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Can neonatal sepsis be predicted in late preterm premature rupture of membranes? Development of a prediction model

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ABSTRACT

Objective: Women with late preterm premature rupture of membranes (PROM) have an increased risk that their child will develop neonatal sepsis. We evaluated whether neonatal sepsis can be predicted from antepartum parameters in these women.

Study design: We used multivariable logistic regression to develop a prediction model. Data were obtained from two recent randomized controlled trials on induction of labor versus expectant management in late preterm PROM (PPROMEXIL trials, (ISRCTN29313500 and ISRCTN05689407). Data from randomized as well as non-randomized women, who consented to the use of their medical data, were used. We evaluated 13 potential antepartum predictors for neonatal sepsis. Missing data were imputed. Discriminative ability of the model was expressed as the area under the receiver operating characteristic (ROC) curve and a calibration with both a calibration plot and the Hosmer and Lemeshow goodness-of-fit test. Overall performance of the prediction model was quantified as the scaled Brier score.

Results: We studied 970 women. Thirty-three (3.4%) neonates suffered neonatal sepsis. Maternal age (OR 1.09 per year), maternal CRP level (OR 1.01 per mmol/l), maternal temperature (OR 1.80 per °C) and positive GBS culture (OR 2.20) were associated with an increased risk of neonatal sepsis. The model had an area under the ROC-curve of 0.71. The model had both a good calibration and accuracy.

Conclusions: Antepartum parameters aid in the more precise prediction of the risk of neonatal sepsis in women with late preterm PPROM.

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1. Introduction

Preterm premature rupture of the membranes (PROM) is an important clinical problem. It complicates 1% to 5% of all pregnancies, and precedes 30–40% of all preterm deliveries [1–3]. Preterm PROM is associated with increased perinatal and maternal morbidity and mortality [4–6]. The risk of infection, resulting in chorioamnionitis and neonatal sepsis, is considered to be the largest threat in patients with late preterm PROM.

While there is no longer a need to administer antenatal corticosteroids for lung maturity, induction of labor is recommended from 34^{+0} weeks onwards [7,8]. However, two randomized controlled trials in The Netherlands showed that induction of labor (IoL) in asymptomatic women did not reduce the risk of neonatal sepsis compared to expectant management (EM) (combined Relative Risk (RR) 0.66, 95% Confidence Interval (CI) 0.30 to 1.5; neonatal sepsis rate of 2.7% (IoL) and 3.8% (EM) [9,10].

In the light of this, expectant management could be advocated in late preterm PROM, while identification of a high-risk subgroup could be helpful in the management of these women. Inducing labor and close monitoring of identified neonates at risk may reduce the incidence of neonatal sepsis even further, whereas EM and less frequent monitoring in low risk women will potentially lead to a reduction of neonatal complications due to prematurity, and of costs.

In this secondary analysis, we assessed the ability of several antepartum clinical parameters to predict neonatal sepsis. The aim was to develop a prediction model based on parameters easily available in routine practice.

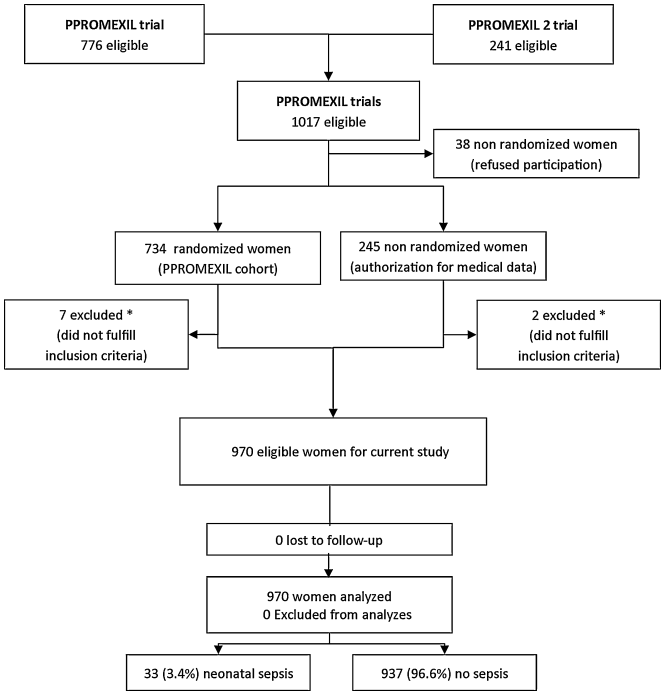

Fig. 1. Trial profile.

