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Full length article

Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 5-year outcomes of the HYPITAT II trial

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ABSTRACT

Objective: To compare effects of immediate delivery vs expectant monitoring on neurodevelopmental and behavioral outcomes at 5 years of age in offspring of women with mild late preterm hypertensive disorders.

Study design: We studied children born during the HYPITAT-II trial, in which 704 women with a hypertensive disorder between 34 and 37 weeks of gestation were randomized to immediate delivery or expectant monitoring. Participating women were asked to complete the Ages and Stages Questionnaire (ASQ) for developmental outcome and the Child Behavior Checklist (CBCL) for behavioral problems when their child was 5 years old. Outcomes were dichotomized and analyzed by logistic regression analysis. We also assessed factors influencing development and behavior at both 2 and 5 years after a hypertensive pregnancy.

Results: Five years after the original study 322(46%) women were contacted for follow-up, of whom 148 (46%) responded. In the delivery group 22%(n = 14/65) of the children had an abnormal ASQ score compared to 21% (n = 13/62) in the expectant monitoring group (p = 0.9). Abnormal CBCL-scores were found in 19% (n = 14/72) of the children in the delivery group versus in 27% (n = 20/75) in the expectant monitoring group (p = 0.3). The main predictor of development and behavior at 2 and 5 years was fetal growth restriction (for abnormal development OR 2.1, CI 1.0–4.4; for behavior problems OR 2.2, CI 1.1–5.5). Higher maternal education decreased abnormal behavior outcomes (OR 0.5, CI 0.2–0.9) and a similar tendency was observed for developmental problems (OR 0.6, CI 0.3 – 1.1).

Conclusion: We did not find different developmental and behavior outcomes at 5 years of age between a management policy of immediate delivery and expectant management in preterm hypertensive disorders. The increased risk of developmental delay at 2 years of age after immediate delivery, we found in the 2 year follow up study, did not persist at 5 years of age.

Introduction

Hypertensive disorders of pregnancy, which include gestational hypertension, preeclampsia, worsening chronic hypertension and superimposed preeclampsia, occur in 10% of all pregnancies [1–3]. These disorders carry both maternal and neonatal risk of mortality and morbidity [4–6]. Delivery of the baby remains the only way to

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definitively treat the disorder and prevent progression. At term this is the preferred management strategy, since it decreases maternal risk on progression of disease and adverse outcomes, without affecting neonatal outcomes [7,8]. However, in preterm pregnancy there are neonatal risks to consider.

Preterm delivery is associated with neonatal mortality and morbidity such as respiratory distress syndrome (RDS), necrotizing enterocolitis and intraventricular hemorrhage [9,10]. In addition, lower gestational age at delivery is known to be associated with long-term complications such as impaired neuromotor development and atypical psychosocial patterns [11,12]. However, delayed delivery increases the risk of maternal complications of the hypertensive disease such as thromboembolic complications, pulmonary oedema, HELLP syndrome, eclampsia, placental abruption, or maternal death [8,13]. Therefore, determining the most suitable course of action in case of a hypertensive disorder before term requires a balanced evaluation of maternal and neonatal risks, both in short and longer term.

This dilemma was addressed in the HYPITAT II study, which compared immediate delivery to expectant monitoring as management strategies in late preterm hypertensive disorders. We found that 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 (RR 3.3; 95% CI, 1.4-8.2). However, adverse maternal outcomes did not differ significantly (1.1% in the immediate delivery group vs. 3.1% in the expectant monitoring group, RR 0.36; 95% CI, 0.12-1.11) [14]. Since immediate delivery did not decrease adverse maternal outcomes but significantly increased RDS, we concluded that expectant monitoring was preferred until delivery was clinically required in a preterm hypertensive pregnancy.

Since children born from a preeclamptic pregnancy are at increased risk of developmental problems [15], we previously investigated the effect of immediate versus deferred delivery in late preterm hypertensive disorders, on developmental and behavioral outcomes at the age of two. Behavioral outcomes were similar but infants in the immediate delivery group showed an increased rate of abnormal development (28% versus 18% in the expectant monitoring group ($p = 0.045$)) [16].

To investigate whether this impaired neurodevelopment in the immediate delivery group at 2 years of age persists at a later age, we repeated this assessment at the age of 5. The aim of this study was to compare long term effects of immediate delivery vs. expectant monitoring on neurodevelopmental and behavioral outcomes at the age of 5 in offspring of women with mild late preterm hypertensive disorders.

