






# Comparison of maternal characteristics, pregnancy course, and neonatal outcome in preterm births with and without prelabor rupture of membranes

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## ABSTRACT

**Objectives:** The aim of this study was to evaluate pregnancy outcome of patients with prelabor rupture of membranes receiving expectant management and giving birth prematurely in comparison to preterm births of patients with intact membranes.

**Material and methods:** It was a retrospective cohort study comparing maternal and neonatal outcome in two groups of preterm births. The first group included 299 consecutive singleton preterm births complicated by prelabor rupture of membranes. The second group consisted of 349 consecutive singleton preterm births without prelabor rupture of membranes.

**Results:** Patients without pPROM underwent Caesarean sections more often than women from the pPROM group (65.3% vs 45.2%;  $p < 0.001$ ). No statistically significant differences regarding the gestational age during delivery were identified. Lower birth weight was detected in the group with no history of pPROM ( $p < 0.001$ ).

No differences regarding early-onset sepsis and higher percentage of late-onset infections was observed in infants with no history of pPROM (8.9% vs 4.7%;  $p = 0.04$ ). Pulmonary hypertension was more common in the infants from the pPROM group (4% vs 1.4%;  $p = 0.049$ ). Neonatal respiratory distress syndrome and respiratory failure were more prevalent in cases of no pPROM history — 20% vs 12.7% ( $p = 0.02$ ) and 40% vs 25.8% ( $p < 0.001$ ), respectively.

**Conclusions:** Development of multiple complications in preterm neonates may be more associated with the management, gestational age at birth, and birth weight than with the occurrence of preterm prelabor rupture of membranes.

**Key words:** pregnancy complications; pregnancy outcome; premature birth; preterm premature rupture of the membranes

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## INTRODUCTION

Prematurity remains the leading cause of neonatal morbidity and mortality worldwide [1]. Preterm prelabor rupture of membranes (pPROM) complicates about 3% of all pregnancies and one-third of pregnancies delivered before term [2]. Even though this complication has been managed for decades, available data on the results of planned early birth compared to expectant management of pPROM do not strongly support any method [3, 4].

### Objective

The aim of this study was to evaluate maternal and neonatal outcome of preterm births complicated by pPROM

and receiving expectant management in comparison to preterm births with intact membranes.

## MATERIAL AND METHODS

### Patient population and data collection

It was a retrospective cohort study comparing maternal and neonatal outcome in two groups of preterm births. The first group included 299 consecutive singleton preterm births complicated by preterm prelabor rupture of membranes. The second group consisted of 349 consecutive singleton preterm births without preterm prelabor rupture of membranes. Patients with fetal congenital defects and multiple pregnancies were excluded from the study. Data was collected from

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maternal and neonatal records of patients managed in a tertiary referral obstetric center between October 2016 and December 2018. Maternal obstetric history, comorbidities, pregnancy course, cervical microbiome, applied management, and delivery mode were examined. Neonatal outcome analysis included neonate's condition, birth weight, length of hospitalization, management in the Neonatal Intensive Care Unit (NICU), and type of applied treatment.

### Patients' management

Preterm prelabor rupture of membranes was diagnosed with a rapid test detecting insulin-like growth factor binding protein (IGFBP-1) and with ultrasound examination. In case of positive result, expectant management was introduced. Cervical specimen collected on admission was cultured and prophylactic antimicrobial agents were administered. The antimicrobial regimen was established based on the local epidemiological data and consisted of intravenous cefuroxime for 10 days. The medication was adjusted in case of drug allergy or detected antimicrobial resistance. Cervical swabs were repeated every two weeks and further treatment was determined depending on the culture results. If no pathological agents were identified, the antimicrobial treatment was withdrawn after administering the prophylactic dose. Serum inflammatory markers were monitored every 2 days. Amniotic fluid index was measured twice a week.

Both groups — with and without pPROM — were monitored with ultrasound examinations and nonstress tests. In case of contractions before completed 35<sup>th</sup> gestational week, accompanied by normal levels of inflammatory markers and normal nonstress test results, intravenous tocolysis was introduced. Antenatal corticosteroids were administered for better fetal maturation in case of preterm birth.

Premature infants were screened for early onset infections by monitoring of inflammatory markers, blood culture, and general condition. Prophylactic antimicrobial management included ampicillin and gentamicin for 48–72 hours.

### Statistical analysis

Statistical analysis was performed using Statistica 13 (StatSoft. Inc.). T-Student test was used for quantitative data comparison between two groups. Two-sided Fisher's exact test was used for comparison of discrete variables. Logistic regression models were employed for multivariable analysis. P value < 0.05 was considered significant.

## RESULTS

### Maternal characteristics

Results of compared maternal characteristics are presented in Table 1. No differences between patients with pPROM and with intact membranes regarding maternal age, parity, and gestational age were observed. One of the

**Table 1. Maternal characteristics and course of pregnancy in preterm births with and without preterm prelabor rupture of membranes**

Parameter	pPROM (n = 299)	No pPROM (n = 349)	No pPROM without hypertension (n = 240)	No pPROM with hypertension (n = 109)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>	p <sup>4</sup>
Mean age [years]	32.6	31.9	31.5	32.8	0.09	0.01	0.79	0.04
Primigravid	132 (44.1)	162 (46.4%)	107 (44.4%)	55 (50.5%)	0.58	0.93	0.26	0.35
GDMG <sup>1</sup>	45 (15%)	50 (14.3%)	30 (12.4%)	20 (18.3%)	0.82	0.32	0.45	0.16
GDMG <sup>2</sup>	26 (8.7%)	17 (4.9%)	10 (4.1%)	7 (6.4%)	0.058	<b>0.04 RR = 2.09 (0.99–4.57)</b>	0.54	0.42
GDM	71 (23.7%)	67 (19.2%)	40 (16.7%)	27 (24.8%)	0.18	0.053	0.89	0.08
PGDM	20 (6.7%)	31 (8.9%)	16 (6.6%)	15 (13.8%)	0.31	1	<b>0.02 RR = 0.49 (0.25–0.97)</b>	<b>0.04 RR = 2.06 (1–4.23)</b>
Pregnancy-induced hypertension	9 (3%)	55 (15.6%)			<0.001 RR = 0.19 (0.09–0.39)			
Pregestational hypertension	15 (5%)	54 (15.5%)			<0.001 RR = 0.32 (0.18–0.58)			
Preeclampsia	0	41 (11.7%)			<0.001			
Hypothyroidism	58 (19.4%)	100 (28.7%)	70 (29%)	30 (27.5%)	<b>0.008 RR = 0.68 (0.50–0.91)</b>	<b>0.011 RR = 0.67 (0.48–0.91)</b>	0.1	0.8

