Effect of Tocolysis on Doppler Measurements of Umbilical, Uterine and Spiral Arteries

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Abstract

Objective: The aim of this study is to assess the relationship between the change in Doppler values of umbilical, uterine and spiral arteries with ritodrine tocolysis and the value of these changes.

Methods: Thirty women with gestational age between 26 and 35 weeks admitted to the Obstetric and Gynecology Clinic and had a diagnosis of preterm labor were enrolled to the study. S/D, PI and RI values of uterine, umbilical and spiral arteries were evaluated with color Doppler ultrasonography before and 24 hours after the tocolytic treatment. Patients were evaluated in two groups according to the time gained with tocolysis, as 2-7 days and more than 7 days. The Doppler variables were compared statistically by using paired t test, Wilcoxon Signed Ranks Test and Mann-Whitney U Test.

Results: It was found that a significant decrease only in uterine artery Doppler values were present in cases with 2-7 days gain with tocolysis. In cases with decrease both in uterine and umbilical artery Doppler values, time gained with tocolysis was more than 7 days. Spiral artery Doppler values were not affected with the tocolytic treatment.

Conclusion: Time gained with tocolytic treatment was longer in patients with a significant decrease in S/D, PI and RI values of uterine and umbilical arteries.

Keywords: Preterm labor, tocolysis, Doppler ultrasound.

Tokolitik tedavinin umbilikal, uterin ve spiral arter Doppler bulgularına etkisi

Amaç: Bu çalışmanın amacı, ritodrin ile tokoliz uygulanan preterm doğum eylemi olgularında umbilikal, uterin ve spiral arter doppler değerlerinde elde edilen değişimleri ve bu değişimlerin değerinin olup olmadığını araştırmaktır.

Yöntem: Tokolitik tedavi ile sadece uterin arter doppler ölçümlerinde tedavi öncesine göre anlamlı düşüş tespit edilenlerde, kazanılan sürenin 2- 7 gün arasında olduğu bulundu. Hem uterin hem de umbilikal arter doppler ölçümlerinde tedavi öncesine göre anlamlı düşüş tespit edilenlerde ise tokoliz ile kazanılan süre 7 günden fazla idi. Spiral arter doppler bulgularının ise tokolizden etkilenmediği bulundu.

Bulgular: Kadın Hastalıkları ve Doğum Polikliniğine başvuran 26-35 haftalar arası preterm eylem tanısı alan 30 gebe çalışmaya alındı. Renkli Doppler Ultrasonografi cihazı ile tokoliz başlamadan önce ve tokolizden 24 saat sonra umbilikal, uterin ve spiral arter S/D, PI ve RI değerlerine bakıldı. Hastalar tokolitik tedavi ile kazanılan süreye göre, 2-7 gün kazanılan ve 7 günden fazla kazanılan olmak üzere iki grupta değerlendirildi. Doppler değişkenleri İki Değer Arasındaki Farkın Önemlilik Testi, Wilcoxon Eşleştirilmiş İki Örnek Testi ve Mann- Whitney U Testi ile karşılaştırıldı.

Sonuç: Preterm eylem olgularında, ritodrin tedavisi ile uterin ve umbilikal arter doppler ölçümlerinde tedavi öncesine göre anlamlı düşüş olanlarda kazanılan süre daha uzundur.

Anahtar Sözcükler: Preterm eylem, tokoliz, Doppler ultrasonografi.

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Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality world wide.[1] It increases the risk of respiratory distress syndrome, leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, cerebral palsy, retinopathy and mental retardation in the newborn.[2] With the improvement of neonatal intensive care facilities the mortality rate of the newborn decreased, but the severe morbidity due to prematurity continued to be a major problem.[3]

Life expectancy of the preterm infants is related to the gestational age and the birth weight. It's less than 10% for infants smaller than 24 weeks of gestation, while increases to 90% around 30 weeks of gestation. Similarly it's around 10% for infants with birth weight less than 500 grams and increases to 90% for infants with birth weight of 1500 grams.[4,5] It's also known that the morbidity due to prematurity decreases by prenatal corticosteroid treatment.[6] Prevention or delay of preterm birth is important for grow up of the gestation and the appearance of the effect of prenatal corticosteroid treatment. Tocolytic treatment is the most common treatment option for this aim.

