

Maternal Leukocytosis After Preterm Premature Rupture of Membranes and Infant Neurodevelopmental Outcome: A Prospective, Population-Based Study (Décrire L'ouverture des Membranes Inopinée le Nouveau-né et L'Organisation des Soins [DOMINOS] Study)

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Abstract

Objective: To evaluate the relationship between maternal leukocytosis in women admitted after preterm premature rupture of the membranes (PPROM) and the neurodevelopmental outcomes of their infants at two years of age.

Methods: A prospective cohort study of women with PPRM occurring between 24 weeks and 33 weeks and 6 days of gestation was conducted in a region of France over two years. The primary outcome was a composite of neurodevelopmental variables, including motor impairment (an inability to stand without support, walk, run, or climb or descend stairs alone), auditory impairment, visual impairment, or the presence of monoplegia, diplegia, or hemiplegia at two years of age. Multiple logistic regression analysis was used to adjust for confounding factors.

Results: Of 394 cases, 6/64 neonates (9.4%) born to mothers with leukocytosis were no longer alive at the two-year follow-up, compared with 14/330 (4.2%) born to mothers with no leukocytosis ($P = 0.09$). At two years of age, 28 (56%), 22 (52%), 34 (49%), and 52 infants (37%) showed at least one of the primary outcome features for PPRM occurring at 24–27, 28–29, 30–31, and 32–33 weeks' gestation, respectively. In univariate analysis, PPRM at

less than 30 weeks, leukocytosis, and cerclage were associated with a higher rate of the primary outcome. In logistic regression analysis, only leukocytosis remained significant (odds ratio [OR] 2.92; 95% confidence intervals [CI] 1.33–6.39, $P = 0.02$). Fewer infants whose mothers had a leukocyte count (WBC) $\leq 15\,000/\text{mm}^3$ at the time of PPRM showed a feature of the primary outcome at two years of age than infants whose mothers had a higher WBC ($P < 0.01$).

Conclusion: Maternal leukocytosis at admission is associated with higher adverse infant neurodevelopmental outcomes at two years of age. Guidelines for the management of women with PPRM who do not begin to labour should include consideration of the degree of leukocytosis.

Résumé

Objectif : Évaluer la relation entre la leucocytose maternelle constatée chez les femmes hospitalisées à la suite d'une rupture prématurée préterme des membranes (RPPM) et les issues neurodéveloppementales constatées chez leurs enfants à deux ans.

Méthodes : Une étude de cohorte prospective qui portait sur des femmes ayant présenté une RPPM entre la 24^e semaine et la 33^e semaine-6^e jour de gestation a été menée dans une région de la France pendant deux ans. Le critère d'évaluation principal consistait en un ensemble de variables neurodéveloppementales, dont les troubles moteurs (incapacité de se tenir debout sans soutien, de marcher, de courir ou de monter ou de descendre un escalier de façon autonome), les troubles auditifs, les troubles visuels ou la présence d'une monoplégie, d'une diplégie ou d'une

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hémiplégie à deux ans. Une analyse de régression logistique multiple a été utilisée pour neutraliser l'effet des facteurs confusionnels.

Résultats : Sur 394 cas, 6/64 nouveau-nés (9,4 %) issus de mères présentant une leucocytose étaient décédés au moment du suivi à deux ans, par comparaison avec 14/330 (4,2 %) nouveau-nés issus de mères ne présentant pas une leucocytose ($P \leq 0,09$). À deux ans, 28 (56 %), 22 (52 %), 34 (49 %) et 52 enfants (37 %) présentaient au moins une des caractéristiques du critère d'évaluation principal en ce qui concerne la RPPM survenant à la 24^e–27^e, 28^e–29^e, 30^e–31^e et 32^e–33^e semaine de gestation, respectivement. Dans le cadre de l'analyse univariée, la RPPM survenant avant la 30^e semaine de gestation, la leucocytose et le cerclage ont été associés à un taux supérieur d'apparition du critère d'évaluation principal. Dans le cadre de l'analyse de régression logistique, seule la leucocytose est demeurée significative (rapport de cotes [RC], 2,92; intervalle de confiance [IC] à 95 %, 1,33–6,39, $P = 0,02$). Un nombre moindre d'enfants dont la mère avait présenté une leucocytémie $\leq 15\,000/\text{mm}^3$ au moment de la RPPM présentaient une caractéristique du critère d'évaluation principal à deux ans, par comparaison avec les enfants dont la mère avait présenté une leucocytémie supérieure ($P < 0,01$).