**Table 1. Maternal characteristics and course of pregnancy in preterm births with and without preterm prelabour rupture of membranes (continued)**

Parameter	pPROM (n = 299)	No pPROM (n = 349)	No pPROM without hypertension (n = 240)	No pPROM with hypertension (n = 109)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>	p <sup>4</sup>
Asthma	9 (3%)	4 (1.2%)	4 (1.7%)	0	0.1	0.4	0.12	0.31
Intrahepatic cholestasis of pregnancy	9 (3%)	18 (5.2%)	13 (5.4%)	5 (4.6%)	0.24	0.19	0.54	1
History of cervical conisation	4 (1.3%)	0	0	0	<b>0.045</b>	0.13	0.58	1
Cervical insufficiency	47 (15.7%)	58 (16.6%)	49 (20.3%)	9 (8.3%)	0.59	0.11	0.1	<b>0.005 RR = 0.4 (0.2–0.81)</b>
Pessary	32 (10.7%)	20 (5.7%)	16 (6.6%)	4 (3.7%)	<b>0.03 RR = 1.87 (1.06–3.33)</b>	0.13	<b>0.03 RR = 2.92 (1.03–9.63)</b>	0.33
Cervical cerclage	10 (3.3%)	16 (4.6%)	15 (6.2%)	1 (0.9%)	0.55	0.15	0.3	<b>0.03 RR = 0.15 (0.01–1.02)</b>
3 <sup>rd</sup> trimester vaginal bleeding	17 (5.7%)	51 (14.6%)	44 (18.3%)	7 (6.4%)	<b>&lt;0.001 RR = 0.39 (0.22–0.67)</b>	<b>&lt;0.001 RR = 0.31 (0.17–0.54)</b>	0.81	<b>0.003 RR = 0.35 (0.15–0.77)</b>
Pathological vaginal microbiome	130 (43.5%)	157 (45%)	108 (44.8%)	49 (45%)	0.75	0.73	0.82	1
Positive amniotic fluid culture <sup>5</sup>	19 (6.4%)	7 (2%)	7 (2.9%)	0	<b>0.008 RR = 3.17 (1.28–8.22)</b>	0.07	<b>0.003</b>	0.1
Suspected intrauterine infection	24 (8%)	16 (4.6%)	14 (5.8%)	2 (1.8%)	0.07	0.4	<b>0.02 RR = 4.38 (1.04–26.7)</b>	0.16
Steroids administration	184 (61.5%)	200 (57.3%)	128 (53.1%)	72 (66%)	0.3	0.07	0.4	<b>0.03 OR = 1.7 (1.06–2.73)</b>
Full prophylactic steroids dose (24 mg) administration followed by birth within 10 days	140 (46.8%)	147 (42%)	90 (37.3%)	57 (52.3%)	0.24	<b>0.04 OR = 1.47 (1.04–2.08)</b>	0.37	<b>0.01 OR = 1.83 (1.16–2.89)</b>
Intravenous tocolysis	105 (35.1%)	83 (23.8%)	74 (30.7%)	9 (8.3%)	<b>0.002 OR = 1.74 (1.23–2.44)</b>	<b>0.31</b>	<b>&lt;0.001 RR = 4.25 (2.22–8.8)</b>	<b>&lt;0.001 RR = 0.29 (0.13–0.52)</b>
Abnormal NST results	48 (16%)	135 (38.7%)	72 (29.9%)	63 (57.8%)	<b>&lt;0.001 OR = 0.3 (0.2–0.44)</b>	<b>&lt;0.001 OR = 0.45 (0.3–0.68)</b>	<b>&lt;0.001 OR = 0.14 (0.09–0.23)</b>	<b>&lt;0.001 OR = 3.2 (2–5.1)</b>
Stillbirth	2 (0.7%)	13 (3.7%)	11 (4.6%)	2 (1.8%)	<b>0.02 RR = 0.18 (0.04–0.78)</b>	<b>0.004 RR = 0.15 (0.03–0.68)</b>	0.29	0.36
Caesarean section	145 (45.2%)	228 (65.3%)	139 (57.7%)	89 (81.7%)	<b>&lt;0.001 OR = 0.5 (0.36–0.69)</b>	<b>0.03 OR = 0.68 (0.49–0.96)</b>	<b>&lt;0.001 OR = 0.21 (0.12–0.36)</b>	<b>&lt;0.001 OR = 3.23 (1.87–5.6)</b>
Emergency Caesarean section	41 (13.7%)	138 (39.5%)	76 (31.5%)	62 (56.8%)	<b>&lt;0.001 OR = 0.24 (0.16–0.36)</b>	<b>&lt;0.001 OR = 0.34 (0.22–0.53)</b>	<b>&lt;0.001 OR = 0.12 (0.07–0.2)</b>	<b>&lt;0.001 OR = 2.85 (1.79–4.54)</b>
Mean gestational age at birth [weeks + days]	33 + 4	32 + 6	32 + 5	33+0	0.2	0.48	0.1	0.48
Birth before completed 34 <sup>th</sup> gestational week	98 (32.8%)	135 (38.7%)	91 (37.8%)	44 (40.4%)	0.12	0.24	0.16	0.72
Birth after completed 34 <sup>th</sup> gestational week	201 (67.2%)	214 (61.3%)	150 (62.2%)	65 (59.6%)	0.12	0.24	0.16	0.72

pPROM — preterm prelabour rupture of membranes; p<sup>1</sup> — statistical significance concerning comparison between all patients with pPROM and all patients without pPROM; p<sup>2</sup> — statistical significance concerning comparison between all patients with pPROM and patients without pPROM but suffering from hypertension; p<sup>3</sup> — statistical significance concerning comparison between patients with and without hypertension among the group with no pPROM; p<sup>4</sup> — statistical significance concerning comparison between patients with and without hypertension among the group with pPROM; GDMG1 — gestational diabetes mellitus treated with diet; GDMG2 — gestational diabetes mellitus treated with insulin; RR — risk ratio; PGDM — pregestational diabetes mellitus; <sup>5</sup>Only the amniotic fluid collected during Caesarean sections was cultured; OR — odds ratio; NST — nonstress test

