Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial

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Summary

Background Robust evidence to direct management of pregnant women with mild hypertensive disease at term is scarce. We investigated whether induction of labour in women with a singleton pregnancy complicated by gestational hypertension or mild pre-eclampsia reduces severe maternal morbidity.

Methods We undertook a multicentre, parallel, open-label randomised controlled trial in six academic and 32 non-academic hospitals in the Netherlands between October, 2005, and March, 2008. We enrolled patients with a singleton pregnancy at 36–41 weeks' gestation, and who had gestational hypertension or mild pre-eclampsia. Participants were randomly allocated in a 1:1 ratio by block randomisation with a web-based application system to receive either induction of labour or expectant monitoring. Masking of intervention allocation was not possible. The primary outcome was a composite measure of poor maternal outcome—maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, and placental abruption), progression to severe hypertension or proteinuria, and major post-partum haemorrhage (>1000 mL blood loss). Analysis was by intention to treat and treatment effect is presented as relative risk. This study is registered, number ISRCTN08132825.

Findings 756 patients were allocated to receive induction of labour (n=377 patients) or expectant monitoring (n=379). 397 patients refused randomisation but authorised use of their medical records. Of women who were randomised, 117 (31%) allocated to induction of labour developed poor maternal outcome compared with 166 (44%) allocated to expectant monitoring (relative risk 0·71, 95% CI 0·59–0·86, p<0·0001). No cases of maternal or neonatal death or eclampsia were recorded.

Interpretation Induction of labour is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks' gestation.

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See Comment page 951

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Introduction

About 6–8% of pregnancies are complicated by hypertensive disorders.[1,2] Such disorders in pregnancy make a substantial contribution to maternal and neonatal morbidity and mortality worldwide.[3] In the Netherlands these disorders are the primary cause of maternal mortality.[4,5] Most hypertensive disorders present after 36 weeks' gestation. For the management of women with gestational hypertension or mild pre-eclampsia at term, evidence for selection of induction of labour versus expectant monitoring is scarce. Induction of labour is thought to prevent severe maternal and neonatal complications such as eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count), placental abruption, maternal death, and asphyxia. Conversely, induction might increase the risk of instrumental vaginal delivery and caesarean section, and thereby generate additional morbidity and costs.[6–8]

To our knowledge, no randomised clinical trial on this subject has yet been published. Strong practice variation exists in the Netherlands for treatment of women with gestational hypertension or mild pre-eclampsia beyond 36 weeks' gestation. Therefore we aimed to assess whether induction of labour in such women reduces poor maternal outcome compared with expectant monitoring.

Methods

Patients

We did a multicentre, parallel, open-label randomised controlled trial in the Netherlands, in which six academic and 32 non-academic hospitals participated. We recruited women with a singleton pregnancy and a fetus in cephalic presentation at a gestational age of between 36 (0 days) and 41 weeks (0 days), and who had gestational hypertension or mild pre-eclampsia. Gestational hypertension was defined as diastolic blood pressure of

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95 mm Hg or higher measured on two occasions at least 6 h apart. Mild pre-eclampsia was defined as diastolic blood pressure of 90 mm Hg or higher measured on two occasions at least 6 h apart, combined with proteinuria (two or more occurrences of protein on a dipstick, >300 mg total protein within a 24-h urine collection, or ratio of protein to creatinine >30 mg/mmol).[9–11]

Patients were excluded if they had severe gestational hypertension or severe pre-eclampsia, defined as systolic blood pressure of 170 mm Hg or higher, diastolic blood pressure of 110 mm Hg or higher, or proteinuria of 5 g or higher per 24 h. Other exclusion criteria were pre-existing hypertension treated with antihypertensive drugs, diabetes mellitus, gestational diabetes needing insulin treatment, renal disease, heart disease, previous caesarean section, HELLP syndrome, oliguria of less than 500 mL per 24 h, pulmonary oedema or cyanosis, HIV seropositivity, use of intravenous antihypertensive drugs, fetal anomalies, suspected intrauterine growth restriction,[12] and abnormalities detected during fetal-heart-rate monitoring.

Patients were seen by research nurses and midwives who provided counselling, obtained informed consent, monitored the study protocol in every centre and collected the data. Before randomisation, cervical length was measured by transvaginal sonography and vaginal digital examination was done. Patient data were then entered into a password-protected web-based database and a web-based application was used for block randomisation with a variable block size of 2–8. Randomisation was stratified for centre, parity, and hypertensive-related disease (gestational hypertension or pre-eclampsia). Women were randomly allocated in a 1:1 ratio to receive either induction of labour or expectant monitoring. In this open-label trial, masking of participants, obstetricians, and outcome assessors was not possible for allocation of the randomisation number or intervention.

The trial was approved by the Institutional Review Board of the University of Leiden, and had local approval from the boards of the other participating hospitals. Written informed consent was obtained from all patients before randomisation. Patients who did not give informed consent for randomisation, but who gave authorisation for the use of their medical records, were treated according to one of the two protocols at the discretion of the attending obstetrician.

