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Use of uterine artery doppler velocimetry values to predict pregnancy in clomiphene citrate-induced intrauterine insemination cycles in patients with polycystic ovary syndrome

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Abstract

Aim: The aim of this study is to investigate the effectiveness of uterine artery Doppler velocimetry values to predict pregnancy in clomiphene citrate-induced intrauterine insemination cycles (IUI) in patients with polycystic ovary syndrome (PCOS).

Materials and Methods: Patients with PCOS who applied to the infertility outpatient clinic between 01/06/2020 and 31/11/2021 were included in this prospective interventional study. For ovulation induction, patients used clomiphene citrate (CC) 50-150 mg daily between days 5 and 9 of the cycle. When at least one dominant follicle of 17 mm or larger was detected in serial transvaginal ultrasound controls, ovulation was triggered and IUI was performed 36 hours later. Uterine artery flow Resistance Index (RI), Pulsatility Index (PI), and systolic-diastolic ratio (S/D) were evaluated with Doppler ultrasound in all patients on the 3rd day of the cycle and the 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 conducted on 56 cycles in which IUI was performed after ovulation induction. In these 56 cycles, 10 pregnancies were obtained and the clinical pregnancy rate was 17.9%. The pregnant and non-pregnant groups were similar in terms of demographic characteristics, basal hormone levels, basal period and trigger day endometrial thickness, follicle number, and mean dominant follicle diameter ($p>0.005$). There was no significant difference in mean uterine artery Doppler values (PI, RI, and S/D) measured on the 3rd day of the cycle and the trigger day between the pregnant and non-pregnant groups ($p>0.005$).

Conclusion: Considering the hormonal changes in stimulated cycles and the effect of CC itself on endometrial receptivity, we think that only uterine artery Doppler values are not effective in predicting pregnancy success in CC-induced IUI cycles in patients with PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women in the reproductive period, with a prevalence ranging from 4% to 12% [1]. Since it was first described in 1935, different classifications have been made for the diagnosis of PCOS in different societies. Among these classification, the most widely used PCOS classification is the Rotterdam criteria. Accordingly, the presence of two of the following three criteria is required for the diagnosis of PCOS; chronic oligo-ovulation or anovulation, clinically or laboratory-confirmed hyperandrogenism, and features of polycystic ovaries on ultrasound [2].

It is known that PCOS is the most common cause of anovulatory infertility in women of reproductive age [3]. Ovulation induction with pharmacological treatment is considered in patients with PCOS who do not ovulate spontaneously despite lifestyle changes and weight loss. According to the recommendations in the international evidence-based guideline for PCOS, published in 2018, letrozole should be considered as the first-line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility [4]. However, Clomiphene citrate (CC) remains the most widely used agent for ovulation induction in patients with PCOS, since the use of Letrozole in ovulation induction is off-label and is not supported by the healthcare system when it is prescribed for ovulation induction in most countries [3].

Factors affecting pregnancy rates in CC cycles, such as age, infertility duration, ovarian reserve, and endometrial

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thickness, have been investigated in previous studies [5,6]. In addition to these, the effect of CC on blood flow in the endometrium was investigated and it was stated that CC has a negative effect on endometrial perfusion in the periovulatory period [7]. In the light of this information, we aimed to evaluate the effectiveness of uterine artery Doppler velocimetry values in predicting pregnancy success in CC-induced intrauterine insemination cycles (IUI) in patients with PCOS.

Materials and Methods

This prospective interventional study was conducted in the Obstetrics and Gynecology Department of Istanbul Umraniye Training and Research Hospital between 01/06/2020 and 31/11/2021. Among the patients who applied to the infertility outpatient clinic during this period, the patients who were diagnosed with PCOS according to the Rotterdam criteria were included in the study. Patients used 50-150 mg CC (*Klomen 50 mg tablet, Koçak Farma İlaç ve Kimya Sanayi A.Ş.*) daily between the 5th and 9th days of menstruation for ovulation induction (OI). Follicle follow-up of the patients was performed at regular intervals by transvaginal ultrasonography. Ovulation was triggered with 250 mcg recombinant human chorionic gonadotropin (rec hCG) (*Ovitrelle 250 microgram/0.5 ml, Merck İlaç Ecza ve Kimya Tic. A.Ş*) when at least one dominant follicle of 17 mm or larger was detected, and IUI was performed by a soft cannula 36 hours after the trigger. None of the patients used medication for luteal support after IUI. Serum beta-hCG tests were performed 14 days after the insemination. Clinical pregnancy was then confirmed via transvaginal ultrasound scanning of the intrauterine gestational sac with fetal cardiac activity. On the 3rd day of menstruation and the trigger day, the endometrial thickness was measured by transvaginal ultrasound, and the uterine artery flow Resistance Index (RI), Pulsatility Index (PI), 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 by 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, at 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 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/m^2) = Body weight (kg)/Height^2(m) The Local Ethics 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.0.01/180)

