The Role of Uterine Artery Doppler and Maternal Serum D-dimer Levels in Prediction of Preterm Labor

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Abstract

Objective: To determine the role of uterine artery Doppler findings and serum d-dimer levels in prediction of preterm labor in women hospitalised for threatening preterm labor.

Methods: 15 (20.27%) and 59 (79.73%) of 74 pregnant women delivered before and after 37 completed weeks respectively. Ultrasonographic length of the cervix, Bishop scores and uterine artery RI values were not significantly different (p = 0.225; 0.59; 0.622 and 0.331) between both groups. Maternal serum d-Dimer geometric means were 1502.57 ng/ml and 1052.41 ng/ml in preterm and term delivery groups respectively. (p=0.023) 4 (%26.7) women in the preterm versus 2 (%3.4) in the term delivery group had bilateral diastolic notches. [p=0.013, RR:4.12 (1.88-9.01)]. Multiple logistic regression analysis revealed bilateral diastolic notches in the uterine arteries as the only significant factor for prediction of preterm delivery with a sensitivity, specificity, positive and negative predictive value of 0.27; 0.97; 0.67 and 0.84 respectively.

Results: This prospective cohort study was conducted in the perinatology unit of the Süleymaniye Maternity Hospital during 30.01.2004 thru 20.07.2006. Pregnant women hospitalised for threatening preterm labor were evaluated with Bishop's cervical score, cardiotocography, cervical length measurment by abdominal ultrasound, bilateral uterine artery Doppler and measurement of serum d-dimer levels. After delivery patients characteristics were compared between women who delivered before completed 37 weeks and those who delivered later. Parameters with significant difference between the two groups were used in a logistic regression model to adjust for confounding. All statistical work was done with Cruncher Statistical System – NCSS 2000 (McGraw Hill) software.

Conclusion: Maternal serum d-Dimer levels and uterine artery Doppler characteristics are two promising parameters that might be helpful to predict preterm delivery. But our conclusions need to be substantiated by large scale prospective studies before to be recommended for routine clinical use..

Keywords: Preterm labor, uterine artery Doppler, serum D-dimer level.

Uterin arter Doppler bulguları ve maternal serum D-dimer Seviyelerinin erken doğum öngörüsündeki rolü

Amaç: Erken doğum tehdidinde serum D-dimer seviyeleri ile uterin arter Doppler bulgularının prognoz tayinindeki rollerinin saptanması.

Yöntem: Prospektif kohort tasarımlı çalışmamıza 30.01.2004 ile 20.07.2006 tarihleri arasında Süleymaniye Doğum ve Kadın Hastalıkları Eğitim ve Araştırma Hastanesi doğum servisinde erken doğum tehdidi nedeniyle yatırılan olgular dahil edildi. Tüm olgularda Bishop skorlama, abdominal ultrasonografi ile serviks boyu ölçümü, kardiotokografi, bilateral uterin arter Doppler tetkiki ve serum D - dimer düzeyleri tayini yapıldı. Gebelik sonuna kadar izlenen olgular, 37. gebelik haftası öncesinde ve sonrasında doğum yapan grup-

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lara ayrılarak, her iki grup arasında EDT nedeni ile hospitalizasyon esnasında saptanan parametreler açısından farklılık olup olmadığı irdelendi. Anlamlı farklılık gösteren parametreler çoklu lojistik regresyon analizine tabi tutuldu. Tüm istatistiki analizler Cruncher Statistical System – NCSS 2000(Mc Graw Hill) yazılımı yardımı ile yapıldı.

Bulgular: Değerlendirmeye alınan toplam 74 olgudan 15'i (%20.27) 37. haftadan önce 59'u (%79.73) 37. haftadan sonra doğum yaptı. Bishop skorları, ultrasonografik serviks boyu ve sağ ve sol uterin arter RI değerleri iki grup arasında anlamlı farklılık göstermedi (p = 0.225; 0.59; 0.622 ve 0.331). Maternal serum D-dimer düzeyi geometrik ortalaması preterm doğum grubunda 1502.57 ng/ml, term doğum grubunda 1052.41 ng/ml bulundu (p=0.023). Bilateral uterin arterlerde diastolik çentikleşme (UADÇ) ED grubunda 4 (%26.7) olguda, kontrol grubunda 2 (%3.4) olguda izlendi. [p=0.013, RR:4.12 (1.88-9.01)]. Çoklu regresyon analizi sonrası sadece UAÇDde gruplar arasında anlamlı farklılık sebat etti. Bilateral UAÇD bulgusunun duyarlık, özgünlük, pozitif kestirim ve negatif kestirim değerleri sırası ile 0.27; 0.97; 0.67 ve 0.84 idi.

