Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 599–605

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Amniopatch treatment for preterm premature rupture of membranes before 23 weeks' gestation and factors associated with its success

Ji-Hee Sung [a], Jin-Yi Kuk [a], Hyun-Hwa Cha [b], Suk-Joo Choi [a, *], Soo-young Oh [a], Cheong-Rae Roh [a], Jong-Hwa Kim [a]

[a] Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Department of Obstetrics and Gynecology, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu, Republic of Korea

ARTICLE INFO

Article history:
Accepted 12 January 2017

Keywords:
Amniopatch
Iatrogenic preterm premature rupture of membranes
Before 23 weeks' gestation
Spontaneous preterm premature rupture of membranes

ABSTRACT

Objective: The purpose of this study is to investigate the factors associated with successful amniopatch treatment in patients with iatrogenic preterm premature rupture of membranes (iPPROM) or spontaneous PPROM (sPPROM) before 23 weeks' gestation.
Materials and methods: This cohort study included 28 women who received amniopatch treatment due to iPPROM or sPPROM at 15–23 weeks' gestation. Patients' clinical characteristics before performing the amniopatch, factors associated with the procedure, pregnancy and neonatal outcomes were compared between the iPPROM and sPPROM groups, and also between the successful and failed groups.
Results: The amniopatch was successful in 6 of 28 patients (21.4%) with a success rate of 36.4% (4/11) and 11.8% (2/17) in the iPPROM group and sPPROM group ($P = 0.174$), respectively. The success group had a longer PPROM-to-delivery interval, fewer cases of clinical chorioamnionitis, larger birth weight, and lower neonatal intensive care unit admission rate than the failed group. The success rate of amniopatch procedure was proportional to maximal vertical pocket prior to procedure, which showed statistically significant association (adjusted odds ratio: 3.62, 95% confidence interval: 1.16–11.31, $P = 0.027$).
Conclusion: The amniopatch treatment success rate was higher in the iPPROM group than the sPPROM group, but was not statistically significant. The neonatal outcome was more favorable when the amniopatch was successful. However, the only predictive factor associated with successful amniopatch was a larger amniotic fluid volume before the procedure.

Introduction

Rupture of fetal membranes before or at the limit of fetal viability, also known as 'pre-viable' preterm premature rupture of membranes (PPROM), complicates about 1–4 in every thousand pregnancies [1,2]. PPROM at this early stage of pregnancy occurs either iatrogenically (iPPROM) or spontaneously (sPPROM). Pre-viable iPPROM may occur after chorionic villus sampling, amniocentesis or fetal therapy procedures, including shunt therapy, fetoscopy, and radiofrequency ablation [3,4]. The etiology of pre-viable sPPROM is more complicated and multifactorial, although intrauterine infection is known to be the most common identifiable cause [2]. Regardless of the type or etiology, the prognosis of pre-viable PPROM is not promising [5–8]. Even with the recent advances in obstetric and neonatal care, the survival rate of neonates born at less than 22–24 weeks of gestation ranges only 40–60% at best [9,10], while survival is virtually impossible when the baby is unavoidably born before 20–22 weeks.

The obstetric management options for pre-viable PPROM include termination of pregnancy, expectant management and aggressive intervention with antibiotics, cerclage, or tocolysis [2,9,11]. In cases with severe oligohydramnios, transabdominal amnioinfusion may be beneficial for preventing pulmonary hypoplasia and prolonging the latency period [12,13]. However, none of these treatments can possibly seal the defect completely. Many experimental and clinical studies have been conducted in order to seal the defected membranes, including evaluation of the amniopatch technique [14–23]. The amniopatch technique was first introduced by Quintero et al. [24] in 1996. It consisted of infusing a platelet concentrate and cryoprecipitate into the amniotic cavity

* Corresponding author. 81 Irwon-ro, Gangnam-Gu, 135-710, Seoul, Republic of Korea. Fax: +82 2 3410 0630.
E-mail address: drmaxmix.choi@samsung.com (S.-J. Choi).

http://dx.doi.org/10.1016/j.tjog.2017.08.005

which may form a plug and seal the defected site, as a result of platelet activation and fibrin formation [24]. The success rate of the amniopatch treatment varies from 10 to 60% depending on the cause of PPROM, with a higher success rate recorded in patients with iPPROM compared to those with sPPROM [3,18,25]. However, the efficacy of amniopatch treatment in patients with iPPROM and sPPROM has only been directly compared in small sample size studies.

Although the success rate of amniopatch in patients with iPPROM is higher than in those with sPPROM, the procedure is assumed to fail in more than 4 out of 10 patients with iPPROM. On the other hand, a few cases with complete sealing of the defected membranes in sPPROM, resulting in prolongation of the pregnancy to the term have been reported [19,26,27]. Therefore, we hypothesized that a subset of the population may benefit from amniopatch treatment when their membranes rupture either iatrogenically or spontaneously. In this study, we aimed to compare the efficacy of amniopatch in patients with iPPROM and sPPROM before 23 weeks' gestation, and investigate the factors associated with the success of amniopatch treatment.