Methods

Study population

Our study population originates from the HYPITAT II trial, which ran from 2009 until 2013 in the Netherlands [14]. The HYPITAT II randomized women with hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, worsening chronic hypertension or superimposed preeclampsia) between 34 + 0 and 36 + 6 weeks of gestation to immediate delivery or expectant monitoring. In the first group labor was immediately induced whereas in the expectant monitoring group induction of labor only occurred if another indication arose or the gestational age of 37 weeks was reached. The Institutional review board of the Academic Medical Center in Amsterdam approved this study (08/244) and participants gave informed consent for this follow-up study at inclusion. Participants were included between 2014 and 2018.

Study procedures

In this follow-up study mothers of the HYPITAT II trial were approached when their infants reached 5 years of age. They were sent three questionnaires to be completed when their child was 5 years old; the Ages and Stages Questionnaire for developmental outcome, the Child Behavior Checklist for behavioral problems and a general background questionnaire. The questionnaires were included in the analysis if they were completed within the recommended age range, as specified per questionnaire.

Ages and stages questionnaire

The Ages and Stages Questionnaire (ASQ) is a questionnaire developed to detect developmental delay by tracking age specific milestones [17–19]. ASQ adjusts for age and was previously validated for the age of 5 [20]. The child should be between 57 and 66 months at time of ASQ completion. Parents were asked to score their child on five domains; communication, gross motor, fine motor, problem solving and personal-social. Each domain consists of 6 questions regarding skills for which parents could indicate if their child already showed it or not, and answer 'not yet', 'sometimes' or 'yes'. Lower scores indicate less attainment of developmental milestones [18]. The questionnaire result was considered abnormal if the score was $\geq$2 SD below the expected mean of the Dutch reference population on one domain or $\geq$ 1 SD below reference on multiple domains [17]. Abnormal ASQ scores can indicate developmental delay.

Child behavior checklist

The Child Behavior Check list (CBCL) checks for behavioral problems in infants between 1.5 and 5 year old [21,22]. It consists of 100 questions in which parents can indicate to what extent certain behavior problems are present currently, or in the last two months. The CBCL assesses seven narrow syndrome scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behavior) and two broadband scales (internalizing and externalizing behavior). A standardized t-score was calculated for each scale. Borderline cut-off points are the 85th percentile (T-score $\geq$ 60) for the broadband scales and 95th percentile (T-score $\geq$ 65) for the narrowband scales [22]. Scores above these cut-off points were defined as abnormal, indicating increased risk of behavioral problems [22].

Statistical analysis

Baseline characteristics and outcomes from the original HYPITAT II study were compared between respondents and non-respondents and between the randomization groups. Continuous variables were expressed as medians and interquartile range (IQR), dichotomous variables in absolute numbers and percentages. T-tests, Mann-Whitney U, Chi-square test or Fisher exact test were used to compare the groups as appropriate.

The primary outcomes, abnormal ASQ and CBCL scores, were compared between randomization groups using Chi-square test. As a secondary analysis an univariable logistic regression was performed to identify predictors of abnormal development or behavioral problems at 5 years of age. Additionally, we merged the current 5-year follow-up cohort to the previously described 2-year follow-up cohort to assess factors of influence on development and behavior at both 2 and 5 years after a hypertensive pregnancy. To address this question, a multi-level analysis using Generalized Estimating Equations with exchangeable correlation matrix structures was performed, which takes into account repeated measures within one individual.

Results

Of the original 704 participants of the HYPITAT II study, 322 (45.7%) parents were approachable for this 5-year follow-up. Of the approached women 148 (45.9%) agreed to participate, of whom 72 (48.6%) were in the delivery group and 76 (51.4%) in the expectant monitoring group. Including twins this resulted in a total of 153 completed questionnaires. Unfortunately, 6 (4.1%) CBCL and 26 (8.3%) ASQ questionnaires were discarded because they were either incomplete or filled in outside the correct age range (Fig. 1).

Baseline characteristics

The baseline characteristics of the respondents and non-respondents, as well as of the two management groups are shown in Table 1. As an effect of randomization, the delivery group showed a significantly lower gestational age at delivery (36 vs. 37 weeks, $p < 0.001$), and a significantly shorter time between inclusion and delivery (2 vs. 7 days, $p < 0.001$) compared to the expectant monitoring group. We found no other significant differences in baseline and in neonatal outcomes between management groups (Table 2).

Developmental outcomes (ASQ)

In the immediate delivery group 21.5% (n = 14) had an abnormal ASQ compared to 21.0% (n = 13) of the expectant monitoring group (absolute difference 0.5%, 95% CI -13.7 to 14.7, p = 0.94, Fig. 2). No statistically significant differences were found among the developmental domains between the management groups (Table 3).

