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The Effect of The Number of Preovulatory Follicles Developed by Ovulation Induction with GND and Clomiphene Citrate for IUI Treatment in Unexplained Infertility on Pregnancy Rates

Açıklanamayan İnfertilitede IUI Tedavisinde GND ve Klomifen Sitrat İle Ovulasyon İndüksiyonu İle Gelişen Preovulatuar Folikül Sayısının Gebelik Oranlarına Etkisi

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ÖZ

Amaç: Bu çalışmanın amacı açıklanamayan infertilitesi olan çiftlerde over stimülasyonlu (OS) aşılamada oluşan dominant folikül sayısının gebelik sonuçlarını etkileyip etkilemediğini araştırmaktır.

Gereç ve Yöntem: Çalışmamıza 24-39 yaşları arasında açıklanamayan infertilitesi olan ve OS ile IUI uygulanan 217 çift katılmıştır. Hastalar klinik olarak gebe olanlar ve olmayanlar olmak üzere 2 gruba ayrılarak yaş, monofollikül ve bifolikül gelişimi, infertilite süresi, tedavi başlama günü, hcg günü, önde gelen folikül çapı, endometrium kalınlığı, dominant folikül sayısı ve tedavi tipi açısından karşılaştırıldı.

Bulgular: Açıklanamayan infertilite nedeni ile IUI yapılan 217 hastada klinik gebelik olan ve olmayan gruplar arasında dominant folikül sayısı açısından anlamlı fark bulunmadı (p=0,73). Endometriyal kalınlık ile tedavi başarısı arasında pozitif ancak düşük bir korelasyon vardı (Spearman's korelasyon katsayısı değeri = 0,14, p=0,03). Alıcı çalışma karakteristik eğrisi analizi, gebelik başarısını öngörmek için endometriyal kalınlık için optimal kesme değerinin 9,5 mm (%55,0 duyarlılık, %65,0 özgüllük) olduğunu ortaya koydu.

Sonuç: Sonuç olarak açıklanamayan infertilitede klinik gebelik oranları açısından gonadotropinlerin oral ajanlara üstünlüğü olmadığı, bu nedenle tedaviye daha az invaziv ve daha az maliyetli oral ajanlarla başlanması gerektiği kanaatindeyiz. Ayrıca over stimülasyonu ile oluşturulan dominant folikül (monofolikül veya bifolikül) sayısının klinik gebelik başarısını etkilemediğini, ancak endometriyal kalınlığın gebelik oranları ile yakından ilişkili olduğunu ve dikkat edilmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: monofolikül, bifolikül, açıklanamayan infertilite, endometrial kalınlık, intrauterin inseminasyon

ABSTRACT

Aim: The aim of this study is to investigate whether the number of dominant follicles formed in IUI with OS affects pregnancy outcomes in couples with unexplained infertility.

Material and Method: 217 couples aged 24-39 years with unexplained infertility and treated with IUI by way of ovarian stimulation participated in our study. The patients were divided into 2 groups of which the first included the clinically pregnant and the second did not, and were compared in terms of age, monofollicle and bifollicle development, infertility duration, treatment initiation day, hcg day, leading follicle diameter, endometrial thickness, number of dominant follicles and treatment type.

Results: Of the 217 patients who underwent IUI for unexplained infertility, no significant difference was found between the groups with and without clinical pregnancy in terms of the number of dominant follicles (p=0.73). There was a positive but low correlation between endometrial thickness and treatment success (Spearman's correlation coefficient value = 0.14, p=0.03). The receiver operating characteristic curve analysis revealed that the optimal cut-off value for endometrial thickness to predict pregnancy success was 9.5 mm (55.0% sensitivity, 65.0% specificity).

Conclusions: As a result, we suggest that gonadotropins are not superior to oral agents in terms of clinical pregnancy rates in unexplained infertility, therefore treatment should commence with less invasive and less costly oral agents. Furthermore, we think that the number of dominant follicles (monofollicles or bifollicles) created by ovarian stimulation does not affect clinical pregnancy success, but endometrial thickness is closely related to pregnancy rates and deserves attention.

Keywords: monofollicle, bifollicle, endometrial thickness, intrauterine insemination, unexplained infertility

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INTRODUCTION

Unexplained infertility accounts for 10-30% of infertile couples and is diagnosed by determining tubal patency and with the normal ovulation function and semen analysis (1). Treatment is usually empirical as no underlying cause can be identified. However, the chance of spontaneous pregnancy is high in untreated couples (2). IUI, by way of ovarian stimulation (OS) with the use of oral agents or gonadotropins, plays an important role in the treatment. Additionally, IUI and IVF are also among the treatment options within a natural cycle.

