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CLINICAL STUDY

Is amniopatch an effective treatment for spontaneous previable premature rupture of membranes? Analysis of perinatal outcome

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ABSTRACT

OBJECTIVES: To characterize the perinatal outcomes of pregnancies complicated by spontaneous previable premature rupture of membranes with a therapeutic intervention in the form of amniopatch (AP) at the 2nd Department of Obstetrics and Gynecology (2008–2019).

MATERIALS AND METHODS: The retrospective analysis of perinatal markers and early neonatal morbidity of pregnancies treated with amniopatch. Discussion comparison with the published papers of cases of spontaneous previable rupture of membranes managed expectantly.

RESULTS: Out of the total number of pregnancies, 53 met the exclusion criteria, of which 35 were terminated by delivering a live newborn, 3 newborns died during the hospitalization. The following incidence of early complications has been reported in live births: 1) Bronchopulmonary dysplasia (10/35–28.57 %), 2) Newborn respiratory distress syndrome (25/35–71.42 %), 3) Neonatal sepsis (15/35–42.85 %), 4) Intraventricular hemorrhage (14/35–40 %), 5) Periventricular leukomalacia (3/35–8.57 %), 6). Necrotizing enterocolitis (2/35–5.71 %), 7) Retinopathy of prematurity (7/35–20 %) and 8) Foetal compression syndrome (16/35–45.71 %). In a discussion comparison with available publications of expectantly managed pregnancies, we observed a statistically significantly lower incidence of respiratory distress syndrome, retinopathy, and chorioamnionitis in our cohort along with a higher incidence of foetal compression defects.

CONCLUSION: Amniopatch can be a therapeutic method for reducing the neonatal mortality associated with RDS, maternal infectious morbidity, and an alternative in patients, who require an active approach to such a compromised pregnancy *(Tab. 12, Fig. 1, Ref. 50)*. Text in PDF *www.elis.sk*

KEY WORDS: spontaneous previable rupture of membranes, amniopatch, expectant management, perinatal morbidity, perinatal mortality.

Introduction

Spontaneous preterm premature rupture of membranes (sPPROM) is defined in our geographical conditions as an impairment of the integrity of amniotic sacs unrelated to the invasive procedure before completing the 24 gestational weeks (gw). Pregnancies complicated by the development of sPPROM compose a relatively small group (less than 1 % of all pregnancies) with an extremely unfavorable prognosis (1). Expectant management (application of tocolysis, corticoid preparation of foetal lungs, antibiotic prophylaxis, monitoring of the fetomaternal unit) is applied only to a limited extent, since in most pregnancies , a spontaneous termination in the form of childbirth or abortion occurs within 7 days of a clinical recording of sPPROM (2). Foetuses that reach the limit of viability defined as the completed 24 gw, generally suffer from complications due to an extreme prematurity manifested by pulmonary hypoplasia (PH) and the resulting changes (newborn respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), disorders of the central nervous system (CNS), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) of the retina, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), infectious complications (neonatal sepsis), limb compression defects (foetal compression syndrome–FCS)), which significantly affect the neonatal mortality and morbidity and almost without exception result in long-term health consequences (3–11). Some

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women opt for an elective termination due to an extremely unfavorable prognosis (12).

The therapeutic alternative is a so-called active management. To date (2021), several techniques have been described for the purpose of artificial closure of a defect in the amniotic sac, referred to in the Anglo-Saxon literature as the so-called "*resealing techniques*" or "*amniotic fluid reparation techniques*" (AFRT) (13–15).

One of the first, historically documented procedures was the sterile, intraamniotic administration of homologous maternal platelets and plasma cryoprecipitate to close a defect in the amniotic sac, secondary restoration of normohydramnios, and a reduction of perinatal morbidity and mortality (16–21).

Tab. 1. Exclusive criteria for enrolling in AP group.

