Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy

HYPITAT-II Study Group; Zwertbroek, Eva F; Franssen, Maureen T M; Broekhuijsen, Kim; Langenveld, Josje; Bremer, Henk; Ganzevoort, Wessel; van Loon, Aren J; van Pampus, Maria G; Rijnders, Robbert J P

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OBSTETRICS

Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 2-year outcomes of the HYPITAT-II trial

Eva F. Zwertbroek, BSc; Maureen T. M. Franssen, MD, PhD; Kim Broekhuijsen, MD, PhD; Josje Langenveld, MD, PhD; Henk Bremer, MD, PhD; Wessel Ganzevoort, MD, PhD; Aren J. van Loon, MD, PhD; Maria G. van Pampus, MD, PhD; Robbert J. P. Rijnders, MD, PhD; Marko J. Sikkema, MD, PhD; Sicco A. Scherjon, MD, PhD; Mallory D. Woiski, MD, PhD; Ben W. J. Mol, MD, PhD; Anneloes L. van Baar, PhD; Henk Groen, MD, PhD; for the HYPITAT-II Study Group

BACKGROUND: Management of preterm hypertensive disorders remains a clinical dilemma. The maternal benefits of delivery need to be weighed against the adverse neonatal consequences of preterm birth. Long-term consequences of obstetric management in offspring of women with hypertensive disorders in preterm pregnancy are largely unknown. We report child neurodevelopmental and behavioral outcomes at 2 years after the Hypertension and Preeclampsia Intervention Trial at near Term (HYPITAT-II) trial, which compared immediate delivery versus expectant monitoring in mild late preterm hypertensive disorders of pregnancy.

OBJECTIVE: To compare effects of immediate delivery vs expectant monitoring on neurodevelopmental and behavioral outcomes at 2 years of age in offspring of women with mild late preterm hypertensive disorders.

MATERIALS AND METHODS: We studied children born in the HYPITAT-II trial, a study in which women (n = 704) with hypertensive disorders of pregnancy who were between 34 and 37 weeks' gestation were randomized to immediate delivery or expectant monitoring. Participating women were asked to complete the Ages and Stages Questionnaire for developmental outcome and the Child Behavior Checklist for behavioral problems when their toddlers were 2 years old.

RESULTS: We approached 545 of 704 randomized women (77%); 330 of 545 (61%) returned the questionnaires. In the immediate delivery group, 45 of 162 infants (28%) had an abnormal Ages and Stages Questionnaire score compared to 27 of 148 (18%) in the expectant monitoring group (risk difference, 9.6%; 95% CI, 0.3−18.0%); $P = .045$. In the pregnancies (n = 94) that delivered before reaching 36 weeks, 27% (n = 25) had an abnormal Ages and Stages Questionnaire score compared to 22% (n = 47) when delivered after 36 weeks (odds ratio, 0.77; confidence interval, 0.44−1.34). An abnormal Child Behavior Checklist outcome was found in 31 of 175 (18%) in the delivery group vs 24 of 166 (15%) in the expectant monitoring group (risk difference, 3.2%; 95% CI, −4.6% to 11.0%). After correction for maternal education, management strategy remained an independent predictor of abnormal Ages and Stages Questionnaire score (odds ratio, 0.48; confidence interval, 0.24 to −0.96, $P = .03$). In multivariable analyses, low birth weight, low maternal education, and immediate delivery policy were all significantly associated with an abnormal Ages and Stages Questionnaire score.

CONCLUSION: In this study, we found that early delivery in women with late preterm hypertensive disorders is associated with poorer neurodevelopmental outcomes in their children at 2 years of age. These findings indicate an increased risk of developmental delay after early delivery compared to expectant monitoring. This follow-up study underlines the conclusion of the original HYPITAT-II study that, until the clinical situation deteriorates, expectant monitoring remains the most appropriate management strategy in the light of short- and long-term neonatal outcomes in women with preterm hypertensive disorders.

Key words: Ages and Stages Questionnaire, behavior, Child Behavior Checklist, chronic hypertension, follow-up, gestational hypertension, hypertensive disorder of pregnancy, HYPITAT-II trial, long-term outcome, neurodevelopment, preeclampsia, superimposed preeclampsia

Hypertensive disorders of pregnancy complicate up to 10% of all pregnancies worldwide, resulting in considerable maternal morbidity and neonatal mortality or morbidity.[1−3]

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The only definitive treatment for a hypertensive disorder is delivery. In women with a hypertensive disorder at term, immediate delivery reduces the risk of adverse maternal outcomes or progression to severe disease without affecting neonatal outcomes.[4] Therefore, immediate delivery is the preferred strategy at term. In women with a hypertensive disorder diagnosed before term, benefits of delivery for the mother need to be weighed against the adverse consequences of iatrogenic preterm birth for the neonate, including neonatal respiratory distress syndrome (RDS), hypoglycemia, and hyperbilirubinemia.[5−7] This issue was addressed in the Hypertension and Preeclampsia Intervention Trial at near Term (HYPITAT-II), which compared immediate delivery to expectant monitoring in women with gestational hypertension or mild preeclampsia. The composite adverse maternal outcome occurred in 1.1% of the 352 women allocated to immediate delivery vs 3.1% of the 351 women allocated to expectant monitoring (relative risk [RR], 0.36; 95% CI, 0.12−1.11). In the immediate delivery group, 5.7% of the neonates were diagnosed with respiratory distress syndrome compared to 1.7% in the expectant monitoring group

AJOG at a Glance

Why was this study conducted?

- To evaluate child behavior and developmental outcome 2 years after an randomized controlled trial comparing immediate vs deferred delivery in preterm hypertensive pregnancy.

Key findings

- Early delivery in women with late preterm hypertensive disorders results in poorer neurodevelopmental outcome of their children at 2 years of age
- No differences in behavior problems between the management strategies were found.
- Immediate delivery, low maternal education, and lower birthweight were predictors of abnormal development.

What does this add to what is known?

- Preterm hypertensive disorders are associated with impaired neurodevelopment at 2 years of age.
- Expectant monitoring should be the preferred management strategy in preterm hypertensive disorders, especially in the light of long-term neonatal consequences.

(RR, 3.3; 95% CI, 1.4−8.2).[8] We concluded that in women with a mild hypertensive disorder diagnosed preterm, immediate delivery is not justified, as it significantly increases the short-term risk of RDS even though it may reduce an already small risk of adverse maternal outcome. As a consequence, expectant monitoring was considered to be the preferred strategy, until the clinical situation of the women required delivery.