Materials and methods

This is a cohort study of women diagnosed with PPROM at 15–23 weeks of gestation between September 2007 and March 2014 at Samsung Medical Center, a tertiary-care referral hospital in Seoul, Korea. This study was approved by the Institutional Review Board for Clinical Research at Samsung Medical Center (IRB No. 2011-10-045).

The diagnosis of ruptured membranes was made by the presence of gross leakage and pooling of amniotic fluid in the vagina with positive nitrazine test or placental alpha microglobulin-1 test result, and/or dye test by amniocentesis. Gestational age was calculated based on crown-rump length measurement made during the first trimester. Patients were placed for at least 2 days of bed rest, in trial with expectation of spontaneous sealing of the membranes. During this waiting period, prophylactic antibiotic treatment, with intravenous cefazolin (1 g every 6 h) and oral clarithromycin (500 mg every 12 h) administration, and the daily amniotic fluid volume measurement was performed. If the amniotic fluid leakage persisted and the amniotic fluid volume continuously decreased, we counseled the patient about the potential benefits and risks of pregnancy continuation, and offered the following options: 1) active treatment with an effort to seal the ruptured membranes using the amniopatch technique; 2) expectant management with prophylactic antibiotics, antenatal corticosteroids and/or tocolytics; or 3) termination of pregnancy. The amniopatch procedure was not offered as a treatment option to patients with regular uterine contractions or vaginal bleeding, major fetal congenital anomalies, or signs or symptoms of clinical chorioamnionitis.

We obtained written informed consent from each patient who chosen the amniopatch treatment. The amniopatch protocol used at our institute is described in detail in a previous report [19]. Briefly, blood products were prepared using the autotransfusion protocol, and an ultrasound-guided amnioinfusion of the platelet concentrate followed by cryoprecipitate was performed using a 20–22 gauge amniocentesis needle. Over the following days, bed rest, prophylactic antibiotic therapy, and daily ultrasound monitoring for amniotic fluid volume were continued. Tocolytics and antenatal corticosteroid were administered when indicated at the discretion of the physician. Primary outcome was achievement of successful amniopatch, determinant by no further additional amniotic fluid leakage and maintenance/increase of amniotic fluid volume after the treatment. Failure of amniopatch treatment was defined as continuous amniotic fluid leakage after the procedure and/or persistent oligohydramnios.

Clinical characteristics of patients before performing an amniopatch included age, parity, gestational age at PPROM, twin pregnancy, and incompetent cervix. Factors associated with the procedures included gestational age at amniopatch, PPROM-to-amniopatch interval, maternal serum white blood cell (WBC) count and C-reactive protein (CRP) level, amounts of blood products infused, maximal vertical pocket (MVP) before and after the procedure. MVP was used in place of amniotic fluid index as a predictor variable because the 4 quadrant assessment was not feasible in twin pregnancies or severe oligohydramnios.

Pregnancy outcomes included termination of pregnancy (TOP), fetal death, stillbirth, live birth, gestational age at delivery, delivery beyond 34 weeks of gestation, delivery beyond 37 weeks of gestation, PPROM-to-delivery interval, amniopatch-to-delivery interval, and clinical and histological chorioamnionitis. TOP was done when pregnant woman refused to maintain the pregnancy. Fetal death was defined as no fetal heart beat in absent of labor while in uterus. Whereas stillbirth included all death of fetus including, death occurring with or immediately after birth. Clinical chorioamnionitis was defined as maternal fever of 37.8 °C or more plus one or more of the following signs: uterine tenderness, malodorous vaginal discharge, maternal serum white blood cell count of more than 15,000 cells/mm^3, maternal tachycardia (>100 beats/min), and fetal tachycardia (>160 beats/min). Histological chorioamnionitis was defined as the presence of acute inflammatory change in one or more placentas. Neonatal outcomes of live-born neonates included sex, birth weight, need of admission to the neonatal intensive care unit, and neonatal mortality. In twin pregnancies, only the neonates with ruptured membranes were included in the analysis.

The Mann–Whitney *U* test was used to compare continuous variables, and the Fisher's exact test was used to compare categorical variables. Conditional exact logistic regression was performed to evaluate the effects of potential confounding variables on the success of amniopatch procedure. The results were considered statistically significant when P values were <0.05.

