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Neonatal outcomes and risk of neonatal sepsis in an expectantly managed cohort of late preterm prelabor rupture of membranes

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ABSTRACT

Objective: Expectant management in patients with prelabor preterm rupture of membranes between between $34^{0/7}$ and $36^{6/7}$ weeks (late preterm pPROM or LpPROM) has been shown to decrease the burden of prematurity, when compared to immediate delivery. As the severity of prematurity depends on gestational age (GA) at PROM, and PROM to delivery interval, we first investigated how such variables affect neonatal outcomes (NO). Second, we assessed the risk of neonatal sepsis.
Study design: retrospective cohort study on neonatal morbidity among singleton infants born to expectantly managed mothers with LpPROM in five hospitals affiliated with three Italian academic institutions. The primary NO was a composite of neonatal death, non-invasive (cPAP) or invasive (mechanical ventilation) respiratory support, hypoglycemia (< 44 mg/dl needing therapy), newborn sepsis, confirmed seizures, stroke, intraventricular hemorrhage (IVH), basal nuclei anomalies, cardiopulmonary resuscitation, umbilical-cord-blood arterial pH < 7.0 or base excess < -12.5, and prolonged hospitalization (≥ 5 days). Univariate analysis described differences in the population according to GA at delivery. Multivariate logistic regression was then used to investigate the effects of GA at PROM, and PROM to delivery interval on the NO.
Results: 258/606 (42.6 %) women with LpPROM were expectantly managed, as they did not deliver within the first 24 h. The median latency duration was 2 (95 %CI 1–3) days, having no effect on neonatal morbidity on multivariate analysis. Multivariate analysis also showed increased risks of adverse NO among PROM at 34 (OR 2.3 95 %CI 1.03–5.1) but not at 35 weeks when compared to 36 weeks, and among women receiving antenatal corticosteroids (OR 3.6 95 %CI 1.3–9.7), while antibiotic treatment showed a non-significant protective effect (OR 0.2 95 %CI 0.04–1.02). Prevalence of neonatal sepsis was 0.8 % (2/258)
Conclusion: Expectant management of LpPROM should be encouraged especially between 34^{+0} and 34^{+6} weeks', when the burden of prematurity is the greatest. Antibiotics may have beneficial effects, while careful consideration should be given to antenatal corticosteroids until future studies specifically address LpPROM.

Introduction

Late preterm (LP) prelabor rupture of membranes (i.e rupture of membranes before the onset of labor between $34^{0/7}$ and $36^{6/7}$ weeks of gestation, or LpPROM) is responsible for approximately 60.000–120.000 deliveries/years in Europe, given a LP birth rate of 3–6% [1,2]

For years LpPROM was considered as an indication to proceed towards delivery, balancing the risks of intraamniotic infection and neonatal sepsis with relative low risks of prematurity [3], until research showed increased rates of adverse neonatal outcomes (NO) in LP births [4]. A large 2016 randomized controlled trial (RCT) evaluating immediate delivery versus expectant management in patients with LpPROM demonstrated lower respiratory distress

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syndrome rates and mechanical ventilation among newborns from expectantly managed patients, without a significant increase in neonatal sepsis or morbidity [2]. A 2018 individual patient data meta-analysis on 3 RCTs also confirmed these results [5]. Therefore, in 2020 the American College of Obstetricians and Gynecologists (ACOG) suggested that care of LpPROM should be individualized through shared decision-making, as both expectant management or immediate delivery are reasonable options, and that the balance between benefit and risk should be carefully considered and discussed with patients. Given the new evidence, in 2020 Italian guidelines were also changed to recommend expectant management of LpPROM as inpatients, granting adequate maternal and fetal surveillance [6].

However, the use of antibiotics to prolong latency and antenatal corticosteroids (ACS) to reduce respiratory morbidity among expectantly managed LpPROM is a matter of discussion. None of the RCTs investigating expectant management systematically utilized antibiotics to prolong latency [2,7–9]. Reduced neonatal respiratory morbidity was shown when a single course of ACS was administered to pregnant women in LP period at risk of preterm birth within 7 days, and who had not received a previous course of ACS [10,11]. However, neonatal hypoglycemia was significantly associated with the treatment; furthermore, the long-term effects of ACS in LP is unknown [12], with recent data suggesting potential downsides on mental and behavioral health [13]. Such uncertainties have raised concerns about LP ACS use [12,13], as also shown by a Delphi survey in Italy [14].

