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MATERNAL-FETAL MEDICINE

Can we predict preterm delivery in patients with premature rupture of membranes?

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Abstract

Purpose To characterize the parameters that predict preterm delivery in patients with preterm, premature rupture of membranes.

Methods This retrospective cohort study included women diagnosed with preterm premature rupture of membranes at 24–34 weeks gestation. Demographics, medical history, laboratory tests, and delivery data were reviewed.

Results Among 258 patients with preterm, premature rupture of membranes during the study period, 141 (54.7%) met the inclusion criteria. Therefore, the final cohort included 141 (54.78%) women, among whom, 32 (22.7%) delivered within the first 24 h of ROM and 109 (77.3%) delivered after 24 h. Univariant analysis revealed that advanced gestational age at the time of preterm, premature rupture of membranes, larger cervical dilation and leukocyte count at admission had significant effects on the likelihood of labor within 24 h. Analysis of the differences between each patient at admission to 24 h before labor in heart rate, temperature (fever), leukocyte counts and amniotic fluid color revealed significant changes in heart rate ($P<0.001$), leukocyte count ($P<0.001$) and in amniotic fluid from clean to meconium or bloody ($P<0.001$). There was no significant change in elevated temperature ($P=0.065$).

Conclusions Our findings indicate that minimal changes in heart rate, body temperature (fever), leukocyte count and amniotic fluid color, within normal ranges, appear 24 h before delivery, among women with preterm, premature rupture of membranes and prolonged latency period. Increased attention to these changes might enable better follow-up and timing of delivery for patients with preterm, premature rupture of membranes before 34 weeks gestation.

Keywords Infection · Latency period · Preterm birth · Preterm · Premature rupture of membranes

Introduction

Premature rupture of membranes (PROM) is defined as rupture of membranes before the onset of labor. Preterm, premature rupture of membranes (PPROM) is defined as rupture of membranes before the onset of labor and before 37 weeks of gestation [1]. The prevalence of PPROM is 3% of all pregnancies [2]. Consequently, PPROM increases the risks of perinatal morbidity such as respiratory distress, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, neurodevelopmental impairment and even mortality [3].

The accepted approach to patients with PPROM before 34 0/7 weeks of gestation is conservative management [1, 4, 5] with close follow-up for signs of infection, which occur in approximately 15–25% of cases [6]; abruption, which occurs in approximately 2–5% [7]; fetal distress; spontaneous preterm labor, or delivery indicated for medical reasons [1]. In 50% of cases of PPROM, birth occurs within a week [8]. Recent data support extending conservative management up to 37 0/7 weeks [9–12] but not beyond 37 0/7 weeks of gestation [1]. Patients with PPROM are usually hospitalized for close follow-up. Fetal heart rate, contractions, ultrasound (for fetal growth estimation and biophysical profile) and signs of infection are monitored [1, 4].

Few studies have attempted to identify factors that predict the length of the latency period between membrane rupture and delivery. Suggested influencing factors include gestational age and cervical length or dilation at admission, amniotic fluid index, and parity, among others [13–19].

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Chorioamnionitis is a common indication for labor induction in patients with PPROM. Specific signs of chorioamnionitis, such as fever, maternal or fetal tachycardia, abdominal pain or offensive smell of the amniotic fluid are indications for immediate delivery [1]. A correlation between intrauterine infection and cerebral palsy has been previously described [20–24]. It is well-established that early detection of intrauterine infection and prompt delivery reduce short- and long-term neonatal complications, but in many cases, clear clinical evidence of infection appears with fetal distress, when it might be too late to prevent adverse effects. If we could predict which of our PPROM patients is likely to develop an indication for delivery and when, we might be able to improve neonatal outcomes. We hypothesized that even minor changes that are still within the normal ranges might reveal clues of an infection or other indication for delivery.

In the current study, we tried to characterize parameters that predict indicated and induced preterm delivery in patients with PPROM, assuming that early identification of these patients might enable better treatment and perhaps prevent maternal and fetal complications.

Materials and methods

This retrospective, single center cohort study included women diagnosed with PPROM at 24–34 weeks of gestation. All study participants were treated according to the accepted maternal–fetal medicine protocols, which are based on CDC recommendations [25]. All women diagnosed with PPROM are hospitalized in the maternal–fetal unit from admission to labor. They receive conservative treatment with antibiotics: azithromycin for latency, IV Ampicillin for 48 h and PO moxypen for 5 days (after group B streptococcus (GBS) culture). They are also given corticosteroids for lung maturation (two doses of 12 mg dexamethasone). Strict daily follow-up of fever, heart rate, amniotic fluid and fetal heart rate monitoring. Weekly: complete blood count to track changes in leukocytes. Indications for labor are gestational age of 34 weeks, spontaneous labor, fetal distress or signs of infection.

