Sonographic evaluation of Myometrial Thickness as a Prognosticator for the Latency Interval in Pregnant Women with Preterm Premature Rupture of Membranes and Oligohydramnios

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Abstract: Objective: Term labor is associated with global thinning of the myometrium. We hypothesized that a thickened myometrium at the time of preterm premature rupture of membranes (PPROM) predicts less myometrial wall stress and, consequently, a longer latency interval. **Study design**: Myometrial thickness was measured prospectively in 100 pregnant women enrolled in the following groups: preterm premature rupture of membranes (**PPROM**), preterm non-labor control group (**P-CTR**), and term non-labor control (**T-CTR**). All preterm premature rupture of membranes (**PPROM**) women had oligohydramnios. Myometrial thickness was measured ultrasonographically at the mid-anterior, fundal, posterior, and lower uterine segment wall in cases and controls. **Setting:** this is study carried out at Al-Azhar hospitals (Al Hussain and Bab Alsheria hospitals) during the period from January 2016 to June 2016. **Results:** Maternal weight, the number of previous pregnancies, gestational age and SEFW; there was no significant difference among the three groups (p>0.05). MT showed a significant difference between both P-CTR group and T-CTR group with post hoc significance =1 and p >0.001. The LUS was significantly thicker in PPROM group compared with both T-CTR and P-CTR groups (p<0.001). PPROM group had an obvious significantly lower AFI compared with both P-CTR group and T-CTR group. Regression analysis suggested that there was a very strong positive person correlation between the latency interval and both the AFI and the fundal MT. **Conclusion:** Significant thickening of the anterior and fundal walls of the uterus follows preterm premature rupture of membranes (**PPROM**). A thick myometrium in non-laboring patients with PPROM is associated with longer latency interval. Sonographic evaluation of MT may represent an alternative clinical tool for the prediction of a short latency interval in women with preterm premature rupture of membranes (**PPROM).**

1. Introduction

Spontaneous rupture of the membranes is a normal component of labor and delivery. Membrane rupture before the onset of labor is considered premature (PROM), and induction of labor is common if the patient is at or close to term. Patient management becomes more challenging when membrane rupture occurs preterm (PPROM), and in the absence of labor. The incidence of PPROM ranges from 2% to 20% and is associated with 18% to 20% of perinatal deaths.[1-3]

Most women with PPROM deliver within 48 hours of rupture, but the neonatal impact and overall outcome depend largely on the gestational age (GA) at rupture.[4,5] Though the physiologic explanation is obscure, the interval from PPROM to delivery varies inversely with GA at rupture.[4] At less than 25 weeks' (w) gestational age (GA), the average interval from rupture to delivery (latency) is 11 days (d).[6]

Although researchers have long investigated ''the timing of birth,'' our understanding of the biological mechanisms regulating the events that prevent and initiate labor remains limited.[7] Not surprisingly, any prediction of the latency interval for women with PPROM is imprecise.

Amniotic fluid volume, GA, cervical length, and presence of intra-amniotic markers of inflammation have various prognostic values.[8-10] Indeed, oligohydramnios is a risk factor for earlier delivery because abruption and infection are each more common when amniotic fluid volume is diminished.[11,12]

Women with PPROM and oligohydramnios at less than 25 w deliver earlier compared to those with adequate amniotic fluid volume (pocket O2 cm).[8] It is thus not surprising to find that 85% of women with adequate amniotic fluid deliver beyond 25 w, and have much lower neonatal morbidity and mortality rates.[8] Nevertheless, prophylactic therapy with broad-spectrum antimicrobial treatment (but no tocolytic therapy) is also associated with longer latency interval than placebo.[13]

Similar to the myocardium, the force of labor is uterine wall tension opposed to the resistance of the cervix, perineum, and pelvis.[14,15] Mathematical modeling reveals that uterine wall stress (defined as

applied force per unit cross-sectional area of material) is directly proportional to both the intracavitary pressure and the radius of the curvature, but inversely proportional to the thickness of the myometrium.16 Thus, the thicker the myometrium, the lower the uterine wall stress.