The aim of the treatment other than to achieve live birth is also to minimize the risk of multiple pregnancy and OHSS (3). There are views suggesting the use of less invasive and more cost-effective treatments when dealing with cases of unexplained infertility (2). However, studies show that although IUI treatment with gonadotropins increases the risk of OHSS and multiple pregnancy, the rates of live births are also higher (1). Therefore, in order to reduce the risk of multiple pregnancy, there are strict cancellation practices when dealing with the formation of more than two follicles, such as cancelling the treatment cycle and imposing a coitus ban (4).

Many studies have investigated factors that affect IUI outcomes in unexplained infertility. One study reported that a women's age, smoking status, and the number of treatment cycles has an affect on conception (5). Another study revealed that higher maternal and paternal ages adversely affected pregnancy and that IUI is an effective method in couples with unexplained infertility (6). In a randomized cohort of women with unexplained infertility, it was shown that biochemical and clinical androgen measurements did not predict the live birth rate after ovarian stimulation treatment (7). In unexplained infertility, the factors affecting the treatment and live birth rates are still controversial because the cause cannot be determined clearly. Many factors have been investigated. However, studies on whether the number of dominant follicles formed in IUI treatment by way of OS affect pregnancy rates are not common in the literature. In this respect, this study is different.

The aim of our study is to investigate whether the number of dominant follicles formed in IUI treatment by way of OS affect pregnancy outcomes in couples with unexplained infertility.

MATERIALS AND METHODS

217 couples aged 24-39 years who applied to the IUI unit of our hospital due to unexplained infertility between January 2021 and January 2022 and were treated with IUI participated in our study. Ethics committee approval was obtained from the ethics committee unit of the city hospital (21/1085). The unexplained infertility diagnosis was made by looking at the couples' semen analysis, hysteresalpingogram, transvaginal ultrasound, serum basal hormone values performed on the 2nd day of the cycle, and serum midluteal phase progesterone values. All of the spouses of the patients had normal spermiogram results based on at least two semen analyzes according to World Health Organization (WHO) 2010 criteria, which were confirmed by the same urologist. In all hysteresalpingograms, there were no abnormalities that could cause uterine and tubal factors. Ovarian, follicular and endometrial pathologies were not observed in transvaginal ultrasounds in any of the women. The serum basal hormones administered on the 2nd day of the cycle consisted of FSH, LH, E2, PRL, and TSH. Couples with PCOS, endometriosis, uterine or tubal factor infertility, decreased ovarian reserve, male factor infertility and those that smoked were excluded from the study. Also, patients with a body mass index >=30 kg/m2 and patients with additional systemic diseases were not included in the study. The patients' age, infertility duration, treatment initiation day, hcg day, leading follicle diameter, endometrial thickness information, applied treatment procedures and pregnancy status were scanned from our hospital archive and recorded. Beginning from the 2nd or 3rd day of the cycle, patients received controlled ovarian stimulation with clomiphene citrate or 37.5-150 IU HMG. From the 6th day of the cycle, transvajinal ultrasound and regular monitoring of serum e2 levels were used to track follicular development. When at least one ≥16-18 mm follicle was seen in the transvaginal ultrasonography, a urinary hCG dose of 10,000 IU was administered.

The patients were divided into groups based on the number of preovulatory follicles developed, including those with 1 preovulatory follicle (monofollicular) and those with 2 preovulatory follicles (bifollicular), as well as those who underwent IUI with clomiphene citrate based medication and those who underwent IUI with gonadotropin based medication. All patients underwent intrauterine insemination 36 hours after hCG administration, and sexual intercourse was allowed after insemination. In addition, patients who received gonadotropin were given 200mg/day vaginal progesterone supplementation for luteal support following the transfer. Clinical pregnancy was defined as the presence of a gestational sac with fetal cardiac activity detected by ultrasound at least 4 weeks after insemination. Pregnant and non-pregnant patients were compared in terms of monofollicle and bifollicle formation, age, infertility duration, treatment initiation day, hcg day, leading follicle diameter, endometrial thickness and treatment type (clomiphene citrate and GND).

Statistical analyses was performed using the Statistical Package for the Social Sciences (SPSS) ver. 21.0 (IBM Corp., Armonk) NY, US). The Kolmogorov-Smirnov test was used to determine the normality of the data. Descriptive parameters were expressed as the medians (interquartile range) for continuous variables and as numbers and percentages for categorical variables. Chi-square test was used to analyze the data and compare the groups (i.e., pregnant vs. non-pregnant). Degrees of association between the achieving pregnancy and endometrial thickness were calculated using Spearman's rank correlation coefficient. Receiver operating characteristic curves were used to determine the cut-off values of the endometrial thickness for achieving pregnancy. A $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 217 women fulfilled the inclusion criteria and enrolled in the study. The clinical characteristics for all patients according to the groups are summarized in Table 1.

