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INVESTIGATION OF FACTORS AFFECTING THE SUCCESS RATES OF IN VITRO FERTILIZATION FOLLOWED BY A FAILED CYCLE

BAŞARISIZ İN VİTRO FERTİLİZASYON SİKLUSU SONRASINDA GEBELİK SONUÇLARINI ETKİLEYEN FAKTÖRLERİN RETROSPEKTİF İNCELENMESİ

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ABSTRACT

Objective: Our aim was to compare the success of the treatment modalities used in in vitro fertilization protocols by comparing the cycles of same patients with failed and successful results to determine the factors affecting the success.

Material and Method: The study was conducted in the In Vitro Fertilization - Fertility Center of the Zeynep Kamil Training and Research Hospital, between March 2007 and March 2011, where a total of 96 patients' files were reviewed retrospectively. The data of the first cycle (Group 1), where the pregnancy was not achieved from the same couples, and the following cycle (Group 2), where pregnancy was achieved were compared. Long, antagonist or microdose protocols have been applied for ovulation induction. The primary outcome was the 'clinical pregnancy' achieved per cycle.

Results: When the duration of gonadotropin use, gonadotropin start dose, total gonadotropin dose, antagonist start days, number of days using antagonist per cycle were compared between the patients who used the same treatment protocol in both cycles, the difference was not statistically significant ($p>0.05$). The effect of protocol changes on pregnancy rates between the two groups was statistically significant ($p<0.05$). It was found that embryo transfer day was more advanced (Group 1: 2.66±0.76 vs Group 2: 3.02±1.1 days) and the number of embryos transferred was less (Group 1: 2.52±0.64 vs Group 2: 2.32±0.7) in pregnancy cycles ($p<0.05$).

Conclusion: The protocol change can positively affect the success rate of the IVF cycle, thus the number of developing follicles

ÖZET

Amaç: İn vitro fertilizasyon protokollerinde kullanılan tedavi modalitelerinin başarısının, tedavinin uygulandığı çiftlerin başarısız oldukları siklusları ile başarılı oldukları siklusları retrospektif olarak karşılaştırarak, başarıyı etkileyen faktörleri incelemektir.

Gereç ve Yöntem: Çalışmamızda Mart 2007-Mart 2011 tarihleri arasında Zeynep Kamil Eğitim ve Araştırma Hastanesi Tüp Bebek Merkezi'ne başvuran, çalışmaya dahil edilme kriterlerini sağlayan 96 hastanın verileri retrospektif olarak değerlendirildi. Aynı çiftlere ait gebelik elde edilmeyen ilk siklus (Grup 1) ile gebeliğin elde edildiği takip eden siklusa (Grup 2) ait veriler karşılaştırılmıştır. Ovulasyon indüksiyonu için uzun, antagonist ve mikrodoz protokolleri uygulanmıştır. Primer sonuç, siklus başına elde edilen 'klinik gebelik' olarak kabul edilmiştir.

Bulgular: Gonadotropin kullanım süresi, gonadotropin başlangıç dozu, toplam gonadotropin dozu, antagonist başlangıç günleri, siklus başına antagonist kullanılan gün sayısı her iki siklusta aynı tedavi protokolünü kullanan hastalar arasında karşılaştırıldığında, aradaki fark istatiksel olarak anlamlı bulunmamıştır ($p>0.05$). Buna karşılık iki grup arasında protokol değişikliğinin yapılmasının elde edilen gebelik oranını arttırması istatiksel açıdan anlamlı bulunmuştur ($p<0,05$). Gebelik elde edilen siklusta daha ileri gündeki embriyonun transfer edildiği (Grup 1: 2,66±0,76 gün vs Grup 2: 3,02±1,1 gün) ve daha az sayıda embriyo transferi yapıldığı (Grup 1: 2,52±0,64 vs Grup 2: 2,32±0,7) tespit edilmiştir ($p<0,05$).

Sonuç: Protokol değişikliği hastanın tedaviye cevabını, dolayısıyla gelişen folikül sayısını ve elde edilen matur oosit sayısını olum-

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and the number of mature oocytes obtained. Beside this, it was shown that embryo transfer count and sufficient quality embryos positively affect the treatment results, and it was emphasized once again that embryo quality is the most important factor for unsuccessful IVF cycles.

Keywords: In vitro fertilization, failed cycle, embryo transfer, treatment protocol, pregnancy

lu yönde etkileyebilir. Ayrıca çalışmamızda matur ve az sayıdaki embriyo transferinin tedavi sonuçlarını olumlu şekilde etkilediği gösterilmiş ve başarısız IVF siklusları için en önemli faktörün embriyo kalitesi olduğu bir kez daha vurgulanmıştır.

