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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

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ABSTRACT

Objective: We recently reported that induction of labour does not improve short term neonatal outcome in women with late preterm premature rupture of membranes (PPROM) as compared to expectant management (PPROMEXIL trial). In this study the neurodevelopmental and behavioural outcome of the children from this trial at 2 years of age was studied.

Study design: We studied outcome of offspring of women randomised in the PPROMEXIL study. These women had >24 h of ruptured membranes and were between 34 and 37 weeks of pregnancy when they were randomised to induction of labour (IoL) or expectant management (EM). Two years after delivery, the parents received the ages and stages questionnaire (ASQ), the child behaviour checklist (CBCL) and a general questionnaire.

Results: Follow-up data were obtained from 234 children (121 after IoL, 113 after EM, response rate 59% (44% of the original 532 randomised women)). In the IoL group 16 children (14%) had an abnormal score in ≥1 domains of the ASQ, versus 27 (26%) in the EM group (difference in percentage −11.4 (95% CI −21.9 to −0.98; $p = 0.033$)). For the CBCL, an abnormal score was found in 13% ($n = 15$) in the IoL group and in 15% ($n = 16$) in the EM group (difference in percentage −2.13 (95% CI −11.2 to 6.94; $p = 0.645$)).

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Conclusion: Although a policy of induction of labour in women with late PPROM does not improve short term neonatal outcome, it might be associated with a decrease in neurodevelopmental difficulties at the age of two years as compared to expectant management. Expectant management did not lead to a difference in behavioural problems.

Introduction

Management of preterm premature rupture of membranes (PPROM) between 34 and 37 weeks' gestation remains a medical dilemma, and recommendations given in international guidelines are not uniform [1–3]. A Cochrane review on the management of PPROM prior to 37 weeks identified insufficient evidence for the management of PPROM in clinical practice [4].

With this lack of knowledge in mind, we conducted a randomised controlled trial under the acronym PPROMEXIL (PPROM Expectant Management (EM) versus Induction of Labour (IoL)) [5]. This trial tested the hypothesis that IoL would reduce the incidence of neonatal sepsis in late preterm women (34–37 weeks' gestation). In total, 532 women were randomised between IoL and EM. Neonatal sepsis was found in 7 neonates (2.6%) in the IoL group and in 11 neonates (4.1%) in the EM group, with a relative risk (RR) of 0.64 (95% confidence interval (CI) 0.25–1.6). Although the overall risk of neonatal sepsis was similar in both groups, the risk of histological chorioamnionitis was reduced in the IoL group. Hypoglycemia and hyperbilirubinemia occurred significantly more often after IoL compared to EM (RR 2.2; 95% CI 1.4–3.4 and RR 1.5; 95% CI 1.1–1.9, respectively). Other neonatal outcomes, such as low Apgar scores, asphyxia, respiratory distress syndrome, intraventricular haemorrhage and neonatal admission, were not different between the two groups. As late prematurity is associated with long-term neurodevelopmental deficits [6], the assessment of neurobehavioural development in early and later childhood seemed appropriate. Moreover, PPROM has been linked to an increased risk of brain damage and neurodevelopmental impairment [7]. Such antenatal exposure to intra-amniotic inflammation and funisitis are primary risk factors for the development of cerebral palsy at the age of 3 years [8].

The present study assessed the effect of IoL or EM on the neurological and behavioural development of toddlers at the age of two years old who were born after a pregnancy complicated by PPROM between 34 and 37 weeks' gestation.

Methods and materials

The details of the PPROMEXIL study have been published previously (PLoS Medicine 2012) [5]. The follow-up study took place between April 2009 and September 2011.

A local research nurse contacted women by telephone to announce the follow-up when the toddler was 23 months old. Three questionnaires and a cover letter were then sent to the participants by mail. One questionnaire consisted of a short list covering general background questions. The developmental and behavioural outcome were tested by using the Ages and Stages Questionnaire (ASQ) and the Child Behaviour Checklist (CBCL) [9–11].

Participants were asked to complete and return the questionnaires within two months (e.g. age of the toddler 23–25 months). Next, the questionnaires were entered in an electronic database. Participants who failed to return the questionnaires within the given timeframe received a reminder by telephone to fill out the questionnaires.

