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Prediction of Latency Interval in Preterm Premature Rupture of Membranes using Sonographic Myometrial Thickness

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Abstract: Despite recent advances in perinatal care, Preterm Premature Rupture of Membranes (PPROM) continues to lead to important obstetric complications. This study was aimed to evaluate the role of sonographic measurement of myometrial thickness in prediction of latency interval in women with PPROM. This analytic- descriptive and case- control study was performed on pregnant women with PPROM presenting to Tabriz Al-Zahra Hospital since 2006 to 2008. Thirty pregnant women with PPROM and 30 pregnant women with normal pregnancy were enrolled. Mean gestational age was 30.60±1.99 week and in case and 31.13±20.01 week in control group (p = 0.307). Mean gravidity was 1.63±0.49 in case and 1.47±0.50 in control group (p = 0.210). Mean parity was 0.53±0.62 in case and 0.57 0.50 in control group (p = 0.819). Mean anterior myometrial thickness was 8.23±2.59 mm in case and 7.71±1.45 mm in control group (p = 0.344). Mean posterior myometrial thickness was 8.90±2.86 mm in case and 8.12±1.54 mm in control group (p = 0.197). Mean fundus myometrial thickness was 9.10±3.54 mm in case and 8.77±1.77 mm in control group (p = 0.648). Mean latency interval of women with PPROM was 18.70±20.68 day and mean sonography to labor interval was 57.30±16.14 day (p<0.01). Mean latency interval of women with PPROM was significantly shorter than mean sonography to labor interval in control group patients (p<0.05). In our study, 50% of women in 10 first days after PPRM labored and only 43.3% of women labored in 7 first days after PPROM. In this study, significant correlation was not found between myocardial sickness in anterior, posterior and fundus with latency interval.

Key words: Complications, perinatal care, ultrasonography, preterm premature rupture of membranes

INTRODUCTION

Despite recent advances in perinatal care, preterm premature rupture of membranes (PPROM) continues to lead to important obstetric complications beginning a high-risk period for both mother and fetus (Mateus *et al*., 2010; Pasquier and Doret, 2008; Park *et al*., 2006; Naylor *et al*., 2001). PPROM is the leading identifiable cause of prematurity (Manuck *et al*., 2009). It is a common event and during the preterm period, it occurs in 1% of all pregnancies (Park *et al*., 2006).

The term latency refers to the time between membrane rupture and delivery. Latency is an important factor for neonatal survival in these patients (Park *et al*., 2006; Mercer, 2003). Studies showed that latency period after PPROM is associated with a higher infant mortality rate specially when occur before 30 weeks' gestation, with pulmonary disease being the major cause of death (Pasquier *et al*., 2007; Hsieh *et al*., 1999; Nelson *et al*., 1994). There is an urgent need for a through evaluation of expectant management of PPROM (Pasquier *et al*., 2007; Hsieh *et al*., 1999; Nelson *et al*., 1994). The risk of chorioamnionitis increases with increasing latency period (Park *et al*., 2006) which worsens the neonatal outcomes (Aziz *et al*., 2009). PPROM is associated with several factors that lead fetal morbidity and mortality. Amnionitis, advanced labor and non-reassuring fetal status usually force the clinician to affect delivery despite fetal immaturity. Also, chorioamnionitis is one of the various causes of neonatal brain damage in this period (Park *et al*., 2006; Salafia *et al*., 1995; Vergani *et al*., 2000; Thorp *et al*., 2001). Having adequate knowledge about latency period after PPROM and conducting appropriate management such as early referring to well-equipped center, clinicians can resolve mater and fetus.

Abdominal (Sfakianaki *et al*., 2008; Gire *et al*., 2002; Durnwald and Mercer, 2008; Buhimschi *et al*., 2003; Bergeron *et al*., 2009; Bujold *et al*., 2009) and transvaginal

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(Eitan *et al*., 2005) ultrasound scans has been used as a valuable method for measurement of myometrial thickness in prediction of maternal conditions (Bergeron *et al*., 2009; Bujold *et al*., 2009; Eitan *et al*., 2005) or pregnancy outcome (Sfakianaki *et al*., 2008; Gire *et al*., 2002; Durnwald and Mercer, 2008; Buhimschi *et al*., 2003).

