Available online at www.sciencedirect.com
ScienceDirect
European Journal of Obstetrics & Gynecology and Reproductive Biology 135 (2007) 21–27
ejog European Journal of Obstetrics & Gynecology and Reproductive Biology
www.elsevier.com/locate/ejogrb

Effect of latency period after premature rupture of membranes on 2 years infant mortality (DOMINOS study)☆

Jean-Charles Pasquier *[a,b,c], Emmanuel Bujold [d], Muriel Rabilloud [e], Jean-Charles Picaud [f], René Ecochard [e], Olivier Claris [g], Stephanie Moret [b], Georges Mellier [b]

[a] Department of Obstetrics and Gynecology, Faculté de Médecine et des Sciences de la santé, Sherbrooke, Quebec, Canada
[b] Department of Obstetrics, Edouard Herriot Hospital, Hospices Civils de Lyon and Claude Bernard University, Lyon, France
[c] Department of Obstetrics and Gynecology, Hôpital Ste-Justine, Université de Montréal, Montreal, Quebec, Canada
[d] Department of Obstetrics and Gynecology, Université de Québec, Quebec, Canada
[e] Department of Biostatistics, Hospices Civils de Lyon, Lyon, France
[f] Department of Neonatology, Arnaud de Villeneuve Hospital and Montpellier University, Montpellier, France
[g] Department of Neonatology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

Received 24 May 2006; received in revised form 14 August 2006; accepted 20 October 2006

Abstract

Objective: To assess the impact of a short latency period after preterm premature rupture of the membranes (PPROM) on infant mortality.
Study design: A prospective cohort study of women with PPROM between $24^{0/7}$ and $33^{6/7}$ weeks' in singleton gestation was performed in all maternity wards of the Rhône-Alpes Region. Neonatal and infant outcomes were compared according to the latency period (<48 h and ≥48 h). The primary outcome was the mortality rate and the secondary outcome was a composite variable of significant neurological disorders at 2 years of age. Outcomes was stratified according to gestational age at rupture. Univariate and multiple logistic regression analyses were used with SAS statistical software.
Results: Out of 471 women recruited in the study at a mean gestational age of 30.5 ± 0.2 weeks, 170 (37%) presented with a <48-h latency period, and 301 (63%), a ≥48-h latency period. While prior to 30 weeks' gestation, the mortality rate was higher in neonates with a short latency period (16.3% versus 7.3%, $p < 0.01$) with pulmonary disease being the major cause of death, a short latency period was associated with a lower mortality rate after 30 weeks' gestation (0% versus 3.7%, $p = 0.02$). After adjusting for confounding factors, a <48-h latency period remained an independent factor associated with infant mortality prior to 30 week's gestation (odds ratio 3.8, 95% confidence interval 1.3–11.7). Significant neurological disorders were not modified by the length of the latency period.
Conclusion: For PPROM that occur before 30 weeks' gestation, a short latency period was associated with a higher infant mortality rate. Inversely, it was associated with a lower mortality rate after 30 weeks'. There is an urgent need for a thorough evaluation of expectant management of PPROM after 30 weeks' gestation.

Keywords: Preterm premature rupture of membranes; Latency period; Perinatal mortality; Neurological disorders

1. Introduction

Preterm premature rupture of membranes (PPROM) occurs in 2–4% of pregnancies and represents one-third of preterm deliveries [1]. Neonates born after PPROM are at great risk of morbidity and mortality associated with prematurity and infection [2,3]. Expectant management with antibiotics and antenatal steroids is recommended to prolong

☆ The study was conducted in the Rhône-Alpes Region and coordinated in Lyon (France).

* Corresponding author at: Dr Jean-Charles Pasquier, Department of Obstetrics and Gynecology, faculté de médecine et des sciences de la santé, 3001, 12e avenue Nord, Sherbrooke, Quebec, Canada J1H 5N4.
Tel.: +1 819 346 1110x13120.
E-mail address: jean-charles.pasquier@usherbrooke.ca (J.-C. Pasquier).

0301-2115/$ – see front matter © 2006 Published by Elsevier Ireland Ltd.
doi:10.1016/j.ejogrb.2006.10.020

the pregnancy and reduce the risks linked with prematurity up to 34 weeks' gestation [4]. While antibiotics have been associated with a longer latency period and a lower rate of neonatal complications, antenatal corticosteroids potentially reduce intraventricular hemorrhage in PPROM before 30–32 weeks' gestation [5–7]. Despite these treatments, expectant management exposes the fetus for a longer period to other antenatal complications such as abruptio placenta, non-reassuring fetal heart rate tracings, cord accident, microbial invasion of the amniotic cavity, and chorioamnionitis., the latter being a major determinant of long-term neurological development of neonates [2]. Few studies have actually provided long term follow-up information based on contemporary management and optimal obstetrical strategy of PPROM remains a controversial subject.

