

Perinatal outcome in preterm premature rupture of membranes before 37 weeks of gestation

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ABSTRACT

Objectives: The aim of this study was to assess the maternal and neonatal outcome in patients with preterm premature rupture of membranes between 22 to 37 weeks of gestation in comparison to preterm birth patients.

Material and methods: Group of PPRM patients consisted of 127 women, the control group counted 141 women who delivered prematurely. The control group was formed by matching patient with the same gestational age at delivery and neonatal birth weight to every woman from study group. In both groups speculum and ultrasound examinations were performed, microbiological swabs were taken. In unclear cases of PPRM tests detecting amniotic proteins, such as PAMG-1 or IGFBP-1, were performed. According to gestational age at delivery, neonates were divided into subgroups: extremely premature infants (< 27 weeks 6 days), moderate premature infants (from 28 weeks 0 days to 33 weeks 6 days), late premature infants (from 34 weeks 0 days to 37 weeks 0 days).

Results: In the study group, median gestational age of delivery was 34 weeks 1 day and the same in control group — 34 weeks and 5 days ($p > 0.05$). Parameters of inflammatory status were more often reported in the PPRM group than in the preterm birth group, even if they weren't statistically significant (positive culture of cervical swab, increased leukocytosis, CRP above 5). The rate of neonate survival was similar in both groups (93.7% and 94.1%). Congenital infection was more often diagnosed in group of neonates from PPRM pregnancies than in neonates from control group; (36% and 21.2% respectively; $p = 0.009$).

Conclusions: Our research appears to be consistent with theory of inflammatory etiology of PPRM. Optimal management of infection in PPRM patients seems to be the most important in efforts to prolong pregnancy.

Key words: 1 preterm delivery; 2 preterm premature rupture of membranes; 3 neonatology outcome

Ginekologia Polska 2019; 90, 11: 645–650

INTRODUCTION

Preterm rupture of membranes (PROM) complicates approximately 2–5% of pregnancies before term and 8% of term gestations [1]. At term it does not significantly influence pregnancy outcome. If it happens before 37 weeks, we describe it as preterm premature rupture of membranes (PPROM) and it increases the risk of preterm labor, intrauterine infection, fetal hypoxia and intrauterine death [1, 2]. Pregnancy outcome in cases of spontaneous PPRM depends on gestational age. Approximately 50% of patients deliver within a week after PPRM, latency in the other half depends on gestational age, fetal condition and presence of infection [3].

Depending on the gestational age, fetal and maternal condition, there is a possibility of conservative management, including steroids administration, antibiotics and magnesium sulfate or active labor induction after steroids

administration [4]. Tocolytics are usually not recommended because uterine contractions are usually correlated to intrauterine infection and prolongation of pregnancy in these cases does not decrease the mortality and morbidity of women and children [5, 6].

Lack of amniotic fluid in the uterus, especially before the 24th week of gestation, disturbs fetal lung development. Alveoli do not form without amniotic fluid even after steroids administration. Respiratory distress in children born after PPRM, after they had spent some time in uterus without amniotic fluid, is often more severe than we expect. Neonates have also higher risk of severe inborn infection. Both factors — respiratory distress and infection — worsen prognosis for the children after PPRM [7, 8].

There are only a few trials trying to compare different approaches to ahydramnios caused by PPRM. They

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concentrate on two topics: sealing the hole in membranes (amniopatch, immunologic sealants, membranes) and supplementing amniotic fluid (amnioinfusion). As of now, there is no answer to if any type of treatment improves pregnancy outcome [9, 10].

Objectives

Authors compared pregnancy outcome in patients who delivered before term with and without PPRM.

