Articles

Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial

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Summary

Background There is little evidence to guide the management of women with hypertensive disorders in late preterm pregnancy. We investigated the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in such women.

Methods We did an open-label, randomised controlled trial, in seven academic hospitals and 44 non-academic hospitals in the Netherlands. Women with non-severe hypertensive disorders of pregnancy between 34 and 37 weeks of gestation were randomly allocated to either induction of labour or caesarean section within 24 h (immediate delivery) or a strategy aimed at prolonging pregnancy until 37 weeks of gestation (expectant monitoring). The primary outcomes were a composite of adverse maternal outcomes (thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death), and neonatal respiratory distress syndrome, both analysed by intention-to-treat. This study is registered with the Netherlands Trial Register (NTR1792).

Findings Between March 1, 2009, and Feb 21, 2013, 897 women were invited to participate, of whom 703 were enrolled and randomly assigned to immediate delivery (n=352) or expectant monitoring (n=351). The composite adverse maternal outcome occurred in four (1·1%) of 352 women allocated to immediate delivery versus 11 (3·1%) of 351 women allocated to expectant monitoring (relative risk [RR] 0·36, 95% CI 0·12–1·11; p=0·069). Respiratory distress syndrome was diagnosed in 20 (5·7%) of 352 neonates in the immediate delivery group versus six (1·7%) of 351 neonates in the expectant monitoring group (RR 3·3, 95% CI 1·4–8·2; p=0·005). No maternal or perinatal deaths occurred.

Interpretation For women with non-severe hypertensive disorders at 34–37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes. However, it significantly increases the risk of neonatal respiratory distress syndrome, therefore, routine immediate delivery does not seem justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered.

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Introduction

Hypertensive disorders of pregnancy, such as gestational hypertension, pre-existing or chronic hypertension during pregnancy, pre-eclampsia, and superimposed pre-eclampsia,[1] occur in roughly 10% of all pregnancies.[2,3] These disorders cause substantial maternal and neonatal morbidity and mortality worldwide.[4,5]

Delivery of the placenta is the only definitive treatment for hypertensive disorders of pregnancy; it will stop progression and therefore has the potential to prevent adverse pregnancy outcomes. However, immediate delivery also has potential disadvantages. First, it can result in preterm or early term birth, which increases the risk of neonatal complications.[6] Second, induction of labour might increase the risk of a need for caesarean section.[7] Therefore, management of hypertensive

disorders should be based on the balance between the risks of immediate delivery versus the risks of continuing the pregnancy. In severe pre-eclampsia before 34 weeks of gestation, delivery decreases the proportion of neonates born small for gestational age, while the effect on other neonatal morbidity and maternal outcomes is uncertain.[8–11] The first HYPITAT study showed that delivery reduces the risk of adverse maternal outcomes for women with mild gestational hypertension or pre-eclampsia beyond 37 weeks of gestation, without affecting neonatal outcomes or risk of caesarean section.[12] However, for women at 34–37 weeks of gestation who have hypertensive disorders, little is known of the risks and benefits of immediate delivery versus continuing pregnancy.[13] Dutch guidelines do not advise about timing of delivery for women with hypertensive disorders of pregnancy and both strategies

are practised in Netherlands.[14] Therefore, we investigated the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes for women with hypertensive disorders between 34 and 37 weeks' gestation.

Methods

Study design and participants

We did an open-label, randomised controlled trial in seven academic hospitals and 44 non-academic hospitals in Netherlands.[15] Women were eligible if they had gestational hypertension, pre-eclampsia, deteriorating pre-existing hypertension, or superimposed pre-eclampsia, and had a gestational age of $34^{0/7}$ weeks up to and including $36^{6/7}$ weeks (in Netherlands, gestational age is routinely measured by first trimester ultrasound).

We defined gestational hypertension as a diastolic blood pressure of 100 mm Hg or more, on at least two occasions, 6 h apart, in women without pre-existing hypertension (defined as a blood pressure ≥140/90 mm Hg before 20 weeks of gestation). We defined pre-eclampsia as a diastolic blood pressure of 90 mm Hg or more on at least two occasions, 6 h apart, combined with proteinuria, also in women without pre-existing hypertension. Proteinuria was defined as a spot protein:creatinine ratio of 30 mg/mmol or more or at least 300 mg protein in a 24-h urine collection. We defined deteriorating pre-existing hypertension as the need for new or additional antihypertensive drugs after 34 weeks of gestation in a woman with pre-existing hypertension, and we defined superimposed pre-eclampsia as new onset proteinuria in women with pre-existing hypertension.

We excluded women with severe hypertensive disorder (systolic blood pressure ≥170 mm Hg or a diastolic blood pressure ≥110 mm Hg despite drugs), severe proteinuria (≥5 g/L), oliguria (<500 mL per 24 h), HELLP syndrome (haemolysis, elevated liver enzyme concentrations, and low platelet count), pulmonary oedema, or cyanosis.[16] Other exclusion criteria were a non-reassuring fetal condition (non-reassuring fetal heart rate tracing, reversed diastolic umbilical artery flow), and maternal or fetal comorbidity that would have affected management or treatment effect (maternal renal or cardiac disease, maternal HIV, fetal chromosomal or structural abnormalities). Women with ruptured membranes or any other contraindication to prolong pregnancy as judged by the attending gynaecologist were also excluded. Women with a multiple pregnancy or a fetus in non-cephalic position were not excluded.

The study protocol was approved by the institutional review board of the Academic Medical Centre in Amsterdam and the boards of directors of all participating centres.[15] Women who gave written informed consent were included in the randomised study, those who did not provide informed consent were asked to provide informed consent to participate in an observational phase of the study.

