ORIGINAL ARTICLE

Sonographic predicting factors of latency interval in pregnancies complicated by preterm premature rupture of membranes

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ABSTRACT

Objectives: Preterm prelabor rupture of membranes (PPROM) is associated with significant perinatal morbidity and mortality. To date, the latency period to delivery cannot be reliably predicted. The aim of this study was to identify potential sonographic predictors of the interval until delivery in cases with PPROM.

Methods: This was a retrospective cohort study of all singleton pregnancies with PPROM between 24^{+0} and 33^{+6} gestational weeks that were admitted in the 3rd Academic Department of Obstetrics and Gynecology Department of the Aristotle University of Thessaloniki between January 2016 and December 2019. Sonographic parameters including the cervical length (CL) and the deepest vertical pool (DVP) of amniotic fluid, as well as the pregnancy outcomes were examined.

Results: In total, 50 women fulfilled the inclusion criteria and were included in the study. The multivariate analysis (multiple linear regression) revealed that only the CL made a unique contribution (p=0.001, beta=0.542) to the latency interval. Moreover, in the subgroup multivariate analyses (binary logistic regression), only the CL correlated significantly with a latency interval greater than 2 days (p=0.008, OR=1.142, 95% CI=1.036-1.262) or latency>7 days (p=0.034, OR=1.076, 95% CI=1.005-1.125).

Conclusions: The CL may be an independent predictor for the latency interval in pregnancies with PPROM between 24 and 34 gestational weeks. Further research is needed on potential sonographic and other biomarkers for the effective prediction of imminent delivery.

KEY WORDS preterm prelabor rupture of membranes, cervical length, ultrasound, amniotic fluid, prediction

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Introduction

Preterm (<37 weeks) prelabor rupture of membranes (PPROM) complicates about 2% of pregnancies and 40% of these cases result in prematurity, thus, contributing to the associated neonatal morbidity and mortality [1-4]. In cases with PPROM after 24 weeks of gestation, all the major guidelines recommend expectant management, at least until 34 weeks [5]. Moreover, antenatal corticosteroids when administered between 24 and 34 weeks improve perinatal outcome, especially when delivery occurs within 2 to 7 days [6]. Furthermore, the administration of magnesium sulfate before 32 weeks of gestation improves neonatal outcome, when given up to 24 hours before delivery [6].

In most countries, women with PPROM are managed as inpatients, however, there are countries that may allow outpatient surveillance in selected cases; a significant proportion of women will deliver within 48 hours or within 7 days from the rupture, however many will remain undelivered, some for more than 2 weeks [7]. Predictive factors of the neonatal outcome in cases with PPROM include gestational age, severe oligohydramnios and cesarean delivery [8]. Therefore, the accurate prediction of the onset of labor in cases with PPROM would be clinically useful for timely administration of antenatal corticosteroids and magnesium sulfate and also for the triage of women that may be safely managed expectantly as outpatients.

It has been shown that ultrasound may be useful in the prediction of the interval between membrane rupture and labor onset, by the measurement of cervical length and presence of funneling and also the amniotic fluid volume at presentation [9], however existing evidence is not definite. Thus, the aim of this study was to investigate sonographic predictive factors for the latency interval in pregnant women with PPROM.

Materials and Methods

Study design, setting and participants

This was a retrospective cohort study including patients with singleton viable pregnancies complicated by PPROM between 24^{+0} and 33^{+6} gestational weeks, that were admitted in the high-risk pregnancy unit of the 3rd Obstetrics and Gynecology Department of the Aristotle University of Thessaloniki, between January 2016 and December 2019. Women with multiple pregnancies, history of cervical surgery and those with missing fetal ultrasound biometry

Table 1. General characteristics of the study population (n=50)