Preterm delivery, be it with or without short-term neonatal morbidity, is associated with long-term neurodevelopmental problems in the offspring.[9−13] Preterm birth is a prevalent outcome of a hypertensive disorder, and accordingly, the hypertensive disorder in itself may contribute to impaired neurodevelopment, as well as through iatrogenic actions. This has been demonstrated for severe early-onset preeclampsia.[14] In late preterm hypertensive disorders, the long-term effects of early vs deferred delivery on the offspring are unknown. We compared neurodevelopmental and behavioral outcomes at 2 years of age in the offspring of mothers with late preterm hypertensive disorders randomized to immediate delivery or expectant monitoring.

Materials and Methods

Study population

Our study population consisted of children born to women who participated in the HYPITAT-II trial. This randomized controlled trial took place from 2009 to 2013 and was described previously.[8] Briefly, the study randomized 704 women with a hypertensive disorder of pregnancy (gestational hypertension, chronic hypertension, or mild preeclampsia) between 34+0 and 36+6 weeks of gestation to immediate delivery or expectant monitoring until 37 weeks of gestation (when delivery was mandated per protocol). Expectant monitoring consisted of close monitoring until 37 weeks or until an indication for delivery occurred, whichever came first. The trial was approved by the Institutional Review Board of the Academic Medical Centre in Amsterdam (08/244), and had local approval from the boards of the other participating hospitals. Informed consent for follow-up was previously obtained at inclusion in the original study. For the current study, we approached randomized women who participated in the HYPITAT-II trial. Children born to these mothers were eligible for participation at the age of 2 years. This follow-up study took place from 2011 to 2015.

Study procedures

When infants were about to reach 2 years of age, the research nurse from the participating hospital contacted the parents to announce the follow-up study. Three paper questionnaires were sent by post: the Dutch versions of the Ages and Stages Questionnaire (ASQ) and the Child Behavior Checklist (CBCL for children between 0.5 and 5 years of age) to assess developmental and behavior problems and a general background questionnaire. Parents were asked to fill out the questionnaires when their child was between 23 and 26 months of age, corrected for prematurity (which is the age range for the version of the ASQ that was used). When the questionnaires were not returned, the parents were reminded by telephone. If the questionnaires were not filled out during the right period, they were not included in the planned analysis.

Ages and Stages Questionnaire

The Ages and Stages Questionnaire is a screening instrument to detect developmental delay in children.[15−17] It has different age versions, each version consisting of age-specific developmental milestones. The 24-month version has previously been validated to identify developmental delay in infants that were born preterm.[18] This parent-completed questionnaire covers 5 developmental domains: communication, gross motor, fine motor, problem solving, and personal social behavior. There are 6 questions per domain with a score of 0, 5 or 10 points, reflecting respectively whether the child is not yet able, sometimes is able, or is fully able to perform the behavior described. Per domain, a maximum score of 60 can be achieved, with lower scores indicating less attainment of developmental milestones.[16] A score $\leq$2 standard deviations (SD) below the mean of a Dutch reference population on 1 domain, or a score $\leq$1 SD below the mean on 2 or more domains, is defined as abnormal.[15] This definition of an abnormal score is specified in the ASQ manual, and indicates a possible delay in development and a need for further assessment.

Child Behavior Checklist

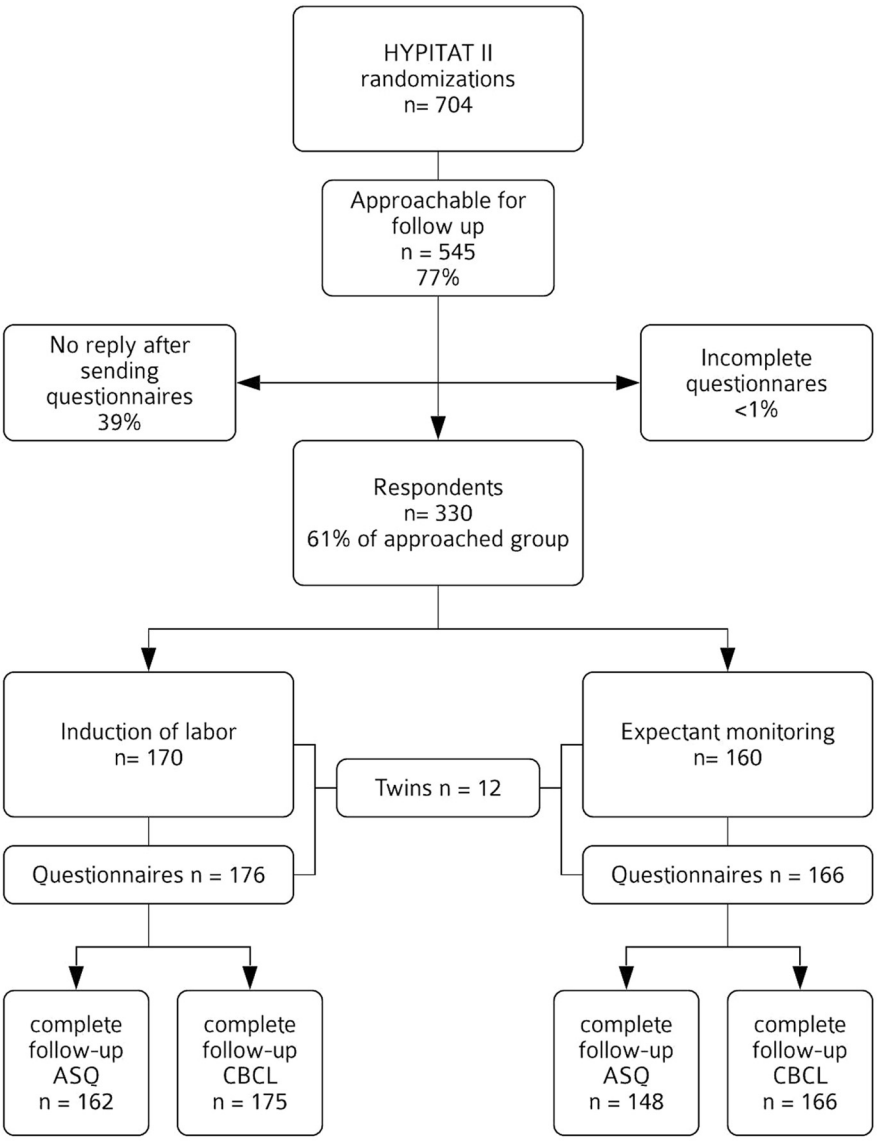
The Child Behavior Checklist (CBCL) assesses behavioral and emotional problems at 1.5−5 years of age.[19,20] The CBCL has 100 questions regarding behavior problems, allowing calculation of an age-adjusted total problem score and subscores for 7 narrow syndrome scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior) and 2 broader scales (internalizing and externalizing behavior). Standardized *T* scores are calculated for each behavior problem.[20] For the narrow syndrome scales, a score above the 93th percentile ($T \geq 65$) is defined as a borderline score, whereas for the broader scales, the borderline cut-off point is a *T* score above the 83rd percentile ($T \geq 60$).[20] A score above the borderline cut-off point indicates a significant risk for behavior problems.