As perinatal well-being varies substantially in the LP period according to the GA at delivery, and use of antibiotics as well as ACS is still debated, we sought to study NO in an expectantly managed Italian LpPROM population.

Materials and methods

We conducted a retrospective multicenter cohort study of all patients diagnosed with LpPROM who delivered from July 1st 2015 to December 31st 2019 in hospitals associated with 3 major Italian academic centers: the University of Modena (Modena Policlinico hospital), the University of Florence (Careggi hospital), and the University of Milan (Carate hospital, Lecco hospital, and Monza hospital).

Women with a singleton viable pregnancy were included if they had experienced pPROM between 34^{+0} and 36^{+6} weeks' gestation and were not in labor within 24 h from the diagnosis. Membrane rupture was confirmed by visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a basic pH test of vaginal fluid. When needed, commercially available test for amniotic proteins (Amnioquick ® Biosynex, Amnisure@ Oiagen) were also utilized to confirm pPROM according to local protocols.

Women were not eligible for the study if any contraindication to expectant management arose when PROM was diagnosed, such as active labor, non-reassuring antenatal testing, signs of intrauterine infection, preeclampsia with severe features, HELLP syndrome or placental abruption. Women with multiple pregnancies or antenatal stillbirths were also excluded.

As national guidelines do no standardize management of LpPROM in Italy, antibiotic therapy with a combination of a beta lactam and a macrolide, administration of ACS, and tocolysis were left at the discretion of each study site. Similarly, cultures for vaginal bacterial colonization/infections and urinary tract infections, markers of inflammation/infection such as white cell blood count and reactive C protein were assessed according to local protocols. All women were managed as inpatients from the diagnosis of PROM until delivery, and they received at least twice daily fetal heart rate monitoring.

Medical records were reviewed by research associates to obtain anonymized data on mothers and their newborns, that were organized in a password protected database.

Our primary aim was to investigate if gestational age at PROM, and if the PROM to delivery interval (ultimately affecting time of delivery) impact infants' health in LpPROM population. Infants' health was measured with a composite adverse NO that included one or more of the following: neonatal death, non-invasive (cPAP) or invasive (mechanical ventilation) respiratory support, hypoglycemia (< 44 mg/dl needing therapy), newborn sepsis, confirmed seizures, stroke, IVH, basal nuclei anomalies, cardiopulmonary resuscitation, umbilical-cord-blood arterial pH < 7.0 or base excess < -12.5, and prolonged hospitalization (≥ 5 days). Our secondary aim was to study the risk of neonatal sepsis, defined as a positive culture of a known pathogen from blood or cerebrospinal fluid for which the baby was treated with antibiotics, and the presence of one or more clinical signs of infection, such as respiratory distress requiring support for more than 1 h, apnea, lethargy, abnormal level of consciousness, circulatory compromise (including hypotension, poor perfusion, need for inotropic support, or volume expansion), temperature instability (temperature <36 °C or ≥38 °C). Rupture of membranes was considered as the delivery indication only when the patient and/or her obstetrician opted to terminate expectant management with an elective delivery. If onset of labor occurred during expectant management, spontaneous preterm labor was considered as the delivery indication; instead, if complications prompting delivery (including suspected intraamniotic infection) arose among expectantly managed PROMs, such deliveries were classified as indicated.

Our secondary aim was to study the risk of intraamniotic infection in an expectantly managed pPROM population. According to ACOG, suspected intraamniotic infection (triple I) was defined as maternal fever without a clear source, plus specific clinical criteria. Fever consisted in a single oral temperature of 39 °C or greater, or an oral temperature of 38–38.9 °C that persists after 30 min; clinical criteria included one or more of the following: maternal leukocytosis (WBC > 15.000 per mm^3), purulent cervical drainage, or fetal tachycardia (>160 bpm for 10 min or longer) [3].