Maternal characteristics	Median	Range	IQR
Age	33.7	15-41.1	6.8
BMI	23	18.6-41	6.78
Weight gain (kg)	9	0-29	7
Latency (days)	5.5	0-29	10.5
		N	%
Smoking	no	27	54
	yes	23	46
GDM	no	46	92
	yes	4	8
Multiparous	no	27	54
	yes	23	46
Last delivery mode (multiparous)	CS	7	30.4
	VD	16	69.6
Fetal and US characteristics	**Median**	**Range**	**IQR**
Days from US to Delivery	3	0-16	3.25
GA at birth	32	24-34	4.75
	Mean	**SD**	
Estimated fetal weight (g)	1646	514	
EFW-centile	35.8	21.6	
Birthweight (g)	1746	523	
Birthweight centile	49.3	28.8	
Cervical length	22.78	11.98	
Deepest pocket	2.1	1.2	
	Number	**Percentage (%)**	
Cephalic presentation	yes	36	72
	no	14	28
Gender	male	29	58
	female	21	42
Funneling	yes	10	20
	no	40	80

BMI: body mass index, US: ultrasound, GDM: gestational diabetes mellitus, EFW: estimated fetal weight
GA: gestational age, SD: standard deviation,

Table 2. Univariate analysis between latency period and each factor

Spearman's correlation	MA	BMI	DP	Cervical length	Weight gain	EFW	BW	GA birth
P values	0.858	0.691	0.892	**<0.001**	0.237	0.04	0.17	0.193
rho	-0.026	-0.058	0.02	**0.626**	-0.17	-0.291	-0.197	-0.187
Mann-Whitney	Smoking	GDM	Parity	Abnormality	Funneling	Gender	Previous delivery mode	
P values	0.742	0.21	0.464	0.116	**0.019**	0.497	0.298	

BMI: body mass index, GDM: gestational diabetes mellitus, EFW: estimated fetal weight GA: gestational age, MA: maternal age DP: deepest pocket

and incomplete outcome data were excluded from the study. The gestational age was determined by first trimester ultrasound (crown-rump length) or by head circumference measurement during the second trimester if there was no first trimester ultrasound available.

According to the local protocol, all women were routinely hospitalized until delivery. In cases where spontaneous delivery did not occur, either induction of labor or cesarean delivery were performed at 34 gestational weeks and the mode of delivery was decided based on standard obstetric indications. The diagnosis of PPROM was made based on clinical history and physical examination. Their management included administration of corticosteroids for fetal lung maturation, antibiotic treatment for 7 days (ceftriaxone, clarithromycin and metronidazole), weekly growth scans and daily non-stress tests after 28 weeks of gestation. All sonographic examinations were performed with an S8 Voluson GE ultrasound, by obstetricians certified in obstetric ultrasonography. Patients' demographic data, somatometric and medical history including maternal age and weight, weight gain, body mass index (BMI), smoking, parity and diagnosis of gestational diabetes mellitus were collected. Sonographic measurements [estimated fetal weight (EFW), presentation, placental position, cervical length (CL), cervical funneling, deepest vertical pool - DVP] were routinely prospectively collected and recorded in an electronic database (Astraia). The cervical length was measured transvaginally, as previously described [10]. The perinatal outcome parameters, including date, indication and mode of delivery, birthweight and neonatal complications were also routinely recorded in the same database.

Statistical analysis

Except for descriptive data (parametric: mean ± SD, non-parametric: median, range, IQR), a normality test was used for selecting parametric and non-parametric variables and their respective analysis. Latency was the dependent variable and was examined both as continuous and binary (latency > 2 days and latency > 7 days). Initially, the association between maternal data, ultrasound parameters, pregnancy outcome and latency was examined separately for each independent variable with parametric and non-parametric tests (Spearman's correlation, t-test, Mann-Whitney test, Chi-square test). Following that, multivariate analysis was performed, including all previously important factors. In all tests the statistical significance was set at 0.05. Finally, women were divided according to gestational age at PPROM, group A: 24^{+0} - 27^{+6} weeks (N= 15) and group B: 28^{+0} - 33^{+6} weeks (N=35). Subgroup analysis included both comparisons between the groups and investigation of the independent variables of latency. The IBM Statistical package for Social sciences (SPSS), version 25.0 was used for statistical analyses.

Results

Overall, 50 women fulfilled the inclusion criteria and were included in the study. The participants' demographic data are presented in Table 1. Of note, no cases of clinically and laboratory confirmed chorioamnionitis were detected in our sample.