Results

During the 7-year study period, 117 patients were diagnosed with PPROM at 15–23 weeks of gestation at Samsung Medical Center, of whom 14 (12.0%) had iPPROM after genetic amniocentesis and 103 (88.0%) had sPPROM. Fourteen patients were transferred to other hospitals before delivery and lost to follow up, 25 patients chose to terminate the pregnancy, and 50 patients were conservatively managed without an amniopatch. The pregnancy outcome such as FDIU, stillbirth and live birth of those who were expectantly managed is shown in the Fig. 1. Finally, 28 patients who selected the amniopatch treatment were included in the final analysis. The median gestational age at PPROM diagnosis and amniopatch procedure was 18.5 weeks (range, 16.3–23.0 weeks) and 20.3 weeks (range, 17.0–23.7 weeks), respectively. A total of 34 amniopatch procedures were performed, including those repeated in 6 patients. The amniopatch treatment was repeated in 6 patients, due to first amniopatch treatment failure in 5 cases and re-rupture despite successful first amniopatch treatment in one patient. The second amniopatch treatment was performed as the patients showed no evidence of chorioamnionitis or preterm labor, and strongly wished to prolong the pregnancy. Among 5 patients with failed first amniopatch treatment, 4 cases were spontaneous PPROM and one case was due to iatrogenic PPROM after performing amniocentesis. In the other one re-ruptured patient, whose membranes ruptured spontaneously before performing an emergency

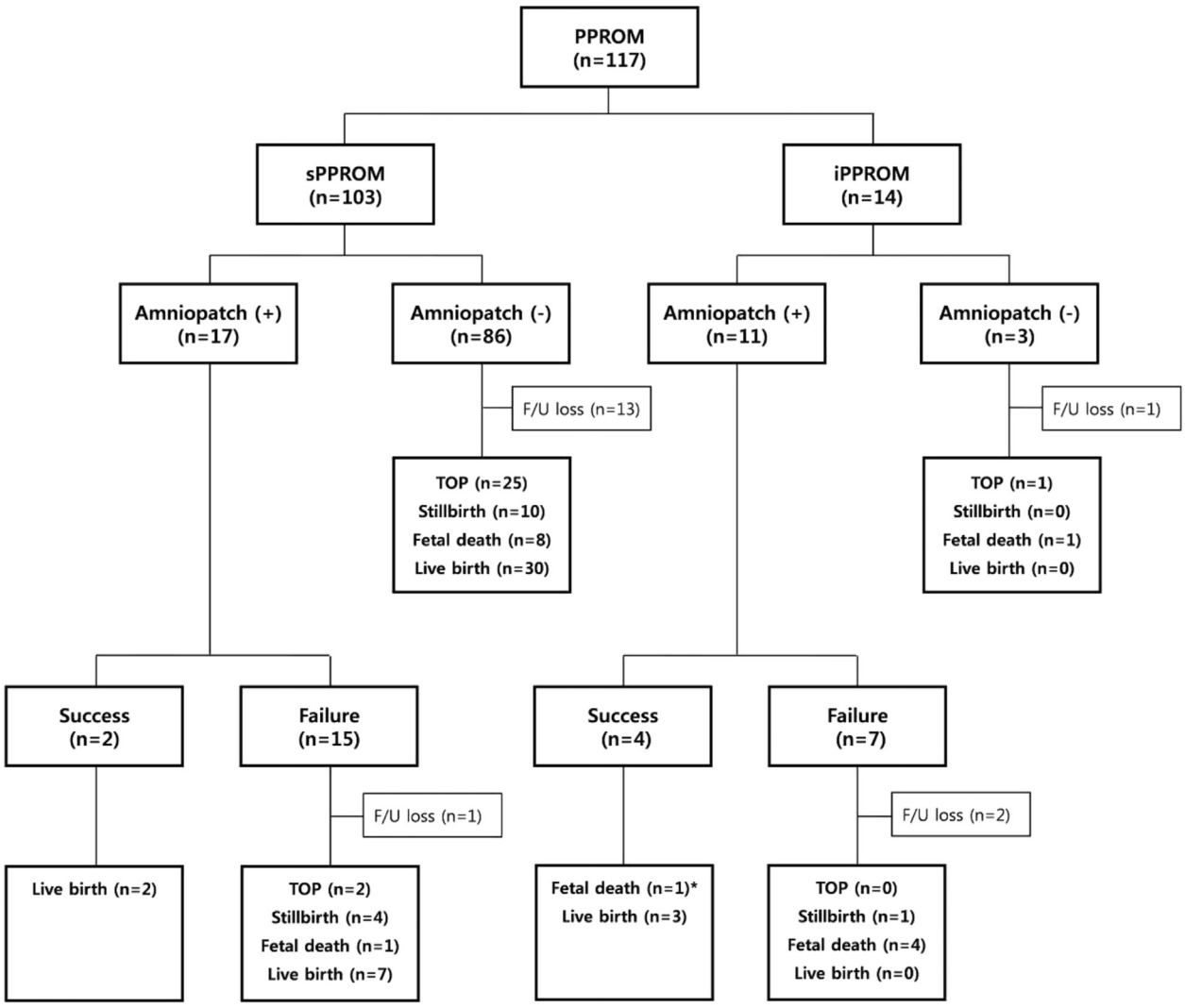

Fig. 1. Study population flowchart. *, fetal death occurred 14 weeks after the amniopatch procedure (19 weeks of gestation).

cerclage due to incompetent cervix, the first amniopatch treatment was successful. However, the amniotic sac re-bulged into the vaginal and eventually emergent cerclage was performed, where the membrane ruptured again 4 days later. The interval between the first and second amniopatch was 7–8 days in all 6 cases.