The Dutch Organisation for Health Research and Development, ZonMW, funded the PPROMEXIL study and its follow-up (Grant numbers 94507212 and 171002215). The funder was not involved in the study design, the analysis or the report. The PPROMEXIL study and its follow-up were approved by the Medical Ethics Committee of Maastricht University Medical Center (MEC 05-240).

Developmental assessment: Ages and Stages Questionnaire (ASQ)

The ASQ is a comprehensive first-level screening questionnaire to detect developmental delay in children [9,10]. The ASQ has been validated to identify mental delay in preterm children at 24 months of age [12]. The questionnaire consists of questions about five developmental domains: communication, gross and fine motor skills, problem solving, and personal-social behaviour. The questionnaire is filled out by the parents. For each domain, a mean score was calculated and compared to the normative mean and standard deviation (SD) as was determined for the US version. A score between one and two SD below the normative mean on any domain, requires further monitoring of the child; a score <2 SD under the normative mean needs referral for further developmental assessment. We defined an abnormal score that reflects a risk for developmental delay as a score <2 SD under the normative mean in at least one domain.

Behavioural assessment: Child Behaviour Checklist (CBCL)

The CBCL consists of 100 items concerning behavioural problems, out of which a total problem score can be calculated [11]. The CBCL adequately assesses behavioural/emotional problems of children of 2–3 years old [13]. It informs on six narrow syndrome scales (anxious/depressed, withdrawn, sleeping problems, somatic problems, aggressive behaviour, destructive behaviour) and 2 broadband scales (internalising and externalising behaviour). For each scale, a standardised *T*-score is calculated. While the borderline cut-off point for the scale scores is the 95th percentile of the reference population, for the broadband dimensions and the total problem score is the 85th percentile. A score $>$97th percentile indicates severe behavioural problems. A score above the borderline cut-off point in one of the two broadband scales or in at least one narrowband scale, is used as an indicator of a significant risk for behavioural problems.

Statistical analysis

Outcomes of the IoL group with the EM group are expressed as medians with interquartile ranges, means with standard deviations and absolute numbers with differences in percentage. The Students *T*-test, Mann–Whitney U test and Chi-square tests were used if appropriate. An univariate regression analysis was performed to test the predictive value of multiple antepartum variables for neurodevelopmental outcome. We considered the following variables as potential predictors for an abnormal ASQ or CBCL score: maternal educational level, gestational age at birth, antenatal administration of corticosteroids, positive vaginal culture for group B streptococcus (GBS), maternal antibiotic

treatment during admission and/or labour, birth asphyxia (arterial pH <7.1 mmol/l at birth), histological chorioamnionitis, neonatal sepsis, neonatal hypoglycemia, neonatal hyperbilirubinemia, respiratory distress syndrome (RDS), neonatal admission to neonatal intensive care unit (NICU), and randomisation allocation. The predictors were introduced in a multivariate logistic regression model, with step-by-step exclusion using the Wald test. A *p*-value <0.20 was used to keep a variable in the model.

All data were analysed using SPSS software (SPSS, version 20.0; SPSS Inc, Chicago, IL).

Results

A total of 532 women randomised in the original PPROMEXIL trial were eligible for participation. Not all participants could be contacted for participation in the follow-up study, due to relocation or other logistic reasons (such as difficulty to obtain contact information). This cumulated in 75% of the women being approached to fill out the questionnaires (Fig. 1).

The response rate was 59% (*n* = 121 in the IoL group and *n* = 113 in the EM group) (44% of the original group of 532 women). Among these responses, 12 ASQs (5.1%) and 9 CBCLs (3.8%) were incomplete. Some of these questionnaires could still be included using ASQ guideline criteria on how to deal with missing data [7]. A total number of 114 ASQs in the IoL group, and 106 ASQs in the EM group were eligible for analysis. For the CBCLs this was 117 in the IoL group and 107 in the EM group.

Forty-five questionnaires (19%) were completed outside the recommended age range (23–26 months). We included the scores of these questionnaires in our analysis. A separate analysis was carried out for questionnaires which were completed within the recommended age range.