Our objective was to evaluate the role of sonographic measurement of myometrial thickness in prediction of latency interval in women with premature rupture of membranes in order to help the clinicians in better decision making.

MATERIALS AND METHODS

This is an analytic- descriptive and case- control study performed on pregnant women with PPROM presenting to Tabriz Al-Zahra Hospital since 2006 to 2008. Thirty PPROM women with pregnancy age of 28-34 weeks admitted in high risk pregnancy ward (Case Group) were compared with a matched group containing 30 healthy pregnant women and the same pregnancy age presenting for routine pregnancy control visits (Control Group).

The exclusion criteria were IUGR, fetal anomalies, uterine anomalies, placenta abruption, placenta anomalies, cervical cerclage, previous uterine scar (except for scar of previous cesarean), very obese patients (for prevention of sonography false results), history of premature delivery, multiple pregnancy, the need for elective induction of delivery for maternal or fetal indications and moderate to severe oligohydramnios. Oligohydramnios was classified as severe (fluid index <2 cm), moderate (fluid index 2-5 cm) or mild (fluid index >5 cm).

PPROM was diagnosed by (1) sterile speculum examination, (2) sonographic report of oligohydramnios, (3) the maternal report indicating the presence of amniorrhea and (4) a combination of vaginal pooling, nitrazine and fetal fibronectin testing (Park *et al*., 2006). All patients with PPROM were admitted in high risk pregnancy ward with following routine services: control of vital signs specially fever (for chorioamnionitis), control of bleeding, amniorrhea and contractions, control of abdominal tenderness (for chorioamnionitis), Fetal Heart Rate (FHR) monitoring, daily Non-Stress Test (NST), biophysical profile (BPP) two times a week, administration of betamethasone 12 mg day^{-1} for two days and antibiotic therapy with ampicillin- gentamicin for 3 days followed by oral amoxicillin for a week.

In the presence of chorioamnionitis with manifestations of maternal fever, fetal tachycardia or uterine tenderness and also in the presence of fetal complications including abnormal FHR or BPP, the pregnancy was terminated and the case was excluded from the study. Otherwise, the patients underwent expectant management.

All patients (cases and controls) underwent trans-abdominal sonography for measurement of amniotic index and myometrial thickness in anterior and posterior aspects and fundus of uterus. The myometrium was defined sonographically as the echo homogeneous layer between the serosa and the decidua (Buhimschi *et al*., 2003). For determination of anterior wall thickness the US probe was located 1 cm upper the umbilicus. For fundus wall thickness, the probe located so that the total uterus curvature to be observable. Posterior wall thickness was determined according where the aorta pulse was detected.

All sonographies were performed by expert sonographists. Then, the time between PPROM beginning and labor in case group and the time between sonography and labor in control group were determined.

Other information collected from patients by questionnaires was including: age, gestational age, gravidity and delivery date. Written informed consent was obtained from all enrollees, according to the criteria of the Ethical Committee of Tabriz University of Medical Sciences.

The collected data were analyzed by SPSS-12 statistical software. The collected data were expressed as percentage and Mean±SD. Continuous (quantitative) variables were compared by Student T-test (Independent samples). Categorical (qualitative) variables were compared by contingency tables and Persian Correlation, Chi-square test or Mann-Whitney-U test. The p-value ≤ 0.05 was considered statistically significant (Park *et al*., 2006; Safaei, 2008).

RESULTS

Thirty women with pregnancy age of 28-34 weeks (Case Group) were compared with a matched group containing 30 healthy pregnant women and the same pregnancy age (Control Group). The characteristics of patients in case and control groups are presented in Table 1.