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM, Armonk, NY, USA). 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.), an independent t-test is 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, 70 OI cycles with CC were performed on 70 infertile couples who met the study criteria. 14 cycles were cancelled because 8 cycles of follicles did not develop, 2 cycles were from spontaneous ovulation, 1 cycle male partner could not give a sperm sample on the day of IUI, and three patients did not come for follicle follow-ups. CC treatment was generally well tolerated and no CC-related adverse events were reported in any patient. The study was carried on with the remaining 56 cycles in which IUI was performed after OI. In these 56 cycles, 10 pregnancies were obtained and the clinical pregnancy rate was 17.9%. 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 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.

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 dominant follicle size were similar in pregnant and the non-pregnant groups ($p>0.005$) (Table 1).

Right uterine artery PI, RI, and S/D values measured on the 3rd day of the cycle in the pregnant group and the non-pregnant group were similar ($p=0.907$, $p=0.488$, $p=0.509$, respectively). Also, the left uterine artery PI, RI, and S/D values measured on the 3rd day of the cycle in the pregnant group and the non-pregnant group were similar ($p=0.193$, $p=0.170$, $p=0.291$, respectively) (Table 2).

Right uterine artery PI, RI and S/D values measured on the trigger day of the pregnant group and the non-pregnant group were similar ($p=0.548$, $p=0.326$, $p=0.501$, respectively). Also, the left uterine artery PI, RI, and S/D values measured on the trigger day of the pregnant group and the non-pregnant group were similar ($p=0.118$, $p=0.172$, $p=0.282$, respectively) (Table 2).

Discussion

In the present study, we tested the effect of uterine artery Doppler values in predicting pregnancy in CC-induced IUI cycles in infertile patients with PCOS. We did not find a significant difference in uterine artery Doppler values measured on the 3rd day of the cycle or the trigger day between the pregnant and non-pregnant groups.

As we know, CC is a selective estrogen receptor modulator used in the treatment of infertility since the 1960s [8]. CC

Table 1. Comparison of demographic and clinical characteristics between pregnant and non-pregnant groups.

	Pregnant Group n=10	Non-pregnant group n=46	p value
Age (Years)	28.60 ± 3.6	29.83 ± 3.3	0.364
BMI (kg/m^2)	25.87±3.7	24.43±4.0	0.302
Duration of infertility (Years)	2.0 ± 0.8	2.9 ± 1.5	0.072
Basal FSH (mIU/mL)	5,82 ± 1,23	5.76 ± 1.40	0.895
Basal LH (mIU/ml)	8.05 ± 3.55	7.64 ± 3.96	0.764
Basal Estradiol (pg/ml)	39.0 ± 18.14	39.59 ± 15.30	0.916
Basal Progesterone (ng/mL)	0.23 ± 0.20	0.26 ± 0.20	0.648
Prolactin (ng/mL)	17.00 ± 7.03	19.12 ± 7.06	0.393
TSH (mU/mL)	1.60 ± 0.53	2.13 ± 0.93	0.86
Basal endometrial thickness (mm)	4.33 ± 1,35	3.73 ± 1,50	0.248
Trigger day endometrial thickness (mm)	11.18 ± 3.18	9.35 ± 3.23	0.109
Number of dominant follicles	1.30 ± 0.48	1.35 ± 0.48	0.777
Mean dominant follicle diameter (mm)	18.55 ± 1.21	19.20 ± 2.11	0.354

Independent t test.

Table 2. Doppler velocimetry of uterine arteries among the pregnant and non-pregnant groups.

	Pregnant Group n=10	Non-pregnant group n=46	p value
Bazal right uterine artery PI	1.83 ± 0.49	1.85 ± 0.50	0.907
Bazal right uterine artery RI	0.80 ± 0.06	0.78 ± 0.07	0.488
Bazal right uterine artery S/D	5.39 ± 1.56	5.02 ± 1.64	0.509
Bazal left uterine artery PI	1.63 ± 0.47	1.91 ± 0.63	0.193
Bazal left uterine artery RI	0.76 ± 0.06	0.79 ± 0.06	0.170
Bazal left uterine artery S/D	4.40 ± 1.21	4.91 ± 1.52	0.291
Trigger day right uterine artery PI	1.91 ± 0.33	2.02 ± 0.56	0.548
Trigger day right uterine artery RI	0.82 ± 0.6	0.80 ± 0.07	0.326
Trigger day right uterine artery S/D	5.94 ± 1.77	5.53 ± 1.70	0.501
Trigger day left uterine artery PI	1.69 ± 0.44	2.01 ± 0.59	0.118
Trigger day left uterine artery RI	0.79 ± 0.06	0.82 ± 0.07	0.172
Trigger day left uterine artery S/D	5.09 ± 1.94	5.82 ± 1.92	0.282

Independent t test.

acts as an estrogen antagonist and causes an increase in the release of gonadotropins from the pituitary by blocking the negative feedback of estrogen. While this effect stimulates follicle development, its anti-estrogenic effect on the cervix and endometrium negatively affects pregnancy success. Despite this, it is still used as a first-line pharmacological treatment for OI in patients with PCOS, as it is cost-effective.

