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Effect of Chorioamnionitis on Mortality, Early Onset Neonatal Sepsis and Bronchopulmonary Dysplasia in Preterm Neonates with Birth Weight of ≤1,500 Grams

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A B S T R A C T

The aim of the study was to investigate the effects of chorioamnionitis on mortality and early onset neonatal sepsis (EONS) and bronchopulmonary dysplasia (BPD) in preterm neonates with birth weight ≤1,500 g. The study included 395 preterm infants born at the Zagreb Clinical Hospital Center, from January 2001 to December 2005. All the placentas from preterm deliveries were sent for pathological examination. The patients were categorized into two groups: one including patients with chorioamnionitis at placental histology (47%) and the other control group without chorioamnionitis (53%). Neonates were distributed into 3 groups according to gestational age: the first group with 132 (33%) infants born at ≤28 weeks of gestation, the second with 202 (52%) infant born from 29 to 32 weeks of gestation and the third with 61 (15%) infants born at ≥33 weeks gestation. Chorioamnionitis was diagnosed significantly more often in the first gestational age group (91/132-69% of infants, $\chi^2=51.307$, $p<0.05$). The outcome was lethal in 67/395 (17%) patients; 55% of them had chorioamnionitis ($\chi^2=2.421$, $p>0.05$). Lethal outcome ensued in 54/132 (41%) infants from the first gestational age group; 30/54 (55%) were born from pregnancies complicated by chorioamnionitis. In comparison with the control group, mortality was significantly higher in the group of premature infants with gestation ≤28 weeks whose placentas showed chorioamnionitis ($\chi^2=7.645$, $p<0.01$). EONS was probable or confirmed in 100/395 (25%) infants; in 66/100 (66%) infants pregnancy was complicated by chorioamnionitis ($\chi^2=22.396$, $p<0.01$). BPD developed in 25/395 (6%) infants; in 12/25 (48%) infants placentas showed chorioamnionitis ($\chi^2=0.022$, $p>0.05$). In conclusion, premature neonates from pregnancies complicated by chorioamnionitis are more often born at ≤28 weeks of gestation. Chorioamnionitis in neonates whose gestation is ≤28 weeks leads to a significantly higher rate of mortality than in neonates with a longer gestation period. A greater incidence of EONS was proven in the group of infants with chorioamnionitis. The difference between the incidence of BPD in preterm infants born from pregnancies complicated by chorioamnionitis and the control group was not significant.

Key words: *chorioamnionitis, early onset neonatal sepsis, bronchopulmonary dysplasia*

Introduction

Chorioamnionitis is an inflammation of the membranes and chorion of the placenta[1]. It is clinically evident in 1–10% pregnancies, while in the most cases the pregnancies up to its manifestation are asymptomatic[2]. Chorioamnionitis is etiologically associated with preterm labour and can be found in 40% of preterm deliveries[3]. Despite great advances in perinatology during the last 20 years, the incidence of preterm labour is still as high as

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10% or even greater. One to two percent of deliveries result in the birth of neonates weighting<1,500 grams[3,4].

The results of studies about the effect of chorioamnionitis on neonatal outcomes are still controversial but many of them point toward higher neonatal mortality and morbidity rates in neonates born from pregnancies with chorioamnionitis[2]. The presence of inflammatory mediators, primarily cytokines in the amniotic fluid and fetal blood associated with chorioamnionitis is an important factor causing the rupture of fetal membranes, thus inducing preterm delivery[5]. The high level of proinflammatory cytokines in fetal blood is associated with higher rates of neonatal mortality and morbidity[2,6].

The aim of this study was to analyse the association between histopathologically confirmed chorioamnionitis on the one hand and mortality and morbidity rates in preterm neonates with birth weight ≤1,500 grams on the other. The analysis of morbidity included cases of early onset neonatal sepsis (EONS) and bronchopulmonary dysplasia (BPD).

Patients/Material and Methods

All preterm neonates with birth weight ≤1,500 grams that were admitted to the Neonatal Intensive Care Unit of the Department of Obstetrics and Gynecology, Zagreb Clinical Hospital Center, from January 2001 to December 2005, were included in this retrospective study. Exclusion criteria included: birth weight >1,500 g, gestation ≥37 weeks, presence of major congenital malformations and incomplete medical records.

