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Neonatal outcome of preterm infants born to mothers with abnormal genital tract colonisation and chorioamnionitis: A cohort study

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ABSTRACT

Purpose: We hypothesised that abnormal genital tract colonisation leading to an in utero inflammation/infection process, contributes to the risk of respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intra ventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC) in preterm infants.

Methods: 396 placentas and umbilical cords of neonates born at 22–32 weeks of gestation were evaluated. Genital tract and amniotic fluid swabs were cultured for aerobic and anaerobic bacteria.

Results: Chorioamnionitis significantly increases the risk for RDS (OR 1.74, 95% CI 1.14–2.65), NEC (OR 3.22, 95% CI 1.36–3.28) and ROP>2 (OR 2.12, 95% CI 1.33–3.36). But the risk for IVH, PDA and BPD did not differ between the groups. *Klebsiella pneumoniae* (OR 5.33, 95% CI 1.06–26.79), *Staphylococcus* sp. (OR 18.39, 95% CI 2.32–145.2) and *Enterococcus faecalis* (OR 10.7, 95% CI 1.27–89.9) showed a significant relationship with intrauterine inflammation processes. *E. faecalis* increased the risk for NEC (OR 6.13, 95% CI 1.059–37.6). We did not note a link between ROP and genital tract colonisation. Interestingly PDA seems to be triggered by the presence of *Pseudomonas aeruginosa* (OR 2.38 95% CI 1.83–3.82).

Conclusion: Our results show a link between *K. pneumoniae*, *Staphylococcus* sp., *E. faecalis* and intrauterine infection. *E. faecalis* increases the risk for NEC, and suggests a direct link between gram + bacteria, chorioamnionitis and NEC.

1. Introduction

Preterm delivery has been linked to multiple causes throughout the last 30 years. Despite ongoing research, infection/inflammation is the main pathologic process, which has a clear proven connection with preterm parturition. Histological diagnosis of *chorioamnionitis* is most frequently connected to intrauterine bacterial infection, and is defined as polymorphonuclear cell infiltration into the free membranes and chorionic plate, and may coexist with umbilical infiltration (funisitis) [1].

Bacteria present in the lower genital tract, may ascend in to the amniotic cavity, and gain access to the foetus [2]. Microbes identified in the amniotic fluid are predominantly responsible for congenital infection [3]. Intrauterine inflammation processes may lead to foetal inflammation response syndrome (FIRS), which is hallmarked by funisitis [4]. It is believed that FIRS, as a result of microbial invasion, leads to multiple organ injury and those newborns with funisitis have worse outcome [5].

It has been implicated that neonatal complications such as chronic lung disease (CLD) may be caused by intrauterine infection and inflammation. *Chorioamnionitis* has also been associated with intraventricular haemorrhage (IVH), and necrotising enterocolitis (NEC) [6,7]. Further on, some studies have stated a "protective" role of infection processes, which may be connected with a decrease in the prevalence of respiratory distress syndrome (RDS) [8].

We hypothesised that abnormal genital tract colonisation leading to an in utero inflammation/infection process, may also contribute to other neonatal outcomes such as patent ductus arteriousus (PDA), retinopathy of prematurity (ROP) above those mentioned in other studies [9–11].

A Medline search of 10 key phrases and personal attendance to 3 recent conferences on closely related topics produced a small number of trials which looked at the link between *chorioamnionitis*, genital colonisation and neonatal outcomes such as respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), patent ductus arteriousus (PDA), retinopathy of prematurity (ROP) and chronic lung disease (CLD) [9–11]. These studies were performed in the late 80, when antibiotic strategies in preterm delivery differed from those implemented currently. Additionally study groups consisted of infants born below 37 weeks of gestation [9–11] or term infants, with no discrimination of extremely low birth weight infants [12]. One study regarding outcomes in 23 to 32-week preterm newborns born to mothers with *chorioamnionitis* was published recently, but the authors did not analyse the link between the presence of specific bacterial in the genital tract of pregnant women and preterm neonatal outcome [13]. Thus, the substantial question remains about the

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association of specific bacterial infection/inflammation and neonatal outcome.

Our primary objectives were to 1) identify genital tract colonisation of women with *chorioamnionitis* and 2) evaluate the link between specific bacterial colonisation of the maternal genital tract, and neonatal outcome of extremely premature infants exposed to *chorioamnionitis*.

Following the STROBE statement we report a cohort study in which we try to determine the link between abnormal genital tract colonisation, *chorioamnionitis* and neonatal outcome [14].

2. Methods

We used a closed, prospective cohort study, enrolling participants at birth and followed them until 40 weeks of post-conceptional age. This type of study is appropriate when an exposure (genital tract colonisation, *chorioamnionitis*) may be associated with a risk for an outcome (PDA, CLD, NEC, and ROP). The incidence of specified neonatal morbidities was compared among two groups of infants; neonates exposed to *chorioamnionitis* and abnormal genial tract colonisation and those born from preterm deliveries complicated by other adverse events.

Data was collected in the Department of Neonatology and Neonatal Intensive Care (Warsaw Medical University) in years 2005–2007, and then analysed throughout the following years. The number of live births at less than 32 weeks of gestation during the study period determined the sample size. To avoid selection bias all three hundred ninety six infants born during the mentioned period at 22 1/7–31 6/7 weeks of gestation were evaluated. Demographic, obstetric and neonatal data were gathered based on chart review. Apart from gestational age, infants were qualified to enter the study based on the following criteria; inborn infants, no known congenital malformations and parental/carer consent. Opposed to other studies we included infants born at 22 1/7–31 6/7 weeks of gestation.

