Effect of uterine artery blood flow on recurrent pregnancy loss

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Summary

We investigated the effect of uterine artery blood flow on recurrent pregnancy loss. One hundred and twelve patients admitted to our clinic were included in the prospective study. The study group consisted of 28 cases with a history of three miscarriages before the 20th gestational week, and the control group consisted of cases with at least one prior live birth without any history of miscarriage or poor obstetric outcome. The mean pulsatility index (PI) , resistance index (RI) and systolic/diastolic ratio (S/D ratio) values of the uterine artery were measured between the 18th and 23rd days of the menstrual cycle via transvaginal Doppler ultrasonography. No statistically significant difference could be detected regarding uterine artery PI (p = 0.703), RI (p = 0.333), and S/D (p = 0.403) values between the study group and the control group ($p > 0.05$). In order to clearly determine etiologic causes of recurrent pregnancy loss, new randomized and controlled clinical trials with large patient populations are needed.

Key words: Recurrent pregnancy loss; Uterine artery; Doppler ultrasonography.

Introduction

Recurrent pregnancy loss is defined as three or more miscarriages before 20 weeks of gestation. Cases with no live birth are referred to as primary and those with live birth as secondary recurrent pregnancy loss. More than 80% of the abortions occur within the first 12 weeks and this rate rapidly decreases thereafter [1]. More than than half of the abortions are caused by chromosomal anomalies. The incidence decreases as gestational age increases. The risk of spontaneous abortion increases with increasing age of parents [2].

The frequency of recurrent pregnancy loss in a fertile population is 1-2% when those with three or more pregnancy losses are taken into consideration. This rate is reported to be 5% when the cases with two or more pregnancy losses are taken into consideration [3]. Using current diagnostic methods, the underlying cause can be determined only in half the cases with recurrent pregnancy loss [4].

Detailed visualization of female internal genital organs has been possible particularly with the use of high resolution transvaginal ultrasound probes [5]. These devices allow close examination of small details since they are placed in close proximity to the organs to be inspected [6]. Hemodynamics of pelvic and genital organs can also be evaluated by Doppler ultrasound (US). Taylor *et al*. was the first to perform ovarian and uterine artery blood flow measurements during the menstrual cycle [7]. Pelvic genital organs can be evaluated by continuous wave, pulsed wave, and color flow mapping methods [8].

In this study, we evaluated the relationship between recurrent pregnancy loss and uterine artery Doppler flow.

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Materials and Methods

Between 2008 and 2010, 112 patients admitted to the 4th Department of Obstetrics and Gynecology at Göztepe Training and Research Hospital were included in this prospective and controlled study. The study group consisted of 28 patients between 18 and 40 years of age who had at least three abortions before 20 weeks of gestation, regular menstrual cycles in the last three months, who did not use hormonal contraception or intrauterine devices, and who were not pregnant at the time of the study.

Four patients with irregular menstrual cycles, three patients who were using hormonal contraception, four patients who were using intrauterine devices, and one patient who was pregnant at the time of the study were excluded from the study. One case with diabetes mellitus, two cases with hypothyroidism and three cases that were found to have consanguineous marriages were also excluded from the study. Two cases had abnormal karyotypes, two cases had IgG anticardiolipin antibodies, six cases had heterozygous and one case had homozygous factor V Leiden mutation, 21 cases had heterozygous and two cases had homozygous MTHFR mutation. These cases were all excluded from the study. One case was excluded because of a previous oophorectomy operation due to an ovarian cyst. Three cases could not be reached during the study.

Using a simple random sampling method, 28 cases were selected as the control group among 128 cases who were admitted to our outpatient clinic for family planning counselling and who had at least one live birth and who no history of abortion or poor obstetric history.

Patient age, age of spouse, number of abortions, abortion week, consanguineous marriage, systemic disorders (diabetes mellitus, thyroid disease, chronic liver, kidney or heart disease), and history of venous thrombosis were all recorded; prolactin levels were measured and karyotype analysis was performed. IgG and IgM anticardiolipin antibodies and lupus anticoagulant were measured. Factor V Leiden (G1691A) mutation, prothrombin G20210A mutation, and MTHFR C677T mutation were investigated in peripheral blood obtained from the patients.

Table 1. — *Age characteristics*.

	Study group (n = 28)	Control group (n = 28)	*p**
Patient age	31.42 ± 3.72	31.10 ± 3.75	0.805
Spouse age	33.85 ± 3.48	34.14 ± 3.00	0.754

* $p < 0.05$ was considered significant.

Table 2. — *PI, RI values and S/D ratios between the study and control group*.