Randomisation and masking

Eligible women were counselled by staff or research nurses or midwives of participating centres collaborating in the Dutch Obstetric Research Consortium. After giving consent but before randomisation, digital vaginal examination and measurement of cervical length by transvaginal ultrasound were done. We randomly assigned participants (1:1) to immediate delivery or expectant monitoring. The randomisation was done with a web-based system by random permuted blocks with variable block size (range 2–4), stratified by centre. Neither participants, gynaecologists, nor outcome assessors were masked to treatment allocation.

Procedures

Women who were assigned to immediate delivery and had a Bishop score[17] of 6 or more had labour induced by amniotomy followed by augmentation with oxytocin if necessary. For women with a Bishop score of less than 6, induction of labour was preceded by cervical priming with either a Foley catheter or prostaglandins, according to local protocol. For women with a contraindication for induction of labour or vaginal delivery as judged by the attending gynaecologist, a caesarean section was planned. All interventions were planned to start within 24 h of randomisation.

Women who were assigned to expectant monitoring were monitored as outpatients (visiting the clinic several times per week), through a home care programme (being visited at home by a trained nurse or midwife several times per week), or in hospital (admitted as inpatients), depending on their condition. Maternal monitoring was done according to local protocol, with at least blood pressure measurements at every outpatient or home visit and at least daily during admission, screening for

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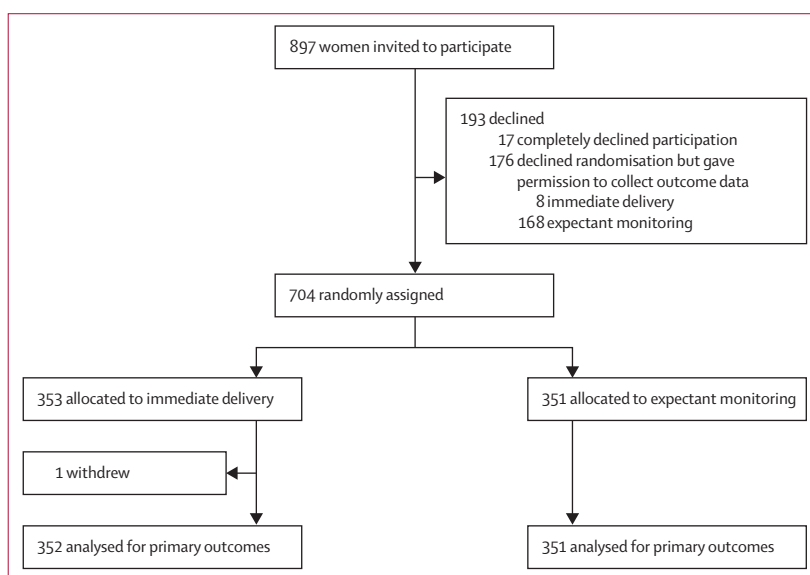

897 women invited to participate

193 declined
  17 completely declined participation
  176 declined randomisation but gave permission to collect outcome data
    8 immediate delivery
    168 expectant monitoring

704 randomly assigned

353 allocated to immediate delivery

351 allocated to expectant monitoring

1 withdrew

352 analysed for primary outcomes

351 analysed for primary outcomes

Figure 1: Trial profile

Articles

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For more details of the **trial** see http://www.studies-obsgyn.nl/hypitat2/page.asp?page_id=642

