5)	0.87 (0.71; 1.05)	0.15	-111 (-264; 43)	30	0.23
Episiotomy‡	328 (14.4)	335 (14.7)	0.97 (0.85; 1.11)	0.71	-30 (-226; 166)	0	0.53
Perineal lacerations III-IV§	68 (3.0)	81 (3.6)	0.84 (0.61; 1.15)	0.28	-57 (-160; 46)	0	0.71
Postpartum haemorrhage (>1000 ml)¶	208 (9.1)	204 (9.0)	0.98 (0.82; 1.17)	0.86	17 (-149; 184)	70	0.067
Postpartum haemorrhage (>2000 ml)¶	42 (1.8)	34 (1.5)	1.23 (0.79; 1.93)	0.36	35 (-39; 109)	0	0.56
Retained placenta (all)	93 (4.1)	90 (3.9)	1.03 (0.78; 1.37)	0.82	13 (-101; 127)	10	0.29
Retained placenta with haemorrhage >1000 ml	62 (2.7)	61 (2.7)	1.02 (0.72; 1.44)	0.93	4 (-90; 98)	0	0.91
Retained placenta with haemorrhage ≤1000 ml	31 (1.4)	29 (1.3)	1.07 (0.65; 1.77)	0.80	9 (-57; 75)	63	0.10
Hypertensive disorders‖	26 (1.1)	66 (2.9)	0.39 (0.25; 0.61)	<0.001	-176 (-257; -94)	0	0.39
Maternal venous thromboembolism	0 (0.0)	1 (0.0)	NE	NE	NE	NE	NE
Maternal admission to intensive care unit	5 (0.2)	2 (0.1)	2.50 (0.49; 12.86)	0.27	13 (-10;36)	0	NE
Maternal death	0 (0.0)	0 (0.0)	NE	NE	NE	NE	NE

Values are numbers (percentages) unless stated otherwise. Relative risk is adjusted for RCT. NE = Not estimated due to zero events in both arms in one or both trials

**In the INDEX trial a combination of epidural and opiates was possible*

‡With and without perineal lacerations III-IV

§With and without episiotomy

¶Based on measured blood loss and not International Classification of Diseases 10th Revision codes reported

‖Hypertensive disorders of pregnancy including eclampsia and HELLP

Because of the low perinatal mortality rate (0.2%, n=9), no interaction analysis on mortality could be performed. Perinatal mortality according to subgroups is presented in S5 Table. In nulliparous women, perinatal mortality occurred in 0% (0/1,219) in the IOL group versus 0.9% (7/1,264) in the expectant management group. In multiparous women the corresponding figures were 0.1% (1/1,062) versus 0.1% (1/1,016).

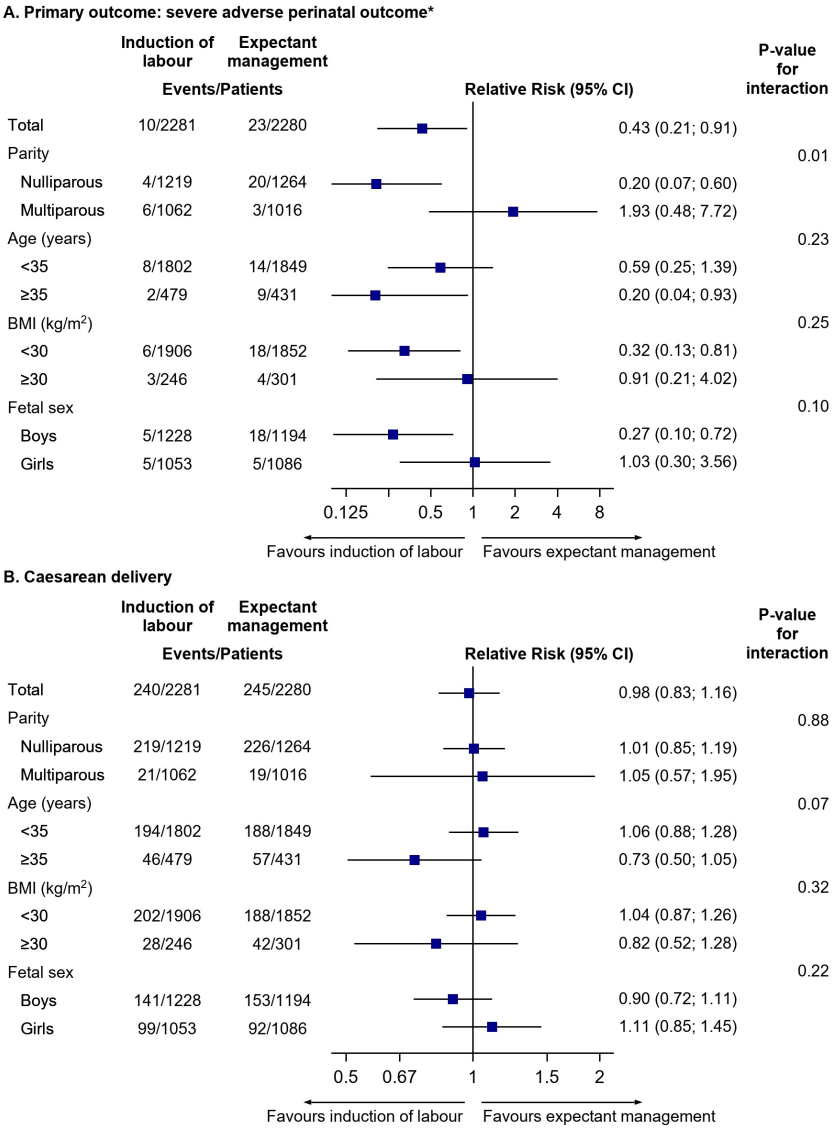

FIGURE 2. Prespecified and post hoc subgroup analysis

**Including perinatal mortality, Apgar<4 at five minutes, HIE II-III, intracranial haemorrhage, neonatal convulsions, meconium aspiration syndrome, obstetric brachial plexus injury, mechanical ventilation within 72 hours.*

There was no significant difference in the treatment effect on cesarean delivery according to parity, maternal age, or BMI (p-value for interaction 0.88, 0.07 and 0.32, respectively) (Figure 2, S5 Table). The rate of cesarean delivery in nulliparous women was 18.0% (219/1,219) in the IOL group and 17.9% (226/1,264) in the expectant management group (RR 1.01 [95%CI 0.85 to 1.19], p-value 0.87) (RR 1.01 [95%CI 0.85 to 1.19], p-value 0.87). Corresponding rates for multiparous women were 2.0% (21/1,062) and 1.9% (19/1,016) (RR 1.05 [95%CI 0.57 to 1.95], p-value 0.87).

For other outcomes, there were no significant interaction effects for parity, except for use of oxytocin. This was used more frequently in nulliparous women, 76% in the IOL group versus 65% in the expectant management group, and corresponding rates for multiparous women were 49% versus 26% (p-value for interaction <0.001) (S5 Table).

DISCUSSION

Summary of evidence

Overall, we found in this IPD-MA that IOL in women with an uncomplicated pregnancy at 41 weeks, reduced the incidence of severe adverse perinatal outcome as compared with expectant management until 42 weeks from 1.0% to 0.4%. The NNT to avoid one of these events is 175 (95%CI 94 to 1,267). The risk of perinatal death was reduced from 0.4% to 0.04% after IOL at 41 weeks with a NNT of 326 (95%CI 177 to 2014). Also, the risk for an infant to be treated in neonatal care for four or more days was lower in the IOL group (NNT 103 [95%CI 59 to 385]). Cesarean delivery or operative vaginal delivery rates were comparable, just as most important maternal adverse outcomes. The low rate of cesarean delivery reflects the low risk population of this IPD-MA. The rate of hypertensive disorders of pregnancy was found to be lower in the IOL group with a NNT of 57 (95%CI 39 to 106).

In the subgroup analysis, we found that nulliparous women had a significantly reduced risk of severe adverse perinatal outcome after IOL at 41 weeks compared with expectant management until 42 weeks. The results indicate that infants of low-risk nulliparous women reaching 41 weeks of pregnancy will probably benefit from IOL at 41 weeks. For infants of low-risk multiparous women, the incidence of a severe adverse perinatal outcome is low. It is not clear if they would benefit from IOL or not. In this IPD-MA, we lack the power to detect a difference in multiparous women regarding severe adverse perinatal outcome, but also with an adequate sample size the NNT or to harm would probably be high. An explanation of the lower incidence of

adverse outcomes in multiparous women might be that women with previous cesarean delivery were excluded from this IPD-MA. Furthermore, multiparous pregnant women at 41 weeks are probably women without major risk factors following from a previous pregnancy. However, there may also be a true difference in risk between nulliparous and multiparous women. The fact that infants of nulliparous women are at increased risk of adverse outcomes in late term pregnancy is in agreement with some but not all previous studies [28-30].

In the post hoc subgroup analysis on fetal sex we found that the boys, rather than girls might benefit from IOL regarding the composite severe adverse perinatal outcome. However, perinatal mortality did not differ by fetal sex, it occurred in five boys and in four girls in our IPD-MA.

The overall better outcome for IOL in our IPD-MA is in line with the latest Cochrane review on IOL at or beyond term, however, no difference between parity was found [9]. The increased risk of stillbirth with advancing gestational age is also shown in a recent large MA of cohort studies by Muglu and colleagues [1]. Several large observational studies are also in line with our findings [31,32]. However, other observational studies are not [33,34]. The Cochrane reviews included RCTs with different timeframes of comparison, and most RCTs had upper limits of expectant management that went far beyond 42 weeks, which could at least partly explain the higher risk of perinatal mortality with a policy of expectant management [8,9].

Strengths and limitations

IPD-MA is believed to be the preferred design for a systematic review of trials [35]. Our IPD-MA included two recently published large RCTs carried out in two high income countries with a study population reflecting the general population in each country. Both RCTs excluded complicated pregnancies. Furthermore, the two countries, according to the Organisation for Economic Co-operation and Development, are comparable in life expectancy, level of education, perinatal mortality and cesarean delivery. The overall similarity between the RCTs enabled us to redefine a primary composite outcome that more accurately reflects seriously affected neonates. We changed from Apgar <7 to Apgar <4 at five minutes because it is associated with an increased risk of long-term adverse neonatal outcome and replaced NICU admission by clearly diagnosed severe neonatal illness and severe complications because NICU admission criteria in Sweden and the Netherlands are not comparable [21]. In addition, the results of this IPD-MA are likely to be applicable to high-income countries due to the equivalence in healthcare status in the included trials but less applicable to low- or

middle-income countries. The heterogeneity between trials for most outcomes was low. Only for one important outcome (Apgar score) heterogeneity was considerable.

Risk of bias assessed by the authors themselves may be considered as not independent, however, the low risk of bias is in agreement with the assessment of the independent reviewers in the Cochrane 2020 updated review of Middleton et al. [9].

There are a few issues, both in the SWEPIS trial and in the INDEX trial which we would like to highlight. In both trials only low-risk women were included, and women with former cesarean delivery or other major uterine surgery were excluded. Thus, how to advise these women is still unclear. The SWEPIS trial was stopped early due to safety reasons; therefore, the magnitude of the risk on perinatal death could be affected and may be overestimated also considering the difference in perinatal mortality rate between the SWEPIS and INDEX trial. Additionally, there was a discrepancy between the enrolment procedure of eligible low-risk women in different centres. In the Stockholm region, inclusion was performed after a routine ultrasonographic assessment, including measurement of fetal abdominal diameter and amniotic fluid, but at other centres this was not performed routinely because it was not mandatory in the study protocol. One could argue that the women included in the Stockholm region (41% of all inclusions) were selected excluding women with fetuses at increased risk of adverse outcome. Perinatal mortality did not occur in the expectant management group in Stockholm centres (0/557; 0.0%) wheras in the other centres there were six cases (6/822; 0.7%). However, there is currently insufficient evidence that routine surveillance with ultrasonographic assessment in late term in order to detect fetuses at risk reduces perinatal mortality [36-39]. In a Swedish retrospective study, a reduction in SGA but no reduction in rates of composite perinatal mortality and morbidity or stillbirth was found with routine ultrasound at 41 weeks compared with indicated ultrasound [38]. Thus, whether the use of routine ultrasonographic assessment at 41 weeks affected the outcome is difficult to determine. Furthermore, it reflects the real clinical situation in Sweden regarding the management of prolonged pregnancy and therefore probably increases the generalisability of the SWEPIS trial to the Swedish population.

In both the SWEPIS and INDEX trials fetal surveillance was performed according to local protocol between 41 and 42 weeks. This could also be considered as a strength, rather than a limitation, because it increases external validity of these pragmatic trials. In the SWEPIS, trial it usually included an antenatal visit performed by a midwife with a clinical assessment and auscultation of fetal heart rate. In the INDEX trial, it generally included clinical assessment and assessment of the fetus with ultrasound, cardiotocography,

and extra checks between 41 and 42 weeks [40]. This could be reflected in the higher rate of medical inductions for fetal and maternal reasons between 41 and 42 weeks in the INDEX expectant management group compared with the expectant group of the SWEPIS trial, though whether this contributed to a lower perinatal mortality rate is unknown and makes us aware that further studies are needed to evaluate the effect of screening regimes in late-term pregnancy.

In the INDEX trial, randomisation was not stratified by parity, which resulted in a small difference in distribution of nulliparous women between the groups (slightly higher rate in the expectant management group), though after adjustment for parity similar results were shown. In addition, due to the healthcare system, a discrepancy between the IOL and expectant management group regarding level of care was present. All induced women were treated in an obstetrician-led secondary care setting while a large proportion of the women in the expectant management group started their delivery in midwifery-led primary care including home births. This might be considered as performance bias, but several studies have shown that the level of care does not seem to influence the delivery outcome. Women at risk of adverse perinatal or maternal outcome are referred to secondary care (hospital); this risk selection is on the basis of the Dutch obstetric care system [41-44]. Also, all babies in the expectant management group with adverse outcome were born in secondary care after referral before or during delivery.

Furthermore, for our combined IPD-MA, a limitation is the low number of included women (*n*=5,161) compared with the recent Cochrane review (*n*=12,479). However, none of the trials except the Gelisen and the INDEX trials in the Cochrane review fulfilled our inclusion criteria for gestational age. Including IPD from trials with induction before or after 41 weeks and an expectant management policy beyond 42 weeks would have caused methodological problems such as selection bias.

Finally, due to the few RCTs eligible for this IPD-MA, the possibility of assessing severe adverse perinatal outcomes with few events and subgroup analysis was limited.

CONCLUSIONS AND IMPLICATIONS

In this study, we found that, overall, IOL at 41 weeks improved perinatal outcome compared with expectant management until 42 weeks without increasing the cesarean delivery rate. This benefit is shown only in nulliparous women, whereas

for multiparous women the incidence of mortality and morbidity was too low to demonstrate any effect. The magnitude of risk reduction of perinatal mortality remains uncertain. Women with pregnancies approaching 41 weeks should be informed on the risk differences according to parity so that they are able to make an informed choice for IOL at 41 weeks or expectant management until 42 weeks.

