

# A Novel Approach to Serial Amnioinfusion in a Case of Premature Rupture of Membranes Near the Limit of Viability

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Am J Perinatol Rep 2018;8:e180–e183.

## Abstract

Prelabor rupture of the membranes (PROM) near the limit of viability is associated with significant risks for both mother and fetus. Preterm labor, intra-amniotic infection, and placental abruption are the immediate risks to the pregnancy; however, the fetus incurs additional risks related to the sequela of persistent oligohydramnios. Transabdominal intra-amniotic infusions have been studied. Results, suggesting that this intervention may prolong the latency period, and potentially, decrease pulmonary hypoplasia in surviving neonates without evidence of increasing risk of intra-amniotic infection. To our knowledge, the use of antibiotic-infused fluid has not been reported in this clinical scenario. Therefore, we present a case of a patient with PROM before the limit of viability who underwent serial transabdominal amnioinfusions with oxacillin-containing normal saline, which resulted in membrane resealing and neonatal survival with no additional maternal morbidity.

## Keywords

- ▶ periviable PROM
- ▶ serial amnioinfusion
- ▶ pulmonary hypoplasia

Prelabor rupture of membranes (PROM) is the rupture of membranes before the onset of labor. It is rare for PROM to occur before the onset of viability. It is estimated to occur in approximately 0.37% of all pregnancies, and it presents a challenging clinical dilemma due to high likelihood of poor neonatal outcome, as well as significant risks to maternal health. PROM, before the onset of viability is frequently associated with subclinical intra-amniotic infection.<sup>1,2</sup> Patients with PROM before the onset of viability face significant risks, including development of chorioamnionitis, preterm labor, abruption, and intrauterine demise. After counseling, patients may elect to continue the pregnancy, and in the absence of clinical signs of infection, labor or vaginal bleeding, the mainstay of therapy involves expectant management until the onset of viability. This conservative management typically involves inpatient admission, latency antibiotics, and steroids for fetal lung maturity. This strategy

however, does not address the issue of the associated sequela for the fetus, of which include severe pulmonary hypoplasia and compressive limb deformities. The exact incidence of pulmonary hypoplasia is unknown and likely underreported. Pulmonary hypoplasia is potentially lethal for the neonate. Factors that affect the severity of pulmonary hypoplasia in the newborn include gestational age at PROM, duration of latency, and the amount of amniotic fluid present around the developing fetus.<sup>3</sup> More than 20 years ago, serial transabdominal intra-amniotic infusions with warmed saline were proposed as an additive management approach to patients with PPRM (Preterm Prelabor Rupture of Membranes). While the data from these trials have been encouraging, lack of safety data and adequate control groups currently prevent this strategy from becoming widely accepted.<sup>4</sup> The case we present is an example of the novel use of serial transabdominal amnioinfusions using oxacillin infused

received  
April 6, 2018  
accepted after revision  
July 21, 2018

DOI <https://doi.org/10.1055/s-0038-1669964>.  
ISSN 2157-6998.

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normal saline, in a patient with PROM before the limit of viability.

## Case Report

Thirty-five year old gravida 3 para 1-0-1-1 was referred to our maternal-fetal medicine office after diagnosis of early mid-trimester oligohydramnios. Oligohydramnios was incidentally found during a routine anatomical survey ultrasound examination at 18 weeks of gestation. She was evaluated for preterm prelabor rupture of membranes (pooling of amniotic fluid in posterior vaginal fornix, arborization *ferning* testing and *nitrazine* testing); this initial evaluation was negative. Two subsequent assessments again showed no evidence of rupture of amniotic membranes. The patient was offered, but declined intra-amniotic dye infusion testing at that time. An ultrasound at 20<sup>6/7</sup> weeks of gestation revealed a single live fetus and an amniotic fluid index of 2.8 cm. There was ultrasound evidence of membrane separation, suggesting a possible membrane rupture distal to the cervical opening ("high amniotic leak"). Fetal kidneys and bladder were seen on ultrasound and appeared normal. Her pregnancy was complicated by a history of gestational diabetes, history of loop electrical excision procedure, herpes simplex type 2, and maternal obesity (pre-pregnancy body mass index [BMI] 34 kg/m<sup>2</sup>). An episode of domestic violence had also been reported. She had early genetic screening with cell free fetal DNA that showed an appropriate fetal fraction, sex chromosomes XY, and low risk for trisomy 13, 18, and 21. A second trimester maternal serum  $\alpha$ -fetoprotein was 2.16 MoM (Multiples of the Median). The patient underwent prenatal counseling with neonatology and maternal-fetal medicine. She expressed wishes for full neonatal resuscitation at 22 weeks and stated an understanding of the prognosis.

