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Neonatal outcomes after elective delivery management of preterm premature rupture of the membranes before 34 weeks' gestation (DOMINOS study)☆,☆☆

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ABSTRACT

Objective: The objective was to compare the impact of the reason for delivery (elective delivery versus spontaneous onset of labor) on neonatal outcome after preterm premature rupture of the membranes (PPROMs).

Study design: A regional prospective cohort study of all women with PPROM at between 24 and 34 weeks' gestation was conducted. We compared the effects of elective delivery ($n = 133$), spontaneous labor ($n = 170$), and admission for medical complications ($n = 169$) like fetal distress, maternal hyperthermia, or placental abruption, on neonatal outcomes. Primary outcome measures were a composite of neonatal mortality and morbidity, which included periventricular leukomalacia, grade III/IV intraventricular hemorrhage, neonatal sepsis, and oxygen requirement at 36 weeks' gestation.

Results: Among 472 cases, mean gestational age at PPROM was 31.2 ± 2.6 weeks. Neonatal outcomes improved as gestational age advanced, but a latency period of over 14 days did not improve outcomes. A logistic regression analysis showed that only elective delivery (OR 0.41, 95%CI: 0.19–0.87, $P = 0.02$), maternal age >35 years (OR 2.13, 95%CI: 1.19–3.85, $P = 0.01$), and gestational age at rupture remained associated with primary outcome.

Conclusion: Elective delivery in women with PPROM can be associated with decreased neonatal morbidity compared to spontaneous labor.

1. Introduction

Preterm premature rupture of the membranes (PPROMs) represents one-third of preterm births and is the leading cause of perinatal mortality and morbidity [1,2]. Recent evidence indicates that PPROM is related to biochemical processes that start several weeks before the rupture of the membranes and progress to inappropriate degradation of the membrane matrices [3]. During the latency period, several events, such as the ascent of pathogenic microorganisms from the lower genital area, could create complications (e.g. intrauterine infection, abruptio placentae, non-reassuring fetal heart rate tracings or uterine contractions) [4,5]. Several studies have shown that intrauterine infection/inflammation could be one of the most important risk factors for the subsequent development of brain white matter lesions in the infant, which may culminate in cerebral palsy [6,7]. Most authors propose the conservative management of women with PPROM before 34 weeks' gestation, associating antibiotic therapy with corticosteroid administration in patients with PPROM before 30–32 weeks' gestation [8–10]. The main benefit of conservative management is prolonging pregnancy, which theoretically has the potential to decrease gestational age-related morbidity associated with prematurity. But the benefit must be balanced with the risks of conservative management, especially clinical chorioamnionitis [11]. While we know that the infection/inflammatory process is linked to poor neonatal outcome, we do not know what the best strategy is to avoid these outcomes. In an effort to diminish the risks of infection linked to a longer latency period, several authors

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have proposed intentional delivery after PPROM and tested the hypothesis in randomized trials. These studies, however, were conducted prior to the beginning of antibiotic therapy and corticosteroid administration in patients with PPROM [12–15].

We conducted a large prospective cohort study on PPROM in Rhone-Alpes region [16,17]. From April 1999 to April 2001, all women with PPROM between 24 and 34 weeks' gestation were systematically approached and contacted by a research nurse to be enrolled in the study. In this area, we observed a heterogeneous attitude toward PPROM with centers proposing intentional delivery for PPROM before 34 weeks of gestation [18,19]. The objective of this study was to assess whether elective delivery (without spontaneous onset of labor and without medical complications) following PPROM, before $33^{6/7}$ weeks' gestation, was associated with improving neonatal outcome.

2. Methods

DOMINOS was an observational prospective study designed to assess several contemporary issues related to preterm premature rupture of the membranes. Between April 1999 and April 2001, all women presenting with PPROM between $24^{0/7}$ and $33^{6/7}$ weeks' gestation at a participating center were prospectively assessed. Detailed information regarding medical and obstetric history, latency period, intrapartum course, and postpartum complications were abstracted directly from maternal charts and completed by direct interview by a specially trained research midwife in each center. If a woman was transferred to another obstetric department, another research midwife continued the follow-up through delivery. Two coordinating research assistants checked all 81 delivery registers three times a year to identify any case omissions and control data quality. For each of 81 centers participating in this network study, institutional review board approval was obtained before enrollment and all mothers participating in the study gave their written informed consent. Neonatal information was noted by pediatricians in charge of the neonate in the Department of Neonatology up to discharge.

