A Randomized Controlled Trial *of* Labor Induction *for* Women Aged *35 or* Over

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On behalf of the 35/39 trial group (Supplementary Appendix Table 1)

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Key words: Induction of labor; stillbirth; cesarean section; maternal age; randomised trial; childbirth experience

ABSTRACT

Background

Women aged 35 years or over have an increased risk of antepartum stillbirth at term. Labor induction would likely reduce stillbirth, but might increase Cesarean delivery, which already is common among older women.

Methods

We conducted a randomized controlled trial involving women in their first pregnancy, aged 35 years or over. Women were randomised to labor induction between 39^{+0} and 39^{+6} weeks or "expectant management", waiting until the spontaneous onset of labor, or until a medical problem arose mandating induction. The primary outcome was Cesarean delivery.

Results

619 women participated. In an intention to treat analysis, there were no significant differences between groups in the proportion of women who had cesarean section (98 (32%) in the induction group versus 103 (33%) in the expectant group (relative risk [RR] 0.99, 95% CI 0.87 – 1.14), or instrumental vaginal delivery (115 (38%) v. 104 (33%), respectively, RR 1.30, 95% CI 0.96 – 1.77). There were no maternal or infant deaths and no significant between group differences in maternal experience or in the frequency of adverse maternal or neonatal outcomes.

Conclusions

Induction of labor at 39 weeks for women of advanced maternal age, as compared with expectant management, had no significant effect on the rate of cesarean section nor adverse short-term effects on maternal or neonatal outcomes. Our trial was not designed or powered to assess effects of this strategy on stillbirth. (ISRCTN11517275)

Introduction

The average age at childbirth in industrialized nations has been steadily increasing for about 30 years[1]. Between 1996 and 2006, births to women aged 35 years or over in the UK rose from 12% to 20% of all births[2]. In 2006, 5.6% of UK live births were to nulliparous women aged 35 years or over.

As compared with younger women, women aged 35 years or over have higher risks of perinatal death, hypertensive disease, gestational diabetes mellitus, placenta praevia and placental abruption[1,3,4]. They are also at increased risk of preterm labor and of bearing macrosomic (>3999g) or low birth weight (<2500g) infants. The women themselves typically believe that their age puts their infant at increased risk[3]. Unsurprisingly, they have higher rates of obstetric intervention.

The Cesarean section rate for nulliparous women in the UK is 38% among those 35 years or over and 50% among those 40 years or over[3]. In nulliparous women, the relationship between maternal age and delivery by emergency Cesarean is linear[5].

Induction at or before the due date in women aged 35 years or over may be beneficial because the gestational age of delivery associated with the lowest cumulative risk of perinatal death is 38 weeks[6]. Nulliparous women have a higher risk of stillbirth than multiparous women for all maternal age groups[7,8]. Induction is currently offered to all women in the UK at 41-42 weeks gestation, when the stillbirth risk is 2 to 3 in 1000[9,10]; older women experience this risk at earlier gestational ages (2.6 in 1000 from 37 weeks onwards)[7]. However, induction carries risks (cord prolapse, uterine hyperstimulation), has a perceived association with Cesarean section and benefits may be offset by longer term adverse child outcomes due to delivery at 'early-term' gestations (37-39 weeks)[11-14].

Some UK obstetricians already induce older pregnant women at the due date (40 weeks) (39% women aged 40-44, 58% women aged 45 and over), but of those who do not, one third are reluctant to offer it for fear of increasing the likelihood of Cesarean delivery, despite believing it would improve perinatal outcomes[15]. However, there is a growing body of evidence that induction of labor

at term for other reasons does not increase Cesarean rates and may even reduce them[16], in which case an effective intervention is being underutilised.

Most trials of induction at or near term have included women with established pregnancy complications, hypertension[17], pre-labor rupture of membranes[18] growth restriction[19], diabetes[20] or macrosomia[21]. The few trials of induction in the absence of pathology[22-25] are relatively small (total n = 1377), date from the 1970s, and may not be applicable to modern obstetric practice. To our knowledge there have been no trials of induction of labor for advanced maternal age. The 35/39 trial was designed to test the hypothesis that induction of labor at 39 weeks among nulliparous women of advanced maternal age would reduce Cesarean delivery.

