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Original Research

Association of cervical length and uterine artery Doppler with threatened preterm labor

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Summary

Background: To assess the association between cervical length (CL) and uterine artery (UtA) Doppler screening at the second trimester with spontaneous preterm birth. *Materials and Methods:* In this case-control study, 162 antenatal women were recruited, among whom 82 women were admitted with preterm labor (case group) and 80 women only received routine antenatal care (control group). After the pulsatility index (PI), resistance index (RI), and CL were measured using transvaginal sonography at 24 weeks of pregnancy, the distribution values of these variables in patients with idiopathic preterm delivery before 37 weeks were compared to those of patients with delivery at or after 37 weeks. *Results:* The present results showed that in the case group ($p = 0.035$), PI values were 1.64 and 1.42 for term and preterm births, while in the control group ($p = 0.543$), PI values were 1.71 and 1.85 for term and preterm births, respectively. Furthermore, mean PI (MPI) values of the case and control groups were 1.43 and 1.73 ($p = 0.007$), respectively. The present findings also indicated that in the case group ($p = 0.081$), CL values were 26.73 and 23.65 for term and preterm births, while in the control group ($p = 0.644$), CL values were 28.33 and 29.3 for term and preterm births, respectively. In addition, mean CL values of the case and control groups were 23.45 and 28.48 ($p = 0.001$), respectively. *Conclusion:* Although UtA Doppler screening at the second trimester can provide nearly estimates of spontaneous birth, the maternal demographic characteristics and previous obstetrics history are important variables to consider when predicting the likelihood of complications in pregnancy.

Key words: Cervical length; Preterm birth; Uterine artery Doppler.

Introduction

Preterm birth is the most important cause of neonatal morbidity and mortality worldwide, especially when it occurs before 34 weeks of pregnancy [1-3]. The prevalence of preterm birth is approximately 6-10% of all births and is responsible for nearly half of all neonatal deaths [4, 5]. The outcome of preterm infants is strongly dependent on gestational age at delivery, with survival rates increasing from 10% at 23 weeks to 95% at 33 weeks of pregnancy [1]. A number of studies have indicated that ischemia due to trophoblast invasion in the myometrial segment of the maternal spiral artery causes increased resistance to blood flow in the uterine artery. Therefore, failure of trophoblast development leads to preterm labor [1-6]. Transvaginal ultrasonography of cervical length is considered a key factor in predicting preterm birth [7, 8]. Furthermore, high-risk pregnancies are commonly associated with the presence of a short cervix and cervical funneling. Additionally, U-shaped cervical funneling has been shown to be clinically associated with preterm birth [9]. Therefore, this study aimed at evaluating the association between cervical length (CL) and uterine artery (UtA) Doppler screening during the second trimester of pregnancy with spontaneous preterm delivery at less than 37 weeks of pregnancy.

Materials and Methods

This case-control study included pregnant women referred to the ultrasound wards of three hospitals affiliated with Tehran University of Medical Sciences, Tehran, Iran, in September 2014 to March 2015. The case group was a representative sample of pregnant women whose pregnancy was terminated prematurely (less than 37 weeks), either through idiopathic or spontaneous abortion. The control group included a representative sample of healthy pregnant women whose pregnancy reached term after 37 weeks.

Eighty-two subjects in the case group and 80 subjects in the control group were enrolled in the study. The participants were compared in terms of the likelihood of preterm delivery and its association with CL and UtA Doppler screening in the second trimester of pregnancy.

The study was approved by the Ethics Committee of Tehran University of Medical Sciences, IR-TUMS-REC-1395-2488. Oral informed consent was obtained from all pregnant women prior to data collection. The objectives of the study were explained to all participants. Individual patient information was kept confidential and data relevant to the study was published as a group.

Gestational age was determined using the last normal menstrual period (LMP) and ultrasound measurement performed at the first

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trimester of pregnancy for all patients. Parity, smoking habits, age, the number of diastolic notch in the uterine artery and pregnancy outcome were also recorded. Pregnant women with fetal abnormalities, uterine anomalies, and a history of cervical conization were excluded from the study. If three same consecutive waves were observed in UtA Doppler screening, presence of the protodiastolic notch, mean resistance index (MRI) and mean pulsatility index (MPI) were recorded in two waves.