Number	Criteria used
1.	Single-foetal pregnancies
2.	sPPROM (to completed 24 gw)
3.	Absence of active vaginal bleeding
4.	Interval between premature rupture of membranes and delivery or abortion >10 days
5.	Presence of ultrasonically verified anhydramnios
6.	Absence of positivity of maternal inflammatory parameter before AP application (without clinically or laboratory manifested inflammatory syndrome)
7.	Normal maternal CM parameters (>25 mm, without funneling)
8.	Absence of severe developmental defects or chromosomal aberrations in the foetus
9.	Performance of amniopatch not more than once

sPPROM – Spontaneous previable premature rupture of membranes; AP – Amniopatch; CM – Cervicometry; Gw – Gestational week

Tab. 2. Monitored parameters of the definitive group of patients.

Number	Monitored parameter
1.	Mean time of occurrence of sPPPROM (gw/d)
2.	Mean time of AP performance (gw/d)
3.	Mean time of termination of pregnancy (gw/d)
4.	Mean LP (AP–delivery/abortion) (gw/d)
5.	Mean LP (PPROM–delivery/abortion) (gw/d)

Tab. 3. Monitored neonatal complications and their definition criteria.

Monitored neonatal complication (ICD–10)	Used diagnostic criteria (Year of publication) (Citation)
BPD (P27.1)	Criteria according to Higgins (2000) (25)
RDS (P22.0)	Vermont Oxford definition criteria (1996) (26)
Neonatal sepsis (P36.0-9)	Criteria according to Singh et al. (1994) (27)
IVH (P52.0-9)	Criteria according to Papile and Burstein (1978) (28)
PVL (P91.2)	Criteria according to Hashimoto (2001) (29)
NEC (P77)	Criteria according to Bell (1978) (30)
ROP (H35.1)	Criteria according to ICROP (1984–1987) (31)
Fetal compression syndrome	Criteria created by the authors of the study–the occurrence of deformities of the fetal locomotor system associated with the persistent oligo- or anhydramniom

BPD – Bronchopulmonary dysplasia; RDS – Respiratory distress syndrome; IVH – Intraventricular haemorrhage; PVL – Periventricular leukomalacia; NEC – Necrotizing enterocolitis; ROP – Retinopathy of prematurity; FCS – Foetal compression syndrome; ICD–10 – International Classification of Diseases (10th Revision); ICROP – International Classification of Retinopathy of Prematurity

Tab. 4. Assessed perinatal parameters of subsets of neonates according to selected neonatal complications of pregnancies complicated by sPPROM treated with AP at the 2nd Department of Obstetrics and Gynecology FM CU and UHB (2008–2019).

Number	Monitored parameter
1.	Mode of delivery (n; %)
2.	Mean time of occurrence of sPPPROM (gw/d)
3.	Mean time of AP application (gw/d)
4.	Mean time of delivery (gw/d)
5.	Median LP value (sPPROM – delivery)

sPPROM – Spontaneous previable premature rupture of membranes; AP – Amniopatch; LP – Latency period; n – Number; % – Percentage; Gw – Gestational week; d – Days

The technique was successfully used for the first time by Rubén A. Quintero (1996) in the case of iatrogenic preterm premature rupture of membranes (iPPROM) in a 23-year-old woman after fetoscopic umbilical cord ligation in an acardiac fetus, and the procedure was termed *amniopatch* (AP) (16). The technique was derived from the peridural application of so-called "*blood patch*" products used to treat post-puncture headaches (22). In 2016, the Cochrane database stated that there was an insufficient verified evidence for common AP application in sPPROM cases (23). This fact classifies AP as an experimental treatment method requiring an individual use and a documented consent of a well-informed patient. Reported cases of membrane closure with a successful prolongation of pregnancy indicate the existence of a subset of patients who may benefit from its application (24).

Material and methods

Of the total number of women diagnosed with sPPROM, who underwent AP at the 2nd Department of Obstetrics and Gynecology (2008–2019), we composed the final set based on the exclusion criteria (Tab. 1).

In the final set, we determined the miscarriage rate (MiR) and live birth rate (LR) after the procedure in absolute values and percentages. We made up two subcategories for live births: 1) Newborns, who survived the initial stay in a hospital facility–survival rate to discharge (SR to discharge) and 2) Newborns, who lived during the initial hospitalization–mortality rate after delivery (MR after delivery) and these subcategories were expressed in absolute values and percentages. We defined the final set by determining the following parameters (Tab. 2).

We characterized live births in terms of early neonatal morbidity during the initial hospitalization (Tab. 3). We expressed the number in absolute numbers and percentages.