Eleven patients in case group were gravid 1, 16 were gravid 2 and 3 were gravid 3. As showed in Table 1, maternal age, gestational age, gravidity, parity and myometrial thickness at anterior and posterior aspects and fundus of uterus were not significantly different in both groups.

In case group, 20 patients (66.7%) were admitted at the first day of amniorrhea, 7 (23.3%) at the second day and 3 (10%) at the third day.

The time interval between amniorrhea and delivery in case group was 18.70±20.68 day (481.00±528.42 h). The

Table 1: Characteristics of patients in case and control groups

Variable	Case group	Control group	p-value
Maternal age (year)	27.20±4.96	26.30±4.17	0.450
Gestational age (week)	30.60±1.99	31.13±2.01	0.307
Gravidity	1.63±0.49	1.47±0.50	0.210
Parity	0.53±0.63	0.57±0.50	0.819

Table 2: Sonographic findings of patients in case and control groups

Variable	Case group	Control group	p-value
Anterior myometrial thickness (mm)	8.23±2.59	7.71±1.45	0.344
Posterior myometrial thickness (mm)	8.90±2.86	8.12±1.54	0.197
Fundus myometrial thickness (mm)	9.10±3.54	8.77±1.77	0.648

time interval between sonography and delivery in control group was 57.30±16.14 day (1445.60±446.72 h). The time between amniorrhea and delivery in case group was significantly shorter than the time between sonography and delivery in control group ($p<0.001$).

The time between hospitalization and delivery in case group (18.70±20.68 day) was significantly shorter than the time between sonography and delivery in control group (57.30±16.14 day) ($p = 0.000$).

The average amniotic fluid index was 8.80±5.61 in case group (range 2-10) and 10.11±1.33 in case group (range 7-12), with no significant difference ($p = 0.217$).

The sonographic findings of patients in case and control groups are presented in Table 2.

In case group we found direct linear relation between duration of amniorrhea and maternal age ($p = 0.022$, $r = 0.417$) and reversed linear relation between amniorrhea to delivery time and gravidity ($p = 0.030$, $r = -0.396$). It seems that the delivery occurs later in women with higher age and PPROM and occurs earlier in women with lower gravidity.

However, there was not significant linear relation between amniorrhea to hospitalization time and GA ($p = 0.631$), gravidity ($p = 0.422$), parity ($p = 0.393$) and amniotic fluid ($p = 0.608$); amniorrhea to delivery time and GA ($p = 0.848$), parity ($p = 0.376$), myometrial thickness at anterior ($p = 0.341$), posterior ($p = 0.496$) and fundus ($p = 0.172$) of uterus and amniotic fluid ($p = 0.190$); GA and myometrial thickness at anterior ($p = 0.299$), posterior ($p = 0.609$) and fundus ($p = 0.807$) of uterus; parity and myometrial thickness at anterior ($p = 0.755$), posterior ($p = 0.594$) and fundus ($p = 0.617$) of uterus; and amniotic fluid and myometrial thickness at anterior ($p = 0.097$), posterior ($p = 0.169$) and fundus ($p = 0.378$) of uterus.

In control group we found reversed linear relation between GA and myometrial thickness at anterior aspect of uterus ($p = 0.001$, $r = -0.576$). Our study showed that with increasing the GA (from 28 to 34 weeks), the myometrial thickness decrease in anterior aspect, but this finding is not true for other aspects of myometrium.

However, there was not significant linear relation between GA and myometrial thickness at posterior ($p = 0.062$) and fundus ($p = 0.462$) of uterus; gravidity and myometrial thickness at anterior ($p = 0.533$), posterior ($p = 0.827$) and fundus ($p>0.05$) of uterus; and parity and myometrial thickness at anterior ($p = 0.829$), posterior ($p = 0.130$) and fundus ($p = 0.180$) of uterus.