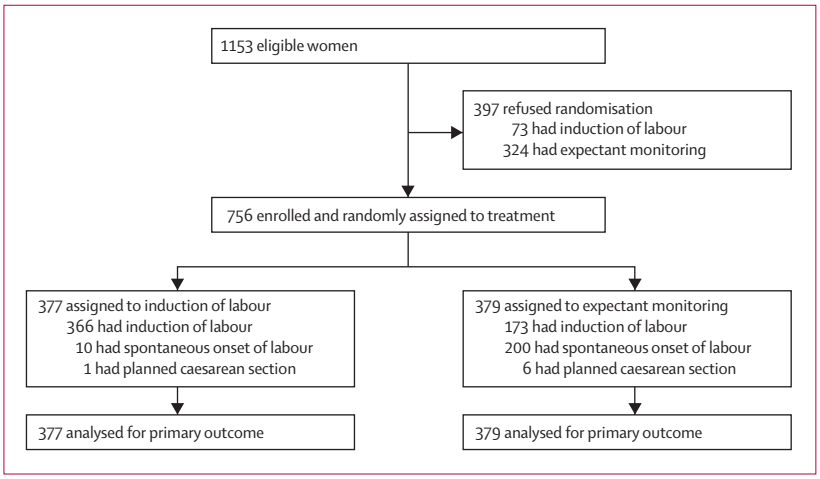

Figure 1: **Trial profile**

Procedures

Patients allocated to induction of labour were induced within 24 h of randomisation. If the patient had a Bishop score[13] of more than 6 at vaginal examination, labour was induced with amniotomy and, if needed, augmentation with oxytocin. If the Bishop score was 6 or lower, cervical ripening was stimulated with intracervical or intravaginal prostaglandins or a balloon catheter. Use of oxytocin or prostaglandins depended on local protocols, which were based on national guidelines of the Dutch Society for Obstetrics and Gynaecology.[14]

Patients allocated to expectant monitoring were monitored until the onset of spontaneous delivery. Maternal monitoring consisted of frequent blood pressure measurements and screening of urine for protein with a dipstick specimen or with the ratio of protein to creatinine. In cases of positive screening for protein, urine was collected for 24 h to quantify proteinuria. Laboratory tests were done on patients with increased blood pressure or proteinuria. Fetal monitoring consisted of assessment of fetal movements as reported by the mother, as well as electronic fetal-heart-rate monitoring and ultrasound examination. Expectant monitoring was done in either a hospital or outpatient setting, dependent on the condition of the patient. Induction of labour was recommended for patients allocated to expectant monitoring if they had systolic blood pressure of 170 mm Hg or higher, diastolic blood pressure of 110 mm Hg or higher, proteinuria of 5 g or higher per 24 h, eclampsia, HELLP syndrome, suspected fetal distress, prelabour rupture of membranes lasting more than 48 h, meconium stained amniotic fluid, or a fetus with gestational age beyond 41 weeks.

The primary outcome was a composite measure of poor maternal outcome, defined as maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, or placental abruption), progression to severe disease (at least one measurement during ante-partum or post-partum [less than 48 h after delivery] period of systolic blood pressure ≥170 mm Hg, diastolic blood pressure ≥110 mm Hg, or proteinuria ≥5 g per 24 h),[9] and major post-partum haemorrhage. In a separate analysis, progression to severe disease was diagnosed from severe hypertension measured on at least two occasions that were a minimum of 6 h apart. Eclampsia was defined as the presence of seizures.[15] The diagnosis of HELLP syndrome was made in patients with decreased platelet count (<100×10⁹/L) and increased liver enzymes (aspartate aminotransferase

	Randomised patients		Non-randomised patients	
	Induction of labour (n=377)	Expectant monitoring (n=379)	Induction of labour (n=73)	Expectant monitoring (n=324)
Nulliparous	269 (71%)	272 (72%)	52 (71%)	248 (77%)
Maternal age (years)	29·0 (26·0–33·0)	29·0 (26·0–33·0)	30·0 (27·0–33·0)	31·0 (29·0–34·0)
Gestational age (weeks)	38·4 (37·6–39·4)	38·6 (37·6–39·4)	38·4 (37·4–39·6)	38·4 (37·4–39·4)
Ethnic origin				
White	317 (84%)	298 (79%)	60 (82%)	261 (81%)
Other	35 (9%)	47 (12%)	11 (15%)	32 (10%)
Unknown	25 (7%)	34 (9%)	2 (3%)	31 (10%)
Education*				
Primary school (4 to 12 years)	6 (2%)	6 (2%)	0	0
Secondary school (12 to 16–18 years)	12 (3%)	12 (3%)	3 (4%)	7 (2%)
Lower professional school	39 (10%)	36 (9%)	6 (8%)	15 (5%)
Medium professional school	112 (30%)	106 (28%)	10 (14%)	64 (20%)
Higher professional school	55 (15%)	58 (15%)	17 (23%)	49 (15%)
University	17 (5%)	12 (3%)	3 (4%)	34 (10%)
Unknown	135 (36%)	149 (39%)	34 (47%)	155 (48%)
Maternal smoking†	52 (15%)	50 (14%)	7 (10%)	23 (8%)
Body-mass index (kg/m^2)				
First antenatal appointment	26·0 (22·8–30·6)	26·0 (22·7–29·7)	24·8 (22·1–28·1)	24·3 (21·9–28·4)
Baseline	32·5 (28·7–36·4)	32·3 (28·5–35·9)	30·1 (27·8–33·3)	30·5 (27·4–34·1)
Blood pressure (mm Hg)				
First antenatal appointment				
Systolic	120 (110–130)	120 (111–130)	120 (110–130)	120 (110–130)
Diastolic	75 (70–80)	75 (70–80)	70 (65–80)	75 (70–80)
Baseline				
Systolic	140 (140–150)	144 (140–150)	140 (137–150)	140 (137–150)
Diastolic	100 (95–100)	100 (95–100)	100 (95–100)	98 (95–100)
Bishop score				
<2	93 (25%)	82 (22%)	..	..
2–6	225 (60%)	244 (64%)	..	..
>6	16 (4%)	12 (3%)	..	..
Unknown	43 (11%)	41 (11%)	..	..
Cervical length with transvaginal sonography (mm)	30·0 (23·0–37·0)	30·0 (22·0–37·0)	..	..
Haemoglobin (mmol/L)	7·5 (7·0–8·0)	7·4 (6·9–8·0)	7·5 (6·9–8·0)	7·6 (7·1–8·1)
Packed cell volume (L/L)	0·36 (0·34–0·38)	0·36 (0·34–0·37)	0·36 (0·33–0·38)	0·36 (0·34–0·38)
Platelets (×10^9/L)	230 (192–277)	232 (192–280)	219 (177–269)	219 (189–263)
Uric acid (μmol/L)	310 (260–360)	310 (270–360)	310 (260–390)	320 (270–370)
Creatinine (μmol/L)	59·0 (52·0–70·0)	60·0 (51·8–70·0)	61·0 (55·0–73·0)	62·0 (54·0–70·0)
Aspartate aminotransferase (U/L)	20·0 (16·0–25·0)	20·0 (16·0–25·0)	20·0 (17·0–26·0)	20·0 (16·0–24·8)
Alanine aminotransferase (U/L)	12·0 (9·0–17·0)	12·0 (10·0–17·0)	13·0 (9·0–18·3)	12·0 (10·0–17·0)
Lactate dehydrogenase (U/L)	294 (199–374)	287 (200–366)	331 (254–395)	316 (226–380)
Diagnosis				
Gestational hypertension	244 (65%)	252 (66%)	45 (62%)	232 (72%)
Pre-eclampsia	123 (33%)	123 (32%)	28 (38%)	84 (26%)
Unknown	10 (3%)	4 (1%)	0	8 (2%)
Proteinuria in women with pre-eclampsia (mg per 24 h)	450 (300–1140)	600 (350–970)	735 (365–1800)	655 (463–1400)