We hypothesized that a thick myometrium at the time of PPROM would be associated with less myometrial wall stress and, consequently, longer latency interval. We tested this hypothesis by measuring MT by ultrasound scanning in patients with PPROM immediately following rupture.

2. Methodology
Patients and protocol

Myometrial thickness (MT) was measured prospectively in 100 pregnant women: PPROM (n = 50), preterm nonlabor control (P-CTR, n = 25), and term nonlabor control (T-CTR, n = 25). We approached women admitted to the Labor and Delivery ward and to the antepartum inpatient High-Risk service at both hospitals. All women solicited for enrollment agreed to participate and provided written informed consent. All women in P-CTR group were recruited from the Ultrasound Unit. Women were enrolled based on the availability of one of the investigators, and all enrolled women were included in the final analysis. For the PPROM group, inclusion required PPROM with singleton from 22 to 34 w GA. Exclusion criteria included: fetal anomalies, suspected fetal growth restriction (IUGR) (sonographic fetal weight!10% percentile for GA), abnormalities of placentation (low lying placenta, abruptio placenta), uterine structural abnormalities, cervical cerclage, previous uterine scar. Management of the patients was left up to the treating team. All patients except one (22 w GA) received corticosteroids for lung maturity and antibiotics per PPROM protocol (ampicillin/erythromycin). In the absence of signs or symptoms of chorioamnionitis (fever over 100.4(F, abdominal tenderness, fetal tachycardia), and/or abnormalities of fetal heart rate (variable or late decelerations), and/or abruption, PPROM was managed expectantly. The diagnosis of PPROM was confirmed by visualization of amniotic fluid ''pooling'' through the cervical os during speculum examination, ''nitrazine,'' ''ferning,'' or amniocentesis-dye positive tests. Tocolysis and/or digital exams were not permitted. Patients received corticosteroids for lung maturity if less than 32 w GA, and antibiotic therapy (ampicillin/erythromycin or clindamycin in the event of allergy to penicillin). Women were monitored by cardiotocography at least twice daily for the presence of fetal heart abnormalities and/or uterine contractions. The ultrasound examination was performed within 12 hours of PPROM. An abdominal ultrasound survey was performed using a 5.0 or 7.5 MHz transabdominal probe. The amniotic fluid index (AFI) was measured using the 4-quadrant technique.17 Oligohydramnios was defined as an AFI less than five cm.17 The myometrium was sonographically identified as the echo homogeneous layer between the serosa and the decidua. The MT was measured at 4 di□erent sites: lower segment (LUS) (approximately 2 cm above reflection of the urinary bladder), mid-anterior wall (with the scan probe 1 cm above the maternal umbilicus), fundus, and posterior walls of the uterus.14 Thickness of the fundus was measured by placing the scan probe above the uterine fundus so that the entire curvature of the uterus was visualized. To assure consistency in the anatomic site, aortic pulsations were identified before evaluation of fundal MT and used as a reference for all subsequent measurements. Measurement of the posterior uterine wall was technically the most challenging. We demarcated the posterior wall using pulsations of the maternal abdominal aorta as an anatomic marker. Each measurement was made from separate scan images. At least 3 measurements were obtained at each site and averaged. We were not aware of the previous numeric evaluation of MT in between measurements. Previous experience demonstrated no di□erences in MT among uterine wall sites.14 The intraobserver coe□cient of variation for assessment of MT varied from 8% to 10% at each uterine site. The placental thickness was measured at the site of umbilical cord insertion. Abdominal wall thickness was estimated at the same site used to evaluate the thickness of the mid anterior uterine wall.

PPROM women were managed expectantly and underwent serial evaluations of fetal well-being up to delivery (spontaneously or for clinical indications consistent with chorioamnionitis or abruption). The latency interval was defined as the period (days or hours) from the time of membrane rupture reported by the patient to delivery. None of the PPROM women were delivered for topics unrelated to PPROM (elective induction at 34-35 w, preeclampsia, or other medical complications of pregnancy).

Ethical Consideration

Agreement for this study was obtained from the hospital's ethical committee; and informed consent was obtained from pregnant women after adequate provision of information regarding the study requirements, purpose and risks.