Anahtar Kelimeler: In vitro fertilizasyon, başarısız siklus, embriyo transferi, tedavi protokolü, gebelik

INTRODUCTION

Infertility is interpreted as a failure of conception despite one year of unprotected sexual intercourse. The fecundability rate for normal couples is approximately 20-25% but almost 90 percent of all would conceive at the end of the year meaning 10-15% would be considered as infertile (1). People who suffer from infertility apply for assisted reproductive technologies (ART). Despite so many techniques existing under ART, in vitro fertilization (IVF) is the most favorable and applicable one with new improvements included day by day.

The success rates associated with IVF depend on many factors, many of which are unknown. The primary indicators of success before starting an IVF cycle are maternal age, ovarian capacity, and previous reproductive performance. Women with young age and normal ovarian capacity are more likely to become pregnant than those with older age and lower capacity. Those who have had a live birth before are more fortunate than nulliparas, while those with previous unsuccessful IVF cycles have lower success (2). Apart from this, basal follicle stimulating hormone (FSH) level, the number of oocytes collected, the number of fertilized embryos and the number of transferred embryos have been shown to have an effect on cycle success.

There are so many protocols for ovulation induction to provide follicular growth but none of them is accepted as the standard protocol, moreover the predictive factors affecting the success rates are still confusing thus the search for correct protocol for correct patient yet goes on. The aim of this study is to compare the success of the treatment modalities used in in vitro fertilization protocols by comparing the cycles of the same patients with failed and successful results to determine the factors affecting the success.

MATERIAL AND METHOD

Approval was obtained from the ethical committee of Zeynep Kamil Training and Research Hospital on 30.06.2011 with the protocol number 10149 and the decision number 128. Following the approval of the local ethics committee, the study was conducted in the Obstetrics and Gynecology Department of Zeynep Kamil Training and Research Hospital. Informed consent of all patients was obtained. Between March 2007 and March 2011, of the total of 96 patients' files were reviewed retrospectively. Ovulation induction protocols who led to pregnancy in the patients second IVF cycle has been compared to the previous cycle protocol which failed. Patients who have an indication for in vitro fertilization therapy, who has a previous history of at least one IVF cycle with primary or secondary infertility, aged between 20-40, has regular menstrual cycle (25-32 days interval), has no hormonal imbalance (FSH<13mU/ml, TSH<4mU/ml, PRL<20ng/ml) and had pregnancy test positive (hcg>5 IU/ml) in the second cycle followed by a failed IVF cycle, has enrolled into the study. Patients with polycystic ovarian syndrome, with endometriosis, with any systemic disease, who have any intracavitary lesions as endometrial polyp, uterine myomas or septum, those who had achieved pregnancy in their first IVF cycle or cancelled IVF because of oocyte or sperm dependent problems and those who do not meet inclusion criteria have been excluded from the study.

Also, cycles with failed fertilization, failure to achieve at least one follicle greater than 18 mm, which had a high risk for ovarian hyper stimulation syndrome (OHSS) and those who had a decrease in estradiol levels more than 50% in two following measurements have been cancelled.

Demographic data for all included patients as age, BMI, previous medical records and also physical and gynecological examinations findings are listed in Table 1. Blood

Table 1: Demographic data for patients included in current study.

	Mean value or percentage
Age (years)	30.96±5.23
BMI (kg/m²)	25.00±2.63
Total years of infertility	7.87±4.14
FSH (mIU/ml)	7.47±5.52
E2 (pg/ml)	50.17±28.47
PRL (ng/ml)	15.8±9.26
TSH (µU/ml)	1.96±1.20
Infertility type	
Primary	89.9%
Secondary	10.1%
IVF indication	
Male factor	66%
Tubal factor	12%
Unexplained reasons	22%

test as AST, ALT, blood glucose level, hormonal test taken in their follicular phase were recorded. All patients had undergone a transvaginal ultrasonography for endometrial thickness and follicular count.

Ovarian stimulation protocols for IVF

In 22 patients, the antagonist protocol was applied, in 71, the long protocol and in three patients, the microdose protocol in their first cycle (failed cycle; Group 1). When all patients are considered, 36 patients had antagonist protocol, 54 patients had long protocol while 6 patients had micro dose protocol in their second cycle in which pregnancy was achieved (achieved pregnancy; Group 2). Patients who had one or more repetitive failed IVF cycles were evaluated before the cycle for change of protocol.