Data are number of patients (%) or median (IQR). Data are at baseline unless otherwise indicated. ..=data unavailable because not routinely measured. *Lower, medium, and higher professional schools denote preparatory, intermediate, and higher vocational education, respectively. †Data are missing for some participants: n=353 for induction of labour (randomised), n=360 for expectant monitoring (randomised), n=67 for induction of labour (non-randomised), and n=303 for expectant monitoring (non-randomised).

Table 1: **Demographic and clinical characteristics of randomised and non-randomised patients**

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI; p value)	Absolute risk reduction (95% CI)
Time between randomisation and onset of labour (days)	0·79 (0·67–1·0)	6·3 (3·7–10·9)	<0·0001*	NA
Gestational age at delivery (weeks)	38·7 (37·9–39·8)	39·9 (38·9–40·4)	<0·0001*	NA
Onset of labour				
Spontaneous	10 (3%)	200 (53%)	0·05 (0·03–0·09; <0·0001)	50·12% (44·64 to 55·24)
Planned caesarean section	1 (<1%)	6 (2%)	0·17 (0·02–1·39; 0·059)	NS
Induction	366 (97%)	173 (46%)	2·13 (1·90–2·38; <0·0001)	–51·44% (–56·54 to –45·93)
Indications that induction of labour was needed†				
Randomised to treatment	366 (100%)	0	NA	NA
Maternal indications	0	94 (54%)	NA	NA
Severe hypertension (mm Hg)	NA	78 (45%)	NA	NA
Severe proteinuria	NA	3 (2%)	NA	NA
HELLP syndrome	NA	7 (4%)	NA	NA
Use of anticonvulsive drugs	NA	37 (21%)	NA	NA
Use of intravenous antihypertensive drugs	NA	28 (16%)	NA	NA
Suspected fetal distress	0	18 (10%)	NA	NA
Time since prelabour rupture of membranes >48 h	0	9 (5%)	NA	NA
Gestational age >41 weeks	0	24 (14%)	NA	NA
Chose induction	0	48 (28%)	NA	NA

Data are median (IQR) or number of patients (%), unless otherwise indicated. NA=not applicable. NS=not stated because indicator was not significantly associated. HELLP=haemolysis, elevated liver enzymes, and low platelet count. *Relative risk and absolute risk reduction not stated because not clinically relevant. †Some patients had more than one clinical feature; percentages are given for women who were induced (366 patients randomised to induction of labour, 173 patients randomised to expectant monitoring).

Table 2: **Pregnancy outcome and onset of labour in randomised patients**

>70 U/L or alanine aminotransferase >70 U/L). Thromboembolic disease was defined as deep-vein thrombosis or pulmonary embolism.[16] Major post-partum haemorrhage was defined as blood loss of more than 1000 mL within 24 h of delivery.[17] Secondary outcome measures were method of delivery, neonatal mortality, and neonatal morbidity. For neonatal morbidity, we used a composite outcome consisting of a 5-min Apgar score of lower than 7, umbilical artery pH of lower than 7·05, or admission to a neonatal intensive care unit.

Statistical analysis

The composite measure of poor maternal outcome in the expectant monitoring group was thought to be 12%, on the basis of data obtained from the National Dutch Perinatal Registry of 2003 and 2004. We anticipated that induction of labour would reduce this occurrence to 6%. A sample size of 720 women, 360 women per treatment group, was needed for 80% power and a 5% type 1 error probability (two-sided).[18] We assumed a 5% protocol violation and planned to randomise 750 women.