Based on the occurrence of the above-mentioned complications, we composed the subgroups of newborns characterized in terms of management, sPPROM, intervention in the form of AP, termination of pregnancy, and the interval between the premature rupture of membranes and termination of pregnancy (Tab. 4).

In the discussion part, we calculated the level of statistical significance of the occurrence of early neonatal complications in comparison with 7 published studies of expectantly managed cases of sPPROM (2009–2021) (32–38) (Tab. 5) using a chi-square test

Tab. 5. Occurrence of early neonatal complications in 7 publications with the issue of pregnancies complicated by sPPROM (expectant management) terminated by delivery (2009 – 2021) (32 – 38).

Publication (Year of publication)	Number of live-born neonates (n) (Citation)	BPD (n; %)	RDS (n; %)	Neonatal sepsis (n; %)	IVH (n; %)	PVL (n; %)	NEC (n; %)	ROP (n; %)	FCS (n; %)
Manuck (2009)	112 (32)	N	N	15 (13.39%)	47 (41.96%)	N	12 (10.71%)	N	8 (7.14%)
Pendse (2021)	82 (33)	N	80 (97.56%)	37 (45.12%)	N	0	4 (4.87%)	N	3 (3.65%)
Danisman (2019)	61 (34)	N	N	10 (16.39%)	34 (55.73%)	N	9 (14.75%)	N	3 (4.91%)
Kiver (2018)	44 (35)	21 (47.72%)	44 (100%)	N	10 (22.72%)	N	N	N	N
Wagner (2016)	40 (36)	13 (32.5%)	N	N	N	1 (2.5%)	3 (7.5%)	7 (17.5%)	N
Esteves (2016)	28 (37)	13 (46.4%)	N	N	8 (28.6%)	3 (10.7%)	N	19 (67.8%)	N
Chauleur (2009)	17 (38)	4 (23.52%)	12 (70.58%)	N	5 (29.41%)	N	N	N	2 (11.76%)

BPD – Bronchopulmonary dysplasia; RDS – Respiratory distress syndrome; IVH – Intraventricular haemorrhage; PVL – Periventricular leukomalacia; NEC – Necrotizing enterocolitis; ROP – Retinopathy of prematurity; FCS – Foetal compression syndrome; N – not given; n – Number; % – Percentage

(2 x 2) with p corrected by Bonferroni correction (necessity of testing multiple, independent hypotheses). We selected the compared studies based on the following criteria: 1) sPPROM (before the end of 24 gw), 2) Expectant management, 3) History without an invasive puncture or fetoscopic procedure, and 4. Availability of data on the incidence of defined neonatal complications in live births.

Tab. 6. Gibbs criteria (1991) of chorioamnionitis (39).

Primary criterion	
Presence of maternal fever (body temperature > 38 °C)	
+ minimum 2 of the secondary criteria	
Number	Secondary criterion
1.	Maternal tachycardia (pulse frequency >100/min)
2.	Fetal tachycardia (pulse frequency >160/min)
3.	Foul smelling amniotic fluid
4.	Uterine tenderness
5.	Uterine hypertonus
6.	Elevated levels of CRP
7.	Maternal leukocytosis (>18x109/l)

°C – Degrees Celsius; min. – minute; CRP – C-reactive protein; l – litre

Tab. 7. Occurrence of chorioamnionitis in patients in 4 publications with the issue of pregnancies complicated by sPPROM (expectant management) terminated by delivery (2009 – 2016) (32, 40 – 42).

Main authors of the study (year of publication)	Number of patients (n) (citation)	Occurrence of clinically manifested chorioamnionitis (n; %)
Manuck (2009)	159 (32)	85 (85/159–53.5%)
McLaughlin (2016)	106 (40)	46 (46/106–43%)
Hunter (2012)	106 (41)	58 (58/106–55%)
Deutsch (2010)	105 (42)	68 (68/105–64.8%)

n – Number; % – Percentage

In the cohort, we determined the incidence of clinically manifested chorioamnionitis based on the Gibbs criteria (1991) (39) (Tab. 6) and compared the result with the incidence of chorioamnionitis in 4 studies on sPPROM managed expectantly (2009–2016) (32, 40–42) (Tab. 7) using chi-square test (2x2). We selected the compared studies based on the following criteria: 1) sPPROM (before the end of 24 gw), 2) Expectant management, 3) History without an invasive puncture or fetoscopic procedure, and 4) Availability of data on the incidence of chorioamnionitis in the patients.