Baseline characteristics

The baseline characteristics between the IoL and EM group (Table 1) were not different and were similar to the original PPROMEXIL trial. When comparing respondents with non-respondents, they were more often Caucasian (90% vs. 79%) and had a higher level of education (38% vs. 25%). There were more smokers in the non-responding group (35% vs. 19%) and the incidence of neonatal sepsis and RDS was lower among respondents than

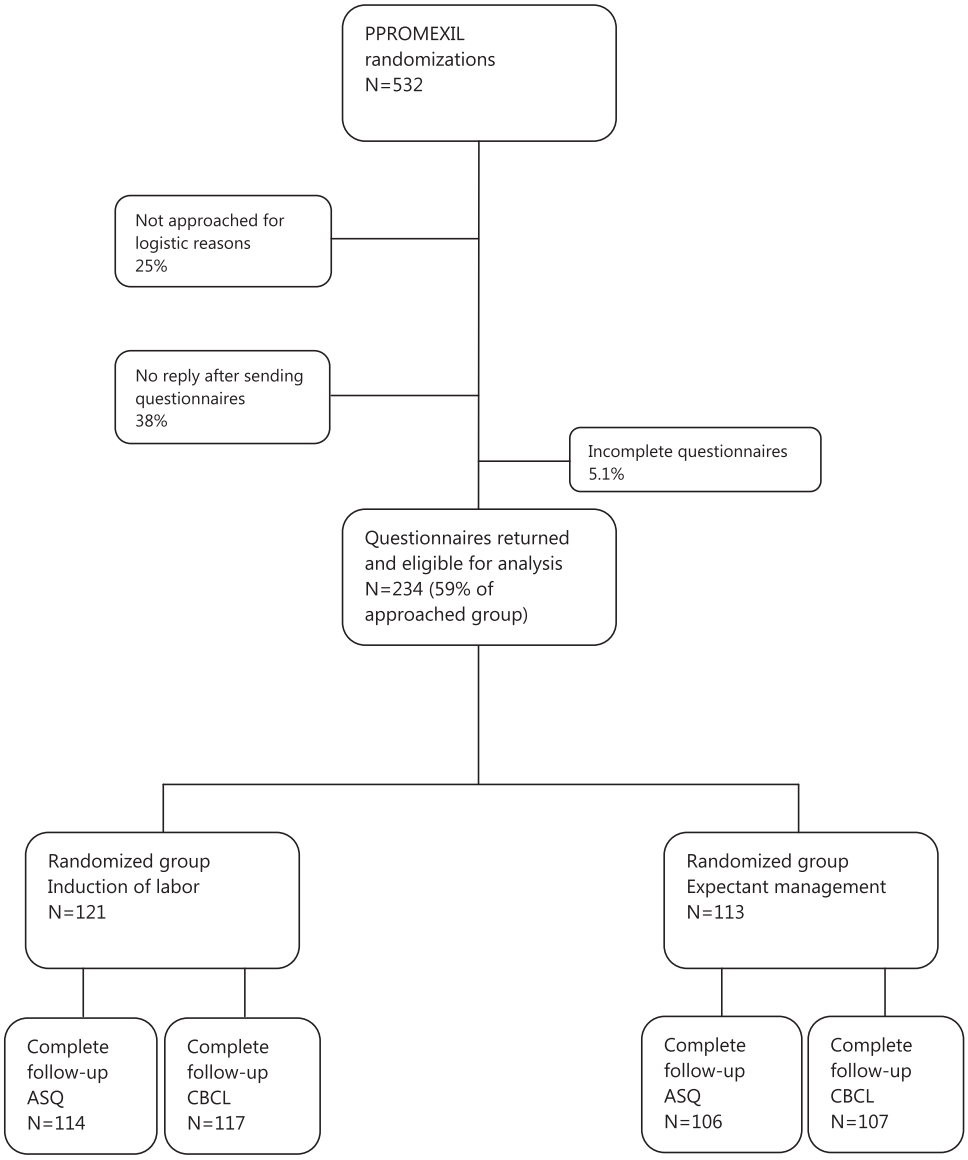

Fig. 1. Inclusion flow chart.

Table 1
Baseline characteristics.