Sonuç: D - dimer ve uterin arter Doppler sonografisi erken doğum öngörüsünde gelecek vaat eden iki parametredir. Ancak rollerinin tam olarak anlaşılabilmesi için daha geniş prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Erken doğum tehdidi, serum D-dimer düzeyi, uterin arter Doppler bulguları.

Introduction

Preterm labor is defined as the presence of three or more uterine contractions in a period of 10 minutes to effect cervical changes or a determination of cervical dilatation 2 cm or above or a cervical effacement 80% or above between 20 and 37 weeks of gestation.[1-3] In spite of the advanced neonatal care, preterm births except congenital malformations account for 70-80% of neonatal mortality.[4] But not enough progression has been achieved in the prediction of preterm labor. Only a small proportion of pregnant women hospitalized with threatened preterm labor actually end up with preterm delivery, and for the rest valuable resources such as manpower, time etc. are wasted.

Preterm delivery is one of the leading causes of neonatal mortality and morbidity. Approximately 5-15% of pregnancies end up with preterm delivery.[5-8] Thereby, early identification of pregnant women with a high risk for preterm delivery is one of the main goals of Obstetrics.

Although most of the clinical studies associate preterm labor with subclinical or clinical inflammation, there are studies suggesting that partial placental ablation, an entity difficult to diagnose, might play a role in a certain proportion of cases of preterm delivery.

In our study, we tried to find out whether umbilical and uterine artery Doppler and maternal serum d-dimer levels used as indirect indicators of silent placental ablation, might help further to identify a subgroup with a high risk for preterm delivery among pregnant women hospitalised for threatened preterm labor.

Methods

Our study is designed as a prospective cohort study.All pregnant women hospitalised because of threatened preterm labor at the Süleymaniye Maternity Hospital Obstetrics Department between 30.01.2004 and 20.07. 2006 are included.

Inclusion Criteria: 20-35 weeks of gestation, 3 or more uterine contractions per 10 minutes, singleton pregnancy, positive fetal heart activity diagnosed by USG and/or NST.

Exclusion criteria: Preterm membrane rupture, placental ablation, fetal distress, cases in the phase of active labor.

All women meeting the inclusion criteria underwent a complete physical examination after recording the medical and obstetrical story. Bishop Scores were acquired by vaginal examination. Blood and urine samples are derived for CBC, Urine analysis, blood group and serum D-Dimer level determinations. D-

Dimer levels are determined by using the Elisa method with VIDAS D-dimer Exclusion test (bioMerieux Clinical Diagnostics, Marcy I'Etoile, France) kit.

Age, gravida, parity, number of abortion, contraction frequency per 10 minutes were noted from the hospital records. Also, applied treatment protocols, duration of treatment and complications were noted. As the part of routine tocolysis regimen, all patients were sedated by 10 mg diazepam IM and hydrated with 1000 cc. Ringer Lactate Dextrose 5% infusion. In the case of persistent uterine contractions, nifedipine 10 mg capsules 4x2 p.o. was delivered for 48 hours. In case of failed therapy, patients were treated with indomethacine (1x100 mg rectally as bolus dose, 4x50 mg per oral as maintenance dose) before 32 weeks of gestation. After 32 weeks ritodrine was used with the following protocol: initial dose of 100 mcg/min., increased by 50 mcg/min. every 20 minutes until the cessation of the contractions. maximum allowed dose: 350 mcg/min.