	Randomised		Not randomised	
	Immediate delivery (n=352)	Expectant monitoring (n=351)	Immediate delivery (n=8)	Expectant monitoring (n=168)
Age				
Mean (SD; years)	30·4 (5·3)	30·4 (5·1)	31·3 (6·3)	31·9 (5·0)
Data missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White ethnic origin	297/342 (87%)	297/344 (86%)	3/7 (43%)	135/160 (84%)
Education				
Primary school (4–12 years)	4/222 (2%)	4/225 (2%)	0/7 (0%)	1/102 (1%)
Secondary school (12–18 years)	13/222 (6%)	12/225 (5%)	0/7 (0%)	2/102 (2%)
Preparatory professional school	24/222 (11%)	19/225 (8%)	1/7 (14%)	4/102 (4%)
Intermediate professional school	102/222 (46%)	105/225 (47%)	4/7 (57%)	32/102 (31%)
Higher professional school	55/222 (25%)	68/225 (30%)	1/7 (14%)	41/102 (40%)
University	24/222 (11%)	17/225 (8%)	1/7 (14%)	22/102 (22%)
Non-smoking or quit before pregnancy	278/338 (82%)	285/338 (84%)	7/8 (88%)	147/164 (90%)
Body-mass index at booking (kg/m²)				
Median (IQR)	25·9 (22·8–30·3)	25·7 (23·1–30·1)	23·8 (21·1–27·5)	24·7 (21·2–29·0)
Data missing	32 (9%)	27 (8%)	0 (0%)	14 (8%)
Blood pressure at booking (mm Hg)				
Mean systolic (SD)	123·4 (14·9)	122·2 (15·3)	113·8 (13·8)	122·9 (13·2)
Systolic data missing	7 (2%)	10 (3%)	0 (0%)	14 (8%)
Mean diastolic (SD)	75·6 (11·8)	75·8 (11·7)	74·6 (7·6)	74·5 (11·0)
Diastolic data missing	6 (2%)	11 (3%)	0 (0%)	14 (8%)
Comorbidity				
Pregestational diabetes	4/352 (1%)	6/351 (2%)	0/8 (0%)	1/168 (1%)
Gestational diabetes	13/352 (4%)	11/351 (3%)	0/8 (0%)	3/168 (2%)
Parity ≥1	142/352 (40%)	145/351 (41%)	2/8 (25%)	43/168 (26%)
History of caesarean section	36/351 (10%)	41/349 (12%)	0/8 (0%)	12/168 (7%)
History of pre-eclampsia	53/351 (15%)	52/350 (15%)	0/7 (0%)	18/168 (11%)
Multifetal gestation	18/352 (5%)	26/351 (7%)	0/8 (0%)	6/168 (4%)
Gestational age at study entry (weeks)				
Median (IQR)	35⁺⁶ᐟ⁷ (35⁺⁰ᐟ⁷–36⁺³ᐟ⁷)	35⁺⁵ᐟ⁷ (35⁺⁰ᐟ⁷–36⁺²ᐟ⁷)	35⁺²ᐟ⁷ (34⁺³ᐟ⁷–36⁺²ᐟ⁷)	35⁺²ᐟ⁷ (34⁺⁵ᐟ⁷–36⁺¹ᐟ⁷)
<34⁺⁰ᐟ⁷	2/352 (1%)	2/351 (1%)	1/8 (13%)	4/168 (2%)
34⁺⁰ᐟ⁷–34⁺⁶ᐟ⁷	77/352 (22%)	73/351 (21%)	1/8 (13%)	61/168 (36%)
35⁺⁰ᐟ⁷–35⁺⁶ᐟ⁷	104/352 (30%)	132/351 (37%)	4/8 (50%)	50/168 (30%)
36⁺⁰ᐟ⁷–36⁺⁶ᐟ⁷	168/352 (48%)	144/351 (41%)	2/8 (25%)	53/168 (32%)
≥37⁺⁰ᐟ⁷	1/352 (<1%)	0/351 (0%)	0/8 (0%)	0/168 (0%)
Diagnosis at study entry				
Gestational hypertension	92/352 (26%)	90/351 (26%)	0/8 (0·0%)	42/168 (25%)
Pre-eclampsia	165/352 (47%)	159/351 (45%)	5/8 (63%)	67/168 (40%)
Deteriorating hypertension	49/352 (14%)	49/351 (14%)	0/8 (0%)	25/168 (15%)
Superimposed pre-eclampsia	46/352 (13%)	53/351 (15%)	3/8 (38%)	34/168 (20%)
Blood pressure at study entry (mm Hg)				
Mean systolic (SD)	142·8 (11·7)	142·8 (12·0)	147·8 (9·2)	143·2 (12·1)
Mean diastolic (SD)	94·8 (7·6)	94·8 (7·9)	100·8 (6·3)	94·4 (6·1)
Data missing	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Antihypertensive drugs at study entry				
None	279/351 (79%)	263/350 (75%)	7/8 (88%)	115/168 (68%)
One oral	47/351 (13%)	60/350 (17%)	1/8 (13%)	27/168 (16%)
Multiple or intravenous	25/351 (7%)	27/350 (8%)	0/8 (0%)	26/168 (15%)
Proteinuria in women with (superimposed) pre-eclampsia				
Median protein:creatinine ratio (mg/mmol; IQR)	63·0 (25·0–40·0)	60·5 (25·0–40·0)	52·0 (52·0–52·0)	70·0 (18·0–55·0)

(Table 1 continues on next page)

	Randomised		Not randomised	
	Immediate delivery (n=352)	Expectant monitoring (n=351)	Immediate delivery (n=8)	Expectant monitoring (n=168)
(Continued from previous page)				
Data missing for protein:creatine ratio	275 (78%)	275 (78%)	7 (88%)	147 (88%)
Median 24 h collection (mg; IQR)	580·0 (390·0–1092·5)	600·0 (400·0–1445·0)	4860·0 (552·0–6140·0)	650·0 (400·0–1390·0)
Data missing for 24 h collection	0 (0%)	3 (1%)	0 (0%)	1 (1%)
Bishop score at study entry				
<2	135\324 (42%)	133\300 (44%)	1\3 (33%)	13\19 (68%)
2–6	172\324 (53%)	151\300 (50%)	2\3 (67%)	5\19 (26%)
≥6	17\324 (5%)	16\300 (5%)	0\3 (0%)	1\19 (5%)
Cervical length at study entry (mm)				
Median (IQR)	35·0 (25·0–40·0)	34·0 (25·0–40·0)	..	38·0 (18·0–55·0)
Data missing	29 (8%)	42 (12%)	8 (100%)	163 (97%)
Estimated fetal weight in bottom 10th percentile at study entry	30\293 (10%)	24\294 (8%)	0\2 (0%)	3\37 (8%)
Antenatal steroids before study entry	26\347 (7·5%)	29\346 (8%)	0\8 (0%)	13\167 (8%)

Data are n/N (%) unless otherwise stated.

Table 1: **Baseline characteristics**

proteinuria twice a week, and laboratory testing if either were abnormal. Fetal monitoring consisted of electronic monitoring of fetal heart rate at least twice a week and assessment of fetal movements as reported by the mother. At 37 weeks of gestation, delivery by induction of labour or caesarean section was planned as for the immediate delivery group.[12] Delivery before 37 weeks of gestation was advised for participants with severe hypertensive disorders (severe pre-eclamptic complaints, severe hypertension, severe proteinuria, anuria [<30 mL/h for ≥4 h], pulmonary oedema, HELLP syndrome, or eclampsia), suspected fetal distress (no fetal movements reported by the mother, non-reassuring fetal heart rate tracing, or absent or reversed diastolic umbilical artery flow), or any other contraindication to prolongation of pregnancy as judged by the attending gynaecologist.

In both groups, drug treatment for hypertension was started according to the Dutch Society for Obstetrics and Gynaecology guidelines,[14,18] which recommend starting antihypertensive drugs if systolic blood pressure is 160 mm Hg or higher, or if diastolic blood pressure is 110 mm Hg or higher.