We compared women with PPROM and onset of labor within more than 24 h (study group) to patients with PPROM who delivered within 24 h of ruptured membranes (control group). Demographics, medical history, laboratory tests, and delivery data were obtained from the electronic medical records. Patients with preterm labor without PROM and women with term PROM were excluded. Multifetal pregnancies were excluded.

We first analyzed the data at admission, comparing control group patients (short latency) to study group patients (long latency). Next, we looked at the differences in these parameters between the time of admission and 24 h before delivery among patients in the long latency group. The rational for this analysis was to find changes that could potentially predict spontaneous labor or an indication for delivery. Finally, we compared the parameters of patients in the short and long latency groups 24 h prior to delivery to identify similarities that could potentially identify patients who will deliver within the next 24 h after being admitted for PPROM.

The study was conducted according to good clinical practice guidelines and was approved by the local Institutional Review Board—the Meir medical center Helsinki committee Informed. Due to the retrospective nature of the study, consent for participation was not required.

Statistical analysis

Power analysis revealed that a sample size of 141 patients was sufficient to detect a 10% difference in parameters that could predict progression to labor, under the assumptions of a type I error (two-sided) of 5% and at least 80% power.

Patients' characteristics were compared between the control group [those who delivered within 24 h (short latency group) and the study group, who delivered after more than 24 h of ruptured membranes (the long latency group)], using student *t* test for continuous variables, and the Chi-square or Fisher's Exact Test for categorical variables. Results were considered significant when the *P* value was ≤ 0.05. Data are presented as numbers and percentages for categorical variables and as means and standard deviations for continuous variables. All statistical analyses were performed using IBM SPSS Statistics for Windows.

Results

Among 258 patients with PPROM during the study period, 141 (54.7%) met the inclusion criteria. Excluded were 23 twin pregnancies and 94 women with PPROM at gestational age beyond 34 0/7 weeks. The final cohort included 141 women. Of these, 32 (22.7%) were in the short latency group and 109 (77.3%) in the long latency group (Fig. 1).

There were no significant differences between the two groups in baseline characteristics stratified by latency period. There was no difference in maternal age and routine prenatal follow-up, including triple test, first and second trimester ultrasound scans and glucose tolerance tests (Table 1).

Among the short latency group, there were significantly more primiparas compared to the long latency group [18 (56.3%) vs. 35 (32.1%), respectively, $P=0.013$]. A history of preterm delivery, prior to 37 weeks, was significantly more prominent among the long latency group 75 (68.8%) vs. 14 (43.8%), $P=0.01$. We compared the baseline characteristics

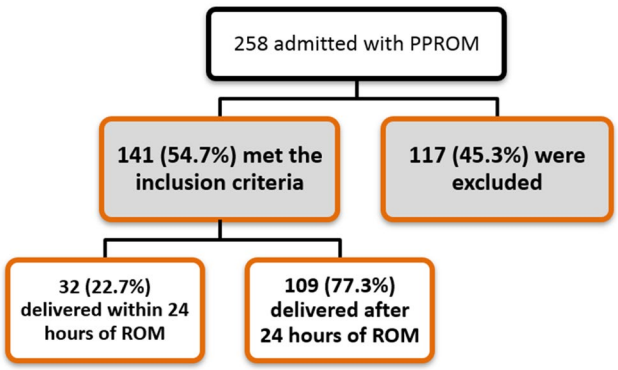

Fig. 1 Patient selection

between the short and long latency groups in each of these subgroups (primiparas, delivery prior to 37 weeks and term delivery) and found no significant differences in baseline characteristics.

Twenty women from the cohort had amniocentesis (AC): 3 (23.1%) from the short latency and 17 (35.4%) from the long latency group ($P=0.297$). Indications for AC were nuchal translucency (NT) 3.3 mm (one patient), triple test (TT) < 1:380 (one patient), seroconversion of CMV (two patients) with no fetal infection, abnormal US findings of transposition of great arteries (one patient), maternal age > 35 years (seven patients), and without known medical indication (eight patients). The average time from amniocentesis to PPROM was 9 weeks.

Univariant analysis revealed that advanced gestational age at the time of PPROM, larger cervical dilatation and leukocyte count at admission had a significant effect on the likelihood of labor onset within 24 h (Table 2).