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SUPPORTING INFORMATION

S1 TABLE. Baseline characteristics per trial in the populations included in the IPD-MA

Variable	SWEPIS Induction group (n=1381)	SWEPIS Expectant management group (n=1379)	INDEX Induction group (n=900)	INDEX Expectant management group (n=901)
Maternal age at randomisation (years)	**n=1381**	**n=1379**	**n=900**	**n=901**
Mean (standard deviation)	31.2 (4.7)	31.1 (4.5)	30.6 (4.8)	30.2 (4.6)
Age ≥35	303/1,381 (21.9)	279/1,379 (20.2)	176/900 (19.6)	152/901 (16.9)
Parity (includes stillbirths and live births)	**n=1381**	**n=1379**	**n=900**	**n=901**
Nulliparous	762/1,381 (55.2)	753/1,379 (54.6)	457/900 (50.8)	511/901 (56.7)
Multiparous	619/1,381 (44.8)	626/1,379 (45.4)	443/900 (49.2)	390/901 (43.3)
BMI at first antenatal visit	**n=1,275**	**n=1,265**	**n=877**	**n=888**
Mean (standard deviation)	24.9 (4.7	25.1 (4.9)	24.5 (4.3)	24.9 (4.7)
BMI ≥30	157/1,275 (12.3)	184/1,265 (14.5)	89/877 (10.1)	117/888 (13.2)
Higher professional education/university	789/1,221 (64.6)	780/1,242 (62.8)	286/900 (31.8)	322/901 (35.7)

Values are numbers (percentages) unless stated otherwise

S2 TABLE. Perinatal outcomes per trial in the populations included in the IPD-MA

Variable	SWEPIS Induction group (n=1,381)	SWEPIS Expectant management group (n=1,379)	INDEX Induction group (n=900)	INDEX Expectant management group (n=901)
Primary outcome				
Primary composite outcome*	8/1,381 (0.6)	15/1,379 (1.1)	2/900 (0.4)	8/901 (1.2)
Subcomponents of primary composite outcome				
Perinatal mortality†	0/1,381 (0.0)	6/1,379 (0.4)	1/900 (0.1)	2/901 (0.2)
Stillbirth	0/1,381 (0.0)	5/1,379 (0.4)	1/900 (0.1)	2/901 (0.2)
Neonatal mortality (Live births with mortality < 28 days)	0/1,381 (0.0)	1/1,374 (0.1)	0/899 (0.0)	0/899 (0.0)
Apgar score <4 at 5 minutes	3/1,381 (0.2)	1/1,374 (0.1)	0/899 (0.0)	3/899 (0.3)
Hypoxic ischemic encephalopathy (HIE) II-III	2/1,381 (0.1)	3/1,374 (0.2)	0/899 (0.0)	0/899 (0.0)
Intracranial haemorrhage	1/1,381 (0.1)	2/1,374 (0.1)	0/899 (0.0)	0/899 (0.0)
Neonatal convulsions	1/1,381 (0.1)	3/1,374 (0.2)	0/899 (0.0)	0/899 (0.0)
Meconium aspiration syndrome (MAS)	2/1,381 (0.1)	3/1,374 (0.2)	0/899 (0.0)	2/899 (0.2)
Tracheal intubation within first 72 hours	3/1,381 (0.2)	5/1,374 (0.4)	3/899 (0.3)	7/899 (0.8)
Obstetric brachial plexus injury	4/1,381 (0.3)	1/1,374 (0.1)	0/899 (0.0)	0/899 (0.0)
Additional secondary neonatal outcome				
Composite outcome with Apgar<7 at 5 minutes instead of <4	21/1,381 (1.5)	26/1,379 (1.9)	13/900 (1.4)	26/901 (2.9)
Admittance to neonatal care (all babies due to illness and not just protocol observation)	55/1,381 (4.0)	82/1,374 (6.0)	24/899 (2.7)	27/899 (3.0)
Admission to a neonatal care unit ≥4 days	21/1,381 (1.5)	36/1,374 (2.6)	3/899 (0.3)	10/899 (1.1)
Neonatal infection or Sepsis‡	12/1,381 (0.9)	22/1,374 (1.6)	37/899 (4.1)	37/899 (4.1)
Apgar score <7 at 5 minutes	18/1,381 (1.3)	16/1,374 (1.2)	11/899 (1.2)	23/899 (2.6)
Humerus fracture	0/1,381 (0.0)	0/1,379 (0.0)	0/900 (0.0)	1/901 (0.1)
Birth weight (g)	**n=1,381**	**n=1,379**	**n=900**	**n=901**
Mean (standard deviation)	3815 (409)	3875 (436)	3685 (417)	3742 (430)
Macrosomia (≥ 4500 g)	68/1,381 (4.9)	114/1,374 (8.3)	24/900 (2.4)	41/901 (4.3)
Small for gestational age§				
<3rd percentile	13/1,381 (0.9)	28/1,379 (2.0)	24/900 (2.7)	17/901 (1.9)
<10th percentile	94/1,381 (6.8)	103/1,379 (7.5)	75/900 (8.3)	85/901 (9.4)
Congenital anomaly¶	14/1,381 (1.0)	17/1,379 (1.2)	16/900 (1.8)	19/901 (2.1)
Boy	781/1,381 (56.6)	756/1,379 (54.8)	447/900 (49.7)	438/901 (48.6

Values are numbers (percentages) unless stated otherwise.

**Including perinatal mortality, Apgar<4 at five minutes, HIE II-III, intracranial haemorrhage, neonatal convulsions, MAS, obstetrical brachial plexus injury, mechanical ventilation within 72 hours*

†stillbirth and neonatal mortality (Live births with mortality < 28 days)

‡In the INDEX trial, neonates with suspected infection are also included

§ According to national gestational and sex specific references (18, 19)

¶ Minor birth anomalies according to EUROCAT excluded (17)

S3 TABLE. Delivery outcomes per trial in the populations included in the IPD-MA

Variable	SWEPIS Induction group (n=1,381)	SWEPIS Expectant management group (n=1,379)	INDEX Induction group (n=900)	INDEX Expectant management group (n=901)
Gestational age at delivery (days)	**n=1,381**	**n=1,379**	**n=900**	**n=901**
Median (interquartile range)	289 (283; 297)	292 (286; 297)	287 (285; 295)	289 (285; 296)
Time from randomization to delivery (days)	n=1,381	n=1,379	n=900	n=901
Mean (standard deviation)	1.76 (1.42)	4.66 (2.64)	2.06 (1.58)	4.16 (3.04)
Onset of birth process	**n=1,381**	**n=1,379**	**n=900**	**n=901**
Spontaneous	195/1,381 (14.1)	920/1,379 (66.7)	260/900(18.9)	664 (73.7)
Induction	1181/1,381 (85.5)	457/1,379 (33.1)	640 (71.1)	237 (26.3)
Scheduled caesarean delivery	5/1,381 (0.4)	2/1,379 (0.1)	0	0
Meconium stained amniotic fluid	233/1238 (18.8)	320/1126 (28.3)	147/900 (16.4)	205/901 (22.6)
Use of oxytocin*	907/1,381 (65.7)	722/1,379 (52.4)	533/900 (59.2)	355/901 (39.4)
Mode of delivery	**n=1,381**	**n=1,379**	**n=900**	**n=901**
Spontaneous vaginal delivery	1150/1,381 (83.3)	1140/1,379 (82.7)	710/900 (78.9)	696/901 (77.2)
Caesarean delivery	143/1,381 (10.4)	148/1,379 (10.7)	97/900 (10.8)	97/901 (10.8)
Operative vaginal delivery	88/1,381 (6.4)	91/1,379 (6.6)	93/900 (10.3)	108/901 (12.0)
Indication for caesarean delivery	**n=143**	**n=148**	**n=97**	**n=97**
Failure to progress†	79/143 (55.2)	83/148 (56.1)	41/97 (42.3)	39/97 (40.2)
Suspected foetal distress	41/143 (28.7)	36/148 (24.3)	24/97 (24.7)	21/97 (21.6)
Suspected foetal distress and failure to progress	6/143 (4.2)	10/148 (6.8)	11/97 (11.3)	11/97 (11.3)
Failed operative vaginal delivery	7/143 (4.9)	12/148 (8.1)	6/97 (6.2)	12/97 (12.4)
Other‡	10/143 (7.0)	7/148 (4.7)	15/97 (15.5)	14/97 (14.4)
Indication for operative vaginal delivery	**n=88**	**n=91**	**n=93**	**n=108**
Failure to progress§	50/88 (56.8)	49/91 (53.8)	39/93 (41.9)	49/108 (45.4)
Foetal distress	33/88 (37.5)	34/91 (37.4)	43/93 (46.2)	37/108 (34.3)
Foetal distress and Failure to progress	5/88 (5.7)	7/91 (7.7)	10/93 (10.8)	22/108 (20.4)
Maternal complication	0/88 (0.0)	1/91 (1.1)	1/93 (1.1)	0/108 (0.0)

Values are numbers (percentages) unless stated otherwise.

**Both induction and/or labour augmentation*

†Including failed induction

‡Including scheduled due to e.g. undetected breech or transverse presentation/maternal indication

§Including maternal distress

S4 TABLE. Maternal outcomes per trial in the populations included in the IPD-MA

Variable	SWEPIS Induction group (n=1,381)	SWEPIS Expectant management group (n=1,379)	INDEX Induction group (n=900)	INDEX Expectant management group (n=901)
Pain treatment (use of epidural/spinal/opiates)*	733/1,381 (53.1)	675/1,379 (48.9)	420/900 (46.7)	383/901 (42.5)
Use of epidural anaesthesia	733/1,381 (53.1)	675/1,379 (48.9)	265/900 (29.4)	231/901 (25.6)
Use of opiates	0/1,381 (0.0)	0/1,379 (0.0)	184/900 (20.4)	173/901 (19.2)
Fever during labour	127/1,381 (9.2)	105/1,379 (7.6)	50/900 (5.6)	46/901 (5.1)
Antibiotics during labour	248/1,381 (18.0)	262/1,379 (19.0)	48/900 (5.3)	35/901 (3.9)
Therapy	95/1,381 (6.9)	80/1,379 (5.8)	33/900 (3.7)	24/901 (2.7)
Prophylaxis	153/1,381 (11.1)	182/1,379 (13.2)	15/900 (1.7)	11/901 (1.3)
Episiotomy†	89/1,381 (6.4)	84/1,379 (6.1)	239/900 (26.6)	251/901 (27.9))
Perineal lacerations III-IV‡	40/1,381 (2.9)	50/1,379 (3.6)	28/900 (3.1)	31/901 (3.4)
Postpartum haemorrhage (>1000 ml) §	131/1377 (9.5)	145/1375 (10.5)	77/900 (9.1)	59/901 (8.0)
Postpartum haemorrhage (>2000 ml) §	27/1,381 (2.0)	18/1,379 (1.3)	15/900 (3.0)	16/901 (2.6)
Retained placenta (all)	52/1,381 (3.8)	57/1,379 (4.1)	41/900 (4.6)	33/901 (3.7)
Retained placenta with haemorrhage >1000 ml	36/1,381 (2.6)	36/1,379 (2.6)	26/900 (2.9)	25/901 (2.8)
Retained placenta with haemorrhage ≤1000 ml	16/1,381 (1.2)	21/1,379 (1.5)	15/900 (1.7)	8/901 (0.9)
Hypertensive disorders¶	19/1,381 (1.4)	42/1,379 (3.0)	7/900 (0.6)	24/901 (1.6)
Maternal venous thromboembolism	0/1,381 (0.0)	1/1,379 (0.1)	0/900 (0.0)	0/901 (0.0)
Maternal admission to intensive care unit	2/1,381(0.1)	0/1,381 (0.0)	3/900 (0.3)	2/901 (0.2)
Maternal death	0/1,381 (0.0)	0/1,379 (0.0)	0/900 (0.0)	0/901 (0.0)

Values are numbers (percentages) unless stated otherwise.

**In the INDEX trial a combination of epidural and opiates was possible*

†With and without perineal lacerations III-IV

‡With and without episiotomy

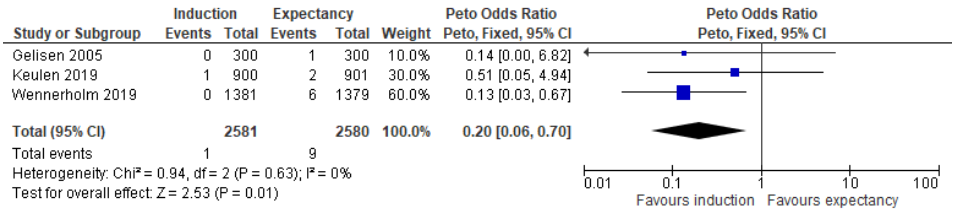
§Based on measured blood loss and not International Classification of Diseases 10th Revision codes reported

¶Hypertensive disorders of pregnancy including eclampsia and HELLP

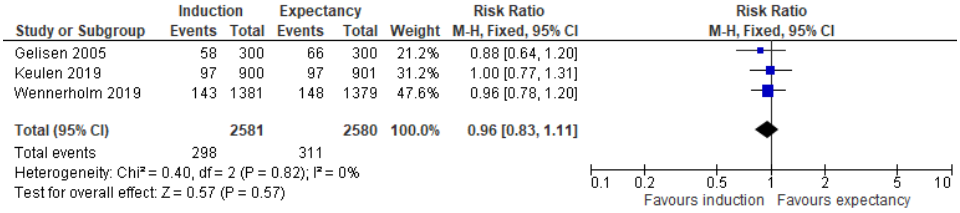
S5 TABLE. Primary outcome: severe adverse perinatal outcome, perinatal mortality and caesarean delivery per subgroup in the population included in the IPD-MA

Variable	Induction group	Expectant management group	Relative Risk (95% Confidence Interval)	*P value*	Risk difference per 10,000 (95% Confidence Interval)	Interaction *P value*
Severe adverse perinatal outcome *						
Parity						0.01
Nulliparous	4/1,219 (0.3)	20/1,264 (1.6)	0.20 (0.07; 0.60)	0.004	-127 (-204; -50)	
Multiparous	6/1,062 (0.6)	3/1,016 (0.3)	1.93 (0.48; 7.72)	0.35	27 (-29; 84)	
Maternal age (Years)						0.23
<35 years	8/1,802(0.4)	14/1,849 (0.8)	0.59 (0.25; 1.39)	0.23	-31 (-82; 19)	
≥35 years	2/479 (0.4)	9/431 (2.1)	0.20 (0.04; 0.93)	0.04	-166 (-308; -25)	
Body mass index (Kg/m2)						0.25
<30	8/1,906 (0.4)	19/1,852 (1.0)	0.32 (0.13; 0.81)	0.02	-66 (-117; -15)	
≥30	3/246 (1.2)	4/301 (1.3)	0.91 (0.21; 4.02)	0.90	-12 (-202; 177)	
Fetal sex						0.10
Boy	5/1,228 (0.4)	18/1,194 (1.5)	0.27 (0.10; 0.72)	0.01	-110 (-187; -33)	
Girl	5/1,053 (0.5)	5/1,086 (0.5)	1.03 (0.30; 3.56)	0.96	2 (-56; 59)	
Perinatal mortality†						
Parity						NE
Nulliparous	0/1,219 (0.0)	7/1,264 (0.6)	0.14 (0.03; 0.60)‡	0.01	-56 (-98; -15)	
Multiparous	1/1,062 (0.1)	1/1,016 (0.1)	0.88 (0.05; 14.17)‡	0.93	-1 (-28; 25)	
Maternal age (Years)						NE
<35 years	1/1,802 (0.1)	4/1,849 (0.2)	0.31 (0.05; 1.78)‡	0.19	-16 (-40; 8)	
≥35 years	0/479 (0.0)	4/431 (0.9)	0.12 (0.02; 0.87‡	0.04	-93 (-178; -7)	
Body mass index (Kg/m2)						NE
<30	1/1,906 (0.1)	5/1,852(0.3)	0.26 (0.05; 1.27)‡	0.10	-22 (-47; 4)	
≥30	0 /246 (0.0)	3/301 (1.0)	0.16 (0.02; 1.57)‡	0.12	-100 (-224; 24)	
Fetal sex						NE
Boy	1/1,228 (0.1)	4/1,194 (0.3)	0.29 (0.05; 1.69)‡	0.17	-25 (-61; 11)	
Girl	0/1,053 (0.0)	4/1,086 (0.4)	0.14 (0.02; 0.99)‡	0.05	-37 (-73; -0)	
Caesarean delivery						
Parity						0.88
Nulliparous	219/1,219 (18.0)	226/1,264 (17.9)	1.01 (0.85; 1.19)	0.95	10 (-292; 312)	
Multiparous	21/1,062 (2.0)	19/1,016 (1.9)	1.05 (0.57; 1.95)	0.87	10 (-108; 128	
Maternal age (Years)						0.07
<35 years	194/1,802 (10.8)	188/1,849 (10.2)	1.06 (0.88; 1.28)	0.56	60 (-139; 258	
≥35 years	46/479 (9.6)	57/431 (13.2)	0.73 (0.50; 1.05)	0.09	-364 (-775; 48)	
Body mass index (Kg/m2)						0.32
<30	202/1,906 (10.6)	188/1,852 (10.2)	1.04 (0.87; 1.26)	0.65	45 (-150; 240)	
≥30	28/246 (11.4)	42 (14.0)	0.82 (0.52; 1.28)	0.38	-254 (-816; 309)	
Fetal sex						0.22
Boy	141/1,228 (11.5)	153/1,194 (12.8)	0.90 (0.72; 1.11)	0.31	-133 (-393; 127)	
Girl	99/1,053 (9.4)	92/1,086 (8.5)	1.11 (0.85; 1.45)	0.45	94 (-148; 335)	
Use of Oxytocin						
Parity						<0.001
Nulliparous	925 (75.9)	817 (64.6)	1.15 (1.10; 1.21)	<0.001	1083 (730; 1437)	
Multiparous	515 (48.5)	260 (25.6)	1.89 (1.68; 2.14)	<0.001	2304 (1900; 2708)	

