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Randomized Trial of Labor Induction in Women 35 Years of Age or Older

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ABSTRACT

BACKGROUND

The risk of antepartum stillbirth at term is higher among women 35 years of age or older than among younger women. Labor induction may reduce the risk of stillbirth, but it also may increase the risk of cesarean delivery, which already is common in this older age group.

METHODS

We conducted a randomized, controlled trial involving primigravid women who were 35 years of age or older. Women were randomly assigned to labor induction between 39 weeks 0 days and 39 weeks 6 days of gestation or to expectant management (i.e., waiting until the spontaneous onset of labor or until the development of a medical problem that mandated induction). The primary outcome was cesarean delivery. The trial was not designed or powered to assess the effects of labor induction on stillbirth.

RESULTS

A total of 619 women underwent randomization. In an intention-to-treat analysis, there were no significant between-group differences in the percentage of women who underwent a cesarean section (98 of 304 women in the induction group [32%] and 103 of 314 women in the expectant-management group [33%]; relative risk, 0.99; 95% confidence interval [CI], 0.87 to 1.14) or in the percentage of women who had a vaginal delivery with the use of forceps or vacuum (115 of 304 women [38%] and 104 of 314 women [33%], respectively; relative risk, 1.30; 95% CI, 0.96 to 1.77). There were no maternal or infant deaths and no significant between-group differences in the women's experience of childbirth or in the frequency of adverse maternal or neonatal outcomes.

CONCLUSIONS

Among women of advanced maternal age, induction of labor at 39 weeks of gestation, as compared with expectant management, had no significant effect on the rate of cesarean section and no adverse short-term effects on maternal or neonatal outcomes. (Funded by the Research for Patient Benefit Programme of the National Institute for Health Research; Current Controlled Trials number, ISRCTN11517275.)

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The average age of women at childbirth in industrialized nations has been increasing steadily for approximately 30 years.[1] Between 1996 and 2006, births to women 35 years of age or older in the United Kingdom increased from 12% to 20% of all births.[2] In 2006, a total of 5.6% of live births in the United Kingdom were to nulliparous women 35 years of age or older.

The risks of perinatal death, hypertensive disease, gestational diabetes mellitus, placenta previa, and placental abruption are higher among women 35 years of age or older than among younger women.[1,3,4] Older mothers are also at increased risk for preterm labor and for bearing infants with macrosomia (>3999 g) or low birth weight (<2500 g). The women themselves typically think that their age puts their infant at increased risk for a poor outcome.[3] Unsurprisingly, rates of obstetrical intervention are higher among older women than among younger women.

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The rate of cesarean section is 38% among nulliparous women in the United Kingdom who are 35 years of age or older and 50% among those who are 40 years of age or older.[3] Among nulliparous women, the relationship between maternal age and delivery by means of emergency cesarean section is linear.[5]

Induction at or before the due date in women 35 years of age or older may be beneficial because the gestational age at delivery that is associated with the lowest cumulative risk of perinatal death is 38 weeks.[6] In all maternal age groups, the risk of stillbirth is higher among nulliparous women than among multiparous women.[7,8] Induction is currently available to all women in the United Kingdom at 41 to 42 weeks of gestation, when the risk of stillbirth is 2 to 3 per 1000 deliveries[9,10]; among older women, this risk is 2.6 stillbirths per 1000 deliveries from 37 weeks of gestation onward.[7] However, induction carries risks (e.g., cord prolapse and uterine hyperstimulation) and has been associated with an increased risk of cesarean section. In addition, its benefits may be offset by longer-term adverse outcomes in children because of delivery at "early-term" gestation (37 to 39 weeks).[11-14]

Some obstetricians in the United Kingdom already induce labor at the due date (40 weeks of gestation); rates of induction are 39% among women 40 to 44 years of age and 58% among women 45 years of age or older. Among obstetricians who do not induce labor in older pregnant women at the due date, one third are reluctant to offer induction because they are concerned about increasing the likelihood of cesarean delivery, even though they think that induction would improve perinatal outcomes.[15] However, there is a growing body of evidence that induction of labor at term for reasons other than older maternal age does not increase rates of cesarean section and may even reduce them[16] and that an effective intervention is therefore being underused.