First, criteria for the diagnosis of PPROM included clinical diagnosis of rupture of the membranes based on a history of amniotic fluid leakage, amniotic fluid drainage from the cervical os during sterile speculum examination, and biochemical tests (diamino oxidase) when there was any doubt about PPROM. Second, gestational age was determined from the last menstrual period or from early ultrasound (US; <16 weeks). The ultrasound result took precedence when the results of the two methods were discordant by more than 7 days. Women with multiple gestations, lethal neonatal anomalies (i.e., major heart malformations and chromosomal anomalies) and spontaneous labor and delivery within 12 h of membrane rupture were excluded.

In 1999, the French College of Obstetricians and Gynaecologists (CNGOF) recommended a short course of antibiotic therapy and antenatal steroids for PPROM before 34 weeks' gestation [20]. The management strategy chosen during the latency period (defined as the interval between PPROM and birth) was left to the discretion of the attending obstetrician, and no specific recommendations were made to the obstetrician and pediatrician from the research team.

For this analysis, reasons for the delivery were grouped into three groups: (i) women who underwent delivery with spontaneous onset of labor; (ii) women who underwent delivery due to medical complications including non-reassuring fetal heart rate, maternal hyperthermia, abruptio placentae, and cord prolapse; (iii) those who underwent elective delivery by the induction of labor or cesarean section before labor without medical complications. The situation of the last group could occur, for example, when pregnancy reached 34 weeks' gestation.

Maternal (age, marital status, employment status, and parity) and obstetrical information (previous cesarean delivery, assisted reproductive technique, and cerclage), latency information (antibiotics, steroids, length, oligohydramnios, and hyperleukocytosis), and labor characteristics (mode of delivery and fetal presentation) were collected. The latency period was divided into four groups: ≤48 h, 3–7 days, 8–14 days, and >14 days. Oligohydramnios at admission was defined as a maximum vertical pocket of <2 cm on US and maternal hyperleukocytosis was noted if the white blood cell (WBC) count was >15,000 mm^{-3}.

The primary outcome was a neonatal composite outcome. The neonatal composite included at least one of the following: death before discharge from the hospital or major adverse outcome of the baby before discharge, periventricular leukomalacia, grade III/IV intraventricular hemorrhage, infectious disease, or oxygen requirement at 36 weeks' gestation [8]. The individual components of the composites were also examined. The diagnosis of neonatal respiratory distress was defined as clinical signs of respiratory distress needing oxygen and continuous nasal pressure or mechanical ventilation with typical radiographic appearance. A positive blood or cerebrospinal fluid culture was interpreted as proven neonatal sepsis. In all participating centers, cranial US was performed by qualified neonatologists who routinely perform the test when necessary (when faced with an abnormality during neonatal examination). Neurological anomalies, grades III and IV intraventricular hemorrhage, as defined by Papile et al., and periventricular leukomalacia on surveillance US were grouped together [21].

In the analysis, maternal, obstetrical, and latency period characteristics were compared with regard to reasons of delivery (elective delivery group versus spontaneous onset of labor group, medical complications group versus spontaneous onset of labor group). The composite factor was presented according to reason for delivery. Univariate analysis was performed to determine the crude odds ratio of the effect of independent factors on primary outcomes. Pearson's Chi-squared test, Fisher's exact test, and analysis of variance were used to ascertain differences among groups when appropriate. Only characteristics found to be significant ($P < 0.2$) in the univariate analysis were introduced in a logistic regression analysis. Using a 5% significance level, this analysis served to examine the contribution of each risk factor to the dependent variable (composite factor). Data were managed and analyzed using SAS statistical software 8.2 (SAS Institute, Inc., Cary, NC, USA).

3. Results

During the 2-year study period, there were 150,255 births in the Rhône-Alpes region. A total of 472 cases of PPROM between $24^{0/7}$ and $33^{6/7}$ weeks' gestation occurred; 170 (36.2%) women gave birth after spontaneous onset of labor, 169 (35.4%) due to medical complications, and 133 (28.4%) gave birth after elective delivery without medical complications. Selected maternal and obstetrical characteristics are shown in Table 1. Gestational age at rupture, latency period duration, and gestational age at delivery were similar in the spontaneous delivery group and the elective delivery group. Women undergoing elective delivery were less likely to present leukocytosis at admission. As anticipated, women undergoing elective delivery were more likely to present a non-vertex presentation, to undergo cesarean section, and to receive antenatal steroids. Gestational ages at rupture and at delivery were younger in the medical complications group than in the spontaneous delivery group. Table 2 shows neonatal outcomes according to the reason for delivery. Respiratory distress syndrome was the most common morbidity consequence noted across each group. We observed that oxygen requirement was more frequent in the medical complica-