CL, known as the distance between the internal OS to the external OS, was measured by transvaginal ultrasound with an empty bladder, after inserting a vaginal probe into the anterior vaginal fornix with light pressure on the cervix. Due to the dynamics of the cervix, measurements were performed three times at five-minute intervals; the shortest length was reported.

With 95% confidential interval (CI), there was an increase in the term group (46%) and preterm group (39%) according to the study by Soares *et al.* [6]. Therefore, the minimum acceptable sample size of 80 patients (80 preterm and 80 term) were estimated based on the sample size formula to compare the proportions.

Data were collected based on observation, examination and ultrasound evaluation. Variables were reported as the mean [standard deviation (SD)] and number (percentage). The *t*-test and Chi-square test were applied to determine significant differences between groups. Data were analyzed using Stata software, version 13, and a *p* value of 0.05 or less was considered statistically significant.

Table 1. — *Comparison of demographic and medical variables between two groups.*

Variables	Case group n=82	Control group n=80	*p* value
Age	28.95 ± 7.83	31.48 ± 6.73	0.035*
BMI	25.31 ± 5.67	25.93 ± 4.67	0.454
Gravidity	2.16 ± 1.28	2.01 ± 0.98	0.417
Parity	1.18 ± 0.87	0.83 ± 0.88	0.017*
Abortion	0.28 ± 0.61	0.31 ± 0.61	0.728
Smoking habit	0 (0%)	0 (0%)	-
Preterm history (%)	18.29%	15%	0.574
GA by sonography	33.13 ± 2.67	33.55 ± 2.85	0.346
CL	23.45 ± 8.43	28.48 ± 6.61	0.001*
Birth weight	2867 ± 498	3073 ± 537	0.013*
MPI	1.43 ± 0.66	1.73 ± 0.74	0.005*
R UtA-PI	1.44 ± 0.80	1.76 ± 0.92	0.011*
R UtA-RI	0.65 ± 0.12	0.69 ± 0.13	0.065
L UtA-PI	1.38 ± 0.64	1.70 ± 0.84	0.004*
L UtA-RI	0.65 ± 0.10	0.69 ± 0.13	0.040*
UmA-PI	0.95 ± 0.20	1.01 ± 0.29	0.459
UmA-RI	0.60 ± 0.08	0.64 ± 0.29	0.741
MRI	0.66 ± 0.12	0.74 ± 0.40	0.046*
Nouch (positive)	10%	7.59%	0.593

** Significant; BMI: body mass index; CL: cervical length; GA: gestational age; L: left; MPI: mean PI; MRI: mean RI; PI: pulsatility index; R: right; RI: resistance index; UmA, Umbilical artery Doppler; UtA: uterine artery Doppler.*

Results

In this study, the mean age values of case and control groups were 28.95 and 31.48 years, respectively. The risk values of preterm delivery in the case and control groups were 37.80% and 16.25%, respectively.

As shown in Table 1, there are significant differences in terms of mean age ($p = 0.035$), parity ($p = 0.017$), CL ($p = 0.001$), birth weight ($p = 0.013$), MPI ($p = 0.005$), the risk of preterm delivery ($p = 0.002$), right UtA-PI ($p = 0.011$), left UtA-PI ($p = 0.004$), and left UtA-RI ($p = 0.040$) between the two groups. In other variables, there are no significant differences between case and control groups ($p < 0.05$).

In Table 2, the association between the CL measurement and UtA Doppler screening with preterm birth was depicted. The results showed that mean values of CL ($p = 0.044$) and MPI ($p = 0.035$) in women with term delivery are significantly higher than in women with preterm delivery. However, there are no significant differences in terms of right UtA-PI ($p = 0.115$), left UtA-PI ($p = 0.230$), right UtA-RI ($p = 0.101$), left UtA-RI ($p = 259$), umbilical artery Doppler-PI (UmA-PI) ($p = 0.364$), UmA-RI ($p = 0.801$), and MPI ($p = 0.138$) between the two groups.