Statistical analysis

Baseline characteristics and outcomes of the original study were compared between respondents and nonrespondents as well as between the 2 randomization groups. Continuous variables were expressed as mean and SD or as medians and interquartile ranges (IQR), as appropriate. *T* tests or Mann−Whitney *U* tests, respectively, were used to compare the groups. Dichotomous variables were expressed in absolute numbers and percentages, and these variables were compared using the χ^2 test or Fisher exact test.

Our primary outcome, abnormal ASQ or CBCL, was compared between the randomization groups using the χ^2 test. The secondary outcomes, abnormal domain or syndrome scores, were compared in the same way. In addition, univariable logistic regression was performed to assess predictors of poor neurodevelopmental or behavioral outcome independently of management strategy. Predictors with a *P* value <.05 were selected for multivariable logistic regression analysis to assess the independence of their effects on abnormal ASQ and CBCL outcomes. Multi-level analysis using generalized estimating equations with independent and exchangeable correlation matrix structures was performed to determine the impact of inclusion of twins in our analysis.

FIGURE 1
Flow chart of inclusions



ASQ, Ages and Stages Questionnaire; *CBCL*, Child Behavior Checklist; *HYPITAT-II*, Hypertension and Preeclampsia Intervention Trial At near Term.

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Results

Of the 704 women randomized in the HYPITAT-II study, we were able to approach 545 women (77%), of whom 330 (61%) agreed to participate in the follow-up study (Figure 1). We received completed questionnaires of 342 children, of whom 24 (7.0%) were twins. Of these 342 children, 176 had been born after randomization to immediate delivery, whereas 166 had been randomized to expectant monitoring. A total of 32 (9.6%) ASQ questionnaires and 1 (0.3%) CBCL questionnaire were excluded because they were incomplete or filled out outside the recommended age range of 23−26 months (for the ASQ). This resulted in a sample of 310 children with complete ASQ and 341

children with complete CBCL questionnaires.

Baseline characteristics

Baseline characteristics of the respondents and nonrespondents, as well as of the 2 management groups (immediate delivery or expectant monitoring), are shown in Table 1. Women who responded were significantly more often Caucasian/white (94% vs 80% $P < .001$), were less likely to have smoked during pregnancy (13% vs 20%, $P = .02$), and had more often finished higher education (44% vs 30%, $P = .003$). Baseline characteristics were compared between immediate delivery and expectant monitoring, and results were not significantly different from the original HYPITAT-II randomized controlled trial.[8]

Among women participating in the current study, those allocated to the expectant monitoring group delivered at a more advanced gestational age (median 37.0 vs 36.1, $P < .001$) than those in the immediate delivery group.

Neonatal outcomes for immediate delivery and expectant monitoring are shown in Table 2. Neonates in the immediate delivery group were less likely to be born small for gestational age (11% vs 18%, $P = .05$) but were more likely to develop transient tachypnea of the newborn (7.4% vs 2.4%, $P = .03$). Respiratory distress syndrome occurred more often in the immediate delivery group (4.5% vs 1.8%, $P = .15$), a difference similar in size to that in the original HYPITAT-II study, even though it did not reach statistical significance in the current comparison. Children in the immediate delivery group were significantly older (24.4 vs 24.1 months, $P = .037$) when the questionnaires were answered.

Developmental outcomes

In the immediate delivery group, 28% of the infants (n = 45) had an abnormal ASQ score, compared to 18% (n = 27) in the expectant monitoring group (difference, 9.6%; CI, −0.3% to 18.0%, $P = .045$) (Figure 2). In all of the developmental subdomains, a trend toward a higher percentage of abnormal outcomes was observed in the immediate delivery group (Table 3). The most pronounced difference was found in the fine motor domain (6.8% vs 2.0%; difference, 4.8%; CI, 0.3−9.3). When the scores were analyzed as continuous values, children in the immediate delivery group had a significantly lower average total score ($P = .02$) and they also had lower average scores on specific domains, such as the fine motor score ($P = .04$) or the personal−social score ($P = .03$).

The uncorrected association between management and the ASQ outcome was statistically significant (OR for expectant monitoring, 0.58; CI, 0.34−0.99). After correction for maternal education, management strategy remained an independent predictor of abnormal ASQ score (OR, 0.48; CI, 0.24−0.96, $P = .03$). When we adjusted for gestational age at delivery, the effect size of randomization allocation on ASQ scores did not change substantially but was no longer statistically significant (OR, 0.62; CI, 0.35−1.1). We performed a sensitivity analysis for gestational age at delivery: In the pregnancies (n = 94) in which infants were delivered before reaching 36 weeks, 26.6% (n = 25) had an abnormal ASQ score compared to 21.8% (n = 47) when delivered after 36 weeks (OR, 0.77; CI, 0.44−1.34). In the pregnancies (n = 94) that delivered before reaching 36 weeks, 29.9% of the children (n = 20/67) in the delivery group had an abnormal ASQ as compared to 18.5% (n = 5/27) in the expectant monitoring group ($P = .26$). In the group who reached a gestational age of >36 weeks at delivery (n = 216), we found an abnormal ASQ score in 26.3% (n = 25/95) in the delivery group as compared to 18.2% (n = 22/121) in the expectant monitoring group ($P = .15$).