Ovarian stimulation was started on the third day of the menstrual cycle. r-FSH stimulation [(Puregon Organon, The Netherlands), (Gonal-F; Serono, Italy)] and HP-hMG [(Menopur; Ferring, Switzerland also A), (Menogon; Ferring, Switzerland also A), (Merional; Aris, Turkey)] or u-FSH (Fostimon; Arista, Turkey) was used. Estimated ovarian response was considered for each case in determining the initial dose. On the stimulation days 6 and 7, follicular number, size and serum estradiol measurements were performed according to ovarian response by USG and stimulation continued until the day of hCG. The hCG application criteria for oocyte maturation were the same in both groups. When three of the leading follicles were 17 mm, ovulation was induced with urinary hCG 10000 IU (Pregnyl amp, Organon, Netherlands) or r-hCG 250µgr (Ovitrelle, Serono, Italy). Oocyte collection was performed 35-36 hours after hCG administration.

Highest quality embryos (type A) were selected as having 4-5 cells on day 2 or > 7 cells on day 3 and less than 20% of fragmentation in equal sized blastomeres without multinucleation. Following the standard IVF procedure, 3 days after oocyte retrieval, embryos were transferred into uterine cavities. In patients who had adequate number and sufficient quality embryos, blastocyst (Day 5) transfer was preferred. In patients who had either inadequate number or insufficient quality embryos, day 3 embryos were transferred. All patients were provided with Progesterone gel (Crinone gel 8%; Serono, Italy) and/or 1500 IU hCG intramuscularly (Pregynl 1500 IU amp; Organon, Netherlands) for every 3 days after oocyte collection. Serum beta-hCG positivity was accepted as chemical pregnancy following embryo transfer (HCG>5 IU/ml). Achieved pregnancy was defined as clinical pregnancy with ultrasonographic evidence of a gestational sac and a positive blood beta-hCG test.

Achieving pregnancy was calculated as the primary outcome and also duration of induction, average daily dose of gonadotropin, duration of GnRH agonist usage, hCG day estradiol level, endometrial status, oocyte count obtained, mature oocyte count and ratio, fertilization rate, embryo quality were reported as secondary outcomes.

SPSS (Statistical Package for Social Sciences) for Windows 16.0 was used for statistical analysis. In the evaluation of the study data, Student t test was used in the comparison of the descriptive statistical methods (mean, standard deviation, frequency) as well as the normal distribution parameters in the comparison of quantitative data; Chi-square test and paired samples t-test were used to compare qualitative data. The results were evaluated with 95% confidence interval and $p<0.05$ significance level.

RESULTS

The data of 96 patients who applied to a tertiary hospital IVF Center between 01.03.2007-31.03.2011 were included in the study. The age distribution of the patients ranged from 21 to 40 years, with a mean age of 30.96±5.23 years. The study groups organized as Group 1 for the first cycles of patients, which is the failure cycle, and for Group 2 for second cycles of the same patients which achieved pregnancy.

The demographic data are shown in Table 1 in terms of age, BMI, day 3 basal hormonal tests, TSH level, total timing for infertility and reason for infertility and indications for IVF therapy.

The information given in Tables 2 to 7 included the duration of use of gonadotropins, total doses, initial doses, starting day and duration of antagonists, day 5 and HCG day of the gonadotropins used in the treatment protocols they received, follicle counts, endometrial thickness and E2 levels, protocol types used for each group, embryo and blastocyst transfer numbers.

When the treatments of patients whose protocol was not changed in both cycles were compared, it was found that the duration of gonadotropin use, the initial dose of gonadotropin, and the total dose did not significantly differ between the two groups ($p>0.05$) (Table 2). In the 20 cycles of all in which the antagonist protocol was applied, the starting days of the antagonist and the total number of days used per cycle were not statistically significant ($p>0.05$).

All patients (n=96) in the study did not show statistically significant difference between endometrial thicknesses on day 5 and HCG day as a result of comparison of cycles for Groups 1 and 2 ($p>0.05$) (Table 3). E2 levels were analyzed on the 5th day, on HCG application day and comparison between the two groups showed no statistically significant difference ($p>0.05$).

No statistically significant difference was found between follicle counts of follicles >14 mm between groups ($p>0.05$) (Table 4). However, when the follicle numbers

Table 2: Comparison of the treatment of patients without protocol changes in both cycles.

