Uterine Artery Doppler Velocimetry During First Trimester of Pregnancy to Predict Decreased Endovascular Trophoblast Invasion Associated with Adverse Pregnancy Outcomes

Gebeliğin İlk Trimesterinde Azalmış Endovasküler Trofoblastik İnvazyonla İlişkili Kötü Gebelik Sonuçlarının Öngörülmesinde Uterin Arter Doppler Hızlarının Değerlendirilmesi

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ABSTRACT Objective: Successful placentation relies on normal trophoblastic invasion of the maternal decidua, myometrium and blood vessels. Uterine perfusion appears to regulate uterine receptivity. This article investigates the relationship between Doppler studies of uterine artery and endovascular trophoblastic invasion in the first trimester of pregnancy. **Material and Methods:** Doppler ultrasound examination of the maternal uterine arteries was performed in women attending for termination of pregnancy for non-medical reasons. We recorded the Doppler flow velocity waveforms using a Shimadzu 2000 ultrasound machine with a 3,5 or 5 MHz probe.Colour Doppler ultrasound was used to identify the main branch of the uterine artery at its junction with the internal iliac artery, from where we obtained blood flow velocity waveforms. High-resistance cases were defined as those presenting with bilateral or unilateral uterine artery notches and a mean RI above the 95th centile. The conceptional products were examined histologically with regard to the extend of decidual endovascular trophoblast invasion. **Results:** At the week 8, there were 19 high-resistance and 17 low-resistence uterine artery blood flow. The proportion of decidual vessels with endovascular trophoblast invasion was significantly higher in the low-resistance pregnancies (65%) compared with high-resistance ones (47%; p= 0.18). **Conclusion:** Interstitial invasion, deeper decidual-myometrial junction invasion and the release of vasoactive mediators may explain changes in arterial resistance and be related to decidual endovascular trophoblastic invasion. Doppler ultrasonography is a non-invasive method for evaluating trophoblastic invasion in early pregnancy. Further studies are necessary to clarify the significance of these observations.

Key Words: Ultrasonography, Doppler, trophoblasts, decidua

ÖZET Amaç: Başarılı plasentasyon, maternal desidua, myometrium ve kan damarlarına trofoblastik yayılımın normal olmasını gerektirmektedir. Uterusta mevcut kan akımı uterusun reseptivitesini etkilemektedir. Bu çalışmada, gebeliğin ilk trimesterinde uterin arter doppler kan akımıyla trofoblastik invazyon arasındaki ilişki incelenmiştir. **Gereç ve Yöntemler:** Tıbbi olmayan nedenlerle gebelik terminasyonu isteyen kadınlarda uterin arter Doppler kan akım çalışmaları uygulandı. 3.5-5 MHz probu olan Shimadzu 2000 marka ultrasonografi aleti ile Doppler akım hızı dalga formları kaydedildi. Kan akım hızı dalga formlarını ölçtüğümüz internal iliak arterden uterin arterin çıkış noktasını tespit için renkli doppler ultrasonografi uygulandı. Tek veya iki taraflı uterin arterde "notch" olanlar ve ortalama rezistans indeksi 95. persentilin üzerinde olanlar yüksek dirençli olgular olarak tanımlandı. Müdahale sonrası elde edilen gebelik ürünleri, histolojik olarak desidual trofoblastik yayılım derinliği açısından incelendi. **Bulgular:** Gebeliğin sonlandırılması amacıyla 8. gebelik haftasında başvuran kadınların uterin arter doppler incelemesinde 19'unda yüksek dirençli akım izlenirken 17'sinde düşük dirençli akım paterni izlenmiştir. Endovasküler trofoblastik invazyon oranı, akım direnci düşük olanlarda belirgin olarak yüksekken (%65), direncin yüksek olduğu kişilerde düşük olduğu bulunmuştur (%47, p= 0.18). **Sonuç:** Arteriyel dirençteki değişimleri, interstisyel yayılım, derin desidual-miyometriyal bileşke yayılımı ve vazoaktif mediatörlerin salınımıyla açıklanabilmektedir ve bu durum desidual endovasküler trofoblast invazyonuyla ilişkili bulunmaktadır. Erken gebelik döneminde trofoblastik invazyonun değerlendirilmesinde ultrasonografik Doppler incelemesi invaziv olmayan bir yöntem olarak kabul edilmektedir. Bu gözlemlerin öneminin kesinleşmesi için daha ileri çalışmalara gerek duyulmaktadır.