**Table 2.** Vaginal microbiome detected in patients from the pPROM and no pPROM group

Pathogen	With pPROM n (%)	Without pPROM n (%)	p
Positive culture	130 (43.5)	157 (45)	0.8
<i>E. coli</i>	43 (14.4)	42 (12)	0.4
<i>S. agalactiae</i>	39 (13)	58 (16.6)	0.2
<i>C. albicans</i>	31 (10.4)	48 (13.8)	0.2
<i>P. bivia</i>	19 (6.4)	19 (5.4)	0.7
<i>E. faecalis</i>	17 (5.7)	14 (4)	0.4
<i>G. vaginalis</i>	7 (2.3)	9 (2.6)	1
<i>K. pneumoanie</i>	5 (1.7)	5 (1.4)	1
<i>E. cloacae</i>	3 (1)	3 (0.9)	1
<i>Ureaplasma</i>	3 (1)	6 (1.7)	0.5
<i>P. melanogenica</i>	2 (0.7)	0	0.2
<i>S. pyogenes</i>	2 (0.7)	0	0.2
<i>B. fragilis</i>	1 (0.3)	0	0.5
<i>B. ovatus</i>	1 (0.3)	0	0.5
<i>C. crusei</i>	1 (0.3)	0	0.5
<i>C. glabrata</i>	1 (0.3)	4 (1.1)	0.4
<i>C. lusitaniae</i>	1 (0.3)	1 (0.3)	1
<i>C. freundii</i>	1 (0.3)	0	0.5
<i>C. krosei</i>	1 (0.3)	1 (0.3)	1
<i>H. influenzae</i>	1 (0.3)	0	0.5
<i>P. mirabilis</i>	1 (0.3)	0	0.5

most relevant differences regarded the occurrence of hypertensive disorders — 24 (8%) patients in the pPROM group and 109 (31%) in the second group ( $p < 0.001$ ). Therefore, additional subgroups in the no pPROM group were analyzed depending on the hypertensive status in order to avoid bias resulting from different hypertensive disorders incidence between pPROM and no pPROM group [5].

Patients with pPROM more frequently had undergone cervical conization in the past (1.3% vs 0;  $p = 0.045$ ). Obstetric pessary had been also more often used during earlier stages of pregnancies complicated by pPROM (10.7% vs 5.7%;  $p = 0.03$ ). Occurrence of cervical insufficiency and treatment with cervical cerclage was similar in both pPROM and no pPROM groups. Gestational diabetes treated with insulin occurred more frequently in the pPROM group compared to no pPROM, no hypertension group ( $p = 0.04$ ). Hypothyroidism (28.7% vs 19.4%;  $p = 0.008$ ), 3<sup>rd</sup> trimester vaginal bleeding (14.6% vs 5.7%;  $p < 0.001$ ), and stillbirth (3.7% vs 0.7%;  $p = 0.02$ ) were more frequent in the preterm pregnancies without pPROM. No differences between pPROM and no pPROM groups regarding the incidence of gestational diabetes treated with diet, asthma, and intrahepatic cholestasis of pregnancy were identified.

Similarly, no statistically relevant differences in the cervical microbiome among two groups were detected. Both

the occurrence of positive culture result and the microbiome composition were comparable. Detected pathogens included *E. coli*, *S. agalactiae*, *C. albicans*, *P. bivia*, *E. faecalis*, *G. vaginalis*, *K. pneumoanie*, *E. cloacae*, *Ureaplasma*, *P. melanogenica*, *S. pyogenes*, *B. fragilis*, *B. ovatus*, *C. crusei*, *C. glabrata*, *C. lusitaniae*, *C. freundii*, *C. krosei*, *H. influenzae*, and *P. mirabilis*. Detailed information on the microbiome is presented in Table 2.

### Management during pregnancy

Distribution of antenatal corticosteroids administration was similar in both groups. However, a difference was identified concerning administration of full prophylactic dose followed by birth within ten days. Patients with pPROM more often received full prophylaxis (46.8%) than patients with preterm birth uncomplicated by pPROM nor hypertension (37.3%) ( $p = 0.04$ ). Intravenous tocolysis (fenoterol, atosiban) was more frequently required and administered in the pPROM patients (35.1% vs 23.8%;  $p = 0.002$ ). Monitoring with the nonstress test resulted in detection of significantly more abnormalities in patients without pPROM than with the amniotic fluid leakage (38.7% vs 16%;  $p < 0.001$ ).

### Mode of delivery

No statistically significant differences regarding the gestational age during delivery were identified.

Patients without pPROM more often underwent Caesarean sections than women from the pPROM group (65.3% vs 45.2%;  $p < 0.001$ ). The difference between emergency Cesarean section was even higher. Almost 40% of patients from the no pPROM group underwent emergency Cesarean section — 31.5% in the hypertension negative subgroup and 56.8% in the hypertension positive subgroup. The high Cesarean section rate resulted from high number of medically indicated preterm deliveries in this group.

Every patient undergoing a Cesarean section had her amniotic fluid collected and cultured. Results showed more frequent prevalence of positive amniotic fluid culture in the pPROM group (6.4%) than in the second group (2%) ( $p = 0.008$ ).

### Birth weight

There was a difference regarding mean birth weight, prevalence of small for gestational age under 10<sup>th</sup> percentile (2.7% in pPROM group vs 8.9% in no pPROM group;  $p = 0.001$ ); extremely low birth weight between 750 and 1000 g (4.3% in pPROM group vs 8.6% in no pPROM group;  $p = 0.04$ ), and incredibly low birth weight under 750 g (2.7% in pPROM group vs 8.3% in no pPROM group;  $p = 0.002$ ). Lower birth weight was detected in the group with no history of pPROM ( $p < 0.001$ ). The Ponderal index was not significantly different, however lower values were observed in the pPROM group and the no pPROM hypertension positive subgroup (Tab. 3).

