Preterm Premature Rupture of Membranes: A Constant Challenge in Perinatal Medicine?

Der vorzeitige Blasensprung: Eine anhaltende Herausforderung in der Perinatalmedizin?

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Two recently published observational studies have focused on the outcome of very preterm respectively of very low birth weight infants after preterm premature rupture of fetal membranes (PPROM). One single center study from the Netherlands enrolling 160 women with PPROM before 24 weeks gestational age, who admitted to the Rotterdam Medical Center between 2002 and 2011, were analyzed [14]. In parallel, there was a publication from the German Neonatal Network (GNN) enrolling about 6,000 very low birth weight infants, whose data were analyzed under the aspect of PPROM as a potential risk factor for adverse neonatal outcomes [5].

The major result from the first study conducted in the Netherlands was the finding that neonatal outcome largely depends on the time of PPROM. Neonates born after a PPROM diagnosed beyond 20 completed weeks gestational age had a greater likelihood to survive compared with those being born after PPROM with onset before 20 weeks gestational age. There was a 24% difference in survival in favor of the first group, which was highly significant. On the other hand, using a quite different approach, the GNN-consortium aimed at investigating risk factors for adverse neonatal outcome including PPROM. Definitions of neonatal variables in both papers were comparable. It could be demonstrated that PPROM as a primary cause of preterm birth was not an independent risk factor for sepsis and other related neonatal complications. In the GNN cohort, gestational age, i.e. the degree of immaturity, was the major risk factor for developing early onset sepsis. The only adverse diagnosis in the German cohort associated with PPROM was an increased risk of bronchopulmonary dysplasia (BPD) by an odds ratio of 1.25, reaching just the level of statistical significance. However, all other major neonatal adverse outcome variables were not associated with PPROM.

What do both aforementioned studies mean for clinical practice in the actual discussion of the scientific community?

The key message of the trial from the Netherlands is to provide a useful basis for prenatal counselling of parents facing the delivery of a very preterm neonate with PPROM. As birth weight and gestational age was comparable in preterms with PPROM before and after 20 weeks, there are 2 major robust conclusions to be drawn from this study:

Firstly, the prognosis of very preterm neonates born after PPROM < 20 weeks is worse than in the group with PPROM > 20 weeks.

Secondly, neonatologists must be aware of the fact that persistent pulmonary hypertension may aggravate the clinical course of affected very preterm neonates with respect to cardiopulmonary function. Several therapeutic options are currently available for persistent pulmonary hypertension in very preterm infants [9, 11]. Apart from cardiopulmonary problems, contractures not being a major challenge actually for neonatal intensive care, but potentially causing some long-term problems must be anticipated [1]. Thus, careful follow-up in affected very preterm neonates seems reasonable. As various therapeutic options for treatment of pulmonary hypertension in very preterm neonates have been proposed, which require high treatment standards, pregnant woman suffering from early PPROM should be allocated to centers being adequately staffed and equipped for diagnosis and treatment of affected very preterm neonates [4].

For further prenatal counselling, the overall survival rate in affected neonates should be discussed. In the paper from the Netherlands, a survival rate of very preterm neonates, who were admitted to neonatal intensive care, was in the range of 70 to 76% still indicating a serious prognosis. However, overall prognosis for survival of very preterm has been substantially improved compared with the data published one or 2 decades ago [2, 7].

The major result from the German trial with enrollment of very low birth weight infants is given by the fact that an increased risk for BPD must be anticipated in very low birth weight infants after PPROM. Thus, strategies for preventing BPD in infants at highest risk should include all current therapeutic options. The authors of the GNN study further conclude that the diagnosis of PPROM is not primarily associated with an increased mortality or other major neonatal complications.

Given the data of both trials, there still is an ongoing discussion as to expectant or intentional treatment in obstetrics should be preferred in case of PPROM. One study from Japan enrolling very preterm neonates after PPROM with an expectant management within 14 days was associated with impaired neonatal outcomes. Mortality was mainly attributed to sepsis and related complications. However, the Japanese data imply on the other hand that prenatal steroid administration was an excellent tool in improving prognosis after PPROM occurring beyond 26 weeks gestational age [3]. Thus, it can be concluded from this study, that survival depends also on obstetrical management.

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However, the problem how to optimize obstetrical management remains. One controlled clinical trial with respect to pregnancy outcomes after midtrimester PPROM from the Netherlands was conducted to answer this question. In pregnancies from 34 to 37 weeks either expectant procedure or induction of labor were compared. Main results include no major differences in early neonatal outcome variables ([12]; PPROMEXIL trial). A further randomized controlled clinical trial addressed the question as to expectant procedure or amnioinfusion improves prognosis in PPROM is ongoing (PPROMEXIL trial III). Again late second trimester PPROM was used as an enrollment criterion [15]. As this trial is still running, no conclusions can be drawn yet.

Finally, long-term outcome of preterm neonates after PPROM needs to be addressed: Outcome data in affected preterms from the PPROMEXIL trial showed that expectant procedure compared with induction of labor was not associated with major changes in major neonatal outcome variables. However, at the age of 2 years, preterm neonates were found to have a decreased risk for neurodevelopmental difficulties when induction of labor was compared with expectant management [13].

Thus, long-term outcome in preterm neonates after PPROM still is controversial. However, as neonates enrolled in the follow-up over a period of 2 years from the PPROMEXIL trial had a mean gestational age of about 35 weeks, these data cannot be applied without some skepticism to the group of very preterm neonates of a gestational age below 32 weeks [13]. Further pathophysiological mechanisms for adverse neurodevelopmental outcome must be considered: PPROM may lead to a fetal inflammatory response secondary to ascending bacterial infection. This may pose affected neonates at an increased risk for neurologic and pulmonary sequelae – mostly periventricular leukomalacia and bronchopulmonary dysplasia. The latter complication has been verified by the GNN data and was discussed before. As periventricular damage may have devastating consequences for neurodevelopmental outcome, this topic deserves a further discussion. Data drawn from animal experiments are suggestive of a direct association of an intrauterine inflammatory response secondary to chorioamnionitis – a typical complication after PPROM – and cerebral white matter damage [16]. Thus, clinical studies focused on the association of risk for periventricular leukomalacia in PPROM exposed very preterm neonates: PPROM especially before 20–22 weeks of gestation is clearly associated with an increased risk for periventricular lesions as an independent factor apart from the degree of prematurity [6, 8]. Long-term follow up of preterm neonates suffering from periventricular leukomalacia following among others PPROM confirm the serious consequences with respect neurodevelopmental impairments: cerebral palsy in 84% and mental retardation in about 50% was described in a large cohort from an Austrian single-center study using strictly defined neonatal and follow-up variables [10].

To sum up, PPROM still represents a major challenge in perinatal medicine. Adequately powered obstetrical controlled clinical trials on medical treatment in case of PPROM and the optimum timing of delivery and studies in affected neonates for prevention of periventricular damage and bronchopulmonary dysplasia are mandatory.

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