Data collection was the responsibility of the local investigators of each centre, who were supported by research nurses or midwives. At study entry, we collected data for maternal characteristics, obstetric history, present pregnancy, fetal condition, and Bishop score. For the remainder of pregnancy, we collected data for severity of disease and use of health resources (eg, number of outpatient visits, drug prescriptions, maternal laboratory tests), and for delivery we collected data for onset, course, and mode of delivery. We collected data for maternal outcome until final discharge and at 6 weeks after birth; we collected data for neonatal outcomes until final discharge from hospital.

	Immediate delivery (n=352)	Expectant monitoring (n=351)	Relative risk (95% CI)
Time between randomisation and delivery (days)*	2·0 (1·0–3·0; 351)	7·0 (4·0–11; 350)	
<35+0/7	2·0 (1·0–3·0; 79)	10 (5·0–16; 75)	
35+0/7–35+6/7	2·0 (1·0–3·0; 103)	9·0 (6·0–12; 132)	
≥36+0/7	2·0 (1·0–2·0; 169)	5·0 (3·0–7·0; 144)	
Steroids between randomisation and delivery	4/347 (1%)	3/346 (1%)	
Onset of delivery			
Spontaneous	6/352 (2%)	25/351 (7%)	0·24 (0·10–0·58)
Induction of labour	319/352 (91%)	284/351 (81%)	1·12 (1·05–1·19)
Caesarean section	27/352 (8%)	42/351 (12%)	0·64 (0·40–1·02)
Indication for non-spontaneous onset†			
Randomisation	344/352 (98%)	0/351 (0%)	
Reaching 37 weeks of gestation	1/352 (<1%)	187/351 (53%)	
Maternal HDP	0/352 (0%)	98/351 (28%)	
Maternal comorbidity	0/352 (0%)	5/351 (1%)	
Fetal compromise	1/352 (<1%) ‡	24/351 (7%)	
Elective or not specified <37 weeks of gestation	0/352 (0%)	19/351 (5%)	

Data are median (IQR; N), or n/N (%). HDP=hypertensive disorders of pregnancy. *Mean difference 5·6 (95% CI 5·00-6·16). †Some women had more than one indication. ‡Patient mistakenly treated with expectant monitoring.

Table 2: **Onset of delivery for randomly assigned women**

Outcomes

The primary maternal outcome measure was a composite of adverse maternal outcomes, defined as one or more of thromboembolic complications, pulmonary oedema, HELLP syndrome, eclampsia, placental abruption, or maternal death. The primary neonatal outcome was neonatal respiratory distress syndrome, defined as the need for supplemental oxygen for more than 24 h

	Immediate delivery (n=352)	Expectant monitoring (n=351)	Relative risk (95% CI)	Absolute risk difference (95% CI)
Primary outcome	4 (1%)	11 (3%)	0·36 (0·12 to 1·11)	2·0 (–0·2 to 4·5)
Thromboembolic process	1 (<1%)	1 (<1%)	1·00 (0·06 to 15·88)	0·0 (–1·3 to 1·3)
Pulmonary oedema	0 (0%)	0 (0%)	..	0·0 (–1·1 to 1·1)
HELLP syndrome	3 (1%)	6 (2%)	0·50 (0·13 to 1·98)	0·9 (–0·0 to 0·0)
Eclampsia	0 (0%)	2 (1%)	..	0·6 (–0·6 to 2·1)
Placental abruption	0 (0%)	2 (1%)	..	0·6 (–0·6 to 2·1)
Death	0 (0%)	0 (0%)	..	0·0 (–1·1 to 1·1)
Secondary outcomes				
Instrumental vaginal delivery	32 (9%)	34 (10%)	0·94 (0·59 to 1·49)	0·6 (–3·8 to 5·0)
Caesarean section	107 (30%)	114 (32%)	0·94 (0·75 to 1·16)	2·1 (–4·8 to 8·9)
Onset by caesarean section	27 (8%)	42 (12%)		
Caesarean section after induction or spontaneous onset of labour	80 (23%)	72 (21%)		
Indication for instrumental vaginal delivery				
Failure to progress in second stage	13 (4%)	15 (4%)		
Suspected fetal distress	18 (5%)	12 (3%)		
Failure to progress in second stage and suspected fetal distress	1 (<1%)	3 (1%)		
Maternal complication	0 (0%)	4 (1%)		
Indication for caesarean section		*		
Failure to progress in first stage	28 (8%)	21 (6%)		
Failure to progress in second stage	3 (1%)	2 (1%)		
Failed instrumental delivery	3 (1%)	2 (1%)		
Suspected fetal distress	27 (8%)	33 (9%)		
Failure to progress and suspected fetal distress	12 (3%)	17 (5%)		
Maternal HDP related	6 2%)	8 (2%)		
Maternal comorbidity	6 (2%)	3 (3%)		
Non-cephalic fetal position	14 (4%)	20 (6%)		
History of caesarean section	4 (1%)	5 (1%)		
Elective or not specified	4 (1%)	5 (1%)		

Data are n (%). HDP=hypertensive disorders of pregnancy. HELLP=haemolysis, elevated liver enzyme concentrations, and low platelets. *Two women had a combination of maternal HDP and non-cephalic fetal position.

Table 3: Maternal outcomes

combined with radiographic findings typical for respiratory distress syndrome; all neonates' medical notes were reviewed to confirm the diagnosis.

Secondary maternal outcomes were instrumental delivery and caesarean section. Secondary neonatal outcome measures were a 5-min Apgar score of less than 7, an umbilical artery pH of less than 7·05, admission to a neonatal intensive care unit, death before discharge, suspected or confirmed neonatal infection or sepsis, hypoglycaemia necessitating intravenous glucose, transient tachypnoea of the newborn, meconium aspiration syndrome, pneumothorax or pneumomediastinum, necrotising enterocolitis, intraventricular haemorrhage, periventricular leucomalacia, and convulsions.