Values are numbers (percentages) unless stated otherwise. Relative risk is adjusted for RCT. P-value correspond to the method used to calculate the relative risk/odds ratio. NE= not estimable due to low number of events (total of nine)
**Composite of stillbirth, neonatal mortality, Apgar<4 at five minutes, HIE II-III, intracranial hemorrhage, neonatal convulsions, meconium aspiration syndrome, obstetric brachial plexus injury and mechanical ventilation within 72 hours*
†Stillbirth and neonatal mortality (live births with mortality <28 days)
‡Peto odds ratio



S1 FIGURE. Aggregate meta-analysis of studies comparing induction of labour with expectant management regarding perinatal mortality



S2 FIGURE. Aggregate meta-analysis of studies comparing induction of labour with expectant management regarding caesarean delivery

CHAPTER 5

WHAT WOMEN WANT AND WHY. WOMEN'S PREFERENCES FOR INDUCTION OF LABOUR OR EXPECTANT MANAGEMENT IN LATE-TERM PREGNANCY

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ABSTRACT

Background Both induction of labour at 41 weeks and expectant management until 42 weeks are common management strategies in low-risk pregnancy since there is no consensus on the optimal timing of induction in late-term pregnancy for the prevention of adverse outcomes. Our aim was to explore maternal preference for either strategy and the influence on quality of life and maternal anxiety on this preference.

Methods Obstetrical low-risk women with an uncomplicated pregnancy were eligible when they reached a gestational age of 41 weeks. They were asked to fill in questionnaires on quality of life (EQ6D) and anxiety (STAI-state). Reasons of women's preferences for either induction or expectant management were explored in a semi-structured questionnaire containing open ended questions.

Results Of 782 invited women 604 (77.2%) responded. Induction at 41 weeks was preferred by 44.7% (270/604) women, 42.1% (254/604) preferred expectant management until 42 weeks, while 12.2% (74/604) of women did not have a preference. Women preferring induction reported significantly more problems regarding quality of life and were more anxious than women preferring expectant management ($p<0.001$). Main reasons for preferring induction of labour were: "safe feeling" (41.2%), "pregnancy taking too long" (35.4%) and "knowing what to expect" (18.6%). For women preferring expectant management, the main reason was "wish to give birth as natural as possible" (80.3%).

Conclusion Women's preference for induction of labour or a policy of expectant management in late-term pregnancy is influenced by anxiety, quality of life problems (induction), the presence of a wish for natural birth (expectant management), and a variety of additional reasons.

Keywords Late-term pregnancy, induction of labour, expectant management, preference, anxiety, quality of life

INTRODUCTION

In late-term pregnancy (≥ 41 weeks + 0 days - <42 weeks + 0 days), induction of labour (IOL) is often performed in order to prevent perinatal or maternal adverse outcomes, but the optimal timing of delivery is not yet clear [1, 2] Recent trials show a small difference in the risk of adverse perinatal outcomes in favour of induction at 41 weeks [3, 4]. A Cochrane systematic review concluded that the absolute risk of perinatal mortality is low, and therefore IOL as well as expectant management (EM) are both options for a woman to choose.

As induction of labour intervenes in the normal birth process it might be more painful than labour with a spontaneous onset[5]. The WHO recommends that women should be involved in decision-making when it concerns the use of interventions [6]. Decision making for induction of labour in case of late term pregnancy is mainly based on medical considerations. Women are not routinely involved in the decision making process which implicates unmet expectations and preferences[7]. However, guidelines recommend that women should be offered an IOL somewhere between 41 and 42 weeks gestation, and in a majority of the existing guidelines it is emphasised that the timing of IOL should be decided after discussing the management options and women's preferences in a process of shared decision making [8-11]. According to Elwyn et al. Shared Decision Making is defined as "a dialogue between the patient (woman) and health care professional where women are supported to consider options in order to achieve informed preferences using the best available evidence". This process may improve healthcare experience and outcomes [12-14]. Three important factors in shared decision making are: recognising the need for a decision, understanding the evidence, and integrating women's values and preferences [15].

Recent qualitative systematic reviews on women's experiences of IOL concluded that women's decision making and women's preferences are influenced by the quality of given information, the point of view of the healthcare professional, the opinion of family members and woman's own risk perception [16, 17]. Also, anxiety and quality of life have an influence on women's preferences. People with higher levels of anxiety tend to have more risk aversion and are more willing to accept an intervention [18, 19]. When women are more anxious or when they experience a worsening quality of life, preferences for management may change. On the other hand, being involved in the decision making may reduce anxiety [20]. Some studies focused on women's preferences for either IOL or a policy of expectant management (EM), these studies focused on different methods of IOL, on the provided care and birth experience,

and on women's feelings about being postdate [21-24]. However, women's personal preference as a key influencing factor on decision-making and her motivation for this preference was sparsely explored.

The aim of this study was to compare preferences of women at a gestational age of 41 weeks for a policy of IOL or EM with respect to their experienced quality of life and their state of anxiety. Furthermore, we explored reasons of women for their preference for either management option.

METHODS

Setting and ethics

This survey was part of the INDEX study in which a policy of IOL at 41 weeks + 0-1 days was compared with EM until 42 weeks + 0 days. It consisted of a multicentre randomised controlled trial (RCT) and a prospective cohort study among women with prolonged pregnancy. In the INDEX RCT 1801 women were randomised for IOL at 41 weeks + 0-1 days or EM until 42 weeks+ 0 days. In the INDEX cohort study, 4273 women who fulfilled the criteria for participation in the INDEX RCT but declined randomisation were followed. More detailed information about the RCT and its results was recently published, results of the prospective cohort will follow [3, 25]. Ethical approval was administered by the local ethics committee of the Academic Medical Centre (No NL38455.018.11).

From February 2014 until March 2016 we conducted a survey alongside these studies in a subsample of the participating hospitals and midwifery care practices. This concerned 8 hospitals and 49 midwifery care practices located throughout the country who were willing to distribute the surveys among eligible women. The local caregivers (midwife, obstetrician, resident or nurse) received instructions on how to distribute the survey.

Participants

Women were eligible if they had a low-risk, uncomplicated singleton pregnancy with a stable cephalic presentation at a certain gestational age, based on early ultrasound, of 40 weeks + 5 days to 41 weeks + 0 days and no contraindications to expectant management until 42 weeks.

Questionnaires

Eligible women were approached by their local caregiver at a gestational age of 40

weeks + 5 to 6 days and counselled for the INDEX study. After giving consent to either randomisation for the trial (with immediate randomisation) or participation in the INDEX cohort, women received the survey. Women could choose to complete a digital version or a paper version of the questionnaire, supplied with a self-addressed envelope. The local caregiver provided the e-mail address of the participant/woman to the investigator (JKJK) and the participant received a direct link to a digital questionnaire. In case of non-response a reminder was sent with a maximum of three times. The paper and digital version of the questionnaires were identical. The questionnaires consisted of the validated Six-Dimensional EuroQol questionnaire (EQ-6D) to assess women's quality of life, the validated State-Trait Anxiety Inventory for Adults (STAI state version) to assess women's current feelings of anxiety, and questions on the preference for management of care [26-28].

Preference for management strategy was assessed by three questions. In the first question women were asked to indicate which management strategy they would prefer if they could choose: induction of labour at 41 weeks or expectant management until 42 weeks. Women were asked to answer this question on a 5 point Likert scale (certainly induction at 41 weeks, probably induction at 41 weeks, don't know, probably expectant management until 42 weeks, certainly expectant management until 42 weeks). Women were asked explain their motivation for the preferred management in an open-ended question. We extracted the given answers and categorised them in overarching themes. Answers could cover more than one theme. Per question, a maximum of three different themes was assigned. Thirdly, we asked women to indicate from seven predefined reasons what was the main reason why they chose for the preferred management options ("pregnancy takes too long", "to know what to expect", "a safe feeling", "this is how it happened in my social environment", "want my community midwife as lead professional", "like to give birth as natural as possible", "like to get the chance to give birth at home", or "other reason"; see Appendix). These predefined reasons were extracted from the literature and expert opinion and were tested in a pilot [16, 20].

Outcomes

Preference for management strategy was categorised in one of three groups: preference for IOL ("certainly want induction at 41 weeks" and "probably want induction at 41 weeks"), preference for EM ("certainly want EM until 42 weeks" and "probably want EM until 42 weeks"), or no preference ("don't know"). Women's motivation for this preference was presented in themes. Women's quality of life scores (EQ6D) and anxiety (STAI-state) scores were compared according to their preference for either

IOL or EM. In the six domains of quality of life, we dichotomised into women reporting problems versus reporting no problems and calculated the outcomes for the different groups. For anxiety, the median score and high and low anxiety levels were calculated for the different groups. An anxiety score of ≥41 was used as cut-off point for an increased level of anxiety [29].

Sample size

In the Netherlands, approximately 16% of all pregnancies reach a gestational age of 41 weeks [30]. For a representative survey on preferences of women with a gestational age of 41 weeks a sample size of at least 380 completed surveys was needed to reach a confidence level of 95% and a margin of error of 5%.

Analysis

Demographics and clinical characteristics were extracted from the INDEX study database. Quality of life and anxiety were reported in absolute numbers and percentages or in means and standard deviations. Differences in demographics, clinical characteristics, quality of life, and anxiety among the groups were analysed using Chi-squared test, or Fisher exact test when appropriate, for dichotomous variables or with factorial ANOVA for continuous variables. The significance level was set to 5%.

Women's answers on questions regarding their preferences were analysed and interpreted using Directed Content Analysis.[106] Two authors (JKJK and EdM) read all women's answers on the open-ended questions describing their motivation to prefer either IOL or EM. First the text was coded by highlighting the words that captured the essence and were most descriptive. Then these codes were assembled into themes. A code could fit into a predefined theme ("pregnancy takes too long", "to know what to expect", "a safe feeling", "this is how it happened in my social environment", "want my community midwife as lead professional", "like to give birth as natural as possible", "like to get the chance to give birth at home"), but also new themes were formulated. Results of the coding and theming of JK and EdM were compared, discrepancies discussed and final themes were agreed upon on a consensus base. A maximum of three themes per question was assigned.

One author (JKJK) extracted all free text answers that explained women's motivation. JKJK, EdM and PTN selected the answers which described best women's motivation for reporting verbatim in this publication.

RESULTS

For the survey 782 women were invited to participate, of whom 604 (77.2%) completed the survey, 102 surveys were completed by women in secondary care, 502 by women in midwifery care. From these 604 women 288 participated in the INDEX-trial and had been randomised for either IOL (n=145) or EM (n=143) and 316 women had refused randomisation and participated in the INDEX cohort-study. The reason for refusing randomisation was registered as "not wanting a policy by randomisation" (27.2% (86/316)), a "preference for IOL" (13.3% (42/316)), a "preference for EM" (57.3% (181/316)), and not wanting to be randomised for other reasons (2.2% (7/316)) (Figure 1).

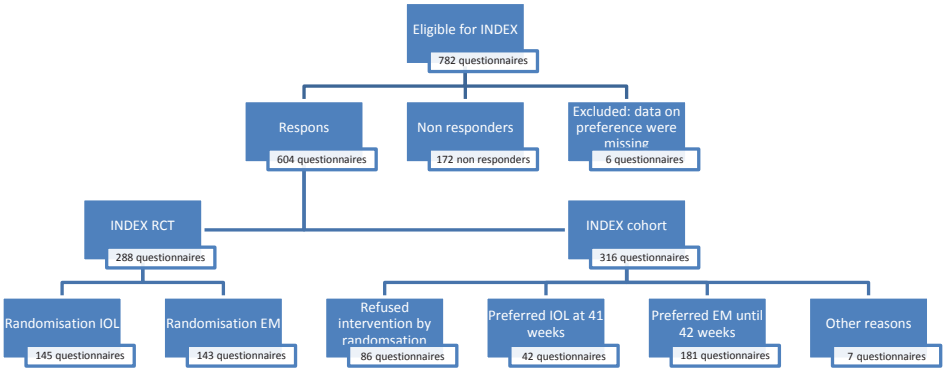

FIGURE 1. Flowchart questionnaires

Preference groups

Participating women were categorized according to their preference into three groups: preference for IOL ("certainly choose for IOL" or "probably choose for IOL"), preference for EM ("certainly choose for waiting until 42 weeks with subsequent IOL" or "probably choose for waiting until 42 weeks with subsequent IOL") or no preference for either management strategy. A total of 270 women had a preference for IOL (164 "certainly", 106 "probably"), 254 women had a preference for EM (117 "certainly ", 137 "probably"), 74 women had no preference for either management strategy. In six questionnaires the preference score was missing. We combined women with a mild or strong preference for either management strategy, as the outcomes for anxiety and quality of life were comparable within these groups. Women with a preference for IOL had higher anxiety scores than women with a preference for EM.

Characteristics of participants

Characteristics of the participants, categorized according to their preference, are reported in Table 1. Baseline characteristics of the participants were comparable with baseline characterises from RCT and cohort. Women who had a preference for EM were on average older (31.4 years versus 30.4 years; p 0.031), more often higher educated (p<0.001) and were more often cohort participants (89.0% cohort versus 11.0% RCT) than women with a preference for IOL (20.4% cohort versus 79.6% RCT; p<0.001). There were no statistically significant differences in ethnicity (p=0.11), parity (p= 0.78) or socio-economic status (p= 0.19). Women who preferred IOL were more anxious (STAI p< 0.001) and reported more problems in different aspect of quality of life (EQ6D mobility p=0.007; self-care p=0.001; usual activities p=0.01; pain/discomfort p=0.004; anxiety/depression p<0.001, cognitive functioning p=0.03) (Table 2).

Preference

From seven predefined reasons, women could indicate the main reason for their preference. The main reasons for women to prefer IOL were "a safe feeling" (41.2% (93/226)), or "the pregnancy takes too long" (35.4% (80/226)). The main reason for women to prefer EM was the wish "to give birth as natural as possible" (80.3% (196/244)) which was also pointed out as main reason of 59.6% (34/57) of the women who did not indicate a preference for either management strategy (Table 3).

