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Use of uterine artery Doppler velocimetry values to predict pregnancy in intrauterine insemination cycles in couples with unexplained infertility

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Ethics Committee Approval
The Local Ethic Committee of Umraniye Training and Research Hospital, Istanbul, Turkey has approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.GP.0.01/178).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: It is known that pregnancy success in IUI cycles performed in couples with unexplained infertility is below 20% even under the best conditions. Predicting the success in IUI cycles and directing patients to appropriate assisted reproductive treatment is essential for the time and budget. In this context, we aimed to investigate the use of uterine artery Doppler velocimetry values to predict pregnancy in intrauterine insemination (IUI) cycles in couples with unexplained infertility.

Methods: In this prospective cohort study, couples with unexplained infertility were randomly assigned to two groups: clomiphene citrate (CC) and gonadotropin. The CC group used 50-150 mg CC daily between the 5th and 9th days of the menstrual period, while the gonadotropin group used 37.5-75 IU of recFSH daily from the 3rd day of the menstrual period until the dominant follicle developed. Ovulation was triggered by recHcg when at least one dominant follicle of 17 mm or larger was detected. Intrauterine insemination was performed 36 hours after the trigger. Uterine artery flow pulsatility index (PI), resistance index (RI) and the systolic-diastolic ratio (S/D) were measured in all patients by Doppler ultrasound on the 3rd day of menstruation and trigger day. Uterine artery Doppler values of the group that achieved pregnancy and those who could not conceive were compared as the main outcome of the study.

Results: The study was designed over 143 IUI cycles, 89 cycles in the gonadotropin group and 54 cycles in the CC group. In 143 IUI cycles, 24 (16%) pregnancies were obtained, seven (12%) in the CC group and 17 (12%) in the gonadotropin group. In both CC and gonadotropin cycles, mean age, BMI, duration of infertility, hormone levels on the third day of menstruation, endometrial thickness on 3rd day of menstruation and on the trigger day, dominant follicle number and mean follicle diameter were similar in the pregnant and non-pregnant groups ($P<0.05$). There was no statistical difference in uterine artery Doppler values (RI, PI and S/D) measured neither on the 3rd day of the cycle nor on the trigger day between pregnant and non-pregnant groups in patients receiving CC or gonadotropin ($P<0.05$).

Conclusion: Considering the hormonal changes in stimulated cycles or other factors that may have an impact on endometrial blood flow and endometrial receptivity, we think that only uterine artery Doppler velocity measurement values are not effective in predicting pregnancy success in CC or gonadotropin-induced IUI cycles.

Keywords: Infertility, Uterine artery, Insemination, Pregnancy

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Introduction

Unexplained infertility, which covers 25 % of infertile couples, is a diagnosis generally used for couples in which all standard tests such as ovulation tests, hormone levels, tubal patency and semen analysis are normal [1]. Impaired endocrinological balance or reproductive physiology, immunologic and genetic disturbances are thought to be the potential causes of unexplained infertility [2]. In this context, blood flows in the uterine or spiral arteries were investigated in patients with unexplained infertility, especially in the last decade. Studies have suggested that endometrial perfusion is impaired in women with unexplained infertility, especially during the peri-implantation period [3, 4]. In the light of this information, we aimed to evaluate the effectiveness of uterine artery Doppler velocimetry values as a predictor of a successful pregnancy in intrauterine insemination cycles in couples with unexplained infertility.