	Number of patients whose IVF protocols did not change between Group 1 and 2	Group 1 (failed cycle)	Group 2 (achieved pregnancy)	p value
Gonadotropin usage days	66	8.92±1.50	8.89±1.25	>0.05
Initial dosage for gonadotropins	66	293.28±83.6	291.42±83.4	>0.05
Total dose of gonadotropins applied	66	2527.30±976.8	2541.73±1049.9	>0.05
Menstrual day antagonist drug added	20	5.7±0.8	5.7±0.57	>0.05
Number of days antagonist drug used	20	4.9±1.3	5.0±1.5	>0.05

*p<0.05 Statistically significant

Table 3: Comparison of endometrial thickness, E2 values and OPU days between Group 1 and Group 2.

	Group 1 (failed cycle; n=96)	Group 2 (achieved pregnancy; n=96)	p value*
Endometrial thickness on day 5	7.32±1.7	7.22±1.87	>0.05
Endometrial thickness on HCG administration day	10.28±2.2	10.2±1.87	>0.05
Oocyte pick up day	12.04±1.2	12.06±1.6	>0.05

*p<0.05 Statistically significant

Table 4: Comparison of follicle characteristics monitored during the cycle, the number of mature oocytes obtained after OPU, transferred embryo characteristics between Group 1 and Group 2.

	Group 1 (failed cycle; n=96)	Group 2 (achieved pregnancy; n=96)	p value
Number of follicles greater than 14mm	4.8±3.1	5.23±3.3	>0.05
Number of follicles greater than 17mm	4.72±0.36	3.76±3.2	**<0.05***
Mature oocyte numbers	8.72±5.05	8.54±4.7	>0.05
Embryo transfer day	2.66±0.76	3.02±1.1	**<0.05***
Number of embryos transferred	2.52±0.64	2.32±0.7	**<0.05***

*p<0.05 Statistically significant

of follicles greater than 17 mm were compared, it was found to be higher than the group 2 with an average of 4.72±0.36 in the first cycle in which pregnancy was not obtained (p<0.05). However, the mature oocyte counts between the two groups were close to each other and there was no statistically significant difference (p>0.05).

When each ovulation induction protocol was evaluated within group 1 and group 2, it was observed that the number of long protocols was lower in the successful cycles, (74%, 56.2% respectively) (Table 5). In contrast, the antagonist protocol and microdose protocol were higher in second group (22.9% to 36% for antagonist protocol and 3.1% to 6.2% on microdose protocol). This increase in the use of antagonist and microdose protocols yielded successful pregnancy results in selected cases, and this difference was statistically significant (p<0.05). Also, no statistically significant change occurred by using step up or step down protocol or continuing with the same gonadotropin dosage for the whole cycle (p>0.05) (Table 6).

The number of embryos transferred and the date of transfer are given in Table 4. It was found that embryo transfer day was more advanced (3.02±1.1 days) and the

Table 5: Type of IVF protocols and their effects on pregnancy outcomes between Group 1 and Group 2.

	Group 1 (failed cycle; n=96)	Group 2 (achieved pregnancy; n=96)	Total number of IVF cycles (n=192)	p value
Number of patients long protocol applied	71 (%74)	54 (%56.2)	125 (65.1%)	**<0.05***
Number of patients antagonist protocol applied	22 (%22.9)	36 (%37.5)	58 (30.2%)	**<0.05***
Number of patients microdose protocol applied	3 (%3.1)	6 (6.2%)	3 (4.7%)	**<0.05***

*p<0.05 Statistically significant

Table 6: Gonadotropin step up / step down doses and its effect on pregnancy outcomes between Group 1 and Group 2 (n=96).

	Group 1 (failed cycle)	Group 2 (achieved pregnancy)	p value*
Number of cycles with step up dosing	6 (%6,2)	9 (%9,4)	>0.05
Number of cycles with step down dosing	39 (%40,6)	41 (%42,7)	>0.05
Number of cycles with no change in Gonadotropin dosing	51 (%53,1)	46 (%47,9)	>0.05

*p<0.05 Statistically significant

number of embryos transferred was less (n=2.32±0.7) in pregnancy cycles (p<0.05). But no significant change was obtained for transferring blastocyst instead of day 3 embryos (p>0.05)

DISCUSSION

Infertility affects approximately 15% of population at the reproductive age and, may cause emotional and social problems. The infertile population refers to assisted reproductive techniques which are mostly expensive, time-consuming and stressful for patients. Accurate information about each patient and choosing the appropriate treatment is inevitable, in order to reduce the financial and moral concerns of the patients and to achieve successful results.