First, we compared the outcome of amniopatch treatment between the sPPROM (n = 17) and iPPROM (n = 11) group. The two groups were similar with respect to clinical characteristics, but the median gestational age at diagnosis of PPROM and amniopatch procedure was higher in the sPPROM group than in the iPPROM group (Table 1). The amniopatch procedure was successful in 6 of 28 patients (21.4%). The success rate in women with iPPROM was higher than in those with sPPROM (36.4% [4/11] vs. 11.8% [2/17]), but the difference was not statistically significant ($P = 0.174$).

Among 28 patients, 3 patients were lost for follow up and 2 patients decided to terminate pregnancy after failing of amniopatch treatment (Fig. 1). Pregnancy and neonatal outcomes were not significantly different between the iPPROM group and the sPPROM group, except for a higher rate of FDIU in the iPPROM group than the sPPROM group (Table 2).

To investigate whether any factors were associated with amniopatch treatment success, we compared clinical characteristics and factors associated with the procedure between the success group (n = 6) and failure group (n = 22) (Table 3). The two groups were similar with respect to patients' characteristics before performing the amniopatch procedure. The median MVP before amniopatch was significantly larger in the success group than the failure group (1.8 cm [0.6–3.1 cm] vs. 0 cm [0–4.3 cm], $P = 0.008$). Although the median MVP measured immediately after the amniopatch was similar in both groups, it became significantly greater by 24 h' period in the success group compared to the failed group, which was consistent after 7 days. Other factors including gestational age at amniopatch, PPROM-to-amniopatch interval, maternal serum WBC count and CRP level, and volume of blood products infused were not significantly different between the success and failure group. Multivariable analysis showed greater MVP before amniopatch in the success group (adjusted odds ratio: 3.62, 95% confidence interval: 1.16–11.31, $P = 0.027$). Amniotic fluid culture was performed in 6 patients, and only 1 patient in the sPPROM group who failed in the amniopatch treatment, had a positive culture for *Ureaplasma urealyticum*.

The live birth rate was 83.3% (5/6) and 31.8% (7/22) in the success group and failure group, respectively (Table 4). One patient in the success group had a stillbirth at 33 weeks of gestation due to fetal death in utero, but the fetal death was unlikely to be associated with the amniopatch procedure because it occurred 14 weeks after treatment (19 weeks of gestation). Of the 6 women in the success group, 2 delivered their infants at term and the other 4 had

Table 1
Clinical characteristics of patients and outcome of amniopatch procedures; spontaneous versus iatrogenic preterm premature rupture of membranes.

	Spontaneous (n = 17)	Iatrogenic (n = 11)	*P* value
Maternal age (year)	33 [26–44]	30 [26–40]	0.082
Multiparity	9 (52.9%)	5 (45.5%)	0.699
Twin	2 (11.8%)	1 (9.1%)	1.000
Cervical incompetence	6 (35.3%)	0 (0%)	0.055
GA at PPROM (week)	20.3 [16.7–23.0]	17.4 [16.3–19.4]	0.002
MVP before amniopatch (cm)	0 [0–4.3]	0.3 [0–3.1]	0.902
GA at amniopatch (week)	20.9 [18.4–23.7]	19.3 [17.0–21.7]	0.004
PPROM-to-amniopatch interval (day)	6 [2–35]	5 [2–25]	0.817
Maternal serum WBC count (/μL)	10,260 [5110–19,520]	7700 [3180–12,550]	0.073
Maternal serum CRP (mg/dL)	0.28 [0.03–2.71]	0.37 [0.05–1.08]	0.824
Volume of blood products			
Platelet concentrate (mL)	30 [4–46]	30 [10–40]	0.458
Cryoprecipitate (mL)	30 [8–50]	30 [15–40]	0.746
MVP immediately after amniopatch (cm)	2.6 [0–5.0]	2.5 [0–4.7]	0.718
MVP 1 day after amniopatch (cm)	0.9 [0–6.4]	1.0 [0–4.8]	0.334
MVP 7 days after amniopatch (cm)	2.1 [0–3.3]	2.4 [0–4.9]	0.211
Result of amniopatch			0.174
Success	2 (11.8%)	4 (36.4%)	
Failure	15 (88.2%)	7 (63.6%)	

Data are expressed in median [range] or number (%).
PTD; preterm delivery, GA; gestational age, PPROM; preterm premature rupture of membranes, WBC; white blood cell, CRP; C-reactive protein, MVP; maximal vertical pocket.

Table 2
Pregnancy outcome and neonatal outcome; spontaneous versus iatrogenic preterm premature rupture of membranes.