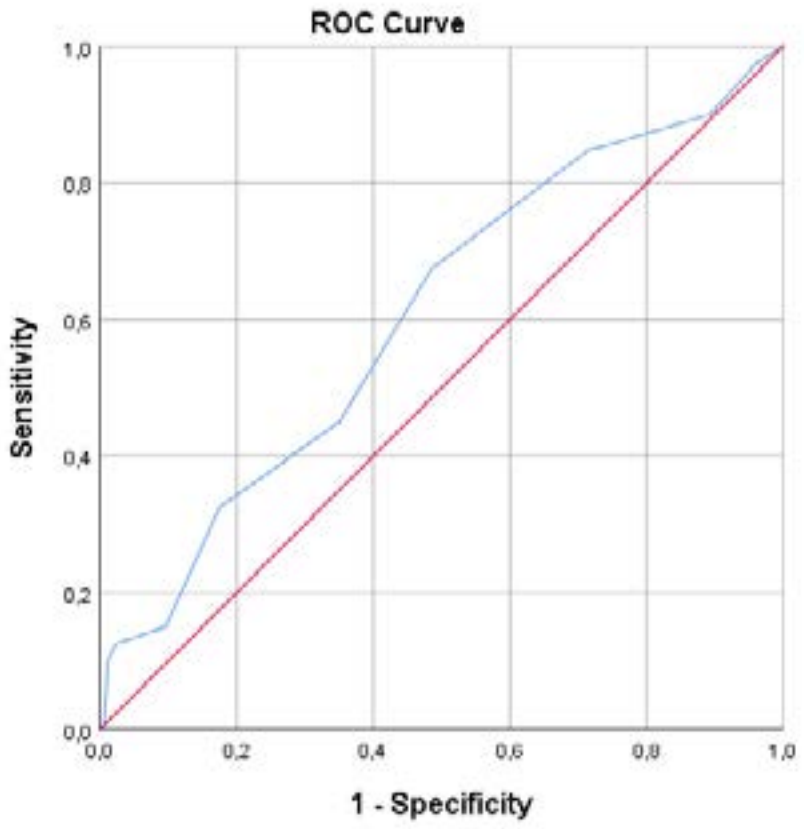
Table 1: Characteristics of patients, overall and according to treatment success.

Characteristic	*All patients (n=217, %100)*	*Pregnant (n=40, %18.4)*	*Non-pregnant (n=177, %81.6)*	*p value*
Age (years)	28.0±8.0	26.0±8.8	28.0±8.0	0.70
Infertility period (years)	3.0±2.0	3.0±1.0	3.0± 2.0	0.13
FSH value (U/L)	6.7±1.9	6.2± 1.3	6.8± 2.0	0.21
Estradiol value (ng/L)	38.0±19.0	35.5±18.7	38.0±18.5	0.77
Medication type (%) Gonadotropin Clomiphene citrate	 65.0 (30.0) 152.0 (70.0)	 13.0 (6.0) 27.0 (12.5)	 52.0 (24.0) 125.0 (57.5)	0.69
Treatment start day	3.0±1.0	3.0±1.0	3.0±2.0	0.79
hCG administration day	13.0±2.0	14.0±3.8	13.0±2.0	0.05
Leading Follicle Diameter (mm)	19.0±2.0	19.0±3.0	19.0±3.0	0.27
Dominants Follicle Count (%) One Two	 136.0 (62.7) 81.0 (37.3)	 26 (11.9) 14(6.5)	 110 (50.8) 67 (30.8)	0.73
Endometrial thickness (mm)	9.0±3.0	9.0±3.0	8.0±3.0	**0.03***

Data are expressed as median mean±standard deviation or number (%).

The groups were not different regarding clinical features except for endometrial thickness (p =0.03). Even though the relationship between endometrial thickness and treatment success (pregnancy) was positive, it was low (Spearman's correlation coefficient value = 0.14, p=0.03). The receiver operating characteristic curve analysis revealed that the optimal cutoff value of endometrial thickness for predicting the achievement of pregnancy was 9.5 mm (55.0% sensitivity, 65.0% specificity). (Fig.1)

Fig.1: Receiver operating characteristics curve of endometrial thickness for determining the treatment success (i.e., pregnant vs. non-pregnant) (area under the curve: 0.60, standard error: 0.05).