2. Materials and methods

For this study we used the data from the PPROMEXIL trials; PPROMEXIL (ISRCTN29313500) [10] and PPROMEXIL-2-trial (ISRCTN05689407) [9]. The PPROMEXIL trials were multicenter, open-label, randomized controlled trials in The Netherlands in which all eight academic and 52 non-academic hospitals participated. Briefly, women with a singleton or twin pregnancy were eligible for the PPROMEXIL trial when they were not in labor 24 h after PPROM between 34^{+0} and 37^{+0} weeks of gestational age. Fig. 1 outlines the study design and selection of patients.

PPROM had to occur after 26^{+0} weeks. Women with a monochorionic multiparty, an abnormal (non-reassuring) cardiotocogram, meconium stained amniotic fluid, major fetal anomalies, signs of intrauterine infections, HELLP syndrome or severe preeclampsia were not included.

Women who consented to participation in the trial were randomly allocated to either induction of labor (IoL-group) or expectant management (EM-group). Patients who did not consent to randomization, but who provided authorization for the use of their medical data, were treated according to their preference (non-randomization group), and had either immediate delivery or expectant monitoring. The management of these women was similar to that of randomized patients. In the present study we combined data from randomized women and women who refused randomization in the same cohort.

On admission a vaginal swab was taken to culture vaginal microorganisms. Immediate delivery was mostly due to induction of labor, but in some cases, for example for breech presentation, planned Cesarean delivery was performed. Expectant management consisted of at least daily maternal temperature monitoring and twice weekly blood sampling for signs of infection. If signs or symptoms of an (intra-uterine) infection developed labor was induced before 37 + 0 weeks of gestational age. Otherwise, if a woman reached 37^{+0} weeks of gestational age, labor was induced or a planned Cesarean section was done. In non-randomized women preferring expectant management labor was induced at 37^{+0} weeks of gestational age, according the national guideline [11]. The details of the trials have been published [9,10,12].

The outcome of interest was early onset neonatal sepsis. This was defined as: (1) positive blood culture taken at birth or (2) two or more symptoms of infection within 72 h plus one of three items: (a) positive blood culture; (b) CRP > 20; (c) positive surface culture of a known virulent pathogen [9,10]. Each case of suspected sepsis was judged by an independent panel of pediatricians (AM and RM). They were unaware of the allocation of randomization or preferred management in non-randomization, and individually adjudicated either neonatal sepsis or no sepsis. In case of disagreement this was resolved by a panel discussion.

Guidelines about the number of potential predictors that can be included in a prediction model have been proposed, including a requirement of 10 events per predictor variable [13]. However, since this is the first study to assess the predictive value of a multivariable model on the probability of neonatal sepsis, with many more potential predictors, we allowed five events per predictor variable to be included in the final model, dictating a maximum of six predictors (N_{cases} = 33). We assumed the following variables as candidate predictors: maternal age, parity (nulliparity versus multiparity), ethnicity, maternal smoking, maternal body mass index (BMI) at start of pregnancy, gestational age (GA) at PROM, antenatal administration of steroids, antepartum administration of antibiotics, and the following variables ascertained on admission: maternal C-reactive protein (CRP) level, maternal white blood cell count, maternal temperature, positive vaginal culture (any pathogenic specimen), positive group B streptococcus (GBS) culture. Antibiotics were given according to local protocol on admission, before signs or symptoms of chorioamnionitis.

Data were incomplete for some variables. The omission of patients from the analysis who have one or more predictor values missing could lead to a loss of precision and subsequently a reduction in statistical power [14–16]. More seriously, using only complete cases could potentially bias results. We assumed these data were missing at random (MAR) [17]. Therefore, we imputed the dataset using regression imputation.