Nowadays, the most commonly studied issue in the obstetric field worldwide is the prevention of preterm birth. Prevention of preterm birth depends mostly on early diagnosis or an accomplished foresight. Studies aiming to determine the high risk pregnancies and the success of tocolytic treatment, evaluated the fetomaternal blood flow with Doppler ultrasonography.[7,8]

The aim of this study is to evaluate the changes in the vascular resistance of umbilical, uterine and the spiral arteries with the application of intravenous ritodrine treatment and to find out value of these changes.

Methods

The study was conducted between April 2003 and January 2004 in Obstetrics and Gynecology clinic and 30 cases with a diagnosis of preterm labor between 26 and 35 weeks of gestation were enrolled. The subjects were enrolled after the institutional review board approval. Routine informed consent was taken from all recipients.

Inclusion criteria were the presence of gestational age between 26 and 37 weeks, intact amniotic membrane, regular contractions 4 times in 20 minutes or 8 times in 60 minutes lasting at least 30 seconds, cervical dilatation less than 4 cm or effacement less than 80%. Pregnancies complicated with multiple gestation, intrauterine growth retardation, preterm premature rupture of membranes, diabetes mellitus, fetal anomaly, oligohydramnios, polyhydramnios, chorioamnionitis and pregnancies with unknown gestational age were not included to the study.

Age, obstetric history and gestational age of cases were recorded. The gestational age was determined by the last menstruation period or by the early ultrasonography done before 20 weeks of gestation. Cervix and vagina of all cases were evaluated for infection via speculum examination and swab was taken from cervical canal for culture and gram staining. Dilatation and effacement of cervix were determined in all cases. Fetal biometry and estimated fetal weight were evaluated via obstetric ultrasonography. Monitorization of uterine contractions and fetal cardiac activity were performed via Spacelabs medical AM67 device for 20 minutes. Tocolysis was started to cases with at least 4 contractions of 25-45 mmHg in amplitude within this time period. Cases with less than 4 contractions of 25-45 mmHg in amplitude within 20 minutes were excluded from the study. Before tocolysis maternal and fetal heart rate were

recorded. Two doses of 12 mg betamethasone (Celestone Chronodose ampul, Eczacıbaşı®) were applied intramuscularly (I.M.) 24 hours apart to cases with gestational age less than 34 weeks for providing pulmonary maturation.

Ritodrine hydrochloride (Pre-par ampoule, Eczacıbaşı®) was applied intravenously (I.V.) as the tocolytic agent. It was not combined with other tocolytic agents. Zero point three mg/ml solution was prepared by tittering 150 mg ritodrine hydrochloride (Pre-par ampoule, Eczacıbaşı®) in 500 ml 5% dextrose. Infusion was started with a dose of 50 microgram/ minute (4 drop/min.) and it was increased 50 microgram every 15 minutes till the cessation of contractions or the appearance of side effects. Contractions were documented cardiotogographically. Maximum dose was determined as 350 microgram/ minute. Intravenous treatment continued for 24 hours and oral treatment was not started afterwards. Blood pressure and pulse rate of cases were recorded during and after the tocolysis non-invasively via Marquette Dash 2000 device. None of the cases delivered within 48 hours of the treatment. As the period for maximum effect of steroid is 7 days, we determined the time needed to delay delivery as 7 days and divided cases into two groups as 2–7 days gained till delivery and more than 7 days gained till delivery.

Doppler measurements were performed by the same operator via ATL HDI 3400, Ultrasound System, Bothell, WA, USA device with 5-2 MHz transabdominal probe. Doppler measurements were recorded after the fetal biometric measurements were taken. Doppler indexes were measured before and at the beginning of tocolysis and 20–24 hours after the cessation of the contractions. Since the contractions affect uterine artery Doppler indexes, measurements before tocolysis were taken in periods between contractions with patient positioned slightly laterally on a flat table with 30° head tilt. Systole/ diastole (S/D) ratio, pulsatility index (PI) and resistance index (RI) of umbilical, uterine and spiral arteries were recorded. Umbilical artery measurement was done 3 times on the free loop of the cord, more than 4 cm far from the placental and fetal insertion site and the mean was taken. Uterine artery measurement was done on both right and left side at the point where uterine artery branches form the internal iliac artery and the mean was taken. Spiral artery measurement was done from the base of glomerular structure formed behind the placenta.

