Research Article

(Amniopatch, a Repairing Technique of Spontaneous Preterm Premature Rupture of Fetal Membranes.)

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Abstract
Objective: The present study aimed to evaluate the efficacy and safety of amniopatch as a repairing technique of spontaneous preterm premature rupture of fetal membranes. **Methods**: Amniopatch, an amnioinfusion of platelet concentrate followed by FFP, was performed in ٢٠ women with sPPROM diagnosed at ٢٤ to ≤ ٣٤ weeks' gestation. Pregnancy outcomes of the cases were compared with the controls who were managed conservatively (n = ٢٥). **Results**: amniopatch was successful in complete sealing of the membrane defect in ٣ cases (representing ١٥٪), while no cases had sealed in the conservative management group. Also, it was found that, ١٥ cases of the amniopatch group (representing ٧٥٪) were found to have statistically significant increase in and restoration of AFI within normal, while, none of the patients in the conservative management group had. Overall, neonatal outcome was similar in the amniopatch and conservatively managed groups. **Conclusion:** The amniopatch procedure was shown to be a safe technique with no maternal or fetal procedure related morbidity or mortality. Although, the overall success rate of amniopatch to seal the membranes among our small number of cases was low, a prospective RCT assessing the value of using amniopatch as a standard management modality to the cases of PPROM is needed to guide practice.
Keywords: Amniopatch, spontaneous preterm premature rupture of fetal membranes

Introduction
Spontaneous Preterm Premature Rupture of Membranes (sPPROM) complicates ٢٪ to ٤٪ of all singleton and ٧٪ to ٢٠٪ of twin pregnancies (Mercer et al., ٢٠٠٠), and occurs in approximately ١٥٠,٠٠٠ pregnancies yearly in the United States (ACOG Practice Bulletin No. ٨٠, ٢٠٠٧).

Eighty-five percent of neonatal morbidity and mortality is a result of prematurity. PPROM is associated with ٣٠-٤٠٪ of preterm deliveries and is the leading identifiable cause of preterm delivery and accounts for approximately ١٨٪ to ٢٠٪ of perinatal deaths in the United States (Spinillo et al., ٢٠٠٤). In addition to preterm delivery, sPPROM is considered the most common cause of oligohydramnios, with its potential consequences in the form of oligohydramnios-related pulmonary hypoplasia and chorioamnionitis. This may result in considerable mortality as well as morbidity in survivors (Magann et al., ٢٠١١).

As the fetal membranes display a poor to virtually absent spontaneous wound healing capacity, In vitro and in vivo studies have been unable to show either significant cell proliferation or an ability of the membranes to cover membrane defects (Devlieger et al., ٢٠٠٠; Gratacos et al., ٢٠٠٦). Absence of obvious leakage is therefore probably prevented by another mechanism. Most probably the fetal membranes slide over each other, so that the amniotic and chorionic defects are no longer aligned (Gratacos et al., ٢٠٠٦).

As a result, the clinical approach in these cases consists of expectant management with the prescription of prophylactic antibiotics and antenatal corticosteroids, or, rather, considering the high risk it poses for serious neonatal handicap, of terminating the pregnancy through induction of labor. A less drastic solution can be the attempt to restore a normal amount of amniotic fluid through amniotic sac tear repair by means

of an infusion of cryoprecipitate and a platelet concentrate (amniopatch) (Quintero ٢٠٠١).

In this study, ٢٠ amniopatch procedures performed on ٢٠ women with sPPROM at ٢٤ to ≤٣٤ weeks' gestation and compared the pregnancy outcomes of these cases with the controls who continued their pregnancies with conservative management, aiming to evaluate the safety and effectiveness of the amniopatch procedure as a repairing technique of sPPROM.

Patients and methods

This clinical trial was conducted on women diagnosed with PPROM at ≥٢٤ to <٣٤ gestational weeks, who were admitted to the Department of Obstetrics and Gynaecology of Minia University Hospital, Minia, Egypt, during the period from January ٢٠١٣ to December ٢٠١٤. Ethical permission was sought from a Local Research Ethics Committee (REC). The pre procedure counseling about the potential benefits and risks of all aspects of the study were clearly stated to the participants giving them the choice to go through the procedure or opt out of it. Gestational age was estimated based on the last menstrual period, when reliable, or on ultrasonography performed during the ١st trimester, and confirmed by an early ٢nd trimester ultrasound. The diagnosis of ruptured membranes was established based on the classic history of sudden gush of watery vaginal discharge and confirmed by examination by a sterile speculum when obvious leakage of amniotic fluid from the cervical os was observed. This was associated by estimation of the volume of amniotic fluid through calculation of amniotic fluid index AFI according to the four quadrant technique (Vermillion et al., ٢٠٠٠), Oligohydramnios was diagnosed when the AFI was below the ١٠th centile for estimated gestational age as described by (Moore and Cayle, ١٩٩٠). Patients who were excluded from the study were those who had positive uterine contractions at the time of admission, symptoms or signs suggestive of clinical chorioamnionitis, major congenital fetal malformations, any vaginal bleeding regardless its cause, uncontrolled medical disorder e.g. severe hypertension, uncontrolled diabetes, chronic renal impairment, and evidence of placental insufficiency due to any cause, evidence of placental anomalies, anterior position of the placenta, multiple gestation, or those who had refused to participate in the study.