Statistical analysis

The data are reported as a mean and standard error of the mean. Continuous normally distributed data were compared using one-way analysis of variance (ANOVA) or one-way repeated measures ANOVA. Statistical analysis of all MT datasets was completed after logarithmic transformation to obtain a

normal distribution (one-way ANOVA). The effect of PPROM on MT at different uterine sites was determined using two-way repeated measures ANOVA. Multivariate analysis with linear regression model was applied to identify any significant associations between maternal, fetal, or labor characteristics as independent variables and MT as the dependent variable. Survival analysis was performed using Graph Pad Software (San Diego, Calif). A $P<0.05$ was considered to indicate statistically significant difference.

3. Results

The present study was carried out at Al-Azhar University Maternity Hospital during the period from January 2016 to June 2016. The study included a total number of 100 pregnant women and they were divided into three groups:

✓ **Group I:** consisted of 50 women with preterm premature rupture of membranes (**PPROM**, n=50) with gestational age from 24 to 34 weeks.

✓ **Group II:** included 25 term non-labor control (**T-CTR**, n=25) with gestational age from 37 to 41 weeks.

✓ **Group III**: included 25 preterm non-labor control (**P-CTR**, n=25) with gestational age from 24 to 34 weeks.

Table (1): Demographic data in PPROM and T-CTR

	Group	*Mean ±SD*	95% Confidence interval CI		*P*
			lower bound	*upper bound*	
Age	PPROM	29.44±6.1	27.68	31.21	0.57
	T-CTR	26.76±5.9	24.32	29.20	
Previous pregnancies	PPROM	2.20±2.1	1.60	2.80	0.61
	T-CTR	1.68±1.8	0.92	2.44	
Maternal weight	PPROM	85.1±6.0	83.62	88.72	0.23
	T-CTR	89.8±4.1	86.56	91.43	

Table (2): Demographic data in PPROM and P-CTR

	Group	Mean ±SD	95% Confidence interval CI		P
			lower bound	*upper bound*	
Age	PPROM	29.44±6.1	27.68	31.21	0.54
	P-CTR	26.56± 5.9	24.72	28.40	
Previous pregnancies	PPROM	2.20±2.1	1.60	2.80	0.57
	P-CTR	1.6±2.5	0.64	2.72	
Maternal weight	PPROM	85.±6.0	83.62	88.72	0.74

Table I & 2 present a series of demographic and ultrasonographic variables assessed at enrollment. Women with PPROM were significantly older compared with those in the P-CTR and T-CTR groups. There were no significant differences among groups regarding gravidity, parity or maternal body weight.

Table (3): The post-hoc Tukey test showing the difference in gestational age between PPROM, P-CTR, and T-CTR groups

Groups	*N*	*Subset for alpha= 0.05*		
		1	*2*	*3*
P-CTR	25	31.04		31.04
T-CTR	25		39.04	39.04
PPROM	50	30.74	30.74	
Significance		0.884	1.000	1.000

Regarding the gestational age, women with PPROM (mean ±SD: 30.7±2.8 w) and P-CTR group (mean ±SD: 31±2.4 w) showed no significant difference with post-hoc significance =0.884 and p >0.05, while there was a significant difference in GA between PPROM and T-CTR group (mean ±SD: 39±1.3w) with post-hoc significance = 1 and p <0.001. As well as between P-CTR group and T-CTR group with post-hoc significance =1 and p<0.001 (Table 3).

Table (4): The post-hoc Tukey test showing the difference in AFI between PPROM and Both P-CTR and T-CTR groups

Groups	N	Subset for alpha= 0.05		
		1	2	3
P-CTR	25	15.20		15.20
T-CTR	25		13.85	13.85
PPROM	50	3.56	3.56	
Significance		1.000	1.000	0.874

PPROM group had an obvious significantly lower AFI (mean ±SD: 3.56±3cm) compared with both P-CTR group (mean ±SD): 15.2±3.4cm) and T-CTR group (mean ±SD: 13.8±5.8cm) with post hoc-significance = 1 and p <0.001.