TABLE 1. Characteristics of participants

Characteristics	Total	Preference for IOL	Preference for EM		No preference	
	(n=604)	(n=270)	(n=254)	*P value**	(n=74)	*P value**
Mean maternal age at inclusion (SD)	30.8 (4.2)	30.4 (4.4)	31.4 (4.0)	**0.031**	30.4 (4.1)	0.50
Ethnicity Caucasian	548 (90.7%)	239 (88.5%)	234 (92.1%)	0.11	69 (93.2%)	0.47
Level of education				**<0.001**		**0.0016**
Lower education	32 (5.3%)	24 (8.9%)	6 (2.4%)		2 (2.7%)	
Medium education	106 (17.5%)	70 (25.9%)	23 (9.1%)		13 (17.6%)	
Higher education	142 (23.5%)	67 (24.8%)	52 (20.5%)		23 (31.1%)	
Unknown/other	324 (53.7%)	109 (40.4%)	173 (68.1%)		36 (48.7%)	
Social Economic Status				0.19		0.81
Low	152 (25.2%)	77 (28.5%)	55 (21.7%)		19 (25.7%)	
Medium	276 (45.7%)	122 (45.2%)	118 (46.5%)		33 (44.6%)	
High	157 (26.0%)	61 (22.6%)	74 (29.1%)		21 (28.4%)	
Unknown	19 (3.2%)	10 (3.7%)	7 (2.8%)		1 (1.4%)	
Parity				0.78		0.32
Nulliparous	309 (51.5%)	135 (50.2%)	129 (51.4%)		42 (56.8%)	
Multiparous	291 (48.5%)	134 (49.8%)	122 (48.6%)		32 (43.2%)	
Origin of participants				**<0.001**		**0.001**
INDEX RCT	288 (47.7%)	215 (79.6 %)	28 (11.0%)		45 (60.8%)	
INDEX cohort	316 (52.3%)	55 (20.4%)	226 (89.0%)		29 (39.1%)	

**reference group = preference for IOL*
response rate preference n=598

TABLE 2. Anxiety and quality of life according to maternal preference

Outcomes	Total	Preference for IOL	Preference for EM		No preference	
	(n=604)	(n=270)	(n=254)	*P value**	(n=74)	*P value**
Anxiety score, STAI STATE (mean, SD)	34.6 (9.8)	37.0 (10.8)	32.1 (8.3)	**<0.001**	34.1 (8.6)	**<0.001**
Lower anxiety score <41 (n,%)	475 (78.8%)	189 (70.0%)	221 (87.0%)	**<0.001**	60 (81.1%)	**<0.001**
median (min-max)	31 (19-40)	32 (19-40)	30 (20-40)		32 (20-40)	
Higher anxiety score ≥41 (n,%)	128 (21.2%)	81 (30.0%)	33 (13.0%)	**<0.001**	14 (18.9%)	**<0.001**
median (min-max)	48 (41-73)	48 (41-73)	46.0 (41-60)		47.0 (41-58)	
Quality of life. EQ6D						
Mobility				**0.007**		0.32
No problems	380 (62.9%)	154 (57.0%)	174 (68.5%)		47 (63.5%)	
Some problems	224 (37.1%)	116 (43.0%)	80 (31.5%)		27 (36.5%)	
Self-care				**0.001**		0.25
No problems	526 (87.1%)	222 (82.2%)	234 (92.1%)		65 (87.8%)	
Some problems	78 (12.9%)	48 (17.8%)	20 (7.9%)		9 (12.2%)	
Usual activities				**0.01**		0.52
No problems	287 (47.5%)	117 (43.3%)	138 (54.3%)		29 (39.2%)	
Some problems	317 (52.5%)	153 (56.7%)	116 (45.7%)		45 (60.8%)	
Pain/discomfort				**0.004**		0.69
No problems	255 (42.2%)	99 (36.7%)	125 (49.2%)		29 (39.2%)	
Some problems	349 (57.8%)	171 (63.3%)	129 (50.8%)		45 (60.8%)	
Anxiety/depression				**<0.001**		0.09
No problems	493 (81.6%)	201 (74.4%)	225 (88.6%)		62 (83.8%)	
Some problems	111 (18.4%)	69 (25.6%)	29 (11.4%)		12 (16.2%)	
Cognitive functioning				**0.03**		0.55
No problems	459 (76.0%)	195 (72.2%)	204 (80.3%)		56 (75.7%)	
Some problems	145 (24.0%)	75 (27.8%)	50 (19.7%)		18 (24.3%)	

**reference group = preference for IOL*

response rate preference n=598

TABLE 3. Main reason for preference of IOL or EM

Main reason	Total (n=527)	Preference for IOL (n=226)	Preference for EM (n=244)	No preference (n=50)
The pregnancy takes too long	84 (15.9%)	80 (35.4%)	1 (0.4%)	3 (5.3%)
To know what to expect	50 (9.5%)	42 (18.6%)	1 (0.4%)	7 (12.3%)
A safe feeling	101 (19.2%)	93 (41.2%)	3 (1.2%)	5 (8.8%)
Usual in my social environment	2 (0.4%)	1 (0.4%)	1 (0.4%)	0
Community midwife as lead professional	12 (2.3%)	3 (1.3%)	8 (3.3%)	1 (1.8%)
To give birth as natural as possible	235 (44.6%)	5 (2.2%)	196 (80.3%)	34 (59.6%)
Chance to give birth at home	43 (8.2%)	2 (0.9%)	34 (13.9%)	7 (12.3%)

From the open-ended questions, in which women explained their motivation for their preferred management, we extracted the given answers and categorised them in overarching themes. We constructed seven new themes ("physical status" ,"fear for complications with IOL", "no advantages of IOL", "does not know", "consensus: waiting until 41+3 or 41+4", "good experiences with IOL", "depending on condition of baby" and "mental status") for answers which could not fit in one of the seven predefined themes. Answers could cover more than one theme. Per question, a maximum of three different themes was assigned. Figure 2 shows the frequency of themes according to preference groups.

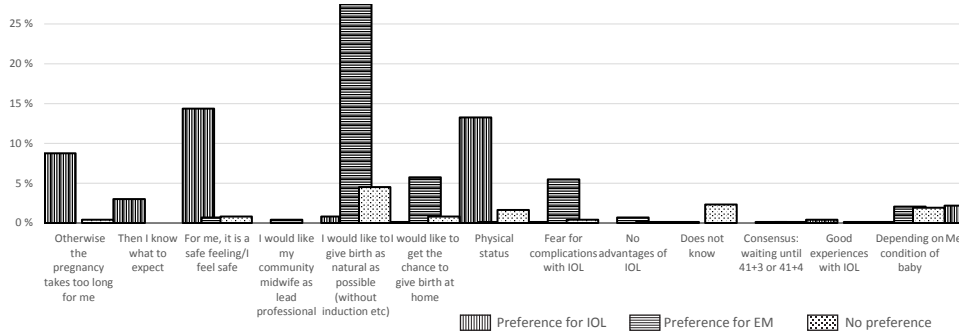

FIGURE 2. Motivation for preferences (multiple answers)

Women's explanation for their preference

In the open-ended question on the reasons for preference, women explained their choice.

5

Preference for IOL

Women who had a preference for IOL made clear that "the pregnancy takes too long":

'Because after due date one is in a kind of waiting mode, every day is one too many…'

'…impatient…'

But for some women their preference will be a result of balancing different conditions:

'It is a balance between waiting as long as possible to give birth naturally, the size and growth of the baby and time of pregnancy being long/good enough.'

Physical and mental state are also reasons why a pregnancy takes too long:

'Because my mental state deteriorates more and more the longer it takes, waiting constantly breaks you down. Also the physical strength does not increase.'

'Physically and mentally it is getting too heavy, then every day is too long… If I wouldn't have physical complaints, it might be different.'

Women with a preference for IOL wanted "to know what to expect":

'…for practical reasons I would consider to be induced at 41 weeks…'

'I am ready for childbirth, and I expect the baby to be ready also.'

"To feel safe" was also an important reason for women with a preference for IOL:

'I worry about the condition of the baby, and for that I do not want to postpone childbirth.'

'I don't want to put my child in danger, because there is a chance that the placenta does not work sufficiently and there is a lack of oxygen! That the most!'

'The fear that something happens with a healthy baby if I wait too long.'

Some women describe that they have to choose between arguments:

'Negative reduction: because waiting until 42 weeks for me is the worst scenario. To be induced scares me a bit, but waiting and not knowing what to expect is worse for me.'

'The baby is ready and has to get out, staying longer inside increases the risk for the baby. Of course I prefer a natural childbirth, but I do not have any problems to be induced for the wellbeing of my child.'

Preference for EM

Women who had a preference for EM explain that they would like to give birth as natural as possible, to get the chance to give birth at home:

'*Because then the chance of a natural childbirth is the highest, and my body is most ready when birth starts spontaneously.'*

'Because I want to await natural course of pregnancy and childbirth, I feel good, and I want to give birth at home.'

'I think that a natural childbirth is best for mother and child. They indicate when the time is ripe (few exceptions). Also less complications and less interventions, in my perception.'

Many women emphasized that the safety of the baby is always more important:

'We prefer a natural childbirth, of course only as long as the baby stays well.'

'As long as the condition of the baby is well, I think it makes sense to let nature by its course, it also seems to be less stressful for myself and the baby.'

'I see childbirth as a natural process. When possible I prefer to wait until the baby and my body starts birth by itself. If waiting is more riskful, then of course I would choose for an induction.'

For some women resistance towards induction of labour is the reason to want a natural childbirth:

'Because the counter effects of an induction are not known yet.'

'Induction of labour is in essence a non-natural way to start childbirth. I have heard a lot of bad experiences of those births, because the body was not 'self-

directing' and thus the pain more intense.'
'I experienced induction of labour and a normal childbirth before. The pain with the induction was much more fierce, and the ability to cope with it much less than with a normal childbirth.'

For a few women *"to feel safe"* was the most important reason for their preference of expectant management:
'To have more time to enjoy the baby in my belly. As long as you feel good, I think the baby is the safest with the mother.'
'Baby is not a computer and does not come exactly on time.'

Women who did not have a preference
Women who indicated that they had no preference for either IOL or EM formulated their argument as a balance, or did not know what to choose for:
'Emotionally both options have pro-and-cons. I prefer week 42, because I want to give birth as natural as possible. But induction at 41 weeks makes that everything is (still) okay with the baby and I can start with 'recuperation', because the physical complaints have increased the last weeks. (and to look forward to the birth of our daughter :-))'
'It is a difficult decision because you don't know what is good to do.'
'It is completely dependent on the situation, how I feel and the condition of the baby.'

DISCUSSION

In this study we explored women's preferences for either IOL at 41 weeks or EM until 42 weeks. It is the first study which gives a broad insight in the motivations behind their preference.

At a gestational age of 41 weeks the main reason for women who preferred IOL was "a safe feeling", followed by: "the pregnancy taking too long", mainly caused by physical complaints, and "knowing what to expect". For women who preferred EM the most important reason was to give birth as natural as possible. Most women with a preference for induction at 41 weeks gave more than one reason for their preference.

In previous research on women's experiences of late-term pregnancy, themes that emerged as important were stress and worry, (mis-)trust in the own body, the feeling

of 'time is up', and mental exhaustion [16, 32] Our study shows similar themes, adds other themes and also explains the preference for one of the management strategies in late-term pregnancy.

Women who had a preference for IOL reported more problems regarding quality of life and were more anxious. This is in line with the reasons women described for their preference for IOL. Previous research showed a significant association between elevated levels of anxiety in pregnancy and negative feelings about the forthcoming birth, Elevated levels of anxiety are also associated with a higher preference for an intervention [19, 29] In our study anxiety could be considered as a motivator to choose IOL, mainly because of worrying about baby's or women's own condition.

Women in our study participated either in the INDEX RCT or in the INDEX cohort study. Women participating in the RCT were significantly more anxious (STAI) and reported more quality of life problems with pain/discomfort and with anxiety/depression than women in the cohort study. There was no difference in the overall level of anxiety between women randomised for IOL or EM. As we expected, women participating in the INDEX RCT more frequently had a preference for IOL (74.7%), compared to women of the INDEX cohort (17.7%). Since IOL at 41 weeks is not a standard procedure in the Netherlands yet, participating in the RCT provided women the opportunity (by chance), to be induced at 41 weeks. This most likely explains the difference in preference for IOL between INDEX RCT and cohort participants. Also women with a strong wish for natural birth did not want to participate in a trial because of the risk of allocation to induction by chance.

A limitation of this study could be that we distributed the questionnaires among participating hospitals and midwifery care practices during a specified timeframe rather than among all participants of the RCT and cohort. However, for a representative survey it was not necessary to include all women participating in both studies. Baseline characteristics are comparable with the entire RCT and cohort population which supports that we obtained data from a representative sample. For the qualitative part of this study of women's explanation for their preferences, we reached data saturation, so even with more available questionnaires it was not expected that more or other themes would have emerged. Though we assessed women's preferences, these preferences are also influenced by what and how information is given by the caregiver [16]. Questionnaires were distributed by 57 different centres, but caregivers with strong preferences for either induction at 41 weeks or expectant management could be underrepresented in the group who counselled women for the INDEX study. Other studies focused only on some elements of our findings (for example "time is up"

or "safety"), in our study we identified a broader range of reasons from women to have a preference for either IOL or EM [17, 24, 33].

Recent evidence from the INDEX and SWEPIS trials showed that IOL at a gestational age of 41 weeks could reduce adverse perinatal outcomes, taking into account that the absolute risk of severe adverse outcome is low [3, 4]. Because of these publications it is expected that guidelines will be adapted in many countries to active offering the option of IOL at 41 weeks to women with otherwise low-risk pregnancies. The authors of the recent Cochrane review on induction of labour at or beyond term concluded that the optimal timing of offering IOL to women warrants further investigation, but also further exploration of risk profiles of women and their values and preferences [1]. The present study aimed to fill this knowledge gap and provide lacking information on women's preferences. An important factor associated with women's preference is anxiety, we also found this association in our study. Women who preferred IOL had higher anxiety levels. To provide adequate information and involving women in the process of shared decision making may reduce anxiety. The outcomes of this study will help to get a better understanding of the underlying motivation of pregnant women for their preference for a policy of induction of labour or expectant management, which is important for caregivers who are involved in the counselling in late-term pregnancy. Our finding that women's preferences were motivated by anxiety, physical problems, concerns about safety, but also a wish to deliver as natural as possible and a variety of factors, emphasises that there is no such thing as 'one size fits all' regarding management in late term pregnancy. A quote of a woman (who did not know what management strategy to prefer) illustrates this well:

> *'...in these cases I don't like standard procedures, but I think that this should be evaluated on a personal level, every pregnancy again. So I think that a standard conclusion that induction at 41 weeks is better, is no good...'*

CONCLUSION

Women vary both in their preference for management strategy at 41 weeks' gestation as well as in their motivations for their preference. Women preferring induction of labour are more anxious and experience more quality of life problems than women preferring a policy of expectant management. Awareness of this variation in women's preference and the motivations behind will help obstetrical caregivers in the process of shared decision making in late-term pregnancy.

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CHAPTER 6

WOMEN'S EXPERIENCES AND PREFERENCES AFTER RANDOMISATION TO ELECTIVE INDUCTION OF LABOUR AT 41 WEEKS OR A POLICY OF EXPECTANT MANAGEMENT UNTIL 42 WEEKS

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ABSTRACT

Objective To evaluate birth experience of women randomised to elective induction of labour (IOL) at 41 weeks or a policy of expectant management (EM) until 42 weeks, and their preference for either strategy in a future pregnancy.

Study design We analysed surveys containing validated questionnaires on birth experience (LADY-X) and satisfaction with birth care (SSQ) two months after childbirth. Anxiety (STAI-State) and women's preference for either management strategy in late-term pregnancy were assessed at randomisation and two months after childbirth.