Characteristics	Respondents[a] $n=233/235$[e] C	Nonrespondents[a] $n=299/303$[e] D	Difference in percent or mean (95% CI) C–D	Induction of labor[b] $n=120/121$[e] E	Expectant management[b] $n=113/114$[e] F	Difference in percent or mean (95% CI) E–F
Maternal age, y	30.2 (27.0–33.5)	28.9 (24.5–32.4)	1.37 (0.47 to 2.27)*	30.4 (27.8–33.8)	30.0 (26.6–33.5)	0.63 (−0.59 to 1.86)
BMI at start pregnancy, kg/m^2	23.7 (21.2–27.3)	23.4 (20.9–26.6)	0.34 (−0.66 to 1.34)*	24.2 (20.8–27.3)	22.8 (21.3–27.1)	0.74 (−0.79 to 2.13)
Maternal smoking	43 (18.9)	98 (35.3)	−16.3 (−23.9 to −8.73)**	23 (19.7)	20 (18.2)	1.48 (−8.71 to 11.7)
Caucasian	204 (90.3)	215 (79.3)	10.9 (4.75 to 17.1)**	105 (92.1)	99 (88.4)	3.71 (−4.01 to 11.4)
Education[c]						
Lower professional school	93 (62.4)	121 (75.2)	−12.7 (−23.0 to −2.49)*	44 (58.7)	49 (66.2)	−7.55 (−23.1 to −7.95)
Higher professional school	56 (37.6)	40 (24.8)		31 (41.3)	25 (33.8)	
Nulliparous	138 (59.2)	161 (54.0)	5.20 (−3.27 to 13.7)	71 (59.2)	67 (59.3)	−0.13 (−12.8 to 12.5)
Twin Pregnancy	2 (0.9)	4 (1.3)	−0.48 (−2.25 to 1.28)	1 (0.8)	1 (0.9)	−0.05 (−.242 to 2.32)
Antibiotic treatment[c]	90 (39.0)	127 (43.1)	−4.09 (−12.5 to 4.36)	48 (40.3)	42 (37.5)	2.84 (−9.74 to 15.4)
Antenatal administration corticosteroids	24 (10.9)	52 (18.5)	−7.60 (−13.7 to −1.47)*	14 (12.6)	10 (9.2)	3.44 (−4.78 to 11.7)
Gestational age at PPROM, d	249 (243–253)	249 (242–253)	1.29 (−0.43 to 3.01)	250 (243–254)	249 (243–253)	0.61 (−1.63 to 2.85)
Gestational age at birth, d	253 (248–258)	254 (249–258)	−0.78 (−1.89 to 0.33)	252 (246–256)	254 (250–254)	−3.15 (−4.63 to −1.67)**
Birthweight, g	2700 (2450–2910)	2670 (2360–2975)	10.62 (−62.5 to 83.7)	2665 (2373–2888)	2730 (2540–2940)	−79.7 (−182.6 to 23.3)
Neonatal sepsis	3 (1.3)	14 (4.6)	−3.34 (−6.11 to −0.57)*	1 (0.8)	2 (1.8)	−0.94 (−3.8 to 1.9)
Respiratory distress syndrome	10 (4.3)	26 (8.6)	−4.31 (−8.39 to −0.23)*	7 (5.8)	3 (2.7)	3.13 (−1.98 to 8.24)
Histologic chorioamnionitis[d]	37 (22.2)	68 (29.8)	−7.67 (−16.3 to 0.99)	19 (20.9)	18 (23.7)	−2.81 (−15.5 to 9.89)
Management						
Induction of labour	120 (51.5)	145 (48.7)	2.84 (−5.72 to 11.4)	NA	NA	NA
Expectant management	113 (48.5)	153 (51.3)		NA	NA	

Data are given according to available data.
Table shows median [interquartile 25th–75th percentile or number (%)].
BMI, body mass index.
[a] Data for randomised patients only, nonrespondents are including nonapproached.
[b] Data for respondent randomised patients only.
[c] Antibiotic treatment either during admission or during labour or both.
[d] Indicates a characteristic with >20% missing data.
[e] N/n; N, women; n, neonates. For neonatal outcome results are calculated for number of neonates.
* p-value <0.05.
** p-value ≤0.001.

among non-respondents (1.3% vs. 4.6% for neonatal sepsis and for RDS 4.3% vs. 8.6%) (Table 1).

Ages and Stages Questionnaire

A significant difference was found in the ASQ outcome between both groups (Table 2). In the IoL group, 16 children (14%) had an abnormal score in ≥1 domain of the ASQ, versus 27 children (26%) in the EM group (difference in percentage −11.4 (95% CI −21.9 to −0.98; $p = 0.033$)) (Fig. 2). The most obvious differences were found in the domains gross motor skills (abnormal score in 2.5% versus 6.3%) and personal-social behaviour (abnormal score in 5.1% versus 13%).