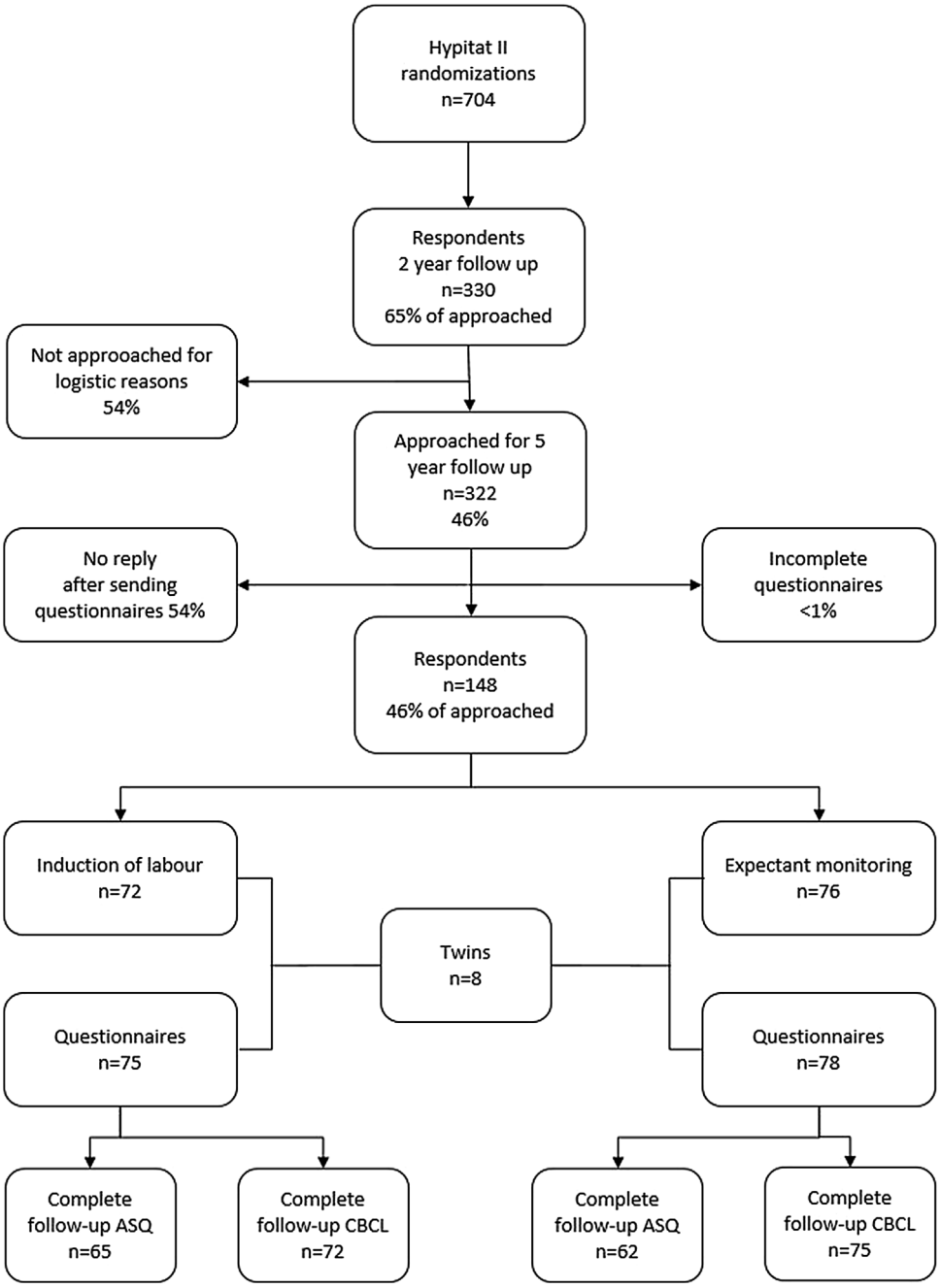

Fig. 1. Flow chart of inclusions.

Table 1
Baseline characteristics.