**Table 3. Neonatal outcome in preterm births with and without preterm prelabour rupture of membranes**

Parameter	pPROM (n = 299)	No pPROM (n = 349)	No pPROM without hypertension (n = 240)	No pPROM with hypertension (n = 109)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>	p <sup>4</sup>
Female infants	114 (38.1%)	150 (43%)	105 (43.6%)	45 (41.3%)	0.23	0.22	0.57	0.73
1 <sup>st</sup> minute Apgar score between 8–10	225 (73.5%)	212 (60.7%)	147 (61%)	65 (59.6%)	<0.001 OR = 1.97 (1.4–2.76)	0.001 OR = 1.92 (1.33–2.78)	0.003 OR = 2.06 (1.3–3.27)	0.81
1 <sup>st</sup> minute Apgar score between 4–7	56 (18.7%)	92 (26.4%)	54 (22.4%)	38 (34.9%)	0.02 OR = 0.64 (0.44–0.94)	0.3	0.001 OR = 0.43 (0.26–0.7)	0.02 OR = 1.84 (1.12–3.03)
1 <sup>st</sup> minute Apgar score between 0–3	10 (3.3%)	45 (12.9%)	39 (16.2%)	6 (5.5%)	<0.001 RR = 0.26 (0.12–0.52)	<0.001 RR = 0.18 (0.09–0.37)	0.39	0.005 RR = 0.34 (0.13–0.8)
3 <sup>rd</sup> minute Apgar score between 8–10	229 (76.6%)	231 (66.2%)	155 (64.3%)	76 (69.7%)	0.004 OR = 1.67 (1.18–2.37)	0.003 OR = 1.8 (1.23–2.61)	0.16	0.4
3 <sup>rd</sup> minute Apgar score between 4–7	55 (18.4%)	87 (24.9%)	57 (23.7%)	30 (27.5%)	0.046 OR = 0.68 (0.46–0.99)	0.14	0.054	0.51
3 <sup>rd</sup> minute Apgar score between 0–3	7 (2.3%)	31 (8.9%)	28 (11.6%)	3 (2.8%)	<0.001 RR = 0.26 (0.11–0.57)	<0.001 RR = 0.26 (0.08–0.47)	0.73	0.007 RR = 0.23 (0.06–0.78)
5 <sup>th</sup> minute Apgar score between 8–10	248 (82.9%)	256 (73.4%)	168 (69.7%)	88 (80.7%)	0.004 OR = 1.77 (1.2–2.6)	<0.001 OR = 2.08 (1.39–3.14)	0.66	0.04 OR = 1.8 (1.04–3.11)
5 <sup>th</sup> minute Apgar score between 4–7	39 (13%)	65 (18.6%)	47 (19.5%)	18 (16.5%)	0.07	0.044 OR = 0.62 (0.39–0.98)	0.42	0.56
5 <sup>th</sup> minute Apgar score between 0–3	5 (1.7%)	27 (7.7%)	25 (10.4%)	2 (1.8%)	<0.001 RR = 0.22 (0.07–0.58)	<0.001 RR = 0.16 (0.05–0.43)	1	0.004 RR = 0.18 (0.03–0.74)
10 <sup>th</sup> minute Apgar score between 8–10	258 (83.6%)	274 (78.5%)	180 (74.7%)	94 (86.2%)	0.01 OR = 1.72 (1.14–2.61)	0.001 OR = 2.1 (1.35–3.26)	1	0.02 OR = 2.09 (1.13–3.88)
10 <sup>th</sup> minute Apgar score between 4–7	29 (9.7%)	51 (14.6%)	48 (15.8%)	13 (11.9%)	0.07	0.001 RR = 0.49 (0.31–0.76)	0.58	0.07
10 <sup>th</sup> minute Apgar score between 0–3	4 (1.3%)	24 (6.9%)	22 (9.1%)	2 (1.8%)	<0.001 RR = 0.2 (0.06–0.58)	<0.001 RR = 0.15 (0.04–0.44)	0.66	0.01 RR = 0.2 (0.03–0.84)
Mean infant's hospitalization duration [days]	20.4	26.6	25.5	28.8	0.03	0.33	0.02	0.046
NICU admission	76 (25.4%)	108 (30.9%)	68 (28.2%)	40 (36.7%)	0.14	0.5	0.04 OR = 0.59 (0.37–0.94)	0.13
Mean birth weight [g]	2416	2075	2136	1943	<0.001	<0.001	<0.001	0.03
Mean length at birth [cm]	49.4	46.9	47.4	45.8	<0.001	0.006	<0.001	0.007
Mean Ponderal Index at birth	20.3	33.4	39.9	19.7	0.33	0.84	0.07	0.08
LBW <sup>5</sup>	106 (35.5%)	125 (35.8%)	87 (36.1%)	38 (34.9%)	0.94	0.86	1	0.9
VLBW <sup>6</sup>	19 (6.4%)	37 (10.6%)	21 (8.7%)	16 (14.7%)	0.07	0.32	0.02 RR = 0.43 (0.22–0.86)	0.13
ELBW <sup>7</sup>	13 (4.3%)	30 (8.6%)	17 (7%)	13 (11.9%)	0.04 RR = 0.51 (0.25–0.99)	0.2	0.01 RR = 0.37 (0.16–0.81)	0.15

Table 3. Neonatal outcome in preterm births with and without preterm prelabour rupture of membranes (continued)