Screening for fetal abnormalities, complete fetal biometrical, cervical length, and fetal and maternal Doppler measurements were done with a high resolution ultrasound device (General Electric MD 400 5 MHz abdominal probe or Voluson 730 Expert 7 Mhz abdominal probe) at our prenatal diagnosis unit. RI and PI values, existence of notch in the right and/or left uterine artery and RI and PI values, lack of diastolic flow and reversed diastolic flow at umbilical artery were noted.

After the estimated birth date, the patients were contacted by phone and a standardized questionnaire containing birth date, birth weight, neonatal intensive care unit necessity in neonatal period, congenital abnormalities noticed after delivery, the mode of delivery, additional health problems during pregnancy and need of hospitalisation, current health condition of the newborn, maternal health problems during and after delivery was used to collect data.

The patients were divided into two groups according to the gestational age at birth. Cases who delivered before and after completed 37 weeks of pregnancy comprised the preterm and term delivery groups respectively. Statistical analysis was performed with the Number Cruncher Statistical System- NCSS 2000 (Mc Graw Hill) software. In data analysis, differences between the groups were checked with independent t test, and Fisher's exact test as well as descriptive statistical analysis expressed as mean ± SD. A multivariate logistic regression model was used to check for confounding factors. Sensitivity, specificity, positive and negative predictive values, relative risks of all factors significantly associated with preterm labor either alone or combined, were calculated. All differences with $p<0.05$ or 95% confidence interval not crossing "1" were considered to be significant.

Results

Eighty-five women hospitalised for threatened preterm labor between 30.01.2004 and 20.07.2006 and meeting the inclusion criteria were allowed to participate in this study. 11 patients were excluded because of address modification or wrong phone number. Thus the study was conducted with 74 patients.

15 patients (20.27%) delivered before 37 weeks (preterm delivery group), and 59 patients (79.73 %) after 37 weeks of gestation (term delivery group).[9] patients delivered vaginally and 6 patients had caesarean section in the preterm delivery group. The indications for caesarean section were breech presentation in 2 patients, two prior caesarean deliveries in 3

patients and elective caesarean section in 1 patient. All patients were operated in the active phase of labor.

Demographical data and gestational age at the initial hospitalization were not different between both groups (Table 1). Mean platelet volume was significantly low in the preterm delivery group (Table 2). Bishop scores, cervical length, the duration of tocolysis and the mean contraction frequency were not significantly different between two groups (Table 3).

Analysis of serum D-Dimer levels, RI and PI values of right and left uterine arteries, RI and PI values of umbilical artery revealed that only the geometrical mean of D-Dimer levels was significantly different. In the preterm delivery group geometrical mean of D-Dimer was 1502.57 ng/ml, whereas the term delivery group had a geometrical mean of 1052.41 ng/ml (p=0.023) (Table 4).

Notching in the right uterine artery only showed no significant difference, whereas notching in the left uterine artery only or in bilateral uterine arteries were significantly different between both groups. Also the finding of any unilateral notching in the right or left uter-

Table 1. Demographic characteristics of preterm and term delivery groups.

	<37 weeks	>37 weeks	t	p
Age	26.8±4.3	26.85±5.63	-0.03	0.976
Gravida	2.67±1.8	2.44±1.7	0.45	0.652
Parity	1.2±1.15	0.88±1.02	1.06	0.295
Abortion	0.47±0.92	0.58±1.21	-0.33	0.744
GAA	213.13±33.36	227.66±20.99	-1.61	0.126

Results are expressed as Median ± Standart deviation. GAA: Gestational age at admission

Table 2. Hematological parameters in preterm and term delivery groups.

	< 37 weeks	> 37 weeks	t	p
Hct	33.47± 3.57	33.64±3.83	-0.15	0.878
MCV	87.75±5.32	87.26±5.32	0.32	0.751
WBC	12.64±2.74	11.44±3.04	1.39	0.169
PLT	256.4±66.25	226.07±67.66	1.56	0.124
MPV	8.46±1.25	9.96±1.79	-3.05	0.003

Hct: Hematocrit, MCV: Mean corpuscular volume, WBC: White blood cell, PLT: Platelet, MPV: mean platelet volume. Results are expressed as Mean ± Standart deviation.