Characteristic	Respondents *n = 148*	Non-respondents *n = 556*	*p*-value	Induction of labour *n = 72*	Expectant monitoring *n = 76*	*p*-value
Maternal characteristics						
Age	30 (27-34)	30 (26-34)	0.35	30 (27-34)	31 (27-34)	0.69
Caucasian	137 (95.1%)	457 (82.2%)	*0.001*	68 (97.1%)	69 (93.2%)	0.28
Smoking	21 (14.7%)	92 (16.5%)	0.46	11 (15.3%)	10 (13.7%)	0.73
Higher education*	38 (43.7%)	126 (35.0%)	0.13	16 (41.0%)	22 (45.8%)	0.65
BMI*	25 (23-29)	26 (23-30)	0.01	26 (23-29)	24 (23–29)	0.80
History of preeclampsia	21 (14.2%)	84 (15.1%)	0.85	9 (12.5%)	12 (15.8%)	0.77
Comorbidity	30 (21.1%)	122 (22.6%)	0.70	12 (17.1%)	18 (25%)	0.25
Diabetes mellitus	1 (0.7%)	9 (1.6%)	0.70	0 (0.0%)	1 (1.3%)	0.33
Gestational diabetes mellitus	3 (2.0%)	21 (3.8%)	0.44	1 (1.4%)	2 (2.6%)	0.59
Pregnancy details						
Nulliparous	91 (61.5%)	326 (58.6%)	0.53	44 (61.1%)	47 (61.8%)	0.93
Twin pregnancy	8 (5.4%)	36 (6.5%)	0.63	3 (4.2%)	5 (6.6%)	0.52
Management			0.68			
Delivery	72 (48.6%)	281 (50.5%)		NA	NA	NA
Expectant	76 (51.4%)	275 (49.5%)		NA	NA	NA
Mode of delivery			0.13			0.80
Spontaneously	97 (58.8%)	392 (59.2%)		44 (61.1%)	43 (56.6%)	
Instrumental	20 (13.5%)	46 (8.3%)		8 (11.1%)	12 (15.8%)	
Primary caesarean	16 (10.8%)	52 (9.4%)		7 (9.7%)	9 (11.8%)	
Secondary caesarean	25 (16.9%)	128 (23.0%)		13 (18.1%)	12 (15.8%)	
Disease characteristics						
Type of hypertension			0.07			0.57
Gestational hypertension	45 (30.4%)	137 (24.6%)		25 (34.7%)	20 (26.3%)	
Preeclampsia	68 (45.9 %)	256 (46.0%)		33 (45.8%)	35 (46.1%)	
Worsening chronic hypertension	24 (16.2%)	73 (13.1%)		10 (13.9%)	14 (18.4%)	
Superimposed preeclampsia	11 (7.4%)	89 (16.0%)		4 (5.6%)	7 (9.2%)	
Diastolic blood pressure at inclusion	96 (90–100)	95 (90–100)	0.01	96 (92–100)	96 (90–100)	0.97
Systolic blood pressure at inclusion	140 (138–150)	140 (135–150)	0.37	140 (138–150)	141 (139–150)	0.40
Gestational age at onset	35 (33–36)	35 (34–36)	0.36	35 (33–36)	35 (33–36)	0.91
Gestational age at inclusion	36 (35–36)	36 (35–36)	0.94	36 (35–36)	36 (35–36)	0.27
Gestational age at delivery	37 (36–37)	37 (36–37)	0.95	36 (35–37)	37 (36–37)	*<0.001*
Days between inclusion and delivery	3(2–7)	3(2–7)	0.75	2 (1–3)	7 (4–11)	*<0.001*
Antenatal steroids	15 (10.2%)	47 (8.5%)	0.55	8 (11.3%)	7 (9.2%)	0.68
Composite adverse maternal outcome	3 (2.0%)	12 (2.2%)	0.92	1 (1.4%)	2 (2.6%)	0.59
Composite adverse neonatal outcome	6 (4.1%)	57 (10.3%)	0.02	3 (4.2%)	3 (4.0%)	0.96

Data were compared between respondents, nonrespondents, and induction of labour and expectant management using Student t, Mann-Whitney U, Chi square or Fishers exact test. Table shows median [interquartile range] or number (%). Data are given according to available data.
*Indicates a variable with >20% missing data.

Table 2
Neonatal outcomes.

