



## SPONTANEOUS MEMBRANOUS RESEALING AFTER SPONTANEOUS PRETERM PREMATURE RUPTURE OF MEMBRANES

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### ABSTRACT

**Objective:** To detect spontaneous amniotic sealing rates after spontaneous preterm premature rupture of membranes (PPROM) between 20 and 34 weeks gestation and to describe the associated factors with resealing.

**Material and Methods:** Patients admitted due to PPRM between 20 and 34 weeks singleton gestation and followed in clinic are included in the study. Primary aim was to describe the spontaneous amniotic resealing rates after PPRM. Secondary aim was to describe the optimal latency time for resealing and obstetrical outcomes at resealed group.

**Results:** Total 114 patients are included in the study. 16 of them were at prior to 24 weeks pregnancy during membrane rupture and 98 were between 24 and 34 weeks. Spontaneous resealing occurred at seven cases. All of them occurred in the first week after membrane rupture. The resealed group had longer durations of pregnancy and better neonatal outcomes.

**Conclusion:** Despite the great efforts to heal amniotic membranes after membrane rupture still there is no proven method primary to heal the membranes. Spontaneous resealing of membranes is the biggest advance of patients for better prognosis after PPRM.

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### INTRODUCTION

Preterm premature rupture of membrane (PPROM) occurs about in 1-3% of pregnancies and that's the leading cause of preterm deliveries. It is described as the rupture of membranes occurring before 37 weeks of gestation in case of the absence of active labor (1). Conservative management is the recommended regimen between 24-34 weeks after PPRM. Delivery is the recommended management if PPRM occurs at or beyond 34 weeks' gestation. Management of PPRM before 24 weeks pregnancy is the most complex issue due to poor prognosis of the newborn in addition to the risk of maternal chorioamnionitis, Termination of pregnancy and conservative management are options for parents after counseling about the prognosis.

The more prematurity is associated with the more neonatal morbidity and mortality. The major neonatal morbidity associated with prematurity includes: pulmonary hypoplasia, respiratory distress syndrome, neonatal intraventricular hemorrhage and periventricular leukomalacia, limb position defects, necrotising enterocolitis, a prolonged stay in the neonatal intensive care unit, neonatal sepsis, neonatal hyperbilirubinemia and hemolytic anemia, as well as cerebral palsy, and other long-term outcomes (2). During conservative management of pregnancies after PPRM, maternal and fetal infections may occur. This is especially true for

chorioamnionitis that may result with maternal sepsis and may conclude major morbidity and mortality (3).

Amount of amniotic fluid after PPRM is an important factor for maternal and neonatal prognosis. A higher mean amniotic fluid volume on ultrasound is associated with longer latency period to delivery and better neonatal outcome (4). Fetal membranes are formed in three layers (amnion, chorion and decidua) in the second and third trimester. They both protect the fetus from environment and also provide an area where amniotic fluid can accumulate and allow fetal movements (5). Lots of different methods have been studied to get higher amniotic fluid levels during management after PPRM to improve overall survival. There are several reports of the clinical use of fibrin glue to seal ruptured fetal membranes, starting from 1979. But still there is no approved effective method to heal the ruptured membranes. Various blood components have already been used in vivo as potential treatments to heal the membranes after PPRM (6).

PPROM may occur spontaneously or iatrogenically. Spontaneous PPRM usually occurs secondary to ascending infection. Iatrogenic PPRM occurs after prenatal invasive procedures such as chorionic villus sampling, amniocentesis or fetoscopy. The defect of membranes is lighter after iatrogenic procedures compared to spontaneous ruptures. If infection is present, the latency period between PPRM and delivery is much shorter and the neonatal mortality rate is four times

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higher than those without sepsis (7). Subclinical amniotic leakage after amniocentesis is more frequent than thought; PPRM following amniocentesis is usually self-limiting and resolves within days to weeks after the procedure, provided to absence of infection (8).

After spontaneous or iatrogenic PPRM, at ongoing pregnancies, spontaneous "resealing" is reported in 7.7% to 9.7% of cases (9). In women with amniotic fluid leakage after amniocentesis, spontaneous sealing of the membranes is commonly observed and, when compared with cases of spontaneous rupture of membranes at the same gestational age, the risk of perinatal loss is substantially lower. This can suggest that the fetal membranes may have the capacity to reseal. Although, resealing rates after amniocentesis is reported in several studies there is not much data about the resealing rates after spontaneous membrane rupture. In this retrospective study we reported spontaneous resealing rates and factors associated with resealing after spontaneous PPRM.

## MATERIAL AND METHODS

This retrospective descriptive study is conducted in Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Unit, Sanliurfa Education and Research Hospital, Sanliurfa, Turkey. Retrospectively collected data is acquired from patients who have been hospitalized due to PPRM during 20-34 weeks gestation, between September 2017 and August 2018. Approval and permission for the study about provision of patient data is taken from institutional board. The unit is a busy tertiary center at east of Turkey getting referral patients from the region with about 45000 deliveries in a year. The patients included in this study are all inpatients and are followed in clinic. Patients who are delivered due to indications not related to PPRM, like severe preeclampsia or abnormal obstetrical Doppler are not included in the study. Multiple pregnancies are not included in the study. If delivery is started spontaneously in 24 hours after membrane rupture, they are defined as preterm labor and are not included in the study.

Diagnosis of membrane rupture is made by either directly visualization of amniotic fluid or by placental alpha microglobulin-1 (PAMG-1) (AmniSure®) test test for suspicious cases.