MATERIAL AND METHODS

The study group consisted of 127 women who were admitted to the Department of Obstetrics of Medical University from October 2009 to 2014 with preterm premature rupture of membranes (between 22 and 37 weeks of gestation). The control group (141 women) was formed by matching patient with the same gestational age at delivery and neonatal birth weight to every woman from study group. According to gestational age at delivery, neonates were divided into subgroups: extremely premature infants (< 27 weeks 6 days), moderate premature infants (from 28 weeks 0 days to 33 weeks 6 days), late premature infants (from 34 weeks 6 days to 37 weeks 0 days).

To confirm PPRM, sterile speculum examinations were performed with the visualization of amniotic fluid leaking from the cervical canal. In unclear cases tests detecting amniotic proteins, such as PAMG-1 (Placental alpha microglobulin-1) or IGFBP-1 (Insulin-like growth factor binding protein 1), were performed. Ultrasound examinations were performed in every patient — fetal well-being, amniotic fluid index and signs of placental abruption were determined. The exclusion criteria included: multiple pregnancy, intrauterine fetal death, fetal congenital malformations, previous cervical surgery and uncertain diagnosis of PPRM.

According to our Department regulation, patients with PPRM before 34 weeks 0 days of gestation were managed expectantly if no maternal or fetal contraindication were present. Induction of labor wasn't offered to these patients unless intrauterine infection was diagnosed. Tocolysis wasn't ordered to pregnant patients with PPRM. A single course of corticosteroids was offered to every pregnant woman between 24 weeks 0 days and 34 weeks 6 days. Prophylactic antibiotics were given to patients in the latent phase of PPRM from 24 weeks 0 days to 33 weeks 6 days. Every week patients were examined vaginally (speculum examination) and had cervical swabs taken. If a microbiological swab was positive, antibiotics were administered. Similarly, CRP and leukocytosis were evaluated every week. Fetal status was assessed every seven days by ultrasound examination. In case of patients with PPRM after 34 weeks 0 days of gestation, who didn't have contraindication to labor, delivery was induced, mostly with Oxytocin infusion (usually after

12 hours of expectancy for spontaneous contractions). Neither tocolysis nor corticosteroids were offered in this group of patients. Maternal infusion of magnesium sulfate as fetal neuroprotection wasn't recommended for patients before 32 weeks 0 days.

Data from medical records were analyzed to compare pregnancy complications and outcome in the study group and control group. Information regarding gestational age at PPRM, laboratory symptoms of infection (CRP > 5, leukocytosis > 15000/dL, positive culture of cervical swab), steroids and antibiotics administration, gestational age at delivery, mode of delivery, indication for cesarean section, birth weight of neonate, respiratory distress syndrome (type of assisted ventilation), leukocytosis and CRP in neonate, results of microbiological tests in neonates, length of hospital stay of neonate was collected. Congenital infection was diagnosed based on a minimum of two signs of infection in clinical examination and/or increased values of inflammatory parameters in neonate. Clinical symptoms of congenital infection were defined as breathing disturbances (tachypnea, apnea), tachycardia, bradycardia, significant variability of heart rate, emesis, hypotonia, muscle tremors, convulsions, instability of body temperature, lethargy, circulation disturbances, and metabolic disturbances.

The normality of the layout of continuous variables was assessed by means of the Shapiro-Wilk test. Statistical characteristics of continuous variables were presented by means of arithmetic means, standard deviations, medians as well as minimal and maximal values. For inter-group comparisons Student's t-test for non-linked variables or U Mann-Whitney test were applied. In order to compare the layouts of discrete variables, Pearson's chi-squared test or Fisher's exact test were used. All calculations were carried out by means of Statistica10 software (StatSoft, the USA), where value $p < 0.05$ was accepted as a statistically significant.