Neonatal outcomes	Immediate delivery *n = 75*	Expectant monitoring *n = 78*	Difference in % or mean (95% CI)	*p*-value
Fetal growth restriction at study entry	5 (6.7%)	3 (3.8%)	2.9 (-4.2 to 10.0)	0.62
Born small for gestational age	9 (12.0%)	15 (19.2%)	−7.2 (-18.6 to 4.2)	0.22
Birth weight (grams)	2550 (2280-2970)	2690 (2269-3070)	−63 (-223 to 97)	0.44
Gestational age at birth (weeks)	36.1 (35.4-36.7)	37.0 (36.1-37.1)	−0.61 (-0.88 to -0.34)	*<0.001*
RDS	4 (5.3%)	1 (1.3%)	4.0 (-1.7 to 9.7)	0.16
5 min Apgar score <7	0 (0.0%)	3 (3.9%)	−3.9 (-8.2 to 0.4)	0.08
Umbilical artery pH < 7.05*	2 (3.5%)	1 (1.5%)	2.0 (-3.0 to 7.0)	0.48
NICU admission	1 (1.3%)	0 (0.0%)	1.3 (1.3 to 3.9)	0.31
Sepsis (suspected infection)	7 (9.3%)	7 (9.0%)	0.3 (-8.8 to 9.4)	0.94
Hypoglycaemia	13 (17.3%)	5 (6.4%)	10.9 (0.8 to 21.0)	0.04
Transient tachypnoea of the newborn	3 (4.0%)	3 (3.8%)	0.2 (-5.9 to 6.3)	0.96
Meconium aspiration syndrome	0 (0.0%)	0 (0.0%)		NA
Pneumothorax or pneumomediastinum	0 (0.0%)	0 (0.0%)		NA
Periventricular leucomalacia	0 (0.0%)	0 (0.0%)		NA
Intraventricular haemorrhage	0 (0.0%)	0 (0.0%)		NA
Convulsions	0 (0.0%)	1 (1.3%)	−1.3 (-3.8 to 1.2)	1.00
Necrotising enterocolitis	0 (0.0%)	0 (0.0%)		NA
Any neonatal morbidity	28 (37.3%)	18 (23.1%)	14.2 (-0.2 to 28.6)	0.12
Age at completion of follow up (month)	61 (60-64)	61 (60-65)	−0.5 (-1.77 to 0.72)	0.41

Data were compared between induction of labour and expectant management using Student t, Mann-Whitney U, Chi square or Fishers exact test.
Table shows median (interquartile range) or number (%).
n = number of neonates born in a certain cohort.
Data are given according to available data.
*Indicates a variable with >20% missing data.

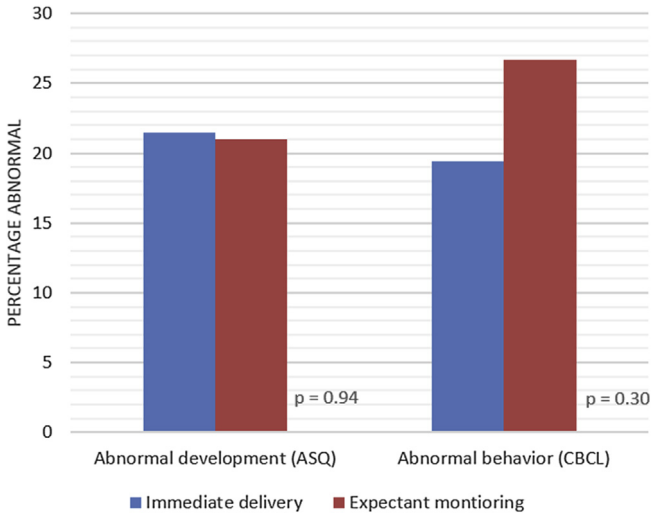

Fig. 2. Number of children with abnormal scores on Ages and Stages Questionnaire (ASQ) or Child Behaviour Checklist (CBCL).
Data were compared with Chi square test.

Behavioral problems (CBCL)

An abnormal CBCL score was found in 19.4% (n = 14) of the immediate delivery group and 26.7% (n = 20) of the expectant monitoring group (absolute difference 7.3%, 95% CI -20.9 to 6.3, p = 0.30, Fig. 2). On the CBCL subscale of somatic complaints 12% (n = 9) of the children in the expectant monitoring group had an abnormal score as compared to 2.8% (n = 2) in the immediate delivery group (absolute difference 9.2%, 95% CI -17.5 to -0.9, p = 0.03, see Table 3). No statistically significant differences were found in other behavioral problem scales.

Predictors of abnormal ASQ or CBCL

Univariable analysis found no significant predictors of abnormal ASQ or CBCL score at 5 years of age in children born after a hypertensive pregnancy. Table 4 shows the results of the multilevel analysis of possible predictors of abnormal ASQ and CBCL scores at both 2 and 5 years after the HYPITAT II study. Fetal growth restriction was associated with abnormal ASQ scores at 2 and 5 years of age (OR 2.1, 95% CI 1.0 to 4.4). Higher birthweight and higher maternal education did not decrease abnormal ASQ outcome rate although their effects bordered on significance (OR 0.7, 95% CI 0.4 to 1.1 and OR 0.6, 95% CI 0.3 to 1.1, respectively). In the analysis of all measurements at 2 and 5 years, abnormal development was not significantly associated with immediate delivery (OR 1.4, 95% CI 0.9 to 2.3) or with the related variable younger gestational age at birth (OR 1.0, 95% CI 0.8 to 1.3). Factors associated with abnormal CBCL scores at 2 and 5 years were fetal growth restriction (OR 2.2, 95% CI 1.1 to 5.5) and maternal education (OR for higher education 0.5, 95% CI 0.2 to 0.9).