Conclusion : La présence d'une leucocytose maternelle au moment de l'hospitalisation est associée à un nombre accru d'issues neurodéveloppementales indésirables chez l'enfant à deux ans. Les lignes directrices sur la prise en charge des femmes présentant une RPPM qui n'entrent pas en travail devraient comprendre la prise en considération du degré de leucocytose.

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INTRODUCTION

Preterm premature rupture of the membranes (PPROM) is responsible for approximately 30% of all preterm births and for more than 50% of adverse outcomes in premature neonates.¹ An expectant management strategy has been recommended for PPRM prior to 32–34 weeks' gestation to decrease complications related to prematurity.²

Administration of corticosteroids to the mother can decrease the risk of intraventricular hemorrhage in neonates born after PPRM occurring before 30–32 weeks of gestation.³ The addition of prophylactic antibiotics during expectant management has been associated with prolongation of pregnancy and with a lower rate of infectious complications.⁴ However, the relationship between the infectious process and PPRM is unclear; intra-amniotic infection may be a result of bacterial invasion before rupture of membranes but may also be a result of bacterial contamination after disruption of the amniotic membrane barrier.^{5,6} After the membranes rupture, microbial invasion of the amniotic cavity detected by amniocentesis is present in approximately 30% of women with PPRM.⁷ Although most women with PPRM and microbial invasion of the amniotic cavity are asymptomatic, approximately 25% of women with PPRM will subsequently develop clinical chorioamnionitis during the time of expectant management. Clinical chorioamnionitis or a fetal inflammatory response is associated with a worse neonatal outcome.^{8–12}

Few tests are available to detect microbial invasion of the amniotic cavity, and the ideal method of predicting chorioamnionitis or neonatal sepsis has not yet been identified.¹³ Efforts should be made to avoid prolongation of pregnancies in the presence of intra-amniotic infection. Since leukocytosis is used as a marker of systemic inflammation, we sought to evaluate the relationship between maternal leukocytosis at the beginning of expectant management of PPRM and neurodevelopmental outcomes in the infant.

MATERIALS AND METHODS

A prospective cohort study of women with PPRM occurring between 24 weeks and 33 weeks and 6 days of pregnancy was conducted from April 1999 to April 2001 in all maternity wards ($n = 81$) of the Rhône-Alpes region in France (DOMINOS study). Research ethics committee approval was obtained, and all participating mothers gave their written informed consent. At the beginning of the study, there was no standardization regarding the use of antibiotics, corticosteroid therapy between 30 and 32 weeks' gestation, and tocolytics in the management of PPRM. Therefore, no specific recommendations for PPRM management were given to collaborating obstetricians. A research study midwife was selected and assigned to each participating centre. At the time of admission, each woman with a singleton pregnancy who presented with PPRM between 24 weeks and 33 weeks and 6 days of gestation was invited to participate in the study by the research study midwife. The inclusion criteria were (1) diagnosis of rupture of membranes based on a history of amniotic fluid leakage, confirmed by vaginal pooling during sterile speculum examination, a positive diamino oxydase test, or demonstration of oligohydramnios on ultrasound and (2) no spontaneous labour within 12 hours of membrane rupture. The exclusion criteria were (1) multiple gestation and (2) the presence of lethal anomalies. Gestational age was calculated from the date of the last menstrual period or from early ultrasound measurements (< 16 weeks' gestation). When the results of the two methods were discordant by more than seven days, the ultrasound measurement was used. In the Rhône-Alpes region, early ultrasound examinations were routinely performed in all maternity wards.