Parameter	pPROM (n = 299)	No pPROM (n = 349)	No pPROM without hypertension (n = 240)	No pPROM with hypertension (n = 109)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>	p <sup>4</sup>
ILBW <sup>6</sup>	8 (2.7%)	29 (8.3%)	21 (8.7%)	8 (7.3%)	<b>0.002 RR = 0.32 (0.13-0.71)</b>	<b>0.003 RR = 0.31 (0.13-0.71)</b>	<b>0.04 RR = 0.37 (0.13-1.05)</b>	0.84
Small for gestational age	8 (2.7%)	31 (8.9%)	17 (7%)	21 (19.3%)	<b>0.001 RR = 0.3 (0.13-0.67)</b>	<b>0.02 RR = 0.39 (0.15-0.9)</b>	<b>&lt;0.001 RR = 0.14 (0.06-0.32)</b>	<b>0.001 RR = 2.72 (1.43-5.2)</b>
Early onset sepsis	23 (7.7%)	31 (8.9%)	23 (9.5%)	8 (7.3%)	0.67	0.44	1	0.55
Late onset sepsis	14 (4.7%)	31 (8.9%)	19 (7.9%)	12 (11%)	<b>0.04 RR = 0.53 (0.27-1)</b>	0.15	<b>0.04 RR = 0.43 (0.19-0.96)</b>	0.42
Pneumonia	13 (4.3%)	22 (6.3%)	15 (6.2%)	7 (6.4%)	0.2	0.34	0.44	1
Adaptive breathing disorders	72 (24%)	83 (23.8%)	55 (22.8%)	28 (25.7%)	1	0.76	0.8	0.59
Pneumothorax	6 (2%)	6 (1.7%)	2 (0.8%)	4 (3.7%)	1	0.31	0.47	0.08
Broncho-pulmonary dysplasia	20 (6.7%)	30 (8.6%)	24 (9.6%)	6 (5.5%)	0.4	0.2	0.82	0.22
Respiratory distress syndrome	38 (12.7%)	70 (20%)	47 (19.5%)	23 (21.1%)	<b>0.02 OR = 0.58 (0.38-0.89)</b>	<b>0.03 OR = 0.6 (0.38-0.95)</b>	<b>0.04 OR = 0.54 (0.31-0.97)</b>	0.77
Pulmonary hypoplasia	2 (0.7%)	0	0	0	0.21	0.51	1	
Pulmonary hypertension	12 (4%)	5 (1.4%)	3 (1.2%)	2 (1.8%)	<b>0.049 RR = 2.8 (0.93-9.05)</b>	0.07	0.37	0.66
Respiratory failure <sup>9</sup>	77 (25.8%)	141 (40.4%)	94 (39%)	47 (43.1%)	<b>&lt;0.001 OR = 0.51 (0.37-0.72)</b>	<b>0.001 OR = 0.67 (0.51-0.85)</b>	<b>0.001 OR = 0.46 (0.29-0.72)</b>	0.56
Circulatory failure	20 (6.7%)	24 (6.9%)	16 (6.6%)	8 (7.3%)	1	1	0.83	0.82
Death	6 (2%)	16 (4.6%)	10 (4.1%)	6 (5.5%)	0.08	0.2	0.09	0.59
Hyperbilirubinemia	182 (60.1%)	180 (51.6%)	122 (50.6%)	58 (53.2%)	<b>0.02 OR = 1.46 (1.07-2)</b>	<b>0.02 OR = 1.5 (1.07-2.12)</b>	0.17	0.73
Anaemia	49 (16.4%)	102 (29.2%)	64 (26.6%)	38 (34.9%)	<b>&lt;0.001 OR = 0.48 (0.32-0.7)</b>	<b>0.004 OR = 0.54 (0.35-0.82)</b>	<b>&lt;0.001 OR = 0.37 (0.22-0.6)</b>	0.13
Hypoglycaemia	51 (17.1%)	47 (13.5%)	26 (10.8%)	21 (19.3%)	0.23	<b>0.047 OR = 1.7 (1.02-2.8)</b>	0.66	<b>0.04 OR = 1.96 (1.05-3.67)</b>
Intraventricular haemorrhage	20 (6.7%)	44 (12.6%)	30 (12.4%)	14 (12.8%)	<b>0.01 RR = 0.53 (0.3-0.9)</b>	<b>0.03 RR = 0.54 (0.3-0.95)</b>	0.07	1
Necrotizing enterocolitis	5 (1.7%)	12 (3.4%)	7 (2.9%)	5 (4.6%)	0.23	0.39	0.14	0.53
Retinopathy	7 (2.3%)	22 (6.3%)	16 (6.6%)	6 (5.5%)	<b>0.02 RR = 0.37 (0.15-0.9)</b>	<b>0.02 RR = 0.35 (0.13-0.9)</b>	0.1	0.8
nCPAP <sup>10</sup>	100 (33.4%)	141 (40.4%)	88 (36.5%)	53 (48.6%)	0.07	0.47	<b>0.006 OR = 0.53 (0.34-0.83)</b>	<b>0.045 OR = 1.64 (1.03-2.59)</b>
Mechanical ventilation	46 (15.4%)	69 (19.9%)	49 (20.3%)	20 (18.3%)	0.15	0.17	0.54	0.77
Parenteral nutrition	88 (29.4%)	138 (39.5%)	86 (35.7%)	52 (47.7%)	<b>0.008 OR = 0.64 (0.46-0.89)</b>	0.1	<b>0.001 OR = 0.46 (0.29-0.72)</b>	<b>0.044 OR = 1.63 (1.03-2.59)</b>

pPROM — preterm prelabour rupture of membranes; p<sup>1</sup> — statistical significance concerning comparison between all patients with pPROM and all patients without pPROM; p<sup>2</sup> — statistical significance concerning comparison between all patients with pPROM and patients without pPROM but suffering from hypertension; p<sup>3</sup> — statistical significance concerning comparison between patients with and without hypertension among the group with no pPROM; OR — odds ratio; RR — risk ratio; <sup>1</sup>LBW — low birth weights; <sup>6</sup>VLBW — very low birth weights; <sup>9</sup>ELBW — extremely low birth weight; <sup>10</sup>LBW — incredibly low birth weight; <sup>10</sup>Defined as persistent hypoxaemia or hypercapnia despite surfactant therapy and "maximal" conventional ventilation, includes both patients with severe adaptive breathing disorders and with respiratory distress syndrome; <sup>10</sup>treatment with neonatal Continuous Positive Airway Pressure