Pregnancy outcome	Spontaneous (n = 17)	Iatrogenic (n = 11)	*P* value
Lost to follow up	1 (5.9%)	2 (18.2%)	0.543
Termination of pregnancy	2 (11.8%)	0 (0%)	0.505
Fetal death	1 (5.9%)	4 (45.5%)	0.022
Stillbirth	4 (23.5%)	1 (9.1%)	0.619
Live birth	9 (52.9%)	3 (27.3%)	0.253
GA at delivery (week)[a]	23.5 [20–39]	22 [17–40]	0.781
Delivery at ≥34 week[a]	2 (14.3%)	1 (11.1%)	1.000
Delivery at ≥37 week[a]	1 (7.1%)	1 (11.1%)	1.000
PPROM-to-delivery interval (day)[a]	25.5 [4–152]	32 [2–158]	0.600
Amniopatch-to-delivery interval (day)[a]	11.5 [2–117]	12 [1–153]	0.877
Clinical chorioamnionitis[a,b]	7/14 (50.0%)	3/8 (37.5%)	0.675
Histologic chorioamnionitis[a,b]	10/14 (71.4%)	3/8 (37.5%)	0.187
Neonatal outcome of live-born neonates	**Spontaneous (n = 9)**	**Iatrogenic (n = 3)**	***P* value**
Gender (male)	6 (66.7%)	2 (66.7%)	1.000
Birth weight (Kg)	0.68 [0.54–3.08]	2.00 [0.93–3.22]	0.064
NICU admission	8 (88.9%)	1 (33.3%)	0.127
Neonatal mortality	3 (33.3%)	0 (0%)	0.509

Data are expressed in median [range] or number (%).
GA; gestational age, PPROM; preterm premature rupture of membranes, NICU; neonatal intensive care unit.
[a] Cases that are lost to follow up and cases who terminated the pregnancies are excluded from the analysis.
[b] Denominators are the numbers of cases with available placental pathology results.

a preterm delivery (24, 27, 33, 33 weeks, respectively), while none in the failure group delivered beyond 37 weeks of gestation. The median ROM-to-delivery interval and amniopatch-to-delivery interval was significantly longer in the success group than in the failure group. Clinical chorioamnionitis occurred in 58.8% of failure group, but none in the success group. Histological chorioamnionitis was diagnosed in 70.6% of patients in the failure group, but only in 1 patient in the success group, who delivered at 24 weeks of gestation after a successful amniopatch performed at 20 weeks of gestation. Neonatal outcomes were more favorable in the success group than the failure group in terms of heavier median birth weight and lower neonatal intensive care unit admission rate.

Discussion

In this study, we described the outcomes of amniopatch treatment in women with iPPROM and sPPROM before 23 weeks' gestation, and investigated the factors associated with a successful amniopatch treatment. Our data showed that although the success rate in the iPPROM group was higher than the sPPROM group, the difference was not statistically significant. Pregnancy and neonatal outcomes were more favorable when the amniopatch treatment was successful, while a larger MVP before the procedure was the only significant predictive factor associated with the success of the amniopatch procedure.

Amniopatch treatment is not a novel technique. It was first introduced in 1996 [24]. However, less than a hundred cases of PPROM treated with amniopatch have been published worldwide for last 20 years [3,19–23,25–32]. Although the size of the study population is not large enough to draw a conclusion, the benefits of amniopatch treatment in terms of prolongation of pregnancy and improvement in perinatal survival in pregnancies with PPROM, are considerably evident. Recently, Kozinsky et al. [18] reviewed the available literature and reported an overall perinatal survival rate of 61.4% after amniopatch treatment in pregnant women with PPROM at 16–25 weeks of gestation, which is higher

Table 3
Clinical characteristics of patients and factors associated with the procedures; success versus failure cases.

	Success (n = 6)	Failure (n = 22)	*P* value
Maternal age (year)	31.5 [30–39]	32.5 [26–44]	0.723
Multiparity	3 (50.0%)	11 (50.0%)	1.000
Twin	1 (16.7%)	2 (9.1%)	0.530
Cervical incompetence	1 (16.7%)	5 (22.7%)	1.000
GA at PPROM (week)	17.4 [16.3–20.3]	18.6 [16.7–23.0]	0.078
Type of PPROM			0.174
Spontaneous	2 (33.3%)	15 (68.2%)	
Iatrogenic	4 (66.7%)	7 (31.8%)	
MVP before amniopatch (cm)	1.8 [0.6–3.1]	0 [0–4.3]	0.008
GA at amniopatch (week)	20.1 [17.2–22.3]	20.4 [17.0–23.7]	0.566
PPROM-to-amniopatch interval (day)	5.5 [1–35]	5.5 [1–25]	0.935
Maternal serum WBC count (/μL)	6950 [5110–10,902]	9610 [3180–19,520]	0.078
Maternal serum CRP (mg/dL)	0.16 [0.07–1.08]	0.30 [0.03–2.71]	0.712
Volume of blood products			
Platelet concentrate (mL)	25 [4–40]	30 [7–46]	0.336
Cryoprecipitate (mL)	33 [20–40]	30 [8–50]	0.460
MVP immediately after amniopatch (cm)	2.9 [2.3–4.5]	2.2 [0–5.0]	0.303
MVP 1 day after amniopatch (cm)	2.5 [1.0–6.1]	0.9 [0–6.4]	0.031
MVP 7 days after amniopatch (cm)	4.2 [1.5–4.9]	0.8 [0–4.3]	0.002

Data are expressed in median [range] or number (%).
PTD; preterm delivery, GA; gestational age, PPROM; preterm premature rupture of membranes, WBC; white blood cell, CRP; C-reactive protein, MVP; maximal vertical pocket.