Results

Of the total number of patients (n=56), we excluded 3 patients (Tab. 1). In the final set (n=53), 18 abortions (MiR – 18/53 – 33.96 %) and 35 live births (LR – 35/53 – 66.03 %) were recorded. Of the 35 live births, 32 survived (SR to discharge – 32/53 – 60.37 %), and 3 did not survive (MR after delivery – 3/35 – 8.57 %) the period from delivery to discharge from the hospital (Fig. 1). The characteristics of the total set (n=53) are processed in Table 8.

In live-born neonates (n=35), we observed the following complications in terms of early neonatal morbidity: 1) BPD (10/35–28.57 %); 2) RDS (25/35 – 71.42 %); 3) Neonatal sepsis (7/35–20 %); 4) IVH (14/35 – 40 %); 5) PVL (3/35 – 8.57 %); 6) NEC (2/35 – 5.71 %); 7) ROP (9/35 – 25.71 %); 8) FCS (16/35 – 45.71 %). In the subgroups of newborns divided upon the occurrence of complications, we recorded the following values of perinatal parameters (Tab. 9).

Based on Gibbs criteria, we did not record a single case of chorioamnionitis in the total group of the patients (Tab. 10).

Tab. 8. Basic characteristics of AP group in 5 defined categories (Tab. 2).

A group of patients with pregnancies complicated by the development of sPPROM who underwent AP at the 2nd Department of Obstetrics and Gynecology FM CU and UHB					
Number of patients (n)	Mean time of occurrence of sPPPROM (gw/d)	Mean time of AP application (gw/d)	Mean time of termination of pregnancy (delivery/abortion) (gw/d)	Median value of LP AP – delivery/abortion (gw/d)	Median value of LP sPPROM – delivery/abortion (gw/d)
53	19+3/136	22+0/154	27+4/193	5+3/38	7+6/55

sPPROM – Spontaneous previable premature rupture of membranes; AP – Amniopatch; LP – Latency period; n – Number; % – Percentage; Gw – Gestational week; d – Days

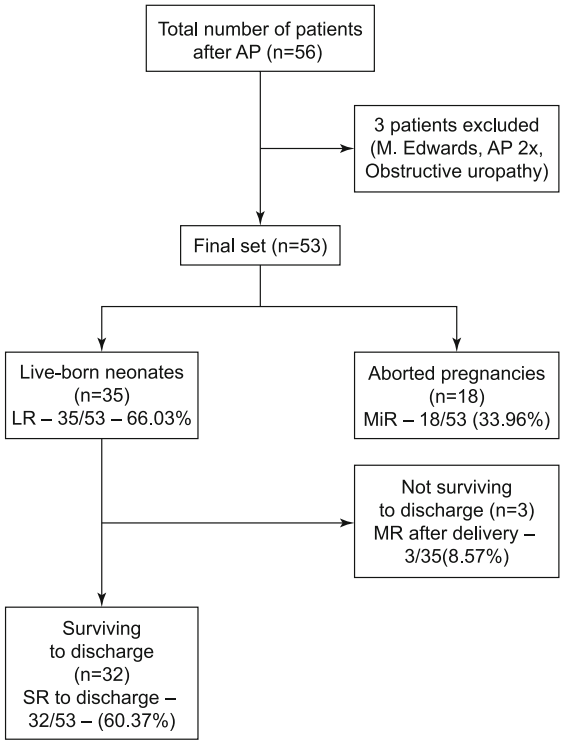

Fig. 1. Composition of patients in AP group according to the outcome of pregnancy. AP – Amniopatch; n – Number; LR –Live-born rate; MiR – Miscarriage rate; SR to discharge – Survival rate to discharge; MR after delivery – Mortality rate after delivery.

Tab. 10. Occurrence of clinically manifested chorioamnionitis in AP group.