Data were analysed on an intention-to-treat basis. All randomised women could be included in the trial analysis because missing data for relevant outcome measures were negligible. Analysis of data included comparison of maternal condition with: laboratory findings at randomisation, maternal mortality and morbidity until hospital discharge and 6 weeks post partum, neonatal mortality and morbidity until hospital discharge, method of delivery, type of hospital care, and days of maternal and neonatal hospital admission.

After we established the distribution using the Kolmogorov-Smirnov test, differences between groups with normally distributed data were tested with the Student's *t* test. For data with a skewed distribution, a non-parametric Mann-Whitney U test was applied. Categorical data were analysed with χ^2 statistics. Calculation of the percentages was based on the number of valid observations. We included footnotes in tables and figures if any observations were missing. Treatment effect is presented as relative risk (RR) with 95% CIs, and where appropriate as absolute risk reduction with 95% CIs, relative risk reduction with 95% CIs, and number needed to treat. Since the randomisation was stratified for centre, parity, and presence of proteinuria, we also did a stratified analysis using logistic regression, presented as odds ratios (ORs) for the primary outcome. A p value of less than 0·05 indicated statistical significance.

We used exploratory subgroup analyses to assess the consistency of the treatment effect in the trial between different categories of patients. Treatment effects are represented by forest plots. Patients were characterised by gestational age of the fetus (36–37, 37–38, 38–39, 39–40, and 40–41 weeks' gestation), parity (nulliparous and multiparous women), hypertensive-related diseases

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI; p value)	Absolute risk reduction (95% CI)
Composite adverse maternal outcome	117 (31%)	166 (44%)	0·71 (0·59–0·86; <0·0001)	12·76% (5·87–19·49)
Maternal death	0	0	NA	NA
Severe hypertension (mm Hg)				
Systolic BP	55 (15%)	88 (23%)	0·63 (0·46–0·86; 0·003)	8·63% (3·05–14·16)
Diastolic BP	62 (16%)	103 (27%)	0·61 (0·46–0·80; <0·0001)	10·73% (4·85–16·52)
Severe proteinuria*	3 (2%)	4 (2%)	0·91 (0·21–4·02; 0·90)	NS
HELLP syndrome	4 (1%)	11 (3%)	0·37 (0·12–1·14; 0·07)	NS
Eclampsia	0	0	NA	NA
Lung oedema	0	2 (1%)	NA	NA
Postpartum haemorrhage	35 (9%)	40 (11%)	0·88 (0·57–1·35; 0·55)	NS
Thromboembolic disease	1 (<1%)	0	NA	NA
Placental abruption	0	0	NA	NA
Severe hypertension measured twice (mm Hg)				
Systolic BP	26 (7%)	44 (12%)	0·60 (0·38–0·95; 0·03)	4·71% (0·57–8·92)
Diastolic BP	28 (7%)	50 (13%)	0·56 (0·36–0·87; 0·01)	5·77% (1·42–10·16)
Drugs				
Oral antihypertensive	67 (18%)	111 (29%)	0·61 (0·47–0·80; <0·0001)	11·52% (5·48–17·45)
Intravenous antihypertensive	13 (3%)	39 (10%)	0·34 (0·18–0·62; <0·0001)	6·84% (3·28–10·59)
Intravenous anticonvulsive	24 (6%)	46 (12%)	0·53 (0·33–0·84; 0·01)	5·77% (1·64–9·98)
Maternal hospital care				
Intensive care	6 (2%)	14 (4%)	0·41 (0·16–1·07; 0·059)	NS
Medium care	14 (4%)	15 (4%)	0·90 (0·44–1·84; 0·777)	NS
Maternal ward	340 (90%)	319 (84%)	1·03 (0·99–1·07; 0·145)	NS
Unknown	17 (5%)	31 (8%)	NA	NA
Duration of hospital stay (days)	2·0 (1·0–3·0)	2·0 (1·0–4·0)	0·12†	NA

Data are number of patients (%) or median (IQR), unless otherwise indicated. NA=not applicable. BP=blood pressure. NS=not stated because indicator was not significantly associated.HELLP=haemolysis, elevated liver enzymes, and low platelet count. *Data are missing for some participants: n=157 for induction of labour, and n=191 for expectant monitoring. †Relative risk and absolute risk reduction not stated because not clinically relevant.

Table 3: **Maternal outcome**

(gestational hypertension and pre-eclampsia), systolic blood pressure at study entry (<140 and ≥140 mm Hg), Bishop score (<2, 2–6, and >6) and vaginal examination (cervical dilatation, effacement, consistence, position, length, and engagement). The engagement process is described with the levels of Hodge.[13] Statistical analyses were done with SPSS software (version 16.0).

This study is registered, number ISRCTN08132825.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Between October, 2005, and March, 2008, we identified 1153 eligible women, of whom 756 gave informed consent for randomisation. We randomly assigned 377 patients to induction of labour and 379 to expectant monitoring (figure 1). Of the 397 patients who refused randomisation, most (82%) had expectant monitoring and only 18% had induction of labour. Baseline characteristics of all eligible women (table 1) showed that women in the randomised group, compared with those in the non-randomised group, had a higher median body-mass index at their first antenatal appointment (26·0 kg/m², IQR 22·8–30·0 *vs* 24·5 kg/m², IQR 22·0–28·1; p<0·0001), smoked more frequently (14% [n=102 patients] *vs* 8% [n=30], p=0·003), and, for those whom information was available, had a lower education level (30% [n=142] *vs* 50% [n=103] had finished higher professional school or university, p<0·0001).