Materials and methods

The study was conducted in Obstetrics and Gynecology Department of Istanbul Umraniye Training and Research Hospital between 01/06/2020 and 31/11/2021. Couples with unexplained infertility were informed about CC and gonadotropin treatments, and the choice of drug to be used by the patient was made according to the couples' own decision. Accordingly, the couples were divided into two groups as clomiphene citrate (CC) and gonadotropin. While the CC group used 50-150 mg CC (Koçak Farma İlaç ve Kimya Sanayi A.Ş.) daily between the 5th and 9th days of menstruation, the gonadotropin group used recombinant follicle stimulating hormone (rec FSH) (Gonal-f Merck İlaç Ecza ve Kimya Tic. A.Ş.) from the 3rd day of menstruation with a daily starting dose of 37.5 or 75 IU/day. The dose was increased by 37.5 IU/day in tandem with follicle development until at least one dominant follicle developed. Ovulation was triggered with 250 mcg recombinant human chorionic gonadotropin (rec hCG) (Gonal-f Merck İlaç Ecza ve Kimya Tic. A.Ş) when at least one dominant follicle of 17 mm or larger was detected, and intrauterine insemination (IUI) was performed by a soft cannula 36 hours after the trigger. The gonadotropin group was given 20 mg of oral dydrogesterone (Abbott Laboraturarları İthalat İhracat ve Ticaret Limited Şirketi) daily for post-insemination luteal support, whereas luteal support was not given to the CC group. Serum beta-hCG tests were performed 14 days after the IUI. Clinical pregnancy was then confirmed via transvaginal ultrasound scanning of intrauterine gestational sac with fetal cardiac activity. Luteal support of the patients who achieved pregnancy in the gonadotropin group was continued until the 10th gestational week.On the 3rd day of menstruation and on the trigger day, the endometrial thickness was measured by transvaginal ultrasound, and the uterine artery flow Pulsatility Index (PI), Resistance Index (RI), and the systolic-diastolic ratio (S/D) were measured by Doppler ultrasound. FSH, LH, estradiol, TSH, prolactin, and progesterone levels of the patients on the 3rd day of menstruation were analyzed with the Abbott Architect i200 SR device in accordance with the manufacturer's recommendations. Transvaginal ultrasound evaluations of the patients were performed by the same specialist and with the same ultrasound device (Hitachi Aloka Prosound F37).Patients under the age of 40, those with a BMI of 29.9 kg/m2 or less, non-smokers, least one tube shown to be open according to the results of hysterosalpingography and whose partner's spermiogram result was normospermic according to WHO 2010 criteria were included in the study. Patients with polycystic ovary syndrome, any systemic or autoimmune disease, congenital uterine anomaly, myoma causing deformation in the uterine cavity, diagnosis of endometrioma or endometriosis, or previous uterine or ovarian surgery were not included in the study.Body mass index (BMI) had been measured as; BMI (kg/m2)

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Statistical analysis

Statistics were performed with the SPSS 25.0 package program. The distribution of the data was found to be normal with the Kolmogorov Smirnov test. In addition to descriptive statistical methods (mean, standard deviation, frequency, etc.), t-test and chi-square tests were also used alongside parametric data while evaluating the findings of this study. Significance has been determined at $P<0.05$ levels for all values.

Results

Between June 2020 and November 2021, 173 ovulation induction (OI) cycles, 97 with gonadotropin and 76 with CC were performed on 173 infertile couples who met the study criteria. Eight cycles were canceled in the gonadotropin group because 2 cycles of follicles did not develop, 4 cycles were from spontaneous ovulation, and 2 cycles were from hyperstimulation. In the CC group, 22 cycles were canceled because 6 cycles of follicles did not develop, 3 cycles were due to spontaneous ovulation, 6 cycles of cystic development, 1 cycle male partner could not give sperm sample on the day of IUI, and six patients did not come for follicle follow-ups. The study was designed with 89 cycles in the gonadotropin group that underwent IUI after OI and 54 cycles in the CC group. In this study, no adverse side effects or undesirable results occurred in any patient due to drugs used for OI or during blood collection for hormone tests or during transvaginal ultrasound examinations.

In this study, 24 pregnancies (16%) were obtained in 143 IUI cycles, 7 pregnancies (12%) in IUI cycles with CC and 17 (19%) in IUI cycles with gonadotropins. Those who became pregnant and those who could not conceive were compared among themselves in terms of age, BMI, duration of infertility, hormone levels on the third day of menstruation, endometrial thickness on the third day of menstruation and on the trigger day, number of dominant follicles, average follicle size, and uterine artery Doppler values on the 3rd day of menstruation and the trigger day.