Behavioral problems

In the immediate delivery, group 18% of children (n = 31) had an abnormal CBCL outcome compared to 15% (n = 24) in the expectant monitoring group (difference, 3.2%; CI, −4.6 to 11.0, $P = .414$) (Figure 2). On the individual syndrome scales, the proportion of children with an abnormal score likewise did not differ significantly between the groups (Table 3). Analysis of the *T* scores as continuous variables showed no statistically significant differences between the groups.

Predictors of abnormal ASQ or CBCL scores

Table 4 shows the results of the univariable analysis of possible predictors of an abnormal ASQ or CBCL outcome independent of the management policy. A normal ASQ score was associated with high birthweight of the child (OR, 0.59; CI, 0.34−0.99), high maternal education (OR, 0.41; CI, 0.20−0.82), and the randomization allocation (OR for expectant monitoring, 0.58; CI, 0.34−0.99). Gestational age at delivery, fetal growth restriction, respiratory distress syndrome and neonatal intensive care unit admission were not significantly associated with abnormal ASQ scores. Maternal smoking during pregnancy (OR, 2.31; CI, 1.10−4.87) and low maternal education (OR for higher education, 0.31; CI, 0.14−0.72) were associated with abnormal CBCL outcome. In a multivariable analysis, birth weight, maternal education, and management policy were all significantly associated with an abnormal ASQ score (Table 5). Maternal education had the strongest influence on CBCL score (OR for higher education, 0.33; CI, 0.14−0.77). Results of multi-level analyses did not suggest any major influence of dependency between twin siblings.

Comment

Principal findings

In this follow-up study of 342 (49%) children born from mothers included in the HYPITAT-II study, infants in the immediate delivery group had more often an abnormal ASQ score compared to children in the expectant monitoring group at 2 years of age. This poorer neurodevelopmental outcome indicates that these children are at increased risk for developmental delay. After adjusting for birthweight and maternal education level, management policy remained a significant predictor of neurodevelopmental outcome of the child. Management strategy directly influenced gestational age at delivery, which

TABLE 1
Baseline characteristics of study participants

Characteristics	Respondents n = 330	Nonrespondents n = 374	*P* value	Immediate delivery n = 170	Expectant monitoring n = 160	*P* value
Maternal characteristics						
Age, y	30 (27–34)	30 (26– 34)	0.68	30 (26–34)	30 (27–34)	.73
Caucasian/white	300 (93.8%)	294 (80.3%)	<0.001	157 (95.2%)	143 (92.3%)	.29
Smoking	42 (13.2%)	71 (19.8%)	0.02	22 (13.4%)	20 (13.0%)	.91
Higher education[a]	95 (43.8%)	69 (30.0%)	0.003	55 (50.0%)	40 (37.4%)	.06
Body mass index[a]	31 (27–35)	31 (28–36)	0.47	31 (27–34)	32 (28–35)	.53
History of preeclampsia	43 (13.1%)	62 (16.6%)	0.18	23 (13.5%)	20 (12.6%)	.61
Comorbidity	67 (21.1%)	85 (23.4%)	0.49	26 (16.0%)	41 (26.5%)	.02
Diabetes mellitus	3 (0.9%)	7 (1.9%)	0.28	1 (0.6%)	3 (1.3%)	.53
Gestational diabetes mellitus	10 (3.0%)	14 (3.7%)	0.60	4 (2.4%)	6 (3.8%)	.46
Pregnancy details						
Nulliparous	207 (62.7%)	210 (56.1%)	0.08	60 (35.3%)	63 (39.4%)	.44
Twin pregnancy	16 (4.8%)	28 (7.5%)	0.15	9 (5.3%)	7 (4.4%)	.70
Management			0.49			
Delivery	170 (51.5%)	183 (48.9%)		NA	NA	NA
Expectant monitoring	160 (48.5%)	191 (51.1%)		NA	NA	NA
Mode of delivery			0.15			.17
Spontaneous	186 (56.4%)	230 (61.7%)		100 (58.8%)	86 (53.8%)	
Instrumental	34 (10.3%)	32 (8.6%)		19 (11.2%)	15 (9.4%)	
Primary cesarean	40 (12.1%)	28 (7.5%)		14 (8.2%)	26 (16.3%)	
Secondary cesarean	70 (21.2%)	83 (22.3%)		37 (21.8%)	33 (20.6%)	
Disease characteristics						
Type of hypertension			0.27			.59
Gestational hypertension	88 (26.6%)	94 (25.1%)		49 (28.8%)	39 (24.4%)	
Preeclampsia	144 (43.6%)	180 (48.1%)		76 (44.7%)	68 (42.5%)	
Worsening chronic hypertension	54 (16.4%)	43 (11.5%)		25 (14.7%)	29 (18.1%)	
Superimposed preeclampsia	44 (13.3%)	56 (15.0%)		20 (11.8%)	24 (15.0%)	
Diastolic blood pressure at inclusion	95 (90–100)	95 (90–100)	0.30	95 (90–100)	95 (90–100)	.08
Systolic blood pressure at inclusion	140 (135–150)	140 (135–150)	0.24	140 (135–150)	142 (135–150)	.19
Gestational age at onset	35 (33–36)	35 (34–36)	0.21	35 (33–36)	35 (33–36)	.35
Gestational age at inclusion	36 (35–36)	36 (35–36)	0.51	36 (35–36)	36 (35–36)	.17
Gestational age at delivery	36 (36–37)	37 (36–37)	0.14	36 (35–37)	37 (36–37)	<.001
Days between inclusion and delivery	3 (2–7)	4 (2–8)	0.228	2 (1–3)	7 (4–11)	.00
Antenatal steroids	31 (9.5%)	31 (8.4%)	0.61	15 (8.9%)	16 (10.2%)	.70
Composite adverse maternal outcome	9 (2.7%)	6 (1.6%)	0.30	2 (1.2%)	7 (4.4%)	.08
Composite adverse neonatal outcome	33 (10.0%)	30 (8.1%)	0.37	22 (12.9%)	11 (6.9%)	.07

Data are median (interquartile range) or number (%). Data were compared between respondents, nonrespondents, and induction of labor and expectant monitoring using Student *t*, Mann–Whitney *U*, χ^2, or Fisher exact test. Data are given according to available data.

NA, not applicable.

[a] Indicates a variable with >20% missing data.