Table 4
Pregnancy outcome and neonatal outcome; success versus failure cases.

Pregnancy outcome	Success (n = 6)	Failure (n = 22)	*P* value
Lost to follow up	0 (0%)	3 (13.6%)	1.000
Termination of pregnancy	0 (0%)	2 (9.1%)	1.000
Fetal death	1 (16.7%)	5 (22.7%)	1.000
Stillbirth	0 (0%)	5 (22.7%)	0.553
Live birth	5 (83.3%)	7 (31.8%)	0.057
GA at delivery (week)[a]	33.0 [24–40]	21 [17–34]	0.001
Delivery at ≥34 week[a]	2 (33.3%)	1 (5.9%)	0.155
Delivery at ≥37 week[a]	2 (33.3%)	0 (0%)	0.059
PPROM-to-delivery interval (day)[a]	106 [31–158]	16 [2–77]	<0.001
Amniopatch-to-delivery interval (day)[a]	87 [30–153]	8 [1–75]	<0.001
Clinical chorioamnionitis[a,b]	0/5 (0%)	10/17 (58.8%)	0.040
Histologic chorioamnionitis[a,b]	1/5 (20.0%)	12/17 (70.6%)	0.116
Neonatal outcome of live-born neonates	**Success (n = 5)**	**Failure (n = 7)**	***P* value**
Gender (male)	4 (80.0%)	4 (57.1%)	0.576
Birth weight (Kg)	2.00 [0.74–3.22]	0.64 [0.54–1.67]	0.018
NICU admission	2 (40.0%)	7 (100%)	0.045
Neonatal mortality	1 (20.0%)	2 (28.6%)	1.000

Data are expressed in median [range] or number (%).
GA; gestational age, PPROM; preterm premature rupture of membranes, NICU; neonatal intensive care unit.
[a] Cases that are lost to follow up and cases who terminated the pregnancies are excluded from the analysis.
[b] Denominators are the numbers of cases with available placental pathology results.

than the 29.3% found following expectant management. The overall procedure-related complication rate was 28.2%, but the risk of fatal neonatal complications was less than 1%, while procedure failure and amniotic fluid leakage relapsed occurred in 50.7% of women.

The amniopatch treatment is less likely to be effective in sPPROM because the characteristics of membrane defects differ from those of iPPROM: 1) membrane defects in sPPROM are usually large, poorly delineated, and located unstably over or near the internal cervical os [3,25], 2) sPPROM is more frequently complicated by intrauterine infection and/or inflammatory reaction, 3) the membranes tend to seal spontaneously more frequently following iPPROM [33]. The success rate of amniopatch treatment between the iPPROM and sPPROM group was not statistically significant in our study, but this may be due to inadequate power.

Only one study has directly compared the efficacy of amniopatch in patients with iPPROM and sPPROM, using an intrauterine endoscopy technique for direct visualization of membrane defects and infusion of platelets, fibrin glue, and powdered collagen slurry at the site of the defect [25]. The procedure was successful in 3 out of 4 patients of iPPROM after amniocentesis, but in none out of the 4 patients with sPPROM. Quintero et al. [3], reported a success rate of 67.9% (19/28) in patients with iPPROM receiving the amniopatch treatment, but they failed to seal the membrane defects in all 12 patients with sPPROM. However, a low success rate does not necessarily mean that the treatment is of no benefit, because complete sealing of the spontaneously ruptured membranes after the amniopatch treatment did occur [26,27]. We previously reported that the treatment success rate was only 14.3%, derived from 7 cases of sPPROM before 23 weeks' gestation [19]. Nevertheless, the neonatal outcome of the treatment group was more favorable compared to the conservative management group in terms of lower incidence of respiratory distress syndrome and early neonatal sepsis.

In this study, we did not compare the outcome between the amniopatch treatment group and the conservative management group. Instead, we compared the outcome between the success group and the failure group in order to precisely evaluate the factors associated with successful amniopatch treatment. Although the amniopatch treatment was successful in only 21.4% of patients, they had a more favorable outcome compared to the failure group. The success group had a higher live birth rate, lower incidence of clinical and histological chorioamnionitis, longer prolongation of pregnancy, larger birth weight, and lower neonatal intensive care unit admission rate. In 2 of the 6 success cases, the pregnancies were prolonged to term after amniopatch treatment, with 1 patient with iPPROM and the other one case with sPPROM delivering at 40 weeks and at 39 weeks of gestation, respectively. Excluding the patients in our study, we found in a review of the available literature, 19 cases of sPPROM in which the amniopatch procedure was performed [3,25–27]. The treatment was successful in only 2 patients, but none of them delivered at term.