The association of each independent variable with the latency period was examined separately for each variable. Among all variables, CL showed a significant positive correlation with the latency interval (p<0.001,

Table 3. Multivariate analysis between latency period and each factor.							
Variables /p values	**Cephalic presentation**	**CL**	**CL>15**	**EFW**	**Funneling**	**model**	
Latency	--	**P<0.001 beta=0.542**	--	P=0.193 beta= -0.16	P=0.987 beta=0.002	**P<0.001, Adjusted R^2= 0.299**	Multiple Linear Regression
Latency<2d	P=0.067 OR=5.963	**p=0.008 OR=1.143**	--	--	--	**p<0.001**	Binary logistic regression
Latency<2d	P=0.062 OR=5.497	--	**P=0.014 OR=10.165**	--	--	**p=0.002**	
Latency<7d	--	**P=0.034 OR=1.076**	--	P=0.081 OR=0.999	P=0.343 OR=0.306	**P=0.002**	
Latency<7d	--	--	**P=0.025 OR=6.011**	**P=0.036 OR=0.999**	P=0.193 OR=0.204	**P=0.005**	

rho=0.626) while EFW (p=0.040, rho= -0.291) showed a significant negative correlation. The absence of funneling also correlated to an increased latency period (absence, Median-MD=8.5 days R=0-29 IQR=12.5 vs presence, MD=3 days R=0-11 IQR=5, p=0.019, Mann-Whitney) (Table 2). The multivariate analysis (multiple linear regression) that included all previous significant factors revealed that only CL makes a unique contribution (p=0.001, beta=0.542) and this model explained 29.9% of the variance of latency (p<0.001).

A subgroup analysis with latency period as a categorical variable was also performed. In particular, participants were separated according to latency period: group A≤2 days and group B >2days and group C≤7 days and group D>7 days. Regarding latency >2 days, cephalic presentation was correlated with latency period >2 days (p=0.030, Chi-square test) and also, there was statistically significant difference in CL between women with latency ≤2 days and >2 days (group A: Mn= 10.25, SD=8.79 vs group B: Mn=25.1. SD=11.04, p=0.001, t-test). Multivariate analysis (binary logistic regression), including the previous factors, revealed that only CL correlated significantly with the presence of latency>2 days (p=0.008, OR=1.143, 95% CI=1.036-1.262). Multivariate analysis for CL=15mm as a cut-off revealed that only CL>15mm correlated independently with latency>2 days (p=0.014, OR=10.165, CI=1.595-64.766) (Table 3).

For latency>7 days, there was statistically significant difference in CL (group C: Mn= 18.07, SD=10.84 vs group D: Mn=28.77, SD=10.81, p=0.001, t-test) and EFW (group C: Mn= 1777 SD=544 vs group D: Mn=1479 SD=430, p=0.041, t-test) between the two groups. Presence of funneling also correlated with latency ≤7days (p=0.016, Chi-square test). Multivariate analysis (binary logistic regression) including the previous factors revealed that only CL was correlated significantly with the presence of latency>7 days (p=0.034, OR=1.076, 95% CI=1.005-1.125). Multivariate analysis (binary logistic regression-hierarchical) for CL=15mm as a cut-off revealed that both CL>15mm (p=0.025, OR=6.011) and EFW (p=0.036, OR=0.999) correlated independently with latency>7 days (Table 3).

Finally, subgroup analysis according to gestational age at PPROM was performed. Patients with PPROM at <28w delivered significantly lower birthweight neonates, (p<0.001, group A:1144±316 gr vs group B:2004±353 gr) and had lower sonographic EFW (p:0.001, group A:1069±244 gr vs group B:1893±383 gr) compared to those with PPROM at later gestational age. However, there were no other differences in measurements between the groups. Furthermore, in group A, a moderate association between CL and latency was identified (p=0.019, r=0.595) and there was significant difference in latency interval (p=0.021) between nullip-

arous (Mn:7.75±6.73 d) and multiparous (Mn:17±6.83 d) women. Multivariate analysis (multiple linear regression) including both parity and CL in the model, explained 48.7% of variance (ANOVA R^2=0.487, p=0.018) without revealing any single independent variable (Parity Beta=0.408, p=0.102, CL Beta=0.415, p=0.096). No other factors correlated significantly with latency in univariate analysis. Regarding patients with PPROM at <28w (group B), only CL correlated strongly and positively with latency (p<0.001, rho:0,644).

