

CASE REPORT

Successful Patching of Iatrogenic Rupture of the Fetal Membranes

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Rupture of the fetal membranes is a common, but potentially serious complication of invasive fetal procedures. Quintero described a technique to seal the fetal membrane defect by means of a bloodpatch, usually called ‘amniopatch’ in this application. The successful use in two consecutive patients with ruptured membranes after a fetoscopic intervention at respectively 17 and 22 weeks’ gestational age is described, together with a literature review of published experience.

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The number of invasive procedures for diagnostic and therapeutic indications is rising. Not only did advanced maternal age increase the demand for genetic amniocentesis, also the number of operative fetoscopic procedures is growing quickly. In only two years, data on more than 200 fetoscopic operations have been published in Europe [1–3] and by March this year, the website based Eurofoetus registry had recorded data on 560 such procedures (www.eurofoetus.org). After withdrawal of the needle or trocar, a surgical defect remains, which may lead to temporary or permanent amniotic fluid leakage (AFL). Subclinical AFL in the immediate postoperative phase occurs probably more often than previously thought [4]. When AFL persists and becomes clinically relevant, this is considered as PPRM (preterm prelabour rupture of the membranes). We introduced the concept of ‘iatrogenic’ PPRM (iPPROM) [5], which compared to spontaneous PPRM (sPPROM) is based on different pathophysiological mechanisms. iPPROM complicates about 1–2 per cent of genetic amniocenteses [6,7], 4 per cent of amniotomies [8] and 6 per cent of fetoscopic laser procedures for twin-to-twin transfusion syndrome [9]. For more complex fetoscopic procedures such as umbilical cord ligation and tracheal occlusion, the risk of iPPROM is reported to be around 30 per cent [10] and 50 per cent [11], respectively. Therefore, iPPROM has been called the ‘Achilles’ heel’ of invasive fetal therapy [12].

Since most invasive procedures are performed in the 2nd trimester of pregnancy, iPPROM usually occurs at an early gestational age. Although the cause of PPRM in the early 2nd trimester differs between spontaneous and iatrogenic cases, its consequences may be comparable. The gestational age at which PPRM occurs, together with the duration of oligohydramnios are the two most important predictors of perinatal mortality and pulmonary hypoplasia [13]. As such, PPRM before 25 weeks’ gestation with severe oligohydramnios for more than 14 days has a predicted perinatal mortality of over 90 per cent [14]. One-third of these deaths occur antenatally [15], mainly because of placental abruption and umbilical cord accidents. Besides the high mortality, there is also significant morbidity in survivors: 67 per cent of neonates suffer from respiratory distress syndrome, 53 per cent have bronchopulmonary dysplasia, 40 per cent intraventricular haemorrhage and 7 per cent sepsis [16]. In addition to the fetal risks, there are also important maternal risks with chorioamnionitis complicating about 50 per cent of cases [17].

Several experimental therapies have been proposed for the treatment of PPRM. On the one hand palliative treatments have been suggested, aiming to restore the amniotic fluid volume and thereby preventing pulmonary hypoplasia, such as serial amnio-infusion [18] or maternal administration of vasopressin to increase fetal diuresis [19]. On the other hand, more cause oriented strategies have been proposed to stop further AFL: fetoscopic closure of the membrane defect [20,21], occlusion of the cervical canal with fibrin glue [22,23] and intra-amniotic injection of blood products (amniopatch) [24]. The preliminary results [25] have shown this last

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technique to be an effective treatment for iPPROM. We report on our experience with amniopatch in two consecutive cases of iPPROM after fetoscopy at 17 and 22 weeks of gestation.