As neonatal outcomes strictly depend on the timing of delivery, in the univariate analysis we compared how maternal characteristics, obstetric features, fetal characteristics, and indication to delivery varied with each completed week of gestation at the time of delivery. Categorical variables were presented as n (%) and tested with Chi square test or Fisher's exact test as appropriate. Normally distributed continuous variables were presented as mean ± SD and compared with One Way ANOVA. Non-normally distributed continuous variables were presented as median (IQR) and tested with One Way ANOVA on ranks. A level of statistical significance of $P \leq 0.05$ was considered. Multivariate logistic regression analysis was used to investigate if GA at PROM and PROM to delivery interval could affect the risk of adverse NO, either independently or through an interaction term. Socio-demographic variables, maternal medical complications, bacterial maternal colonization, fetal complications, indication to delivery, delivery route and delivery site were tested as potential confounders.

The strength of the association between the covariates and the dependent variable was estimated as area under the curve of a receiver operating characteristic (ROC) curve plotted with the true-positive rate compared with the false positive rate. Statistical analyses were performed using Stata 15 (StataCorp, College Station, TX).

Approval from the Institution Review Board was obtained (IRB numbers AOU 0,024,477/20).

Results

The study population consisted in 258 pregnancies, as 348 out of 606 (57.4 %) women diagnosed with pPROM between 34^{+0} and 36^{+6} weeks' gestation delivered in the first 24 h (337 due to spontaneous preterm labor, 11 due to indicated deliveries). Table 1 describes the baseline maternal characteristics of study population according to GA at delivery. Most baseline characteristics were similar across study groups. The majority of patients were enrolled at hospitals affiliated with the Universities of Florence and Milan ($p < 0.01$). Pregnancies achieved through assisted reproduction technologies delivered at earlier GAS ($p < 0.01$). Tocolytics and ACS were more commonly administered at earlier gestations ($p < 0.01$), while delivery indications, onset of labor and route of delivery were similar across study groups. Of note, the majority of deliveries were due to spontaneous preterm labor (122/258, 47.7 %), elective deliveries were 112 (43.7 %), while only 22 (8.6 %) were indicated.

As shown in Table 2, women with early PROM delivered at earlier GAs ($p < 0.01$); the median PROM to delivery interval reached a median of only 2 days (95 %CI 1–3) among women delivered at 34 weeks' gestation, dropping to 1 day for later deliveries. The vast majority (247/258, 95.7 %) of our patients received antibiotic treatment, 103/258 (39.9 %) during expectant management while 121 more (46.9 %) during both expectant management and in labor; antibiotics were administered more frequently among women who delivered earlier ($p < 0.01$). The median duration of antibiotic treatment was only 2 days (95 %CI 1–2) in the entire population, dropping to 1 day (95 %CI 1–1) among those delivered at 37 weeks.

No cases of neonatal death or cardiopulmonary resuscitation were observed. As indicated in Table 3, umbilical cord arterial and venous blood gases showed similar pH across different study groups, although the 5 min Apgar score was slightly higher at later GAs ($p < 0.01$). Deliveries later in pregnancy correlated with higher birth weights, shorter NICU stays, and lower rates of the composite adverse NO ($p < 0.01$). Hypoglycemia complicated births prior to 37 weeks' gestation ($p < 0.01$), while the need for respiratory support was similar across different GA groups. No differences in GA at delivery were observed among the 8 women (3.1 %) diagnosed with suspected triple I, and the 2 (0.8 %) neonates diagnosed with sepsis. No cases of maternal sepsis or maternal positive blood cultures were detected.

Multivariate logistic regression showed that while PROM to delivery interval had no impact on NO ($p = 0.5$), rupture of membranes at 34 ($p = 0.04$), but not at 35 ($p = 0.8$) weeks' gestation was associated with worse NO than PROM at 36 weeks (Table 4). Women with PROM receiving ACS had 3.6 higher odds of experiencing adverse outcomes than pregnancies who did not receive the treatment ($p = 0.01$), while antibiotic treatment showed a non-significant trend towards better NO ($p = 0.05$). No interaction was detected between PROM to delivery interval and GA at PROM; similarly, no interactions were found between administration of ACS, and timing of PROM, PROM to delivery interval, or antibiotic treatment respectively.