All the placentas in cases of preterm delivery were sent for pathological examination. After a gross examination, samples of the free margin of fetal membranes, and the umbilical cord and at least 2 samples of the full thickness of placental tissue were taken for microscopic examination. Chorioamnionitis was diagnosed when an acute inflammatory infiltrate consisting of neutrophils was found in the amniotic membranes and chorion of the placenta[7,8]. According to histopathological findings, the infants included in the study were divided into two main groups: one including pregnancies complicated by chorioamnionitis and the other representing the control group (pregnancies without chorioamnionitis). According to the gestational age, that was estimated by early ultrasonography or based on the last menstrual period, the infants were divided into three groups: I – group of infants born at ≤28 weeks of gestation, II – group of infants born from 29 to 32 weeks of gestation and III – group of infants born at ≥33 weeks of gestation.

All newborns included in the study had their blood and gastric aspirate sampled for microbiological analysis right after delivery using standard diagnostic culture techniques. The criteria for EONS were positive microbiological findings or clinical evidence of infection in the first three days of life along with a positive sepsis screen (raised level of C reactive protein, abnormal number of white blood cells and raised ratio of immature to total neutrophils)[9]. BPD was diagnosed in premature newborns that were treated with supplemental oxygen for at least 28 days and still depended on it at/after 36 postmenstrual weeks and that had characteristic radiographic findings of chronic lung disease.

Statistics

The statistical analysis was performed with SPSS version 12.0 (SPSS, Inc, Chicago, IL) with χ^2-test. A p value of<0.05 was considered significant.

Results

During the five year period 491 preterm newborns with birth weight ≤1,500 grams were admitted to the Neonatal Intensive Care Unit of the Departement of Obstetrics and Gynecology of the Zagreb Clinical Hospital Center; 395 of them were included in this study. An inflammation of fetal membranes was diagnosed in 184/395 (47%) placentas. The group of infants with the pathological diagnosis of chorioamnionitis and the control group were compared for mortality and morbidity.

There were 132/395 (33%) infants in the gestational age group I (gestation duration 28 weeks or less), 202/395 (52%) infants were in the gestational age group II (29 to 32 weeks of gestation), and 61/395 (15%) infants were in the gestational age group III (gestation of 33 weeks or longer).

The differences between the number of infants with chorioamnionitis at placental histology and the number of control group infants for all three gestational age groups are shown in Figure 1. A statistically significant between-group difference regarding the presence of histologic chorioamnionitis was found only among infants whose gestational age at birth was 28 weeks or less (χ^2=51.307, p<0.05).

The overall mortality rate was 17% (67/395) and chorioamnionitis was diagnosed in 37 of 67 infants that died (55%) (χ^2=2.421, p>0.05). However, in the gestational age group I infants (28 weeks of gestation or less) with le-

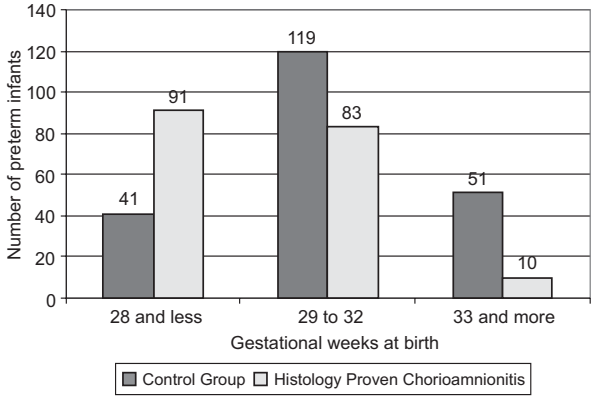

Fig. 1. Gestational weeks at birth and the number of preterm infants in the histological chorioamnionitis group and the control group; in the gestational age group 28 weeks and less chorioamnionitis was diagnosed significantly more often (χ^2=51.307, p<0.05).

thal outcome, there were significantly more infants from pregnancies complicated by chorioamnionitis than the control group infants (30/54; 55%) (χ^2=7.645, p<0.01).

EONS was present in 100/395 (25%) infants included in the study and in 66 (66%) of them an inflammation was diagnosed at placental histology. EONS was found statistically more often in infants with chorioamnionitis than in the control group. (χ^2=22.396, p<0.01).