In the CC-induced cycles, mean age, BMI, infertility duration, hormone levels on the third day of menstruation, endometrial thickness in the basal period and on the trigger day, dominant follicle number, and mean follicle size were similar in pregnant and the non-pregnant groups (Table 1). There was no significant difference in the mean uterine artery Doppler values

(PI, RI and S/D) measured on the 3rd day of menstruation and on the trigger day between the pregnant and the non-pregnant groups (Table 2).

Table 1: Comparison of demographic and clinical characteristics between pregnant and non-pregnant groups in CC group

	Pregnant Group n=7	Non-pregnant Group n=47	*P*-value
Age (Years)	29.29 (5.62)	29.17 (5.64)	0.960
BMI (kg/m2)	26.11 (5.64)	25.46 (4.29)	0.717
Duration of infertility (Years)	2.5 (1.3)	3 (2.3)	0.561
Basal FSH (mIU/mL)	6.80 (2.76)	7.06 (2.24)	0.783
Basal LH (mIU/ml)	4.67 (1.64)	5.75 (2.73)	0.317
Basal Estradiol (pg/ml)	40.71 (16.87)	43.66 (20.36)	0.718
Basal Progesterone (ng/mL)	0.29 (0.25)	0.21 (0.13)	0.238
Prolactin (ng/mL)	16.11 (5.87)	16.79 (6.57)	0.797
TSH (mU/mL)	1.86 (1.16)	2.20 (1.38)	0.532
Basal endometrial thickness (mm)	3.2 (1.0)	3.6 (1.0)	0.352
Trigger day endometrial thickness (mm)	7.9 (1.7)	9.2 (2.6)	0.221
Number of dominant follicles	1.2 (0.4)	1.4 (0.5)	0.492
Mean dominant follicle diameter (mm)	19.7 (1.5)	19.5 (2.0)	0.845

Independent t test

Table 2: Doppler velocimetry of uterine arteries among the pregnant and non-pregnant groups in the CC group

	Pregnant Group n=7	Non-pregnant Group n=47	*P*-value
Right uterine artery PI on the 3rd day of menstruation	1.73 (0.55)	1.83 (0.57)	0.663
Right uterine artery RI on the 3rd day of menstruation	0.76 (0.08)	0.77 (0.08)	0.879
Right uterine artery S/D on the 3rd day of menstruation	4.70 (1.88)	4.90 (1.86)	0.797
Left uterine artery PI on the 3rd day of menstruation	1.75 (0.63)	1.81 (0.62)	0.813
Left uterine artery RI on the 3rd day of menstruation	0.75 (0.11)	0.77 (0.09)	0.509
Left uterine artery S/D on the 3rd day of menstruation	4.64 (2.09)	4.89 (1.87)	0.741
Trigger day right uterine artery PI	2.06 (0.64)	2.08 (0.88)	0.970
Trigger day right uterine artery RI	0.83 (0.07)	0.81 (0.06)	0.661
Trigger day right uterine artery S/D	6.29 (1.80)	5.48 (1.82)	0.275
Trigger day left uterine artery PI	1.99 (0.78)	2.18 (0.64)	0.477
Trigger day left uterine artery RI	0.82 (0.07)	0.82 (0.07)	0.940
Trigger day left uterine artery S/D	5.96 (2.06)	5.41 (1.88)	0.475

Independent t test

In gonadotropin-induced cycles, mean age, BMI, infertility duration, hormone levels on the third day of menstruation, endometrial thickness in the basal period and on the trigger day, dominant follicle number, and mean follicle size were similar in pregnant and the non-pregnant groups (Table 3). There was no statistical difference in the mean uterine artery Doppler values (PI, RI and S/D) measured on the 3rd day of menstruation and on the trigger day between the pregnant and the non-pregnant groups (Table 4).