METHODS

We performed a multi-center randomized controlled trial of induction of labor between 39^{+0} and 39^{+6} weeks gestation or expectant management in nulliparous pregnant women aged 35 years or over. The original and final trial protocols are available on line at NEJM.org. Professor James Thornton and Dr. Kate Walker take responsibility for the accuracy and completeness of reporting and for the fidelity of the report to the study protocol.

Participants

Nulliparous women aged 35 years or over on their expected due date, with a singleton live fetus in a cephalic presentation were recruited between August 2012 and March 2015 from 38 UK National Health Service hospitals and 1 UK primary care trust. Women were ineligible if their pregnancy was complicated by a known lethal fetal congenital abnormality or if they had any contraindications to labor (e.g. evidence of fetal compromise), vaginal delivery (e.g. placenta praevia) or expectant management (e.g. gestational diabetes).

Women with a previous myomectomy, no ultrasound (for gestational age estimation) before 22 weeks, or who had undergone in vitro fertilization using donor eggs were also excluded. The study

was approved by the Derby Research Ethics Committee, and participants gave written informed consent.

Women were randomized at 36^{+0} – 39^{+6} weeks gestation. Randomization was individual, using a 1:1 ratio, based on a computer generated pseudo-random code using random permuted blocks of randomly varying size generated by the Nottingham Clinical Trials Unit. The randomization was stratified by center and maternal age (3 strata: 35-37, 38-39, 40 years or over). After gaining consent, research staff at individual sites logged into an internet based randomization system to access the randomised treatment allocation. Neither participants nor treating clinicians were masked to the allocated group.

Women were randomly allocated to either induction of labor between 39^{+0} and 39^{+6} weeks gestation, or to expectant management i.e. awaiting spontaneous onset of labor unless a situation developed necessitating delivery either by induction or Cesarean. Women randomized to the expectant group were offered induction between 41^{+0} and 42^{+0} (i.e. 7-14 days after the due date), with the exact time determined by their preference and the consultant's usual practice. No additional monitoring prior to 42^{+0} was offered unless it was the consultant's usual practice. If the patient declined the offer of induction at 42 weeks, she was offered a scan for growth and amniotic fluid volume and daily or alternate daily cardiotocography monitoring according to the consultant's usual practice. In the induction group, local policies for induction of labor were followed. Each unit recorded its regimen for use of prostaglandin and oxytocin and Bishop score cut-off for amniotomy, prior to starting the trial. Staff within a given unit were encouraged to use the same induction protocol for all participants and also for those women who for whatever reason required induction in the expectant management group.

The primary outcome was Cesarean delivery. The maternal secondary outcomes were mode of delivery other than Cesarean (vaginal delivery, assisted vaginal delivery, vaginal breech delivery), onset of labor, indication for induction of labor, method of induction of labor, indication for

cesarean section, intrapartum complications, and postpartum morbidity (need for blood transfusion, systemic infection). Postpartum hemorrhage was defined as blood loss of ≥ 500ml at vaginal delivery or ≥ 1000ml at cesarean delivery. The neonatal secondary outcomes were livebirth/stillbirth, birth weight, neonatal intensive care admission, birth trauma and two composite outcomes for serious neonatal morbidity (direct trauma and hypoxic trauma). The composite neonatal direct trauma outcome included subdural hematoma, intracerebral or intraventricular haemorrhage, spinal-cord injury, basal skull fracture, peripheral nerve injury or long bone fracture. The composite neonatal hypoxia outcome included seizures, hypotonia, abnormal level of consciousness, and the use of cooling. The components of the two perinatal composite outcomes (trauma and hypoxia) were prespecified in the statistical analysis plan before the trial allocation code was broken. Data were collected immediately following hospital discharge by the research midwife at each center. Other secondary outcomes included maternal delivery expectation/experience measured by the Childbirth Experience Questionnaire [26] sent one month after the birth. This measure assesses four domains of childbirth experience (Own capacity, Professional support, Perceived safety and Participation). Responses were scored according to the author's instructions (Supplementary Appendix Table 2). Scores on each domain ranges from 0 to 4; higher scores indicate better childbirth experience.

Additional secondary outcomes pertaining to resource use and baseline and postnatal health status were collected to allow a future cost-utility analysis to be performed.

Statistical analysis

The power calculation was based on Cesarean delivery rates in women with singleton cephalic pregnancies in labor at term from a Scottish 2004-2008 cohort of all deliveries which were 23% among women 35-39 years of age and 27% among women aged 40 years or older (Gordon Smith, unpublished data , Dec 2011). Assuming a Cesarean delivery rate of 25% in controls, a sample size of 630 women was calculated to provide 80% power with a two-sided significance level of 5% to test

the hypothesis that induction of labor reduces the cesarean section rate to 16%, a 36% relative reduction (or a 9% absolute reduction).