Most trials of induction at or near term have involved women with established complications of pregnancy such as hypertension,[17] prelabor rupture of membranes,[18] fetal growth restriction,[19] diabetes,[20] or fetal macrosomia.[21] The few trials of induction that did not involve women with complications[22-25] were relatively small (a total of 1377 women in four trials), date from the 1970s, and may not be applicable to modern obstetrical practice. Trials of induction of labor in women of advanced maternal age are lacking. The 35/39 trial was designed to test the hypothesis that induction of labor at 39 weeks of gestation would reduce the rate of cesarean delivery among nulliparous women of advanced maternal age.

METHODS

STUDY DESIGN AND OVERSIGHT

We performed a multicenter, randomized, controlled trial comparing the rate of cesarean section between women assigned to induction of labor between 39 weeks 0 days and 39 weeks 6 days of gestation and those assigned to expectant management. Eligible women were nulliparous, were to be 35 years of age or older on their expected due date, and had a singleton live fetus in a cephalic presentation. Participants were recruited between August 2012 and March 2015 at 38 National Health Service (NHS) hospitals and 1 Primary Care Trust organization in the United Kingdom.

Women were ineligible to participate in the trial if their pregnancy was complicated by a known fetal congenital abnormality that would lead to neonatal death or if they had any contraindications to labor (e.g., evidence of fetal compromise), vaginal delivery (e.g., placenta previa), or expectant management (e.g., gestational diabe-

tes). Women who had undergone a myomectomy, who had not undergone ultrasonographic examination (for estimation of gestational age) before 22 weeks of gestation, or who had undergone in vitro fertilization with the use of donor eggs were also excluded.

The original trial protocol was published in 2012.[26] The original and final trial protocols are available with the full text of this article at NEJM.org. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the trial protocol. The Nottingham Clinical Trials Unit provided the trial database, computerized randomization program, and statistical support. The trial was approved by the East Midlands–Derby NHS research ethics committee, and all participants provided written informed consent.

PARTICIPANTS

Women underwent randomization at 36 weeks 0 days to 39 weeks 6 days of gestation. Individual women were assigned in a 1:1 ratio according to a computer-generated code with the use of random permuted blocks of randomly varying size generated by the Nottingham Clinical Trials Unit. The randomization was stratified into three categories according to trial center and maternal age (35 to 37 years of age, 38 to 39 years of age, and 40 years of age or older).

After obtaining consent, research staff at individual sites logged into an Internet-based randomization system to access the randomized assignments. Both participants and treating clinicians were aware of these assignments.

Women were randomly assigned to either induction of labor between 39 weeks 0 days and 39 weeks 6 days of gestation or to expectant management (i.e., waiting for the spontaneous onset of labor unless a situation developed necessitating delivery either by means of induction or cesarean section). Women who were randomly assigned to the expectant-management group could undergo induction between 41 weeks 0 days and 42 weeks 0 days of gestation (i.e., 7 to 14 days after the due date), with the exact time determined by their preference and the physician's usual practice. No additional monitoring before 42 weeks 0 days of gestation was offered unless it was the physician's usual practice. If the woman declined to undergo induction at 42 weeks of gestation, she could undergo scanning to determine fetal growth and amniotic-fluid volume and daily or every-other-day cardiotocographic monitoring according to the physician's usual practice. In the induction group, local policies for induction of labor were followed.

Before the trial began, each unit recorded its regimen for the use of prostaglandin and oxytocin and the Bishop cutoff score for amniotomy (scores range from 0 to 13, with higher scores indicating greater favorability for induction). Staff within each unit were encouraged to use the same induction protocol for all participants, including women in the expectant-management group who required induction for any reason.

TRIAL OUTCOMES

The primary outcome was cesarean delivery. The secondary maternal outcomes were the method of delivery other than cesarean section (i.e., unassisted vaginal delivery, assisted vaginal delivery [with the use of forceps or vacuum], and vaginal breech delivery), the onset of labor (i.e., spontaneous labor, induction of labor, elective or emergency cesarean, or no labor), the indication for induction of labor, the method of labor induction, the indication for cesarean section, intrapartum complications, and postpartum complications (e.g., systemic infection or the need for a blood transfusion). Postpartum hemorrhage was defined as a blood loss of 500 ml or more at vaginal delivery or 1000 ml or more at cesarean delivery.