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TABLE 2
Neonatal outcomes

Neonatal outcomes	Immediate delivery n = 176	Expectant monitoring n = 166	Difference in % or mean (95% CI)	*P* value
Fetal growth restriction at study entry	20 (13.5%)	12 (8.9%)	4.6 (−2.7 to 11.9)	.22
Born small for gestational age	19 (10.8%)	30 (18.4%)	−7.6 (−1.5 to −0.1)	.05
Birthweight (g)	2593 (2352−2916)	2670 (2272 − 3055)	−62 (−172 to 46)	.26
Gestational age at birth (wk)	36.1 (35.4−36.6)	37.0 (36.1−37.1)	−0.67 (−0.86 to −0.50)	<.001
RDS	8 (4.5%)	3 (1.8%)	2.7 (−1.0 to 6.4)	.15
5-min Apgar score <7	10 (5.7%)	4 (2.4%)	3.3 (−0.8 to 7.4)	.13
Umbilical artery pH <7.05[a]	3 (2.2%)	3 (2.3%)	−0.1 (−3.6 to 3.4)	.94
NICU admission	13 (7.4%)	6 (3.6%)	3.8 (−1.0 to 8.6)	.13
Sepsis	16 (9.1%)	11 (6.6%)	2.5 (−3.2 to 8.2)	.39
Hypoglycemia	23 (13.1%)	25 (15.5%)	−2.4 (−9.8 to 5.0)	.61
Transient tachypnea of the newborn	13 (7.4%)	4 (2.4%)	5.0 (0.5 to 9.5)	.03
Meconium aspiration syndrome	0 (0%)	1 (0.6%)	−0.6 (−1.8 to 0.6)	.49
Pneumothorax or pneumomediastinum	2 (1.1%)	1 (0.6%)	0.5 (−1.4 to 2.4)	.99
Periventricular leukomalacia	2 (1.4%)	0 (0%)	1.4 (−0.5 to 3.3)	.50
Intraventricular hemorrhage	2 (1.2%)	0 (0%)	1.2 (−0.4 to 2.8)	.50
Convulsions	2 (1.1%)	1 (0.6%)	0.5 (−1.4 to 2.4)	.99
Necrotizing enterocolitis	0 (0%)	0 (0%)		NA
Any neonatal morbidity	58 (38.7%)	47 (34.6%)	4.1 (−7.1 to 15.3)	.47
Age at completion of follow up (mo)	24 (24−25)	24 (23−24)	0.28 (0.02−0.55)	.04

Data were compared between induction of labor and expectant monitoring using Student *t*, Mann−Whitney *U*, χ^2, or Fisher exact test. Table shows median (interquartile range) or number (%). Data are given according to available data.

n, Number of neonates born in a certain cohort; *NICU*, neonatal intensive care unit; *RDS*, respiratory distress syndrome.

[a] Indicates a variable with >20% missing data.

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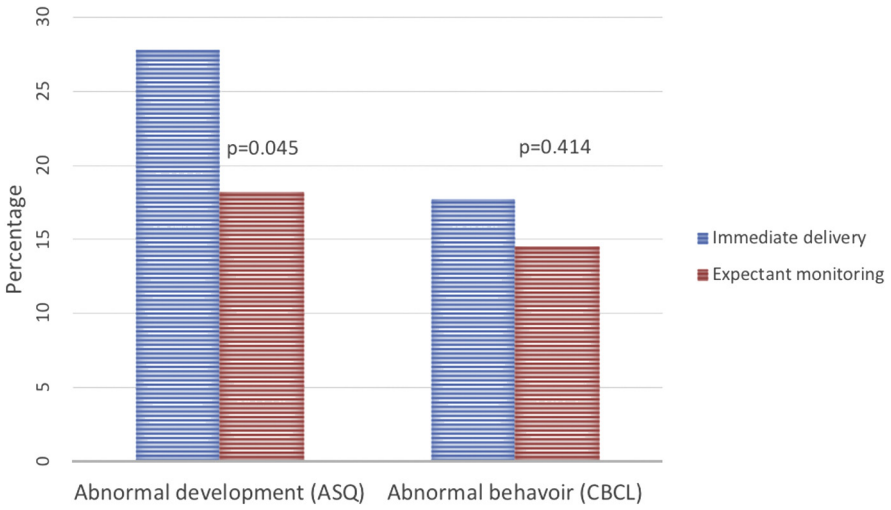
together affect development. We did not find differences in behavioral problems as measured by the CBCL.

Results of the study in context of what is known

The children in both management groups of our study, born preterm due to hypertensive disease, have an increased rate of abnormal neurodevelopmental scores (18% vs 28%) as compared to their 2-year-old peers in the Netherlands (eg, an abnormal score of 2 SD below the mean will be found only in 2.3% of a general population).[15] This finding strengthens previous studies reporting the association between both premature birth and a less optimal developmental outcome, and hypertensive disorders and impaired development later in life.[10,11,21−25] As reported in a previous preeclampsia study, timing of delivery matters: children born preterm had more often abnormal ASQ scores than children born at term.[14] This finding is supported in our study in a late preterm population: we show a difference in developmental outcome when comparing early vs deferred delivery in late preterm hypertensive disorders, a finding that has not previously been demonstrated.

Development of the child is known to be associated with maternal lifestyle factors, such as smoking and socioeconomic status or education.[26] Similar to what is reported in the literature, we found that lower maternal education and smoking were associated with poorer development and behavior. Besides lifestyle factors, gestational age at birth is known to influence developmental outcomes later in life.[14,26] Although in our study population gestational age was not an independent predictor of development, a trend was seen toward more abnormal development with lower gestational age at delivery. Neonatal complications related to preterm delivery such as hypoglycemia and respiratory distress syndrome are also known to be associated with long-term neurodevelopmental problems.[10,27,28] We were not able to demonstrate this association between, for example, hypoglycemia and abnormal ASQ scores, which could be due to the low frequency of those neonatal morbidities in our population. Low birthweight and severe growth

FIGURE 2
Number of children with abnormal scores on Ages and Stages Questionnaire (ASQ) or Child Behavior Checklist (CBCL)



Data were compared with χ^2 test. *n*, Number of neonates with completed questionnaire.