The mean gestational age was significantly advanced in the short latency group, 32.13 (±2.0) weeks compared to 30.18 (±2.6) weeks in the long latency group ($P \leq 0.001$). A total of 80 (93%) women with PPROM who were dilated 0–1 cm at admission had longer latency period. Among patients dilated 2–3 cm at admission, 10 (34.5%) had spontaneous labor in less than 24 h ($P<0.05$). All patients dilated > 4 cm at admission delivered within 24 h ($P<0.001$).

Blood leukocyte count on admission was higher among patients with shorter, as compared to longer latency periods (11.83 ± 4.2 vs. 10.55 ± 2.5, respectively; $P=0.044$).

There were no significant differences in body temperature (fever), heart rate, leukocyte count, amniotic fluid color and fetal monitoring 24 h before labor between groups (Table 3).

In the short latency group, 27 (87.1%) patients labored spontaneously. Induction of labor was significantly more frequent in the longer latency group (41.3% vs. 12.9%, $P=0.003$; Table 4). Indications for the induction of labor included gestational age 34 weeks in 39.4% and meconium-stained or bloody amniotic fluid in 20% in the short latency group and 18.2% in the long latency group.

Table 1 Basic characteristics of the participants

Characteristic	Latency < 24 h ($N=32$)	Latency > 24 h ($N=109$)	P-value*
Maternal age (mean ± SD)	34.06 (±5.4)	35.17 (±6.1)	0.353
Primiparous, *n* (%)	18 (56.3%)	35 (32.1%)	0.013
Previous pregnancy outcome, *n* (%)			0.01
Preterm birth	14 (43.8%)	75 (68.8%)	
Term birth	18 (56.3%)	34 (31.2%)	
Mode of previous delivery *n* (%)			0.235
Spontaneous vaginal	13 (92.9%)	50 (71.4%)	
Vacuum extraction	0 (0%)	2 (2.9%)	
Cesarean section	1 (7.1%)	18 (25.7%)	
Triple test, *n* (%)			0.278
Normal	27 (100%)	72 (91.1%)	
Elevated AFP > 2.5 MoM	0 (0%)	4 (5.1%)	
Elevated BHCG > 2.5 MoM	0 (0%)	3 (3.8%)	
Amniocentesis *n* (%)	3 (23.1%)	17 (35.4%)	0.297
Glucose challenge test (GCT) *n* (%)			0.148
GCT < 140	18 (72.0%)	66 (79.5%)	
GCT > 140	7 (28.0%)	10 (12.0%)	
Oral glucose tolerance test (OGTT) *n* (%)			0.693
Normal	5 (71.4%)	9 (56.3%)	
Abnormal	2 (28.6%)	7 (43.8%)	

*Pearson's Chi-square, Fisher exact test or *t* test, as appropriate

Table 2 Clinical and obstetrical parameters according to labor onset

Characteristic	Latency < 24 h ($N=32$)	Latency > 24 h ($N=109$)	P value*
Gestational age at PPROM, weeks (mean ± SD)	32.13 (±2.0)	30.18 (±2.6)	< 0.001
Gestational week at PPROM, *n* (%)			0.002
24–27	2 (6.3%)	19 (17.4%)	
28–30	3 (9.4%)	37 (33.9%)	
31–34	27 (84.4%)	53 (48.6%)	
Amniotic fluid color at admission, *n* (%)			0.891
Clean	29 (90.6%)	92 (90.2%)	
Meconium	1 (3.1%)	2 (2%)	
Bloody	2 (6.3%)	8 (7.8%)	
Dilation at admission, *n* (%)			< 0.001
0–1 cm	17 (58.6%)	80 (93%)	
2–3 cm	10 (34.5%)	6 (7%)	
> 4 cm	2 (6.9%)	0 (0%)	
Leukocytes at admission (mean ± SD)	11.83 (±4.2)	10.55 (±2.5)	0.044
Heart rate at admission (mean ± SD)	87.67 (±14.3)	89.02 (±12.8)	0.621
Temperature at admission, °C (mean ± SD)	36.58 (±0.5)	36.58 (±1.1)	0.993

*Pearson's Chi-square or *t* test, as appropriate

Table 3 Clinical and obstetrical parameters according to labor onset

Characteristic	Latency < 24 h ($N=32$)	Latency > 24 h ($N=109$)	P value*
Amniotic fluid 24 h before labor, *n* (%)			0.617
Clean	23 (88.5%)	77 (88.5%)	
Meconium	1 (3.8%)	1 (1.1%)	
Bloody	2 (7.7%)	9 (10.3%)	
Temperature 24 h before labor, °C (mean ± SD)	36.71 (±0.5)	36.818 (±0.7)	0.407
Heart rate 24 h before labor (mean ± SD)	88.70 (±18.7)	86.74 (±13.3)	0.528
Leukocytes 24 h before labor (mean ± SD)	12.24 (±4.2)	11.65 (±3.06)	0.431
Fetal heart rate monitor 24 h before labor, *n* (%)			0.754
Normal	19 (73.1%)	71 (77.2%)	
Decelerations	7 (26.9%)	20 (21.7%)	
Tachycardia	0 (0%)	1 (1.1%)	