There was no significant difference in AFI between P-CTR group and T-CTR group with post hoc significance =0.874 and p >0.05. (Table 4).
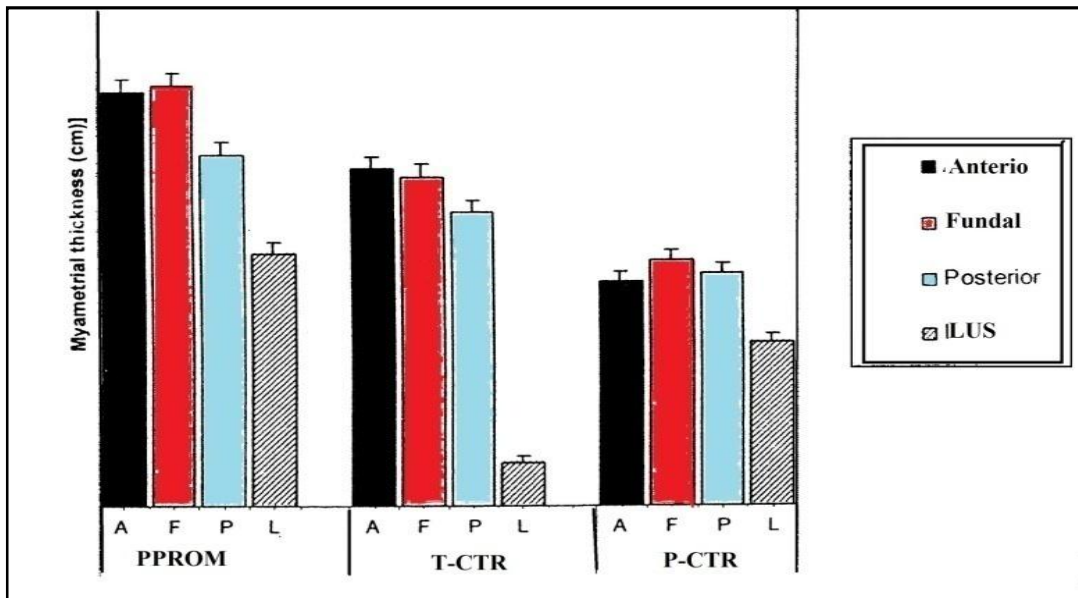
Sonographic estimated myometrial thickness (MT)

Figure (1): Bar chart representing MT at different uterine sites in the three groups.

Figure 1 illustrates representative ultrasound images of the anterior uterine wall of a woman in the P-CTR and PPROM groups. Both women had similar GA at MT assessment (27 w).

Sonographic evaluation of the myometrial wall at term (T-CTR) demonstrated that MT for each patient was uniform between uterine body sites. The mean ±SD were the following: anterior wall (8.8±0.3mm), fundal wall (8.7±0.2mm), and posterior wall (8.2±0.2mm). At term, all uterine body sites were significantly thicker than LUS: (4.6±0.2mm) [p<0.001].

Similarly, MT assessment in the PPROM group revealed uniform thickness at each site of the uterine body anterior wall (9.9±1.8mm), fundal wall (10±2.1mm), posterior wall (9.0±1.6mm), [p=0.07]. Although the LUS was thinner in PPROM women compared to the other sites (4.6±1.7mm) sites [p<0.001].

In the P-CTR group the differences in MT between sites including LUS did not reach the statistical significance anterior wall (7.2±0.2mm), fundal wall (7.5±0.2mm), posterior wall (7.3±0.3mm) and LUS (6.3±0.1 mm) [p> 0.05].

Among groups, MT was significantly thicker at the anterior site in PPROM group (9.9± 1.8mm) compared with P-CTR group (7.2±0.2mm) and T-CTR group (8.8±0.3mm) with post hoc significance

=1 and p <0.001. This diˉerence was maintained at the fundal site (PPROM vs. P-CTR, *P*<.001; PPROM vs. T-CTR, *P* <.001). The posterior wall site was only marginally thicker in PPROM women compared with both control groups (*P* =.05). LUS was significantly thicker in PPROM compared with P-CTR (*P* <0.001)

and T-CTR (*P* <0.001) women. MT of the LUS at term was not diˉerent from P-CTR (*P* =.07).

Regression analysis suggested that there was a direct correlation between latency interval and fundal MT with a very strong +ve Pearson correlation=0.895 and a highly significant p-value <0.001 as shown in figure (2).