DISCUSSION

Morphologic studies suggest dramatic, asymmetric uterine growth during pregnancy that is caused by muscle cell hypertrophy. This growth is most marked at the fundus (Buhimschi *et al*., 2003). Term labor is associated with global thinning of the myometrium. It has been 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 (Buhimschi *et al*., 2005). There is significant and widespread thinning of the myometrium during active labor. Descent of the fetal head during the second stage of labor is associated with a significant relative thickening of the anterior and fundal myometrium. These findings suggest the directionality of the expulsive force vectors (fundal dominance) is not determined by asymmetric myometrial growth but, rather, may be a function of increased myometrial mass that results from increased surface area at the fundus (Buhimschi *et al*., 2003). Buhimschi *et al*. (2003) used abdominal ultrasound scans on 52 term pregnant women to investigate the changes in myometrial thickness. Myometrial Thickness (MT) was measured at the low segment and mid anterior, fundal and posterior uterine walls. The myometrium was significantly thinner during active labor compared with nonlabor at each site studied. The thickness of the low segment was not affected by labor status. Similarly, the MT of the anterior uterine wall was unaffected by contractions. There was no change in MT measured immediately before and after rupture of the amniotic membranes, despite a significant decrease of the amniotic fluid index (Buhimschi *et al*., 2003).

A retrospective cohort study of all women diagnosed with PPROM during 1998-2006 showed that the overall rate of PPROM was 1.4%, of which 46% occurred at <34 weeks. Overall, the latency period exceeded 48 h in about 73.4% of cases. The duration of the latency period was 0-59 days. Gestational age at admission, oligohydroamnios, cervical dilatation >1 cm, fetal growth restriction and nulliparity were significantly associated with shorter duration of the latency period (Melamed *et al*., 2009). In Gire *et al*. (2002) study in pregnancies affected by PPROM, the median time interval between admission and delivery (latency period) was 48 h (Gire *et al*., 2002). The median latency period in our study was 10 days. In

Hsieh *et al.* (1999) study, regardless of the gestational age at PPROM, the mean latencies of singleton and twin pregnancies were statistically similar (4.4±3.3 vs. 3.4±2.9 days, non significant) (Hsieh *et al.*, 1999).

In our study, the mean time interval of vaginorrhea to delivery in patients with PPROM was 18.70±20.68 days. In Hsieh *et al.* (1999) study, 50% of women delivered within 48 h after PPROM and 91.7% within 7 days. In this study, 50% of women delivered within 10 days after PPROM and only 43.3% delivered within 7 days.

Nelson *et al.* (1994) evaluated expectant management of PPROM between 20 and <36 weeks' gestation. Over 47.8% of the patients continued their pregnancy beyond 48 h and in 12.9% of cases expectant management of preterm premature rupture of membranes prolonged the pregnancy by = 7 days. The maternal infection rate is greater before 28 weeks' gestation and is associated with higher fetal-neonatal mortality. Status has little impact on outcome. Expectant management is not detrimental to quality of survival. Survival probability increases at a more rapid rate with preterm premature rupture of membranes after 22 weeks of gestation (Nelson *et al.*, 1994).

In this study, the time between amniorrhea and delivery in case group was significantly shorter than the time between sonography and delivery in control group. Also, the time between hospitalization and delivery in case group was significantly shorter than the time between sonography and delivery in control group. These findings were expected and indicate that the sampling was correct and there was not premature delivery in control group.

In this study, 10% of women delivered within 48 h after PPROM and 56.7% delivered within 7 days.

Degani *et al.* (1998) measured Myometrial Thickness (MT) in singleton uncomplicated pregnancies to achieve baseline reference values for further studies in high-risk pregnancies. MT of the upper uterine segment remains fairly constant in the first and second trimesters, whereas a significant linear trend was found between a decreasing thickness of the lower uterine segment and advancing gestational age. MT was significantly increased behind the placental insertion site (Degani *et al.*, 1998).