Child Behaviour Checklist

For the CBCL, 15 children (13%) in the IoL group and 16 children (15%) in the EM group had an abnormal score in ≥1 narrow- or

Table 2
Neonatal outcomes.

Characteristic	Induction of labour $N=121$	Expectant management $N=113$	Difference in percent or mean (95% CI; p-value)
Gestational age at birth, d	252 (246–256)	254 (250–254)	−3.15 (−4.63 to −1.67; <0.001)
Birth weight, g	2665 (2373–2888)	2730 (2540–2940)	−79.7 (−182.6 to 23.3; 0.129)
Neonatal sepsis	1 (0.8)	2 (1.8)	−0.94 (−3.8 to 1.9; 0.52)
Hospital admission	119 (98.3)	109 (96.5)	1.89 (−2.21 to 5.98; 0.363)
Admission NICU	9 (7.4)	4 (3.5)	3.90 (−1.89 to 9.68; 0.195)
5-min Apgar score <7	0 (0.0)	0 (0.0)	NA
Asphyxia[a]	4 (4.4)	4 (4.7)	−0.26 (−6.46 to 5.93; 0.934)
Hyperbilirubinemia	43 (37.7)	35 (31.5)	6.19 (−6.22 to 18.6; 0.331)
Hypoglycemia	20 (17.5)	10 (9.2)	8.37 (−0.47 to 17.2; 0.068)

Data are given according to available data.
Table shows median [interquartile 25th–75th percentile or number (%)].
[a] Indicates a characteristic with >20% missing data.

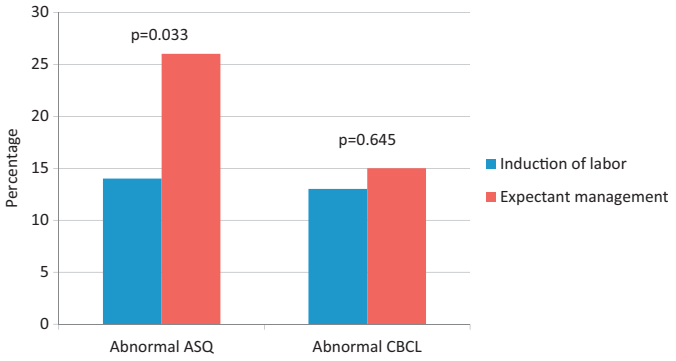

Fig. 2. Abnormal ASQ and CBCL scores in ≥1 areas.

broadband scale (difference in percentage −2.13 (95% CI −11.2 to 6.94; $p = 0.645$)) (Fig. 2).

When outcomes for only those questionnaires that had been completed between 23 and 26 months ($n = 189$) were analysed, similar results were found (more often abnormal ASQ outcome in the EM group compared with the IoL group ($p = 0.035$) and no significant difference in CBCL outcome between the groups ($p = 0.783$)).

In a univariate regression analysis, we assessed which factors were correlated with an abnormal ASQ or CBCL outcome, independently of randomisation allocation. Table 3 shows that neonatal sepsis, admission to NICU, hyperbilirubinemia, hypoglycemia, presence of histological chorioamnionitis and gestational age at birth were not significantly related to an abnormal ASQ or CBCL outcome.

EM was associated with an abnormal ASQ outcome. Lower maternal level of education was significantly correlated with an abnormal outcome of the CBCL (Table 3). Antenatal administration of corticosteroids was not statistically significantly associated with abnormal CBCL outcome ($p = 0.07$).

In multivariate analysis, neonatal hypoglycemia and no maternal antibiotic treatment were correlated with an abnormal ASQ score (odds ratios (OR) 3.7 and 0.43, respectively) (Table 4). An abnormal CBCL score was influenced by maternal education level (OR 0.14, 95% CI 0.01–1.42), antenatal administration of corticosteroids (OR 10.7, 95% CI 1.7–69) and management strategy (IoL) (OR 0.24, 95% CI 0.04–1.5) (Table 5).

Table 3
Univariate analysis of possible factors of influence on ASQ or CBCL, randomised women only.