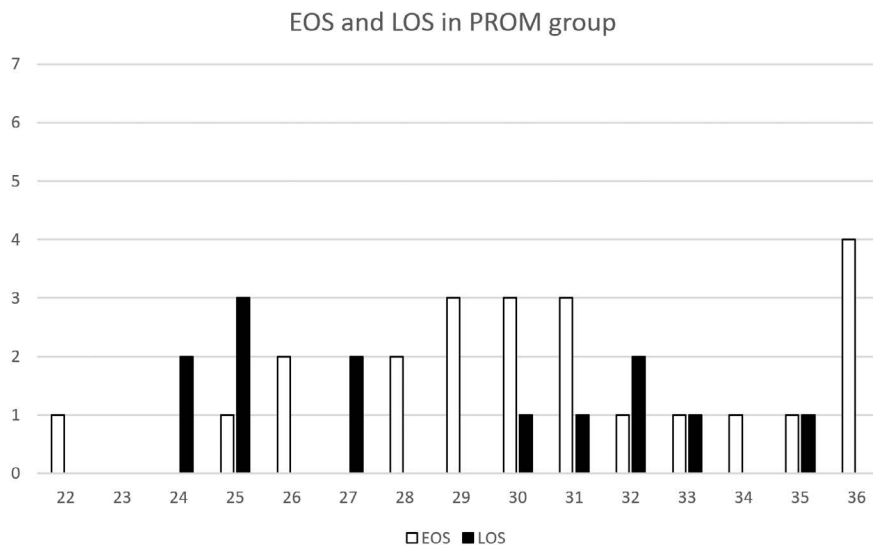
### Infections

On the basis of the nonstress test (fetal tachycardia), elevated maternal body temperature, maternal heart rate and inflammatory markers, patients with pPROM were more often suspected of developing intrauterine infections (8%) compared to the no pPROM group (4.6%), however this difference was not statistically significant ( $p = 0.07$ ). This observation did not correspond with the results of early or late-onset sepsis rates in the neonates. No differences regarding early-onset sepsis were identified and higher percentage of late-onset infections was observed in infants with no history of pPROM (8.9% vs 4.7%;  $p = 0.04$ ) (Tab. 3). The largest difference was observed between infants of patients with pPROM and patients without pPROM but

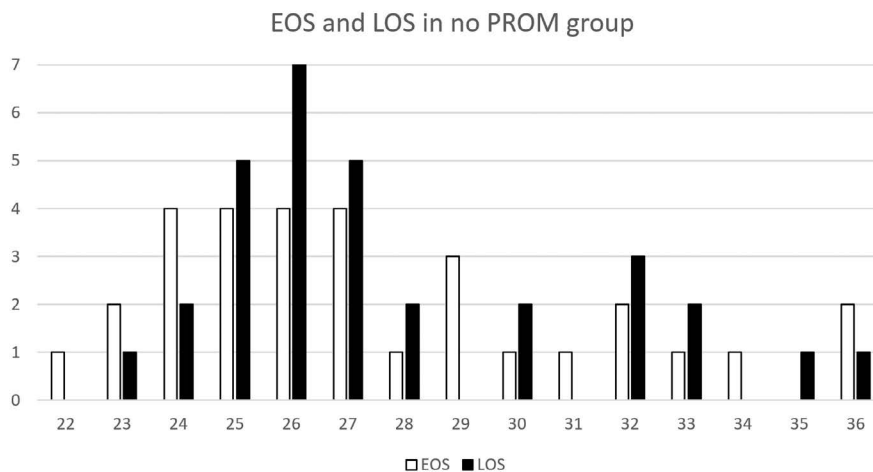
with hypertension (4.7% vs 11%). Figures 1 and 2 show the distribution of early and late-onset sepsis depending on the gestational week at birth and pPROM status. No difference in gestational age at birth among mentioned subgroups were identified.

### Neonatal respiratory complications

Pulmonary hypertension was more common in the infants from the pPROM group (4% vs 1.4%;  $p = 0.049$ ). Surprisingly, the distribution of other respiratory complications was similar between the groups or higher in the group with no history of pPROM (Tab. 3). Identified statistically significant differences regarded the occurrence of respiratory failure, which was defined as persistent hypoxemia or hypercap-



**Figure 1.** Occurrence of early onset sepsis and late-onset sepsis in the pPROM group depending on the gestational week at birth



**Figure 2.** Occurrence of early onset sepsis and late-onset sepsis in the no pPROM group depending on the gestational week at birth

nia despite surfactant therapy and “maximal” conventional ventilation and included both patients with severe adaptive breathing disorders and with respiratory distress syndrome. This condition affected over 40% of infants in the no pPROM group and 25.8% of infants from the pPROM group ( $p < 0.001$ ). Neonatal respiratory distress syndrome was also more prevalent in case of no pPROM history (20% vs 12.7%;  $p = 0.02$ ). The prevalence of neonatal respiratory distress syndrome in both pPROM and no pPROM groups depending on the gestational age at birth is presented in Figure 3 and Figure 4. No statistically significant differences in occurrence of pulmonary hypoplasia, bronchopulmonary dysplasia, use of neonatal continuous positive airway pressure (nCPAP) nor mechanical ventilation between the pPROM and no pPROM group during the observation time were detected.

### Other neonatal complications

Preterm neonates of patients without pPROM obtained more frequently lower Apgar score results, more often developed intraventricular hemorrhage ( $p = 0.01$ ), retinopathy ( $p = 0.02$ ), and anemia ( $p < 0.001$ ), required longer infant’s hospitalization ( $p = 0.03$ ), and parenteral nutrition ( $p = 0.008$ ) (Tab. 3). Hyperbilirubinemia was more frequently diagnosed in the pPROM group ( $p = 0.02$ ). Figures 5 and 6 show the distribution of neonatal complications depending on the gestational age at birth.