RESULTS

Average patient age at admission to hospital was 30.2 ± 5.4 years in the study group and 29.8 ± 4.8 years in the control group ($p > 0.05$). As far as gravidity was concerned, 48% of the patients in study group and 43.3% of the patients in control group were nulliparous, while 52% and 56.7% had had at least one delivery ($p > 0.05$). In the study group of 127 women median gestational age of delivery was 34 weeks 1 day (23 weeks and 5 days to 37 weeks 0 days) and the same in the control group — 34 weeks and 5 days, from 22 weeks and 4 days to 37 weeks and 0 days ($p > 0.05$). Median gestational age of delivery in subgroups was: before 27 weeks and 6 days — 26 weeks and 0 days in PPRM group and 25 weeks 5 days in control group ($p > 0.05$), from 28 weeks and 0 days to 33 weeks and 6 days — 31 weeks and 4 days in both groups ($p > 0.05$) and from

34 weeks and 0 days to 37 weeks and 0 days — 35 weeks and 3 days in PPRM group and 35 weeks 4 days in control group ($p < 0.05$).

The median gestational age of PPRM in the study group was 33 weeks 5 days (from 21 weeks and 4 days to 36 weeks and 6 days). In details: in the group of patients who delivered before 27 weeks 6 days — 24 weeks 6 days, from 28 weeks 0 days to 33 weeks 6 days — 30 weeks 1 day, from 34 weeks 0 days to 37 weeks 0 days — 35 weeks 2 days. The median time from PPRM to delivery was 1 day (0 to 71 days); 9 days in patients, who delivered before 28 weeks of gestation; 11 days in patients who delivered from 28 weeks and 0 days to 33 weeks and 6 days and 1 day in patients who delivered after 33 weeks and 6 days. In the analyzed group 42 patients (33%) delivered on the day, when PPRM occurred, while 85 (66.9%) delivered later. Among 42 pregnant women who delivered on the day of PPRM, gestational age of 36 (85.7%) of them was greater than 33 weeks 6 days of gestation, when in 6 (14.3%) of them was between 28 weeks 0 days and 33 weeks 6 days. None of PPRM patients who delivered before 28 weeks of pregnancy delivered on the day when PPRM occurred.

Positive culture of cervical swabs were noted in 62 patients with PPRM (49%) and in 51 patients in the control group (36%) ($p > 0.05$, $p = 0.101$); in 3 patients (27%), who delivered before 28 weeks of gestation in the PPRM group and in 5 patients (50%) in the control group ($p > 0.05$); in 27 patients (56%), who delivered from 28 weeks 0 days to 33 weeks 6 days in the PPRM group and in 16 patients (36%) in the control group ($p = 0.06$); in the group of patients who delivered from 34 weeks 0 days to 37 weeks 0 days — in 32 pregnant in the PPRM group (47%) and in 30 patients (35%) in the control group ($p < 0.05$). Increased leukocytosis was noted at least once during latent period in 65 women with PPRM (51.2%), in the control group leukocytosis greater than 15000 was found in 43 patients (30.7%) ($p < 0.001$). In details, in the study and in the control group in 6 patients (54%) versus 3 patients (33%) who delivered before 28 weeks of pregnancy, in 30 patients (62%) versus 18 patients (38%) who delivered from 28w0d to 33w6d and in 29 patients (43%) versus 22 patients (27%) who delivered later ($p > 0.05$; $p < 0.05$; $p < 0.05$; respectively) increased leukocytosis was noted. CRP above 5 was observed in 77 patients (68.7%) in the study group versus 29 patients (56.9%) in the control group ($p < 0.001$ and $p > 0.05$). CRP wasn't evaluated in 15 patients (12%) from the study group and in 90 patients (63.8%) from the control group.

During latent time prophylactic antibiotics were used in 73 patients (57.5%) in the group of PPRM patients. Additionally, antibiotics were administered if increased CRP, leukocytosis or positive microbiological swab was observed. To conclude, antibiotics were given to 99 patients in the

PPROM group before delivery (78%), while in the control group 50 patients (35.5%) ($p < 0.001$).