The secondary neonatal outcomes were live birth or stillbirth, birth weight, admission to a neonatal intensive care unit, birth trauma, and two composite outcomes for serious neonatal complications (direct trauma and hypoxia). The composite outcome for neonatal direct trauma included subdural hematoma, intracerebral or intraventricular hemorrhage, spinal cord injury, basal skull fracture, peripheral-nerve injury, and long-bone fracture. The composite outcome for neonatal hypoxia included seizures, hypotonia, abnormal level of consciousness, and the use of cooling. The components of the two neonatal composite outcomes (trauma and hypoxia) were prespecified in the statistical analysis plan before the trial randomization code was broken. Data were collected immediately after the mothers' hospital discharge by the research midwife at each center.

Other secondary outcomes included the mothers' expectations and experience of childbirth, as measured with the use of the Childbirth Experience Questionnaire,[27] which was sent to the women 1 month after the birth. This measure assesses four domains of the experience of childbirth: the woman's own capacity (her sense of control and personal feelings during childbirth), professional support (the woman's receipt of information and midwifery care), perceived safety (the woman's sense of security and memories from the childbirth), and participation in the birth (the woman's ability to influence the birthing process). Responses were scored according to the instructions of the authors of the questionnaire (Table S2 in the Supplementary Appendix, available at NEJM.org). Scores in each domain range from 0 to 4, with higher scores indicating a better childbirth experience. Data on additional secondary outcomes pertaining to resource use and the women's baseline and postnatal health status were also collected but are not reported here.

STATISTICAL ANALYSIS

The power calculation was based on rates of cesarean delivery among women who were pregnant with a singleton in cephalic presentation and who were in labor at term in the cohort of all delivering women in Scotland between 2004 and 2008; 23% of the women in this cohort were 35 to 39 years of age and 27% were 40 years of age or older (Smith G: unpublished data). We calculated that, assuming a rate of cesarean delivery of 25% among controls, a sample size of 630 women would provide 80% power to test the hypothesis that induction of labor would reduce the rate of cesarean section to 16%, a 36% relative reduction (or a 9-percentage-point absolute reduction), at a two-sided significance level of 5%.

In this intention-to-treat analysis, participants were assessed according to their assigned group, regardless of their adherence to the assignment, and according to a prespecified 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 trial center and maternal age (the center was accounted for with the use of robust standard errors and a clustered sandwich estimator in Stata software). We also had planned a sensitivity analysis to investigate the effect of missing data on our results, but this analysis was unnecessary because there were minimal missing data.

For analyses of the method of delivery (other than by cesarean section), we used a multinomial logistic-regression model to calculate relative risks and 95% confidence intervals after adjustment for trial center and maternal age, using vaginal delivery as the reference group. For intrapartum complications, postpartum complications, and the composites of serious neonatal complications, we used the same generalized linear model that was used for the primary outcome to calculate relative risks and 95% confidence intervals. For individual birth trauma outcomes, we summarized the frequency of these events in each group.

To assess the women's experience of childbirth as measured with the use of the Childbirth Experience Questionnaire,[27] we performed a complete case analysis, using the unpaired t-test, to compare the mean subscale scores and the mean total score (the average of the four individual subscale scores) between women in the induction group and those in the expectant-management group. A Mann–Whitney U test was used to calculate P values. In cases in which there were a few missing items, the half-scale method was used so that when the respondent had answered at least half the items in the scale, the sum of the scores was divided by the number of answered items.

For the primary outcome, a prespecified subgroup analysis according to maternal age (35 to 37 years, 38 to 39 years, or 40 years of age or older) was performed by including an interaction term in the model. An independent data and safety monitoring committee met regularly throughout the trial. No interim analyses were performed. All analyses were performed with the use of Stata software, version 13.

RESULTS

ENROLLMENT

Recruitment took place from August 2012 through March 2015. Recruitment according to trial center is shown in Table S3 in the Supplementary Appendix. One woman in the induction group withdrew consent for her data to be used. The numbers of participants who were randomly assigned to each group and who received the