Table (5): The linear regression model with the latency interval as a dependent variable *Coefficient*

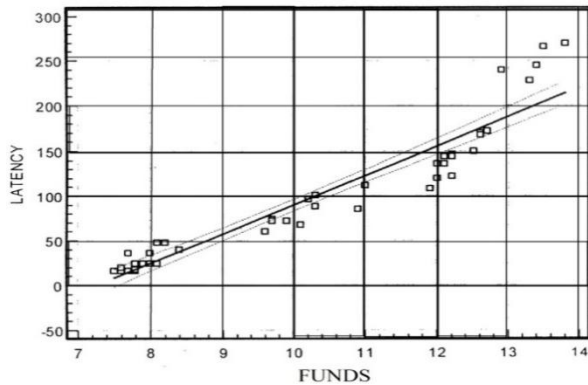| Model		Unstandardized Coefficients		95% Confidence Interval For B	
		B	Std. Error	Lower Bound	Upper Bound
1	(Constant) Fundus	-237.463 32.720	15.606 1.529	-268.841 29.645	-206.085 35.794

Figure (2): A scatter diagram showing the relation between fundal MT and latency interval in women with PPROM

By using the linear regression model, we modeled the latency interval as a dependent variable and the fundal MT as a predictor (constant), and an equation was made from coefficients seen in the table (5) to calculate the latency interval in hours from the sonographic assessment of fundal MT in millimeters.

There was a direct +ve correlation between the latency interval and anterior MT with person correlation = 0.866 and p<0. 001. Posterior wall is positively correlated to the latency interval with Pearson correlation =0.868 and p <0.001. LUS is positively correlated to the latency interval with pearstm correlation =0.813 and p <0.00I.

There was a direct correlation between latency interval and AFI with Pearson correlation =0.710 and P<0.001. This means that the more the increase in the AFI the more the increase in time of the latency interval. There was a +ve person correlation between the latency interval and GA with person correlation = 0.769 and p 0.00l. This means that the more the

increase in the gestational ages the more the increase in the latency interval.

4. Discussion and Conclusion

We demonstrate in the present investigation that uterine wall thickness is altered in women with PPROM, and correlates with latency interval. This finding has both clinical and physiologic implications.

PPROM and associated preterm delivery are considered the leading causes of perinatal morbidity and mortality in the US.[18,19] Clinically, the GA at PPROM, SEFW, fetal presentation, fetal lung maturity, the absence of intra-amniotic inflammation, the degree of cervical dilatation, and state of myometrial contractility are carefully evaluated before deciding on a course of management. In the absence of clinical symptoms or laboratory signs of chorioamnionitis, the management of pregnancy with PPROM is usually expectant, based on the assumption that even a minor delay in the interval to delivery will be beneficial to the fetus.[20]

Even though we have searched for factors that predict the onset of preterm labor, the thickness of the myometrium following PPROM has never been tested. Digital cervical examination, home uterine monitoring of uterine contractility, and thickness of LUS have each been studied.[21-24] The digital cervical examination and frequency of uterine contractions have weak prognostic values.[24] Not only are a digital cervical examination of women with PPROM and frequency of uterine contractions poorly predictive, but a digital exam may increase the risk of ascending infection.[25] Conversely, vaginal bleeding, risk scoring schemes, and fetal breathing activity are also predictive of the onset of labor, but either has poor sensitivity and specificity or are accurate only at late stages in the pathogenic process.[26] Despite being ineˉective, many of the previously listed prediction

strategies are widely used in the clinical practice. The most recent e□orts to estimate the predictive value of LUS thickness in women with intact membranes also proved to be unsuccessful.23

There has been much attention focused on the sonographic assessment of cervical length since shortening is associated with an increased risk of preterm delivery in both nulliparous and multiparous women.21,22,27 The preterm delivery prediction study conducted by the NICHD Maternal Fetal Medicine Unit Network concluded that the most powerful factors associated with preterm birth before 32 w are a positive fetal fibronectin test and a cervical length less than 10th percentile either alone or in combination with other maternal serum biochemical tests.28 Cervical length measurement after PPROM may also be useful for predicting preterm birth, as the risk of ascending infection remains low.9 Unfortunately, the modest sensitivity with high specificity of cervical length evaluation may reflect the fact there are several di□erent patterns of ''normal'' change in cervical length. These patterns may vary from a gradual to an accelerated change or even a precipitous decrease in cervical length at term.29