Steroids were administered in 66 patients before 34 weeks 6 days in the study group (52%), and in 49 patients in the control group (35%) ($p < 0.05$); in a group of women who delivered before 28w0d in 10 (90%) in the PPRM group and in 7 (70%) in the preterm delivery group; in a group of patients who delivered from 28w0d to 33w6d in 41 (85%) in the study group and in 27 (56%) in the control group. Patients who delivered after 33w6d received steroids in 22% (15 pregnant) in the PPRM group and in 18% (15 pregnant) in the control group ($p > 0.05$, $p < 0.05$, $p > 0.05$; respectively).

In the study group 77 patients (61%) delivered vaginally — 73% (8 pregnant women) before 28w0d, 59% (28 pregnant) from 28w0d to 33w6d and 60% (41 pregnant women) from 34w0d to 37w0d. In the remaining 50 women (39%), cesarean sections were performed. In the control group, 38 patients delivered vaginally (27%) — 30% (3 pregnant women) before 28w0d, 29% (13 pregnant women) from 28w0d to 33w6d and 27% (22 pregnant women) from 34w0d to 37w0d. Cesarean sections were performed in 103 patients (73%). The cesarean section rate was higher in the control group ($p < 0.001$) and in the subgroups this trend was also observed ($p = 0.05$, $p < 0.05$, $p < 0.05$).

The cesarean section in the study group was performed most frequently due to fetal distress (28 women — 58.3%) or intrauterine infection (10 women — 20.8%), but also due to fetal malpresentation (9 women — 18.8%), placental abruption (2 women — 4.2%), preeclampsia (1 woman — 2.1%), threatening rupture of uterus (4 women — 8.3%) and maternal indications (8 women — 16.7%), fetal indications (1 woman — 2.1%). Indications for cesarean sections in the control group was mostly fetal distress (66 women — 64.7%). Other indications were: intrauterine infection (3 women — 2.9%), fetal malpresentation (8 women — 7.8%), placental abruption (6 women — 5.9%), preeclampsia (15 women — 14.7%), threatening rupture of uterus (4 women — 3.9%) and maternal indications (13 women — 12.7%), fetal indications (4 women — 3.9%). In three cases, indications for cesarean section were unknown. The group of extremely preterm infants consisted of 11 neonates (9%) in the PPRM group and 10 neonates (7%) in the preterm delivery group, moderate preterm infants — 48 (38%) in the PPRM group and 47 (33%) in the preterm delivery group, late preterm infants — 68 (53%) in the PPRM group and 84 (60%) in the control group ($p > 0.05$, $p > 0.05$, $p < 0.05$).

The average birth weight was similar in the study and the control group (2117.9 g and 2245.0 g respectively, $p > 0.05$). In extremely preterm infants it was 938 g and 832 g ($p > 0.05$), in moderate preterm infants 1717 g and 1766 g ($p > 0.05$) and in late preterm infants 2589 g and

2667 g ($p > 0.05$) in the PPROM group and the control group respectively.

The rate of neonate survival to discharge was similar in both groups (93.7% and 94.1% respectively; $p > 0.05$). Rates of survival increased with increasing gestational age in both groups; in the PPROM group: 73% (< 28w0d), 94% (from 28w0d to 33w6d), 99% (from 34w0d to 37w0d) and in the control group: 60%, 94%, 97% respectively ($p < 0.05$, $p > 0.05$, $p > 0.05$).

Incidence of neonatal respiratory distress syndrome was similar in both groups (42.5% vs 45%; $p > 0.05$). In extremely preterm infants in 90% (10 neonates) and in 89% (8 neonates) ($p > 0.05$), in moderate preterm infants in 35 (73%) and in 35 neonates (74%) ($p > 0.05$), in late preterm infants in 10 neonates (15%) and in 21 neonates (25%) ($p > 0.05$) in the PPROM group and the control group respectively.