Discussion

The findings of this large retrospective cohort study confirmed among women with singleton gestations and ruptured membranes between $34^{0/7}$ and $36^{6/7}$ weeks of gestation, that regardless of obstetric management, birth within 1 week of the PROM diagnosis occurs in the majority of patients [3]. Of the 606 initial cases of PROM, 348 (57.4 %) delivered within the first 24 h mainly due to prompt onset of spontaneous labor, leaving 258 (42.6 %) candidates for expectant management. Even in this population delivery occurred not long after PROM, as the median latency period was 1 day (95 %CI 1–2), with the exception of 34 weeks deliveries being 2 days (95 %CI 1–3). Interestingly, besides spontaneous preterm labor (122, 47.7 %) and indicated deliveries (22, 8.6 %), patients and/or obstetricians opted to electively terminate expectant management in nearly half of the cases (112, 43.7 %). Increased maternal satisfaction has been shown with immediate delivery after PROM at term [15]; furthermore, obstetricians may be less comfortable with the risks of placental abruption, ascending infection, and cord prolapse associated with expectant management in a population that historically has been considered at low risk of prematurity. Due to the short time to delivery interval, GA at PROM was the main determinant of GA at delivery, and it was therefore found to be inversely associated with neonatal morbidity on multivariate analysis: as PROM at 34 weeks was associated with worse NO, expectant management may be particularly advantageous between 34^{+0} and 35^{+0} weeks. Finally, our cohort is representative of the LP population: adverse respiratory outcomes were comparable to the ones detected in the UK population (11.8 %) and to our previous report [24,25].

Table 1
Baseline maternal characteristics of women with late preterm PROM according to gestational age at delivery.

	34 w (34)	35 w (65)	36 w (135)	37 w (24)	Total (258)	P
Hospital						< **0.01**
Careggi	20 (58.8 %)	29 (44.6 %)	53 (39.2 %)	0	102 (39.5 %)	
Carate-Lecco-Monza	12 (35.3 %)	29 (44.6 %)	60 (44.4 %)	16 (66.7 %)	117 (45.3 %)	
Modena	2 (5.9 %)	7 (10.8 %)	22 (16.4 %)	8 (33.3 %)	39 (15.2 %)	
Non Caucasian	8 (24.2 %)	6 (9.2 %)	17 (12.7 %)	41(4.1 %)	32 (12.5 %)	0.1
Maternal age	33.5 ± 6.5	32.5 ± 6.6	32.8 ± 5.6	32.6 ± 5.6	32.8 ± 5.9	0.8
Pre pregnancy BMI	23.7 ± 5	23.3 ± 5	23 ± 4.7	24.5 ± 4.3	23.3 ± 4.8	0.5
Nulliparity	25/29 (86.2 %)	48/52 (92.3 %)	100/114 (87.7 %)	16/21 (76.2 %)	189/216 (87.5 %)	0.3
Previous Spontaneous Preterm Birth	3/29 (10.3 %)	1/52 (1.9 %)	7/114 (6.1 %)	0/21	11/216 (5%)	0.2
Prior Cesarean Delivery	5 (15.7 %)	6 (9.2 %)	10 (7.4 %)	2 (8.3 %)	23 (8.9 %)	0.6
ART (assisted reproductive technologies)	4 (11.8 %)	10 (15.4 %)	4 (3%)	0	18 (6.7 %)	<**0.01**
Cholestasis	0	1 (1.5 %)	3 (2.2 %)	0	4 (1.6 %)	0.7
Hypertensive disorders	2 (5.9 %)	2 (3.1 %)	5 (3.7 %)	0	9 (3.5 %)	0.5
Diabetes	11 (32.3 %)	11 (16.9 %)	24 (17.8 %)	3 (12.5 %)	49 (19 %)	0.2
IUGR	2 (5.9 %)	2 (3%)	4 (3%)	0	8 (3.1 %)	0.5
Progesterone treatment	7 (20.6 %)	13 (20 %)	16 (11.9 %)	1 (4.2 %)	37 (14.4 %)	**0.1**
Positive vaginal culture	0/6 (0%)	1/12 (8.3 %)	10/25 (40 %)	2/8 (25 %)	22/52 (42.3 %)	0.4
Positive Urine culture	0/18	2/17 (11.8 %)	0	0	1/43 (2.3 %)	0.4

Categorical variables were tested with Chi square test or Fisher's exact test as appropriate. Normally distributed continuous variables were tested with One Way ANOVA. Non-normally distributed continuous variables were tested with One Way ANOVA on ranks.