In the literature, there are many Doppler studies conducted in spontaneous cycles to understand the etiology of PCOS. In 2009, Mala et al. stated in their Doppler study that uterine artery PI and RI were significantly higher in women with PCOS compared to controls [9]. Likewise, in the study conducted by Resende et al., it was found that uterine artery PI in women with PCOS was statistically significantly higher than in the control group [10]. Similarly, in a different study, it is found that uterine artery PI in women with PCOS was statistically significantly higher than in the control group. Although there was no significant difference in total testosterone levels, they argued that dehydroepiandrosterone sulfate (DHEAS), which was found to be significantly higher in the PCOS group, modulates uterine arterial blood flow directly or indirectly and may be responsible for high uterine artery PI in women with PCOS [11]. In support of these results, another study reported that PCOS patients had higher PI in the uterine artery compared to the control group, and DHEAS might be responsible for the high PI detected in the uterine arteries [12].

In addition to the above studies comparing uterine artery blood flow in women with and without PCOS in natural cycles, there are studies in the literature comparing patients in stimulated cycles. In this context, the study by Zaidi et al. is one of the first to examine blood flow in the uterus and ovaries in CC-stimulated cycles. They serially evaluated blood flow in the uterine arteries in CC-induced cycles of six women with PCOS. Uterine artery PI, which was detected higher on basal ultrasound scan before CC administration compared with women without PCOS, has been attributed to the high androgen levels that are typical of women with PCOS. In these six women, an increase in uterine artery PI was observed during the follicular phase of the CC-stimulated cycle, this increase continued until about 4 days before the LH surge, and then a decrease was observed throughout the luteal phase. It has been suggested that the increase in FSH and estrogen levels due to CC administration is effective in this change in uterine artery blood flow [13]. Pinkas et al. compared the uter-

ine artery Doppler values of women with PCOS and the control group in gonadotropin-induced cycles. They stated that there was no significant difference between PCOS and control groups in terms of PI and RI of uterine arterial blood flow throughout the treatment cycle [14].

In a study by Palomba et al., uterine artery RI evaluated both in the natural and in the CC-stimulated cycles, was found to be significantly higher in patients with PCOS compared to the control group without PCOS. In the same study, patients with PCOS who were able to conceive and could not become pregnant with CC treatment were compared. The uterine artery RI, which was evaluated in both basal, periovulatory, and luteal periods of stimulated cycles, was found to be significantly lower in the pregnant group than in the non-conceiving group [15]. Contrary to this study, we could not detect a significant difference between pregnant and non-pregnant groups in terms of uterine artery Doppler values evaluated both at basal period and on trigger day in CC-induced IUI cycles in patients with PCOS. We attributed these different results to the fact that patients in the aforementioned study used a fixed dose of 150 mg daily for CC, Palomba et al. did not use any medication to trigger ovulation and left the couples to intercourse instead of IUI.

In this prospective interventional study, although the same gynecologist performed all ultrasonographic evaluations with the same ultrasound device to avoid interobserver variability, a limited number of participants and the lack of evaluation of endometrial and sub-endometrial blood flows are limiting factors.

It is known that many factors affect pregnancy success in infertility treatments. In CC-stimulated cycles, on the one hand, increased serum estradiol levels can alter blood flow to the endometrium by acting on specific receptors in the uterine artery walls, while CC itself can cause histological endometrial abnormalities and delayed endometrial maturation, possibly by depletion of the cytosolic estrogen receptors on endometrial cells [16, 17].

Conclusion

We could not find a significant difference in uterine artery Doppler values evaluated neither on the 3rd day of the cycle nor on the trigger day between pregnant and non-pregnant groups in CC-induced IUI cycles in infertile patients with PCOS. Of course, considering the BMI and current hyperandrogenic status of patients, and the different doses of CC used for OI, we think that uterine arterial blood flow Doppler values alone are insufficient to predict pregnancy success in CC-induced IUI cycles in infertile patients with PCOS.

Ethics approval

The Local Ethics Committee of Umraniye Training and Research Hospital, Istanbul, Turkey have approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.GP.0.01/180).

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