In our hospital, it is routine policy, to obtain a vaginal swab from each woman admitted to hospital with preterm labour. In women who subsequently do not deliver prematurely, but require permanent hospital care, weekly bacterial cultures are evaluated. In this study we evaluated vaginal swabs taken closest to the delivery date, regardless of the mode of delivery. Amniotic fluid cultures were obtained during caesarean sections; 258 (67%) deliveries. Microbiological evaluation was carried out at the hospital Microbiology Laboratory.

According to the unit's protocol, all placentas following preterm birth below 32 weeks of gestation are sent for investigation, thus all 396 placentas were initially evaluated in the hospital's Pathology Department. All cases were examined by one pathologist, who was blinded to clinical outcome to avoid bias. A protocol adapted from Bendon was used [15]. At least 2 membrane rolls, 2 complete sections of umbilical cord (1 from the placental and one from the foetal end of the cord), and 3 transmural parenchymal sections were sent for pathological evaluation in each case. Placental infection was diagnosed according to the maternal and foetal inflammation response, as suggested by the Amniotic Fluid Infection Nosology Committee [16].

After receiving the histological evaluation reports (approximately 2 weeks) recruited neonates were assigned to one of the following study groups based on exposure to *chorioamnionitis* (CA) reported by the pathologist. This cohort study consisted of the following groups; infants born to mothers with histological evidence of intrauterine infection were allocated to the study group and preterm infants born to mothers with no report of CA were included in the control group. Genital tract colonisation was not a determinant of group allocation, thus we cannot separately analyse the outcomes of infants born to mothers with CA and normal genital flora.

Neonatal outcome data was collected based on hospital records. RDS was defined as a documentation of a chest radiograph consistent with RDS within the first 24 h. PDA was diagnosed by an echosonographer blinded to clinical outcome, based on the Skinner criteria [16]. IVH grade 3 or 4 was considered, if present during an ultrasonography examination based on Volpe criteria [17]. NEC stage 2 or greater was recorded if diagnosed clinically by the attending neonatologist [18]. All neonates were reviewed by the same ophthalmologists who diagnosed ROP based on widely accepted criteria [19]. CLD was identified if oxygen requirement was present at 36 weeks of life.

3. Statistics

Data analyses were performed with Satistica Software (version 10). Frequencies and means between groups were compared using chi-square test for discrete variables and t-tests and Wilcoxon rank sum tests for continuous variables. Statistical significance was defined as a p-value less than .05. To determine the odds ratios (ORs) for neonatal outcomes a logistic regression analyses, adjusted for gestational age, premature rupture of membranes, antenatal steroids and mode of delivery was performed. The study was approved by the Warsaw Medical University Ethics Committee.

4. Results

Initially we included 396 infants. One infant died in the study group and twelve infants in the control group and they were excluded from the study. Infants transferred to their local hospital were also followed up. Finally the study evaluated 383 mother/infant dyads with a delivery at <32 weeks of gestation and placental pathology available. The mean birth weight was comparable but we noted a significant difference in mean gestational age. We did not note any difference in Apgar scores at 1 and 5 min of age. Neither was there a difference in the length of premature rupture of membranes (PROM) (Table 1). Our data shows a relationship between neonatal morbidity and intrauterine inflammation. *Chorioamnionitis* significantly increases the risk for RDS (OR 1.74, 95% CI 1.14–2.65), NEC (OR 3.22, 95% CI 1.36–3.28) and ROP >2 (OR 2.12, 95% CI 1.33–3.36). Intrauterine infection seems to increase the occurrence of IVH≥3 (OR 1.29, 95% CI 0.85–1.96) and BPD (OR 1.75, 95% CI 0.99–3.07) but this is not statistically significant. However presence of histological signs of inflammation alone seem to be protective against PDA (OR 0.84, 95% CI 0.54–1.29) but this is a non-significant relationship (Table 2).

Table 1
Demographic and obstetric factors in women and neonates.

	Study group (n = 141) (min; max)	Control group (n = 242) (min; max)	p value
Birth weight, g ± SD	1305.7 (500; 1470)	1357.4 (160; 1920)	0.27
Gestational age (wks) ± SD	28.7 (23; 32)	29.5 (22; 32)	0.0034*
Apgar score at 1′ (median) (min; max)	6 (1; 10)	6 (1; 10)	0.26
Apgar score at 5′ (median) (min; max)	7 (1; 10)	7 (1; 10)	0.22
Gender			
Male (%)	79 (55)	136 (56)	0.8
Female (%)	62 (45)	106 (44)	
Mode of delivery SVD (%)	61 (43)	64 (25)	0.0001
CS (%)	81 (57)	190 (75)	0.0001
Antenatal steroids (%)	67 (47)	254 (49)	0.119
No PROM (%)	103 (73)	164 (68)	0.1793
PROM<18 h (%)	18 (12)	24 (9)	
18 h<PROM<24 h (%)	4 (2)	6 (2)	
PROM>24 h (%)	16 (13)	48(21)	

PROM: premature rupture of membranes.
SVD: spontaneous vaginal delivery.
CS: caesarean section.
* p<0.05.