After counseling she was offered an amnioinfusion and intra-amniotic dye instillation testing to confirm suspected diagnosis of PPRM. The patient proceeded with amnioinfusion and intra-amniotic dye installation at 21<sup>6/7</sup> weeks of gestation. Under ultrasound guidance a 22-gauge-needle was inserted into the intra-amniotic cavity, and 15 mL of clear yellow fluid was removed for purposes of genetic and infection testing. 40 mL of warmed 0.9% sodium chloride solution containing 1,000 mg/L oxacillin was infused at this time. 5 mL of indigo carmine was added for the intra-amniotic dye instillation test. A total of 400 mL of warmed 0.9% sodium chloride solution containing 1,000 mg/L oxacillin was infused. The patient then ambulated for 30 minutes and tampon testing confirmed rupture of fetal membranes. She was admitted to the hospital for latency antibiotics and serial intra-amniotic infusions. Acyclovir prophylaxis was started after clinical exam confirmed no active herpes lesions were seen. She completed a 7-day-course of latency antibiotics consisting of ampicillin and azithromycin. Beta-methasone was administered at 23 weeks of gestation.

At 22<sup>6/7</sup> weeks of gestation, she underwent a second amnioinfusion. At this time, 800 mL of warmed 0.9% sodium chloride solution containing 1,000 mg/L oxacillin were infused to obtain a normal maximum vertical pocket (MVP).

The plan was for serial intra-amniotic infusions until 26 weeks of gestation. However, at 23<sup>6/7</sup> weeks, the patient denied continued leakage of fluid and MVP was normal. At this time, it was suspected that the amnion had resealed and decision was made to cease further intra-amniotic infusions unless symptoms of leakage of fluid returned or oligohydramnios again developed. Amniotic fluid testing returned with no evidence of intra-amniotic infection. Genetic testing with karyotype and microarray also confirmed no genetic abnormalities in the fetus. At 27 weeks of gestation she developed gestational hypertension without clinical or laboratory evidence for preeclampsia.

The patient was expectantly managed in the hospital. Fetal status remained reassuring with appropriate fetal growth on serial ultrasounds. Additionally, the MVP remained normal for the duration of her pregnancy. At 33<sup>0/7</sup> weeks, she was given a second course of betamethasone. An external cephalic version was performed at 34 weeks due to breech presentation. She underwent a successful induction of labor at 34<sup>2/7</sup> weeks. She was given penicillin in labor for group B streptococcus prophylaxis. She delivered a vigorous male infant, with a birth weight of 2,160 g, Apgar's scores of 9 at 1 and 5 minutes of life. The placenta weighed 390 g and had evidence of moderate acute inflammation (grade 3) at the chorion, but no evidence of inflammation elsewhere on the amnion, or umbilical cord. The newborns initial white blood cell count was  $11.7 \times 1,000 \mu\text{L}$ . He was given ampicillin and gentamycin for 48 hours until negative blood cultures per our neonatal intensive care protocol. The newborn stayed in the hospital for 9 days and had no immediate complications.

## Discussion

Premature rupture of membranes near the limit of viability occurs in less than 1% of all pregnancies.<sup>5</sup> Identified risk factors for PPRM before the limit of viability include a history of preterm delivery or PPRM in previous pregnancy, short cervical length, cerclage, intra-amniotic procedures, antepartum vaginal bleeding, low body mass index, low socioeconomic status, illicit drug use and tobacco use.<sup>6-9</sup> Most studies of PPRM before the limit of viability are retrospective and only include cases of expectant management. With a paucity of evidence to guide clinical management, this diagnosis creates a challenging clinical dilemma for clinicians and patients alike.

The expected clinical course in a patient with rupture of membranes before viability is variable and depends on the gestational age at rupture, the length of latency period, and the presence or absence of oligohydramnios.<sup>5</sup> Data from an investigation by Falk et al showed that length of latency does not appear to vary by gestational age at rupture. They showed the median latencies of 8 days (range: 1-161 days) with PROM < 20 weeks, 4.5 days (range: 2-106 days) with PROM between 20-21 weeks, and 12.0 days (range: 1-112 days) with PROM between 21-23 weeks.<sup>10</sup> Patients, who choose expectant management must be counseled on the serious maternal and perinatal risks. Maternal risks include

development of chorioamnionitis (31.8%) and subsequent development of endometritis (1%), abruption (9.3%), sepsis (1%), death (1/619 cases).<sup>11</sup> There is a high rate of perinatal death with 31.6% stillbirth rate, and 29.7% neonatal death rate. Survival for a live birth in the setting of PPRM before the onset of viability is estimated at 44%.<sup>12</sup> Beyond high rates of death among the survivors, there is a significant risk for pulmonary hypoplasia and fetal skeletal deformities.