The purpose of this study was to assess the effect of expectant management and latency period on infant outcomes in women who experienced PPROM between 24 and $33^{6/7}$ weeks' gestation.

2. Materials and methods

A prospective cohort study on all cases of PPROM between $24^{0/7}$ and $33^{6/7}$ weeks' gestation between April 1999 and April 2001 was conducted in all 81 maternity hospitals of the Rhône-Alps region in France (DOMINOS) [8]. DOMINOS received Ethics Committee approval, and all mothers gave informed consent. DOMINOS was an observational cohort study and management strategy was left to the discretion of the attending obstetrician. Two assistant researchers checked all 81 delivery registers three times a year to control the quality of the data.

The criteria for the diagnosis of PPROM included: (1) clinical diagnosis of rupture based on history of amniotic fluid leakage, amniotic fluid draining from the cervical os during sterile speculum examination and biochemical tests and (2) no spontaneous labour and delivery within 12 h of membrane rupture. Multiple gestation and fetuses with lethal anomalies were excluded. Gestational age was determined by the last menstrual period, or early ultrasound ($<$16 weeks) when the results of the two methods were discordant by more than 7 days. After admission for PPROM, a research study midwife enrolled the women in the study. If a woman was transferred, another research midwife continued the follow-up through to delivery. Paediatricians took over surveillance in the Department of Neonatology up to discharge. At this time, a questionnaire with an information letter and stamped envelope was stapled in the infant's health book for the 2-year obligatory visit. This questionnaire was written by a group of paediatric experts and was designed for accurate data collection from a large number of physicians in a large geographic area.

The mother was contacted at 23 months to remind her of the 2-year visit. During the 2-year obligatory visit, the physician in charge of the infant completed the questionnaire after his/her own examination and discussion with the parents, then mailed it to the Coordinating Centre in Lyon. If by 26 months the information was not obtained, the mother was contacted by mail again, and then by phone. After this, if there was still no information, a close relative previously designated by the mother was contacted by mail and by phone.

If no questionnaire was returned to the Coordinating Centre, to avoid loss to follow-up for infant mortality at 2 years of age, a specific mortality survey was organized. Letters were sent to the City Hall of the infants' place of birth to establish if they were alive or not, and if they were dead to know the date of their death (data available in France).

The primary outcome of this study was the mortality rate at 2 years of age. The secondary outcome was the occurrence of significant neurological disorders grouped in a composite of variables, including motor impairment (not able to stand without support, walk, run, climb and descend stairs alone), auditory problems, vision difficulties, the presence of monoplegia, diplegia, hemiplegia or quadriplegia.

The maternal and obstetrical characteristics included maternal age, marital life, employment status, number of previous pregnancies, second or third trimester vaginal bleeding, cerclage, and gestational age at the time of rupture. The latency period was defined as the interval between PPROM and birth; i.e. birth time (date, hour and minute) minus PPROM time (date, hour and minute). During the latency period, the following characteristics were noted: oligohydramnios at admission, defined as the index of amniotic fluid $<$5 cm on ultrasound, maternal white blood cell (WBC) count $>$15,000/mm^3. A woman was classified in the ''corticosteroids'' and in the ''initial antibiotic therapy'' category if she had received at least one dose of corticosteroids or antibiotic during the first 2 days after PPROM.

Women were divided into two groups according to latency period. The cut-off limit of 48 h was predetermined because we believe that foetuses delivered in the first 48 h did not receive the expected benefit of expectant management and cumulated the worst conditions: young gestational age at birth, partial exposure to antibiotic and partial exposure to steroid treatments. In contrast, foetuses delivered after at least 48 h latency period should have received the entire effect of steroids, the benefits of antibiotics and were older at birth.

Maternal and obstetrical characteristics were compared between the groups. Mortality rates stratified by gestational age at rupture in four classes (24–27, 28–29, 30–31 and 32–33 weeks' gestation) were compared for latency periods ($<$48 h and $\geq$48 h). In the second part of the study, the same design served to analyze the occurrence of significant neurological disorders in surviving infants at 2 years of age. Pearson's Chi-square test, Fisher's exact test, the Mann–Whitney test, and analysis of variance (ANOVA) were used when appropriate. Significance and odds ratios (OR) with 95% confidence interval (CI) were calculated. Step-wise forward logistic regression to investigate the interaction between these variables was performed for the primary and