	Study group (n = 28) Mean, SD (range)	Control group (n = 28) Mean, SD (range)	*p**
Pulsatility index	2.28 ± 0.35	2.32 ± 0.39	0.703
Resistance index	0.85 ± 0.03	0.84 ± 0.04	0.333
Systolic/diastolic ratio	7.12 ± 1.78	6.73 ± 1.72	0.403

* $p < 0.05$ was considered significant.

All cases were evaluated during the secretory phase of the menstrual cycle between days 18 and 23. Measurements were performed using a Logiq P5 (General Electric, CA, USA) Doppler US device and 7.5 Mhz endovaginal probe after the patients were placed in the lithotomy position on a gynecologic examination table. US scanning gel was applied to the probe which was then covered with a sterile condom. After applying lubricating gel, the probe was gently inserted into the vagina. The probe was positioned as to obtain sagittal images in which caudal structures are displayed at the right, and cranial structures are displayed at the left side of the monitor. After repositioning the probe by rotating 90 degrees, a coronal view was acquired in which the right side of the patient was displayed on the right side and the left side of the patient was displayed on the left side of the monitor. After orientation to the pelvis minor and determination of anatomic landmarks (cervix, ovary, pelvic wall), the US probe was moved into the lateral fornix of vagina. Examination was performed with minimal possible pressure of the probe. Doppler signal was recorded from the uterine artery at the isthmus level. After locating the artery on real-time imaging, Doppler wave and gate were adjusted as to detect Doppler shift. The mean pulsatility index (PI), resistance index (RI), and systolic/diastolic ratio (S/D ratio) values for bilateral uterine arteries were automatically calculated by the computer. All measurements were performed twice by the same investigator and average values were used in the analysis.

NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) was used in statistical analyses of the data. Along with descriptive statistics, the Student's t test was used in comparison of variables with normal distribution. The level of significance was set at 0.05.

Results

Age of the patients ranged between 20 and 39 years; mean age was 31.42 ± 3.72 years in the study group and 31.10 ± 3.75 years in the control group. There was no significant difference between the groups with respect to age. Mean age of the spouses was 33.85 ± 3.48 years in the study group and 34.14 ± 3.00 years in the control group; no significant difference was found between the groups. Age characteristics of the groups are shown in Table 1.

Mean number of abortions was 3.53 ± 0.88 in the study group. Mean parity was 1.96 ± 0.69 in the control group. No statistically significant difference was found between the study and control groups with respect to PI values of the uterine artery. Mean PI was 2.28 ± 0.35 in the study group and 2.32 ± 0.39 in the control group. There was no statistically significant difference between the study and control groups with respect to RI values of the uterine artery. Mean RI was 0.85 ± 0.03 in the study group and 0.84 ± 0.04 in the control group. There was no statistically significant difference between the study and control groups with respect to S/D ratio. Mean S/D ratio was 7.12 ± 1.78 in the study group and 6.73 ± 1.72 in the control group (Table 2).

Discussion

Abortion is the most common complication occurring during pregnancy and it constitutes the major reason for bleeding during the first and second trimester. The probability of abortion decreases as gestational age increases. The risk of abortion is 11.5% where the gestational sac is visualized but not the embryo itself; the risk is 5% when a fetal heart beat is detectable and the risk is below 3% at the 11th week of gestation [9]. The risk of spontaneous pregnancy loss increases with age. In our study, both patients in the study and control groups were under 40 years of age and no statistically significant difference was found between the groups with respect to age.

Among all the factors investigated, genetic, anatomic, and immunological factors are considered definitive causes of recurrent pregnancy loss. Alloimmunopathology, hereditary thrombophilia, endocrinopathies, infections, and environmental factors are still investigated. After a detailed investigation, definitive cause of recurrent pregnancy loss could not be explained in about more than half of the couples. In our study, 3.5% of the cases had a systemic disorder, 38% had anti-phospholipid syndrome and hereditary thrombophilia, and 2.3% had abnormal karyotype. None of the cases had a history of exposure to radiation, chemicals or drugs.

The ovary and uterus are two organs in which marked neoangiogenesis occurs under physiological conditions in adults. Blood flow curves of the uterine arteries reflect the vessel anatomy of uterine vasculature and furthermore provide clues about functional status of the same arterioles. Color and pulsed transvaginal Doppler US is a simple, fast, and reproducible examination method. Compared to B- and M-mode US, color Doppler and other methods used in blood flow measurements cause higher exposure to US waves. Measurement of uterine perfusion is an invasive method to examine the intrauterine environment but it can also provide additional information about pathophysiology of recurrent pregnancy loss and endometrial implantation. Rhythmic changes in uterine blood supply during the menstrual period could be related with blood progesterone/estrogen ratio. The higher estrogen to progesterone ratio, the higher is the quantity of blood flow through the uterine vascular bed. Proges-

terone antagonizes uterine vasodilator effects of estrogen and the degree of inhibition depends on ratio of these two steroids [10, 11].