Statistical analysis

We postulated that immediate delivery could reduce the risk of adverse maternal outcomes from 5% in the expectant monitoring group to 1% in the immediate delivery group. This estimate was based on the 3·4% risk of composite adverse maternal outcome in the expectant monitoring group of the first HYPITAT study, and assuming a slightly higher risk of adverse maternal outcomes at earlier gestational ages.[12] To assess such a difference with a two-sided test with an α of 5% and a β of 20% and assuming 10% of participants would deviate from protocol, we needed to enrol 680 women (two groups of 340). This sample size was also sufficient to study the primary neonatal outcome, which we anticipated to occur in 8% of neonates in the delivery group and in 3% of the expectant group.[19]

We compared baseline characteristics for randomised and non-randomised women; non-randomised women were not further analysed for the present study. We did the statistical analyses by intention to treat.[20] We calculated risks with the number of valid observations (data available). For neonatal outcomes in multifetal gestations, the outcome was deemed present if at least one neonate was affected. We calculated effect sizes as relative risks (RRs)

	Immediate delivery (n=352)	Expectant monitoring (n=351)	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to harm
Primary outcome	20/352 (5·7%)	6/351 (1·7%)	3·3 (1·4 to 8·2); p=0·005	4·0 (1·2 to 7·1)	25
Secondary outcomes					
5 min Apgar score <7	14/351 (4·0%)	10/350 (2·9%)	1·4 (0·6 to 3·1)	1·1 (−1·7 to 4·0)	..
Umbilical artery pH <7·05	6/270 (2·2%)	6/263 (2·3%)	2·0 (0·3 to 3·0)	0·1 (−2·9 to 2·8)	..
NICU admission	26/352 (7·4%)	13/350 (3·7%)	2·0 (1·0 to 3·8)	3·7 (0·3 to 7·2)	27
Perinatal death	0/352 (0·0%)	0/351 (0·0%)	..	0·0 (−1·1 to 1·1)	..
Suspected or confirmed infection or sepsis	36/351 (10·3%)	22/348 (6·3%)	1·6 (1·0 to 2·7)	3·9 (−0·2 to 8·1)	..
Hypoglycaemia (intravenous glucose)	64/350 (18·3%)	53/348 (15·2%)	1·2 (0·9 to 1·7)	3·1 (−2·5 to 8·6)	..
Transient tachypnoea of the newborn	20/349 (5·7%)	6/348 (1·7%)	3·3 (1·4 to 8·2)	4·0 (1·2 to 7·1)	25
Meconium aspiration syndrome	0/351 (0·0%)	1/349 (0·3%)	..	0·3 (−1·6 to 0·8)	..
Pneumothorax or pneumomediastinum	3/351 (0·9%)	1/348 (0·3%)	3·0 (0·3 to 28·5)	0·6 (−0·9 to 2·2)	..
Periventricular leucomalacia	4/303 (1·3%)	2/284 (0·7%)	1·9 (0·4 to 10·2)	0·6 (−1·4 to 2·7)	..
Intraventricular haemorrhage	3/339 (0·9%)	0/335 (0·0%)	..	0·9 (−0·4 to 2·6)	..
Convulsions	4/351 (1·1%)	1/348 (0·3%)	4·0 (0·5 to 35·3)	0·9 (−0·6 to 2·6)	..
Necrotising enterocolitis	1/351 (0·3%)	0/348 (0·0%)	..	0·3 (−0·8 to 1·6)	..
Any neonatal morbidity*	131/267 (49·1%)	89/245 (36·3%)	1·4 (1·1 to 1·7)	12·7 (4·2 to 21·0)	8

Data are n (%). NICU=neonatal intensive care unit. *Classified as normal if umbilical artery pH was missing and other components were normal, classified as normal if periventricular leucomalacia or intraventricular haemorrhage, or both, were missing but no cerebral imaging had taken place; includes respiratory distress syndrome; some had more than one type of morbidity; not prespecified.
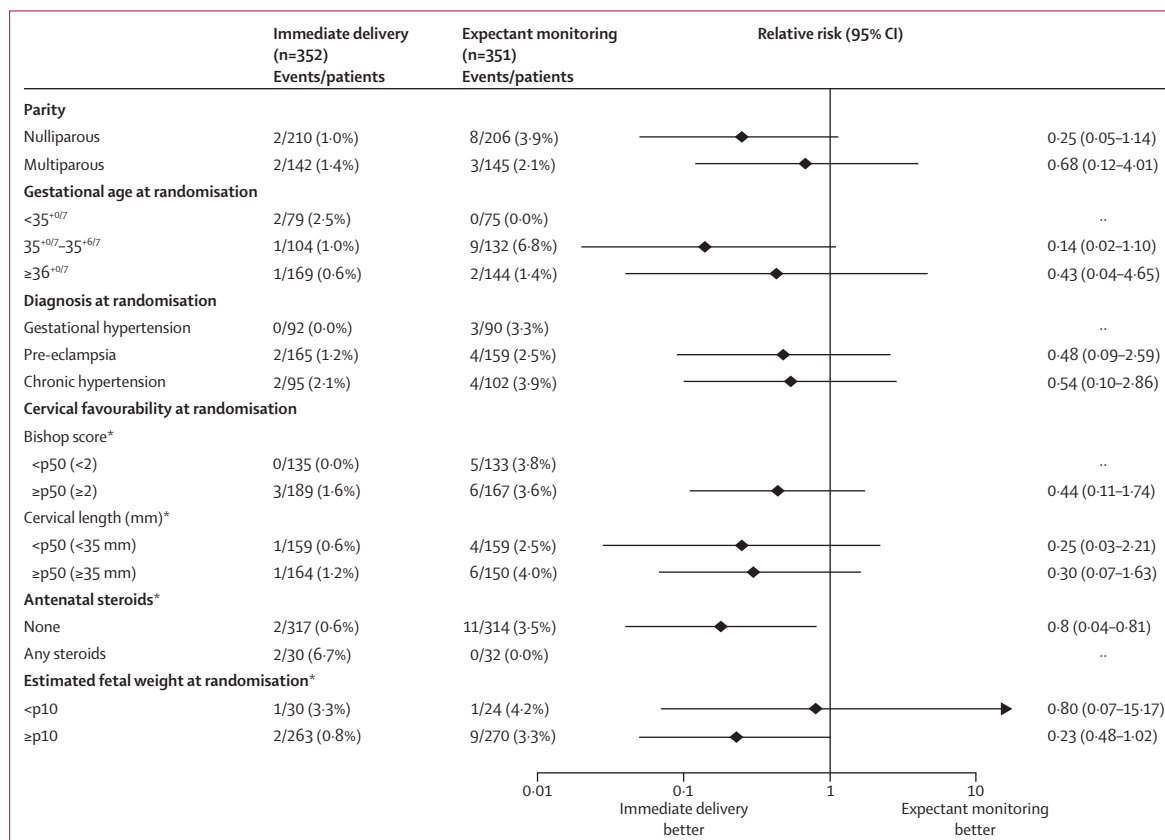
Table 4: Neonatal outcomes