Comment

Principal findings

In this follow-up study of the children 5 year after the HYPITAT II trial we found no difference in developmental and behavioral outcome between the two management groups (immediate delivery vs. expectant monitoring). We did find that fetal growth restriction was associated with poorer developmental and behavioral outcome at 2 and 5 years old. Additionally, maternal education predicted development at age 2 and behavioral outcome at 2 and 5 years old. In the 2-year follow-up data immediate delivery (and a slightly lower gestational age at delivery as a result of that) was associated with poorer development. At 5 years of age the effects of obstetric management on development did not persist.

Results in the context of what is known

Our cohort still showed a higher risk of abnormal development (21.3%) compared to the standard Dutch population, in which an abnormal score is expected for 2.3%) [17]. This strengthens previous studies that both hypertensive disorders and preterm birth are associated with increased risk of abnormal development [23–29]. For behavioral outcomes the gap between the reference and the study population was less pronounced: by definition 17% of the reference population had a score above the borderline cut-off, compared to 16.1% in the 2-year follow-up [17]. In this 5-year follow-up abnormal behavior scores varied from 19.4% in the delivery groups vs. 26.7% in the expectant monitoring group. This indicates a slightly elevated rate of behavior problems in our study compared to their 5 year old peers.

This study did not confirm that gestational age at delivery is one of the main predictors of developmental and behavioral outcomes

Table 3
Abnormal scores per problem area compared between groups.

Variable	Immediate delivery	Expectant monitoring	Difference in percent (95% CI)	*p*-value
Problem area ASQ	*ASQ n = 65*	*ASQ n = 62*		
Communication	5 (7.7%)	3 (4.8%)	2.9 (-5.5 to 11.3)	0.51
Gross motor	3 (4.6%)	2 (3.3%)	1.3 (-5.5 to 8.1)	0.72
Fine motor	5 (7.8%)	5 (8.1%)	−0.3 (-9.7 to 9.1)	0.96
Problem solving	1 (1.6%)	4 (6.5%)	−4.9 (-11.8 to 2.0)	0.17
Personal social	1 (1.6%)	3 (4.8%)	−3.2 (-9.3 to 2.9)	0.29
total score	3 (4.9%)	3 (5.0%)	−0.1 (-7.6 to 7.4)	0.98
Syndrome scale CBCL	*CBCL n = 72*	*CBCL n = 75*		
Emotionally reactive	6 (8.3%)	7 (9.3%)	−1.0 (-10.2 to 8.2)	0.83
Anxious/depressed	4 (5.6%)	3 (4.0%)	1.6 (-5.3 to 8.5)	0.66
Somatic complaints	2 (2.8%)	9 (12.0%)	−9.2 (-17.5 to -0.9)	0.03
Withdrawn	3 (4.2%)	3 (4.0%)	0.2 (-6.2 to 6.6)	0.96
Sleep problems	1 (1.4%)	1 (1.3%)	0.1 (-3.5 to 3.8)	0.98
Attention problems	6 (8.3%)	5 (6.7%)	1.6 (-6.9 to 10.1)	0.70
Agressive behavior	3 (4.2%)	3 (4.0%)	0.2 (6.2 to 6.6)	0.96
Internalizing	9 (12.5%)	6 (8.0%)	4.5 (-5.3 to 14.3)	0.37
Externalizing	6 (8.3%)	8 (10.7%)	−2.4 (-11.9 to 7.1)	0.63
Total problem score	14 (19.4%)	20 (26.7%)	−7.3 (-20.9 to 6.3)	0.30

Data were compared with Chi-square test.
n = number of neonates with complete questionnaire.

Table 4
Predictors of abnormal Ages and Stages Questionnaire and Child Behaviour Checklist scores at 2 and 5 year follow up.