CASE SERIES

Amniopatch procedure

The amniopatch procedure consists of the consecutive injection of platelets and cryoprecipitate in the amniotic cavity at a place that can be needled safely, regardless of the site of the previous invasive procedure or presumed site of rupture. The blood products are preferentially from the patient herself (autologous patch). Heterologous CMV-negative platelets and cryoprecipitate are used when the patient is ineligible for apheresis because of unsuitable veins or positive serology (CMV, Hepatitis B and C, HIV, Syphilis). Through a 20-gauge needle some of the remaining amniotic fluid is aspirated for culture and subsequently 100 ml of Hartmann[®] solution is instilled to create a pocket in which the infusion needle can be stabilized. Thereafter, half to one unit de-leucocytized, irradiated platelets (1.10^9 – 2.10^9 platelets/ml) followed by half to one unit cryoprecipitate is injected. During the procedure, fetal heart rhythm is monitored by ultrasound scan and if necessary infusion is slowed down or discontinued. Before removal of the needle, diluted indigo carmine is instilled to document arrest of AFL.

Case 1

A 27-year-old gravida-2 para-1 underwent a fetoscopic occlusion and transection of the umbilical cord by laser for a monoamniotic acardiac twin pregnancy at 17.2 weeks of gestation. At 16 weeks, she had experienced an episode of vaginal bleeding and at the time of the procedure a retro-membranous haematoma of 5 by 1.5 cm was still present. Deferral of the intervention had been advised because in the presence of a haematoma, visibility is known to be limited and the risk of miscarriage and ruptured membranes is presumed to be increased. However, the patient insisted on an immediate intervention. The procedure had been successfully performed through insertion of a 3-mm trocar with exchange amnio-infusion with warmed Hartmann[®] (Amniomat[®], Karl Storz, Tuttlingen, Germany) [26] to enhance visibility. The night after the procedure, she reported AFL without signs of infection of labour. Actim[®]PROM test (Medix Biochemica, Finland; dipstick test for PROM based on monoclonal antibodies against insulin-like growth factor binding protein-I) was positive. Initially, expectant management was instituted, since we [10] as well as others [27] have observed spontaneous disappearance of AFL after fetoscopy. Conservative management consisted of bed rest, prophylactic erythromycin (500 mg orally, TPD) and follow up of infection parameters. None the

less, AFL and oligohydramnios (deepest vertical pocket <2 cm) persisted for a week. Because of the reported poor outcomes for PPROM at this gestational age, the following options were offered: further expectant management, termination of pregnancy or an attempt for active treatment with amniopatch. The limited reported experience of this experimental procedure was extensively discussed as well as the procedure related risk of intra-uterine fetal death (IUFD) [28]. The patient opted for the amniopatch procedure. An autologous amniopatch was placed at a gestational age of 18.4 weeks with immediate cessation of AFL, documented by the fact that no leakage of blue stained fluid occurred and Actim[®]PROM test turned out negative. The amniotic fluid cultures remained sterile. One week later, ultrasound scan demonstrated improvement of amniotic fluid volume. A few strands were visualized in the amniotic fluid without evidence of ‘amniotic band syndrome’: the fetus moved unrestrictedly, no constriction of fetal limbs was observed and Doppler examination was normal. The patient was discharged and further care was provided at her local hospital. At 30.5 weeks of gestation, 11 weeks after the amniopatch, AFL recurred. On admission, there were no clinical signs of chorioamnionitis and lung maturation and prophylactic antibiotics were started. However, the patient developed chorioamnionitis the following week (fever, raised inflammatory parameters, fetal tachycardia followed by contractions) and a Caesarean section was performed. A boy with a birth weight of 1610 g and pH of 7.36 was born without deformations or signs of amniotic band syndrome. Pathologic examination of the placenta confirmed early signs of chorioamnionitis. A perinatal *Escherichia coli* sepsis was diagnosed which was treated with ampicillin. The baby was ventilated for 5 days and discharged from neonatal intensive care after 2 weeks. Ultrasound of the brain at the age of 1 month showed no abnormalities and the child develops normally at 1 year of age.