Participants were analyzed according to their allocated group (intention to treat), regardless of adherence with allocation and according to a pre-specified statistical analysis plan. For the primary outcome , a generalized linear model (with a binomial family and a log link) was used to calculate relative risk and 95% confidence intervals after adjustment for center and age (center was accounted for using robust standard errors using the vce cluster command in Stata). We had planned also a sensitivity analysis to investigate the impact of missing data on our results, but this was unnecessary as there were minimal missing data.

For analyses of mode of delivery (if not by cesarean section), we used a multinomial logistic regression model to calculate relative risk and 95% confidence intervals after adjustment for center and age, using vaginal delivery as the reference group. For intrapartum complications, postpartum morbidity and the serious neonatal morbidity composites, we used the same generalized linear model as for the primary outcome to calculate relative risk and 95% confidence intervals. For individual birth trauma outcomes, we summarized the frequency of these events in each group. For maternal experience measured by the Childbirth Experience Questionnaire (CEQ)[26] a complete case analysis was performed comparing the mean subscale scores and mean total score (average of the 4 individual subscale scores) for women in the treatment group versus women in the control group, using an unpaired t test. A Mann Whitney U test was used to calculate p values. Where there were a few missing items, the half-scale method was used so that when the respondent had answered at least half of the items in the scale, the sum of the scores were divided by the number of answered items [87].

For the primary outcome, a prespecified subgroup analysis by maternal age (35-37, 38-39, 40 years or over) was performed by including an interaction term in the model. An independent Data

Monitoring Committee met regularly throughout the study. No interim analyses were undertaken. All analyses were performed in Stata (version 13).

RESULTS

Recruitment took place between August 2012 and March 2015. Recruitment by trial center is shown in Supplementary Appendix Table 3. One woman in the treatment group withdrew consent for her data to be used. The number of participants randomly assigned to each group and whether they received the intended treatment is shown in Figure 1. Uptake was 13.6% (619/4642). Of the 46% of non-participants (n=1804) who expressed a preference for one of the management strategies, 1595 (88%) preferred expectant management. Non-adherence was more common in the induction group vs expectant arm group (13.4% vs. 5.4%) (Table 2).

The baseline characteristics were similar between groups (Table 1).

There was no significant difference between the induction group and the expectant management group in the frequency of Cesarean section (98 (32%) versus 103 (33%); relative risk (RR) 0.99, 95% CI 0.87 – 1.14). The frequency of assisted vaginal delivery was 115 (38%) in the induction arm, versus 104 (33%) in the expectant management arm (RR 1.30, 95% CI 0.96 – 1.77). There were no significant differences between groups in other maternal outcomes (Table 3) or neonatal outcomes (Table 4). Serious adverse events were reported in 10 (3%) women in the induction group versus 23 (7%) in the expectant management group; most of these were included as predefined secondary outcomes (Supplementary Appendix Table 4). The groups did not differ materially in the methods of induction (Supplementary Appendix Table 5).

Subgroup analysis of the primary outcome by maternal age showed no significant difference in the treatment effects by age (p interaction 0.65), (Table 3).

In total, 512 (83%) women returned the Childbirth Experience Questionnaire. There were no significant differences in subgroup or total CEQ scores (indicating childbirth experience) between the two groups (Supplementary Appendix Table 6).

DISCUSSION

In this multicenter randomized trial involving women aged 35 years or over, induction of labor at 39 weeks gestation, as compared with expectant management had no significant effect on the cesarean section rate. Moreover, maternal and neonatal outcomes, and women's experience of labor, did not significantly differ between these strategies.

Our trial had some limitations. For one, it was restricted to nulliparous women in the UK who did not have high risk pregnancies. Thus the results may not be generalizable to older multiparous women and also may not apply to all nulliparous pregnant women aged 35 years or over.

Although we found no significant between group difference in maternal experience of labor, this finding may not apply to women with a preference for one or other strategy.

The time gap between randomization (36 weeks) and intervention (39 weeks) in our trial was imposed by the practical constraints of NHS maternity services. This limitation might not apply in other settings. This interval inevitably resulted in some women in the intervention arm entering labor spontaneously prior to their date for induction. Such "non-adherence" reduced the power of the trial but would not have biased the test for a difference between the groups because the analysis was by intention to treat.