	Abnormal ASQ					Abnormal CBCL				
Variable	n (%) 2 year	n (%) 5 year	OR	95% CI	*p*-value	n (%) 2 year	n (%) 5 year	OR	95% CI	*p*-value
Type of hypertension (PE YN)					0.31					0.72
Gestational hypertension	15 (17.5%)	7 (16.7%)	1	reference		16 (17.8%)	11 (23.9%)	1	reference	
Preeclampsia	26 (26.5%)	14 (25.5%)	1.58	(0.88-2.83)		27 (18.0%)	13 (18.8%)	0.88	(0.50–1.54)	
Chronic hypertension	21 (23.6%)	6 (20.0%)	1.39	(0.73-2.65)		12 (11.8%)	10 (31.3%)	0.77	(0.40–1.46)	
Gestational age at delivery					0.34					0.72
<35	14 (38.9%)	0(0%)	1.56	(0.73–3.37)		9 (23.7%)	2(16.7%)	1.28	(0.54–3.02)	
35-36	11 (19.0%)	4(13.3%)	0.73	(0.36–1.51)		10 (16.1%)	9(27.3%)	1.23	(0.61–2.47)	
36-37	28 (23.1%)	13(28.9%)	1.19	(0.68–2.09)		18 (13.3%)	14(25.9%)	0.99	(0.55–1.77)	
>37	19 (20.0%)	10 (25.6%)	1	reference		18 (17.0%)	9(18.8%)	1	reference	
Time between inclusion and delivery			0.98	(0.93–1.03)	0.49			1.03	(0.98–1.09)	0.27
Birth weight (kg)			0.70	(0.44–1.10)	0.13			0.72	(0.43–1.20)	0.21
Twin			0.83	(0.34–2.03)	0.69			0.58	(0.20–1.74)	0.33
yes	6 (21.4%)	1 (9.1%)				3 (11.1%)	2 (15.4%)			
no	66 (23.4%)	26 (22.4%)				52 (16.6%)	32 (23.9%)			
FGR			2.1	(0.99–4.42)	0.05			2.19	(1.05–5.54)	0.04
yes	10 (34.5%)	3 (37.5%)				8 (25.8%)	3 (42.9%)			
no	48 (21.2%)	21 (20.8%)				33 (13.1%)	25 (20.7%)			
SGA			1.53	(0.83–2.78)	0.17			1.56	(0.82–2.97)	0.17
yes	14 (32.6%)	6 (27.3%)				11 (22.4%)	7 (29.2%)			
no	58 (21.9%)	21 (20.0%)				43 (14.9%)	27 (22.0%)			
Adverse neonatal outcome			0.74	(0.31–1.77)	0.50			1.06	(0.44–2.53)	0.90
yes	7 (21.2%)	0 (0%)				7 (20.6%)	1 (14.3%)			
no	65 (23.6%)	27 (22.7%)				48 (15.6%)	33 (23.7%)			
RDS			0.30	(0.04–2.45)	0.26			0.34	(0.04–2.71)	0.31
yes	1 (11.1%)	0 (0%)				1 (9.1%)	0 (0%)			
no	71 (23.6%)	27 (22.0%)				54 (16.4%)	34 (23.8%)			
Apgar			1.47	(0.51–4.30)	0.47			1.24	(0.42–3.67)	0.69
yes	5 (35.7%)	0 (0%)				3 (21.4%)	1 (33.3%)			
no	67(22.7%)	27 (22.0%)				52 (16.0%)	33 (23.1%)			
Umbilical artery PH			0.45	(0.05–3.95)	0.47			NA	NA	NA
yes	1 (16.7%)	0 (0%)				0 (0%)	0 (0%)			
no	58 (24.1%)	26 (25.7%)				47 (17.9%)	31 (27.2%)			
NICU			0.62	(0.1–2.22)	0.47			0.80	(0.23–2.83)	0.73
yes	3 (16.7%)	0 (0%)				3 (15.8%)	0 (0%)			
no	69 (23.6%)	27 (21.4%)				52 (16.1%)	34 (23.3%)			
Sepsis			1.01	(0.46–2.20)	0.98			1.54	(0.70–3.40)	0.28
yes	8 (29.6%)	1 (7.1%)				6 (22.2%)	4 (28.6%)			
no	63 (22.3%)	26 (23.0%)				48 (15.3%)	30 (22.6%)			
Hypoglycemia			1.46	(0.77–2.74)	0.25			1.42	(0.74-2.73)	0.29
yes	11 (26.2%)	6 (37.5%)				9 (18.8%)	6 (33.3%)			
no	60 (22.5%)	21 (18.9%)				45 (15.4%)	28 (21.7%)			
Transient tachypnoea of the newborn			1.68	(0.61–4.67)	0.32			1.75	(0.59–5.24)	0.32
yes	5 (31.3%)	2 (33.3%)				5 (29.4%)	1 (16.7%)			
no	66 (22.5%)	25 (20.7%)				49 (15.2%)	33 (23.4%)			
Antenatal steroids			1.19	(0.56–2.50)	0.65			1.45	(0.72–2.94)	0.30
yes	9 (30.0%)	2 (13.3%)				8 (23.5%)	4 (26.7%)			
no	63 (22.9%)	24 (21.6%)				46 (15.2%)	30 (22.9%)			
Management policy			1.42	(0.89–2.26)	0.14			1.06	(0.65–1.72)	0.81
Induction	45 (27.8%)	14 (21.5%)				24 (14.4%)				
Expectant	27 (18.2%)	13 (21.0%)				31 (17.7%)				
Education*			0.60	(0.33–1.09)	0.09			0.45	(0.23–0.88)	0.02
High	13 (14.6%)	8 (22.9%)				8 (8.1%)	7 (18.4%)			
Low	34 (29.3%)	6 (15.0%)				28 (22.0%)	9 (18.0%)			
Maternal smoking			1.26	(0.64–2.45)	0.50			1.55	(0.82–2.91)	0.18
yes	12 (30.0%)	3 (17.6%)				12 (27.9%)	3 (15.8%)			
no	57 (22.1%)	23 (21.9%)				41 (14.3%)	31(25.2%)			

