

## Amniopatch, a repairing technique for premature rupture of amniotic membranes in second trimester

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**Abstract.** Rupture of the amniotic sac complicates approximately 0.8-1% of amniocentesis procedures carried out between the 15<sup>th</sup> and 18<sup>th</sup> gestational weeks. Spontaneous PROM during the second and third trimester is, however, more frequent. In both cases the rate of fetal morbidity and mortality are very high. Infusion of an autologous platelet concentrate followed by cryoprecipitates (amniopatch) restore the amnio-chorial link interrupted by the iatrogenic trauma, thus making the amniotic repair processes even more effective. Five cases of premature membrane rupture in pregnancies ranging from 17 to 23 weeks have been treated with complete closure of the rupture and restoration of a normal amount of amniotic fluid in two cases and incomplete in the other three cases. Neonatal outcome, in accordance to the gestational stage reached by the patient, was good in three cases (41,32 and 27 weeks), complicated by brain hemorrhage in the fourth and an abortion in fifth case. Amniopatch is able to physiologically facilitate this process and significantly prolong the pregnancy, improving neonatal outcome.

**Key words:** Amniopatch, premature rupture of membranes, amniocentesis

Rupture of the amniotic sac complicates approximately 0.8-1% of amniocentesis procedures carried out between the 15<sup>th</sup> and 18<sup>th</sup> gestational weeks. Spontaneous rupture of amniotic membranes during the second and third trimester is, however, more frequent, occurring in approximately 10-12% of pregnancies. In both cases the rate of fetal morbidity and mortality are very high due to the high incidence of infection, miscarriage, pre-term delivery and neonatal pulmonary hypoplasia common in early gestation. The defect of amniotic membranes is either produced traumatically, by introduction of the needle during amniocentesis (iatrogenic), or it can occur spontaneously: the first case affects the anterior uterine wall while the second occurs more frequently at the caudal portion of the amniotic sac, near the cervical internal os. Continuous leakage of amniotic fluid causes severe oligohydramnios, affecting both the evolution of the pregnancy as

well as fetal prognosis. The most frequent consequence is miscarriage, which happens in the days immediately following the procedure (80% of cases occur within 7 days), and is often associated with ascending amniotic infection (chorioamnionitis). The possibility that the pregnancy will continue until the fetus reaches sufficient maturity is very low, and damage resulting from fetal prematurity is common, including pulmonary hypoplasia and intraventricular hemorrhage. As a result, the clinical approach in these cases can consist of simply awaiting a spontaneous closure, which is possible but rare, with the prescription of prophylactic antibiotics and, or, rather, considering the high risk it poses for serious neonatal handicap, of terminating the pregnancy through the induction of an abortive labour. A less drastic solution can be the attempt to restore a normal amount of amniotic fluid through the intrauterine injection of saline solution

(amnioinfusion) or amniotic sac tear repair by means of an infusion of a platelet concentrate (amniopatch). Amnioinfusion of saline solution, when repeated at regular intervals, has been used successfully to prolong pregnancy from as early as the 17<sup>th</sup> week, though it is a complicated procedure with high risk of amniotic infection. For PROM procedures during early labour and the expulsive stage, proceeding with the continuous intraamniotic infusion of saline solution by means of a permanently placed transcervical catheter significantly reduces decelerations in fetal cardiac frequency, and consequently, the need for operative vaginal delivery and cesarean section, resulting in improved neonatal outcome.

The first proposals of a method that favors repairing membranes go back to 1986 (Baumgarten) and 1994 (Uchida) and were based on the transcervical instillation of fibrin. Intraamniotic infusion of a platelet concentration with the aim of sealing a solution of continuity of the amniotic sac which was produced during a fetoscopy for tying off the umbilical cord of an acardiac fetus in a monoamniotic twin pregnancy, was proposed for the first time in 1996 by Quintero. The case reports by the Quintero group on the combined use of platelet concentrate and autologous cryoprecipitates with endoscopic location of the rupture site go back to 1999. Young then reports in 2001 on his experience with the application, under endoscopic guidance, of a mix of platelets, fibrin glue, and microfibrillar collagen directly on the membrane rupture site.

Spontaneous repair of membranes after hyatrogenic rupturing is possible thanks to the amniotic cells' regenerative abilities, which are less efficient than in other more vascularized endothelia, and to platelet activation by damaged amnion and chorion, with deposits of a fibrin grid that guides amniocytes and fibroblasts to close the rupture. Poor vascularization of amniotic membranes makes this procedure rather ineffective, especially in those cases where needle-related trauma causes the amnion to detach from the chorion, resulting in a reduced incidence of platelets and coagulation factors reaching the rupture site through the bloodstream. A crucial point is the detachment of the chorion from the amnios which is continuously observed in iatrogenic rupture and is extremely rare in

spontaneous ruptures, which are the result of ascending infection that is often undetected and is located at the caudal portion of the sac near the cervix and vagina. Even the simple infusion of saline solution, which brings intraamniotic pressure values nearly back to normal, aids the two membranes in fusing themselves back together and closing the rupture. Infusion of a platelet concentrate followed by cryoprecipitates that contain fibrinogen, fibronectin, growth factors PDGF, TGF-beta, von Willebrand factor, F VIII and F XIII in high concentrations restore the amnio-chorial link interrupted by the iatrogenic trauma, thus making the amniotic repair processes even more effective.