	Immediate delivery (n=352) Events/patients	Expectant monitoring (n=351) Events/patients	Relative risk (95% CI)	
Parity				
Nulliparous	2/210 (1·0%)	8/206 (3·9%)		0·25 (0·05–1·14)
Multiparous	2/142 (1·4%)	3/145 (2·1%)		0·68 (0·12–4·01)
Gestational age at randomisation				
<35+0/7	2/79 (2·5%)	0/75 (0·0%)		..
35+0/7–35+6/7	1/104 (1·0%)	9/132 (6·8%)		0·14 (0·02–1·10)
≥36+0/7	1/169 (0·6%)	2/144 (1·4%)		0·43 (0·04–4·65)
Diagnosis at randomisation				
Gestational hypertension	0/92 (0·0%)	3/90 (3·3%)		..
Pre-eclampsia	2/165 (1·2%)	4/159 (2·5%)		0·48 (0·09–2·59)
Chronic hypertension	2/95 (2·1%)	4/102 (3·9%)		0·54 (0·10–2·86)
Cervical favourability at randomisation				
Bishop score*				
<p50 (<2)	0/135 (0·0%)	5/133 (3·8%)		..
≥p50 (≥2)	3/189 (1·6%)	6/167 (3·6%)		0·44 (0·11–1·74)
Cervical length (mm)*				
<p50 (<35 mm)	1/159 (0·6%)	4/159 (2·5%)		0·25 (0·03–2·21)
≥p50 (≥35 mm)	1/164 (1·2%)	6/150 (4·0%)		0·30 (0·07–1·63)
Antenatal steroids*				
None	2/317 (0·6%)	11/314 (3·5%)		0·8 (0·04–0·81)
Any steroids	2/30 (6·7%)	0/32 (0·0%)		..
Estimated fetal weight at randomisation*				
<p10	1/30 (3·3%)	1/24 (4·2%)		0·80 (0·07–15·17)
≥p10	2/263 (0·8%)	9/270 (3·3%)		0·23 (0·48–1·02)