All patients were counseled about the potential risks and benefits of pregnancy continuation, the nature and technical aspects of the procedure, the following options were offered to the patients and their families:

(١) Expectant management with prophylactic antibiotics and antenatal corticosteroids.

(٢) Active treatment with an effort to seal the ruptured membranes using the amniopatch technique.

Patients who were offered amniopatch treatment were those who agreed, consenting and fulfilling the criteria for application of the procedure. It is mentioned that other, as yet potentially undefined side effects cannot be excluded, and a written informed consent was obtained.

Participants were divided into two groups as follow:

Control Group: included ٢٥ patients under expectant management. Those were the patients who refused to undergo the amniopatch technique and consented to undergo watchful waiting with bed rest, prophylactic antibiotic, and antenatal corticosteroids.

Study Group: included ٢٠ patients under amniopatch trial.

Ultrasonography was performed, using (Toshiba, Japan) machine, consisting of a transabdominal convex array transducer with a frequency of ٣.٧٥ MHz.

<u>The amniopatch technique was done at our hospital as follows:</u>

All women were started on a regimen of hospital bed rest and received antibiotic prophylaxis consisting of ampicillin ٢g IV every ٦hours for ٤٨ hours, followed by erythromycin ٢٥٠mg every ٦hours for ٥days. Antenatal corticosteroids were given in the form of dexamethasone ٦mg

intramuscular every ١٢hours for ٤٨ hours i.e. in four divided doses. Fetal heart rate was monitored daily with daily assessment of the biophysical profile and calculation of AFI. The patients were observed for the appearance of any signs or symptoms of chorioamnionitis, screened and treated for urinary tract infection, vaginal infection or any systemic infection if present. Sterile vulval pad was put and noticed for the presence or absence of continuous leakage, any change in the color or the characteristic odor of the amniotic fluid.

During this waiting period, preparation of one unit of cross matched fresh frozen plasma FFP and ٢ units of platelets concentrates took place. Amnioinfusion technique was performed using a ٢٢-gauge spinal needle. Transplacental passage was avoided whenever possible. Color Doppler ultrasound was used to avoid funipuncture and to confirm correct needle placement by injection of ٥–١٠ ml of normal saline, which produces color signals. The needle was connected to a tubing extension attached to a three-way stopcock and ٥٠–٢٠٠ ml of normal saline was infused to create an adequate pocket in which the infusion needle can be stabilized. After injection of normal saline, alternate infusions of ٢٠ mL of platelets, normal saline (which does not contain Calcium, needed for the clotting process), and ٢٠ mL of (FFP). The infused substances were warmed to a temperature of ٣٧°c. Avoiding contact between the blood products prevents clotting in the lines.

During infusion, the fetal heart rate as well as the accumulation of amniotic fluid was monitored by ultrasound. Usually a total of around ٦٠-٨٠ mL of platelets, ١٠٠-١٥٠ mL of FFP and ١٠٠-١٥٠ mL of amnioinfusion fluid was used throughout the procedure. The last step consisted of flushing the tubing and needle with another ٢-٣ ml of normal saline and then removing the needle.

There was no specific time schedule but the procedure could easily take up to ٤٠ to ٦٠ minutes, because the products were infused slowly. We offered one attempt, but if the initial one did not arrest amniotic fluid leakage, patients were counseled to have another trial, but none of them agreed. It is not necessary to know the exact location of the point where the rupture took place.
Anti- D immuoprophylaxis was given to non-sensitized RH negative patients immediately after the procedure according to the (RCOG, ٢٠١٠).

Over the following ٧ days, bed rest and prophylactic antibiotic therapy were continued. Daily ultrasound monitoring for AFI as well as continuous electronic fetal heart rate and uterine contraction monitoring were performed. Success of treatment was defined to achieve two goals:

١- **primary goal** was to have no further leakage of amniotic fluid.
٢- **secondary goal** was to restore and maintain AFI within normal ranges on follow-up ultrasounds.