Statistical analyses were carried out by employing the Statistical Package for Social Sciences soft-ware10.0 for Windows package software (SPSS, Inc., Chicago, IL, USA). The mean gestational ages of two groups were compared by Mann- Whitney U Test. The Doppler measurements before and after the treatment were compared by paired t test for 30 cases and by Wilcoxon Signed Ranks Test for two groups. Results were evaluated in 95% confidence interval and the p value less than 0.05 was accepted as significant.

Results

The mean age of cases was 25.37 ± 4.92 (18-39) and the mean gestational age was 31.87 ± 2.73 (26-35). The gravity of cases ranged between 1 and 7 and the parity ranged between 0 and 3. Nine cases were nullipara, while 19 cases were multipara and 2 cases were grand-multipara (Table 1). The distribution of cases in groups with 2-7 days gain and >7 days gain, according to the gestational age, are presented in Table 2. The mean gestational ages of the cases with 2-7 days gain and > 7 days gain with tocolysis were 32.63 ± 2.44 and 31.59 ± 2.80

Table 1. Demographic characteristics of the cases.

		Characteristics of cases treated with tocolysis
Yaş (yıl)		25.37± 4.92 (18-39)
Gravity**	Nullipar	9
	Multipar	19
	Grandmultipar	2
Parity**	0	11
	1	16
	2	2
	3	1
Gestational Age (weeks)		31.87 ± 2.73 (26-35)

** Results are given as mean ± standard deviation (minimum-maximum)*
***Given as case number.*

respectively. There was no significant difference between the two values (p=0.342).

The Doppler findings of umbilical, uterine and spiral arteries before and after the tocolysis are presented in Table 3. There was a statistically significant difference for the umbilical and uterine artery S/D, PI and RI values before and after the treatment, while no difference was found for the spiral artery.

In cases with 2-7 days gain with tocolysis, there was no difference between the umbilical artery S/D, PI and RI values before and after the treatment but statistically significant decrease was present for the uterine artery (Table 4).

In cases with >7 days gain with tocolysis, statistically significant decrease was present both for the umbilical and uterine artery S/D, PI and RI values (Table 5).

In cases with 2-7 days gain and > 7 days gain with tocolysis, the difference between the uter-

Table 2. Distribution of cases with 2–7 days and >7 days gain with tocolysis, according to the gestational age

Gestational Age	Cases with 2- 7 days gain	Cases with > 7 days gain	Total
26-29 weeks**	2	7	9
30-34 weeks**	4	11	15
35 weeks**	2	4	6
Total	8	22	30
Mean gestational age*	32.63±2.44	31.59±2.80	p=0.342

**Results are given as mean ± standard deviation..*
***Given as case number..*

Table 3. Doppler findings of uterine artery, spiral artery and umbilical artery in cases

	Before treatment	After treatment	P
Umbilical Artery			
S/D	2.74 ± 0.58	2.36 ± 0.41	0.001*
PI	1.09 ± 0.27	0.90 ± 0.21	0.000*
RI	0.65 ± 0.08	0.57 ± 0.06	0.000*
Uterine Artery			
S/D	2.72 ± 0.89	2.30 ± 0.61	0.003*
PI	1.13 ± 0.41	0.94 ± 0.35	0.002*
RI	0.61 ± 0.11	0.53± 0.11	0.002*
Spiral Artery			
S/D	1.70 ± 0.27	1.62 ± 0.32	0.275
PI	0.55 ± 0.15	0.51 ± 0.19	0.304
RI	0.42 ± 0.12	0.37 ± 0.11	0.600

**p<0.05*

ine S/D, PI and RI values taken before and after the treatment are presented in Figure 1.