Table 2
Management of patients with late preterm PROM according to gestational age at delivery.

	34 w (34)	35 w (65)	36 w (135)	37 w (24)	Total (258)	P
Indication to delivery						0.5
Spontaneous labor	13 (38.2 %)	30 (46.9 %)	70 (52.2 %)	9 (37.5 %)	122 (47.7 %)	
P PROM (no suspected triple I)	18 (52.9 %)	28 (43.7 %)	55 (41 %)	11 (45.8 %)	112 (43.7 %)	
Indicated	3 (8.9 %)	6 (9.4 %)	9 (6.8 %)	4 (16.7 %)	22 (8.6 %)	
Labor						0.4
No labor	5 (14.7 %)	5 (7.8 %)	11(8.1 %)	1 (4.2 %)	22 (8.5 %)	
Spontaneous	13 (38.2 %)	30 (46.1 %)	70 (51.8 %)	9 (37.5 %)	122 (47.3 %)	
Induced	16(47.1 %)	30 (46.1 %)	54 (40.1 %)	14 (58.3 %)	114 (44.2 %)	
Mode of delivery						0.08
Spontaneous vaginal	24 (70.6 %)	54 (83.1 %)	111 (82.2 %)	19 (79.2 %)	208 (80.6 %)	
Operative vaginal	0	3 (4.6 %)	7 (5.2 %)	3 (12.5 %)	13 (5%)	
Cesarean Section	10 (29.4 %)	8 (12.3 %)	17 (12.6 %)	2 (8.3 %)	37 (14.4 %)	
pPROM						
Gestational age at p PROM	34 (34 – 34)	35 (34.6–35)	36 (36 – 36)	36.8 (36.6–36.8)	35.5 (36.6–36.8)	< **0.01**
pPROM to delivery interval (days)	2 (1–3)	1 (1–3)	1 (1–2)	1 (1–3)	1 (1–2)	**0.049**
Suspected triple I	0	4 (6.1 %)	3 (2.2 %)	1 (4.2 %)	8 (3.1 %)	0.3
Antibiotic treatment						<**0.01**
No antibiotic	3 (8.8 %)	2 (3%)	5 (3.7 %)	1 (4.2 %)	11 (4.3 %)	
Antibiotic during expectant management	20 (58.8 %)	29 (44.6 %)	53 (39.3 %)	1 (4.2 %)	103 (39.9 %)	
Antibiotic in labor	1 (2.9 %)	1 (1.5 %)	17 (12.6 %)	4 (16.7 %)	23 (8.9 %)	
Antibiotic during expectant management and labor	10 (29.5 %)	33 (50.9 %)	60 (44.4 %)	18 (74.9 %)	121 (46.9 %)	
Duration of antibiotic treatment	2 (1–2)	2 (1–2)	2 (1–2)	1 (1–1)	2 (1–2)	**0.047**
Beta-lactamic	9 (26.5 %)	28 (43.1 %)	75 (55.6 %)	23 (95.8 %)	287 (47.4 %)	< **0.01**
Gentamicin	0	1 (1.5 %)	0	1 (4.2 %)	2 (0.8 %)	0.1
Macrolide	17 (50 %)	30 (46.1 %)	56 (41.5 %)	11 (45.8 %)	114 (44.2 %)	0.8
Tocolysis	6 (17.6 %)	2 (3.1 %)	1 (0.7 %)	1 (4.3 %)	10 (3.9 %)	< **0.01**
Antenatal corticosteroids						
No administration	19 (55.9 %)	52 (80 %)	129 (95.5 %)	24 (100 %)	224 (86.8 %)	< **0.01**
Before 34 weeks	12 (35.3 %)	8 (12.3 %)	4 (3%)	0	24 (9.3 %)	
After 34 weeks	3 (8.8 %)	5 (7.7 %)	2 (1.5 %)	0	10 (3.5 %)	

Categorical variables were tested with Chi square test or Fisher's exact test as appropriate. Normally distributed continuous variables were tested with One Way ANOVA. Non-normally distributed continuous variables were tested with One Way ANOVA on ranks.

Table 3
Neonatal outcomes of pregnancies with late preterm PROM according to gestational age at delivery.