The results of blood tests, including white blood cell counts (WBC), were recorded with clinical data such as maternal age, marital status, employment status, parity, prior amniocentesis, cervical cerclage, vaginal bleeding in the first trimester, age at PPRM, latency period, oligohydramnios at admission, antibiotic and corticosteroid use during the latency period, and mode of delivery. If the woman was transferred to another hospital, another research midwife continued the follow-up to delivery. In neonatal units,

Table 1. Characteristics of pregnancies with and without leukocytosis

	No leukocytosis WBC < 15 000 n = 330 n (%)	Leukocytosis WBC > 15 000 n = 64 n (%)	<i>P</i>
Maternal characteristics			
Maternal age (years ± SD)	30.9 ± 0.30	28.5 ± 0.65	0.02
Marital status	278 (92)	53 (95)	0.55
Unemployment	63 (21)	12 (22)	0.87
Nulliparity	127 (40)	29 (50)	0.16
Pregnancy characteristics			
Amniocentesis	29 (9)	3 (5)	0.32
Cerclage	14 (4)	4 (7)	0.42
Vaginal bleeding in first trimester	33 (11)	6 (11)	1.0
At admission			
Age at PPRM (years)			
24–27	45 (14)	15 (26)	
28–29	41 (13)	3 (5)	
30–31	68 (22)	14 (25)	
32–33	159 (51)	25 (44)	0.06
Oligohydramnios	33 (15)	6 (15)	0.94
Antibiotics given	263 (83)	47 (81)	0.68
Corticosteroids given	252 (80)	45 (78)	0.71
Caesarean section	178 (57)	32 (56)	0.86
Mean latency period			
< 3 days	171 (56)	27 (50)	
3–7 days	69 (23)	18 (33)	
8–14 days	26 (9)	5 (9)	
> 14 days	38 (13)	4 (7)	0.32

WBC: White blood cell count; SD: standard deviation; PPRM: preterm premature rupture of membranes.

clinical data and the results of cerebral ultrasonography were recorded up to the time of discharge. At the time of discharge, a questionnaire and an information letter and stamped envelope were stapled to the infant's health book for use at the obligatory visit at two years of age. This questionnaire had been developed by a group of pediatric experts and structured to allow the accurate collection of data from a large number of physicians in a large geographic area. The physician in charge of the infant's care was asked to complete the questionnaire after examination of the infant and discussion with the parents during the obligatory visit when the child reached two years of age. The physician was asked to mail the completed questionnaire to the coordinating centre in Lyon. The mother was contacted by mail at 23 months after delivery to remind her of the two-year visit. If no information was obtained by 26 months, the mother was again contacted by mail and then by telephone.

After this, if there was still no information received, a close relative previously identified by the mother was contacted by mail and by telephone. If no questionnaire was returned to the coordinating centre, a specific mortality survey was organized to avoid loss to follow-up for two-year infant mortality. Letters were sent to the city hall in the infant's place of birth, asking whether the infant was alive or not, and, if not, asking for the date of the infant's death (such information is always available in France).

The primary outcome was the occurrence of significant neurological disorders grouped in a composite of variables, including impaired motor function (not able to stand without support, walk or run, or climb or descend stairs alone), auditory difficulties, difficulties with vision, or the presence of monoplegia, diplegia, hemiplegia, or quadriplegia. The secondary outcome was infant death by two years of age.

Table 2. Infant outcomes at two years of age

	PPROM at 24–27 weeks n = 47	PPROM at 28–29 weeks n = 37	PPROM at 30–31 weeks n = 61	PPROM at 32–33 weeks n = 136 n (%)
Motor abilities				
Standing without support* n (%)	43 (91)	36 (97)	60 (100)	134 (99)
Walking* n (%)	43 (93)	36 (97)	59 (98)	134 (99)
Mean age for walking (months \pm SD)	16.7 \pm 0.5	16.1 \pm 0.5	15.5 \pm 0.3	14.6 \pm 0.2
Climbing/descending stairs alone* n (%)	35 (74)	27 (73)	47 (78)	116 (87)
Running* n (%)	42 (89)	34 (92)	57 (93)	133 (98)
Piling 6 cubes* n (%)	382 (70)	27 (77)	52 (88)	114 (86)
Senses				
Speaking in sentences with several words n (%)	23 (50)	18 (50)	32 (53)	89 (59)
No hearing aid* n (%)	41 (98)	37 (100)	47 (100)	122 (100)
No vision problems* n (%)	36 (90)	31 (89)	46 (85)	105 (93)
Diplegia, monoplegia, hemiplegia or quadriplegia n (%)	3 (7)	0 (0)	4 (7)	1 (1)
Composite outcome of significant neurological disorders n (%)*	28 (56)	22 (52)	34 (49)	52 (37)

*Composite outcome of significant neurological disorders was defined as the presence of any of the following: impaired motor function (not able to stand without support, walk, run, or climb or descend stairs alone), auditory difficulties, difficulties with vision, or the presence of monoplegia, diplegia, hemiplegia or quadriplegia.
PPROM: Preterm premature rupture of membranes; SD: standard deviation.