Discussion

In spite of improvements in neonatal intensive care facilities, preterm birth is still the leading cause of perinatal morbidity and mortality. Prevention of preterm birth gained importance with the decrease of incidence of other causes of perinatal morbidity and mortality. Recent studies aimed to determine the high risk pregnancies for preterm birth.

Ritodrine and other tocolytic agents are often used to prevent preterm birth. Ritodrine acts through Beta-1 and Beta-2 receptors. Beta-2 receptors are present on uterus, bronchi and smooth muscle cells of vascular wall. Ritodrine by acting through Beta-2 receptors on vascular smooth muscle cells leads to vasodilatation and decrease in vascular resistance.[9] The increase in uterine perfusion is supplied by more than one mechanism with the I.V. administration of betamimetics. Increase in heart rate and cardiac output, decrease in peripheral vascular resistance and uterine relaxation are some of the mechanisms. Ritodrine administration decreases diastolic period by increasing maternal and fetal heart rate, as a result increases the end diastolic flow.[10] Eventually umbilical and uterine artery S/D ratios decrease. In studies, the I.V. administration of ritodrine is found to increase the uterine perfusion.[11,12]

Studies tried to determine the high risk pregnancies by evaluating the changes in Doppler variables of umbilical and uterine arteries before and after the tocolytic treatment.

Table 4. Comparison of changes in doppler measurements of umbilical and uterine arteries before and after the tocolysis in cases with 2-7 days gain.

	Before treatment	After treatment	Difference	P
Umbilical Artery				
S/D	2.76 ± 0.45	2.43 ± 0.49	0.325	0.128
PI	1.12 ± 0.28	0.98 ± 0.30	0.140	0.208
RI	0.65 ± 0.07	0.58 ± 0.07	0.64	0.107
Uterine Artery				
S/D	2.87 ± 0.78	2.14 ± 0.53	0.731	0.012*
PI	1.18 ± 0.35	0.91 ± 0.42	0.277	0.050*
RI	0.62 ± 0.08	0.52 ± 0.11	0.105	0.012*

*$p<0.05$

Table 5. Comparison of changes in Doppler measurements of umbilical and uterine arteries before and after the tocolysis in cases with >7 days gain

	Before treatment	After treatment	Difference	P
Umbilical Artery				
S/D	2.73 ± 0.63	2.33 ± 0.39	0.400	0.007*
PI	1.08 ± 0.28	0.87 ± 0.16	0.213	0.002*
RI	0.65 ± 0.09	0.57 ± 0.06	0.077	0.001*
Uterine Artery				
S/D	2.66 ± 0.95	2.36 ± 0.64	0.306	0.014*
PI	1.11 ± 0.44	0.96 ± 0.31	0.154	0.009*
RI	0.60 ± 0.12	0.54 ± 0.11	0.063	0.011*