### Multivariable analysis

In the bi-variable logistic regression models pPROM was not associated with the occurrence of early-onset sepsis or the late-onset sepsis after adjustment for ges-

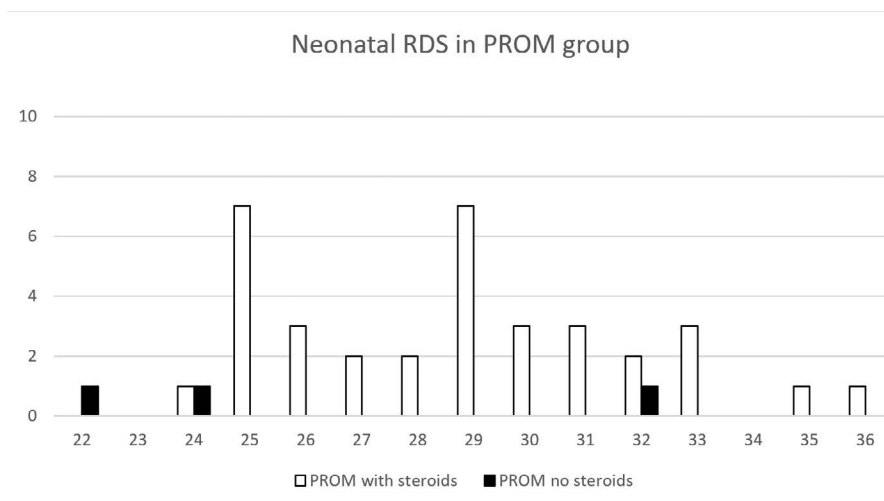


Figure 3. Neonatal Respiratory Distress Syndrome in the pPROM group depending on the gestational week at birth

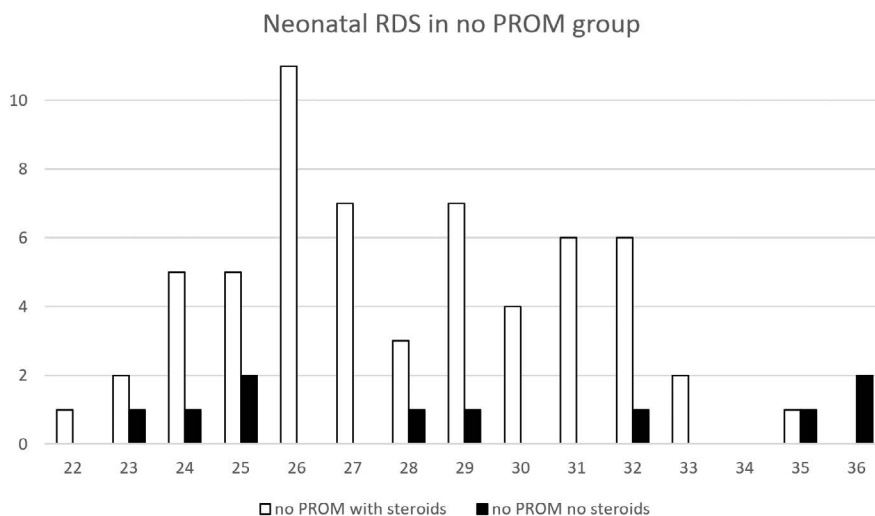


Figure 4. Neonatal Respiratory Distress Syndrome in the no pPROM group depending on the gestational week at birth



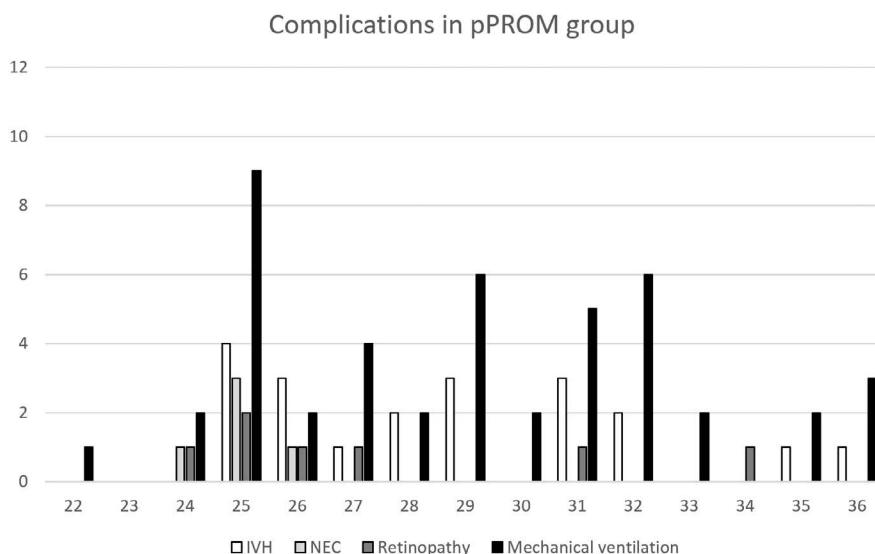


Figure 5. Occurrence of neonatal complications in the pPROM group depending on the gestational week at birth

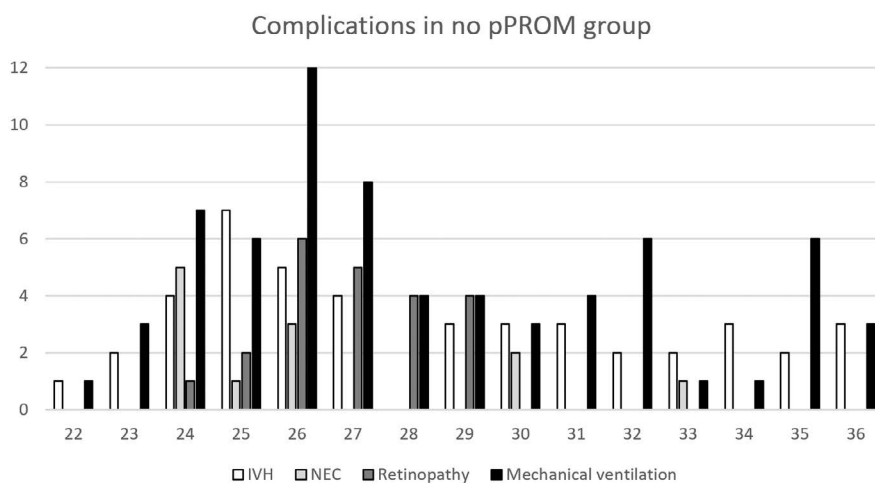


Figure 6. Occurrence of neonatal complications in the no pPROM group depending on the gestational week at birth

tational age at birth ( $p < 0.001$ ) or lower birth weight ( $p < 0.001$ ).

Similarly, the occurrence of the respiratory distress syndrome was independent from pPROM after adjustment for gestational age at birth ( $p < 0.001$ ) or lower birth weight ( $p < 0.001$ ).

PPROM occurrence was associated with reduced probability of respiratory failure (odds ratio 0.44 with 95% confidence interval 0.29–0.66;  $p < 0.001$ ) even after adjustment for gestational age at birth ( $p < 0.001$ ).