	34 w (34)	35 w (65)	36 w (135)	37 w (24)	Total (258)	P
Neonatal outcomes						
Birth weight	2377 (2070–2620)	2500 (2340–2670)	2770 (2535–2970)	3020 (2720–3290)	2640 (2430–2870)	< **0.01**
Female	14 (41.2 %)	27 (41.5 %)	61 (45.2 %)	12 (50 %)	114 (44.2 %)	0.8
Arterial Ph	7.31 ± 0.08 n=21	7.29 ± 0.06 n = 35	7.27 ± 0.08 n=69	7.26 ± 0.08 n = 8	7.28 ± 0.07 n = 133	0.2
Venous Ph	7.30 ± 0.04 n=14	7.29 ± 0.1 n = 35	7.30 ± 0.09 n = 82	7.28 ± 0.07 n=24	7.30 ± 0.08 n=155	0.6
Arterial BE excess	−1.9 ± 2.9 n = 22	−2.1 ± 7.1 n = 35	−1.6 ± 5.2 n = 68	5.3 ± 2.4 n = 8	−1.4 ± 5.6 n = 133	<**0.01**
Venous BE excess	2.6 ± 2.4 n=14	4.3 ± 3.2 n = 35	4.2 ± 3.2 n = 81	4.9 ± 2.5 n=24	4.1 ± 3.1 n=154	0.2
Apgar score 5′	9 (9–10)	10 (9–10)	10 (9–10)	10 (10–10)	10 (9–10)	<**0.01**
Newborn sepsis	1 (2.9 %)	1(1.5 %)	0	0 (0%)	2 (0.8 %)	0.4
Respiratory support						0.5
No support	28 (82.3 %)	56 (87.5 %)	122 (91 %)	22 (95.6 %)	228 (89.4 %)	
Non invasive	6 (17.7 %)	8 (12.5 %)	11 (8.3 %)	1 (4.4 %)	26 (10.2 %)	
Invasive	0 (0%)	0 (0%)	1 (0.7 %)	0	1(0.4 %)	
Jaundice	18 (52.9 %)	29 (45.3 %)	49 (36.6 %)	9 (39.1 %)	105 (41.2 %)	0.3
Hypoglycemia	5 (14.7 %)	10 (15.6 %)	24 (18 %)	0	39 (15.4 %)	**0.04**
NICU length of stay (days)	7 (5–11)	5 (4–7)	4 (3–6)	3 (3–4)	4 (3–6)	<**0.01**
Prolonged neonatal hospitalization (> 5 days)	25(73.5 %)	28 (43 %)	42 (31.1 %)	4 (16.7 %)	99 (38.4 %)	<**0.01**
Neonatal Stroke	0	1 (1.5 %)	1 (0.7 %)	1 (4.1 %)	3 (1.1 %)	0.4
Composite neonatal outcome	26 (76.5 %)	35 (53.8 %)	63 (46.7 %)	6 (25 %)	130 (50.4 %)	<**0.01**
Maternal outcomes						
Maternal post partum fever (>38 °C)	2 (5.9 %)	1 (1.5 %)	1 (0.7 %)	0	4 (1.5 %)	0.2
Maternal post partum antibiotics	3 (8.8 %)	1 (1.5 %)	1(0.7 %)	0	5 (1.9 %)	0.08
Clinical endometritis	1 (2.9 %)	0	0	0	1 (0.4 %)	0.2

Categorical variables were tested with Chi square test or Fisher's exact test as appropriate. Normally distributed continuous variables were tested with One Way ANOVA. Non-normally distributed continuous variables were tested with One Way ANOVA on ranks.

The 0.8 % prevalence of neonatal sepsis detected in our cohort is lower than the 3% reported in the PPROMT trial and the 4% detected in the PPROMEXIL trial. Instead, intraamniotic infections were equally rare in the 3 populations, the prevalence being 1% in our cohort, 2% in the PPROMT trial and 6% in the PPROMEXIL trial, although the studies adopted different definitions. Such differences can't be simply attributed to the shorter latency period detected in our cohort, as in the PPOMT and the PPROMEXIL trials neonatal sepsis was similar among expectantly managed women and those undergoing immediate delivery. We can speculate that the lower rates of neonatal infections may be due to a more extensive use of antibiotics. In our cohort 95.7 % of women received antibiotic treatment as opposed to 86 % in the PPROMT trial and 41 % in the PPROMEXIL trial. Administration of broad-spectrum

Table 4
Multivariate analysis on the risk factors for adverse neonatal outcomes.