0·01   0·1   1   10
Immediate delivery better   Expectant monitoring better

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

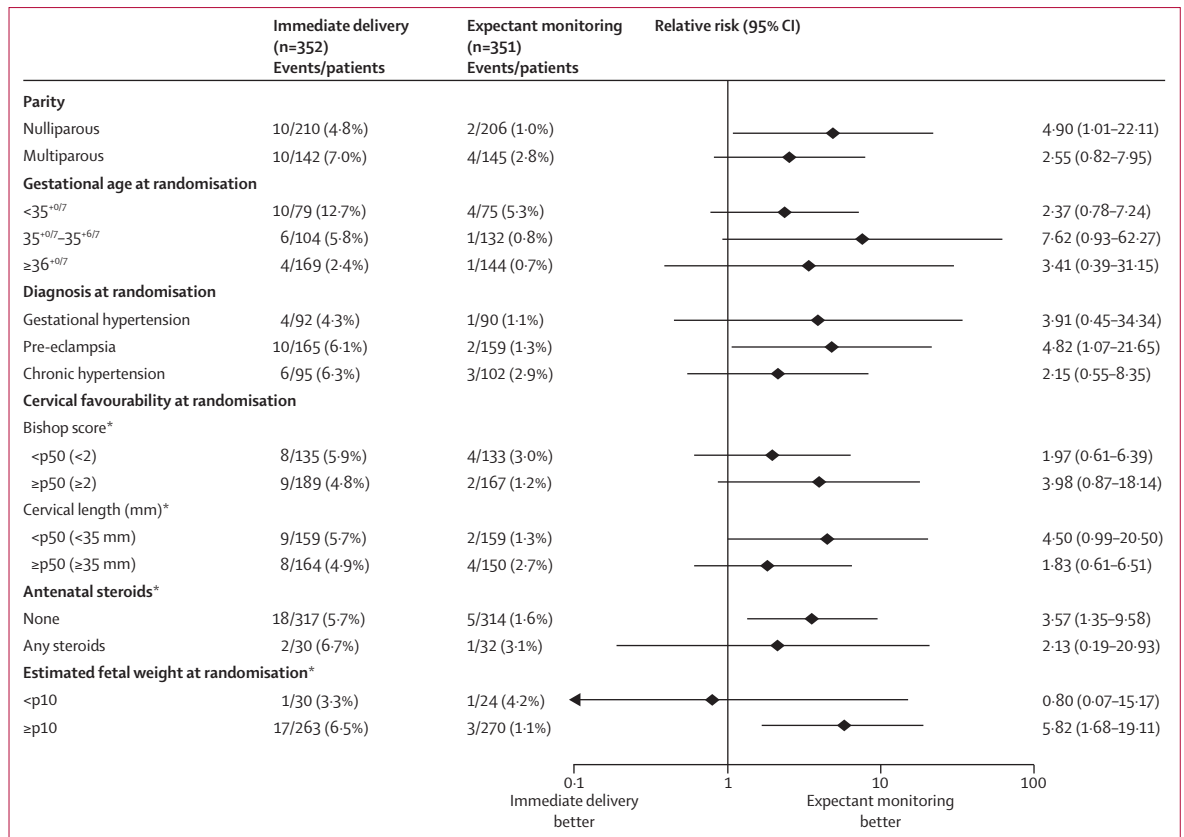|	Immediate delivery (n=352) Events/patients	Expectant monitoring (n=351) Events/patients	Relative risk (95% CI)	
Parity				
Nulliparous	10/210 (4·8%)	2/206 (1·0%)		4·90 (1·01–22·11)
Multiparous	10/142 (7·0%)	4/145 (2·8%)		2·55 (0·82–7·95)
Gestational age at randomisation				
<35+0/7	10/79 (12·7%)	4/75 (5·3%)		2·37 (0·78–7·24)
35+0/7–35+6/7	6/104 (5·8%)	1/132 (0·8%)		7·62 (0·93–62·27)
≥36+0/7	4/169 (2·4%)	1/144 (0·7%)		3·41 (0·39–31·15)
Diagnosis at randomisation				
Gestational hypertension	4/92 (4·3%)	1/90 (1·1%)		3·91 (0·45–34·34)
Pre-eclampsia	10/165 (6·1%)	2/159 (1·3%)		4·82 (1·07–21·65)
Chronic hypertension	6/95 (6·3%)	3/102 (2·9%)		2·15 (0·55–8·35)
Cervical favourability at randomisation				
Bishop score*				
<p50 (<2)	8/135 (5·9%)	4/133 (3·0%)		1·97 (0·61–6·39)
≥p50 (≥2)	9/189 (4·8%)	2/167 (1·2%)		3·98 (0·87–18·14)
Cervical length (mm)*				
<p50 (<35 mm)	9/159 (5·7%)	2/159 (1·3%)		4·50 (0·99–20·50)
≥p50 (≥35 mm)	8/164 (4·9%)	4/150 (2·7%)		1·83 (0·61–6·51)
Antenatal steroids*				
None	18/317 (5·7%)	5/314 (1·6%)		3·57 (1·35–9·58)
Any steroids	2/30 (6·7%)	1/32 (3·1%)		2·13 (0·19–20·93)
Estimated fetal weight at randomisation*				
<p10	1/30 (3·3%)	1/24 (4·2%)		0·80 (0·07–15·17)
≥p10	17/263 (6·5%)	3/270 (1·1%)		5·82 (1·68–19·11)

0·1   1   10   100
Immediate delivery better   Expectant monitoring better

Figure 3: **Risk of neonatal respiratory distress syndrome in subgroups**
*Data are missing for some participants.

with 95% CIs. When relevant, we also calculated the absolute risk difference with 95% CIs, and the number needed to harm. Finally, we assessed the consistency of the treatment effect across prespecified subgroups of parity, gestational age, type of hypertensive disorder, Bishop score, administration of antenatal corticosteroids, and suspected fetal growth restriction. We did the statistical analyses with SPSS (version 20).

The trial was registered with the Netherlands Trial Register (NTR1792).

Role of the funding source

The funding source 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 March 1, 2009, and Feb 21, 2013, 897 women were invited to participate (figure 1). Of the 193 women who did not give informed consent to be randomly assigned, 176 gave informed consent for us to extract data from their medical files; 168 of them (95%) were monitored expectantly.

704 women gave informed consent to be randomly assigned and were allocated to immediate delivery (n=353) or expectant monitoring (n=351). One woman withdrew after being randomised to immediate delivery, which left 352 women in the immediate delivery group and 351 women in the expectant monitoring group.

When compared with randomly assigned women, women who declined to be randomly assigned more often finished higher education, were more often non-smokers, were more often nulliparous, and had a lower gestational age. Otherwise, baseline characteristics were much the same in randomly assigned and not randomly assigned women (table 1).

As expected, spontaneous onset of labour was significantly less common in the immediate delivery group than in the expectant monitoring group (table 2). Labour was induced significantly more often in the immediate delivery group than in the expectant monitoring group, but onset of delivery by caesarean section did not differ significantly between groups (table 2). In the expectant monitoring group, 187 (53%) of 351 women delivered because they had reached 37 weeks, whereas 127 (36%) were delivered for various maternal and fetal indications before 37 weeks. As a result, the median time between randomisation and delivery was

significantly greater in the expectant monitoring group than in the immediate delivery group (p<0·0001; table 2); the difference was limited by the fact that 144 (41%) of 351 of the women in the expectant group had a gestational age of 36 weeks or more at study entry.

The primary maternal outcome occurred in four (1·1%) of 352 women in the immediate delivery group compared with 11 (3·1%) of 351 women in the expectant monitoring group (RR 0·36, 95% CI 0·12–1·11; p=0·067; table 3). Individual components of the composite outcome tended to occur more often in the expectant monitoring group than the immediate delivery group, but none of the differences were statistically significant (table 3). In the immediate delivery group, HELLP syndrome was the most common maternal adverse outcome, followed by thromboembolic disease. In the expectant monitoring group, HELLP syndrome was the most common maternal adverse outcome, followed by eclampsia and placental abruption, and thromboembolic complications. No cases of pulmonary oedema or maternal death were reported. None of the adverse maternal outcomes led to neonatal complications (appendix). The primary neonatal outcome occurred in 20 (5·7%) of 352 neonates in the immediate delivery group versus six (1·7%) of 351 neonates in the expectant monitoring group (RR 3·3, 95% CI 1·4–8·2; p=0·005; number needed to harm 25; table 4). All babies with respiratory distress syndrome needed continuous positive airway pressure for more than 24 h, surfactant, or both.