Since the maternal leukocyte count varies considerably during normal pregnancy, we defined maternal leukocytosis as a WBC greater than 15 000/mm³. ANOVA and Pearson χ^2 , Fisher exact, and Mantel-Haenszel tests were performed when appropriate. Logistic regression analyses were used to adjust for significant confounding factors selected from marital status, employment status, parity, amniocentesis before PPRM, presence of cervical cerclage, vaginal bleeding in the first trimester, gestational age at PPRM, latency period, oligohydramnios at admission (defined as an amniotic fluid index of 5 cm or less), leukocytosis at admission, administration of antibiotics and corticosteroids during the latency period, and mode of delivery. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of 150 255 patients who gave birth between April 1999 and April 2001, 471 consecutive patients who met the inclusion criteria delivered after PPRM between 24 weeks and 33 weeks and 6 days of gestational age. All of these eligible patients consented to participate in the study. Three hundred ninety-four women (84%) had WBC recorded at admission, and 64 of these (16%) had a leukocytosis. Six of the 64 neonates born to mothers with leukocytosis (9.4%) were no longer alive at the two-year follow-up compared with 14 of 330 neonates (4.2%) born to mothers with no leukocytosis ($P = 0.09$). Of the 374 surviving infants, mean

gestational age at the time of rupture of membranes was no different in the group without leukocytosis (30.6 ± 0.1 weeks) and in the group with leukocytosis (30.1 ± 0.4 weeks) ($P = 0.16$). Maternal age was lower in women with leukocytosis ($P = 0.02$) (Table 1). The latency period was 153 ± 14 hours (mean \pm standard deviation) in the group without leukocytosis and 123 ± 20 hours in the group with leukocytosis ($P = 0.39$).

At two-year follow-up, 281 surviving children (75.1%) were examined as described. When compared with infants who attended the two-year follow-up assessment, infants lost to follow-up were more likely to have mothers who were multiparous (73% vs. 54%, $P < 0.01$) and who lived alone (13% vs. 5%, $P = 0.02$). However, gestational age at the time of rupture of membranes and the incidence of maternal leukocytosis were similar in the two groups. The primary outcome is presented in Table 2. For gestational age at rupture of 24–27, 28–29, 30–31, and 32–33 weeks, 26 (60%), 19 (54%), 29 (53%), and 44 (37%) respectively were judged to have a feature of the composite outcome ($P = 0.02$) at two years of age. The occurrence of a composite outcome was significantly more common in children whose mothers had leukocytosis ($n = 26$, 66.7%) than in those whose mothers did not ($n = 92$, 42.2%) (odds ratio [OR] 2.74; 95% confidence intervals [95% CI] 1.33–5.62, $P < 0.01$). Using univariate analysis, gestational age at rupture of membranes beyond 30 weeks' gestation (OR 0.61; 95% CI

Table 3. Univariate analysis for infant outcome at two years of age

	OR	95%CI	P
Maternal			
Maternal age > 35 years	0.85	0.46 – 1.58	0.62
Married	0.71	0.21 – 2.38	0.58
Unemployed	1.21	0.66 – 2.20	0.54
Nulliparous	0.81	0.49 – 1.32	0.39
Pregnancy			
Amniocentesis	0.68	0.29 – 1.62	0.39
Cerclage	3.47	1.07 – 11.2	0.03
Vaginal bleeding after 1 st trimester	0.59	0.25 – 1.39	0.22
At admission			
PPROM ≥ 30 weeks	0.57	0.33 – 0.96	0.04
Oligohydramnios	0.91	0.40 – 2.07	0.22
WBC > 15 000	2.74	1.37 – 5.62	< 0.01
Latency period ≥ 72 hours	0.71	0.43 – 1.17	0.32
Antibiotics given	1.28	0.66 – 2.47	0.46
Corticosteroids given	1.67	0.92 – 3.06	0.09
Caesarean section	1.11	0.68 – 1.84	0.67

OR: Odds ratio; CI: confidence interval; PPRM: preterm premature rupture of membranes; WBC: white blood cell count