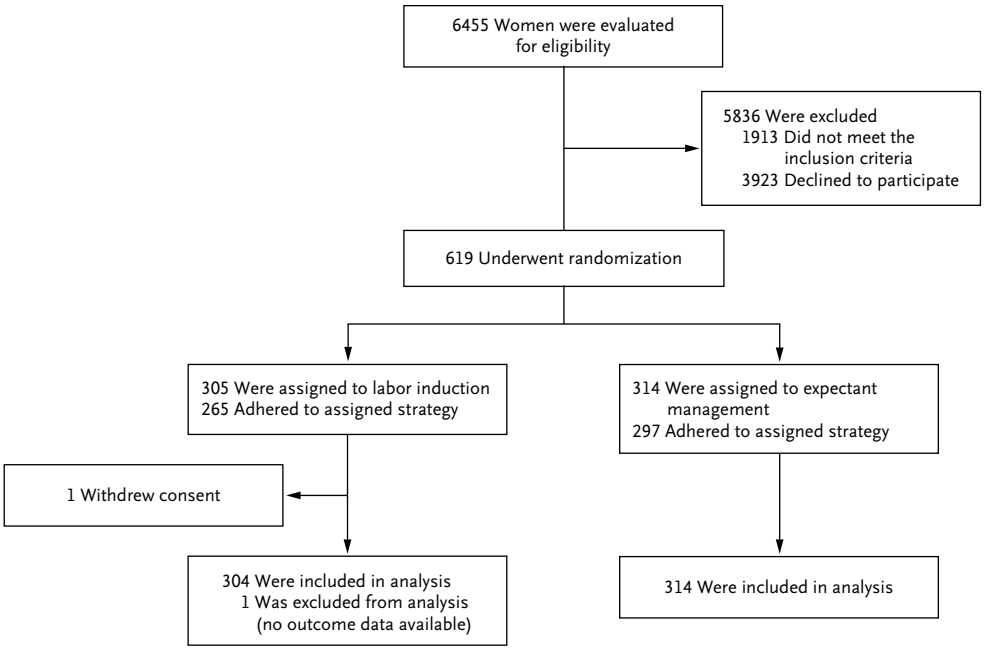

Figure 1. Enrollment, Randomization, and Assessment.

intended strategy are shown in Figure 1. A total of 619 of 4542 women who were eligible to participate in the trial (14%) underwent randomization. Among the 46% of eligible nonparticipants who expressed a preference for one of the management strategies, 1595 of 1804 women (88%) preferred expectant management.

The baseline characteristics were similar in the two groups (Table 1). Nonadherence was more common in the induction group than in the expectant-management group (13% vs. 5%) (Table 2). There was no significant difference between the induction group and the expectant-management group with respect to the frequency of cesarean section (98 of 304 women [32%] vs. 103 of 314 women [33%]; relative risk, 0.99; 95% confidence interval [CI], 0.87 to 1.14). A total of 115 of 304 women (38%) in the induction group, as compared with 104 of 314 women (33%) in the expectant-management group, had assisted vaginal delivery (relative risk, 1.30; 95% CI, 0.96 to 1.77).

Table 1. Baseline Characteristics of the Participants.*

Variable	Induction Group (N=305)	Expectant-Management Group (N=314)
Maternal age at expected date of delivery — yr		
Mean ±SD	37±2.2	37±2.2
Range	35–45	35–44
Current smoker — no. (%)	9 (3)	5 (2)
Body-mass index ≥30 — no. (%)*	85 (28)	83 (26)
Race — no. (%)†		
White	279 (91)	291 (93)
Other	26 (9)	21 (7)
Unknown	0	2 (1)
Assisted conception — no. (%)	40 (13)	48 (15)
Medical history — no. (%)		
Any disease	48 (16)	50 (16)
Renal disease	0	1 (<1)
Hypertension	4 (1)	3 (1)
Other condition	46 (15)	46 (15)

* Body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was self-reported.

OUTCOMES

There were no significant between-group differences in maternal outcomes (Table 3) or neonatal outcomes (Table 4). Serious adverse events were

Table 2. Method of Delivery and Indication for Induction of Labor.

Variable	Induction Group (N=305)	Expectant-Management Group (N=314)
Women who received assigned care — no. (%)*	264 (87)	297 (95)
Onset of birth process		
Spontaneous labor — no. (%)	62 (20)	144 (46)
≤39 wk 6 days of gestation — no.	37	
≥40 wk of gestation — no.	25	
Induced labor — no. (%)	237 (78)	154 (49)
≤39 wk 6 days of gestation — no.	222	
≥40 wk of gestation — no.	15	
Elective cesarean section — no. (%)	3 (1)	9 (3)
≤39 wk 6 days of gestation — no.	2	
≥40 wk of gestation — no.	1	
Emergency cesarean section without labor — no. (%)	2 (1)	7 (2)
≤39 wk 6 days of gestation — no.	2	
≥40 wk of gestation — no.	0	
Indication for induction of labor — no.		
Random assignment to induction	208	0
>41 wk of gestation	7	45
Preterm (<37 wk of gestation) prelabor rupture of membranes	1	1
Term (>37 wk of gestation) prelabor rupture of membranes >24 hr before induction	10	35
Fetal growth restriction	1	7
Reduced fetal movements	3	17
Pregnancy-induced hypertension	8	12
Preeclampsia	8	9
Obstetrical cholestasis	0	3
Gestational diabetes	1	2
Suspected fetal distress	0	5
Request of mother	0	17
Other indications	7	25