DISCUSSION

In our study, we investigated whether the number of dominant follicles formed in IUI treatment by way of OS affects pregnancy outcomes in couples with unexplained infertility. We did not detect a significant difference in the number of dominant follicles between the groups with and without clinical pregnancy (p=0.73). Similarly, we did not observe a statistically significant difference among age, duration of infertility, treatment initiation day, hCG day, leading follicle diameter, and treatment type (clomiphene citrate and GND). However, there was a positive but low correlation between endometrial thickness and treatment success (pregnancy), and we demonstrated that the optimal thickness was 9.5 mm.

In studies conducted in unexplained infertility, factors affecting pregnancy success have been investigated in various ways. In one study, it was reported that gonadotropins were more effective than oral agents in couples with unexplained infertility (1). The cohrane analysis of Cantineau et al. in 2021 demonstrated that gonadotropins increase the chance of live birth more than oral agents, but may also cause an increase in the risk of multiple pregnancy (8). Similarly, a meta-analysis conducted by Wessel et al. reported that gonadotropins were more successful than oral agents in unexplained infertility and the risk of multiple pregnancy could be disregarded (9). However, another study showed that women's age and smoking had a negative effect on pregnancy outcomes and stated that as the number of treatment cycles increased, the pregnancy rate also increased. BMI, treatment regimens, the type of infertility, endometrial thickness, and the timing of insemination did not have any significant prognostic value (5). Furthermore, a comprehensive study conducted by Huang et al. showed that IUI with oral agents was not significantly different from gonadotropin cycles, and IUI with oral agents was recommended due to the fact that it controlled the rate of multiple pregnancy in unexplained infertility (10). One study reported that, in unexplained infertility, the success of IUI increased as the duration of infertility shortened (11). Correspondingly, another study found that infertility duration and age were associated with pregnancy rates (12). In contrast, in our study, we demonstrated that infertility duration, treatment initiation day, hcg day, leading follicle diameter and treatment type (clomiphene citrate and GND) had no effect on clinical pregnancy outcomes. In these studies, IUI success was generally shown as a live birth. However, we defined the success of IUI as clinical pregnancy. This situation and the fact that our study is a retrospective study are the limitations of our article.

While several studies reported that there were no difference in pregnancy rates between IUI performed on the day of hCG and IUI performed 36 hours after hCG (13, 14), another study found that IUI performed after ovulation had higher pregnancy rates than IUI performed on the day of ovulation (15). Therefore, in order to increase the sucess rate of our study, we performed the IUI 36 hours after hCG administration. Moreover, a study on the leading follicle diameter on the hCG day suggested that lead follicle diameter associated with increased pregnancy rates was 19-20mm (16), while another study suggested that it was 21-22mm (17). However, we did not find a significant difference between leading follicle diameter and clinical pregnancy rates in our study.

There are contradictions about the effect of endometrial thickness on pregnancy success in IUI cycles in unexplained infertility. In a randomized controlled study conducted by Quaas et al., although it was thought that increased endometrial thickness was associated with high live birth rates, it was reported that there were significant live pregnancy rates even in thin endometrium and that the cycle should not be canceled due to thin endometrium (18). Nonetheless, another studystated that endometrial thickness was important for achieving viable pregnancy, and in patients with unexplained infertility, the optimal thickness for IUI treatment was considered to be 7.7 mm (19). A meta-analysis that was conducted revealed that there was no connection between endometrial thickness and pregnancy rates in IUI cycles (20). On the other hand, a study conducted by Danhof et al. stated that there is no evidence of a significant connection between endometrial thickness and ongoing pregnancy (21). In contrast, Li et al. demonstrated that clinical pregnancy rates improved as the endometrial thickness increased (22). In our study, we demonstrated that there is a positive but low correlation between endometrial thickness and treatment success (clinical pregnancy), and the optimal thickness is 9.5 mm. Moreover, a strong aspect of our study is that there are no studies investigating the impact of the number of dominant follicles (monofollicle or bifollicle) on clinical pregnancy rates in IUI treatment by way of OS for unexplained infertility. There is a recent study in the literature on this subject. Merviel et al. reported that the highest chance of pregnancy with IUI was during the first two cycles and with bifollicular response to stimulation in women with unexplained infertility (23).

In conclusion, we suggest that gonadotropins are not superior to oral agents in terms of clinical pregnancy rates in unexplained infertility, therefore we recommend that treatment should be initiated with less invasive and less costly oral agents. Furthermore, we think that the number of dominant follicles (monofollicle or bifollicle) created by ovarian stimulation does not affect the success of clinical pregnancy, however, we consider that endometrial thickness is significantly correlated with pregnancy rates and, thus, we believe it should be given careful consideration.

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