Results The response rate was 88% (330/375). Most women in both groups reported a positive birth experience (IOL median score 0.94 (IQR 0.89-1.00) versus 0.97 (IQR 0.86-1.00) for EM; p=0.56). This corresponds with the high satisfaction scores of both groups (IOL median score 38 (IQR 34-41) versus 39 (IQR 35-41) for EM; p=0.50). Anxiety before and after childbirth was associated with a less positive birth experience (p<0.001). This association was stronger for women who gave birth by caesarean section (p=0.03). The preferred management strategy in both groups was IOL before and after childbirth, with a decrease in the preference for IOL after childbirth (IOL group: 79.3% to 72.1% and EM group: 69.9% to 56.3%; p=0.04) favouring preference for EM (IOL group: 6.9% to 14.0% and EM group: 12.6% to 22.2%; p=0.008).

Conclusion The vast majority of women randomised to IOL at 41 weeks or to EM until 42 weeks had positive birth experiences. Increased maternal anxiety is associated with a less positive birth experience, with the association stronger after caesarean section. In this study population most women preferred a policy of elective induction at 41 weeks before and after childbirth, with a small increase in the preference for expectant management after childbirth.

Keywords Birth experience, anxiety, preference, induction of labour, expectant management, late-term pregnancy

INTRODUCTION

A systematic Cochrane review on 'induction of labour (IOL) for improving birth outcomes for women at or beyond term' concluded that a policy of elective induction of labour is associated with fewer perinatal deaths and fewer caesarean sections, though the absolute risk of perinatal death was low [1]. It was suggested in the systematic review that further research is needed on timing of induction and women's values and preferences for different strategies.

Recently, some studies were published on timing of induction [2, 3]. Perinatal and maternal outcomes after elective IOL at 41 weeks were compared with a policy of expectant management (EM) until 42 weeks. The results of a meta-analysis on this comparison showed a small, but significant lower rate of adverse perinatal outcomes after elective induction at 41 weeks, though this decrease was only observed for nulliparous women, not for multiparous women.

For optimal counselling it is important to inform women not only about the risks and benefits of elective induction and a strategy of EM, but also to take into account her wellbeing, including possible feelings of anxiety and their preference for either strategy, as was already suggested in the Cochrane review [4]. Outcome measures that matter to women, such as experience, are increasingly important in health care [5]. Women's experiences of IOL have been evaluated in several studies [6]. Results indicate that experience of IOL may be influenced by the content and quality of the given information, women's share in the decision-making process, the extent to which adequate support was received and women's level of anxiety [7-11]. In a recently published study, we showed that anxiety is also related with women's preferences in late-term pregnancy: women preferring IOL at 41 weeks were more anxious than women preferring EM until 42 weeks [12]. In a Swedish prospective cohort study (N=936) published in 2011, women's experiences with IOL were compared with experiences of women with a spontaneous onset of labour [13]. IOL was associated with a less positive birth experience, but in a subgroup analysis of women beyond 41 weeks of gestation there was no difference in birth experience between woman with or without IOL.

Several qualitative studies focused on women's experiences in late-term pregnancy in order to get a better understanding how caregivers could support women with a gestational age beyond 41 weeks [6-8, 14, 15]. Women reported feelings of "time is up", but women vary in their philosophies and ideologies, therefore woman centred care

with good information and involvement in shared decision making were important issues for women in late-term pregnancy. We identified one Norwegian RCT (N=508) published in 2007, comparing IOL at 41 weeks with EM until 42 weeks and 6 days, they assessed women's birth experience and preference for either IOL or EM in a future late-term pregnancy 6-8 months after childbirth [16]. In this trial, women allocated to the IOL group reported that they had shorter labour and experienced more intense and more frequent contractions compared to women in the EM group. Most women in the IOL group (74%) would prefer IOL again in a future pregnancy, while 38% of the women in the EM group preferred EM again in a future pregnancy. In this study, analysis was according to intention to treat. Birth experience after planned IOL at 41 weeks versus birth experience after a policy of EM until 42 weeks, taking into account the actual onset of labour, has not been studied yet as such to our knowledge.

In the present study we compared birth experience of women who were randomised for IOL at 41 weeks or a policy of EM until 42 weeks. We also assessed the association between actual onset of labour, maternal anxiety and birth outcomes and birth experience. We stratified according to parity and actual onset of labour. Furthermore, we assessed women's preference for either IOL or EM in case of a future late-term pregnancy.

With this information, we aim to get better insight in women's experiences after planned elective IOL at 41 weeks or a policy of EM, and in the possible association between the actual onset of labour, parity, mode of delivery, maternal anxiety and birth experience within the allocation groups. This may support health care professionals in the counselling process of women in late-term pregnancy.

METHODS

Setting and design

This study was performed alongside the INDEX RCT: a multicentre RCT comparing IOL at 41 weeks with a policy of EM until 42 weeks [2]. Between May 2012 and March 2016 a total of 1801 women gave informed consent for randomisation to a policy of either IOL or EM, data on pregnancy and childbirth were prospectively collected and registered in a case report form. Counselling and inclusion was done by midwives in 123 primary care midwifery practices and by clinical midwives, residents or gynaecologists in 26 hospitals (secondary care) participating in the INDEX project. From May 2014 until the end of the inclusion period, the participating centres invited included women

also to fill out validated questionnaires on anxiety, satisfaction with care and questions on women's preferences. This was actually done in 46 midwifery practices and eight hospitals. Women received [a set of] questionnaires at time of inclusion and two months after childbirth. Ethical approval was obtained by the local ethics committee of the Amsterdam UMC, University of Amsterdam (No NL38455.018.11).

Participants

Women with a singleton, uncomplicated low-risk pregnancy with a fetus without known congenital anomalies presenting in a cephalic position were asked at a gestational age of 40 weeks and 5 days to 41 weeks and zero days to participate in the INDEX RCT. When they agreed upon randomisation either elective IOL was planned at 41 weeks and zero to 1 day, or pregnancy was managed expectantly until 42 weeks and zero days.

Questionnaires

During counselling for the INDEX RCT by the local caregiver, women were also informed on the questionnaires. After women gave their consent and after randomisation they were given a link to a digital composite questionnaire or an identical paper version for women who had no internet access, or did not want to complete online questionnaires. Women received the composite questionnaire twice; the first at inclusion in order to fill in immediately after randomisation, and the second two months after childbirth. The paper version of the questionnaire was supplied with a self-addressed envelope. At time of inclusion the local caregiver asked the participating woman for her email address, or house address if she didn't have access to email, and sent this to the study office. Two months after inclusion women received the second questionnaire by email or postal mail. Women who did not respond received a reminder twice. In the Supplement the specifications of the different questionnaires are presented (Supplementary Table 1).

At inclusion the State-Trait Anxiety Inventory for Adults (STAI state, 20 questions) was used to assess women's present feelings of anxiety (situational stress) [17]. The Six Simple Questions (SSQ) questionnaire was used to assess women's satisfaction with care. This validated questionnaire covers six domains of satisfaction with pregnancy or childbirth care in six questions [18]. Quality of life was measured with the Five-Dimensional EuroQol instrument (EQ-5D) [19]. Preference for policy in late-term pregnancy was evaluated by questions regarding the preferred management strategy in the current pregnancy (tick box), the main reasons for this preference (open ended question) and the most important reason for the preferred management option (tick

box) (Supplementary Table 1). The predefined reasons had been extracted from the literature and expert opinion and tested in a pilot [20].

Two months after childbirth the same composite questionnaires as distributed after randomisation were sent to the participating women. A questionnaire was added on women's birth experience and the survey was completed with questions on women's preference for management in an imaginary next late-term pregnancy. Women's birth experience was measured with the Labor and Delivery IndeX (LADY-X), a validated questionnaire evaluating women's experiences of childbirth in seven questions which were identified by women as covering the most important domains of childbirth experience (Supplementary Table 1) [21].

For this study we used the pre- and post childbirth questionnaires on anxiety (STAI-state) and preference, and the post childbirth questionnaires on birth experience (LADY-X) and satisfaction (SSQ).

Outcomes

The primary outcome of this study was birth experience assessed with the LADY-X, a birth specific utility measure reflecting the course of labour and birth. Secondary outcomes included women's anxiety and women's preference for either IOL or EM in a future late-term pregnancy. Satisfaction with received care (SSQ) was used to triangulate the primary outcome; birth experience and satisfaction with care are not interchangeable but these concepts are closely related [18, 22].

Sample size

In the Netherlands at the time of inclusion, approximately 16% of all pregnancies reached a gestational age of 41 weeks. For a representative survey on preferences of women with a gestational age of 41 weeks a sample size of at least 380 completed surveys was needed to reach a confidence level of 95% and a margin of error of 5%.

Statistical analysis

The sum score for the LADY-X questionnaire for measuring birth experience was calculated with preference weights per attribute constructed from a comparable target sample of women who recently gave birth [23]. Scores for experience range from 0.00 for the worst to 1.00 for the best experience. For satisfaction with care we calculated sum scores, ranging from 6 for the lowest to 42 for highest satisfaction. Preference for either IOL or EM was expressed in percentages. Anxiety was expressed in mean scores (with standard deviations).

Analysis was primarily according to intention to treat, subsequently we stratified for actual onset of labour. We reported demographic and clinical characteristics, experience, preference, anxiety and satisfaction with care in absolute numbers with percentages or in means with standard deviations. Comparisons between categorical variables were calculated using Chi-squared test or Fisher exact test when appropriate. For continuous variables, a t-test or Mann-Whitney U test was used for normal and non-normal distributions. The association between birth experience and allocation of IOL or EM, parity, SES, actual onset of labour, mode of delivery (vaginal or caesarean section), maternal anxiety and adverse perinatal and/or maternal birth outcomes on women's birth experience was analysed in a linear regression model. Despite the non-normal distribution for birth experience scores, the residuals in the adjusted linear regression model were approximately normal such that this model was used for adjusted associations. We fitted a linear regression model on the birth experience scores using parity, SES, onset of labour, mode of delivery, maternal anxiety and adverse perinatal and/or maternal birth outcomes as predictors. We considered a p-value < 0.05 to indicate statistical significance. Women's preference before and after birth was assessed with the McNemar test with two tailed p-value. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 26.0 [24].

RESULTS

From May 2014 until the end of the inclusion period 891 women were included in the trial, though a total of 375 women were asked to participate in the survey studies of the INDEX trial. Two months after childbirth 330 (88%) women filled out the post childbirth questionnaires which were used for analysis of birth experience. From the included women, 171 were allocated to IOL at 41 weeks, and 159 to EM until 42 weeks (Figure 1).

Baseline characteristics were comparable between the two groups (Table 1). In the IOL group, 27.5% of the women went into spontaneous labour before the planned IOL and 72.5% was electively induced as planned, in the EM group 70.4% of the women went into spontaneous onset of labour and 29.6% of the women had elective or medically indicated IOL.

Women in both groups had a positive birth experience based on high sum scores in both groups: 0.94 (IQR 0.89 - 1.00) in the IOL group versus 0.97 (IQR 0.86 - 1.00), p-value 0.56) in the EM group (Table 2). A higher score indicates a more positive experience with a minimum score of 0.00 and a maximum score of 1.00. Most women

rated their experiences in all seven domains as "best" (IOL group between 63.1% and 80.8%, versus EM group between 58.7% and 85.7%). The sum score was also high. The satisfaction scores corresponded with the high scores for birth experience (38 in the IOL group versus 39 in the EM group; p-value 0.50); a higher sum-score indicates a higher satisfaction with a minimum sum score of 6 and a maximum sum score of 42. In the IOL group between 83.5% and 93.9% of the women rated their satisfaction as "good" (highest level) in all six domains, versus 83.3% and 95.6% in the EM group. After stratification to onset of labour within the IOL and EM group no differences in experience were observed (p-value 0.17) (Table 3). After stratifying the whole cohort according to onset of labour, birth experience was slightly more positive after spontaneous onset of labour compared to elective induction of labour, though this did not reach significance (p-value 0.05). In the EM group women reported more serious concerns on the child's condition (13.5% compared to 3.8% in the IOL group). The reported quality of life was equally high in both groups (IOL group 0.92 (SD 0.11) and EM group 0.92 (SD 0.11), p-value 1.00).

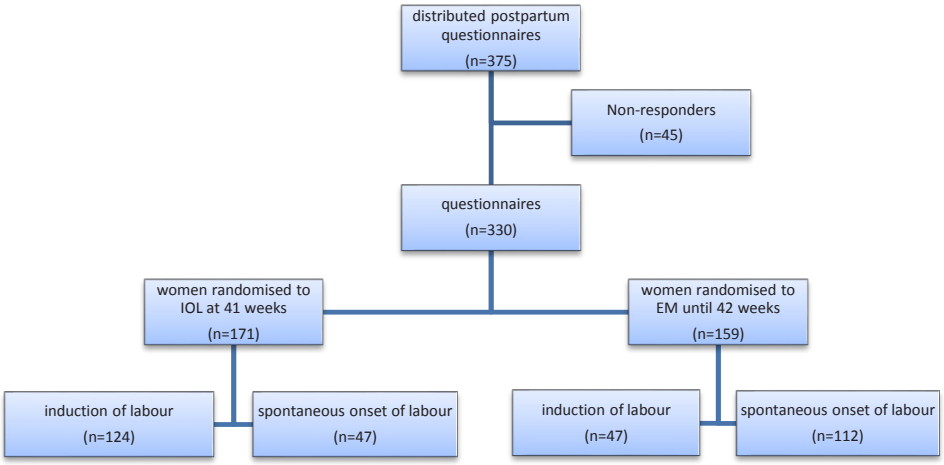

FIGURE 1. Flowchart

TABLE 1. Baseline characteristics

	IOL at 41 weeks (n=171)	EM until 42 weeks (n=159)	*P value* *
Maternal age in years (mean, SD)	30.4 (4.6)	30.2 (4.1)	0.05
Ethnicity			0.76
Caucasian	153 (89.5%)	146 (91.8%)	
Other	15 (8.8%)	11 (6.9%)	
Unknown	3 (1.8%)	2 (1.3%)	
Highest level of education			0.88
Primary school	0	1 (0.6%)	
Secondary school	5 (2.9%)	2 (1.3%)	
Lower / medium professional education	65 (38.0%)	63 (39.6%)	
Higher professional education / university	52 (30.4%)	63 (39.6%)	
Other / unknown	19 (28.7%)	30 (18.9%)	
Social economic status			0.28
Low	36 (21.1%)	47 (29.6%)	
Medium	82 (48.0%)	68 (42.8%)	
High	46 (26.9%)	39 (24.5%)	
Unknown	7 (4.1%)	5 (3.1%)	
Parity			0.09
Nulliparous	85 (49.7%)	94 (59.1%)	
Multiparous	86 (50.3%)	65 (40.9%)	
Body Mass Index (BMI) at start of pregnancy			0.61
<18.5	6 (3.5%)	2 (1.3%)	
18.5-<25	94 (55.0%)	86 (54.1%)	
25-<30	48 (28.1%)	49 (30.8%)	
≥30	21 (12.3%)	21 (13.2%)	
Unknown	2 (1.2%)	1 (0.6%)	
Level of care at onset of labour			<0.001
Primary care	47 (27.5%)	111 (69.8%)	
Secondary care	124 (72.5%)	48 (30.2%)	
Level of care at time of delivery			<0.001
Primary care	19 (11.1%)	48 (30.2%)	
Secondary care	151 (88.3%)	111 (69.9%)	
Onset of labour			<0.001
Spontaneously	47 (27.5%)	112 (70.4%)	
Induction	124 (72.5%)	47 (29.6%)	
Mode of delivery			0.52
Spontaneously	138 (80.7%)	122 (76.7%)	
Vaginal instrumental	14 (8.2%)	21 (13.2%)	
Caesarean section	19 (11.2%)	16 (10.1%)	
Pain treatment during labour†	64 (37.4%)	64 (40.3%)	0.57
Adverse perinatal outcome‡	0	0	
Adverse maternal outcome§	16 (9.4%)	12 (7.5%)	