*Pearson's Chi-square or *t* test, as appropriate

Non-reassuring fetal heart rate (NRFHR) was found in 40% of the short latency group and in 27.3% of the long latency group. Signs of infection were seen in 20% of the short latency group and 15.2% of the long latency group (Table 4).

The data suggest a trend toward increased rates of cesarean deliveries in women with PPROM and latency period longer than 24 h, as compared to the short latency group (42.6% vs. 25.8%, respectively; $P=0.127$), as well as more vacuum assisted deliveries among this population (6.5% vs. 1.9%, $P=0.127$; Table 4).

There were no significant differences between the groups in neonatal outcomes (Table 5). Estimated fetal weights upon admission were similar between groups (48.53 ± 27.0 g vs. 40.6 ± 20.8 g) in the short and the long latency groups, respectively.

None of the results that were significant in univariant analysis remained significant in multivariant analysis.

In a different analysis, we compared the changes in each patient between admission and 24 h before onset of labor in body temperature (fever), heart rate, leukocyte count and amniotic fluid color. We found significant changes in heart rate ($P<0.001$), leukocyte counts ($P<0.001$) and amniotic fluid color from clean to meconium-stained or bloody ($P<0.001$). There was no significant change in temperature ($P=0.065$; Table 6).

Table 4 Clinical and obstetrical parameters of the study group according to labor onset

Characteristic	Latency < 24 h (*N* = 32)	Latency > 24 h (*N* = 109)	*P* value*
Onset of labor *n* (%)			0.003
Spontaneous	27 (87.1%)	60 (57.7%)	
Induced	4 (12.9%)	44 (42.3%)	
Reasons for induction, *n* (%)			0.064
34 weeks	0 (0%)	13 (29.5%)	
Amniotic fluid color	1 (20%)	6 (13.6%)	
NRFHR	2 (40%)	9 (20.5%)	
Signs of infection	1 (20%)	5 (11.4%)	
Unknown reason	0 (0%)	11 (25%)	
Gestational week at delivery (mean ± SD)	32.29 (± 2.1)	31.96 (± 2.2)	0.458
Mode of delivery, *n* (%)			0.127
Spontaneous vaginal	21 (67.7%)	60 (55.6%)	
Vacuum extraction	2 (6.5%)	2 (1.9%)	
Cesarean section	8 (25.8%)	46 (42.6%)	

NRFHR nonreassuring fetal heart rate

*Pearson's Chi-square or *T* test as appropriate

Table 5 Neonatal outcomes

Characteristic	Latency < 24 h (*N* = 32)	Latency > 24 h (*N* = 109)	*P* value*
Birth weight, g (mean ± SD)	2040 (± 596.0)	1829 (± 461.8)	0.073
Percentile (mean ± SD)	48.53 (± 27.0)	40.6 (± 20.8)	0.088
5-min Apgar < 7, *n* (%)	1 (3.2%)	2 (1.9%)	1

**t* test

Table 6 Change in parameters between admission and 24 h before labor

Characteristic	At admission	24 h before labor	*P* value*
Fever (median ± SD)	36.6 ± 1.0	36.7 ± 5.1	0.065
Heart rate (median ± SD)	87 ± 13.1	88 ± 14.8	< 0.001
Leukocytosis (median ± SD)	10.43 ± 3.0	11.53 ± 3.3	< 0.001
Amniotic fluid color *n* (%)			< 0.001
Clean	121 (90.3%)	100 (88.5%)	
Meconium	3 (2.2%)	2 (1.8%)	
Bloody	10 (7.5%)	11 (9.7%)	

*Pearson or Spearman as appropriate

Discussion

The optimal time to deliver patients with PPROM is not clear. On one hand, efforts are made to prolong the pregnancy as much as possible in an attempt to prevent complications of prematurity. However, it is well-known that delivery in the presence of chorioamnionitis might be too late in terms of preventing neonatal complications and long-term morbidities. In this study, we investigated parameters that might predict preterm delivery in patients with PPROM, to determine who would spontaneously deliver or have an indication for labor induction within the next 24 h. Early detection of signs that precede fully-developed chorioamnionitis or fetal distress might enable earlier deliveries and even reduce sequelae of these complications in patients with PPROM before 34 weeks of gestation. We found that 22.7% of patients delivered within the first 24 h of ROM and 77.3% delivered after a latency phase of more than 24 h. Other studies have shown that 50% will go into labor within 24 to 48 h and most (70–97%) within 7 days [1, 14, 19, 26, 27]. The difference between our results and those of other studies is probably related to the longer latency period (48 h vs. 24 h).