BPD developed in 25/395 (6%) premature infants in the study, 12/25 (48%) of them with chorioamnionitis. As the mortality rate was high many premature infants did not survive long enough to develop BPD, so death was included as an outcome. Analysing composite outcome of BPD or death, there were 90/395 (23%) infants who developed BPD or died, and 48/90 (53%) were born from pregnancies complicated by chorioamnionitis. We did not find statistically significant difference between the group with chorioamnionitis and the control group regarding the incidence of BPD or death (χ^2=0.022, p>0.05; χ^2= 2.135, p>0.05).

Discussion

With the advances of neonatal care the survival rate of very low and extremely low gestational age newborns has greatly improved, so that nowadays 80% of preterm neonates with birth weight of 500 to 1000 g survive, but the rate of infants with disabilities is increasing as well[4,6]. Chorioamnionitis is an important risk factor for neonatal mortality and morbidity[10]. In this study, chorioamnionitis was histopathologically confirmed in 47% of placentas, the result that is in accordance to other similar studies that showed chorioamnionitis in 33% to 50% of placentas of prematurely born infants with very low birth weight[11–13]. Similarly to other studies, our study also showed that pregnancies complicated by acute chorioamnionitis significantly more often result in the very premature birth, at 28 or less weeks of gestation[3,14,15].

In other studies the mortality rate in premature newborns ranged from 4% to 21%, while in this study it was found to be 17%[10,12,16]. The reported effects of intrauterine infection on the mortality rate are controversial, so that some authors found an association of intrauterine infection with higher mortality rate, while others concluded that the risk of lethal outcome was lower in the presence of intrauterine infection[13,17]. We found statistically higher mortality rate in the group of infants with chorioamnionitis in comparison with the control group only in premature newborns with gestation of 28 weeks or less. The mortality rate did not differ significantly between infants with chorioamnionitis and control group infants in two other gestational age groups with longer duration of gestation. We speculate that inflammatory mediators produced during the maternal and fetal inflammatory responses contributed to the significantly higher mortality of infants with chorioamnionitis, combined with extremely low gestational age that is, itself, associated with high mortality.

In most studies, the frequency of EONS ranged from 3% to 20%[18–21]. In our study the incidence of EONS was found to be 25%, with a significant difference between the group of infants with chorioamnionitis and the control group of infants. This result is similar to the results of other authors[13].

We found that 6% of premature infants included in the study developed BPD. This percentage was lower than expected 15% to 50%, as reported in other studies[22]. Statistically significantly higher incidence of BPD or death in the group of preterm infants with chorioamnionitis was not found. Some authors found an association between intrauterine infection and development of BPD, while others did not[11,22–24]. Dexter et al. did not find a corellation between development of BPD and intrauterine infection[19]. In their study of 241 preterm infants Kent and Dahlstrom analysed the composite outcome of BPD and/or lethal outcome from RDS in the first few days of life, and showed the result of 33%, and no correlation between chorioamnionitis and development of BPD. The study found that the main predictor for the development of BPD is low gestational age[11]. Van Marter et al. found that premature newborns exposed to chorioamnionitis have a lower risk for developing BPD in addition to the mechanical ventilation shorter than 7 days. They found that, in addition to chorioamnionitis, there is a greater risk for developing BPD in the presence of mechanical ventilation longer than 7 days or postnatal infection[25]. The results of Watterberg et al. show that preterm neonates born from pregnancies complicated by chorioamnionitis have a lower incidence of the respiratory distress syndrome (RDS) but that the incidence of BPD is higher[23]. They conclude that the prenatal inflammatory process improves the maturation of fetal lungs, leading to a smaller incidence and milder clinical picture of RDS. The presence of postnatal inflammation contributes to an increase in the changes in the lung tissue, promoting the development of BPD[23,26]. Been et al. found that the histological chorioamnionitis is associated with the deteriorated response to exogenous surfactant in infants with gestational age<32 weeks[27]. An overview of literature shows that there is no consensus about the effects of chorioamnionitis on the fetal lung maturation and the development of BPD. Jobe explains that BPD is a complex lung development/injury/repair syndrome, which is affected by chorioamnionitis in an inconsistent way because of different organisms, duration of exposure and different fetal/maternal responses. BPD is also affected by multiple postnatal modulators, such as ventilation time, oxygen exposures, postnatal sepsis, patent ductus arteriosus and nutrition[28]. A recent meta-analysis of 59 studies with 15295 patients included showed that chorioamnionitis is significantly associated with BPD, but it cannot be definitively considered as a risk factor for BPD[29].