Variable	Any abnormal ASQ domain	OR (95% CI) [p-value]	Any abnormal CBCL domain	OR (95% CI) [p-value]
Gestational age at birth (wks)				
34–34+6	6 (26%)	0.99 (0.68 to 1.45) [$p = 0.64$]	7 (27%)	0.73 (0.48 to 1.11) [$p = 0.35$]
35–35+6	8 (14%)		7 (12%)	
36–36+6	22 (22%)		13 (13%)	
37–37+6	7 (19%)		4 (11%)	
>38	0 (0.0%)		0 (0.0%)	
Asphyxia (ph <7.1)[a]				
Yes	0 (0.0%)	N/A [$p = 0.15$]	1 (13%)	0.86 (0.10 to 7.3) [$p = 0.89$]
No	33 (21%)		23 (14%)	
Antenatal steroids				
Yes	7 (30%)	1.9 (0.74–5.1) [$p = 0.17$]	6 (25%)	1.9 (0.74–5.1) [$p = 0.07$]
No	34 (18%)		22 (12%)	
Antibiotic treatment				
Yes	19 (21%)	1.2 (0.61–2.4) [$p = 0.60$]	14 (16%)	1.2 (0.61–2.4) [$p = 0.45$]
No	24 (19%)		17 (13%)	
Chorioamnionitis[a]				
Yes	7 (19%)	0.92 (0.36–2.3) [$p = 0.85$]	5 (14%)	1.2 (0.41–3.7) [$p = 0.71$]
No	25 (20%)		14 (11%)	
Positive GBS culture				
Yes	9 (20%)	1.1 (0.68–1.7) [$p = 0.98$]	5 (11%)	0.80 (0.44–1.47) [$p = 0.48$]
No	34 (19%)		26 (15%)	
Neonatal sepsis				
Yes	2 (40%)	8.6 (0.76–98) [$p = 0.24$]	0 (0.0%)	N/A [$p = 0.37$]
No	41 (19%)		31 (14%)	
RDS				
Yes	0 (0.0%)	N/A [$p = 0.11$]	0 (0.0%)	N/A [$p = 0.22$]
No	43 (20%)		31 (14%)	
Hypoglycemia				
Yes	8 (29%)	1.8 (0.74–4.5) [$p = 0.19$]	4 (14%)	1.03 (0.33–3.2) [$p = 0.96$]
No	33 (18%)		26 (14%)	
Hyperbilirubinemia				
Yes	18 (24%)	1.5 (0.76–3.1) [$p = 0.23$]	13 (18%)	1.6 (0.74–3.5) [$p = 0.23$]
No	23 (17%)		17 (12%)	
Admission NICU				
Yes	1 (9.2%)	0.4 (0.05–3.2) [$p = 0.37$]	0 (0.0%)	N/A [$p = 0.14$]
No	42 (20%)		31 (15%)	
Management policy				
Induction of labour	16 (14%)	0.48 (0.24–0.94) [$p = 0.03$]	15 (13%)	0.83 (0.39–1.8) [$p = 0.63$]
Expectant management	27 (26%)		16 (15%)	
Maternal educational level[a]				
Lower professional school	22 (26%)	0.54 (0.23–1.3) [$p = 0.16$]	18 (20%)	0.23 (0.07–0.82) [$p = 0.02$]
Higher professional school	9 (16%)		3 (5.5%)	

Percentages are given between abnormal and normal scores. Percentages are given according to available data.
RDS: respiratory distress syndrome.
[a] Indicates a characteristic with >20% missing data.

Table 4
Multivariable analysis of possible factors of influence on ASQ, randomised women only.

Variable	Regression coefficient	Odd-ratio (95% CI)	*p*-Value
Intercept	−1.164		
Hypoglycemia	1.304	3.7 (0.83–16)	0.09
Antibiotic treatment	−0.842	0.43 (0.13–1.43)	0.17

All potential variables as shown in table were introduced in the model.

Comment

This study suggests that expectant management of women with late preterm PROM results in poorer neurodevelopmental outcome of their children at two years of age when compared to women in whom labour was induced. There were significantly more children with abnormal test scores on the ASQ questionnaires in the EM group, indicating an increased risk of development delay. No significant differences were found in the incidence of behavioural problems of the children at two years of age. These results are based on responses to postal questionnaires validated for screening and answered by parents. Due to financial restraints, we were unable to physically test the toddlers. As such further research is needed to confirm the findings from this trial.