Table 3. The duration of tocolysis (hours), contraction frequency per 10 minutes, Bishop score, cervical length in preterm and term delivery groups.

	< 37 weeks	> 37 weeks	t	p
Duration (hours)	36.0±27.44	39.97±35.19	-0.41	0.686
Freq of contractions	3.6±2.41	3.78±1.69	-0.34	0.739
Bishop score	2.4±2.03	1.8±1.62	1.22	0.225
Servical length	34.0±7.38	34.98±5.96	-0.54	0.59

The duration of tocolysis (hours), contraction frequency per 10 minutes, Bishop score, cervical length in preterm and term delivery groups. Results are expressed as Mean ± Standart deviation.

Table 4. Geometrical mean of serum D-Dimer (ng/ml), Doppler indices of uterin arteries and umblical artery.

	<37 weeks	>37 weeks		
	Mean±SD	Mean±SD	t	p
D-Dimer	1502.57	1052.41	2.32	0.023
Right UA PI	0.86±0.4	0.83±0.35	0.37	0.714
Right UA RI	0.54±0.13	0.52±0.12	0.50	0.622
Left UA PI	0.95±0.45	0.91±0.52	0.33	0.741
Left UA RI	0.58±0.15	0.54±0.12	0.98	0.331
Umb A PI	1.07±0.41	0.97±0.24	0.93	0.368
Umb A RI	0.65±0.15	0.65±0.17	0.10	0.92

UA: Uterin artery, Umb A: Umblical artery, PI: Pulsatily Index, RI: Resistance Index. Results are expressed as Mean ± Standart deviation.

ine arteries showed no significant difference between two groups (Table 5).

In a multivariate logistic regression model with the preterm delivery as the dependent variable, notching in bilateral uterine arteries remained as the only factor significantly associated with preterm delivery. (Odds Ratio = 12.667, 95% CI: 2.017 – 79.533)

To determine the diagnostic significance of notching in bilateral uterine arteries, sensitivity, specificity, positive and negative predictive values and accuracy were calculated and found to be 0.27, 0.97, 0.67, 0.84 and 0.82 respectively (Table 7).

At a threshold of 1700 ng/ml for serum D-dimer level, elevated serum D- dimer and notching in the uterine arteries combination is significantly frequent in preterm delivery group (Table 8). The corresponding values for sensitivity, specificity, positive and negative predictive values and accuracy of elevated serum D-dimer levels and notching in the uterine artery are shown at Table 9.

Discussion

Plasma D-Dimer level is considerably elevated and used as a helpful biomarker in clinical sit-

Table 5. The frequency of notch in bilateral uterin arteries in preterm and term delivery groups.

		<37 weeks		>37 weeks		P
Right UA	Normal	11	%73.3	54	%91.5	
	Notch	4	%26	5	%8.5	0.075
Left UA	Normal	11	%73	56	%94.9	
	Notch	4	%26	3	%5.1	0.027
Bilat UA	Normal	11	%733	57	%96.6	
	Notch	4	%26	2	%3.4	0.013
Each UA	Normal	11	%733	53	%89.8	
	Notch	4	%267	6	%10.2	0.110

UA: Uterin artery, Bilat: Bilateral

Table 6. Multivariate logistic regression analysis.

	RR	SD	p	OR	%95 CI
d-Dimer	-0.001	0.001	0.059	0.999	0.998–1.00
Bilateral UA	2.539	0.937	0.007	12.667	2.017–79.53
Funneling	9.048	25.923	0.727	8.63	0.028–98.82

UA: Uterin artery, OR: Odds Ratio

Table 7. Clinical diagnostic significance of notch in uterin artery.

Notch +	Sensitivity	Specificity	PPV	NPV	Accuracy	RR-%95 CI
Right UA	0.27	0.92	0.44	0.83	0.78	2.63 (1.05-6.51)
Left UA	0.27	0.95	0.57	0.84	0.81	3.48 (1.50-8.05)
Bilateral UA	0.27	0.97	0.67	0.84	0.82	4.12 (1.88-9.01)
UA	0.27	0.90	0.40	0.83	0.77	2.33 (0.91-5.90)

UA: Uterin artery PPV: positive predictive value, NPV: negative predictive value, RR: Risk ratio, CI:Confidence interval

Table 8. Serum D-Dimer level, notch in uterin artery and the combination of these parameters in preterm and term delivery groups.