Table 3: Comparison of demographic and clinical characteristics between pregnant and non-pregnant groups in the gonadotropin group

	Pregnant Group n=17	Non-pregnant Group n=72	*P*-value
Age (Years)	28.9 (4.6)	29.56 (5.07)	0.649
BMI (kg/m2)	25.7 (4.0)	24.70 (4.01)	0.717
Duration of infertility (Years)	2.3 (1.0)	2.6 (1.2)	0.516
Basal FSH (mIU/mL)	6.48 (1.65)	6.99 (2.13)	0.362
Basal LH (mIU/ml)	5.89 (2.54)	6.76 (2.92)	0.261
Basal Estradiol (pg/ml)	42.53 (20.89)	39.71 (21.12)	0.621
Basal Progesterone (ng/mL)	0.19 (0.9)	0.22 (0.13)	0.388
Prolactin (ng/mL)	17.51 (5.39)	17.74 (6.12)	0.889
TSH (mU/mL)	2.09 (1.02)	1.98 (0.82)	0.652
Basal endometrial thickness (mm)	3.8 (1.3)	3.9 (1.2)	0.795
Trigger day endometrial thickness (mm)	10.1 (2.3)	10.1 (2.0)	0.965
Number of dominant follicles	1,4 (.5)	1.2 (0.4)	0.111
Mean dominant follicle diameter (mm)	18.4 (1.7)	18.4 (1.5)	0.952

Independent t test

Table 4: Doppler velocimetry of uterine arteries among the pregnant and non-pregnant groups in the gonadotropin group

	Pregnant Group n=17	Non-pregnant Group n=72	*P*-value
Right uterine artery PI on the 3rd day of menstruation	1.81 (0.62)	1.77 (0.45)	0.782
Right uterine artery RI on the 3rd day of menstruation	0.77 (0.10)	0.78 (0.07)	0.405
Right uterine artery S/D on the 3rd day of menstruation	5.08 (2.20)	4.72 (1.42)	0.405
Left uterine artery PI on the 3rd day of menstruation	1.94 (0.76)	1.85 (0.54)	0.575
Left uterine artery RI on the 3rd day of menstruation	0.77 (0.10)	0.78 (0.08)	0.782
Left uterine artery S/D on the 3rd day of menstruation	5.03 (2.01)	4.93 (1.71)	0.831
Trigger day right uterine artery PI	1.80 (0.44)	1,90 (0.50)	0.485
Trigger day right uterine artery RI	0.76 (0.07)	0.79 (0.11)	0.382
Trigger day right uterine artery S/D	4.63 (1.67)	5.33 (1.61)	0.114
Trigger day left uterine artery PI	1.85 (047)	1.88 (0.52)	0.848
Trigger day left uterine artery RI	0.77 (0.07)	0.78 (0.07)	0.598
Trigger day left uterine artery S/D	5.03 (1.47)	5.18 (1.70)	0.728

Independent t test

Discussion

In this study, we investigated the effect of uterine artery Doppler values in predicting pregnancy in patients with unexplained infertility who underwent IUI after OI. We did not find a significant difference in uterine artery Doppler values measured neither on the 3rd day of the stimulated cycle, nor on the trigger day between the pregnant and non-pregnant groups in patients receiving CC or gonadotropin.

In the literature, there are many studies investigating Doppler values of uterine, endometrial or ovarian arteries in spontaneous or stimulated menstrual cycles. In these studies, different results were reported according to the characteristics of the patients included in the study, the agents used in assisted reproductive treatments, and the different days in which Doppler values were evaluated during the cycle.

Kupesic and Kurjak [5] investigated blood flow in the uterine and spiral arteries in both spontaneous and stimulated cycles. They stated that the uterine artery blood flow pulsatility index decreased in spontaneous menstrual cycles one day before ovulation, but this change did not occur in stimulated cycles. In 2000, Hsieh et al. [6] compared the PI and RI at different sampling sites of the uterine and spiral arteries in the early and mid-menstrual phases during IUI cycles after OI. They stated that there was no significant difference in the PI and RI values of the uterine and spiral arteries at different sampling sites and phases of the stimulated cycles.