A group of patients with pregnancies complicated by the development of sPPROM who underwent AP at the 2nd Clinic of Obstetrics and Gynecology FM CU and UHB

Number of patients (n)	Occurrence of clinically manifested chorioamnionitis (n; %)
53	0 (0/53 – 0%)

sPPROM – Spontaneous previable premature rupture of membranes; AP – Amniopatch; n – Number; % – Percentage

Discussion

Amniopatch as an experimental therapeutic method is currently predominantly used in cases of iPPROM after a transabdominal puncture or fetoscopic procedures, where its success rate reaches 58–66 % (20, 43).

The role of AP in sPPROM cases remains unclear to date, as only a limited number of small cohorts and isolated case reports have been published in the absence of large, randomized, controlled studies. Since randomization in the clinical management of sPPROM is difficult to achieve due to ethical, medical-social, and financial conditions, it was not possible to compare our group with our own control group managed expectantly while maintaining the uniformity of the therapeutic procedure. To evaluate the success rate of AP in terms of perinatal results and early neonatal complications, we decided to compare our group with the available studies dealing with the issue of conservative management of sPPROM.

Tab. 9. Occurrence of early neonatal complications in live-born neonates from pregnancies complicated by sPPROM treated with AP at the 2nd Department of Obstetrics and Gynecology FM CU and UHB (2008–2019).

Number of live-born neonates (n)	BPD (n; %)	RDS (n; %)	Neonatal sepsis (n; %)	IVH (n; %)	PVL (n; %)	NEC (n; %)	ROP (n; %)	FCS (n; %)
35	10 (28.57%)	25 (71.42%)	7 (20%)	14 (40%)	3 (8.57%)	2 (5.71%)	9 (25.71%)	16 (45.71%)

Evaluated perinatal parameters of subsets of neonates according to selected neonatal complications from pregnancies complicated by the development of sPPROM treated with AP at the 2nd Department of Obstetrics and Gynecology FM CU and UHB (2008 – 2019)

Monitored complication	Number of neonates (n; %)	Delivery mode (n; %)	Mean time of occurrence of sPPPROM (gw/d)	Mean time of AP application (gw/d)	Mean time of delivery (gw/d)	Median value of LP (sPPROM – delivery) (d)
BPD	10 (28.57%)	SC (9–90%) Vag. (1–10%)	18+6/132	21+3/150	27+0/189	57
RDS	25 (71.42%)	SC (24–96%) Vag. (1–4%)	20+0/140	22+1/155	27+5/194	57
Neonatal sepsis	7 (20%)	SC (5–7.42%) Vag. (2–28.57%)	21+5/152	23+3/164	25+6/181	18
IVH	14 (40%)	SC (12–85.71%) Vag. (2–14.28%)	19+6/139	22+2/156	26+6/188	50.5
PVL	3 (8.57%)	SC (3–100%)	18+3/129	21+2/149	25+5/180	57
NEC	2 (5.71%)	SC (2–100%)	19+5/138	21+3/150	24+5/173	35
ROP	9 (25.71%)	SC (8–88.88%) Vag. (1–11.11%)	20+0/140	22+1/155	25+5/180	43
FCS	16 (45.71%)	SC (16–100%)	19+3/136	21+5/152	29+1/204	63

BPD – Bronchopulmonary dysplasia; RDS – Respiratory distress syndrome; IVH – Intraventricular haemorrhage; PVL – Periventricular leukomalacia; NEC – Necrotizing enterocolitis; ROP – Retinopathy of prematurity; sPPROM – Spontaneous previable premature rupture of membranes; AP – Amniopatch; LP – Latency period; Gw – Gestational week; n – Number; % – Percentage; CS – Cesarean section; Vag. – Vaginal delivery

Tab. 11A. Comparison of the occurrence of early neonatal complications (BPD, RDS, Neonatal sepsis) among live-born neonates from AP group with neonates from published cases of sPPROM managed expectantly.