Case 2

A 33-year-old woman, gravida-1 para-0, underwent a fetoscopic laser ablation of vascular anastomoses for severe twin-twin transfusion syndrome with hydrops of the recipient at 21.6 weeks of gestation. The patient had previously undergone two amniodrainages and was referred for recurrent polyhydramnios and deteriorating cardiac function of the recipient. An uncomplicated coagulation of vascular anastomoses was performed through a single 3-mm port. iPPROM occurred within 24 h after the procedure. Ultrasound scan showed an anhydramnios in both gestational sacs, despite clear bladder filling in the ex-donor. Initially, expectant management was instituted as above, but no improvement in amniotic fluid volume occurred after 1 week. The patient opted for an amniopatch, which was placed in the recipient’s sac at 23 weeks of gestation. After the procedure the patient had only one brief episode of blue stained vaginal fluid leakage. On ultrasound scan, fluid restitution was observed with fibrin clots



Figure 1. Ultrasound image of clot against the fetal membranes.

against the fetal membranes in both amniotic sacs (Figure 1). This probably indicates that an unintentional septostomy had been performed at the time of one of the previous procedures. The patient was discharged and received further care at her local hospital. Unfortunately at 27 weeks of gestation, 5 weeks after the fetoscopy, IUID of the ex-recipient was diagnosed. The ex-donor however, showed normal growth, amniotic fluid and Doppler indices. At 30 weeks of gestation, AFL recurred. The patient declined further conservative management and was delivered by Caesarean section of a girl with a birth weight of 970 g, pH of 7.38 and Apgar score 10 at 5 min. The baby did not need to be ventilated and had an uneventful neonatal course. Neonatal brain scan showed no abnormality and the child is currently developing normally at the age of 1, 5 years.

DISCUSSION

We described the use of amniopatch in two patients with iPPROM after fetoscopic surgery. Preoperatively, both patients had predisposing factors to develop iPPROM: one patient had a retromembranous haematoma and the second patient underwent two earlier amniodrainages. In both patients, AFL ceased shortly after application of the patch until 30 weeks of gestation, when AFL recurred and both patients were delivered.

Thus far, experience with amniopatch as a treatment of iPPROM is limited to 11 cases (Table 1): five after amniocentesis and six after fetoscopic surgery. Successful sealing of the cavity occurred in 10 of the 11 patients. There was one pregnancy termination for unrelated but worsening uropathy, one miscarriage of twins due to an incompetent cervix and 3 IUIDs. Seven patients (64 per cent) were delivered in the 3rd trimester with an average gestational age of 34 weeks, which is a remarkable figure as most of these pregnancies had additional risk factors.

For sPPROM, the amniopatch has been shown to be far less effective with persistent AFL in three cases treated between 17 and 22 weeks of gestation [29]. Our experience is similar with continued AFL despite two attempts to seal the defect. In sPPROM, the membrane defect is not iatrogenic, ill defined, larger and situated in the lower uterine segment [29] with an increased risk of ascending infection, as far as infection not already triggered membrane rupture. Concomitant infection may cause failure of an amniopatch procedure, as bacterial fibrinolytic enzymes such as streptokinases will cause rapid clot degradation. Conversely, iatrogenic membrane defects are usually well demarcated, relatively small and operators tend to insert their trocars high in the uterine cavity under sterile conditions.

However, the procedure may have its side effects. In the 11 reported cases with iPPROM treated with amniopatch, 3 IUIDs [25,28] occurred. There may be several reasons for this, some related to the background pathology, others to the procedure itself. One explanation may be the secretion of vaso-active substances (serotonin, bradykinine, ADP) by activated platelets, since one fetus developed a severe bradycardia minutes after administration of three times the usual dose of platelets and subsequently died [25]. Severe bradycardia and hypotension are well known side effects of platelet transfusion. Since probably only few if any platelets are required to seal the defect, it seems warranted to limit the amount of platelets used. Also, IV injection of indigo carmine has uncommonly been reported to have similar side effects probably due to its intrinsic serotonergic properties [30]. Therefore, it may be prudent to avoid indigo carmine if not strictly necessary, although it has not been associated with any documented fetal risks and its use is still recommended for amniocentesis in multiple pregnancies [31]. We did not observe any fetal heart rate changes during the amniopatch procedure. In our second patient an IUID was diagnosed at 27 weeks. Intrauterine death of one twin complicates 1 in 5 fetoscopic laser interventions for twin-twin transfusion [32] and this delayed IUID may fit into the observed remote fetal deaths after TTTS therapy.