Wakeman et al. [7] evaluated uterine and ovarian blood flow during the follicular phase of the menstrual cycle, in women who could and could not conceive. They found that in the late follicular phase of natural conception cycles, there is an increased uterine artery peak systolic rate compared to non-conception cycles, which is not seen in CC-induced cycles where conception occurs. Akihito et al. [8] examined the blood flow of the endometrium in both CC-stimulated cycles and spontaneous menstrual cycles; they revealed that CC-stimulated cycles have lower endometrial perfusion in the periovulatory period than spontaneous cycles.

In a study published by Güzel et al. [9] in 2015, no significant difference was found in uterine artery or ovarian artery Doppler values between pregnant and non-pregnant

groups in CC-induced cycles. Kim et al. [10] compared uterine artery Doppler values, endometrial and subendometrial blood flow parameters in the pregnant and non-pregnant groups in CC-stimulated IUI cycles. While they found that the uterine artery Doppler values were similar in the pregnant and non-pregnant group, they found that the endometrial vascularization index (VI), flow index (FI) and vascularization flow index (VFI) scores were higher in the pregnant group. Similar to the results of the two studies above, we did not detect any difference in uterine artery Doppler values in the pregnant and non-pregnant groups in CC-stimulated IUI cycles in this study.

Ivanovski et al. [11] investigated uterine and arcuate artery Doppler values on the trigger day for predicting the success in vitro fertilization cycles. They found that the mean uterine artery PI and RI were significantly lower in the pregnant group compared to the non-pregnant group. Similarly, in a study published in 2015, the effect of uterine and arcuate artery Doppler values measured on the trigger day in predicting pregnancy in patients receiving in IVF treatment was investigated. In this study, the mean PI and RI of both uterine and arcuate arteries were found to be significantly lower in pregnant women than in non-pregnant women [12]. Apart from the IVF treatment cycles mentioned above, Yaltı et al. [13] investigated the pulsatility index of the uterine, and ovarian arteries on the trigger day in patients who conceived and did not become pregnant among patients who underwent IUI after OI with gonadotropin. In this study, which included 57 patients, right, left and mean uterine artery PI and right, left and mean ovarian stromal artery PI were found to be significantly lower in the pregnant group than in the non-pregnant group. Unlike these studies, we did not find any difference in uterine artery Doppler values in gonadotropin-induced IUI cycles in pregnant and non-pregnant women in our study.

In 2004, Ng et al. [14] compared endometrial and subendometrial blood flows in natural and stimulated cycles in the same patients undergoing IVF treatment. This study revealed that endometrial and subendometrial Doppler flow indices were significantly lower in stimulated cycles than in natural cycles and were reduced in approximately 60% of patients after ovarian stimulation. Again, the same authors evaluated uterine artery Doppler values, endometrial and subendometrial blood flows in infertile patients undergoing IVF treatment in both natural and gonadotropin-induced cycles in 2006. It has been reported that the increased serum E2 concentration in stimulated cycles, it causes vasodilation in the myometrium and a decrease in blood flow towards the endometrial and subendometrial regions. Therefore, uterine blood flow measurement may not reflect endometrial and subendometrial blood flow, especially in stimulated cycles [15].

Limitations

The limited number of participants and the lack of evaluation of endometrial and subendometrial blood flows are limiting factors for this study.

Conclusion

We could not find a significant difference in uterine artery Doppler values measured neither on the 3rd day of the menstrual cycle nor on the trigger day between pregnant and non-pregnant groups in patients receiving CC or gonadotropin. Considering the hormonal changes in stimulated cycles or other factors that may have an impact on endometrial blood flow and endometrial receptivity, we believe that only uterine artery Doppler values are not effective in predicting pregnancy success in CC or gonadotropin-induced IUI cycles.

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