		<37 Weeks		>37 Weeks		P
D-dim(+)	D-dimer +	3	20.0%	7	11.9%	
	D-dimer -	12	80.0%	52	88.1%	0.414
UA	Notch	4	26.7%	6	10.2%	
	Normal	11	73.3%	53	89.8%	0.110
D-Dim(+)+ UA	Patolojik	1	6.7%	1	1.7%	
	Normal	14	93.3%	58	98.3%	0.013
D-dim(+) veya UA	Patolojik	6	40.0%	12	20.3%	
	Normal	9	60.0%	47	79.7%	0.110

D-Dimer (+) ? 1700 ng/ ml, UA: Uterin artery

Tablo 9. Diagnostic significance of serum D-Dimer, notch in uterin arteries and the combination of these parameters for preterm delivery.

	Sensitivity	Specificity	PPV	NPV	Accuracy	RR -%95 CI
D-dim(+)	0.20	0.88	0.30	0.81	0.74	1.60 (0.54- 4.69)
Çent(+)	0.27	0.90	0.40	0.83	0.77	2.33 (0.91-5.90)
D-dim(+)+ Notch(+)	0.07	0.98	0.50	0.81	0.80	2.57 (0.59-11.10)
D-dim(+) veya Notch(+)	0.40	0.80	0.33	0.84	0.72	2.07 (0.85-5.03)

D-Dimer (+) ≥ 1700 ng/ ml, Notch (+): notch in uterin arteries, Sen: sensitivity, Spe: specifity, PPV: positive predictive value, NPV: negative predictive value, Acc: Accuracy, RR: Risk ratio, CI: Confidence interval

uations such as acute pulmonary embolism, disseminated intravascular coagulation and abruptio placenta.[10,11] Although serum D-Dimer levels increase with gestational age, there is no convincing data derived from large scale studies.

Kline et al. showed that mean plasma D-Dimer levels increase from 430 ng/ml in the preconceptional period to 579 ng/ml in the first, 832 ng/ml in the second and 1159 ng/ml in third trimester of pregnancy in a study designed with 50 and completed 18 cases.[12]

Francalanci et al. showed that plasma D-Dimer levels increase by gestational age and second and third trimester levels of plasma D-dimer are significantly higher than healty non-pregnant women.[13]

Chabloz et al., exploring the correlation between d-Dimer and Thrombocyte Activating Factor Inhibitor (TAFI) levels, have determined the 5-95% confidence limits of plasma D-dimer levels at first, second and third trimester as 139-602 ng/ml, 291-1232 ng/ml and 489-2217 ng/ml. The mean maternal plasma D-dimer level and 5-95% confidence interval during delivery were 1581 ng/ml and (678 - 5123 ng/ml) respectively. Statistical significance of this finding.[14]

Haznedaroglu et al, found mean maternal plasma D-Dimer levels in preterm delivery, term delivery and non pregnant women to be 203.2±127.4 ng/ml, 69.5±25.1 ng/ml and 34.2±7.6 ng/ml respectively. The difference was significant.[15]

In another study performed to evaluate the clinical use of D-Dimer in preterm delivery, mean plasma D-Dimer level in the preterm delivery and term delivery groups were significantly different and 2544 ng/ml and 1750±839 ng/ml respectively.[16]

In a cohort of pregnant women hospitalised for threatened preterm delivery, we found a sig-

nificant difference in the geometric means of the initial serum D-Dimer levels of preterm and term delivery groups, 1502.57 ng/ml and 1052.41 ng/ml respectively (p=0.023). But this difference lost its significance in multivariate logistic regression analysis.

Abnormal Doppler waveform of uterine arteries indicates an increased impedance secondary to the reduced trophoblastic invasion of the tunica muscularis of the spiral arteries.[17,18] This might lead to abnormal uteroplacental blood perfusion which in turn might cause a tendency to some serious pregnancy complications such as preeclampsia, intrauterine growth retardation and abruptio placentae.[19] A literature survey about the relationship between preterm delivery and Doppler indices of uterine arteries, revealed many studies which nevertheless contained considerable differences from our study in terms of study design research methodology, screened parameters and statistical evaluation.