Conclusion

The study proves that premature neonates from pregnancies complicated by histological chorioamnionitis are more often than not born with 28 or less weeks of gesta-

tion. Histological chorioamnionitis in neonates with 28 or less weeks of gestation leads to a significantly higher mortality than is the case with neonates with a longer gestation period. A greater incidence of EONS was proven in the group of infants with chorioamnionitis. Preterm infants born from chorioamnionitis-complicated pregnancies did not show a greater incidence of BPD.

The histological evaluation of changes in the placenta, fetal membranes and umbilical cord gives a valuable insight into important pathophysiological processes during the prenatal period, which can have an important impact on neonatal mortality and morbidity. Chorioamnionitis must not be regarded only as an isolated process during the fetal period but should be observed in continuum with postnatal insults. Early detection and treatment of clinically silent chorioamnionitis could be a way towards decreasing the rate of preterm deliveries and reducing all the other negative consequences. A further evaluation of the effects of chorioamnionitis on neonatal mortality and morbidity is needed.

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UTJECAJ KORIOAMNIONITISA NA MORTALITET, RANU SEPSU I BRONHOPULMONALNU DISPLAZIJU U NEDONOŠČADI PORODNE TEŽINE ≤1,500 GRAMA

SAŽETAK

Cilj ove retrospektivne studije je istražiti utjecaj korioamnionitisa na mortalitet, ranu novorođenačku sepsu (EONS) i bronhopulmonarnu displaziju (BPD) u nedonoščadi porodne težine ≤1,500 g. U studiju je uključeno 395 nedonoščadi rođenih u Kliničkom bolničkom centru Zagreb, u periodu od siječnja 2001. do prosinca 2005. Ispitanici su podijeljeni u 2 skupine prema nalazu patohistološkog pregleda posteljice, plodovih ovoja i pupkovine: u skupinu čija je trudnoća komplicirana korioamnionitisom i kontrolnu skupinu bez korioamnionitisa. Korioamnionitis je potvrđen u 184 (47%) ispitanih posteljica. Nedonoščad je podijeljena prema gestacijskoj dobi: bilo je 132 (33%) gestacije ≤28 tjedana, 202 (52%) gestacije 29 do 32 tjedna i 61 (15%) gestacije ≥33tjedna. U skupini nedonoščadi s gestacijom ≤28 tjedana bilo je 91/132 (69%) nedonošče rođeno iz trudnoće komplicirane korioamnionitisom (χ^2=51,307, p<0,05). Smrtni ishod je uslijedio u 67 (17%) ispitanika, a 37/67 (55%) je bilo u skupini s korioamnionitisom (χ^2=2,421, p>0,05). U skupini nedonoščadi čija je gestacija ≤28 tjedana umrlo je 54/132 (41%) ispitanika, a 30/54 (55%) je rođeno iz trudnoće komplicirane korioamnionitisom. Utvrđen je statistički značajno viši mortalitet u skupini nedonoščadi gestacije ≤28 tjedana koja je u trudnoći

bila izložena korioamnionitisu (χ^2=7,645, p<0,01). EONS je utvrđen u 100 (25%) ispitanika, a 66/100 (66%) je bilo iz skupine čija trudnoća je opterećena korioamnionitisom, što je pokazalo statistički značajnu razliku u odnosu na kontrolnu skupinu (χ^2=22,396, p<0.01). BPD je razvijen u 25 (6%) ispitanika, a 12/25 (48%) je pripadalo skupini koja je u trudnoći izložena korioamnionitisu (χ^2=0,022, p>0,05). Trudnoće kompliciranе korioamnionitisom statistički značajno češće završavaju porodom ≤28 tjedana gestacije. Utvrđen je statistički značajno veći mortalitet u nedonoščadi gestacije ≤28 tjedana ukoliko su bila izložena korioamnionitisu. U skupini nedonoščadi rođenih iz trudnoće s korioamnionitisom je statistički značajno češća pojava EONS-a. Nedonoščad čije su majke u trudnoći imale korioamnionitis nema statistički značajno češću pojavnost BPD-a.