This trial was powered to detect a 36% relative difference (9% absolute difference) in Cesarean section rates, but we cannot rule out a smaller effect. The observed confidence intervals suggest that the plausible effect of induction ranges from a 28% percent decrease to a 36% percent increase in Cesarean delivery.

The rate of assisted vaginal delivery appeared higher in the induction group than the expectant management group, although differences were not statistically significant. In populations with higher rates of second stage cesarean sections, the rate of cesarean delivery with induction of labor might be higher than in the present report.

The current trial included participants from 38 UK NHS hospitals and one UK primary care trust, representing a mixture of secondary and tertiary level units. The results are generalizable to countries with similar demographics to the UK.

The design was pragmatic; units were encouraged to use their usual method of induction for women in both arms requiring induction. There is considerable heterogeneity in methods employed for induction across the world. Different methods of induction have differing efficacy[10]. Most participating units used prostaglandin ripening followed if necessary by amniotomy and oxytocin infusion. It is unclear whether the results of this trial would be generalizable to centers using other methods of induction.

Previous studies of induction of labor in women of advanced maternal age have been observational and have found an increased risk of cesarean delivery associated with induction[27-29]. Numerous randomized trials have assessed effect of labor induction at term for other indications, and these have been included in three recent meta-analyses, all of which demonstrated a reduction in cesarean delivery in women assigned to induction of labor[30,31,16]. The present results likewise did not indicate an increase in caesarean rates with induction as compared with expectant management.

Our trial does not address whether induction of labor at 39 weeks can prevent stillbirths. However it supports the safety of performing of a larger trial to test the effects of induction on stillbirth and uncommon adverse neonatal outcomes in women aged 35 years or over, although such a trial would need to be extremely large.

Although some observational studies have suggested a possible association between delivery at 'early-term' gestations (37-39 weeks), versus 'late-term' gestations (40-41 weeks)[11-14] and subtle long-term impact on children's development and educational attainment, data are lacking from randomized trials to inform outcomes of infants after discharge from the hospital.

In summary, induction of labor at 39 weeks for women of advanced maternal age, as compared with expectant management, had no significant effect on the rate of cesarean section nor adverse short-term effects on maternal or neonatal outcomes.

Protocol

The full trial protocol is published in an open access journal[32].

Sources of support

The National Institute for Health Research – Research for Patient Benefit Programme funded the study. The Nottingham Clinical Trials Unit provided the trial database, computerised randomisation programme and statistical support.

Funding

The National Institute for Health Research – Research for Patient Benefit Programme.