Our study showed that advanced gestational age at PROM, larger dilatation and higher blood leukocyte count at admission predict delivery within 24 h. Advanced gestational age and dilation at admission, as parameters influencing the timing of labor were described in other studies [14–16, 28].

In this study, we did not find significant changes in body temperature (fever), heart rate and leukocyte count 24 h before labor between the short and late latency groups. Therefore, we can assume that none of these parameters will help us identify patients who will enter spontaneous labor or require induction within 24 h of admission with PROM. This assumption led us to investigate the changes in body temperature, heart rate and leukocyte count between admission and 24 h prior to labor in each subject.

Our novel and interesting finding is that 24 h prior to delivery in women with PPROM, after a latency period, there are mild elevations in heart rate and in leukocyte counts, which are statistically significant and within the normal ranges, as compared to the levels of those parameters in the same patients at admission.

Leukocyte count and heart rate are rarely investigated as isolated parameters. Usually they are estimated as part of the evaluation of chorioamnionitis, which is a major criterion for induction of labor in cases of PPROM [1]. The main reason to induce patients with chorioamnionitis is based on increased neonatal morbidity and mortality from periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, and bronchopulmonary dysplasia

[29–32]. To recognize signs of infection, potential risks factors such as fever, heart rate, leukocytosis and fetal heart rate are tracked. In light of our results, we should increase awareness regarding elevated leukocyte count and heart rate during hospitalization, even within the normal limits, as compared to those values at admission, as they might be the first signs of imminent intrauterine infection.

Patients with PPROM are treated with corticosteroids for fetal lung maturity based on the accepted protocol. Elevated leukocyte count secondary to steroid treatment has been previously described and is well-established [33]. Since all the patients received the same treatment whether delivered within the first 24 h or after a longer latency period, we believe that the significant differences in leukocytes between the groups were not related to the steroid treatment.

Changes within normal limits have been shown in studies from other disciplines. A retrospective case–control study found that long-term variations in blood hemoglobin levels within the normal range may detect gastrointestinal bleeding in the early development of colorectal cancer [34]. They realized that these small changes within normal hemoglobin range can easily be missed by physicians, but the understanding of its importance and use of computerized alert algorithms may change health care management and the patient prognosis.

Santillan et al. evaluated the risk of epithelial ovarian cancer recurrence in patients with changes in cancer antigen 125 (CA-125) levels that remained below the upper limit of normal. In their retrospective cohort design, they concluded that among patients with epithelial ovarian cancer in complete clinical remission, a progressive increase in serum CA-125 levels within normal range can predict disease recurrence [35].

The strengths of the current study are its novelty. The study introduces a new perspective for observing common parameters such as heart rate and leukocyte levels and their changes within the normal ranges. These factors are part of routine follow-up and can be soft indicators of imminent infection that might lead to induction of labor.

Some limitations are inherent to this study's retrospective design. Adequate sample size was calculated to detect a hypothesized 10% difference between patient groups but unfortunately was not large enough to remain significant on multivariate analysis.

We believe that additional studies with a larger sample size will be needed to reveal significant changes within the normal limits in parameters such as body temperature (fever), heart rate and blood leukocyte counts.

Conclusions

Our findings indicate that minimal changes in heart rate, body temperature (fever), leukocyte count and amniotic fluid color within the normal ranges, appear 24 h before delivery among women with PPROM and prolonged latency period. We believe that increased awareness and understanding of these changes that remain within the normal limits, might enable better follow-up and more precise timing of delivery for patients with PPROM before 34 weeks of gestation.

Author contributions YY: Project development, Data Collection, management and analysis, Manuscript writing. OW: Project development, Data collection, management and analysis. ER: Data collection. TB-S: Conceptualized the project, Data analysis Manuscript editing.

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Compliance with ethical standards

Conflict of interest Yael Yagur declares that she has no conflict of interest. Omer Weitzner declares that he has no conflict of interest. Eyal Ravid declares that he has no conflict of interest. Tal Biron-Shental declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were approved by the local institutional ethics committee—The Meir Medical Center Helsinki committee, and are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to retrospective study design, consent for participation was not required.

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