	Composite adverse neonatal outcome	
	Adjusted OR (95 %CI)	P
Gestational age at pPROM		
34	2.3 (1.03–5.1)	**0.04**
35	1.1 (0.6–2)	0.8
36	§	
pPROM to delivery interval	1 (0.9–1.1)	0.5
Antenatal corticosteroids	3.6 (1.3–9.7)	**0.01**
Antibiotic treatment	0.2 (0.04–1.02)	**0.05**

Multivariate logistic regression models investigating the role of GA at PROM and PROM to delivery interval on neonatal outcomes. The following variables were tested as potential confounders: maternal age, parity, race, education, BMI, wait gain, smoking, utilization of assisted reproductive technologies, hypertensive disorders, cholestasis, diabetes mellitus, tocolysis, positive urine cultures, delivery indication, delivery hospital. The area under receiver operating characteristic (ROC) curve was respectively 0.65 for composite adverse neonatal outcomes.

antibiotics to women with pPROM reduces maternal and neonatal infections, drops gestational age-dependent morbidity and prolongs pregnancy [16,17]. The ACOG does not recommend latency antibiotics to women with LpPROM and negative GBS culture [18]. However, ascending infections can be caused by pathogens other than GBS in the LP period, such as E. Coli, Enterococcus, Klebsiella, Lysteria monocytogenes, or S. Aureus [19]. An individual patient data meta-analysis on LpPROM management showed that immediate delivery decreased the risk of neonatal sepsis among women with positive vaginal cultures at randomization [20]. Therefore, broad-spectrum antibiotic prophylaxis may effectively prevent neonatal infections, especially among women colonized with bacteria other than GBS [21,22]. Despite the short-term benefits, antimicrobials did not show improvement in perinatal mortality and long-term outcomes, and they may negatively affect infants' microbiome, breastfeeding and maternal bonding [23]. Therefore, treatment should be prescribed for the shortest possible time and targeted to the identified or most prevalent pathogens.

Our multivariate analysis demonstrated that women with LpPROM receiving ACS had 3.6 higher odds of experiencing adverse outcomes than pregnancies who did not receive the treatment (p = 0.01). The Antenatal Late Preterm Steroid (ALPS) trial showed that pregnant women between $34^{0/7}$ and $36^{6/7}$ weeks of gestation who had not received a previous ACS, and were at risk of preterm birth within 7 days, presented lower neonatal respiratory morbidity when they received a single course of corticosteroids [10]. The trial showed an increased rate of neonatal hypoglycemia in newborns of mothers exposed to corticosteroids. In our cohort, hypoglycemia was included in the composite NO; when mothers received ACS 32 % (11/34) of their newborns presented low blood glucose, as opposed to 12.8 % (28/219) among those not receiving the treatment. Hypoglycemia may be only part of the problem: a previous observational study on LpPROM also identified ACS as a risk factor for adverse neonatal outcome, even after adjustment for GA at delivery and acute histologic chorioamnionitis [26]. The risk of chorioamnionitis does not increase with maternal steroid use in case of PROM [27]; however, corticosteroids may delay recognition of subclinical inflammation/infection, a condition associated with neonatal morbidities and known to be more common in case of PROM than among women with intact membranes [28]. As we encourage further studies to specifically address the use of ACS in LpPROM, caution should be considered when administering such treatment, especially at 36 weeks' gestation, also given the potential downsides on long term mental and behavioral health [29].

The main strengths of our study include the large sample size, the multicenter design, the uniformity in the adopted definitions (i.e suspected triple I). However, we acknowledge several limitations. The approach to LpPROM is not standardized in terms of antibiotics and corticosteroid use; similarly, the optimal duration of the latency period was not prespecified.

In conclusion, using data from a large retrospective cohort, we showed that expectant management of LpPROM is associated with low rates of neonatal sepsis, that neonatal outcome mainly depend on gestational age at PROM due to a short latency period, and that antibiotics, but not maternal corticosteroids may decrease neonatal morbidities. Expectant management should be especially recommended between 34^{+0} and 35^{+0} weeks', when NO are the worst.

Declaration of Competing Interest

The authors declare no conflict of interest.

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