Outcome data were available for all patients who were randomised (table 2). Median time between randomisation and onset of labour was almost 1 week shorter in the induction group than the expectant monitoring group (table 2). Of the women allocated to induction of labour, few had spontaneous onset of labour (table 2). For those whose labour was induced (n=366 patients), 288 (79%) were induced within 24 h of randomisation, 65 (18%) were induced 24–48 h after randomisation, 11 (3%) were induced 2–4 days after randomisation, and two (1%) were induced 4 days after

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI; p value)
Spontaneous	273 (72%)	253 (67%)	1·09 (0·99–1·19; 0·091)
Vaginal instrumental delivery	50 (13%)	54 (14%)	0·93 (0·65–1·33; 0·694)
Caesarean section	54 (14%)	72 (19%)	0·75 (0·55–1·04; 0·085)*
Clinical features indicating that caesarean section was needed			
Arrest of first stage of labour	15 (28%)	24 (33%)	NA
Arrest of second stage of labour	3 (6%)	7 (10%)	NA
Failed instrumental delivery	4 (7%)	2 (3%)	NA
Fetal distress	17 (31%)	20 (27%)	NA
Failure to progress and fetal distress	12 (22%)	8 (11%)	NA
Maternal complication	2 (4%)	7 (10%)	NA
Elective	1 (2%)	4 (6%)	NA

Data are number of patients (%), unless otherwise indicated. NA=not applicable. *Absolute risk reduction is 4·67% (95% CI −0·65 to 9·98).

Table 4: **Method of delivery**

randomisation. In 17 (5%) women the period between randomisation and successful induction was longer than expected (3 days) because the induction method with prostaglandins failed (median 4·0 days, IQR 4·0–6·5). These women were given lengthened treatment with prostaglandins, followed by treatment with oxytocin; five women delivered spontaneously, five had an instrumental delivery (four due to failure to progress, and one due to fetal distress), and seven had a caesarean section (six due to failure to progress, and one due to fetal distress). During induction with prostaglandins, one patient developed an allergic reaction against latex and consequently induction was discontinued. This patient then underwent a planned caesarean section because of suspected cephalopelvic disproportion.

Almost half of women allocated to expectant monitoring had their labour induced (table 2), of whom 125 (72%) had at least one medical reason for induction, and the remainder chose to be induced (table 2). Six patients had planned caesarean section, and in four of these patients, pregnancy was complicated by severe hypertension, of whom two also developed HELLP syndrome. One planned caesarean section was done because abnormalities were detected during fetal-heart-rate monitoring, and another was done for a patient with a history of total hip replacement on both sides and a triple pelvic osteotomy, who had a hip luxation during expectant monitoring.

The number of missing values for each of the variables of the primary outcome ranged from 0% for maternal mortality and eclampsia to 2% for post-partum haemorrhage. Occurrence of the primary outcome of the composite poor maternal outcome was significantly lower for women allocated to induction of labour than for those allocated to expectant monitoring (table 3; OR 0·58, 95% CI 0·43–0·78, p<0·0001). Therefore, allocation to induction of labour corresponded to a relative risk reduction of 29·14% (95% CI 13·40–44·50), and a number needed to treat of 8 (95% CI 5–17). A similar treatment effect was shown by stratified analysis (OR 0·56, 95% CI 0·41–0·77, p<0·0001). No women who were randomised died from hypertensive disease in pregnancy, eclampsia, or placental abruption. One woman died 9 months post partum from sudden unexpected death due to epilepsy.

Overall, 2% (n=15) of patients developed HELLP syndrome, and the difference between intervention groups was not significant (table 3). One patient allocated to labour induction had a pulmonary embolism, and pulmonary oedema occurred in two women allocated to expectant monitoring, one of whom developed acute respiratory distress syndrome (table 3). Progression to severe disease occurred in 88 women in the induction group and in 138 women in the expectant monitoring group (23% *vs* 36%; RR 0·64, 95% CI 0·51–0·80, p<0·0001); several women had more than one severe disease at the same time. The treatment effect was similar when progression to severe disease was diagnosed from high blood pressure measured on at least two occasions more than 6 h apart (11% [n=42] *vs* 19% [n=73]; 0·58, 0·41–0·82, p=0·002). Significantly fewer women randomised to induction, compared with those allocated to expectant monitoring, were prescribed both oral and intravenous antihypertensive drugs (20% [n=77] *vs* 33% [n=124]; 0·63, 0·49–0·81, p<0·0001) and prophylactic anticonvulsive drugs.

Although fewer patients had caesarean sections in the induction group than in the expectant monitoring group, the difference was not significant (table 4). Most caesarean sections were done for patients with arrest of the first stage of labour, failure to progress, or fetal distress (table 4). In both the induction and expectant monitoring groups, the proportion of caesarean sections was higher for women with a composite poor maternal outcome (23% [n=27] *vs* 27% [n=45]; 0·85, 0·56–1·29, p=0·44) than for those who were not classed as having poor maternal outcome (10% [n=27] *vs* 13% [n=27]; 0·82, 0·50–1·35, p=0·44). Occurrence of vaginal instrumental delivery was much the same between the induction and expectant monitoring groups (table 4).