BPD	Number of live-born neonates (n)	Occurrence of clinically manifested BPD (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	10 (28.57%)		
Comparison with published studies (2016 - 2018)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of BPD (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Kiver (2018)	44 (35)	21 (47.72%)	0.08255	No
Wagner (2016)	40 (36)	13 (32.5%)	0.7128	No
Esteves (2016)	28 (37)	13 (46.4%)	0.143507	No

RDS	Number of live-born neonates (n)	Occurrence of clinically manifested RDS (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	25 (71.42%)		
Comparison with published studies (2009 – 2021)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of RDS (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Pendse (2021)	82 (33)	80 (97.56%)	0.000084	Yes
Kiver (2018)	44 (35)	44 (100%)	0.000554	Yes
Chauleur (2009)	17 (38)	12 (70.58%)	0.792149	No

Neonatal sepsis	Number of live-born neonates (n)	Occurrence of manifested neonatal sepsis (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	7 (20%)		
Comparison with published studies (2009 – 2021)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of neonatal sepsis (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Manuck (2009)	112 (32)	15 (13.39%)	0.33886	No
Pendse (2021)	82 (33)	37 (45.12%)	0.010211	No
Danisman (2019)	61 (34)	10 (16.39%)	0.655928	No

BPD – Bronchopulmonary dysplasia; RDS – Respiratory distress syndrome; AP – Amniopatch; sPPROM – Spontaneous previable premature rupture of membranes; n – Number; % - Percentage

The evaluation of the success rate of AP depends on the set criteria, which are defined in each published study. As the criterion of success in terms of perinatal outcomes, we determined a statistically significantly lower incidence of early neonatal complications (Tab. 3) in newborns until their discharge from the hospital facility and a lower incidence of chorioamnionitis.

In the postoperative patients, we did not observe a significantly higher incidence of complications (placental abruption, umbilical cord compression, chorioamnionitis, postpartum sepsis) compared to expectant management, which indicates a good safety profile of the method. The above fact is currently documented (2021) by the single randomized comparative study comparing the effect of AP versus expectant management in cases of pregnancies complicated by premature rupture of membranes between 24 and 34 gw by Maged et al (44).

When comparing the cohort results in the categories of early neonatal morbidity with 7 published studies of sPPROM cases managed expectantly (2009 - 2020) (32–38), we found a statistically significant difference in the categories of RDS, ROP, and FCS. There was a statistically significantly lower incidence of RDS and ROP cases in live births in the AP group with a higher incidence of FCS. The other evaluated categories did not record statistically significant differences in the compared groups (Tabs. 11A, B, C).

We associate the reduced incidence of RDS with a longer duration of pregnancy and a larger residual volume of amniotic fluid, potentiating the maturation of foetal lungs with a consequent better postnatal function requiring a lower rate of ventilation support and oxygen therapy. The reduced need for oxygen directly proportionally reduces the formation of free radicals in foetal tissues involved in the pathogenesis of ROP through their proangiogenic action. The increased incidence of FCS is attributed to the prolonged artificial maintenance of oligohydramnios with an unequal increase in intrauterine pressure and restriction of foetal movements. This fact is evidenced by several published studies showing the relationship between the length of pregnancy, the severity of oligohydramnios, and the risk of developing FCS (45–47).

When evaluating the incidence of infectious complications in the form of clinically manifested chorioamnionitis, we did not record a single case in our cohort. In comparison with 4 publications of sPPROM cases managed expectantly (2009–2016) (32, 40–42), we found a statistically significantly lower incidence of chorioamnionitis in the patients, who underwent AP (Tab. 12).

The reduced incidence of chorioamnionitis in the patients after AP (homologous platelets and plasma cryoprecipitate) may be related to the anti-infective and immunomodulatory effects of

Tab. 11B. Comparison of the occurrence of early neonatal complications (IVH, PVL, NEC) among live-born neonates from AP group with neonates from published cases of sPPROM managed expectantly.