The clinical management after PPROM is complicated by the absence of a gold standard method to predict pathogenic processes leading to parturition.26 Our understanding of the mechanisms that determine the length of the latency interval after PPROM is hindered by the fact that the human myometrium and cervix appear to have redundant and parallel mechanisms to ensure adequate length of gestation.30 Furthermore, the impact of pregnancy and labor on the uterus and cervix di□er significantly.31,32 The prevailing theories surrounding PPROM latency interval may well overestimate the importance of the cervix, leaving the role played by myometrial activation largely unexplored. Markers with prognostic value in predicting the latency interval (chorionic-decidual and myometrial cell activation) would be beneficial as aides to clinical management, as well as to enhance our understanding of the mechanisms triggering preterm labor contractions and PPROM.26

Our previous sonographic observation14 that the myometrium thins symmetrically during active labor with the least amount of thinning at the uterine fundus stimulated us to rethink the mechanisms responsible for the uniform dispersion of the contractile forces that ensure e□cient fetal expulsion. Consistent with our previous report, we now demonstrate that women with spontaneous PPROM and in the absence of myometrial activation have a thicker anterior and fundal wall compared with women who have intact membranes. Sudden decompression of the uterine sac,

which had been filled with a minimally compressible fluid that normally opposed thickening, is the most likely physiologic explanation.33 We assume that women with a long latency interval after spontaneous PPROM are in a state of myometrial quiescence or incomplete myometrial activation, and demonstrate that the long latency and presumed myometrial quiescence are associated with a greater thickness of the anterior and fundal wall myometrium. These observations are consistent with previous interpretations that the mechanisms underlying physical disruption of amniochorion integrity are complex, and collagenolytic activation of matrix metalloproteinases can occur in the absence of uterine contractility (myometrial activation).34 It is possible that those women with PPROM and thin myometrium already experienced functional complete myometrial activation that allows for coordinated tone, contractions, and shorter latency interval.

Sonographic evaluation of cervical length in women with PPROM is reported to have maximum sensitivities and specificities of 63% and 81%, respectively.29 We find that the sonographic measurement of fundal MT less than 8.1 mm has a similar sensitivity and specificity (55.6%, respectively, 88.9%). However, we further determined that a MT 12.1 mm or more is 93.7% sensitive and 63.6% specific for the prediction of a latency period longer than 120 h. Unfortunately, no cervical length data are currently available for comparison at 120 h. As a corollary to these findings, survival analysis revealed that a thickened myometrium in nonlaboring women with PPROM was associated with latency longer than 120 h. This is consistent with our previous report demonstrating that only active myometrial contractility is associated with widespread thinning of the myometrium independent of ROM,14 and explains why nonactive laboring women (thick myometrium) have longer latency periods than those with MT less than 12.1 mm. Given the likely heterogeneity in the causes of preterm labor, our present and previous reports raise more questions. We have insu□cient data at this time to determine how MT changes longitudinally over the course of the latency period in women who will undergo spontaneous onset of uterine contractions. Further, we still do not know the appropriate method to predict latency in women with PPROM. Studies combining cervical length and MT sonography, fetal fibronectin, proteomic analysis of the amniotic fluid at the time of PPROM, and development of highly sensitive noninvasive uterine contraction monitoring methods are warranted. Transabdominal ultrasound evaluation of MT and surface electromyographic analysis of uterine contractions remain the only noninvasive methods to evaluate choriodecidual myometrial

activation.26,31 While transabdominal sonography is unsatisfactory for cervical assessment; it is well accepted by the patients for MT evaluation.35 The sensitive biochemical assays for b-human chorionic gonadotropin (b-hCG) hormone, cytokines, and corticotrophin releasing hormone (CRH), as well as serial evaluation of vaginal amniotic fluid combined with the cervical length and MT sonography, may provide the context required for a reassessment of the mechanisms responsible for early or delayed delivery of the fetus.

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