Logistic regression analysis showed that after adjusting for potential confounding variables, there is a significant relationship between CL, preterm birth, and left UtA-PI with premature pregnancy termination. As shown in Table 3, for each unit increases in CL, the odd of premature pregnancy termination decreased 0.089 times (95% CI: 0.873-0.959, $p = 0.001$). However, there was a positive association between preterm birth and left UtA-PI with the odd of premature pregnancy termination, suggesting that for each unit increase in preterm labor (95% CI: 1.456-7.710, $p = 0.004$) and left UtA-PI (95% CI: 1.044-2.945, p

Table 2. — *Association between CL and UtA Doppler screening in both the case and control group.*

Variables	Delivery < 37 weeks (preterm)	Delivery ≥ 37 weeks (term)	*p* value
CL	23.65 ± 8.45	26.73 ± 7.64	0.044*
MPI	1.42 ± 0.74	1.64 ± 0.70	0.035*
R UtA-PI	1.43 ± 0.78	1.66 ± 0.90	0.115
R UtA-RI	0.64 ± 0.12	0.68 ± 0.13	0.101
L UtA-PI	1.47 ± 0.75	1.56 ± 0.76	0.230
L UtA-RI	0.65 ± 0.13	0.68 ± 0.11	0.259
UmA-PI	0.94 ± 0.18	0.99 ± 0.27	0.364
UmA-RI	0.66 ± 0.39	0.61 ± 0.08	0.801
MRI	0.72 ± 0.52	0.70 ± 0.15	0.138

** Significant; BMI: body mass index; CL: cervical length; GA: gestational age; L: left; MPI: mean PI; MRI: mean RI; PI: pulsatility index; R: right; RI: resistance index; UmA, Umbilical artery Doppler; UtA: uterine artery Doppler.*

Table 3. — *Adjusted logistic regression coefficients of premature pregnancy.*

Variables	S.E.	Sig.	Exp (B)	95% CI
CL	0.024	0.000	0.915	0.873-0.959
Preterm	0.425	0.004	3.350	1.456-7.710
L UtA-PI	0.265	0.034	1.753	1.044-2.945

CL: cervical length; CI: confidential interval; L: left; PI: pulsatility index; S.E.: standard error; Sig,: significance; UtA, uterine artery Doppler.

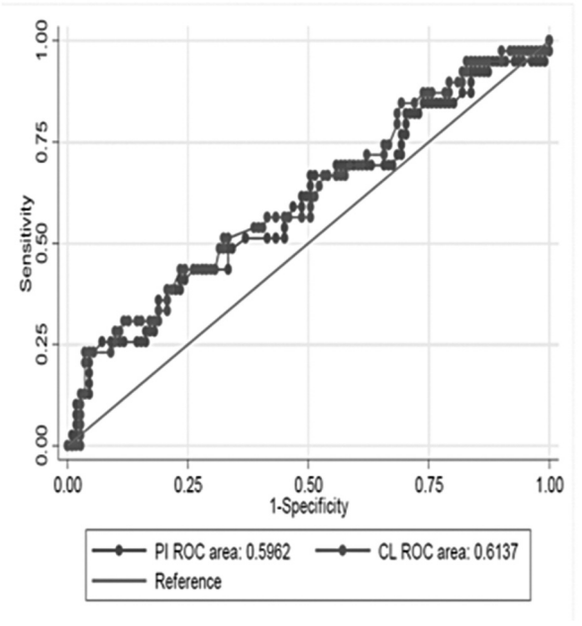

Figure 1. — Comparison of AUC between PI and CL for prediction of preterm birth. AUC: area under curve; CL: cervical length; PI: pulsatility index.

= 0.034), the odds of premature pregnancy termination increases significantly.

As shown in Figure 1, the results revealed no statistical difference in the prediction power of preterm birth between CL and PI [area under curve (AUC)= 0.613 and 0.596, respectively, $p = 0.792$].

Discussion

The present study showed a significant relationship between decreased CL and unchanged mean PI measured in the second trimester with late preterm (between 34 to 37 weeks). During normal development of the placenta, trophoblast invasion of the myometrium and blood vessels occurs [2]. Recent evidence has indicated that failure of physiological transformation of the spiral arteries, especially in the myometrial segment, is closely associated to spontaneous preterm delivery [2].