* A total of 41 women in the induction group (13%) did not adhere to the assigned care strategy, including 25 women who labored spontaneously at 40 or more weeks of gestation, 15 who were induced at 40 or more weeks of gestation, and 1 who had an elective cesarean section after 40 weeks of gestation. Reasons for nonadherence included personal and family issues, hospital and logistic issues, research and clinical staffing issues, and various combinations of these factors. A total of 17 women in the expectant-management group (5%) did not adhere to the assigned care strategy because they requested induction or delivery by means of cesarean section before 41 completed weeks of gestation.

reported in 10 women in the induction group (3%) and in 23 women in the expectant-management group (7%); most of these events were included in the prespecified secondary outcomes (Table S4 in the Supplementary Appendix). The groups did not differ materially with respect to the methods of induction (Table S5 in the Supplementary Appendix). A subgroup analysis of the primary outcome according to maternal age showed no significant difference in the treatment effects according to age (P=0.65 for the interaction) (Table 3).

Table 3. Maternal Outcomes.*

Outcome	Induction Group (N=304)	Expectant-Management Group (N=314)	Relative Risk (95% CI)†	P Value
Method of delivery				
Cesarean section — no. (%)	98 (32)	103 (33)	0.99 (0.87–1.14)	0.92
Age 35–37 yr‡	44 (26)	52 (29)	0.89 (0.67–1.19)	0.45
Age 38–39 yr ‡	29 (39)	27 (39)	1.00 (0.70–1.41)	0.99
Age ≥40 yr‡	25 (42)	24 (38)	1.13 (0.75–1.70)	0.56
Assisted vaginal delivery — no. (%)	115 (38)	104 (33)	1.30 (0.96–1.77)	0.08
Indication for cesarean section — no.				
Failure of labor to progress				
First stage	39	34		
Second stage	5	7		
Failed delivery with use of instruments	4	7		
Suspected fetal distress	43	48		
Maternal complications	8	2		
Patient choice	2	6		
Other§	32	29		
Epidural use — no. (%)	105 (35)	90 (29)		
Gestational age at onset of labor — wk				
Mean	39	40		
Range	37–42	36–42		
Complications — no.				
Placental abruption	0	0		
Cord prolapse	1	0		
Postpartum hemorrhage¶	95	90	1.09 (0.85–1.40)	0.47
Shoulder dystocia	6	9	0.68 (0.25–1.83)	0.45
Blood transfusion required	10	17	0.61 (0.30–1.21)	0.16
Systemic infection‖	12	10	1.24 (0.45–3.37)	0.68

* CI denotes confidence interval.
† Shown is the relative risk of the outcome in the induction group as compared with the expectant-management group, after adjustment for trial center and maternal age.
‡ P=0.65 for the interaction, according to maternal age.
§ Other indications for cesarean section are provided in Table S7 in the Supplementary Appendix.
¶ Postpartum hemorrhage was defined as blood loss of 500 ml or more at vaginal delivery or 1000 ml or more at cesarean delivery.
‖ Systemic infection was defined by a temperature of 38°C or higher.

In total, 512 women (83%) returned the Childbirth Experience Questionnaire. There were no significant differences between the two groups in the subgroup scores or total scores (indicating level of satisfaction with the childbirth experience) (Table S6 in the Supplementary Appendix).

DISCUSSION

In this multicenter, randomized trial involving women 35 years of age or older, induction of labor at 39 weeks of gestation, as compared with expectant management, had no significant effect on the rate of cesarean section. Moreover, mater-