### DISCUSSION

Certain differences regarding maternal comorbidities and past medical history, pregnancy course, delivery mode,

and neonatal complications between patients giving birth before term with pPROM and with intact membranes, were identified in this study.

The largest difference in maternal comorbidities was observed in case of the prevalence of pregnancy-induced hypertension (3% vs 15.6%), pregestational hypertension (5% vs 15.5%), and preeclampsia (0 vs 11.7%), which were less common in the pPROM group. Analogous results were reported by other authors: 5.8% vs 7.6% of hypertensive disorders in the Bouvier et al. study [6] and 14.5% vs 52% of pregnancy-induced hypertension incidence in the pPROM and control groups described by Dannapaneni et al. [7]. Similarly, Pharande et al. observed lower prevalence of hypertensive disease of pregnancy in patients with pPROM

than with the intact membranes (7.6% vs 26.7%) [8]. Hypothyroidism was also more prevalent in the group without pPROM (19.4% vs 28.7%), which stands in contrast to results of other studies. In a systematic review by Maraka et al., the pooled relative risk of prelabor rupture of membranes in women with subclinical hypothyroidism was 1.43% according to data from six randomized trials and cohort studies [9]. In a prospective cohort study by Johnson et al. patients with subclinical hypothyroidism presented significantly more frequent history of pPROM (13%) compared to euthyroid women (1.4%) [10]. However, most studies indicate association between hypothyroidism and increased risk of prematurity, which might explain different proportions in our study focusing exclusively on the analysis of patients with preterm births [11]. Bouvier et al. emphasized the meaning of gestational diabetes in possible pathogenesis of pPROM due to sterile inflammation as they reported both higher rates of gestational diabetes and insulin intake in the pPROM group [6]. Our results confirm these findings only partially as insulin intake was more common among patients with pPROM (8.7%) than among the subgroup without pPROM and without hypertension (4.1%). No other significant differences in gestational diabetes incidence were observed.

Analyzed past medical history included treatment for cervical intraepithelial lesion (CIN) before pregnancy. In a systematic review based on 21 observational studies, the relative risk of pPROM was enhanced in these women (RR 2.36) [12]. Our results confirm this statement as the incidence of conization before gestation was more frequent in the pPROM group. In a recent study by Maina et al. the incidence of pPROM among patients with the history of excisional treatment was also increased (13.13% vs 2.71%) [13]. Another analyzed factor was cervical insufficiency in current pregnancy. Differences in cervical insufficiency and treatment with cervical cerclage were not significant, but the positive history of pessary application in current pregnancy was higher in the pPROM group.

Gestational age at birth did not differ between the groups. However, the group without pPROM was characterized by lower birth weight, higher occurrence of small for gestational age, extremely low birth weight, and incredibly low birth weight. These differences were still significant after subgroup analysis with the consideration of hypertensive disorders distribution. This was not observed in the Pharande et al. study, but comparable results were obtained by other authors [8, 14].

Pathological cervical microbiome was detected in 43.5% patients with pPROM and 45% without pPROM. In a study by Swiatkowska-Freund et al. the incidence of positive cervical swabs in the pPROM group was 49% [15]. As the prevalence concerns almost half of the patients, these results support introduction of standard antimicrobial prophylaxis

as prevention of ascending infection route due to ruptured membranes. In this study mentioned prophylaxis was introduced in every patient with pPROM on admission or after pPROM occurrence during earlier hospitalization. Combined with strict monitoring of maternal inflammation parameters and fetal well-being, this early antimicrobial intervention, adjusted when needed after the antibiogram results analysis, could be the reason that the early onset-sepsis (EOS) rates were similarly distributed among the groups with and without pPROM (7.7% vs 8.9%). Similar observations regarding prophylaxis utility can be made based on other studies, in which antimicrobial prophylaxis was introduced in less than 50% or in over 80% of patients and the rates of EOS cases strongly varied [8, 15]. What is more, in a study by Hanke et al., it was proved in a multivariable logistic regression that pPROM is not an independent risk factor for EOS in infants with extremely low birth weight [16]. The proportion of infants exposed to prenatal antibiotic treatment in this study exceeded 80%. The number of neonates exposed to tocolytic treatment of mothers was also relatively high (68.1%) and higher than in the control group. Concerning the low EOS rate and more frequent use of intravenous tocolysis in patients with pPROM than with the intact membranes, our results are consistent with other studies reporting administration of intravenous tocolysis in pPROM [16, 17].

The occurrence of late-onset sepsis (LOS) in our study was higher in the group of premature infants without the history of pPROM. The association between LOS incidence, pPROM occurrence, gestational age at birth and birth weight were examined in a multivariable analysis in order to determine LOS risk factors. Eventually, no relation between LOS incidence and pPROM was observed. This indicates more relevant factors associated with LOS other than pPROM. As the mean hospitalization duration of infants from the no pPROM group was significantly longer, it is possible that the risk of LOS depends on the number of required neonatal procedures and time of observation under strict medical supervision.

Regarding the incidence of neonatal respiratory complications, our study showed increased risk of pulmonary hypertension in the pPROM group. As patients with fetal congenital defects were excluded from the study, this result does not represent pulmonary hypertension caused by diagnosed congenital heart disease. This result is also compatible with other studies reporting compromised lung development due to oligohydramnios [8, 18, 19]. Pulmonary hypertension is also associated with prematurity and its treatment side effects e.g. by mechanisms including ventilator-induced lung injury and oxidant stress [20]. On the contrary, the incidence of respiratory distress syndrome (RDS) and respiratory failure was higher in the group with

intact membranes (12.7% vs 20% and 25.8% vs 40.4%, respectively). This result could be associated with lower birth weight and increased cesarean section rate (45.2% vs 65.3%) including emergency cesarean sections (13.7% vs 39.5%) in the group without pPROM [21, 22]. Administration of antenatal corticosteroids, including the full prophylactic dose was comparable between the groups (46.8% vs 42%). Multivariable analysis confirmed higher incidence of RDS associated with lower birth weight and earlier gestational age at birth.

## CONCLUSIONS

Development of multiple complications in preterm neonates, including sepsis and respiratory complications, may be more associated with the management, gestational age, and birth weight than with the occurrence of preterm prelabor rupture of membranes.

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