Failure of the procedure was considered when either one or both goals were not achieved.

Tocolytics were given in case of regular uterine contractions noticed during the procedure. Maternal vital signs were closely monitored and follow up of fluid leakage, vaginal bleeding and uterine contractions were observed. Patients in the conservative management group were treated in the same manner as the amniopatch group in terms of antenatal corticosteroid, antibiotics, and maternal-fetal monitoring.

Neonatal outcome for the cases (amniopatch group, n = ٢٠), was compared to control subjects who continued their pregnancies without amniopatch treatment (conservative management group, n = ٢٥) during the study period as regard the duration of pregnancy, estimation of the latency period, Apgar score at ١ and ٥ minutes, neonatal birth weights, the need for NICU admission and its duration, and the status of the neonate at the time of discharge whether living or dead. Maternal outcome was also observed regarding the development of clinical chorioamnionitis, preterm labor, placental abruption, and mode of delivery. Descriptive statistics were used to summaries all study observations. Quantitative data presented as range, mean and standard deviation while

qualitative data presented as frequency distribution. Mann- Whitney test and Friedman tests were used to compare the continuous variables, the proportion were compared using chi square and fisher exact and z tests. Probability of less than ٠.٠٥ was considered cutoff for significance. Logistic regression analysis and Receiver Operator Characteristic (ROC) Curves were used to test the predictive value of amniopatch technique in the management of PPROM for the various clinical outcomes. Data entered and analyzed by SPSS (Statistical package for social sciences) version ١٩ and graphics were done using excel.

Results

The results of the present study show that there was statistically significant difference as regard the increase in AFI in the amniopatch group immediately after and over the ١st week of follow up after doing the procedure when compared to its level before; P value is (٠.٠٠١).

Table (١): Amniotic fluid index (AFI) changes among the amniopatch group before, after, and during the follow up period

AFI	Before amniopatch	After amniopatch	Within ١-٧ days	P
Range	٠-٥	٦-١٠	٠-١٠	٠.٠٠١*
Mean ±sd	٣±١.٣	٨.٥±١.٢	٥.٦±٢.٧	

Table (٢): Comparison between study and control groups as regard success in sealing of the fetal membranes (no leakage).

Success rate	Management group	Conservative group	P
Success	٣(١٥٪)	٠(٠.٠٪)	٠.٠٤*
Failure	١٧(٨٥٪)	٢٥(١٠٠٪)	

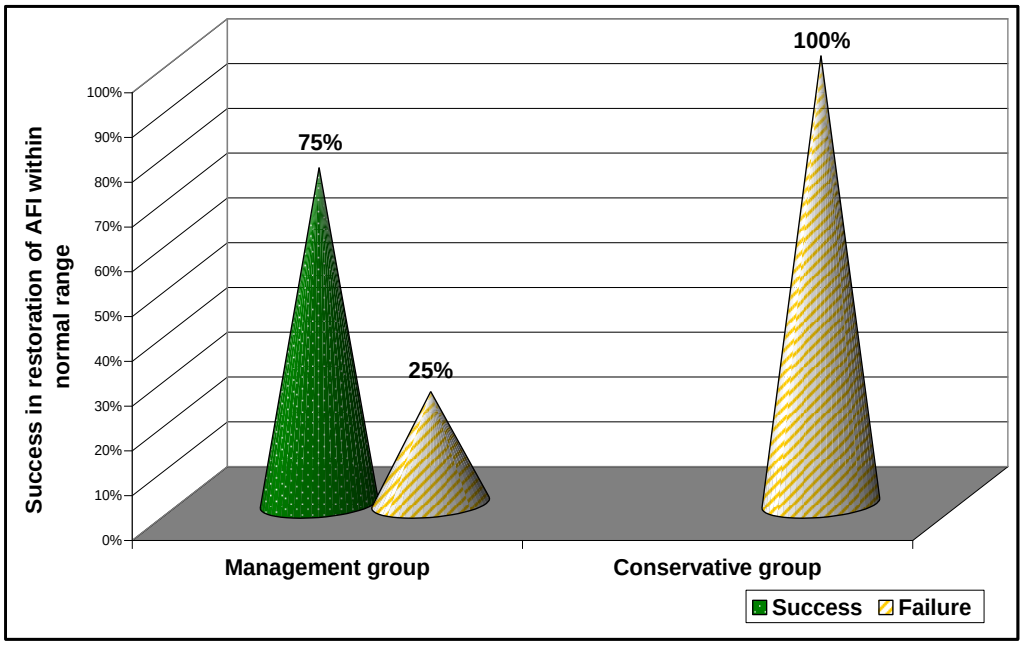

Figure (١): Comparison between study and control group as regard success in restoration of AFI within normal ranges.