* *Fisher's exact test or Chi-square*

† *Pain treatment during labour: spinal, epidural, opiates*

‡ *Adverse perinatal outcome: perinatal mortality or 5 minutes Apgar <7, and/or neonatal intensive care unit admission, and/or meconium aspiration syndrome, and/or plexus brachialis injury, and/or intracranial haemorrhage.*

§ *Adverse maternal outcome: post partum haemorrhage ≥1000mL, and/or manual removal of placenta, and/or obstetric anal sphincter injury, and/or intensive care admission, and/or maternal death*

TABLE 2. Birth experience, anxiety, satisfaction with care and future preference of women according to allocation in the INDEX RCT

Outcomes	Allocation IOL at 41 weeks (n=171)	Allocation EM until 42 weeks (n=159)	*P value* allocation IOL vs allocation EM
Birth Experience (median, IQR) (high= better experience)	0.94 (0.89-1.00)	0.97 (0.86-1.00)	0.56*
Availability of professionals			0.29*
At all times	105 (80.8%)	108 (85.7%)	
Most of the times	25 (19.2%)	18 (14.3%)	
Rarely	0	0	
Information provided			0.52*
Very well informed	86 (66.2%)	88 (69.8%)	
Adequately informed	39 (30.0%)	34 (27.0%)	
Inadequately	5 (3.8%)	4 (3.2%)	
Professionals' response to needs			0.13*
Very well responded	89 (68.5%)	95 (75.4%)	
Reasonably responded	30 (23.1%)	29 (23.0%)	
Not at all	11 (8.5%)	2 (1.6%)	
Emotional support by professionals			0.04*
Very well supported	90 (69.2%)	101 (80.2%)	
Adequately supported	35 (26.9%)	23 (18.3%)	
Inadequately supported	5 (3.8%)	2 (1.6%)	
Feelings of safety			0.71*
Very safe	95 (73.1%)	94 (74.6%)	
Reasonably safe	30 (23.1%)	30 (23.8%)	
Not safe enough	5 (3.8%)	2 (1.6%)	
Concerns about child's condition			0.22*
No concerns	82 (63.1%)	74 (58.7%)	
Some concerns	43 (33.1%)	35 (27.8%)	
Many concerns	5 (3.8%)	17 (13.5%)	
Duration until first contact with child			0.73*
Not long	117 (90.0%)	115 (91.3%)	
Quite long	8 (6.2%)	7 (5.6%)	
Very long	5 (3.8%)	4 (3.2%)	
Anxiety (median, IQR) (high= more anxious)	28.00 (22.00-34.25)	28.00 (23.00-35.00)	0.96*
Satisfaction with care† (median, IQR) (high= higher satisfaction)	38.00 (34.00-41.00)	38.50 (35.00-41.00)	0.50*
Preference for management before childbirth	(n=145)	(n=143)	
Preference for IOL	115 (79.3%)	100 (69.9%)	
Undecided	20 (13.8%)	25 (17.5%)	
Preference for EM	10 (6.9%)	18 (12.6%)	
Preference for management after childbirth	(n=129)	(n=126)	
Preference for IOL	93 (72.1%)	71 (56.3%)	
Undecided	18 (14.0%)	27 (21.4%)	
Preference for EM	18 (14.0%)	28 (22.2%)	

** Mann Whitney U test*

† Satisfaction with care consists of: appropriate and adequate control over care, person(s) responsible for care caring and compassionate, problems have been dealt with effectively, needs addressed with appropriate consideration, overall organization of care appropriate, would choose the same type of care for next pregnancy

IQR: Inter Quartile Range

TABLE 3. Birth experience, anxiety, satisfaction with care and women's preference for management in a future pregnancy according to onset of labour in the INDEX RCT

Outcomes	Allocation IOL at 41 weeks (n=171)			Allocation EM until 42 weeks (n=159)		
	Onset of labour		*P value*	Onset of labour		*P value*
	Spontaneous	Induction	SOL vs IOL	Spontaneous	Induction	SOL vs IOL
Birth Experience (median, IQR) (high= better experience)	0.94 (0.92-1.00)	0.94 (0.87-1.00)	0.17*	0.97 (0.86-1.00)	0.93 (0.85-0.98)	0.17*
Availability of professionals			0.23*			0.30*
At all times	29 (87.9%)	76 (78.4%)		79 (87.8%)	29 (80.6%)	
Most of the times	4 (12.1%)	21 (21.6%)		11 (12.2%)	7 (19.4%)	
Rarely	0	0		0	0	
Information provided			0.36*			0.16*
Very well informed	24 (72.7%)	62 (63.9%)		66 (73.3%)	22 (61.1%)	
Adequately informed	8 (24.2%)	31 (32.0%)		22 (24.4%)	12 (33.3%)	
Inadequately	1 (3.0%)	4 (4.1%)		2 (2.2%)	2 (5.6%)	
Professionals' response to needs			0.80*			0.91*
Very well responded	22 (66.7%)	67 (69.1%)		68 (75.6%)	27 (75.0%)	
Reasonably responded	8 (24.2%)	22 (22.7%)		21 (23.3%)	8 (22.2%)	
Not at all	3 (9.1%)	8 (8.2%)		1 (1.1%)	1 (2.8%)	
Emotional support by professionals			0.61*			0.58*
Very well supported	24 (72.7%)	66 (68.0%)		73 (81.1%)	28 (77.8%)	
Adequately supported	8 (24.2%)	27 (27.8%)		17 (18.9%)	6 (16.7%)	
Inadequately supported	1 (3.0%)	4 (4.1%)		0	2 (5.6%)	
Feelings of safety			0.40*			0.69*
Very safe	26 (78.8%)	69 (71.1%)		68 (75.6%)	26 (72.2%)	
Reasonably safe	6 (18.2%)	24 (24.7%)		21 (23.3%)	9 (25.0%)	
Not safe enough	1 (3.0%)	4 (4.1%)		1 (1.1%)	1 (2.8%)	
Concerns about child's condition			0.51*			0.36*
No concerns	22 (66.7%)	60 (61.9%)		56 (62.2%)	18 (50.0%)	
Some concerns	11 (33.3%)	32 (33.0%)		21 (23.3%)	15 (38.9%)	
Many concerns	0	5 (5.2%)		13 (14.4%)	4 (11.1%)	
Duration until first contact with child			0.12*			0.92*
Not long	32 (97.0%)	85 (87.6%)		82 (91.1%)	33 (91.7%)	
Quite long	1 (3.0%)	7 (7.2%)		5 (5.6%)	2 (5.6%)	
Very long	0	5 (5.2%)		3 (3.3%)	1 (2.8%)	
Anxiety (median, IQR) (high= more anxious)	31.00 (21.50-38.50)	27.00 (22.05-33.00)	0.39*	28.50 (23.00-36.00)	27.50 (23.00-3100)	0.43*
Satisfaction with care† (median, IQR) (high= higher satisfaction)	38.00 (33.00-41.00)	38.00 (34.50-41.00)	0.97*	39.00 (35.00-41.00)	38.00 (34.25-41.75)	0.44*
Preference for management before childbirth						
Preference for IOL	30 (81.1%)	85 (78.7%)		66 (66.0%)	34 (79.1%)	
Undecided	4 (10.8%)	16 (14.8%)		21 (21.0%)	4 (9.3%)	
Preference for EM	3 (8.1%)	7 (6.5%)		13 (13.0%)	5 (11.2%)	
Preference for management after childbirth						
Preference for IOL	25 (75.8%)	68 (70.8%)		45 (50.0%)	26 (72.2%)	
Undecided	4 (12.1%)	14 (14.6%)		22 (24.4%)	5 (13.9%)	
Preference for EM	4 (12.1%)	14 (14.6%)		23 (25.6%)	5 (13.9%)	

** Mann Whitney U test*

† Satisfaction with care consists of: appropriate and adequate control over care, person(s) responsible for care caring and compassionate, problems have been dealt with effectively, needs addressed with appropriate consideration, overall organization of care appropriate, would choose the same type of care for next pregnancy

IQR: Inter Quartile Range

IOL: Induction of labour

SOL: Spontaneous onset of labour

EM: Expectant management

We examined possible associations between pregnancy management allocation, parity, SES, actual onset of labour, mode of delivery, maternal anxiety and adverse perinatal and/or maternal outcomes and women's birth experience (data not shown). Anxiety (both anxiety in pregnancy as well as anxiety after childbirth) and mode of delivery were associated with the quality of the birth experience. Higher scores of anxiety were associated with a less positive birth experience; one unit higher on the anxiety score reduced scores on birth experience with 0.3% (β -0.003 (95%CI: -0.005 to -0.002; p-value <0.001). Because the variable 'mode of delivery' had a significant effect in univariate analysis (data not shown), interaction between anxiety and mode of delivery was tested (Table 4). We found a statistically significant interaction between anxiety and mode of delivery (β -0.004 (95%CI: -0.009 to 0.00; p-value 0.03). Anxiety is a stronger predictor of a less positive birth experience if delivery had taken place by caesarean section, with a score reduction of 0.7% per higher unit on the anxiety score (β -0.007). There was no association with parity and SES, the association with actual onset of labour almost reached statistical significance with a p-value of 0.05. No adverse perinatal outcomes occurred in this survey cohort of the INDEX RCT. Adverse maternal outcomes occurred in 9.4% in the IOL group and in 7.5% in the EM group; we did not find an association with the overall birth experience (p-value 0.44) Because allocation (to IOL or EM) and onset of labour were closely interrelated and actual onset of labour was considered a more relevant outcome for clinical practice, allocation was excluded in the interaction analysis (Table 4).

TABLE 4. Association between patient characteristics and birth experience as estimated in the linear regression model.

Variables	ß	*P value*	95% Confidence Interval for ß	
			Lower Bound	Upper Bound
(Constant)	1.070	<0.001	0.992	1.148
Social economic status	-0.004	0.61	-0.020	0.012
Parity	0.021	0.14	-0.007	0.049
Onset of labour	-0.027	0.05	-0.055	0.000
Mode of delivery (vaginal or CS)	0.001	0.99	-0.138	0.140
Anxiety	-0.003	<0.001	-0.005	-0.002
Adverse maternal outcome	-0.021	0.44	-0.073	0.032
Interaction mode of delivery - anxiety	-0.004	0.03	-0.009	0.000

There was a change in the preference of women regarding management in late-term pregnancy after childbirth in the whole cohort (p-value < 0.001); 74.7% of women had a preference for IOL before childbirth versus 64.3% after childbirth, while 9.7% of the women had a preference for EM before childbirth versus 18.0% after childbirth. In total, 72 women changed their preference after childbirth: 8% (n=20) changed

their preference towards IOL and 20% (n=52) towards EM. We also observed a small significant difference between pre- and post childbirth management preference within both management groups. In the group of women randomised to IOL the percentage of women who preferred IOL after childbirth decreased from 79.3% to 72.1% while the percentage of women with a preference for EM increased from 6.9% to 14.0% (p-value 0.04). In the group of women randomised to EM the preference for IOL decreased from 69.9% to 56.3% % with an increase in the preference for EM from 12.6% to 22.2% (p-value 0.008) (Table 2).

DISCUSSION

Overall birth experience in this study was comparable between women allocated to elective IOL at 41 weeks or EM until 42 weeks. Maternal anxiety before and two months after childbirth was associated with a less positive birth experience, with the association stronger after caesarean section. In this RCT population, a vast majority of women preferred elective IOL, both before childbirth (74.7%) and two months after childbirth (64.3%). A small but significant proportion of women changed their preference towards EM after childbirth.

Strengths and limitations

A limitation of our study was the distribution of the questionnaires in a subsample of women participating in the INDEX RCT and not among all randomised women. A smaller sample size was needed for a representative survey compared to the sample size needed for the INDEX RCT (N=1801), which evaluated the effect of induction of labour versus a policy of EM on adverse perinatal outcome. However, the study population concerned a random sample during time of inclusion and the response rate was high (88%). Furthermore, baseline characteristics were comparable with the INDEX RCT. Our actual sample size was lower than expected considering the many participating centres in the RCT but not all centres actively distributed the survey's among the women who were included in the trial. This could have affect the outcomes of the comparison of birth experiences between the study groups due to a limited sample size. For women's preferences we could demonstrate clinical relevant differences between groups.

The incidence of adverse perinatal outcomes in a low risk population is usual low. In this study population we did not have any cases of adverse perinatal outcomes. Therefore, it was not possible to assess the effect of adverse perinatal outcomes

on women's birth experience, which could be negatively affected in case of fetal or neonatal death or severe morbidity.

Another limitation of this study is that the women participating in the RCT could be considered as a self-selected population: at the time of inclusion for the INDEX RCT it was not possible for all women to choose for elective IOL at 41 weeks because the national guideline advised to start induction of labour for low risk women at a gestational age of 42 weeks. Only by participation in the RCT they had a 50% chance to receive elective IOL, therefore a large proportion of the women in this cohort had a preference for IOL at 41 weeks. The majority of women who refused randomisation had a preference for EM [2]. Also, when women completed the questionnaires at a gestational age of 41 weeks, they already knew whether they were allocated to IOL or EM. This may have affected women's opinion.

In the EM group approximately 40% of women were transferred from primary to secondary care during labour. Referral during labour is associated with a more negative birth experience, [25]. Medical interventions, women's perceived health after childbirth and experiences with the health care process were the most important factors affecting the birth experience of referred women [26]. In our analysis we have taken medical interventions and women's experiences with the health care process into account. We also assessed women's perceived health using the validated EQ5D questionnaire but we found no differences between the groups.

A strength of this study is that we first performed intention-to-treat analysis of women's experiences in the allocated IOL and EM groups, and subsequently within both management groups according to actual onset of labour (spontaneous or induction).

Another strength is that we have used two validated tools to assess women's birth experience; the LADY-X questionnaire which was developed using the outcomes that women themselves considered as the most important birth outcomes and the SSQ evaluating satisfaction and experience with care in pregnancy and after childbirth [18, 27]. Both questionnaires had comparable results indicating a high internal validity.

Interpretation

Overall, most women reported a positive birth experience, which is in concordance with other studies [9, 16]. The results of our study suggest that there is no difference in birth experience between women allocated to a policy of IOL at 41 weeks compared to women allocated to EM until 42 weeks. In a similar study (survey alongside RCT)

of Heimstad et al. (N=508), 84% of women in whom delivery was induced reported a positive labour induction experience. Women randomised to IOL experienced shorter duration of labour, but more intense contractions compared to women randomised to EM [16]. However, the questionnaires used by Heimstad et al were not comparable to our questionnaires, we did not assess "labour induction experience" and neither did we examine duration and intensity of labour, we asked women to evaluate the whole birth experience. We found that maternal anxiety before and after childbirth, was associated with women's birth experience, with a stronger association after caesarean section. A recently published longitudinal study among 167 women confirmed the association of anxiety with birth experience [28]. Women's experiences after IOL have been described in more studies [7].

In our study more women initially preferred IOL. The study of Heimstad et al. also found that most women in their population preferred IOL at 41 weeks [16]. A small proportion of women in both allocated groups changed their preference after giving birth, which indicates that preference for either strategy cannot be considered as a static characteristic of women [12].

Childbirth experience is an important patient reported outcome in contemporary medicine [29]. Therefore, for women approaching a gestational age of 41 weeks who have to balance the managements options elective IOL and EM, not only risks and benefits are relevant, but also the (expected or previous) childbirth experience and women's preference for a strategy [30-32]. In a recent individual patient data meta-analysis on the comparison of elective induction at 41 weeks versus expectant management until 42 weeks, a benefit of IOL at 41 weeks was only found for nulliparous women, not for multiparous women [3]. With this information and the personal preference together with the previous and/or expected experience, women and their counsellors can discuss the management options so that women can make a balanced decision for the management strategy in late-term pregnancy.