No fetal or neonatal deaths occurred in either of the intervention groups, and the difference in composite neonatal morbidity was not significant between the interventions (table 5). However, a lower number of neonates had an arterial pH of less than 7·05 in the induction group than the expectant monitoring group (table 5). Both groups had similar proportions of neonates who had a 5-min Apgar score of lower than 7 or were admitted to an intensive care unit; table 5 shows the reasons for admission to an intensive care unit and total admission time. In the induction group, neonates were born at an earlier stage of pregnancy than in the expectant monitoring group, and therefore their birthweight was significantly lower.

In almost all subgroups a trend toward a better maternal outcome was found for patients who were induced than those who had expectant monitoring (figure 2). Only women randomised at a gestational age of 36–37 weeks or with cervical dilatation of more than 2 cm might benefit from expectant monitoring (figure 2). Subgroup analyses on the risk of caesarean section showed that the favourable effect of induction of labour was not present in women who were multiparous, had a Bishop score of 2–6, had cervical dilatation of 1 cm, or had median or anterior position of the cervix (figure 3).

The proportion of patients who had the composite poor maternal outcome in the non-randomised group was 43% (n=31) for those allocated to induction and 38% (n=123) for those allocated to expectant monitoring. The occurrence of caesarean sections in these patients was 4% (n=3) for those allocated to induction and 16% (n=52) for those allocated to expectant monitoring.

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI; p value)
Birthweight (g)	3220 (2890–3565)	3490 (3080–3810)	<0·0001*
Composite adverse neonatal outcome	24 (6%)	32 (8%)	0·75 (0·45–1·26; 0·276)†
Fetal deaths	0	0	NA
Apgar score of <7 after 5 min	7 (2%)	9 (2%)	0·79 (0·30–2·09; 0·632)
Arterial pH <7·05‡	9 (3%)	19 (6%)	0·46 (0·21–1·00; 0·043)§
Admission to intensive care	10 (3%)	8 (2%)	1·26 (0·50–3·15; 0·625)
Neonatal hospital care			
Medium care	68 (18%)	69 (18%)	0·99 (0·73–1·34; 0·952)
High care	12 (3%)	10 (3%)	1·21 (0·53–2·76; 0·656)
Intensive care	10 (3%)	8 (2%)	1·26 (0·50–3·15; 0·625)
Duration of stay in a neonatal medium, high, or intensive care unit (days)	3·0 (2·0–6·0)	4·0 (2·8–7·0)	0·077*
Reasons for admission to an neonatal intensive care unit¶			
Asphyxia	3 (1%)	3 (1%)	NA
Low birthweight	3 (1%)	0	NA
Hypoglycaemia	0	2 (1%)	NA
Infant respiratory distress syndrome	1 (<1%)	1 (<1%)	NA
Meconium aspiration	0	1 (<1%)	NA
Neonatal sepsis	0	1 (<1%)	NA
Hyperbilirubinaemia	2 (1%)	0	NA
Persistent pulmonary hypertension	0	1 (<1%)	NA
Down syndrome with congenital heart defect	1 (<1%)	0	NA
Inguinal hernias	1 (<1%)	0	NA
Interhemispheric cyst	1 (<1%)	0	NA

Data are median (IQR) or number of patients (%), unless otherwise indicated. NA=not applicable. *Relative risk and absolute risk reduction not stated because not clinically relevant. †Absolute risk reduction is 2·08% (95% CI –1·71 to 5·91). ‡Data are missing for some participants: n=311 for induction of labour, and n=301 for expectant monitoring. §Absolute risk reduction is 3·42% (0·06 to 7·02). ¶Some neonates had more than one clinical feature to indicate that admission to a neonatal intensive care unit was needed.

Table 5: **Neonatal outcome**

Discussion

The results of this study show that induction of labour was associated with a lower composite risk of poor maternal outcome, which was mainly ascribed to progression to severe disease, than was expectant monitoring. Overall, 13 per 100 fewer women allocated to induction of labour had a poor maternal outcome, corresponding with a number needed to treat of eight. Surprisingly, fewer caesarean sections were needed in the induction group than the expectant monitoring group. Adverse neonatal outcomes did not differ significantly between the groups.

The number of women with progression to severe disease was higher than expected from the sample size calculation before the trial began. Consequently, we recorded a high occurrence of the primary outcome with both interventions. This underestimation might be attributable to the absence of some useful data in the National Dutch Perinatal Registry, on which the calculation was based. First, systolic blood pressure was part of our primary outcome, but this variable was not recorded in the registry, and therefore not considered in the sample size calculation. We decided to include systolic blood pressure in our primary composite outcome since accumulating evidence suggests that systolic blood pressure is a risk factor for serious maternal morbidity, especially cerebrovascular accidents.[19,20] Second, the large number of women with high blood pressure in the trial might be explained by the fact that we used only one measurement of severe hypertension to fulfil the definition of progression to severe disease, whereas two measurements are needed for diagnosis, according to the National Dutch Perinatal Registry. Use of an endpoint based on a minimum of two measurements of high blood pressure at least 6 h apart might have underestimated the occurrence of severe hypertension, since in clinical practice the decision to treat a patient with antihypertensives or induction of labour is often based on only one measurement. However, when we recalculated the occurrence of the primary endpoint with progression to severe disease diagnosed from at least two measurements of high blood pressure, the treatment benefit of induction was also clear.