This follow-up study is an essential part of the original PPROMEXIL trial, since intervention in pregnancy could affect the developmental outcome in early and later childhood and should therefore be assessed accurately. A great advantage of the present study is its prospective character. Although we had a limited budget, we were able to carry out this follow-up study as a part of the randomised PPROMEXIL trial. Two validated questionnaires (ASQ and CBCL) were used to assess the (neuro)developmental outcome as well as the behavioural development.

The main problem that we encountered was the large amount of centres (60 hospitals) that included patients, resulting in participants living all across the country. Regularly, it was difficult for the research staff to contact all the participants. This caused a significant loss-to-follow-up. Furthermore, a substantial number of parents had moved and new contact data could not be traced. The response rate was comparable between the IoL and EM group.

In the group of respondents, less women smoked, women completed a higher level of education and more women had a Caucasian ethnicity. It is known that these characteristics are associated with a better response rate [14,15]. Furthermore, women with a healthy child seem more likely to respond to the questionnaires [16]. Indeed, neonatal sepsis and RDS occurred less frequently among the respondents. Therefore, our data might underestimate the effect on the developmental outcome at the follow-up, as these facts could theoretically improve follow-up results.

In the multivariate analysis, a low level of maternal education, antenatal administration of corticosteroids and management strategy (IoL) seem associated with an abnormal CBCL outcome. In the PPROMEXIL study, only a minority (11%) of pregnant women, received antenatal corticosteroids (betamethasone 11.4 mg twice, interval of 24 h) <34 weeks' gestation due to PPROM or threatened preterm labour. Antenatal corticosteroids significantly reduce the risk of neonatal mortality and morbidity in preterm birth before 34 weeks' gestation [17]. Corticosteroids are therefore useful in the management of women who are at immediate risk of preterm birth before 34 weeks of gestation (with or without PPROM). However, based on this finding and results from some other studies [18,19], further investigation of the possible adverse effects of antenatal corticosteroids on brain development is needed.

Table 5
Multivariable analysis of possible factors of influence on CBCL, randomised women only.

Variable	Regression coefficient	Odd-ratio (95% CI)	*p*-Value
Intercept	−0.138		
Induction of labour	−1.433	0.24 (0.04–1.5)	0.13
Antenatal steroids	2.371	10.7 (1.7–69)	0.01
Higher educational level	−1.975	0.14 (0.01–1.42)	0.10

All potential variables as shown in Table 4 were introduced in the model.

In this study, hypoglycemia was associated with a significantly increased risk of an abnormal ASQ outcome. Antibiotic treatment of women with PPROM resulted in significantly less women whose children had abnormal ASQ scores. Based on these results, antibiotic treatment of women presenting with PPROM seems in place. This recommendation is in line with the recommendation from a recent Cochrane review (2013) [20].

Chorioamnionitis might play a role in long-term childhood development, with a higher risk of adverse neonatal outcome (particularly cerebral palsy) [21–23]. In the present follow-up study, histological chorioamnionitis did not seem related to adverse developmental outcome. However, the effect of chorioamnionitis on brain development could still play a role in the difference in developmental outcome that we found. However, the relation between clinical and histological chorioamnionitis and the lack of a uniform definition of chorioamnionitis make comparisons of different studies difficult [21].

It is very likely that other unidentified causes will also play a role in the differences in developmental outcome that were found in this study.

We executed this follow-up study when toddlers where two years old. Possibly, this age is rather young to assess (neuro)developmental and behavioural problems, as problems may not yet have become evident at this age. Yet, we expected to achieve a higher response rate at this age compared to waiting until the children became older. Furthermore, we expected that major problems would already have become evident at this age. Further follow-up of the children, e.g. at 9–10 years of age, with assessment of school performance and motor function skills, might show whether the observed neurodevelopmental delay persists into late childhood.

Conclusion

Neurodevelopmental problems at two years of age seem to occur more often after EM compared to IoL of women with late preterm PROM. The negative effects of late prematurity (increased risks of hypoglycemia and hyperbilirubinemia) after IoL must be weighed against the negative effects of EM (slightly higher risk of abnormal ASQ outcome at two years of age).

Further follow-up is needed in order to determine whether the problems which are seen at two years of age are indeed related to difficulties in daily functioning at school age.

Conflict of interest

None.

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