Assisted ventilation was used in 48 neonates (38%) in the study group and in 59 children (42%) in the control group ($p > 0.05$); in 10 neonates (90%) and in 8 neonates (80%) in extremely preterm infants ($p > 0.05$), in 32 neonates (66%) and in 34 neonates (74%) in moderate preterm infants ($p > 0.05$), in 6 neonates (9%) and in 17 neonates (20%) in late preterm infants ($p = 0.059$). Congenital infection was diagnosed more often in the group of neonates from PPROM pregnancies (45 neonates) than in neonates from the control group (29 neonates); (36% and 21.2% respectively; $p = 0.009$). In detail, infection was present in 6 (55%) extremely preterm neonates in the PPROM group and in 3 (37%) in the control group ($p > 0.05$), in 25 (52%) moderate preterm neonates in the PPROM group and in 14 (31%) in the control group ($p < 0.05$) and in 13 (19%) late preterm neonates in study group and in 11 (13%) in preterm delivery group ($p > 0.05$). Differences were also noted regarding leukocytosis in neonate above 15 000/dL (61.5% and 49.2% respectively), but it was not statistically significant ($p = 0.059$). In detail, high leukocytosis was found in extremely preterm in 66% (6 neonates) and 37% (3 neonates) ($p > 0.05$), in moderate preterm infants in 56% (26 neonates) and in 40% (18 neonates) ($p > 0.05$) and in late preterm infants in 60% (40 neonates) and in 50% (41 neonates) ($p > 0.05$) in the PPROM group and the control group respectively.

Number of neonates with CRP above 5 was similar in both groups (22.3% and 24.4% respectively; $p > 0.05$). In extremely preterm infants CRP was above 5 in 33% (3 neonates) versus 37% (3 neonates) ($p > 0.05$), in moderate preterm infants 38% (17 neonates) versus 35% (15 neonates) ($p > 0.05$) and in late preterm infants 12% (8 neonates) versus 17% (14 neonates) ($p > 0.05$) in the PPROM group and the control group respectively.

Antibiotic therapy was administered in 88 (69%) of neonates from the study group versus 80 (61%) neonates from the control group ($p = 0.04$). In extremely preterm

infants antibiotics were given to 10 neonates (90%) and in 9 neonates (90%) ($p > 0.05$), in moderate preterm infants in 47 neonates (98%) and in 44 neonates (94%) ($p > 0.05$) and in late preterm infants in 31 neonates (45%) and in 28 neonates (34%) ($p > 0.05$) in the PPROM group and the control group respectively.

Median hospital stay of the neonates in the study group was 11 days (0 to 79 days) and in the control group — 8 days (0 to 82 days), and the difference wasn't significant ($p > 0.05$). In extremely preterm infants it was 67 and 54 days ($p > 0.05$), in moderate preterm infants 25 and 30 days ($p > 0.05$) and in late preterm infants 8 and 9 days ($p > 0.05$) in the PPROM group and control group respectively.

DISCUSSION

According to Romero's definition preterm labor results from "pathological activation" of one or more components of "common pathway of parturition". Uterine myometrial contractility, cervical ripening and membranes rupture, if activated synchronously are said to be the most important factors leading to preterm delivery. Asynchronous activation of one of these components results in cervical insufficiency, preterm uterine contractions or preterm premature rupture of membranes [11, 12]. So far there are many dimensions identified as responsible or connected with mentioned above clinical situations [12]. Prostaglandins and matrix-degrading enzymes (mediators of infection) are considered to be crucial factors in collagen degradation and weakening of membranes, which leads to its rupture [13]. Clinical studies have confirmed infectious theory — bacteria's have the ability to cross even intact membranes and positive amniotic fluid cultures are identified in 12.8% of patients with preterm birth and 32% with preterm premature rupture of membranes according to Romero's researches [14]. Caroll S.G. et al. [15] showed that positive culture of swabs from the vagina predicts 53% of intraamniotic infections. In our study we haven't examined amniotic fluid for presence of microbial invasion, but we also observed positive culture of cervical swab significantly more frequent in group of patients with rupture of membranes than in patients with preterm birth. Similarly, increased leukocytosis and CRP were noted more often in groups of pregnant women with PPROM than in groups of patients with preterm birth. CRP isn't routinely ordered in case of patients with risk of preterm delivery, that's why increased value of this marker was observed only in 13% of patients among the patients in this group. According to literature neither CRP nor leukocytosis are considered to be highly specific in detecting intrauterine infection and are not even recommended in some countries to be assessed. The estimated sensitivity rate of leukocytosis in detecting chorioamnionitis is 29–47% [16], when specificity of CRP is 38–55% [17]. Antibiotics were applied