Future research

Considering the importance of patient reported outcomes, including experience besides clinical outcome measures, future research on management strategies in late-term pregnancy should include both. Owing to the fact that preferences for management strategies differ between women and in our study the majority of women had a preference for IOL, women's experiences and preferences should also be assessed in a population where women's preference for either induction or a strategy of EM is more balanced [33].

CONCLUSION

In our study we found no major differences in birth experience between women who were randomised for IOL at 41 weeks or a policy of EM until 42 weeks. In both groups, the vast majority of women had a positive birth experience. Maternal anxiety before and two months after childbirth, was associated with a less positive birth experience, with a stronger association after caesarean section. In this study population most women preferred induction of labour, however after childbirth a small proportion changed their preference towards EM.

The results of this study may provide caregivers with more insight in the different aspects of birth experience, and the association of anxiety with women's birth experience. The awareness of differences between women and their preferences could help caregivers in the counselling process of women who have to make an informed choice for either induction of labour or expectant management in late-term pregnancy.

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SUPPLEMENT

SUPPLEMENTARY TABLE 1. Questionnaires

Questionnaire	Questions / aspects	Response categories
Lady-X **(birth experience)** **After birth**		-"good", -"sufficient" -"insufficient".
	Availability of competent professionals during labour	
	Information provided during labour	
	Professionals' responses to women's needs during labour	
	Professionals' emotional support of women during labour	
	Feelings of safety during labour	
	Concerns about child's condition during labour	
	Duration until first contact with the child after childbirth	
SSQ **(satisfaction with care)** **After birth**		7-point Likert scale: strongly disagree - strongly agree
	Experience has shown that I can have appropriate and adequate control over my care	
	The person(s) responsible for my care are/ were caring and compassionate	
	Problems that have arisen up to now have not been dealt with effectively.	
	My needs have been addressed with appropriate consideration for my time	
	The overall organization of my care has not been appropriate	
	I would choose the same type of care for my next pregnancy	
Preference **Before and after birth**		
	<u>At 41 weeks (before childbirth):</u> What management strategy would you prefer if you could choose? <u>2 months after childbirth:</u> If you had the choice between IOL at 41 weeks or EM in a future pregnancy, what would you choose?	- certainly induction at 41 weeks - probably induction at 41 weeks - don't know - probably EM until 42 weeks - certainly EM until 42 weeks
	Why would you choose this?	(open question)
	What is the main reason for this choice?	-"pregnancy takes too long" -"to know what to expect" -"a safe feeling" -"this is how it happened in my social environment" -"want my community midwife as lead professional" -"like to give birth as natural as possible" -"other reason"
STAI **(anxiety)** **Before and after birth**	20 statements which evaluate how women feel	-"not at all" -"somewhat" -"moderately so" -"very much so"

CHAPTER 7

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis explores perinatal and maternal outcomes as well as maternal perspectives of a policy of induction of labour at 41 weeks compared to expectant management until 42 weeks, in women with low-risk pregnancies. With the results of these studies, caregivers can counsel women approaching a gestational age of 41 weeks. Women can use this evidence based information to make an informed choice for the management strategy that fits them best. Furthermore, the results of these studies will add to the body of knowledge of late-term pregnancy that can be used in guidelines for the management in late-term pregnancy.

GENERAL DISCUSSION

The 41-42 weeks dilemma

After publication of the Cochrane review in 2006 on induction of labour to improve birth outcomes at or beyond term, many guidelines recommended to offer induction of labour after a gestational age of 41 weeks [1-10]. These recommendations are, however, based on trials comparing different timeframes, which we showed in the review on timing of induction of labour (chapter 2) [11]. Only one trial compared induction of labour at 41 weeks with expectant management until 42 weeks. In this trial of Gelisen et al. different techniques of induction of labour were compared, the study was not powered for perinatal outcomes [12]. No other trials were available and high quality evidence was lacking for the recommendation to induce labour at 41 weeks instead of inducing at 42 weeks [11]. In the Netherlands uncomplicated pregnancy until 42 weeks is considered as low-risk and expectant management until 42 weeks has been common practice until recently. After the Cochrane publication the Netherlands Society of Obstetrics and Gynaecology released a new guideline for the management of post-term pregnancy. It recommended to inform women of the risks of continuing pregnancy beyond 42 weeks, and in case women would request elective induction of labour between 41 and 42 weeks, this could be performed. No recommendation was given on the exact timing of induction of labour [9]. The discussion on the optimal timing of induction of labour continued, which increased the demand for more evidence for either strategy. This evidence was expected to come from a trial with adequate sample size among low-risk women. In the Netherlands, with its strict division between low- and high-risk pregnancies, it was assumed that a policy of expectant management would not give more adverse perinatal outcomes than a policy of elective induction. Besides clinical outcomes, also women's perspectives like childbirth experience and preferences were considered essential for the counselling of women approaching late-term pregnancy. All these aspects were taken into account

in the design of the INDEX-study.

Interpretation of the results

Clinical outcomes

Most pregnancies beyond 41 weeks will end with the birth of a healthy baby after either induction of labour at 41 weeks (98.3%) or expectant management until 42 weeks (96.9%), as was shown in the INDEX trial (chapter 3) [13]. Elective induction at 41 weeks significantly reduced the low risk of adverse perinatal outcome with 1.4% (from 3.1% to 1.7%) but there was no significant difference in severe adverse perinatal outcome (0.4% and 1.3% respectively), the study was not powered for the low incidence of severe perinatal outcome. No differences in caesarean section rates or maternal outcomes were found. In an individual participant data meta analysis (IPD-MA) (chapter 4) we combined data from the INDEX trial and the SWEPIS trial, a recent Swedish trial with the same comparison on low-risk women [13, 14]. The primary outcomes (a composite of adverse perinatal outcomes) of both individual trials were not comparable, therefore we altered some of the components of the primary outcome in order to be able to align both studies. This resulted in a composite of severe adverse perinatal outcome, and as a result avoided former comments of surrogate endpoints. After elective induction at 41 weeks the overall composite of severe adverse perinatal outcome was significantly reduced compared to expectant management, though this reduction was only seen in nulliparous women. For multiparous women there were very few adverse perinatal outcomes, with the point estimate in favour of expectant management, though the incidence was too low in both groups to assess any difference. The increased risk of adverse perinatal outcomes only for nulliparous women was also found in a recent Swedish Medical Birth Register study [15]. Perinatal mortality is an important component of adverse perinatal outcomes and the rate of fetal mortality increases from 41 weeks onwards [16, 17]. In the IPD-MA eight out of nine cases of perinatal mortality concerned fetal mortality. Nevertheless, the magnitude of the absolute risk of perinatal mortality —as was shown in the IPD-MA— is uncertain, therefore the generalisability for the Netherlands can be questioned. First, due to the early stopping of the SWEPIS trial the risk could be overestimated. Second, expectant management in the SWEPIS trial was not comparable to Dutch regular care in late-term pregnancy. When a pregnancy is managed expectantly in the Netherlands it is usual care to perform cardiotocography and transabdominal ultrasound in late-term pregnancy [18]. In approximately 59% of the women in the SWEPIS trial (all from the outer Stockholm area) no additional monitoring was performed in pregnancies from 41 weeks onwards. All perinatal mortality occurred outside the Stockholm area. Although there is no difference between the overall incidence of perinatal mortality

in the Netherlands and Sweden (2018: 0.49% and 0.47%, respectively) [18], the rates of perinatal mortality in the INDEX trial were 0.11% in induction group versus 0.22% in expectant management group and in the SWEPIS trial 0% in induction group versus 0.44% in expectant management group. The perinatal mortality rate in the IPD-MA was 0.04% in induction group versus 0.35% in expectant management group. Perinatal mortality occurred only in the outer Stockholm area (0.73%; 6/822). The fetal deaths in the INDEX trial could not be explained, the only clues were a small for gestational age (5th to 10th centile) diagnosis for one neonate, and one placenta showed signs of chorioamnionitis. According to the reporting in the SWEPIS trial of the fetal deaths, one neonate was post mortem diagnosed with a non-lethal cardiac malformation and one neonate was small for gestational age (centile unmentioned), the neonatal death was caused by hypoxic ischemic encephalopathy in a large for gestational age neonate (centile unmentioned). For all other cases of perinatal mortality no reason was found. An in-depth analysis of these cases using audit techniques could give more insight in possible mechanisms, but this has not been performed yet. The proportion of induction on fetal indication in the expectant management groups differs substantially between INDEX and SWEPIS (15.6% versus 3.9%), this could be a reflection of the difference in fetal monitoring strategies.

The caesarean section rate was equal in both groups, in the INDEX trial as well as in the IPD-MA. This is in line with the results of other trials where the risk of caesarean section was equal or decreased after induction of labour [19-21]. But these trials had a high- or medium-risk population. In the largest trials of these (N=6106), elective induction at 39 weeks was compared with expectant management between 40+5 and 42+2 weeks of gestation [19]. The rate of caesarean section was significantly lower in the induction group (18.6%), compared to the expectant management group (22.2%), no differences in perinatal outcomes were observed. Whether this population was comparable to the low-risk Dutch population is questionable: the median BMI was 30.5, 40.8% of women were single, 48.7% was not employed, and only 45.9% had a private insurance for prenatal care. Whether the provided care could be compared to Dutch care is unknown. However, some cohort studies concluded that the caesarean section rate was higher after elective induction compared to spontaneous onset of labour [15, 22-24]. A possible explanation could be that in RCTs intended management strategies are compared, whereas in cohort studies the actual start of labour was taken into account.

Additional differences in secondary outcomes were hypertensive disorders which occurred more in the expectant management group, though whether this resulted in

more cases of clinical relevant preeclampsia is not clear yet. In the induction group more pain treatment was used during labour. Though this may not be considered as an adverse outcome, it is known that induced labour is likely to be experienced as more painful than spontaneous labour [25].

Women's perspectives

In two studies we assessed women's preferences for management strategy in late-term pregnancy. In the first survey we assessed preference and motivations of women with a gestational age of 41 weeks from both cohort and trial. Induction of labour at 41 weeks was preferred by 45% of these women (chapter 5) [26]. In the second survey we assessed birth experience and preference for a future pregnancy after childbirth of women who had participated in the trial, 75% of these women preferred induction at 41 weeks (chapter 6). Women's preference for elective induction or expectant management was dependent on the studied population. From all women who declined participation in the INDEX trial only 14% preferred induction at 41 weeks, which is in contrast to the 75% of all women who agreed to participate in the INDEX trial and preferred elective induction [13]. This is in line with other studies in which not all women prefer the same management strategy [27, 28]. We found in our survey on women's preference for either management strategy in late-term pregnancy clear evidence that women who preferred induction at 41 weeks had higher anxiety scores and reported more quality of life problems than women who preferred expectant management (chapter 5) [26]. In this survey women participating in both trial and cohort were asked for their preference at a gestational age of 41 weeks (45% preferred induction at 41 weeks, 42% preferred expectant management and 12% was undecided), and for the motivations of their preference in pregnancy. In open and tick box questions women could indicate the reason for their preference. Women who preferred induction reported a "safe feeling" (41.2%),"pregnancy taking too long" (35.4%) and "knowing what to expect" (18.6%) as main arguments. Stress and worry, (mis-)trust in their own body, the feeling of 'time is up' and mental exhaustion were themes that emerged from other studies [29-31]. For women preferring expectant management, the main reason was "wish to give birth as natural as possible" (80.3%), which was also described in other studies [29, 31-33]. In our survey, women gave a clear explanation of their preferences. In the arguments for a preferred management strategy we found large variations between women; every woman has a different balance of arguments. With this large variety in reasons for women's preference for a management strategy, a woman-centred approach seems the most appropriate care since this will imply individual counselling and women's involvement in the decision making process [29]. In the survey alongside the trial, the majority of women (75%) had a preference for

elective induction at 41 weeks. Since expectant management was usual care at the time of the trial, elective induction was only possible after randomisation in most participating hospitals (chapter 6). After childbirth women's preferred management strategy for a next pregnancy was also more in favour of induction at 41 weeks. The proportion of women preferring elective induction at 41 weeks in a future pregnancy, however, was smaller compared to the proportion of women preferring induction in pregnancy. No difference in birth outcomes was observed between women who had changed preference after childbirth and women who had not changed their preference. The change in preference suggests that some women had experiences that resulted in a greater preference for expectant management in the future. The key issue is that preferences may change within and between women before and after the experience of childbirth (chapter 5 and 6).

In the survey evaluating the birth experience of women participating in the INDEX trial, we focused on women's experience with the perinatal period and the quality of care during childbirth, the communication with caregivers and the information provided. Women reported good birth experience both after induction at 41 weeks and after expectant management until 42 weeks (chapter 6). Most women in this survey preferred elective induction at 41 weeks before childbirth. In other studies women were more ambiguous about postdate induction of labour [34-37]. The different aspects of birth experience and women's opinions on induction of labour have been evaluated in several reviews [31, 32, 38, 39]. From these reviews it can be concluded that women need tailored care and involvement in the decision process regarding induction of labour. Furthermore, women are in need of support in the challenging period of (approaching) childbirth, also women who prefer no interventions during labour —unless necessary— need support.

We found that women with higher levels of anxiety in pregnancy prefer more often elective induction of labour and have more negative birth experience, especially after a caesarean section (chapter 5 and 6). The association between a more negative birth experience and both higher levels of maternal anxiety and caesarean section was described elsewhere [40]. Anxiety is known to influence women's preference for intervention; higher levels of anxiety in pregnant women may contribute to greater use of interventions in pregnancy and labour like induction of labour and pain relief [41]. Anxiety during pregnancy is an often occurring phenomenon, with concerns about the forthcoming birth and the health of the baby as important factors [42, 43]. Causes of anxiety in late-term pregnancy and the association between anxiety and birth experience need further exploration.

Methodological considerations

In this thesis we addressed the 41-42 weeks dilemma with clinical outcomes from randomised trials and women's perspectives from surveys. The main problem in studies evaluating rare clinical outcomes like perinatal mortality or severe perinatal morbidity is the difficulty to perform adequately powered trials with adequate sample sizes to study relevant subgroups like e.g. nulliparous and multiparous women. For this reason often composite adverse outcomes are chosen which are frequently questioned because some components, like Apgar score, are considered surrogate endpoints. The size of the INDEX trial was also too small to assess the risk of perinatal mortality. With the IPD-MA we created a larger population in which we found a significant risk difference for perinatal mortality as well as for severe adverse perinatal outcome. Nevertheless, the magnitude of the risk of perinatal mortality is still unclear due to problems with the generalisability because of the early termination of the SWEPIS study, the lower risk of perinatal mortality in the expectant management group of the INDEX study compared to the SWEPIS trial and the lack of monitoring in the expectant management group of the SWEPIS trial in the outer Stockholm region, which accounted for 59% of the inclusions.

Another issue of generalisability is the skewed distribution of women's preferences in the studied populations. The majority of women who participated in the INDEX trial had a preference for induction at 41 weeks. Women who preferred induction may have a different risk profile compared to women who prefer expectant management, although baseline characteristics were similar. Furthermore, birth experience was assessed in a population of women who mostly preferred induction. This may have affected the results.

The sample size of the birth experience study was perhaps too small to detect some relevant differences between groups, we found no significant difference between the groups. For our survey studies we asked the participating centres in a certain time frame to invite all women who were randomised to fill out the questionnaires, however, less surveys were distributed than expected. Distribution of the survey among all participants of the trial and cohort would have enabled detection of possible differences and/or the performance of subgroup analyses on parity, women's preference and onset of labour.