*$p<0.05$

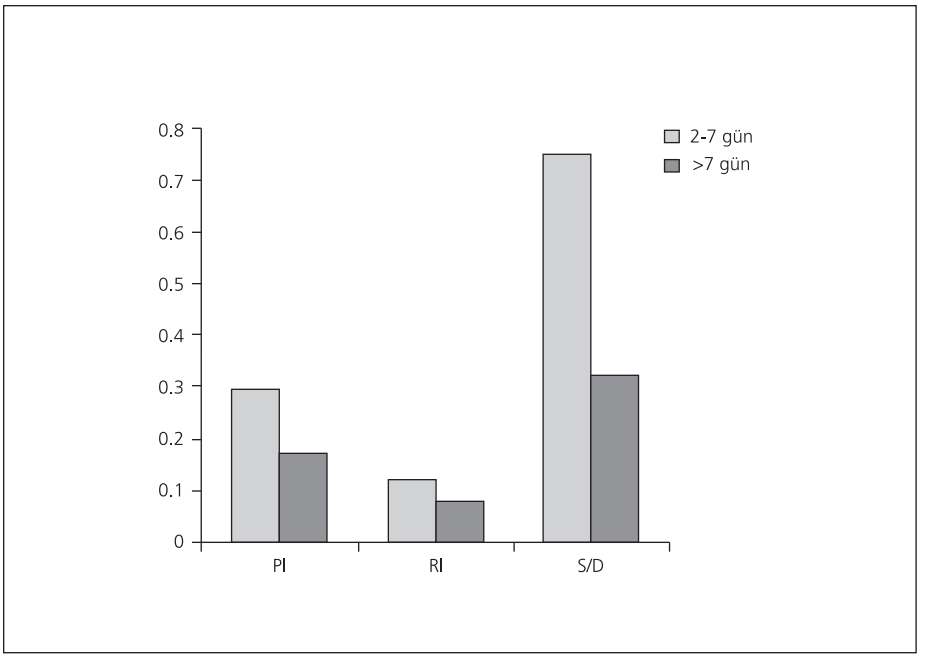

Figure 1. Comparison of changes in doppler measurements of umbilical and uterine arteries before and after the tocolysis in cases with 2-7 days gain and with >7 days gain

Brar et al[7] in a study conducted with 92 preterm labor cases of 29-36 weeks of gestation found that cases with high umbilical and uterine artery S/D ratio were more prone to preterm delivery than cases with normal values and concluded that Doppler measurements of umbilical and uterine artery should also be included in the evaluation of preterm labor cases.

Çankaya at al[8] in a study conducted with 62 preterm labor cases of 26-35 weeks of gestation, measured umbilical and both uterine artery S/D ratios and PI values before and during the tocolytic treatment. In cases with high uterine artery S/D ratio before treatment, rate of tocolysis failure was found to be statistically significantly high and in cases with preterm delivery there was no significant change in umbilical artery S/D ratios.

We evaluated the effect of ritodrine on uteroplacental and fetoplacental vascular resistance in cases with preterm labor. We administered I.M. betamethasone to achieve pulmonary maturation in cases with gestational age less than 34 weeks. In studies conducted with pregnancies complicated with absent end diastolic flow in umbilical artery, administration of betamethasone returned end diastolic flow and decreased resistance;[13] however in pregnancies with intrauterine growth retardation or with no complications, betamethasone administration didn't lead to any change in umbilical artery flow rate or pulsatility if the Doppler measurements were normal before the treatment.[14,15] In studies evaluating the effect of betamethasone treatment on uterine artery Doppler measurements couldn't find any change.[15] Doppler measurements of umbilical and uterine artery before the treatment were normal in our study, so in cases receiving betamethasone and ritodrine treatment, the changes in Doppler measurements were attributed to the ritodrine treatment.

The optimum effect of betamethasone administered 12 mg, 24 hours apart for pulmonary maturation is seen 24 hours after the second dose and lasts for 7 days.[16] The aim of tocolysis is to gain this time. Corticosteroids increase pulmonary surfactant secretion and decrease the incidence of neonatal mortality, necrotizing enterocolitis and cerebral hemorrhage.[17] With this knowledge, the cases were divided into two group as 2-7 days gain with tocolysis and >7 days gain with tocolysis for the evaluation of changes in Doppler measurements.

We couldn't find any change in spiral artery S/D, PI and RI values before and after the treatment. This situation can be explained as: During the development of placenta, trophoblastic cells take place of endothelial cells of the spiral arteries starting from the fourth weeks of gestation. This event converts the spiral arteries to low resistant vessels unaffected from vasomotor control.[18]

If the time gained was not considered, a significant decrease was present in uterine and umbilical artery S/D, PI and RI values after the treatment compared to before treatment values. If the time gained was considered, in cases with 2-7 days gain, a significant decrease was present in only uterine artery whereas in cases with >7 days gain, a significant decrease was present both in uterine and umbilical arteries.

We found the time gained with tocolysis was more, if a significant decrease in Doppler measurements after the treatment was present compared to before treatment values in both uterine and umbilical arteries. This study holds out that tocolysis will be successful in cases with significant decrease in uterine and umbilical artery Doppler measurements after the treatment. However it should be supported by prospective studies done in large group of cases.

Conclusion

In cases with preterm labor, the time gained with ritodrine treatment was longer, in the presence of significant drop in Doppler measurements of umbilical and uterine arteries compared with before treatment values. If the result of this study is supported by other prospective studies done in larger group of cases, Doppler measurements can be used in determining the success of tocolytic treatment.

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