Louis-Sylvestre et al. [33] examined the interaction between platelet rich plasma, amniotic fluid and human amnion/chorion in vitro. Neither amniotic fluid nor intact amnion/chorion caused platelet adhesion or aggregation. Although platelet activating factor has been demonstrated to be present in amniotic fluid [34], its concentration is too low to trigger platelet aggregation [35]. Hence, platelets can reach the membrane defect prior to activation and aggregation elsewhere in the amniotic cavity and injection at the exact site of the membrane defect is therefore not required. Platelets and plasma were demonstrated to seal the defect caused in the chorion and amnion by a 22-gauge needle (0.73 mm). The by trauma exposed connective tissue between amnion/chorion caused platelet adhesion and activation as confirmed by light and electron microscopy. However, it remains unclear whether this platelet-cryoprecipitate plug also stimulates chorion and/or amnion to regenerate. No dose-response relationship

Table 1. Published cases of iPPROM treated with amniopatch

Intra-uterine procedure	Time IPPROM (weeks)	Time patch (weeks)	Time between patch and delivery (weeks)	Delivery (weeks)	Outcome	Authors
1 Fetoscopic cord occlusion TRAP	18	20.5	17.1	37.6	Elective repeat Caesarean section. No neonatal problems	[24]
2 Genetic amniocentesis	16.3	16.5	20	37	Normal delivery. No neonatal problems	[37]
3 Amniocentesis obstructive uropathy	12.3	17.5	3.2	21	Termination of pregnancy worsening obstructive uropathy	[25]
4 Fetoscopic laser TTTS	17.1	17.5	4.2	22	Miscarriage twins	[25]
5 Genetic amniocentesis	16	17	20	37	Normal delivery. No neonatal problems	[25]
6 Genetic amniocentesis	15.2	16.4–17.2	2.1	19.3	IUFD	[25]
7 Genetic amniocentesis	17.1	20.6	11.4	32	Induction pre-eclampsia. Uneventful neonatal course	[20]
8 Operative fetoscopy bladder obstruction	18.7	NA	NA	19.4	IUFD	[28]
9 Operative fetoscopy TTTS	16.1	NA	NA	34.1	Both alive and well	[28]
10 Fetoscopic cord occlusion TRAP	17.2	18.5	12	30.5	Caesarean section chorioamnionitis. Except for <i>E. coli</i> sepsis, uneventful neonatal course	Current series
11 Fetoscopic laser TTTS	22	23	7	30	UFD 1 twin. Elective Caesarean section. Uneventful neonatal course	Current series

TRAP=twin reversed arterial perfusion sequens, TTTS=twin-twin transfusion syndrome, IUFD=intrauterine fetal death, NA=not available

was observed between platelet concentration and the time needed to seal the defect. Platelet concentrations used varied between $0.02 \times 10^9/\text{ml}$ and $2 \times 10^9/\text{ml}$, which demonstrates that probably relatively few platelets are required to achieve sealing. Reddy et al. [36] showed that platelets alone could not seal a standardized membrane defect. Moreover, addition of platelets seemed to decrease the sealing abilities of cryoprecipitate in vitro.

In conclusion, the intra-amniotic injection of blood products appears to be a successful treatment for iPPROM in the 2nd trimester of pregnancy. Given the high risk of iPPROM, it has become an important adjunct for the fetoscopic surgery program. Further in vitro research will help to establish the mode of action and the exact nature and quantity of blood products required, potentially limiting its fetal side effects.

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