Percentages are given according to available data. *Indicates a variable with >20% missing data.

at the age of 5, as we found no significant relationship. A possible explanation might be that literature mainly focuses on preterm versus term delivery, while all participating infants in this trial were delivered preterm between 34–37 weeks [15,30]. The small range of gestational ages might have contributed to the lack of a significant relation.

In literature both fetal growth restriction and birth weight are associated with poor neurodevelopment [31,32]. Our 2-year follow-up study found birth weight as a predictor of development in consensus with literature. The current study showed a trend towards improved development with increasing birthweight and birthweight above the 10th centile. We found that fetal growth restriction was significantly associated with abnormal development and behavior problems at both 2 and 5 years of age.

Besides the perinatal situation, maternal education, lifestyle factors and socio-economic status are known to be associated with development, as we also reported for the outcomes at 2 year [27]. Additionally, the association between maternal education and behavioral outcomes at 2 and 5 years old emerged. A possible explanation for poorer developmental outcome at 2 years of age in the immediate delivery group, and the absence of this difference at 5 years could be that environmental factors such as maternal education and socio-economic status become more important for development at older ages [33]. Additionally, if a developmental

delay is noticed early, early interventions at daycare or school can improve later development [34,35].

Strengths and limitations

Considering that obstetric interventions might influence outcomes in childhood, the HYPITAT II trial preplanned this long-term follow-up. The prediction of developmental outcomes in infancy is still challenging due to intensive neurodevelopmental processes occurring in this period [36]. Assessing the data from two time points makes it possible to monitor the progression of development in one child, having both short and long term follow-up.

This study was limited by a low follow-up rate due to logistic reasons. At 5 years after the original trial contact data were no longer up to date, making it difficult to approach all participants of the original study. As a result, our study may have insufficient power to detect subtle differences. Also, there is evidence of selective participation in this follow-up study: in the respondents group less adverse neonatal outcomes were observed, which may have influenced the results. Nevertheless, this is the only randomized controlled trial comparing two management strategies in preterm hypertensive disorders with a long term follow-up at two time points. Given the limitations of the study budget we performed a questionnaire study. Clinical examination rather than a questionnaire study would have been the most reliable tool to assess development and behavior, although parent completed screening questionnaires are proven to be reliable to detect developmental delay and behavior problems [37,38].

Implication for clinical practice

The principal findings of the HYPITAT II and the 2-year follow-up study underline that in preterm hypertensive disorders expectant monitoring should be the management strategy of choice. The results of the 5-year follow-up indicate that the neonatal morbidity and impaired development at 2 years imposed by immediate delivery, diminish at later age. Apparently, long-term developmental and behavioral consequences of immediate delivery versus expectant management for the neonate are minimal in late preterm pregnancy. Expectant management poses the risk of progression of maternal disease and fetal growth restriction, which are both associated with poorer development. In the preferred general policy of expectant management in preterm hypertensive disorders, immediate delivery can be safely considered when maternal or fetal condition deteriorate without too much hesitation because of worries about the long-term effect on infant development.

Future perspectives

Longer and more detailed follow-up studies are needed to assess the effect of management in late preterm hypertensive disorders of pregnancy on behavior, cognitive and social-emotional development. In addition, other long term morbidity (cardiovascular, metabolic, respiratory, reproductive etcetera) that may result from prematurity should be addressed in follow up studies. We encourage researchers to integrate a long term follow up when designing an (obstetrical) clinical trial to evaluate these valuable parameters.

Conclusion

Neurodevelopmental and behavioral problems at the age of 5 are not associated with management strategy in late preterm hypertensive disorders. This study therefore underlines the conclusion of the original HYPITAT II study and its 2-year follow-up that expectant management is the preferred management strategy until progression of disease or term gestational age indicate otherwise.

Registration and funding

Registered in the Netherlands Trial Registry (NTR1792). URL: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1792. Funded by ZonMw (grant 171102012).

Declaration of competing interests

The authors have no conflicts of interest in connection with this article

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.11.001.

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