Implications for practice

The implication for obstetrical care and counselling is the fact that clinical outcomes and women's perspectives are important issues to discuss with women when they have

to decide on the management strategy to follow in late-term pregnancy. In a process of shared decision making women are actively engaged in decisions about her own care. This is considered an important component in good maternity care, which may reduce negative experiences [29, 31, 38, 44, 45]. Shared decision making starts with the principle that the decision making power lies with the mother [46]. In this process first the caregiver explains to the woman that a decision needs to be made and her opinion is important in this [47]. Secondly, pros and cons of induction and expectant management are explained, tailored to the personal profile of the pregnant woman. Third, women's preferences and other aspects which are known to influence women's birth experience can be discussed and weighed, taking into account women's values and risk perception. The caregiver supports the woman in her deliberation. Finally, caregiver and woman discuss the woman's wish to make the decision, they make or defer the decision, and discuss follow-up.

When more women are offered elective induction, it could have implications for the organisation of care. In 2019 approximately 28,000 women had reached the gestational age of 41 weeks in the Netherlands, of whom 13,000 nulliparous women [48]. About 30% of women have been induced between 41 and 42 weeks of gestation. If all, or a part of these women would be induced at 41 weeks many logistic issues should be considered like capacity of care, continuity of care and the possibility of redistribution of primary and secondary care in case of a low-risk elective induction [49].

The results of these studies give a clear view on the 41-42 weeks dilemma. Information for women on clinical outcomes could be provided with info graphs, decision aids and other tools, so that caregivers could provide this information in an understandable, uniform and unbiased way. Because caregivers have their own preferences and risk perception on this subject, they should be aware of the impact of their view on the weighing process of the women who they counsel. The use of unbiased information tools will help caregivers in the counselling process.

Implications for research

Since a large proportion of the eligible women for inclusion in the INDEX trial declined randomisation we also collected data of these women in order to compare baseline characteristics and outcomes of both groups. In other cohort studies a spontaneous onset of labour was associated with a lower caesarean section rate, analysis according to actual onset of labour and parity could give more insight in the possible contribution of induction or spontaneous onset of labour on the caesarean section rate. Women who participated in the INDEX trial and women who did not want to be randomised

differ in their preference for elective induction or expected management. This may have impact on both clinical outcomes and women's birth experience. Results of the INDEX cohort study are to be expected soon. Further exploration of women's perspectives at the border of late-term pregnancy is needed in order to better understand women's values.

A cost effectiveness study on induction of labour at 41 weeks versus expectant management until 42 weeks will give insight in the financial effects of both management strategies. The results of this study will follow.

Future research should also focus on which individual women and children are at risk for adverse outcomes. A treatment selection marker analysis on data from the existing trials could explore the likelihood of a pregnant woman and her baby will benefit from induction at 41 weeks. Furthermore, the possible difference in risk according to fetal sex could be explored. In a non pre-specified subgroup analysis of the IPD-MA male fetus had a significant higher risk on adverse perinatal outcome than girls with a policy of expectant management. Though, the interaction was non-significant and in the cases with perinatal mortality fetal sex did not differ in this subgroup analysis, the increased risk which was found warrants further investigation.

Moreover, benefit is expected from studies focusing on predictive biomarkers for spontaneous onset of labour, as well for adverse perinatal outcomes.

Patient preference trials could give more insight in outcomes in a real-world situation. Taking into account women's preference for a management strategy in a research setting will show the effects for women who choose the strategy of their preference, this will reflect the effect in daily practice. Possible differences in outcomes between preferred management strategies in the 41-42 weeks timeframe could be assessed for both nulliparous as multiparous women, or other subgroups based on fetal sex. The process of shared decision making could be included in the evaluation in order to get more insight in the effects of counselling of women approaching late-term pregnancy.

CONCLUSION

With the studies in this thesis we have tried to add evidence to the body of knowledge of late-term pregnancy.

When a woman reaches a gestational age of 41 weeks, she needs to be informed on the current evidence of the management options in late-term pregnancy using absolute risks according to parity. These options, with their benefits, harms and uncertainties, should be discussed during the counselling process. Since the absolute risks are small, women can be supported in their choice for either a policy of elective induction of labour or expectant management, in line with her own values and preferences.

The results of these studies may support caregivers in the counselling process, and are suitable to use in the development of guidelines for late-term pregnancy.

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CHAPTER 8

SUMMARY

This thesis aims to assess clinical outcomes as well as to explore women's perspectives on a policy of induction of labour at 41 weeks versus expectant management until 42 weeks.

Chapter 2 describes the identification of the existing evidence for elective induction of labour at 41 weeks by reviewing reviews on the comparison of induction of labour at 41 weeks versus expectant management until 42 weeks. The risk of adverse perinatal outcomes increases gradually beyond term and more steeply after 42 weeks. Reviews concluded that induction of labour at or beyond 41 weeks will reduce adverse perinatal outcome without an increase in caesarean section, but were not specific on the exact timing. Many (22) trials have been performed to compare different timings of induction, but the timeframes of comparison were heterogeneous. Only one trial with limited sample size compared induction of labour at 41 weeks with expectant management until 42 weeks before publication of the INDEX trial. The existing reviews did not provide the needed evidence for a recommendation to induce labour at 41 weeks instead of 42 weeks.

Chapter 3 presents the results of the INDEX trial; we analysed perinatal and maternal outcomes in a randomised non-inferiority trial with low risk women comparing elective induction of labour at 41 weeks with expectant management until 42 weeks. Non-inferiority was not proven, instead the risk of adverse perinatal outcome in the expectant management group was significantly increased, though absolute risks were low. Because the chances of a good outcome were high in both groups either induction at 41 weeks and expectant management until 42 weeks are options that can be supported. With the results of this study women can decide what management strategy would fit them best.

Chapter 4 presents the results of an individual participant data meta analysis of randomised controlled trials comparing induction of labour at 41 weeks with expectant management until 42 weeks, and the identification of possible relevant subgroups at risk. Individual participant data were available from two trials. The risk on severe adverse perinatal outcomes was reduced after induction of labour at 41 weeks for nulliparous women, not for multiparous women. The magnitude of the risk of perinatal mortality is still unclear, due to early stopping of one of the trials and problems with generalisability. The absolute risks according to parity can be used to inform women approaching a gestational age of 41 weeks in the process of shared decision making.

Chapter 5 reports on what management strategy in late-term pregnancy women want and why. To get an insight in women's preferences we asked them at 41 weeks if they would prefer elective induction of labour or a policy of expectant management in late-term pregnancy. The most important reasons to prefer elective induction at 41 weeks were a "safe feeling", "pregnancy taking too long" and "knowing what to expect". Women who prefer expectant management report as most important reason that they want to deliver as natural as possible. Some women are indecisive what to prefer. Women's personal preferences are beside the risks and benefits of management strategies an important component in decision making.

Chapter 6 evaluates women's experiences and preferences after a policy of elective induction of labour at 41 weeks or expectant management until 42 weeks. In this chapter we assessed birth experience and preference for either management strategy before and after birth of a subset of women who were randomised in the INDEX trial. Most women had a good birth experience, we could not distinguish differences between groups. Increased maternal anxiety is associated with a less positive birth experience, with the association stronger after caesarean section. Women who participated in the trial had more often a preference for induction of labour, therefore in this cohort, the majority of women preferred induction, but after childbirth a small proportion of women changed towards a preference for expectant management.

CHAPTER 9

SUMMARY IN DUTCH
SAMENVATTING IN HET NEDERLANDS

In dit proefschrift zijn zowel studies naar klinische uitkomsten als het perspectief van de vrouw opgenomen waarin een beleid van electieve inleiding bij 41 weken vergeleken werd met een afwachtend beleid tot 42 weken.

Hoofdstuk 2 beschrijft de identificatie en evaluatie van de studies die zijn opgenomen in systematic reviews waarin een beleid van electieve inleiding bij 41 weken wordt vergeleken met een afwachtend beleid tot 42 weken. Het risico op slechte perinatale uitkomsten stijgt gradueel na de à terme datum, met een scherpere stijging na 42 weken. Reviews concludeerden dat een inleiding vanaf 41 weken het risico op slechte perinatale uitkomsten reduceert, zonder een stijging van het sectio percentage. Echter, de exacte timing van de inleiding wordt daarbij niet nader gespecificeerd. De geïncludeerde trials vergelijken verschillende momenten van inleiding met verschillende termijnen van afwachten. Slechts één trial met een beperkte studiegrootte vergeleek inleiden bij 41 weken met een afwachtend beleid tot 42 weken voor publicatie van de INDEX trial. De bestaande reviews gaven ten tijde van publicatie onvoldoende bewijs voor het adviseren van een inleiding bij 41 weken in plaats van afwachtend beleid tot 42 weken.

Hoofdstuk 3 bevat de perinatale en maternale uitkomsten van de INDEX trial, een gerandomiseerde, gecontroleerde non-inferiority trial. In deze trial werd een electieve inleiding bij 41 weken vergeleken met een afwachtend beleid tot 42 weken bij laagrisico zwangeren. Non-inferioriteit werd niet aangetoond, het risico op een slechte perinatale uitkomst was significant verhoogd in de afwachtgroep maar het absolute risico was klein. Omdat de kans op een goede uitkomst groot was in beide groepen, kan zowel de keuze voor een inleiding bij 41 weken als voor een afwachtend beleid tot 42 weken ondersteund worden. Met de resultaten van deze studie kunnen vrouwen een keuze maken voor het beleid dat hen het beste past.

Hoofdstuk 4 geeft de resultaten weer van een individuele participant data meta analyse van gerandomiseerde studies die inleiden bij 41 weken vergeleken met een afwachtend beleid tot 42 weken. Mogelijke relevante subgroepen met een verhoogd risico op een slechte uitkomst werden geïdentificeerd. Data van individuele participanten waren beschikbaar van twee studies. Bij nulliparae was het risico op een slechte perinatale uitkomst verlaagd na een inleiding bij 41 weken maar niet bij multiparae. De grootte van het risico op perinatale sterfte blijft onduidelijk vanwege het voortijdig stoppen van één van beide studies en systematische beleidsverschillen in de controlegroep van deze studie. De absolute risico's die passen bij de pariteit kunnen gebruikt worden om vrouwen te informeren tijdens het proces van gezamenlijke besluitvorming wanneer

zij een zwangerschapsduur van 41 weken naderen.

Hoofdstuk 5 beschrijft welk beleid in de laat terme zwangerschap vrouwen prefereren en de redenen hiervoor. Om inzicht te krijgen in de voorkeur van vrouwen hebben wij bij een zwangerschapsduur van 41 weken gevraagd of zij een electieve inleiding of een afwachtend beleid prefereerden. De meest belangrijke reden voor een voorkeur voor inleiding waren "een veilig gevoel", "de zwangerschap duurt te lang" en "dan weet ik waar ik aan toe ben". Vrouwen die een voorkeur hadden voor een afwachtend beleid gaven als belangrijkste reden dat zij zo natuurlijk mogelijk wilden bevallen. Sommige vrouwen gaven geen voorkeur aan. De persoonlijke voorkeur van de vrouw is een belangrijk onderdeel in de besluitvorming naast de mogelijke risico's of voordelen van een beleid.

Hoofdstuk 6 evalueert de bevalervaringen en beleidsvoorkeuren van vrouwen die meededen aan het INDEX vragenlijst onderzoek en waren gerandomiseerd voor electieve inleiding bij 41 weken of een afwachtend beleid tot 42 weken. De meeste vrouwen hadden een goede bevalervaring, er was geen verschil in uitkomst tussen de twee groepen. Verhoogde maternale angst is geassocieerd met een slechtere bevalervaring, deze associatie is sterker na een sectio. Vrouwen die deelnamen aan de trial hadden vaker een voorkeur voor inleiden bij 41 weken, ook in dit cohort. Postpartum veranderde een klein deel van deze vrouwen hun voorkeur naar een afwachtend beleid.

CHAPTER 10

ADDENDUM

ABBREVIATIONS

BMI	body mass index
CAMO	composite adverse maternal outcome
CAPO	composite adverse perinatal outcome
CS	caesarean section
EDD	estimated due date
EM	expectant management
GA	gestational age
ICD	international classification of diseases
IOL	induction of labour
IPD-MA	individual participant data meta analysis
IQR	inter quartile range
ITT	intention to treat
LADY-X	labor and delivery index (questionnaire on birth experience)
MAS	meconium aspiration syndrome
NICU	neonatal intensive care unit
NNT	number needed to treat
OASIS	obstetric anal sphincter injuries
RCT	randomised controlled trial
SES	socio-economic status
SOL	spontaneous inset of labour
SSQ	six simples questions (questionnaire on satisfaction of care)
STAI	state-trait anxiety inventory for adults (questionnaire on anxiety)

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PORTFOLIO

Courses

2014	Evidence based searching
2014	Searching for a Systematic Review
2015	Scientific writing in English for Publication
2015	BROK (Basiscursus Regelgeving Klinisch Onderzoek)
2016	Practical Biostatistics
2017	Oral Presentation in English
2018	Project Management
2019	World of Science (2 days)
2019	BROK herregistratie

Seminars, workshops and master classes

2012	Consortiumdagen (3 days)
2012	Annual CAPHRI research meeting
2018	Annual CaRe Meeting (APH) (2 days)

Presentations

2015	Poster presentation (Review) ECIC Porto
2016	Oral presentation (Review) Kennispoort Conference
2017	Oral presentation (RCT) ICM Toronto
2017	Oral presentation (RCT) Consortiumdag
2018	Oral presentation (RCT) Kennispoort Conference
2018	Oral presentation (RCT) PAOG Nascholing 'Te klein, te laat, te zwaar'
2019	Oral presentation mini symposium 'Let's talk about risk'
	"The INDEX study: CAPO, SAPO and the perspectives of risk"
2020	Oral presentation (IPDA) Perinatale zorg 3.0

International conferences

2014	ICM Prague
2015	ECIC Porto
2017	SMFM Las Vegas
2017	ICM Toronto

Tutoring, Mentoring

2016-2017	Bachelor student Midwifery AVAG

Supervising

2019	Master student Medicine Radboud University
2020	2 bachelor students Midwifery AVAG

PUBLICATIONS

Alkmark M, **Keulen JKJ**, Kortekaas JC, Bergh C, Van Dillen J, Duijnhoven RG, Hagberg H, Mol BW, Molin M, Van der Post JAM, Saltvedt S, Wikström AK, Wennerholm UB, De Miranda E. Induction of labour at 41 weeks or expectant management until 42 weeks: A systematic review and an individual participant data meta-analysis of randomised trials. *PLoS Med. 2020;17(12):e1003436*

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CURRICULUM VITAE

Judit Keulen werd op 8 november 1970 na een zwangerschapsduur van 41 weken en 3 dagen thuis in goede conditie geboren. Zij was het eerste kind van haar liefhebbende ouders. De basisschool heeft zij gedeeltelijk aan een internationale school in Parijs gevolgd. In 1989 voltooide zij het gymnasium aan het Alberdingk Thijm College te Hilversum. Hierna heeft zij een jaar in California gewoond. In 1993 studeerde zij af aan de Kweekschool voor Vroedvrouwen te Amsterdam (thans Academie Verloskunde Amsterdam Groningen). Zij werkte enkele jaren als waarneemster te Kampen, Elburg en Hoofddorp, waarna zij in 1995 associeerde in een eerstelijns praktijk in Amsterdam. In 2006 verhuisde zij naar Maastricht waar zij sindsdien in de eerstelijn werkt. In 2011 voltooide zij haar Master Verloskunde aan de Universiteit van Amsterdam.

Judit is getrouwd met Ralph Graven, zij hebben samen drie kinderen: Evelien (2002), Matthijs (2004) en Anouk (2006).


41
42