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TABLE 3
Abnormal scores per problem area compared between groups

Variable	Immediate delivery	Expectant monitoring	Difference in % (95% CI)	*P* value
Problem area ASQ	ASQ n = 162	ASQ n = 148		
Communication	13 (8.0%)	6 (4.1%)	3.9 (−1.4 to 9.2)	.15
Gross motor	12 (7.4%)	7 (4.7%)	2.7 (−2.6 to 8.0)	.33
Fine motor	11 (6.8%)	3 (2.0%)	4.8 (0.3 to 9.3)	.04
Problem solving	5 (3.1%)	4 (2.7%)	0.4 (−3.3 to 4.1)	.84
Personal social	9 (5.6%)	3 (2.0%)	3.6 (−0.6 to 7.8)	.11
total score	26 (15.9%)	13 (8.8%)	7.1 (−0.1 to 14.3)	.05
Syndrome scale CBCL	CBCL n = 175	CBCL n = 166		
Emotionally reactive	7 (4.0%)	10 (6.0%)	−2.0 (−6.6 to 2.6)	.39
Anxious/depressed	1 (0.6%)	1 (0.6%)	0.0 (−1.6 to 1.6)	.89
Somatic complaints	7 (4.0%)	8 (4.8%)	−0.8 (−5.2 to 3.6)	.71
Withdrawn	4 (2.3%)	3 (1.8%)	0.5 (−2.5 to 3.5)	.78
Sleep problems	5 (2.9%)	2 (1.2%)	1.7 (−1.2 to 4.7)	.45
Attention problems	12 (6.9%)	9 (5.4%)	1.5 (− 3.6 to 6.6)	.58
Agressive behavior	4 (2.3%)	6 (3.6%)	−1.3 (−4.9 to 2.3)	.53
Internalizing	11 (6.3%)	14 (8.4%)	−2.1 (−7.6 to 3.4)	.45
Externalizing	18 (10.3%)	12 (7.2%)	3.1 (−2.9 to 9.1)	.32
Total problem score	9 (5.1%)	10 (6.0%)	−0.9 (−5.8 to 4.0)	.72

Data were compared with χ^2 test.

ASQ, Ages and Stages Questionnaire; *CBCL*, Child Behavior Checklist; n, number of neonates with complete questionnaire.

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restriction are also known to increase the risk of abnormal neurologic development.[29] We found that birthweight was an independent predictor of abnormal neurodevelopment, even after correction for maternal education and management policy. As a result of all these findings, clinicians should keep in mind that in gestational ages between 34 and 37 weeks, low birthweight, growth restriction, and early induction of labor all can have long-term negative effects on the development of the child.

Clinical implications

The implications of this study are 2-fold. First, expectant monitoring of a late preterm hypertensive disorder seems to be preferential in light of short- and long-term neonatal outcomes. The increased risk of neurodevelopmental delay at 2 years after immediate delivery should be kept in mind when considering maternal benefits of delivery against the consequences of preterm delivery for the neonate. More elaborate follow-up examinations and longer follow-up are needed to investigate the severity of the delay as well as the persistence of the delay and group differences in neurodevelopmental outcome at 2 years of age and later in life. Obstetric decision making benefits from increasing knowledge of long-term consequences of the intervention chosen.

Second, structural follow-up, in these children born late preterm at risk for impaired neurodevelopment, is needed to allow early intervention in childhood.[30,31] Long-term consequences of abnormal ASQ scores at 2 years of age are unknown in children born from a hypertensive pregnancy. Nevertheless, 18% of children with abnormal screening questionnaire results receive a diagnosis of developmental delay requiring treatment after referral and further examination.[15] The difference that we found between our groups (18% vs 28%) therefore seems clinically relevant. A developmental delay at a young age may have lifelong consequences since these children are at increased risk of persisting problems and delays at later ages.[32] Therefore, it seems important to

TABLE 4
Univariable analysis of possible confounders on ASQ and CBCL scores

	Abnormal ASQ				Abnormal CBCL			
Variable	n (%)	OR	95% CI	*P* value	n (%)	OR	95% CI	*P* value
Type of hypertension				.32				.39
Gestational hypertension	15 (17.5%)	1.00	Reference		16 (17.8%)	1.00	Reference	
Preeclampsia	26 (26.5%)	1.68	(0.85–3.30)	.13	27 (18.0%)	1.02	(0.51–2.01)	.97
Chronic hypertension	21 (23.6%)	1.44	(0.69–3.03)	.33	12 (11.8%)	0.62	(0.28–1.40)	.25
Gestational age at birth (/wk)				.11				.50
<35	14 (38.9%)	2.55	(1.10–5.88)		9 (23.7%)	1.52	(0.62–3.75)	
35–36	11 (19.0%)	0.94	(0.41–2.14)		10 (16.1%)	0.94	(0.40–2.19)	
36–37	28 (23.1%)	1.20	(0.63- 2.31)		18 (13.3%)	0.75	(0.37–1.53)	
>37	19 (20.0%)	1	Reference		18 (17.0%)	1	Reference	
Birthweight (kg)		0.59	(0.34–0.99)	.05		0.63	(0.35–1.12)	.11
Twin		0.89	(0.35–2.29)	.81		0.63	(0.18–2.17)	.46
Yes	6 (21.4%)				3 (11.1%)			
No	66 (23.4%)				52 (16.6%)			
FGR		1.95	(0.85–4.47)	.11		2.30	(0.95–5.56)	.07
Yes	10 (34.5%)				8 (25.8%)			
No	48 (21.2%)				33 (13.1%)			
SGA		1.72	(0.86–3.47)	.13		1.66	(0.79–3.49)	.19
Yes	14 (32.6%)				11 (22.4%)			
No	58 (21.9%)				43 (14.9%)			
Adverse neonatal outcome		0.87	(0.36–2.10)	.76		1.39	(0.57–3.37)	.47
Yes	7 (21.2%)				7 (20.6%)			
No	65 (23.6%)				48 (15.6%)			
RDS		0.41	(0.05–3.29)	.40		0.51	(0.06–4.08)	.53
Yes	1 (11.1%)				1 (9.1%)			
No	71 (23.6%)				54 (16.4%)			
Apgar		1.89	(0.61–5.83)	.26		1.44	(0.39–5.33)	.59
Yes	5 (35.7%)				3 (21.4%)			
No	67 (22.7%)				52 (16.0%)			
Umbilical artery pH		0.63	(0.07–5.51)	.68		NA	NA	.59
Yes	1 (16.7%)				0 (0%)			
No	58 (24.1%)				47 (17.9%)			
NICU		0.65	(0.18–2.30)	.50		0.97	(0.27–3.46)	.97
Yes	3 (16.7%)				3 (15.8%)			
No	69 (23.6%)				52 (16.1%)			