We found that fewer caesarean sections were needed in the induction group than the expectant monitoring group. Randomised trials in women with post-term pregnancies or those with pre-labour rupture of membranes at term showed similar proportions of caesarean section done for women receiving induction of labour and expectant monitoring.[21,22] The association of induction of labour with increased numbers of caesarean sections is based on results from non-randomised studies alone.[6–8] The reduced risk of caesarean section that we recorded after induction of labour could be caused by decreased occurrence of severe maternal morbidity with this intervention. To support this theory,

	Induction of labour (N=377) Event/n	Expectant monitoring (N=379) Event/n	Relative risk (95% CI)	Relative risk (95% CI)
Gestational age at randomisation (weeks)				
36–37	18/40 (45%)	15/35 (43%)		1·05 (0·63–1·76)
37–38	32/96 (33%)	41/92 (45%)		0·75 (0·52–1·08)
38–39	27/99 (27%)	40/93 (43%)		0·63 (0·43–0·94)
39–40	27/83 (33%)	43/103 (42%)		0·78 (0·53–1·15)
40–41	13/59 (22%)	27/56 (48%)		0·46 (0·26–0·79)
Parity				
Nulliparous	83/269 (31%)	123/272 (45%)		0·68 (0·55–0·85)
Multiparous	34/108 (31%)	43/107 (40%)		0·78 (0·55–1·13)
Pregnancy-related hypertension*				
Gestational hypertension	75/244 (31%)	96/252 (38%)		0·81 (0·63–1·03)
Pre-eclampsia	41/123 (33%)	67/123 (54%)		0·61 (0·45–0·82)
Systolic blood pressure at baseline (mm Hg)				
<140	8/66 (12%)	29/73 (40%)		0·31 (0·15–0·62)
≥140	109/311 (35%)	137/306 (45%)		0·78 (0·64–0·95)
Bishop score at baseline*				
<2	36/93 (39%)	45/82 (55%)		0·71 (0·51–0·97)
2–6	66/225 (29%)	98/244 (40%)		0·73 (0·57–0·94)
>6	5/16 (31%)	5/12 (42%)		0·75 (0·28–2·02)
Cervical dilatation at baseline (cm)*				
0	62/174 (36%)	86/163 (53%)		0·68 (0·53–0·87)
1	34/121 (28%)	48/131 (37%)		0·77 (0·53–1·10)
2	16/53 (30%)	25/55 (45%)		0·66 (0·40–1·10)
>2	4/16 (25%)	3/17 (18%)		1·41 (0·37–5·37)
Cervical effacement at baseline*				
≤25%	53/169 (31%)	78/161 (48%)		0·65 (0·49–0·85)
>25%	62/192 (32%)	81/199 (41%)		0·79 (0·61–1·03)
Cervical consistence at baseline*				
Stiff	22/61 (36%)	36/65 (55%)		0·65 (0·44–0·97)
Moderate to very weak	92/301 (31%)	125/297 (42%)		0·73 (0·59–0·90)
Engagement at baseline*				
Hodge 1	102/316 (32%)	127/304 (42%)		0·77 (0·63–0·95)
>Hodge 1	9/32 (28%)	25/48 (52%)		0·54 (0·29–1·00)
Cervical position at baseline*				
Posterior	65/207 (31%)	96/188 (51%)		0·62 (0·48–0·79)
Median to anterior	50/153 (33%)	62/168 (37%)		0·89 (0·66–1·20)
Cervical length at baseline (cm)*				
<4	90/285 (32%)	118/291 (41%)		0·78 (0·63–0·97)
≥4	24/68 (35%)	38/64 (59%)		0·59 (0·41–0·87)

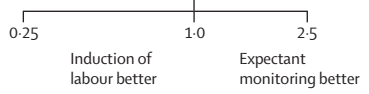

Figure 2: **Risk of composite poor maternal outcome**
*Data are missing for some participants.

stratified analysis in women with and without poor maternal outcome showed that an increased proportion of women with poor maternal outcome needed caesarean section, but no difference was recorded between those receiving induction of labour or expectant monitoring in either group of women.

In this trial, the primary outcome was defined as a composite measure of poor maternal outcome consisting of several conditions. We decided to include progression to severe hypertension because this disease is associated with severe maternal morbidity, such as eclampsia, pulmonary oedema, and cerebral encephalopathy or haemorrhage.[23–25] If we had restricted our primary outcome to conditions of severe morbidity, such as eclampsia, we would have had to extend the power of the study substantially. Such a target was not feasible for our study group. Moreover, since induction of labour reduces the risk of progression to severe disease, and because this intervention probably reduces the risk of caesarean section, we think that a larger study excluding progression to severe disease is not needed.

Major post-partum haemorrhage was also part of our composite primary outcome, because it has been recognised as an important risk factor in pregnant women with hypertensive disorders.[26–28] We postulated that induction of labour would reduce the risk of progression to severe disease and thereby reduce the risk of major post-partum haemorrhage. We recorded 10% of women with a major post-partum haemorrhage, which exceeded the 1·33% risk of haemorrhage (>1000 mL) that has been reported in low-risk populations,[29] but induction of labour did not reduce the occurrence of severe haemorrhage.