IVH	Number of live-born neonates (n)	Occurrence of clinically manifested IVH (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	14 (40%)		
Comparison with published studies (2009 – 2019)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of IVH (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Manuck (2009)	112 (32)	47 (41.96%)	0.836893	No
Danisman (2019)	61 (34)	34 (55.73%)	0.137718	No
Kiver (2018)	44 (35)	10 (22.72%)	0.097269	No

PVL	Number of live-born neonates (n)	Occurrence of manifested PVL (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	3 (8.57%)		
Comparison with published studies (2016 – 2021)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of PVL (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Pendse (2021)	82 (33)	0 (0%)	0.040648	No
Wagner (2016)	40 (36)	1 (2.5%)	0.514156	No
Esteves (2016)	28 (37)	3 (10.71%)	0.885534	No

NEC	Number of live-born neonates (n)	Occurrence of manifested NEC (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	2 (5.71%)		
Comparison with published studies (2009 – 2021)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of NEC (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Manuck (2009)	112 (32)	12 (10.71%)	0.582494	No
Pendse (2021)	82 (33)	4 (4.87%)	0.787222	No
Danisman (2019)	61 (34)	9 (14.75%)	0.314637	No

IVH – Intraventricular hemorrhage; PVL – Periventricular leukomalacia; NEC – Necrotizing enterocolitis; AP – Amniopatch; sPPROM – Spontaneous previable premature rupture of membranes; n – Number; % – Percentage

Tab. 11C. Comparison of the occurrence of early neonatal complications (ROP, FCS) among live-born neonates from AP group with newborns from published cases of sPPROM managed expectantly.

ROP	Number of live-born neonates (n)	Occurrence of manifested ROP (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	35	9 (25.71%)		
Comparison with published studies (2016)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of ROP (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Wagner (2016)	40 (36)	7 (17.5%)	0.386315	No
Esteves (2016)	28 (37)	19 (67.85%)	0.000823	Yes

FCS	Number of live-born neonates (n)	Occurrence of manifested FCS		
AP group (2nd Department of Obstetrics and Gynecology)	35	16 (45.71%)		
Comparison with published studies (2009 – 2021)				
Compared studies (year of publication)	Number of live-born neonates (n) (citation)	Occurrence of FCS (n; %)	p (Bonferroni correction of p: 0.0012)	Statistical significance
Manuck (2009)	112 (32)	8 (7.14%)	0.00001	Yes
Pendse (2021)	82 (33)	3 (3.65%)	0.000001	Yes
Danisman (2019)	61 (34)	3 (4.91%)	0.000001	Yes

ROP – Retinopathy of prematurity; FCS – Fetal compression syndrome; AP – Amniopatch; sPPROM – Spontaneous previable premature rupture of membranes; n – Number; % – Percentage

Tab. 12. Comparison of the occurrence of chorioamnionitis in patients from AP group with patients from published cases with sPPROM managed expectantly (2009 – 2016) (32, 40 – 42).

	Number of patients (n)	Occurrence of clinically manifested chorioamnionitis (n; %)		
AP group (2nd Department of Obstetrics and Gynecology)	53	0 (0%)		
Compared studies (2009 – 2016)				
Main authors of the study (year of publication)	Number of patients (n) (citation)	Occurrence of clinically manifested chorioamnionitis (n; %)	p: 0.005	Statistical significance
Manuck (2009)	159 (32)	85 (53.5%)	0.0	Yes
McLaughlin (2016)	106 (40)	46 (43%)	0.0	Yes
Hunter (2012)	106 (41)	58 (55%)	0.0	Yes
Deutsch (2010)	105 (42)	68 (64.8%)	0.0	Yes

AP – Amniopatch; n – Number; % – Percentage

so-called "*patch*" components that act in the amniotic fluid after application. The anti-infective effect of platelet concentrates and human plasma has been observed in several studies dealing with their use in the treatment of surgical wounds (48 – 50).

These results may indicate the clinical significance of AP as a medical treatment to reduce an early neonatal mortality associated with RDS and infectious morbidity in mothers diagnosed with sPPROM. The interpretability of the results obtained is partially limited by the absence of randomization, relatively small size of the compared groups, the heterogeneity of the exclusion criteria of the cohorts, and the diversity of the therapy administered. Early neonatal morbidity and mortality and overall perinatal outcomes in each cohort are likely to be affected by different levels of neonatal intensive care in each country.

The created cohort can be a valuable basis for the comparison with future publications to evaluate the overall clinical applicability of AP. The potentially broad clinical application of AP based on the principles of Evidence-Based Medicine (EBM) requires enough data obtained from randomized controlled studies. By means of the above findings, we point out that amniopatch may be a suitable therapeutic alternative in patients diagnosed with sPPROM, who require an active approach to such a severely compromised pregnancy.

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