Anahtar Kelimeler: Ultrasonografi, Doppler, trofoblast, desidua

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Successful placentation relies on normal trophoblastic invasion of maternal decidua, myometrium and blood vessels. Preeclampsia and fetal growth restriction have been reliably associated with failures in the trophoblastic invasion of spiral arteries and Doppler studies have shown that impedance of flow in the uterine arteries is increased under these conditions.[1,2] A few previous studies have investigated the relationship between uterine artery Doppler indices and histological features of placentation in normal and preeclamptic pregnancies.[3]

There are only a few first trimester screening studies and most of these have shown that, even in this early stage, impedance to flow in the uterine arteries is increased in pregnancies that develop adverse outcomes.[4] Trophoblastic invasion of decidual maternal vessels can be observed as endovascular trophoblast on histological examination of the products of conception obtained from early pregnancy losses or termination.[5,6]

In this prospective study, we evaluated the resistance in the uterine arteries of women in the first trimester of pregnancy by Doppler assessment of uterine artery resistance and endovascular trophoblastic invasion.

MATERIAL AND METHODS

For this prospective study, 36 subjects were enrolled in the Gaziosmanpasa University Faculty of Medicine Department of Obstetrics and Gynecology. All patients had experienced regular menstrual cycles and had precisely recorded the dates of their last menstruel periods. We obtained informed written consent from each women.

Doppler ultrasound examination of the maternal uterine arteries was performed in women attending for termination of pregnancy. Blood flow evaluations were performed in the morning to avoid fluctuation due to circadien rhythm of uterine artery blood flow.[7] We recorded the Doppler flow velocity waveforms using a Shimadzu 2000 ultrasound machine with a 3,5 or 5 MHz probe. Colour Doppler ultrasound was used to identify the main branch of the uterine artery at its junction with the internal iliac artery, from where we obtained blood flow velocity waveforms. Waveforms were recorded from both uterine arteries. The quality of the flow velocity was maximized by using the smallest possible angle of insonation, and accepting only those waveforms with sharp and definite outlines. After a consecutive series of four or more uniform waveforms had been obtained the analysis were performed by the mean value from both uterine arteries. The presence or absence of diastolic notch in each uterine waveform was also measured.[8] High-resistance cases were defined as those presenting with bilateral or unilateral uterine artery notches and a mean RI above the 95th centile. Centiles calculated by Hollis et al were employed.[9]

The conceptional products were obtained at the time of termination of pregnancy and fixed in formalin. Histological sections were reviewed by a pathologist blinded to the clinical details. The implantation site was identified by the presence of interstitial extravillus trophoblast surrounding decidual vessels. The presence or absence of endovascular trophoblast invasion were determined by examining decidual vessels in implantation site (Figure 1).[6]

The mean resistance index was calculated as the mean value from both left and right uterine arteries. Demographic characteristics and histological findings between groups were compared by Mann-Whitney and Student's t-tests.

RESULTS

A total of 36 unselected pregnant women were enrolled in this study. Nineteen of them were with

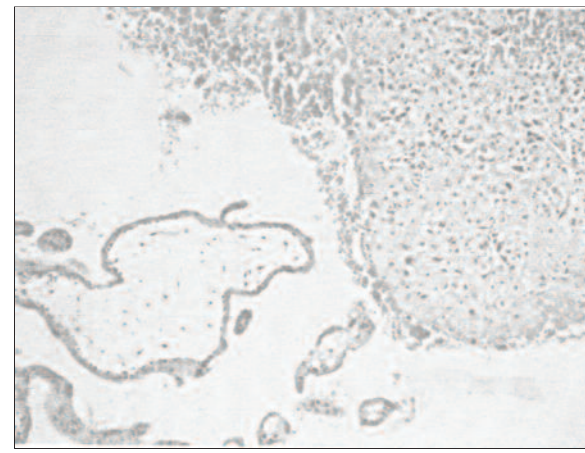

FIGURE 1: Normal formation of decidua and chorion villus (HE, ×20).

high-resistance uterine artery flow and 17 with low-resistance flow. Median age at termination of pregnancy was 29 years (range 19-41), gravidity 3 (range 1-7), parity 1 (0-3) and gestational age at ultrasound scan 8 weeks (range 6-10). The median interval between the ultrasound scan and procedure was two days (range 1-4). There was no significant difference in these parameters between the groups (Table 1).

Histological features of the trophoblastic invasion are determined in Table 2. While pregnancies with a high-resistance uterine artery flow were associated with lower proportion of implantation site, low-resistance uterine artery flow predicted higher proportion of implantation (Figure 2). Although the results were not statistically significant further study will elucidate the significance of these observations.

DISCUSSION

In this prospective study we suggested that assessment of the uterine artery resistance values would be useful test for determining trophoblastic invasion of the decidual vessels which states fetal well being.

Different studies have stated that increased impedance to flow in the uterine arteries is associated with increased risk for subsequent development of preeclampsia, intrauterine growth restriction and perinatal death.[10] These findings have been confirmed by more recent studies. Prefumo et al. supported the use of uterine artery Doppler for the non-invasive assessment of trophoblast invasion in early pregnancy.[11] Measurements of the velocity of blood following through the uterine arteries have been used to estimate uteroplacental blood flow. The defect of placentation is considered to be the major etiological factor in the development of preeclampsia and intrauterine growth restriction.[12]

TABLE 1: Demographic characteristics of pregnants.