Five cases of premature membrane rupture in pregnancies ranging from 17 to 23 weeks have been treated at the Center for Ultrasound and Prenatal Diagnosis at the Maria Vittoria Hospital in Turin, Italy. In three cases the rupture was caused during an amniocentesis procedure, while the other two were of spontaneous origin. A clinical diagnosis was made with direct visualization of the amniotic fluid in the posterior vaginal fornix with the use of a speculum, by ultrasound measurement of the larger vertical amniotic pocket (less than 1 cm), and confirmed by a positive PROM test (detection test of insulin-like growth factor binding protein-1 in vaginal fluid). All cases were verified to be free of clinical signs of concomitant infection (fever, positive vaginal cultures) and an ultrasound scan was done to evaluate the anatomy and biometric parameters of the fetuses who were confirmed to be normal and in correspondence with anamnestic gestational age.

The protocol followed included a waiting period of at least three days with the administration of prophylactic antibiotics, tocolysis for those cases beyond the 20<sup>th</sup> week, and daily ultrasound monitoring of the AFI before initiation of amnioinfusion, in order to detect any signs of oligohydramnios progressive reduction and therefore spontaneous repair. In all cases treated the patients were transferred to other hospitals so the time between the PROM and amnioinfusion was longer than normal, on average over five days. After a detailed informative interview, in which the potential risks and benefits of the pregnancy continuation must be clarified and realistic evaluations must be done about the neonatal outcome for both mortality

and morbidity, a written informed consent form was obtained.

The first step, which took place at our hospital's blood bank consisted of drawing 350–400ml of blood in quadruple bags according to autotransfusional protocols, which was then immediately followed by reinfusion of the autologous erythrocytes. The laboratory procedures that follow consist with the production of CP (30 ml/Plt volume tot.  $81.4 \times 10^9$ ), of PPP (frozen at  $-80^\circ$ ) and, on the following day, of cryoprecipitate which is stored at  $-80^\circ$  until use. The presence of any residual amniotic pocket, and area access are evaluated by ultrasound. When no pocket is present, the complete lack of fluid makes it very difficult to distinguish the interfaces between fetal components, umbilical cord and uterine wall: to do this it is useful to employ a colorDoppler which allows both avoidance of the funiculus and also verification of the exact position of the needle tip through repeated injections of small amounts of saline solution which produce a visible color signal. A 22-gauge amniocentesis needle is used which is connected to an intravenous tubing set and a three-way stopcock. The concentrated platelets (30 ml) and cryoprecipitates (20 ml) are slowly rewarmed and drawn into two 50 ml syringes, which are connected with a 20ml. syringe of saline solution through the three-way stopcock, and the mix is stored at a temperature of  $37^\circ$ . The needle is introduced with extreme care, and once the tip has been verified to be free 5cc. of saline are slowly injected in order to create the pocket in which the autologous platelet concentrate is infused first, and the cryoprecipitates immediately after, with each infusion taking place over a 15 minute period. It is not necessary to know the exact location of the point where the rupture took place: the prior patient's data are used in attempting to puncture as close as possible to the target area. The last step consists of flushing the tubing and needle with another 2–

3 ml. of saline and then removing the needle. Over the following days, bed rest and antibiotic therapy are continued, myorelaxants can be prescribed if needed, and in the case of uterine contractions continuous tocolysis is initiated. Over the first seven days the AFI is monitorized by ultrasound, as are fetal vital signs (heartbeats and fetal movements), persistent vaginal leakage of amniotic fluid (PROM Test), and the possible insurgence of vaginal infection (vaginal cultures).

The results observed after the amniopatch were complete closure of the rupture and restoration of a normal amount of amniotic fluid over the next seven days in two cases, which ended in a spontaneous delivery at the 41<sup>st</sup> week and a TC at the 27<sup>th</sup> week; in the other three cases in which closure of the amniotic sac was incomplete, one still reached the 32<sup>nd</sup> week, with TC for the insurgence of unstoppable labour, in another it was necessary to apply two more amniopatches and the pregnancy was concluded with a TC at the 26<sup>th</sup> week, and in the last the patient requested a voluntary release from the hospital and then miscarried in another hospital three weeks later, at the 22<sup>nd</sup> week. Neonatal outcome, in accordance to the gestational stage reached by the patient, was good in three cases (41, 32 and 27 weeks), and unfortunately complicated by brain hemorrhage in the case that had concluded with the TC at the 26<sup>th</sup> week. The time period between the amniopatch and the stage at which birth occurred was notably higher in the iatrogenic rupture cases compared to cases of premature spontaneous rupture (13.6 weeks vs 3 weeks) (Table 1).

There are too few cases to be able to draw conclusions, however, when considered along with similar experiences reported in medical literature, some preliminary considerations can be made. PROM caused by invasive diagnostic procedures happen in what had been up to that moment completely normal conditions, without the presence of any pathological fac-

Table 1

Case	Gestational age	PROM	N. patch	Delivery	Outcome
ME	19	hyatrogenic	1	Ces.sect. 32 w	good
VD	17	hyatrogenic	1	Sp.deliv.41 w.	good
GM	23	spontaneous	1	Ces.sect. 27 w.	good
LA	21	hyatrogenic	3	Ces.sect. 26 w.	Brain hemorr.
BS	19	spontaneous	1	Sp.abort. 22 w.	Miscarriage

tors that could possibly interfere with a physiological, albeit highly inefficient repair process which the amniotic membranes have demonstrated, even experimentally, to possess (Louis-Sylvestre et al.). Amniopatch is able to physiologically facilitate this process and significantly prolong the pregnancy, improving neonatal outcome. Spontaneous rupture, on the other hand, is almost always the final result of an undetected infection, and so the amniopatch approach fails. Lastly, the fact that both in existing literature and in the cases we observed there was always an amniocorial detachment created by the first injection highlights the importance of proper technique when invasive procedures are carried out: it is fundamental to avoid cases where the gestational stage is excessively early and the union between amnios and chorion is not yet complete. And remember that avoiding puncturing areas where membranes do not appear perfectly fused is much simpler than repairing the damage already done!

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