Kurjak *et al*. performed transvaginal colour Doppler US in 100 infertile patients and 150 control patients to determine changes in blood flow of the uterine and ovarian arteries during the menstrual cycle. They found a statistically significant difference between the study and control groups with respect to mean RI of the uterine artery [12]. Zaidi *et al*. investigated whether or not pregnancy and implantation success rates could be predicted by the assessment of blood flow in the uterine artery on the day hCG was administered to patients undergoing IVF treatment. They suggested that the success of the implantation could be predicted by measuring the uterine artery PI [13]. Yokota *et al*. studied 63 infertile patients and investigated PI values of the uterine and ovarian arteries on the day of ovulation using transvaginal color Doppler US. They noted that measurement of uterine artery PI by transvaginal color Doppler US could be of benefit in patients with infertility of unknown etiology [14].

Hoozemans *et al*. assessed 83 patients undergoing IVF-ET treatment by serial Doppler US examinations performed at different times of the cycle and reported that uterine artery Doppler US cannot predict which women could conceive and which of the pregnancies would end in miscarriage [15]. Wakeman *et al*. studied 192 women in the follicular phase of the menstrual cycle and they compared uterine and ovarian blood flows using transvaginal Doppler US between patients who conceived in a natural menstrual cycle with those who did not. Transvaginal US was performed between the 3rd and 12th day of the cycle. They did not find any statistically significant difference between pregnant and non-pregnant cycles in terms of utero-ovarian blood flow parameters [16].

In this study, we did not find statistically significant difference in terms of PI, RI values, and S/D ratio between the control and study group with a history of recurrent pregnancy loss. Some studies in the literature suggest that no significant relation exists between recurrent pregnancy loss and PI, RI values, and S/D ratio measured by transvaginal Doppler US during the luteal phase of the menstrual cycle but there are also studies which assert the contrary. Ferreira *et al*. compared 43 women with recurrent pregnancy loss and 43 women with no history of abortion and at least one child born at term.The uterine artery PI and flow velocity wave (FVW) patterns were investigated, and a higher PI, incidence of FVW of the A and uterine artery impedance were found among women with recurrent pregnancy loss [17]. Nakatsuka *et al*. examined uterine artery blood flow in 104 pregnant women between the 4th and 5th weeks of gestation using transvaginal Doppler US. Uterine artery PI value was found to be significantly higher in the study group with recurrent pregnancy loss compared to the control group. They suggested that uterine artery PI value could be an independent indicator in cases with recurrent pregnancy loss and that it could be used to detect patients with recurrent pregnancy loss caused by the impairment in uterine perfusion [18]. Lazzarin and colleagues compared uterine artery PI values between a control group consisting of 50 subjects who did not have a history of miscarriage and who had at least one live birth with a study group consisting of 230 cases with recurrent pregnancy loss with unknown etiology. They used transvaginal US in mid-luteal phase. They found significantly higher uterine artery PI values in patients with recurrent pregnancy loss (2.60 ± 0.7) compared to the control group (2.08 ± 0.47). They emphasized that increased uterine artery blood flow resistance is an independent risk factor in cases with recurrent pregnancy loss [19]. By using uterine artery Doppler US in the mid-luteal phase, El Mashad *et al*. compared patients who had three or more recurrent pregnancy losses with a control group. They found significantly higher uterine artery PI values in the study group (2.71 ± 0.259) compared to the control group (2.06 ± 0.194) ($p < 0.01$). As a result, they suggested that the uterine artery PI value could be used to determine patients with recurrent pregnancy loss caused by impairment in uterine perfusion [20].

Frates *et al*. examined 96 cases with a history of recurrent pregnancy loss during the first trimester of their pregnancies and found that uterine artery RI values decreased significantly from the 6th week until the 13th week of gestation. They noted that uterine artery RI value in the first trimester is of no use in predicting pregnancy outcomes in cases with recurrent pregnancy loss [21]. However in the English literature the number of studies that have similar results with Frates *et al*. and our study on uterine artery Doppler flow and recurrent pregnancy loss is limited.

Conclusion

Early pregnancy loss is a distressing condition for the entire family. Most families have the fear that this problem will reoccur. Early pregnancy loss is also an important issue for physicians dealing with reproductive health, because its etiology is unknown and diagnostic methods and treatment options are limited. In this study, we found no statistically significant difference between women with and without a history of recurrent pregnancy loss in terms of uterine artery PI, RI values, and S/D ratio. However, randomized and controlled studies on wider patient populations are needed to elicit etiological factors of recurrent pregnancy loss and to propose standardized treatment protocols.

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