Table (٣): shows that the amniopatch procedure had relative risk for success in restoration of AFI within normal ranges ٤ times than conservative management, and had relative risk for success in sealing of the membranes (as evidenced by no further leakage with restoration of AFI within normal ranges) ١.١ times than the conservative management

Table (٤): The relative risk of the amniopatch procedure in relation to success rate.

	Relative risk	٩٥٪ CI	P
Amniopatch for success in restoration of AFI within normal ranges.	٤	١.٨-٨.٥	٠.٠٠١*
Amniopatch for success in sealing of the membranes (no leakage).	١.١	٠.٩-١.٤	٠.٠٤*

Table (٥): Comparison between the amniopatch and the control groups in neonatal outcome regarding the Apgar score at ١ and ٥ minutes.

Data	Amniopatch group	Control group	P
-Apgar score at ١ minute. **- Mean ±SD**	٠-٦ ٤.٦±١.٦	٠-٦ ٤.٧±١.٧	٠.٥
-Apgar score at ٥ minutes. **- Mean ±SD**	٣-٨ ٦.٧±١.٤	٣-٨ ٦.٨±١.٥	٠.٥

Table (٦): Comparison between the amniopatch and the control groups in neonatal outcome regarding the need for NICU admission and its duration.

Data	Management group	Conservative group	P
The NO. of neonates indicated for NICU admission	٩(٤٧.٤٪)	١٤(٥٦٪)	٠.٣
-Duration of NICU admission (days) **-Mean±SD**	٢-٢١ ٨.٤±٧.٢	٢-٢٨ ١٠.٦±٨.٢	٠.٣

Table (٧): Comparison between study and control group in neonatal outcome regarding the status at time of discharge.

Status at discharge	Amniopatch group	Control group	P
Living	١٤(٧٠٪)	٢٠(٨٠٪)	٠.٤
Dead	٦(٣٠٪)	٥(٢٠٪)	

Discussion

In the present study, amniopatch procedure was applied to ٢٠ cases of sPPROM with gestational ages ranging from ٢٤ to ≤ ٣٤ weeks' gestation. Success of the amniopatch procedure was measured by the restoration of AFI within normal ranges, and the ability of this technique to reseal the membrane defect which was clinically evident by cessation of vaginal leakage of amniotic fluid associated with restoration of AFI within normal ranges. When compared to

the conservative management group, ١٥ cases of the amniopatch group (representing ٧٥٪) were found to have statistically significant increase in, and restoration of AFI within normal ranges P value is (٠.٠٠١), while, none of the patients in the conservative management group had (٧٥٪ success rate in the amniopatch group vs. ٠٪ in the conservative management group). As regard the efficacy in sealing the membrane defect, ٣ cases (representing ١٥٪) of the amniopatch group had successful sealing of the membranes with no amniotic fluid leakage and restoration of amniotic fluid volume within normal ranges, while, no cases of the conservative management group had, and this difference was statistically significant P value is (٠.٠٤).

From the above data, it can be concluded that, although, only ١٥٪ of the cases of amniopatch group had successful sealing of the membrane defect, ٧٥٪ of these cases had restored AFI within normal ranges, this indicates that partial sealing might have been occurred that resulted in reaccumulation of AFI to regain its normal values but without cessation of amniotic fluid leakage.

There was no statistically significant difference between the amniopatch and control groups as regard the development of maternal complications in the form of chorioamnionitis and placental abruption, the duration of maternal hospital stay or the mode of delivery.

It was found that both the amniopatch and the conservative management protocols resulted in statistically significant prolongation of the latency period, although, the latency period was more prolonged in the amniopatch group than the conservative group, this difference did not reach the level of significance.

In the present study, there was no cases of intrauterine fetal deaths, ٥ cases of neonatal deaths with overall neonatal survival rate was ٧٥٪, this is in agreement with the study done by (Kwak et al., ٢٠١٣) as regard the neonatal survival rate but they had one case of stillbirth in their study.

It is noted that the present study is limited by the relatively small group size with heterogeneous patient characteristics. Specifically, (١) patients who were offered amniopatch treatment were selected according to patient's preference, not by specific criteria; (٢) amounts of infused normal saline, platelet concentrate and cryoprecipitate were variable; (٣) 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.

Therefore, further prospective studies with larger numbers of subjects are needed to establish whether this treatment could be considered as an optional treatment for women with sPPROM who desire to continue their pregnancies and more extended and detailed follow up for their neonates to compare their physical and neurodevelopmental wellbeing with those whom mothers managed conservatively.

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