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Figure Legend

Figure 1: Participant Flow

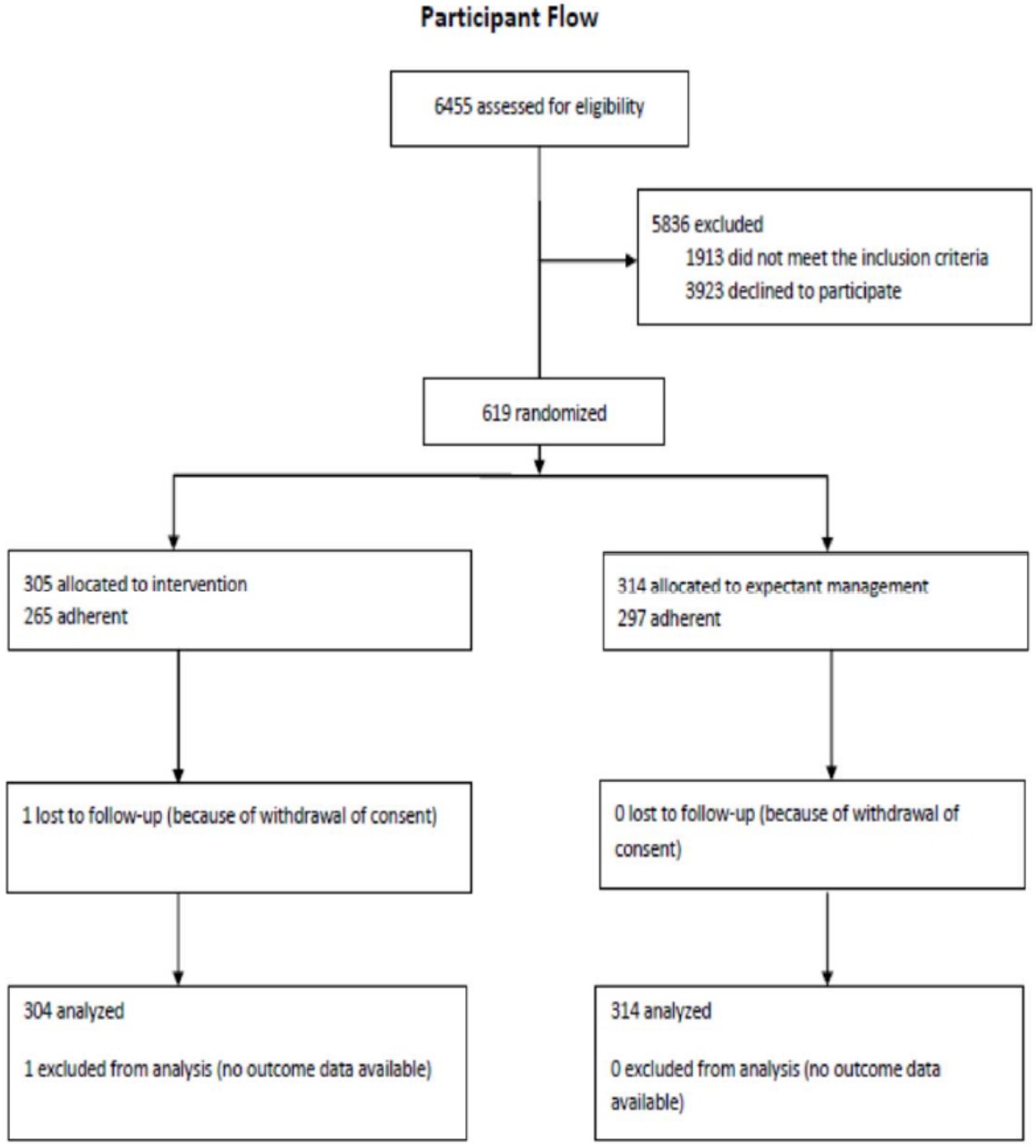

Table 1: Baseline characteristics of the study groups.*

	Induction group	Expectant group
Participants	305	314
Maternal Age in years		
Mean [SD] range	37 [2.2] 35 – 45	37 [2.2] 35-44
Current smoker	9 (3)	5 (2)
BMI		
≥30	85 (28)	83 (26)
Ethnicity**		
White	279 (91)	291 (92)
Other	26 (9)	21 (7)
Unknown	0	2 (1)
Assisted conception	40 (13)	48 (15)
Medical history		
Any disease	48 (16)	50 (16)
Renal disease	0	1
Hypertension	4 (1)	3 (1)
Other	46 (15)	46 (15)

*all data are N (%) unless specified.
**ethnicity self reported.

Table 2: Mode of delivery and indications for induction of labor

Group	Induction group	Expectant group
Total Number allocated	305	314
N (%) received allocated management	264 (87)	297 (95)
Onset of labor (N)		
Spontaneous labor	**62 (20)**	**144 (46)**
Spontaneous labor ≤ 39^{+6}	37	
Spontaneous labor ≥ 40 weeks	25	
Induction of labor	**237 (78)**	**154 (49)**
Induction of labor ≤ 39^{+6}	222	
Induction of labor ≥ 40 weeks	15	
Elective CS	**3 (1)**	**9 (3)**
Elective CS ≤ 39^{+6}	2	
Elective CS ≥ 40 weeks	1	
Emergency CS (no labor)	**2 (1)**	**7 (2)**
Emergency CS (no labor) ≤ 39^{+6}	2	
Emergency CS (no labor) ≥ 40 weeks	0	
Indication for induction		
Randomized to induction	208	0
Gestational age >41 weeks	7	45
Preterm (<37 weeks) pre-labor rupture of membranes	1	1
Term (>37 weeks) pre-labor rupture of membranes > 24 hours	10	35
Fetal growth restriction	1	7
Reduced fetal movements	3	17
Pregnancy induced hypertension	8	12
Pre-eclampsia	8	9
Obstetric cholestasis	0	3
Gestational diabetes	1	2
Suspected fetal distress	0	5
Maternal request	0	17
Other	7	25

Total non-compliance in the induction group = 41 (13.4%), comprising those who labored spontaneously ≥ 40 weeks (n = 25), those who were induced ≥ 40 weeks (n = 15) and those who had an elective CS ≥ 40 weeks (n=1). Total non-compliance in the expectant management group = 17 (5.4 %), comprising those who were induced or delivered by CS for maternal request (n = 17).