Table 4. Neonatal Outcomes.*

Outcome	Induction Group (N=304)	Expectant-Management Group (N=314)	Relative Risk (95% CI)†	P Value
Liveborn infants — no.	304	314		
Death — no.				
Stillbirth (delivered with no signs of life after 24 wk of gestation) — no.	0	0		
Before discharge from hospital	0	0		
Female sex — no. (%)	152 (50)	167 (53)		
Clinical measurements				
Mean birth weight ±SD — g	3352±425	3428±466		
Birth weight <2500 g — no.	4	6	0.68 (0.19–2.4)	0.56
Apgar score at 5 min — no.				
<4	0	1		
4–7	11	11	1.04 (0.40–2.69)	0.94
Umbilical-cord-blood arterial base deficit >15 mmol/liter — no.	0	1		
Umbilical-cord-blood arterial pH <7.00 — no.	1	1	0.89 (0.05–14.6)	0.93
Admission to NICU for >4 days — no.	6	7	0.88 (0.26–3.06)	0.85
Complication — no.				
Composite outcome‡				
Hypoxia	2	2	1.03 (0.14–7.50)	0.98
Hypotonia ≥2 hr	1	0		
Required intervention — no.				
Tube feeding >4 days	0	2		
Intubation and ventilation >24 hr	1	2	0.51 (0.45–5.82)	0.59
Cooling	1	2	0.52 (0.47–5.68)	0.59
Oxygen	9	7	1.32 (0.58–2.99)	0.50
CPAP	4	4	1.02 (0.22–4.86)	0.97

* CPAP denotes continuous positive airway pressure, and NICU neonatal intensive care unit.
† Shown is the relative risk of the outcome in the induction group as compared with the expectant-management group, after adjustment for trial center and maternal age.
‡ The composite outcome for direct trauma includes subdural hematoma, intracerebral or intraventricular hemorrhage, spinal cord injury, basal skull fracture, peripheral-nerve injury, and long-bone fracture. The composite outcome for hypoxia includes seizures, hypotonia, abnormal level of consciousness, and the use of cooling. No cases of direct trauma, seizures, or abnormal level of consciousness were reported.

nal and neonatal outcomes and women's experience of childbirth did not differ significantly between the groups assigned to these strategies.

Our trial had some limitations. It was restricted to nulliparous women in the United Kingdom who did not have high-risk pregnancies. Thus, the results may not be generalizable to older multiparous women and may not apply to all nulliparous pregnant women who are 35 years of age or older. Although we found no significant between-group difference in the women's experience of childbirth, this finding may not apply to women who have a preference for one strategy or the other.

The maximum time gap between randomization (36 weeks of gestation) and intervention (39 weeks of gestation) in our trial was imposed by the practical constraints of NHS maternity services. This limitation might not apply in other clinical settings. Because of this interval,

some women in the intervention group entered labor spontaneously before their date for induction. Such "nonadherence" reduced the power of the trial but would not have biased the test for a difference between the groups because we used an intention-to-treat analysis.

This trial was powered to detect a 36% relative difference (9-percentage-point absolute difference) in the rates of cesarean section, but we cannot rule out a smaller effect. The observed confidence intervals suggest that the rate of cesarean delivery could range from a 28% lower rate to a 36% higher rate with induction than with expectant management.

The rate of assisted vaginal delivery appeared to be higher in the induction group than in the expectant-management group, although the difference was not significant. In countries with higher rates of cesarean sections in the second stage of labor, the rate of cesarean delivery with induction of labor might be higher than the rate that we report in this article.

The current trial included participants from 38 NHS hospitals and 1 Primary Care Trust organization in the United Kingdom; these hospitals represent a mixture of secondary- and tertiary-level units. The results are generalizable to countries with demographic characteristics that are similar to those of the United Kingdom.

The design of our trial was pragmatic; in both trial groups, units were encouraged to use their usual method of induction in women who required induction. There is considerable heterogeneity in the methods used for induction around the world. These 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 that use other methods of induction.

Previous studies of induction of labor involving women of advanced maternal age have been observational and have shown an increased risk of cesarean delivery associated with induction.[28-30] Numerous randomized trials have assessed the effect of labor induction at term for other indications, and these trials have been included in three recent meta-analyses, all of which showed a lower rate of cesarean delivery among women assigned to induction of labor than among women assigned to expectant management.[16,31,32] Our results similarly did not indicate a higher rate of caesarean delivery among women who received induction than among women who received expectant management.

Our trial did not address whether induction of labor at 39 weeks of gestation can prevent stillbirths. It does, however, provide support for the safety of performing a larger trial to test the effects of induction on stillbirth and uncommon adverse neonatal outcomes in women 35 years of age or older, although such a trial would need to be extremely large.

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

In summary, in women of advanced maternal age, induction of labor at 39 weeks of gestation, as compared with expectant management, had no significant effect on the rate of cesarean section and was not associated with adverse short-term effects on maternal or neonatal outcomes.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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