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identify offspring at risk for impaired neurodevelopment due to pregnancy complications, since these children may benefit from early intervention in childhood.[30,31] In addition, in current clinical practice, professionals might not be aware of the potential developmental risks posed by early induction in these children, resulting in a late preterm birth. With a screening approach that uses screening instruments, as in this study, and in cases of borderline

TABLE 4
Univariable analysis of possible confounders on ASQ and CBCL scores *(continued)*

	Abnormal ASQ				Abnormal CBCL			
Variable	n (%)	OR	95% CI	*P* value	n (%)	OR	95% CI	*P* value
Sepsis		1.46	(0.61–3.50)	.39		1.58	(0.61–4.11)	.35
Yes	8 (29.6%)				6 (22.2%)			
No	63 (22.3%)				48 (15.3%)			
Hypoglycemia		1.22	(0.58–2.58)	.60		1.27	(0.57–2.80)	.56
Yes	11 (26.2%)				9 (18.8%)			
No	60 (22.5%)				45 (15.4%)			
Transient tachypnea of the newborn		1.56	(0.53–4.66)	.42		2.33	(0.79–6.91)	.13
Yes	5 (31.3%)				5 (29.4%)			
No	66 (22.5%)				49 (15.2%)			
Antenatal steroids		1.44	(0.63–3.31)	.39		1.71	(0.73–4.02)	.22
Yes	9 (30.0%)				8 (23.5%)			
No	63 (22.9%)				46 (15.2%)			
Management policy		0.58	(0.34-0.99)	.05		0.79	(0.44–1.40)	.41
Expectant	27 (18.2%)				24 (14.4%)			
Delivery	45 (27.8%)				31 (17.7%)			
Education[a,b]		0.41	(0.20–0.84)	.02		0.31	(0.14–0.72)	.01
Higher	13 (14.6%)				8 (8.1%)			
Lower	34 (29.3%)				28 (22.0%)			
Maternal smoking		1.51	(0.72–3.16)	.27		2.31	(1.10–4.87)	.03
Yes	12 (30.0%)				12 (27.9%)			
No	57 (22.1%)				41 (14.3%)			

Percentages are given according to available data.

ASQ, Ages and Stages Questionnaire; *CBCL*, Child Behavior Checklist; *CI*, confidence interval; *OR*, odds ratio.

[a] Indicates a variable with >20% missing data; [b] Higher education denotes university or higher vocational training; lower education denotes vocational training or lower.

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TABLE 5
Joint effects of factors of influence on abnormal ASQ and CBCL results in multivariable logistic regression analysis

Variable	OR	95% CI	*P* value
ASQ			
Higher maternal education	0.36	(0.17–0.74)	.01
Expectant monitoring	0.47	(0.23–0.96)	.04
Birthweight (kg)	0.46	(0.24–0.90)	.02
CBCL			
Higher maternal education	0.33	(0.14–0.77)	.01
Smoking during pregnancy	1.92	(0.75–4.94)	.17

ASQ, Ages and Stages Questionnaire; *CBCL*, Child Behavior Checklist.

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abnormal outcomes, further neurodevelopmental examinations may be feasible.

Research implications

We investigated children at 2 years of age, which is still rather young, as some problems might not yet be apparent. However, some children did already show clear indications of major developmental problems. School assessment and more detailed neuropsychological and socio-emotional assessments later in life are important to investigate whether these problems persist, and whether other (or subtle) developmental difficulties appear in this population. Considering that

longitudinal follow-up studies are needed to investigate developmental problems, a 5-year follow-up study of the current cohort has been planned, and data collection has already started.

Strengths and limitations

This follow-up study was a preconceived part of the HYPITAT-II study, considering that obstetric interventions may affect development in childhood. It is unique that we have 2-year follow-up data of a large cohort of children born to women participating in a randomized controlled trial on management of hypertensive disorders in preterm period of pregnancy.[14] In addition, validated questionnaires were used to assess the behavioral and neurological development of toddlers. Unfortunately, we were unable to perform physical examinations of the children, because of financial limitations. It was challenging to contact participants of the original study, for logistic reasons; for example, many different hospitals included patients, and after 2 years, some participants had moved. The follow-up rate may have influenced the results, because the original randomization was not maintained. Nevertheless, the response rate to this follow-up study was relatively good, providing sufficient power to demonstrate these important differences in the development of these children.

Conclusion

Neurodevelopmental problems at 2 years of age occur more often after immediate delivery compared to expectant monitoring in preterm hypertensive disorders of pregnancy, corrected for birth weight and maternal educational level. There was no indication of behavioral problems associated with immediate delivery. This study underlines the conclusion of the original HYPITAT-II study that, until the clinical situation deteriorates, expectant monitoring remains the most appropriate management strategy for preterm hypertensive disorders. Although induction of labor may reduce the small risk of adverse maternal outcomes, it is also associated with an increase in the risk of neonatal respiratory distress syndrome and poor neurodevelopment at 2 years of age. These findings are apparent even though gestational age differences between the management groups were relatively small. Further studies are needed to assess more long-term effects of hypertensive disorders in pregnancy. ■

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Contribution to authorship

JL, MMP, and BWJM wrote the grant application and obtained funding for the study. All authors recruited participants. EFZ was responsible for data collection and checking. EFZ performed the analyses under HG's supervision. EFZ, HG, ALvB, MTMF, KB, and BWJM interpreted the data. EFZ drafted the manuscript, and all authors contributed to review and revision. All authors have seen and approved the final version.