0.38–0.99, $P = 0.05$) and cervical cerclage (OR 3.44; 95% CI 1.19–9.90, $P = 0.02$) were also associated with the primary outcome at two years of age (Table 3). In a multiple logistic regression model, including gestational age at rupture, cerclage, bleeding in the first trimester, latency period, administration of corticosteroids in the latency period, and maternal leukocytosis at admission, only maternal leukocytosis remained significantly associated with the composite outcome at two years of age (adjusted OR 2.92; 95% CI 1.33–6.39, $P = 0.02$). Furthermore, the occurrence of the composite outcome was directly associated with the severity of maternal leukocytosis: a feature of the composite outcome was present in 42% of women with WBC < 15 000/mm³ (92/218), in 63% (17/27) of women with WBC between 15 000/mm³ and 20 000/mm³ (OR 2.3; 95% CI 1.02–5.32), and in 75% (9/12) of women with WBC > 20 000/mm³ (OR 4.11; 95% CI 1.08–15.60).

DISCUSSION

Our study demonstrates that leukocytosis at the time of admission in women with PPRM is associated with adverse neurodevelopmental outcomes at two years of age in surviving infants. Moreover, this association followed a gradient effect: the more severe the leukocytosis, the worse the infant outcome at two years of age. These results are concordant with the findings of Yoon et al., that an elevated maternal WBC was linked with a trend towards a higher rate

of significant neonatal morbidity (OR 1.5; 95% CI 0.4–5.1).¹³ In their study, the association did not reach statistical significance, but the ability of the study to demonstrate a difference was limited by the number of patients included (90 women with PPRM) and by the fact that blood for WBC measurement was drawn at the time of amniocentesis and not necessarily at admission. Finally, maternal leukocytosis was defined as a WBC equal to or greater than 13 000/mm³, whereas we used 15 000/mm³. The authors did not report neonatal outcomes at a higher level of maternal leukocytosis but showed a direct relationship between the severity of leukocytosis and the likelihood of histological evidence of acute chorioamnionitis, which has been linked with neonatal morbidity.¹³ These findings are also in agreement with those of prior investigations demonstrating that the development of chorioamnionitis in pregnancies complicated by PPRM is associated with more neonatal morbidities, and with the findings of several studies reporting linkage between maternal inflammatory responses (clinical chorioamnionitis) and cerebral palsy.^{9,14}

The leading cause of PPRM is a local inflammatory or infective process that can expand and reach the fetus, the mother, or both.⁵ In pregnancies complicated by preterm labour or PPRM, Yoon et al. found that both antenatal exposure to intra-amniotic inflammation and evidence of a systemic fetal inflammatory response were strong and independent factors for the development of cerebral palsy.¹⁵

Their results also suggested that it is the fetal rather than the maternal inflammatory response that predisposes to cerebral palsy. In our series, amniocentesis was not performed, and information about placental pathology was not collected; therefore, we could not explore the fetal side of the inflammatory process.

In our study, the maternal WBC was measured at the time of admission for PPRM. Any maternal inflammatory process observed could be linked to the inflammation that led to the rupture itself. It is thus possible that adverse infant outcomes originate from an initial inflammatory or infectious process preceding rupture of the membranes and are not exclusively secondary to events that occurred during the latency period. Some data show that intra-amniotic infection or inflammation is present in the second trimester in women who will subsequently develop PPRM, suggesting that PPRM could be a long infectious or inflammatory process that begins in early pregnancy.^{16,17}

The chief limitations of our study are firstly that WBC was not measured in all patients and secondly that 24.9% of infants were lost to follow-up. However, we found no difference in infant outcomes between mothers who had an initial WBC measurement and those who did not, and we also found no difference in the rate of associated maternal leukocytosis between infants followed at two years and those lost to follow-up. The tool developed to assess neurodevelopment at the obligatory visit at two years of age has not been validated in other studies, but was developed and approved by a group of pediatricians and obstetricians prior to the beginning of this study. We do not believe that these limitations could have led to significant biases in our results.

CONCLUSION

The management of PPRM remains a controversial subject. We have found that a maternal inflammatory response at the time of admission for PPRM was the most important predictor of adverse neurodevelopmental outcomes at two years of age in surviving infants. The knowledge that early maternal inflammation after PPRM is associated with poorer long-term neurodevelopmental outcome could modify the current management strategy, which is based mostly on gestational age. Further studies will be required to explore whether administration of antibiotics and corticosteroids antenatally and expectant management remain beneficial strategies in women with PPRM and leukocytosis.

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