Table 3: Maternal outcomes

	Induction group n = 304	**Expectant group n= 314**	**Relative Risk induction versus expectant[a]**	**95% Confidence Interval**
Cesarean section	**98 (32)**	**103 (33)**	**0.99**	**0.87 – 1.14**
Cesarean section (women aged 35-37 years)[b]	**44 (26)**	**52 (29)**	**0.89**	**0.67 – 1.19**
Cesarean section (women aged 38-40 years)[b]	**29 (39)**	**27 (39)**	**1.00**	**0.70 – 1.41**
Cesarean section (women aged 40+)[b]	**25 (42)**	**24 (38)**	**1.13**	**0.75 – 1.70**
Assisted vaginal delivery	**115 (38)**	**104 (33)**	**1.30**	**0.96 – 1.77**
Indication for cesarean section				
Arrest of first stage of labor	39	34		
Arrest of second stage of labor	5	7		
Failed instrumental delivery	4	7		
Suspected fetal distress	43	48		
Maternal complications	8	2		
Elective	2	6		
Other[c]	32	29		
Epidural use	105 (56)	90 (47)		
Gestational age at onset of labor Mean Min; Max	 39 37-42	 40 36-42		
Placental abruption	0	0		
Cord Prolapse	1	0		
Postpartum hemorrhage[d]	95	90	**1.09**	**0.85 – 1.40**
Shoulder dystocia	6	9	**0.68**	**0.25 – 1.83**
Requiring blood transfusion	10	17	**0.61**	**0.30 – 1.21**
Systemic infection – temp ≥38°C[e]	12	10	**1.24**	**0.45 – 3.37**

a=RR of cesarean section in induction of labor group compared to the expectant management group, after adjustment for center and age.
b= p interaction by maternal age 0.65d= Postpartum hemorrhage was defined as blood loss of ≥ 500ml at vaginal delivery or ≥ 1000ml at cesarean delivery.
c= A breakdown of reasons for "other" indications for cesarean section is given in Supplementary Appendix 7
d= Postpartum hemorrhage was defined as blood loss of ≥ 500ml at vaginal delivery or ≥ 1000ml at cesarean delivery.
e= Systemic infection was defined as a temperature of ≥ 38°C

Table 4: Neonatal outcomes

Outcome	Induction group	Expectant group	Relative Risk[a] (95% C.I.)	P-value
Live birth	304	314		
Stillbirth (baby delivered with no sign signs of life after 24 weeks)	0	0		
Birth weight grams – Mean [SD]	3352 (425)	3428 (466)		
Sex – Female	152 (50)	167 (53)		
Death before discharge from hospital	0	0		
Birth weight < 2.5kg	4	6	0.68 (0.19-2.4)	0.56
Apgar <4 at 5 minutes	0	1		
Apgar between 4-7 at 5 minutes	11	11	1.04 (0.40 – 2.69)	0.94
Cord blood artery Base Deficit > 15	0	1		
Cord blood artery pH < 7.00	1	1	0.89 (0.05 – 14.6)	0.93
NICU admission – duration >4 days	6	7	0.88 (0.26 – 3.06)	0.85
***Composite outcome (direct trauma)**	0	0		
****Composite outcome (hypoxia)**	2	2	1.03 (0.14 – 7.50)	0.98
Seizures	0	0		
Hypotonia for at least 2 hours	1	0		
Abnormal level of consciousness	0	0		
Tube feeding for > 4 days	0	2		
Intubation and ventilation for > 24 hours	1	2	0.51 (0.45 – 5.82)	0.59
Cooling required	1	2	0.52 (0.47 – 5.68)	0.59
Oxygen required	9	7	1.32 (0.58 – 2.99)	0.50
CPAP	4	4	1.02 (0. 22 – 4.86)	0.97

a=RR for each outcome is the RR of having the particular outcome of interest in the Induction of labor group compared to effective management group. RR is adjusted for centre and age.
*Composite outcome for trauma includes subdural haematoma, intracerebral or intraventricular haemorrhage, spinal-cord injury, basal skull fracture, peripheral nerve injury or long bone fracture
**Composite outcome for hypoxia includes seizures, hypotonia, abnormal level of consciousness or whether cooling required