References

1. Abalos E, Cuesta C, Carroli G, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the world health organization multicountry survey on maternal and newborn health. BJOG 2014;121(Suppl 1):14–24.
2. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 2011;25:391–403.
3. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009;33:130–7.
4. Koopmans CM, Bijlenga D, Groen H, et al. 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. Lancet 2009;374:979–88.
5. Consortium on Safe Labor, Hibbard JU, Wilkins I, et al. Respiratory morbidity in late preterm births. JAMA 2010;304:419–25.
6. Teune MJ, Bakhuizen S, Gyamfi Bannerman C, et al. A systematic review of severe morbidity in infants born late preterm. Am J Obstet Gynecol 2011;205:374.
7. Melamed N, Klinger G, Tenenbaum-Gavish K, et al. Short-term neonatal outcome in low-risk, spontaneous, singleton, late preterm deliveries. Obstet Gynecol 2009;114:253–60.
8. Broekhuijsen K, van Baaren GJ, van Pampus MG, et al. 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. Lancet 2015;385:2492–501.
9. Langenveld J, Ravelli AC, van Kaam AH, et al. Neonatal outcome of pregnancies 0complicated by hypertensive disorders between 34 and 37 weeks of gestation: a 7 year retrospective analysis of a national registry. Am J Obstet Gynecol 2011;205:540.
10. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ 1988;297:1304–8.
11. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics 2006;117:2231–43.
12. Watchko JF, Jeffrey Maisels M. Enduring controversies in the management of hyperbilirubinemia in preterm neonates. Semin Fetal Neonatal Med 2010;15:136–40.
13. Bhutani VK, Maisels MJ, Stark AR, et al. Management of jaundice and prevention of severe neonatal hyperbilirubinemia in infants > or = 35 weeks gestation. Neonatology 2008;94:63–7.
14. Warshafsky C, Pudwell J, Walker M, Wen SW, Smith GN; Preeclampsia New Emerging Team. Prospective assessment of neurodevelopment in children following a pregnancy complicated by severe pre-eclampsia. BMJ Open 2016;6:e010884.
15. Steenis LJ, Verhoeven M, Hessen DJ, van Baar AL. Parental and professional assessment of early child development: the ASQ-3 and the Bayley-III-NL. Early Hum Dev 2015;91:217–25.
16. Squires J, Twombly E, Bricker D, Potter L. The ASQ-3 user's guide. 3rd ed. Baltimore, MD: Brookes; 2009.
17. Kerstjens JM, Bos AF, ten Vergert EM, de Meer G, Butcher PR, Reijneveld SA. Support for the global feasibility of the ages and stages questionnaire as developmental screener. Early Hum Dev 2009;85:443–7.
18. Simard MN, Luu TM, Gosselin J. Concurrent validity of ages and stages questionnaires in preterm infants. Pediatrics 2012;130:e108–14.
19. Koot HM, Van Den Oord EJ, Verhulst FC, Boomsma DI. Behavioral and emotional problems in young preschoolers: cross-cultural testing of the validity of the child behavior checklist/2-3. J Abnorm Child Psychol 1997;25:183–96.
20. Achenbach T, Verhulst F. Achenbach System of Empirically Based Assessment (ASEBA). Updated 2013. Available at: http://www.aseba.nl/. Accessed October 19, 2017.
21. Ratsep MT, Hickman AF, Maser B, et al. Impact of preeclampsia on cognitive function in the offspring. Behav Brain Res 2016;302:175–81.
22. Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 2012;129:e1121–8.
23. Many A, Fattal A, Leitner Y, Kupferminc MJ, Harel S, Jaffa A. Neurodevelopmental and cognitive assessment of children born growth restricted to mothers with and without pre-eclampsia. Hypertens Pregnancy 2003;22:25–9.

24. Tuovinen S, Raikkonen K, Kajantie E, et al. Hypertensive disorders in pregnancy and intellectual abilities in the offspring in young adulthood: the Helsinki Birth Cohort Study. Ann Med 2012;44:394–403.
25. Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr 2009;154:169–76.
26. Johnson S, Evans TA, Draper ES, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed 2015;100:F301–8.
27. Bird TM, Bronstein JM, Hall RW, Lowery CL, Nugent R, Mays GP. Late preterm infants: birth outcomes and health care utilization in the first year. Pediatrics 2010;126:e311–9.
28. van der Heyden JL, Willekes C, van Baar AL, et al. Behavioural and neurodevelopmental outcome of 2-year-old children after preterm premature rupture of membranes: follow-up of a randomised clinical trial comparing induction of labour and expectant management. Eur J Obstet Gynecol Reprod Biol 2015;194:17–23.
29. van Wyk L, Boers KE, van der Post JA, et al. Effects on (neuro)developmental and behavioral outcome at 2 years of age of induced labor compared with expectant management in intrauterine growth-restricted infants: long-term outcomes of the DIGITAT trial. Am J Obstet Gynecol 2012;206:406.
30. Reynolds AJ, Temple JA, Ou SR, et al. Effects of a school-based, early childhood intervention on adult health and well-being: a 19-year follow-up of low-income families. Arch Pediatr Adolesc Med 2007;161:730–9.
31. Reynolds AJ, Temple JA, Robertson DL, Mann EA. Long-term effects of an early childhood intervention on educational achievement and juvenile arrest: a 15-year follow-up of low-income children in public schools. JAMA 2001;285:2339–46.
32. de Kleine MJ, den Ouden AL, Kollee LA, et al. Development and evaluation of a follow up assessment of preterm infants at 5 years of age. Arch Dis Child 2003;88:870–5.

Author and article information

From Obstetrics and Gynaecology (Ms Zwertbroek and Drs Franssen and Scherjon), University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; Obstetrics and Gynaecology (Dr Broekhuijsen), Leiden University Medical Center, Leiden, The Netherlands; Obstetrics and Gynaecology (Dr Langenveld), Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands; Obstetrics and Gynecology (Dr Bremer), Reinier de Graaf Gasthuis, Delft, The Netherlands; Obstetrics and Gynecology (Dr Ganzevoort), Amsterdam UMC, Amsterdam, The Netherlands; Obstetrics and Gynecology (Dr van Loon), Martini Hospital, Groningen, The Netherlands; Obstetrics and Gynecology (Dr van Pampus), OLVG, Amsterdam, The Netherlands; Obstetrics and Gynecology (Dr Rijnders), Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands; Obstetrics and Gynecology (Dr Sikkema), ZGT Almelo, Almelo, The Netherlands; Obstetrics and Gynecology (Dr Woiski), Radboud University Medical Center, Nijmegen, The Netherlands; Obstetrics and Gynaecology (Dr Mol), Monash University, Melbourne, Australia; Child and Adolescent Studies (Dr van Baar), Utrecht University, Utrecht, The Netherlands; Epidemiology (Dr Groen), University Medical Centre Groningen, Groningen, The Netherlands.

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Corresponding author: Eva Zwertbroek, BSc. e.f.zwertbroek@umcg.nl