in groups of PPRM patients more often than in control groups. Antibiotics weren't offered routinely to everyone. Due to hospital regulation, antibiotics were offered prophylactically or in case of increased inflammatory indicators or symptoms of infection.

Nowadays, according to Polish Society of Gynecologists and Obstetricians the most optimal approach to management of PPRM patients is expectant management with antibiotics therapy to prolong latency of pregnancy. After 34 weeks of pregnancy induction of delivery with oxytocin is indicated only if intrauterine infection is suspected. Regardless of clinical management birth in 7 days following rupture of membranes occurs in 50% patients [3]. The median length of latency from PPRM to delivery in the examined group was 1 day (from 0 to 71 days). Comparing to other publications, median latency time in the PPRM group was short because in the evaluated group nearly half consisted of patients after 34 weeks of gestation, where due to hospital regulation and ACOG recommendations active management was recommended. In patients with PPRM before 28 weeks of gestation median latency time was 9 days and 11 days if delivery took place between 28 + 0 to 33 + 6, similar results were presented by A. Peaceman. In a group of 1377 patient's median latency time between 24–28 weeks was approximately 9 days, and between 30–31 weeks was 6 days [18].

The difference in the frequency of cesarean section was observed in the research. This operative procedure was more often performed in group of patients with intact membranes than in PPRM group. The main indication for cesarean section in both groups was fetal distress, while in the group of PPRM patients could have been related to active management (induction of delivery) in case of patients after 34 weeks of gestation. Threatening intrauterine infection was the second main indication for cesarean section in the PPRM group, what is consistent with published data.

Congenital infection was more often detected in all subgroups of neonates from the study group than the control group, what is consistent with fact of higher incidence of increased parameters of inflammation and positive cervical swabs in pregnant with PPRM. As a consequence of this, antibiotics were also more often administered in the study group. Comparable results were published by Moratti [19]. According to data published by Bengtson and Dale [20, 21] respiratory distress syndrome incidence in neonates from pregnancies complicated by PPRM is evaluated to be 10–40%. In general, in our study we noticed high ratio of respiratory distress, comparable in both groups of neonates (42.5% and 45%). In case of extremely and moderate preterm neonates, it was a result of early gestational age at delivery and impossibility of steroids administration. In the group of neonates delivered after 34 weeks of gestation, res-

piratory distress syndrome was more often observed in the control group, which is probably connected with the high percentage of cesarean section performed in this group.

Considering neonatal survival rate, we haven't found significant difference between both groups of patients. Neonatal death mostly occurred in cases of neonates born before 26 weeks of gestation with low birth weight. Glass estimates that extremely premature infants with extremely low birth weight have 30–50% risk of mortality and 20–50% risk of morbidity in survivors [22]. Probably, if patients with PPRM (especially after 28th week of pregnancy) are appropriately covered with antibiotics, which increases the latent time of pregnancy and offers the possibility of steroids and magnesium sulfate administration, the presence of PPRM doesn't influence the rate of mortality in neonates.

CONCLUSIONS

Our research appears to be consistent with theory of inflammatory etiology of PPRM. Optimal management of infection in PPRM patients seems to be the most important in efforts to prolong latency of pregnancy and decrease mortality and morbidity in neonates.

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