Discussion

This study has shown that: 1) in cases with PPROM between 24 and 34 weeks, the measurement of CL may predict the latency interval, 2) a short CL may be an independent predictor for early delivery in such cases and 3) there is a moderate positive linear correlation between CL and latency interval.

This study is clinically relevant as there is uncertainty on the best approach in cases with PPROM, regarding the timely use of antenatal corticosteroids and magnesium sulfate, as well as the option and the appropriate antibiotic scheme. To date, few studies have addressed this issue.

The value of CL in the second trimester of pregnancy on the prediction of preterm delivery is well established [11]. In addition, we found that CL in PPROM may be an accurate predictor for the latency interval until delivery. Our results are consistent with those from the study by Lee et al., who conducted a retrospective analysis in 121 cases of PPROM and found that the combination of CL and DVP may accurately predict the latency interval with a reported sensitivity of 82.2% and specificity of 75.9% [12].

We also found that cervical funneling was correlated with the latency interval in the univariate analysis, but no such correlation was identified in the multivariate model. Evidence from a prospective study on PPROM concluded that the use of transvaginal ultrasonography for CL measurement in those cases may predict an early delivery but cannot predict the risk of chorioamnionitis or neonatal sepsis [13]. The same study mentioned that funnelling was present in cases with short CL, but it was not identified as an independent predictor for the latency interval.

With regard to DVP, we found that it is not an accurate predictor for early delivery in cases of PPROM. This may be related to the small sample size of our study and is in contrast with previously published data. Thus, in the study by Melamed et al., gestational age on admission (Hazard ratio - HR = 1.29; 95% CI = 1.22-1.37), oligohydroamnios (HR = 1.49; 95% CI = 1.18-1.87), cervical dilation >1 cm (HR = 0.65; 95% CI = 0.52-0.83), fetal growth restriction (HR = 2.94; 95% CI = 1.24-6.94) and nulliparity (HR = 1.28; 95% CI = 1.12-1.63) were associated with shorter latency interval until delivery [9]. As already mentioned, the residual amniotic fluid may play a crucial role in the neonatal outcomes, as it has a direct impact on survival rates and increases the risk of developing respiratory distress syndrome [14].

Regarding antibiotics, following the publication of the study of Lee et al. we routinely adopted the antibiotic scheme of ceftriaxone, clarithromycin and metronidazole for 7 days [15]. This scheme was implemented universally during the study period, so by following this policy we minimized the risk of bias. A Cochrane review concluded that for cases with PPROM the use of antibiotics was associated with a statistically significant reduction in chorioamnionitis (Relative Risk – RR= 0.66; 95% CI= 0.46-0.96) and a reduction in the delivery rate within 48 hours (RR= 0.71; 95% CI= 0.58-0.87) and 7 days of randomisation (RR= 0.79; 95% CI= 0.71-0.89) [16]. Moreover, the incidence of neonatal infections was reduced (RR= 0.67, 95% CI= 0.52-0.85) [16].

This study has certain limitations. First, the retrospective study design may preclude some causal associations, however all relevant data are routinely prospectively collected. Second, some self-reported data may be associated with recall bias, mostly regarding the medical and obstetric history, however this is a standard limitation even in prospective studies. Third, our findings were based on a sample of pregnant women in a single center; however, the latter covers a population of more than 2 million people in northern Greece. Finally, history of preterm birth could be considered a plausible source of bias. However, only one patient reported previous preterm birth.

To conclude, we found that the CL at the time of diagnosis of PPROM may be an accurate predictor for cases complicated by PPROM. With regard to the available international campaigns for the prevention and elimination of the incidence of preterm delivery, more biomarkers are needed for high-risk pregnancies. Moreover, the healthcare policy planners need to establish recommendations on the proper surveillance of pregnancies

complicated with PPROM and thus minimize the adverse outcomes of prematurity. ■

Conflict of interest
The authors declare no conflict of interest.

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no.

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