The risk of caesarean section did not differ significantly between groups (table 3). With regard to secondary neonatal outcomes, admission to a neonatal intensive care unit, transient tachypnoea of the newborn, and suspected or confirmed infection or sepsis were significantly more common in the delivery group than in the immediate delivery group (table 4). Most other types of neonatal morbidity occurred more often in the delivery group, although none of these differences were statistically significant. In a post-hoc analysis, the overall risk of neonatal morbidity was higher in the delivery group than in the expectant group (table 4).

Subgroup analyses suggested that the direction of the effect of immediate delivery on adverse maternal outcomes was the same in all subgroups except women with gestational age less than 35$^{+0/7}$ (figure 2). Neonatal respiratory distress syndrome was more common in babies in the immediate delivery group than in neonates in the expectant monitoring group, for all subgroups except for women with suspected fetal growth restriction, although the study was not powered to detect significant differences in these analyses (figure 3).

Discussion

In our study population, immediate delivery led to fewer adverse maternal outcomes than expectant monitoring. But although the RR suggests a large effect, the fact that

the absolute risk of adverse maternal outcomes was lower than assumed in our sample size calculation resulted in a difference that was not statistically significant. The effect of immediate delivery on maternal outcomes therefore remains uncertain. However, given the low absolute risk, the potential benefit of immediate delivery on maternal outcomes is small. Additionally, immediate delivery significantly increased the risk of neonatal respiratory distress syndrome. In our opinion, routine immediate delivery is therefore not justified and expectant monitoring can be considered for pregnant women with late preterm hypertensive disorders. (panel).

However, the absolute numbers of adverse maternal events were low in both groups. If HELLP syndrome, which could be considered an indicator of severe disease rather than an adverse outcome as such, had not have been included in the primary outcome, adverse maternal outcomes would be even rarer (one *vs* five), thus limiting the potential benefit of immediate delivery. Women in the expectant monitoring group were carefully monitored and delivered if their clinical situation deteriorated; more than a third of women in the expectant group developed

See **Online** for appendix

an indication for delivery before reaching 37 weeks of gestation. Therefore, interpretation of these results should take into account local options for monitoring and emergency intervention.

The proportions of neonates of different gestational ages with respiratory distress syndrome accorded with previous studies.[19,22,23] Although median time from randomisation to delivery differed between the two groups by only 5 days, this resulted in a significant difference in respiratory distress syndrome and a few secondary neonatal outcomes. In addition to these short-term outcomes, we will assess the long-term paediatric outcomes at 2 and 5 years of age.

We did not detect an effect of immediate delivery on risk of caesarean section. This observation, in a study population with a disorder that might progress in late preterm pregnancy, is consistent with evidence that induction of labour at term does not increase the risk of caesarean section.[7] We think that the absence of an effect in our study was a result of progression to severe disease in the expectant monitoring group, resulting in a perceived lack of time for cervical ripening or induction of labour, thereby more often leading to the decision to do a caesarean section.

Although our analyses suggested some different effects in different subgroups, the study was not powered or designed for subgroup analyses, and the results should be interpreted with caution.

One possible limitation was the inclusion of previously normotensive women with gestational hypertension or pre-eclampsia, as well as women with deteriorating chronic hypertension or superimposed pre-eclampsia. We chose this population because the traditional distinction between these syndromes is based on arbitrary criteria; restricting inclusion to one of those syndromes would not necessarily reduce heterogeneity with regard to underlying pathophysiology.[24] Additionally, the use of less restrictive exclusion criteria makes our results more relevant to clinical practice. This decision was supported by similar effects of treatment in subgroups of patients with different hypertensive disorders.

The generalisability of our results is limited by the use of 100 mm Hg as the cutoff for gestational hypertension, as opposed to the more generally accepted cutoff of 90 mm Hg. However, in view of our results, we believe that expectant monitoring can also be considered for women with gestational hypertension and a diastolic blood pressure of 90–100 mm Hg, who probably have an even lower risk of adverse maternal outcomes than patients in our study population.

By contrast with the first HYPITAT trial,[12] the primary maternal outcome of HYPITAT-II did not include progression to severe disease. The higher risk of adverse maternal outcomes at earlier gestational ages made it feasible to study a composite without this surrogate of maternal complications.[25]

Further studies of this subject are needed because the uncertainty around our point estimates were wide and the risk of adverse maternal outcomes in the expectant monitoring group was lower than anticipated. Because circulating angiogenic factors have been identified as potential biomarkers for progression to severe disease in women with hypertensive disorders of pregnancy, future research should include assessment of their clinical utility to identify a subgroup of high-risk women that might benefit from immediate delivery.[26] Additional data are also needed to establish whether are subgroups of women exist who have hypertensive disorders between 34 weeks and 37 weeks of gestation and who would benefit from immediate delivery, and which subgroups could be monitored safely, avoiding as many preterm births as possible. Finally, the best indications for delivery need to be established for women with hypertensive disorders of pregnancy who are managed expectantly.

For women with hypertensive disorders between 34 and 37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes. However, it increases the risk of neonatal respiratory distress syndrome. In our opinion, routine immediate delivery is therefore not justified and a strategy of expectant monitoring can be considered as long as gynaecologists take local circumstances into account and are aware of the risk of complications and initiate delivery if the clinical situation deteriorates.

HYPITAT-II collaboration (women randomly assigned)
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