In 15-20% of pregnancies with preterm delivery, an abnormal placenta is present [3, 9]. Several maternal pathological complications are associated with an abnormal development of the placental vasculature and consequently with preterm delivery, such as chronic hypertension, inherited and acquired thrombophilias, diabetes mellitus, autoimmune disorders (particularly systemic lupus erythematosus), and antiphospholipid syndrome (APS) [10].

UtA Doppler screening is considered an efficient tool for the prediction of preterm labor [9]. The mean value of UtA-PI gradually decreases from the first trimester to the late stages of pregnancy, and UtA-PI Doppler measurements are significantly higher in the first trimester than in the second trimester during normal pregnancy [11]. As such, reference ranges of mean PI are important values that can be used to detect placenta-associated diseases, such as pregnancy induced hypertension (PIH) and fetal growth restriction (FGR) [12]. A number of studies have indicated that in iatrogenic preterm delivery due to pre-eclampsia and intrauterine growth restriction (IUGR), increased UmA-PI and impaired trophoblastic invasion of the myometrial segments of spiral arteries were observed [3-8].

Li *et al.* found that UtA-PI and UmA-PI screening in high risk pregnancies at 23-24 weeks was associated with increasing adverse outcomes of pregnancy, including progressive pre-eclampsia, but it was not useful in predicting essential hypertension [13]. The association between abnormal UmA Doppler with pre-eclampsia and preterm delivery has also been discussed in several studies, in which they have reported similar values for UtA-RI in the first trimester for both term and preterm births [2-4, 6].

Another study reported that UtA-PI at 28 weeks is associated to SGA fetuses, early onset pre-eclampsia, and other poor perinatal outcomes, however UmA-PI provides insufficient evidence for the prediction of pregnancy results [14]. Thilaganathan *et al.* showed that there is no significant increase in RI and early diastolic notches at 18-23 weeks of pregnancy in preterm delivery [2]. Furthermore, a study by Nicolaides *et al.* mentioned that UmA Doppler at 11-14 weeks showed an early diastolic notch in uterine arteries associated with pregnancy complications. Consequently, they stated that early diastolic notch is not a useful marker in screening test for poor outcomes in pregnancy [8].

Although an increased UmA-PI is observed in infants born before 33 weeks compared to full-term infants, there are other important factors to consider, including maternal age, smoking, and previous obstetrics history [5]. For both pre-eclampsia and IUGR, UtA Doppler showed more consistent results in the second trimester than in the first trimester [9].

Studies have indicated that a CL of less than 23 mm is associated with spontaneous preterm birth [5]. Although measurement of CL at 20-24 weeks of pregnancy can be a useful tool to indicate an association between a short cervix and preterm labor [15], neither UtA Doppler nor CL measured in the first trimester are considered useful tools to predict preterm birth [3]. A funnel-shaped cervix and shortened CL with fundal pressure may also be considered as powerful indicators for predicting preterm birth, but cannot be utilized to predict spontaneous preterm labor [15].

Berghella *et al.* showed in a meta-analysis that transvaginal sonography CL (cervical length) screening in singleton pregnancies in symptomatic pregnant women with threatened preterm labor between 24 and 35 weeks was useful in estimating and decreasing threatened preterm labor before 37 weeks [16]. Another study showed a significant correlation between spontaneous preterm delivery before 34

weeks in asymptomatic women with short cervical length (< 20 or < 25) in singleton pregnancy; the correlation was not significant for spontaneous delivery before 37 weeks [17].

The present results showed a significant decrease in CL in patients with premature delivery at less than 37 weeks, as well as a significant association between a not increased MPI and threatened preterm labor. Although other studies have suggested a correlation between increased MPI and threatened preterm labor, the present authors believe that the difference in this study is that the authors considered patients with threatened preterm labor only if subjects delivered preterm, and another one reached to term delivery and it is not contrary to increased MPI in true preterm labor.

The main limitation of the current study was the small sample size, which limited the analysis of the interaction between CL and MPI. More research with a larger sample size is necessary to clarify the interaction between MPI and CL in threatened preterm labor. As such, the correlations between preterm labor with CL and MPI were reported separately. Moreover, the sample size in this study was not sufficient to allow for the statistical analysis of preterm birth in the case and control groups separately.

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