According to current studies, couples that achieve pregnancy in the previous IVF cycle, have a higher chance of having pregnancy in the next IVF cycle (3). In our study, we aimed to investigate the difference between the procedures applied and factors changed in the cycles of patients who got pregnant in the second cycle but failed in the first cycle. The results showed that, the most important factors that increase the success of subsequent IVF cycles following the failed IVF cycle are; choosing the personalized IVF protocols, delayed transfer of embryos (letting the viable embryos survive) and preferring fewer embryo numbers to transfer. The most important difference of our study is the comparison of failed and successful cycles of the same couples.

Kalu et al. investigated the effect of the success of the second IVF cycle on the following IVF cycle, and determined that the age factor was important in predicting success in the next cycle and that the younger age increased the probability of successful pregnancy in the next cycle (4). But they compared different couples and did not clarify each patient's outcomes in the following cycles and did not mention the before and after success rates.

Using gonadotropins at different doses after failed cycles may positively affect pregnancy success rates. In the study of Baker et al. comparing the similar IVF protocols in Europe and the USA on 297 patients, the higher initial dose of FSH and the total dose of FSH used throughout the cycle were statistically significant in increasing pregnancy success (5). However, in the current study, there was no statistically significant difference between the initial FSH dose, the total FSH dose, and the duration of FSH use in Group 1 and Group 2 (Table 2). We think that this result may be due to the number of groups evaluated in our study.

Jun et al. emphasized that obtaining higher numbers of follicles per cycle increased the mature oocyte count and was related to consequently higher pregnancy rates (6). In our current study, unlike their findings, Group 1 which presents the failed cycle was with higher follicle numbers, and there was no significant difference between Group 1 and 2 in mature oocyte numbers (p>0.05).

In order to analyze endometrial receptivity or endometrial factor, studies compare endometrial thickness or estradiol level on day 5 and/or HCG administration day. Kasius et al. (7) showed an increase in pregnancy rates on patients with endometrial thickness more than 10 mm on HCG administration day while Pappageorgiou et al. (8) claimed that E2 levels more than 90 percentile cause an increase in total number of oocytes and embryos obtained from patients. In the present study, there was no correlation between both E2 levels/endometrial thickness and pregnancy rates.

Performing the transfer of the highest viability embryo in the IVF cycle is now leading the modern approach to embryo transfer. Although 2ET is still permitted in some countries and situations today, because of the increase in the number of multiple pregnancies and the associated complications, limiting the number of embryo transfers is preferred. Also, the antagonism between embryos in multiple embryo transfer may decrease the chance of pregnancy (9, 10). As a matter of fact, in our study results, fewer embryos were transferred in the cycles with pregnancy compared to the cycles without pregnancy, and it was found to be statistically significant and consistent with the clinical results.

As is known, embryo transfers are usually performed on the 2nd and 3rd days in conventional IVF treatment. Blastocyst transfer corresponds to the 5th day. Feil et al., in their studies comparing the embryo grade and transfer day in the cycles, they performed single embryo transfer on day 2 and 3 and blastocyst transfers on the 4th and 5th day, did not find a significant difference on pregnancy results, whereas embryo grade was the most important parameter affecting pregnancy outcomes (11). In our study, blastocyst transfer rates were higher in successful cycles (58.6% and 41.4%, respectively). However, this difference was not statistically significant.

In the studies comparing ovulation induction protocols, Marci et al. found initial FSH dosage and total FSH dose were lower in antagonist protocol which did not resulted in a success of pregnancy rates (12). Also, Tazegul et al. compared antagonist protocol and microdose protocol in recurrent IVF failure patients and found no change between groups in terms of pregnancy rates (13). In the present study, results showed that after the failure of the IVF cycle, personalization of the treatment and changing the protocol from long to microdose or antagonist or vice versa may benefit clinically in terms of pregnancy outcomes.

Despite the long follow up and reaching the first and second cycle data of the same patients there were still limitations on the study, which are the retrospective nature and the risk of influence on results related to small patient numbers and predominance of male factor infertility.

Our results show that treatments given after a failed IVF cycle should be personalized on a patient-by-patient basis. A change in the protocol may positively affect the patient's response to treatment, thus the number of developing follicles, and the number of mature oocytes obtained.

Ethics Committee Approval: Ethics committee approval for this study was received from Zeynep Kamil Training and Research Hospital Ethics Committee. (Date: 30.06.2011, No: 10149/128)

Informed Consent: Written consent was obtained from the participants.

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