	High-resistance (n= 19)	Low-resistance (n= 17)
Maternal age	28.2 (19-34)	30.6 (20-41)
Gravidity	3 (1-4)	2 (1-3)
Parity	1 (1-2)	1 (0-3)
Gestational age	7.2 (6-9)	9.1 (7-10)

TABLE 2: Histological findings of conceptional products with high and low resistance uterine artery blood flow.

	High-resistance (n= 19)	Low-resistance (n=17)	p
Endovascular trophoblast invasion (+)	9/19 (47%)	11/17 (65%)	0.18
Endovascular trophoblast invasion (-)	10/19 (53%)	6/17 (35%)	0.49

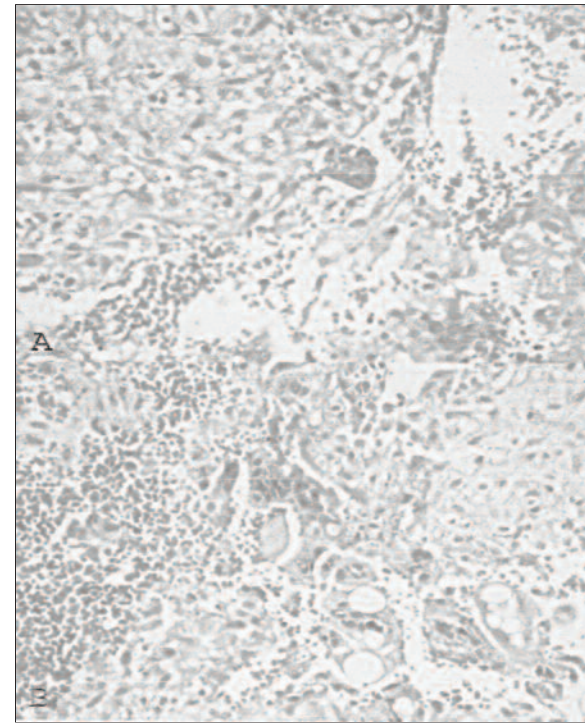

FIGURE 2A, B: Decidual implantation sites of syncytiotrophoblasts (HE, ×40).

In the present study we examined the trophoblastic invasion by determining decidual endovascular trophoblast invasion in specimens of curettage materials of pregnancy. We identified the implantation site in all of cases while Prefumo et al. reported 80% identification ratio by performing the same method.[11] Trophoblastic invasion was observed in 55% of cases. Previous studies have reported similar results in normal pregnancies undergoing elective termination.

Based on the studies from the assisted reproductive medicine programme, uterine artery indices are good indicators of the probability of subsequent pregnancy.[13] However because of the discrepancies between the time of ovulation induction and pulsed Doppler ultrasonography, uterine arterial blo-

od resistance has not proved as a prognostic indicator for implantation.Although not statistically significant the higher percentage of invaded vessels (65%) in the low-resistance cases as opposed to the high-resistance ones (47%; p= 0,18) provides correlation between uterine artery Doppler findings and extent of trophoblastic invasion.

Decline in endometrial receptivity, which is associated with a decrease in uterine perfusion, may play an important role in the decrease of implantation rates with age. However we did not find such elevation of the uterine arterial pulsatility indices in our subjects. We determine that ageing affects uterine perfusion less than other factors. Direct channels through the trophoblast plugs develop gradually between 8 and 12 weeks of gestation, and are unlikely to allow any substantial blood flow before this latter date.[14] This delayed onset of intervillous blood flow protects from oxidative damage to the trophoblast.

During Doppler flow examinations, inefficient placentation in the first and the second trimesters of pregnancies with increased resistance to blood flow in uterine arteries, predisposes to complications such as preeclampsia and intrauterine growth restriction.[15] Early embryonic development occurs in a low oxygen environment and it has been postulated that the yolk sac has an essential role in transport of nutritive substances to the embryo.[16] Placenta replaces the yolk sac as a main source of nutriotional supply after week nine of gestation.[17] Doppler velocimetry of intraplacental,chorionic and yolk sac hemodynamics may be new tools to detect placental dysfunction during the ongoing trophoblast invasion when therapeutic measures would still be possible. Therefore, interstitial invasion, deeper decidual-myometrial junction invasion and the release of vasoactive mediators may explain changes in arterial resistance and be related to decidual endovascular trophoblastic invasion.

In conclusion, we propose the use of uterine artery Doppler invesitigation for the non-invasive assessment of trophoblast invasion in early pregnancy. Further study will elucidate the significance of these observations.

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