In the subgroup analyses we found that the beneficial effect of induction of labour was absent in women with fewer than 37 weeks' gestation, but the result is unreliable because of the low number of women in this subgroup. Our study was not sufficiently powered to detect

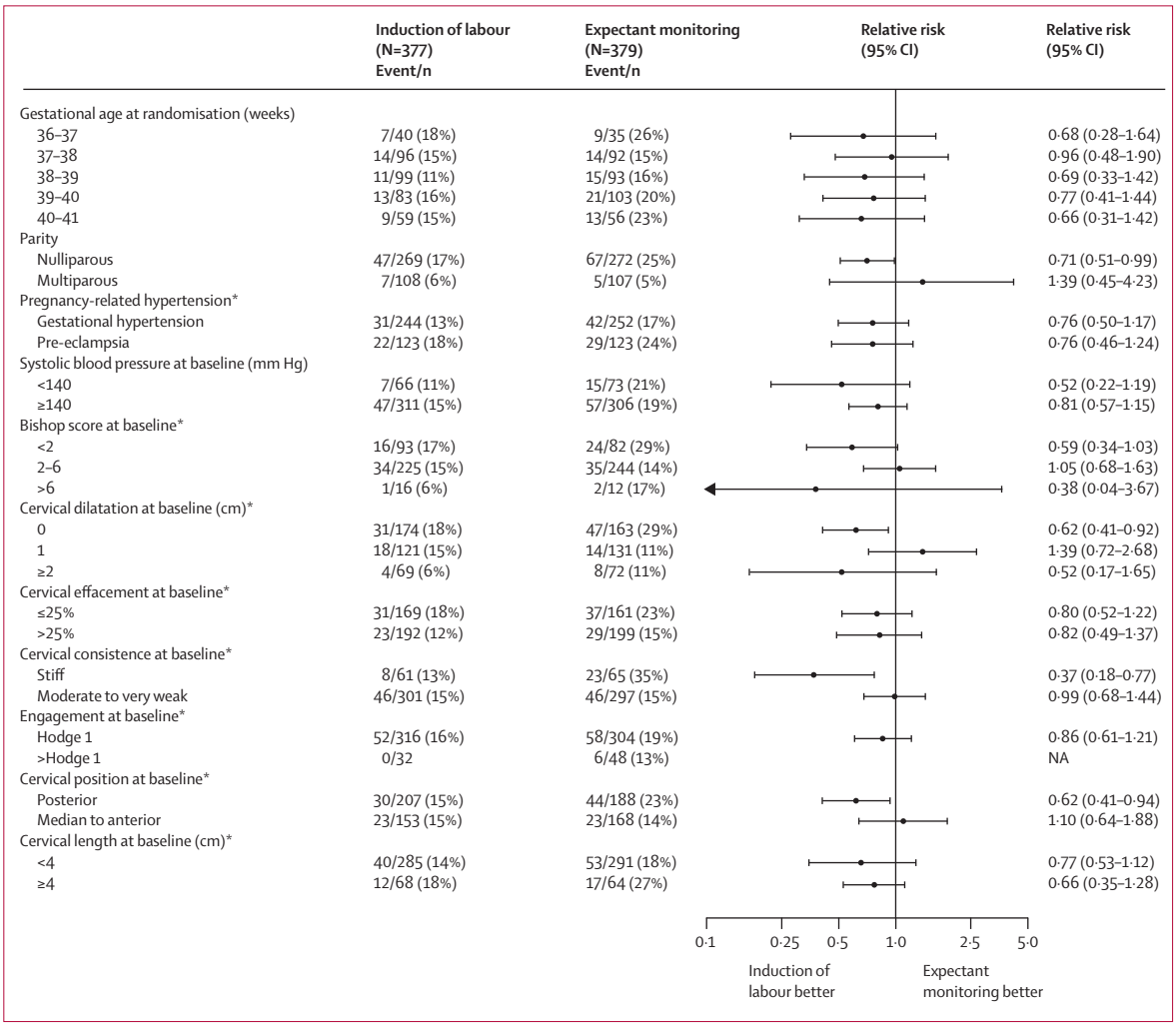

Figure 3: **Risk of caesarean section**
NA=not applicable. *Data are missing for some participants.

differences in subgroup analyses,[30] and consequently we are hesitant to extrapolate trial results to women with a gestational age of 36–37 weeks.

The treatment effect that we found was pronounced in women with an unfavourable cervix (eg, cervical dilation 0 cm, cervical effacement ≤25%, or posterior position of cervix).[31] This paradoxal finding is explained by the fact that in such women who were allocated to expectant monitoring, time to delivery was longer relative to those with a favourable cervix, thereby increasing the risk that the maternal condition could deteriorate. Since the effect of an unfavourable cervix was reduced in women allocated to induction of labour, the benefit of induction increases in women with an unfavourable cervix.

Effective management of women with hypertensive disease beyond 36 weeks' gestation is strongly controversial in the Netherlands. In most participating centres, the protocol recommended expectant monitoring, which was the preferred policy in the non-randomised groups of women. In the USA and other developed countries, induction of labour in women with gestational hypertension or mild pre-eclampsia at term is already general practice, but until now this recommendation has not been based on the results of randomised clinical trials.[1,32]

The results of our trial are important for both developed countries in which induction of labour in women with hypertensive disease beyond 36 weeks' gestation has been controversial, and for developing countries in which maternal morbidity and mortality rates are substantially increased.[3] Our finding that induction of labour was associated with a reduced risk of severe hypertension or HELLP syndrome and subsequent reduced need for caesarean section, emphasises the importance of frequent blood pressure monitoring during the concluding weeks of pregnancy. We believe that induction of labour should be advised for women with gestational hypertension and a diastolic blood pressure of 95 mm Hg or higher or mild pre-eclampsia at a gestational age beyond 37 weeks.

Contributors
MGvP, BWJM, and JAMvdP wrote the grant application and obtained funding for the study. All authors participated in the study design, recruited patients, and collected data. CMK analysed and interpreted the data. HG and BWJM provided background knowledge to the data analysis and interpretation. CMK drafted the report, and all authors contributed to review and revision. All authors have seen and approved the final version.

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Conflicts of interest
We declare that we have no conflicts of interest.

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