Axt-Fleidner et al. assessed the role of uterine artery colour Doppler waveform analysis in the prediction of adverse pregnancy outcome defined as delivery before 34 weeks, intrauterine fetal death, preeclampsia associated with placental abruption and/or intrauterine growth retardation. The sensitivity, specificity, positive and negative predictive value, and relative risk of notching in both uterine arteries were 83, 79, 33, 97 and 12.2, respectively.[20]

Park et al. performed a study in a low risk population and defined the abnormal waveform as two SDs higher than the mean S/D ratio at same gestational week and/or diastolic notching. They showed that delivery before 34 weeks was significantly more frequent in women with an abnormal waveform. RR for preterm birth, was 2.67 (1.24 – 5.74) and 5.88 (2.46 – 14.7) in women with unilateral and bilateral abnormal uterine artery Doppler waveforms respectively.[21]

In another study performed in a high risk population and with the abnormal waveform defined as early diastolic notching in any uterine arteries, the frequency of delivery before 37 weeks of gestation was 16 % in the normal and 41 % in the abnormal waveform group [OR: 7.9 (4.6–13)].[22]

Agar et al. showed that RI, PI and S/D values are significantly different in preterm and term delivery groups. The mean S/D, mean RI and mean PI were 2.16±0.38, 0.36±0.14 and 0.44± 0.17 in the term delivery, and 2.56±0.20, 0.65± 0.09 and 0.54±0.21, in the preterm delivery groups respectively. In the analysis of ROC curve, RI was found to be the most valuable predictor for preterm delivery with 95.8 % sensitivity, 87.7% specificity, 70% positive predictive and 84% negative predictive value.[23]

One study performed in normal pregnant population showed that uterin artery PI was significantly higher in preterm delivery group (< 33 weeks of gestation) than term delivery group, but ROC curve analysis could not prove its prognostic significance either alone or in combination with other parameters.[24]

Another study performed in normal population suggested that the mean PI was 1.06 (0.6 – 2.05) and 1.02 (0.49 – 3.2) in preterm and term delivery groups, respectively.[25]

Irion et al. defined the presence of a protodiastolic notch, peak sistolic/Protodiastolic velocities >2.5, peak systolic/end diastolic velocities >90.centile as abnormal uterine artery Doppler waveform and concluded that these are insignificant as predictive factors in preterm delivery.[26]

We found no significant difference between preterm and term delivery groups in terms of RI and PI values of the of uterin vessels. But the

frequency of prediastolic notching in the uterine artery Doppler waveform in the preterm and term delivery groups were 26.7% (4 cases) and 5.1% (3 cases) respectively, expressing a statistical significance (p=0.027). The preterm delivery rate was also high in patients with bilateral prediastolic notching in uterine arteries (26.7% and 3.4%, p=0.013). After multivariate logistic regression the association of bilateral notching in uterine arteries with the preterm delivery remained significant.

We did not compare a high risk population with a normal population, on the contrary a comparison of patients delivered preterm and term in a high risk population hospitalised for threatened preterm delivery. Also the study group was relatively small. We consider that the differences from the results in the literature are mainly based on these factors. The OR of bilateral prediastolic notching in uterine arteries for preterm delivery was 12.677 (2.017–79.533). The sensitivity, specificity, positive and negative predictive value and relative risk of bilateral notching in the uterine arteries were 0.27, 0.97, 0.67, 0.82 and 4.12 (1.88 -9.01), respectively. The low sensitivity of this finding restricts its clinical value in the prediction of preterm delivery, requiring large scale prospective studies to prove its usefulness.

Conclusion

Maternal serum D-Dimer levels of preterm and term delivery groups were significantly different, but this association lost its significance in the multivariate logistic regression model. The OR for prediastolic notching in uterine arteries for preterm birth was 12 (2.017–79.533). But the low sensitivity of this finding restricts its clinical usefulness. We think that large scale prospective studies are needed to prove the validity of these findings.

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