The only predictive factor associated with a successful amniopatch procedure in our study was a greater MVP before the procedure. The success of amniopatch may also be influenced by other factors, such as the size and location of the membrane defects, and associated intrauterine infection. The size and location of the membrane defects were not identifiable in our study because we did not perform fetoscopy to visualize them directly. However, the higher success rate in patients with a greater amniotic fluid volume before the procedure may suggest that the patients in the success group had a smaller defect size than the failure group. A significantly lower incidence of clinical and histological chorioamnionitis in the success group compared to the failure group may be indirectly suggesting that intrauterine infection may be one of the factors associated with the success of amniopatch treatment. However, whether the low incidence of chorioamnionitis is a predictive factor or a result of successful treatment is unclear. In our study, amniotic fluid culture before the amniopatch procedure was performed only in 6 patients. However, in the majority of the remaining patients, amniotic fluid culture was not possible due to the inadequate amniotic fluid volume remaining in the uterine cavity. Although maternal serum WBC count and CRP level were correlated with intrauterine infection and outcomes of PPROM, they were not significantly different between the groups.

Our study had several limitations. Firstly, because of its retrospective nature, this study is prone to information bias and selection bias. Specifically, patients who were offered amniopatch treatment were selected at the discretion of the attending physician, and not by using specific criteria. Therefore, there is a chance that the treatment might have been offered to patients who were more likely to succeed with the treatment. Secondly, despite larger sample size than that of previous studies, our study was still underpowered to test our hypothesis.

In conclusion, although the success rate of amniopatch procedure was not high in our small number of patients, it could be considered as an optional treatment for women with PPROM before 23 weeks' gestation who desire to continue with their pregnancy, especially in women with iPPROM in whom the amniotic fluid volume is adequate and shows no signs of intrauterine infection. However, further research, especially randomized trials, is strongly needed to justify our conclusion.

Ethics statement

This study was approved by the Institutional Review Board for Clinical Research at Samsung Medical Center (IRB No. 2011-10-045).

Funding

This study was supported by grants of the Korea Healthcare Technology R&D Project (grant number: A102065 and grant number: HI14C0306) through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea.

Author contribution

Research conception & design: Choi SJ. Data acquisition: Sung JH, Kuk JI. Data analysis and interpretation: Choi SJ, Sung JH. Statistical analysis: Choi SJ, Sung JH. Drafting of the manuscript: Choi SJ, Kuk JI, Sung JH. Critical revision of the manuscript: Oh SY, Roh CR, Kim JH. Receiving grant: Oh SY, Choi SJ. Approval of final manuscript: all authors.

Conflict of interest

The authors report no conflicts of interest.

References

[1] Yeast JD. Preterm premature rupture of the membranes before viability. Clin Perinatol 2001;28(4):849–60.
[2] Practice bulletins no. 139: premature rupture of membranes. Obstet Gynecol 2013;122(4):918–30.
[3] Quintero RA. Treatment of previable premature ruptured membranes. Clin Perinatol 2003;30(3):573–89.
[4] Abboud P, Zejli A, Mansour G, Monnoyer Y, Houareau LG, Bart H, et al. [Amniotic fluid leakage and premature rupture of membranes after amniocentesis. A review of the literature]. J Gynecol Obstet Biol Reprod (Paris) 2000;29(8):741–5.
[5] Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003;101(1):178–93.
[6] Soylu H, Jefferies A, Diambomba Y, Windrim R, Shah PS. Rupture of membranes before the age of viability and birth after the age of viability: comparison of outcomes in a matched cohort study. J Perinatol 2010;30(10):645–9.
[7] Hunter TJ, Byrnes MJ, Nathan E, Gill A, Pennell CE. Factors influencing survival in pre-viable preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2012;25(9):1755–61.
[8] Azria E, Anselem O, Schmitz T, Tsatsaris V, Senat MV, Goffinet F. Comparison of perinatal outcome after pre-viable preterm prelabour rupture of membranes in two centres with different rates of termination of pregnancy. BJOG 2012;119(4):449–57.
[9] Miyazaki K, Furuhashi M, Yoshida K, Ishikawa K. Aggressive intervention of previable preterm premature rupture of membranes. Acta Obstet Gynecol Scand 2012;91(8):923–9.
[10] Margato MF, Martins GL, Passini Junior R, Nomura ML. Previable preterm rupture of membranes: gestational and neonatal outcomes. Arch Gynecol Obstet 2012;285(6):1529–34.
[11] Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol 2009;201(3):230–40.
[12] Gramellini D, Fieni S, Kaihura C, Faiola S, Vadora E. Transabdominal antepartum amnioinfusion. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet 2003;83(2):171–8.
[13] Harman CR. Amniotic fluid abnormalities. Semin Perinatol 2008;32(4):288–94.
[14] Haller CM, Buerzle W, Kivelio A, Perrini M, Brubaker CE, Gubeli RJ, et al. Mussel-mimetic tissue adhesive for fetal membrane repair: an ex vivo evaluation. Acta Biomater 2012;8(12):4365–70.
[15] Mann LK, Papanna R, Moise Jr KJ, Byrd RH, Popek EJ, Kaur S, et al. Fetal membrane patch and biomimetic adhesive coacervates as a sealant for fetoscopic defects. Acta Biomater 2012;8(6):2160–5.
[16] Papanna R, Mann LK, Moise KY, Johnson A, Moise Jr KJ. Absorbable gelatin plug does not prevent iatrogenic preterm premature rupture of membranes after fetoscopic laser surgery for twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 2013;42(4):456–60.
[17] Engels AC, Van Calster B, Richter J, DeKoninck P, Lewi L, De Catte L, et al. Collagen plug sealing of iatrogenic fetal membrane defects after fetoscopic surgery for congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 2014;43(1):54–9.
[18] Kozinszky Z, Sikovanyecz J, Pasztor N. Severe midtrimester oligohydramnios: treatment strategies. Curr Opin Obstet Gynecol 2014;26(2):67–76.
[19] Kwak HM, Choi HJ, Cha HH, Yu HJ, Lee JH, Choi SJ, et al. Amniopatch treatment for spontaneous previable, preterm premature rupture of membranes associated or not with incompetent cervix. Fetal Diagn Ther 2013;33(1):47–54.

