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

Der vorzeitige Blasensprung: Eine anhaltende Herausforderung in der Perinatalmedizin?

L. Gortner

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 PPRM 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 PPRM 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 PPRM. Neonates born after a PPRM diagnosed beyond 20 completed weeks gestational age had a greater likelihood to survive compared with those being born after PPRM 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 PPRM. Definitions of neonatal variables in both papers were comparable. It could be demonstrated that PPRM 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 PPRM 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 PPRM.

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 PPRM. As birth weight and gestational age was comparable in preterms with PPRM 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 PPRM < 20 weeks is worse than in the group with PPRM > 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 PPRM 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 PPRM. 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 PPRM 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 PPRM. One study from Japan enrolling very preterm neonates after PPRM 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 PPRM occurring beyond 26 weeks gestational age [3]. Thus, it can be concluded from this study, that survival depends also on obstetrical management.

Bibliography

DOI <http://dx.doi.org/10.1055/s-0042-104244>
Klin Padiatr 2016; 228: 53–54
© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 0300-8630

Correspondence

Prof. Dr. Ludwig Gortner
Clinics for Paediatrics and
Adolescent Medicine
University Hospital of the
Saarland
Building 9
66421 Homburg/Germany
ludwig.gortner@uks.eu

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.

References

- 1 Darin N, Kimber E, Kroksmark AK *et al*. Multiple congenital contractures: birth prevalence, etiology, and outcome. *J Pediatr* 2002; 140: 61–67
- 2 Ernest JM. Neonatal consequences of preterm PROM. *Clin Obstet Gynecol* 1998; 41: 827–831
- 3 Fujiwara A, Fukushima K, Inoue H *et al*. Perinatal management of preterm premature ruptured membranes affects neonatal prognosis. *J Perinat Med* 2014; 42: 499–505
- 4 Gortner L. Adjunctive therapies for treatment of severe respiratory failure in neonates. *Klin Padiatr* 2015; 227: 51–53
- 5 Hanke K, Hartz A, Manz M *et al*. Preterm prelabor rupture of membranes and outcome of very-low-birth-weight infants in the German Neonatal Network. *PLoS One* 2015; 10: e0122564
- 6 Hatzidaki E, Giahnakis E, Maraka S *et al*. Risk factors for periventricular leukomalacia. *Acta Obstet Gynecol Scand* 2009; 88: 110–115
- 7 Lindner W, Pohlandt F, Grab D *et al*. Acute respiratory failure and short-term outcome after premature rupture of the membranes and oligohydramnios before 20 weeks of gestation. *J Pediatr* 2002; 140: 177–182
- 8 Manuck TA, Varner MW. Neonatal and early childhood outcomes following early vs. later preterm premature rupture of membranes. *Am J Obstet Gynecol* 2014; 211 (308): e301–e306
- 9 Patry C, Hien S, Demirakca S *et al*. Adjunctive Therapies for Treatment of Severe Respiratory Failure in Newborns. *Klin Padiatr* 2015; 227: 28–32
- 10 Resch B, Resch E, Maurer-Fellbaum U *et al*. The whole spectrum of cystic periventricular leukomalacia of the preterm infant: results from a large consecutive case series. *Childs Nerv Syst* 2015; 31: 1527–1532
- 11 Steiner M, Salzer U, Baumgartner S *et al*. Intravenous sildenafil i.v. as rescue treatment for refractory pulmonary hypertension in extremely preterm infants. *Klin Padiatr* 2014; 226: 211–215
- 12 van der Ham DP, Vijgen SM, Nijhuis JG *et al*. Induction of labor versus expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks: a randomized controlled trial. *PLoS Med* 2012; 9: e1001208
- 13 van der Heyden JL, Willekes C, van Baar AL *et al*. Behavioural and neurodevelopmental outcome of 2-year-old children after preterm premature rupture of membranes: follow-up of a randomised clinical trial comparing induction of labour and expectant management. *Eur J Obstet Gynecol Reprod Biol* 2015; 194: 17–23
- 14 van der Marel I, de Jonge R, Duvekot J *et al*. Maternal and neonatal outcomes of preterm premature rupture of membranes before viability. *Klin Padiatr* 2015; 228: 69–76
- 15 van Teeffelen AS, van der Ham DP, Willekes C *et al*. Midtrimester preterm prelabour rupture of membranes (PPROM): expectant management or amnioinfusion for improving perinatal outcomes (PPROMEXIL - III trial). *BMC pregnancy and childbirth*. 2014; 14: 128
- 16 Yoon BH, Kim CJ, Romero R *et al*. Experimentally induced intrauterine infection causes fetal brain white matter lesions in rabbits. *Am J Obstet Gynecol*. 1997; 177: 797–802