After appropriate counseling, patients that desire conservative management and are absent of clinical signs of infection, labor, or vaginal bleeding, undergo the mainstay of therapy—expectant management until the onset of viability, at which point inpatient admission, latency antibiotics, and steroids are typically recommended.<sup>2</sup> This strategy however, does not address the issue of associated oligo or anhydramnios, or the subsequent fetal sequela of severe pulmonary hypoplasia and compressive limb deformities. The exact incidence of pulmonary hypoplasia is unknown and likely underreported, but some data suggest that it is found in 9 to 20% of newborns delivered after periviable PROM prior to 26 weeks of gestation. Pulmonary hypoplasia is lethal in 50 to 100% of cases.<sup>3,13–15</sup> Factors that affect the risk of pulmonary hypoplasia in the newborn include gestational age at rupture of membranes, duration of latency, and the amount of remaining amniotic fluid. Although, there are no reliable methods for diagnosing pulmonary hypoplasia in utero, several groups demonstrated association between persistent severe oligohydramnios and worse perinatal outcome.<sup>12</sup>

The novel use of serial transabdominal amnioinfusion to prolong latency and prevent the development of pulmonary hypoplasia was first introduced over 20 years ago.<sup>16</sup> Since this paper, further studies into this approach have shown promise. The theoretical benefit of amnioinfusion or the introduction of physiologic solution into the amniotic cavity is proposed to be 3-fold. First, it provides a dilution of preexisting intra-amniotic bacteria. Second, it washes out and dilutes inflammatory cells and mediators (prostaglandins, leukotrienes, cytokines, interleukins among others). Lastly, it increases the intra-amniotic fluid volume and intrauterine pressure. In theory, washing out or diluting the preexisting intra-amniotic bacteria and inflammatory cells may be beneficial to prolong the latent period and the presence of fluid may promote lung development and prevent positional contractures.<sup>17</sup> Some additional secondary benefits have been proposed and include increasing the ability to test fetal genetics, improving ultrasound imaging and decreasing the risk of cord compression. Recently, a Cochrane review assessed the efficacy of this approach with the data from two randomized control trials and concluded that the small number of subjects in those studies precluded a definitive answer in regards to the efficacy of the intervention.<sup>4</sup> A systematic review and meta-analysis suggested a better shortterm prognosis in women with PPRM, who underwent serial amnioinfusion as seen in the reviewed observational studies, but not in the randomized control trials (RCT). The intervention group had significant latency prolongation and improved perinatal and neonatal survival and experienced less pulmonary hypoplasia. These results

intensify in the significantly lower gestational ages at rupture of membranes in the intervention group, compared with the control group in the observational studies.<sup>17</sup> These results from the meta-analysis of RCTs, demonstrated a trend toward benefit, but the results were not statistically significant. This is possibly because of lack of power in these studies due to the small number of participants. This review also revealed a large variation in the interventions timing, continuation, and other interventions performed (hospitalization, antepartum monitoring, antibiotic prophylaxis choice, and steroid administration).<sup>17</sup>

Our case report describes a unique approach to intra-amniotic fluid infusion in a patient with PPRM before the onset of viability. This case adds a novel approach to amnioinfusion with the addition of oxacillin to the intra-amniotic fluid infusion. This technique has been used in other intrauterine intervention procedures such as meningomyelocele repair. Administration of antibiotic in intra-amniotic fluid infusion was used as part of the standard protocol for the Management of Myelomeningocele Study (MOMS) trial and most institutions performing these procedures are using this mixture to replace amniotic fluid prior to completing closure of the hysterotomy.<sup>18</sup> The addition of oxacillin solution may have aided in the significant prolongation of latency for our patient. This conclusion cannot be drawn definitively but should be considered in further study into the potential benefits of serial amnioinfusion are undertaken. While PPRM before the onset of viability remains a rare event, it has serious morbidity for both mother and fetus. Evidence continues to suggest that serial intra-amniotic fluid infusion is a permissible treatment option for well counseled patients choosing to continue their pregnancy.

#### Conflict of Interest

None.

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