Patients with the diagnosis of PPRM were routinely hospitalized. They were given the option about the termination of pregnancy if the membrane rupture occurred prior to 23 weeks pregnancy. Only ongoing pregnancies are included in the study group, terminated pregnancies are not included. After 23 weeks of pregnancy, all patients were managed conservatively and followed in clinic. All patients were followed up to 34th gestational week unless there was an additional indication of emergency delivery. Patients with the diagnosis of "resealing" were discharged to outpatient care after 10 days hospitalization and antibiotic therapy. They were not delivered electively at 34th gestational week and are followed till spontaneous labor.

In these patients the diagnosis of "resealing" was determined by daily inquiry of cessation of vaginal loss of amniotic fluid and by findings on speculum examination of absence of leakage. The diagnosis of cessation of amniotic fluid leakage was based on the patients' history, repeat vaginal examinations and ultrasonographic improvement of amniotic fluid.

Demographic data of patients, gestational ages at hospitalization and delivery, delivery indications and total follow-up time to delivery of each case are recorded. Amniotic resealing rates are calculated. Neonatal outcomes for resealed and non-resealed patients are recorded.

## RESULTS

During this period total 137 pregnant patients were admitted for PPRM between 20 and 34 weeks gestation. 15 patients rejected hospitalization and were discharged prior to 34th gestational week. Three patients were delivered due to abnormal obstetric Doppler and fetal growth retardation. Two patients were delivered due to severe preeclampsia and they are excluded from the study. Three pregnancies were twins and are not included in the study. Total 114 patients are included in the study. Gestational ages of 16 cases were between 20 and 24 weeks. 98 cases were between 24-34 weeks gestation at admission (Table 1). Mean maternal age was  $28 \pm 2$ , 6 years. Median gravida was three (1-12). Mean body mass index was 25.4. Mean follow-up time to delivery was  $10.5 \pm 4.7$  days (2 - 112days).

**Table 1** Gestational age at onset of rupture and resealing rates

	Reseal (n=7)	Non - seal (n=107)	
20-24 weeks	1 (6.25 %)	15 (93.75 %)	n=16
24 - 34 weeks	6 (6.12 %)	92 (93.88 %)	n=98

Total 7 spontaneous amniotic resealing cases were identified (6.1%). One of them was prior to 24 weeks pregnancy and other six cases were after 24 weeks pregnancy. All amniotic resealing were identified in the first week after membrane rupture. Cessation of amniotic fluid leakage is identified in first 72 hours after hospitalization. All resealed patients are followed in clinic for 10 days and discharged after the improvement at amniotic fluid volume on ultrasonography. Resealed patients and obstetric outcomes are reported in Table 2. All were delivered alive and expect one them all were delivered at term. Only one patient delivered at 30th week of pregnancy due to preterm labor. Birth weight of resealed patients were significantly higher than the others. The mean birth weight at resealed patients was 2871gr however in non-resealed patients that was 1647gr.

**Table 2** Obstetric outcomes of resealed patients.

	Gestational age at PPRM (weeks)	Gestational age at delivery (weeks)	Birth weight (grams)	Follow-up time to Delivery (weeks)
Case 1	22	38	3100	16
Case 2	29	39	3450	10
Case 3	27	39	2900	12
Case 4	32	38	3100	6
Case 5	24	30	1800	6
Case 6	30	38	2950	8
Case 7	29	37	2800	8

## DISCUSSION

Because the canalicular stage of fetal lung development is completed at about 24-26 weeks (10) and compromise of this stage is strongly associated with pulmonary hypoplasia, amniotic fluid is crucial for pregnancies. In addition, PPRM continues to be one of the most complex subjects in obstetric management because of the tight association of membrane rupture with prematurity. Spontaneous resealing still seems to be the greatest advance for patients complicated with this

situation. In our study, resealing rate was 6.1% after PPRM. Obstetric outcomes of them were significantly better than the others.

Spontaneous amniotic resealing is a known entity for a long time especially after PPRM due to prenatal invasive procedures. Contemporarily by the use of intrauterine surgical procedures more commonly, the efforts are concentrated to heal the membranes after PPRM. The ability of fetal membranes to heal spontaneously after fetoscopy appears limited due to lack of vascularity. However amniotic fluid leakage following amniocentesis is usually self-limiting and resolves within days to weeks after the procedure, provided there is no locus of infection (8). This variation about the membrane healing after this two separate procedures seems to be associated with the size of the defect at membranes. The lower incidence of resealing after spontaneous ruptures may be due to larger defects on membranes and the presence of infection in case of spontaneous PPRM.

Actually, active healing of amniotic membrane defects could not be demonstrated in vitro on animal models (11). However, the amniotic fluid leakage may be concealed, or the membranes may reseal with retraction and sliding or scarring in the myometrial and decidual layers of the uterus, rather than an active healing mechanism at the level of the fetal membranes (12). All resealing in our study were identified in the first week after membrane rupture. The leakage stopped in a few days after membrane ruptures. No resealing is identified even in long term followed-up patients. This supports the hypothesis of retraction or scarring at the rupture site.

Our results indicate that "resealing" is a desired situation after membrane rupture. The gestational age at membrane rupture does not seem to be associated with the chance of resealing. That may come up at all gestational ages. The results in the neonates were improved after resealing. The longer latency time to spontaneous labor supports the absence of infection at resealed patients.

The major limitations of the study are its retrospective design and small study population. Also, it should be noted again that our study includes only spontaneous PPRM patients, any iatrogenic PPRM case is not included in the study.

In conclusion, further research are required to clarify the intrinsic resealing mechanisms after membrane rupture. This will help us to produce novel interventions to repair, seal, or heal the membrane defects in vivo. Strategies to heal defects in the fetal membranes will improve the poor outcomes associated to PPRM. Meanwhile, observing the patients about resealing particularly for 48-72 hours after membrane rupture is the best management strategy, especially before making the decision of pregnancy termination at non-viable period of fetuses.

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