[20] Deprest J, Emonds MP, Richter J, DeKoninck P, Van Mieghem T, Van Schoubroeck D, et al. Amniopatch for iatrogenic rupture of the fetal membranes. Prenat Diagn 2011;31(7):661–6.
[21] Mandelbrot L, Bourguignat L, Mellouhi IS, Gavard L, Morin F, Bierling P. Treatment by autologous amniopatch of premature rupture of membranes following mid-trimester amniocentesis. Ultrasound Obstet Gynecol 2009;33(2):245–6.
[22] Cobo T, Borrell A, Fortuny A, Hernandez S, Perez M, Palacio M, et al. Treatment with amniopatch of premature rupture of membranes after first-trimester chorionic villus sampling. Prenat Diagn 2007;27(11):1024–7.
[23] Young BK, Roman AS, MacKenzie AP, Stephenson CD, Minior V, Rebarber A, et al. The closure of iatrogenic membrane defects after amniocentesis and endoscopic intrauterine procedures. Fetal Diagn Ther 2004;19(3):296–300.
[24] Quintero RA, Romero R, Dzieczkowski J, Mammen E, Evans MI. Sealing of ruptured amniotic membranes with intra-amniotic platelet-cryoprecipitate plug. Lancet 1996;347(9008):1117.
[25] Young BK, Mackenzie AP, Roman AS, Stephenson CD, Minior V, Rebarber A, et al. Endoscopic closure of fetal membrane defects: comparing iatrogenic versus spontaneous rupture cases. J Matern Fetal Neonatal Med 2004;16(4):235–40.
[26] Contino B, Armellino F, Brokaj L, Patroncini S. Amniopatch, a repairing technique for premature rupture of amniotic membranes in second trimester. Acta Biomed 2004;75(Suppl. 1):27–30.
[27] Ferianec V, Krizko Jr M, Papcun P, Svitekova K, Cizmar B, Holly I, et al. Amniopatch - possibility of successful treatment of spontaneous previable rupture of membranes in the second trimester of pregnancy by transabdominal intraamiotic application of platelets and cryoprecipitate. Neuroendocrinol Lett 2011;32(4):449–52.
[28] Sipurzynski-Budrass S, Macher S, Haeusler M, Lanzer G. Successful treatment of premature rupture of membranes after genetic amniocentesis by intra-amniotic injection of platelets and cryoprecipitate (amniopatch): a case report. Vox Sang 2006;91(1):88–90.
[29] Sener T, Ozalp S, Hassa H, Yalcin OT, Polay S. Maternal blood clot patch therapy: a model for postamniocentesis amniorrhea. Am J Obstet Gynecol 1997;177(6):1535–6.
[30] Richter J, Henry A, Ryan G, DeKoninck P, Lewi L, Deprest J. Amniopatch procedure after previable iatrogenic rupture of the membranes: a two-center review. Prenat Diagn 2013;33(4):391–6.
[31] Pathak B, Khan A, Assaf SA, Miller DA, Chmait RH. Amniopatch as a treatment for rupture of membranes following laser surgery for twin-twin transfusion syndrome. Fetal Diagn Ther 2010;27(3):134–7.
[32] Lewi L, Van Schoubroeck D, Van Ranst M, Bries G, Emonds MP, Arabin B, et al. Successful patching of iatrogenic rupture of the fetal membranes. Placenta 2004;25(4):352–6.
[33] Gold RB, Goyert GL, Schwartz DB, Evans MI, Seabolt LA. Conservative management of second-trimester post-amniocentesis fluid leakage. Obstet Gynecol 1989;74(5):745–7.