Latency period was defined as the time between onset of PPROM to either spontaneous delivery, labor induction at 34 weeks, or indicated delivery prior to 34 weeks because of suspected chorioamnionitis or nonreassuring fetal heart rate (Melamed *et al.*, 2009). Latency period after PPROM is associated with a higher infant mortality rate specially when occur before 30 weeks' gestation, with pulmonary disease being the major cause of death (Pasquier *et al.*, 2007; Hsieh *et al.*, 1999; Nelson *et al.*, 1994). There is an urgent need for a thorough evaluation of expectant management of PPROM (Pasquier *et al.*, 2007; Hsieh *et al.*, 1999; Nelson *et al.*, 1994). The risk of chorioamnionitis increases with increasing latency period (Park *et al.*, 2006) which worsens the neonatal outcomes (Aziz *et al.*, 2009).

In one study MT was measured sonographically in 76 pregnant women enrolled in the following groups: PPROM, preterm non-labor control group (P-CTR) and term non-labor control (T-CTR). All PPROM women had oligohydramnios. Significant thickening of the anterior and fundal walls of the uterus follows PPROM. A thick myometrium in nonlaboring patients with PPROM was 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 PPROM (Buhimschi *et al.*, 2005). Bergeron *et al.* (2009) used sonographic evaluation of the lower uterine segment to study the degree of thinning. There was a discrepancy between the full thickness and the myometrial layer, which could be representative of the lower uterine segment resistance. Their findings emphasize the need for a consensus on sonographic measuring techniques for the prediction of uterine rupture (Bergeron *et al.*, 2009).

In this study, the relation of latency period with MT in anterior, posterior and fundus of myometrium was not significant ($p>0.05$). In Buhimschi *et al.* (2005) study, women in the PPROM group displayed uniform thickness of the uterine body (anterior: 10.6±0.6 mm, fundal: 10.7±0.7 mm, posterior: 8.9±0.5 mm, $p = 0.078$). At midanterior site the myometrium of the PPROM group was thicker compared to both control groups. There was a positive correlation between fundal MT and latency period ($r = 0.43$, $p = 0.02$) that persisted after adjusting for GA. A fundal MT less than 12.1 mm was 93.7% sensitive and 63.6% specific for the identification of women whose latency period was less than 120 h (Buhimschi *et al.*, 2005).

Among premature infants born at <34 weeks after PPROM, gestational age at diagnosis is independently associated with neonatal white matter damage (Locatelli *et al.*, 2005). Infectious morbidity in patients with preterm prelabor rupture of membranes and preterm delivery remained an important risk factor for obstetrical and neonatal complications (Furman *et al.*, 2000). The frequency and severity of neonatal complications after PPROM vary with the gestational age at which rupture and delivery occur. In particular, the risk of complications increases with decreasing gestational age at membrane rupture and delivery (Park *et al.*, 2006; Mercer, 2003).

All laboring women had uncomplicated labor patterns when studied and were delivered spontaneously.

There are some latency-period complications including: spontaneous onset of labor, chorioamnionitis, abruptio placentae, fetal distress and umbilical cord prolapse. Admittedly, the infection/inflammation process plays a key role during the latency period. Conservative management of PPROM is recommended and is associated with significant pregnancy prolongation. This strategy allows a gain in fetal maturity, but increases the risk of complications. The prediction of infection seems to be essential. Fetal pulmonary maturity can be evaluated with a rapid screening test and can yield arguments for the management strategy (Pasquier and Doret, 2008). However, Manuck *et al.* (2009) study on 306 pregnant women with PPROM at 22-34 weeks' gestation showed that latency does not appear to worsen outcomes in pregnancies that are complicated by PPROM (Manuck *et al.*, 2009).

We excluded very obese patients for prevention of sonography false results. However, Joy *et al.* (2009) suggested that BMI is not associated with latency during conservative management of PPROM before 32 weeks' gestation (Joy *et al.*, 2009).

CONCLUSIONS

In this study, significant correlation was not found between myometrial tickness in anterior, posterior and fundus with latency interval. We recommend further studies about abdominal sonographic measurement of myometrial thickness for prediction of latency period in large samples of patients with PPROM.

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