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The Efficacy of Decreased Ovarian Reserve on in Vitro Fertilization Outcome

Azalmış Over Rezervinin İn Vitro Fertilizasyon Sonucu Üzerindeki Etkileri

***Özlem KARA*[1] *İdil DURAN*[2]**

ÖZ

Amaç: Biz bu çalışmada mikrodoz ve antagonist rejimlerin IVF-ICSI sonucu üzerindeki etkilerini karşılaştırmayı amaçladık.
Araçlar ve Yöntem: Çalışma 2018-2022 yılları arasında Maltepe Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi Tüp Bebek Kliniği'nde gerçekleştirildi. Hastaların dosyaları retrospektif olarak incelendi ve yaş, infertilite süresi, bazal FSH düzeyi, vücut kitle indeksi, antral folikül sayısı (AFC), antimüllerian hormon (AMH) düzeyi, toplanan oosit sayısı, metafaz 2 oosit sayısı, fertilizasyon ve gebelik oranları değerlendirildi. Grup 1'deki hastalara (n=124) gonadotropin releasing hormon (GnRH) mikrodoz protokolü, Grup 2'deki (n=136) hastalara ise antagonist protokol uygulandı.
Bulgular: Hastaların yaş, infertilite süresi, bazal FSH düzeyi vücut kitle indeksi, AFC ve AMH düzeyi gibi parametreler açısından gruplar arasında anlamlı fark yoktu (p>0.05). Elde edilen oosit sayısı, metafaz 2 oosit sayısı, fertilizasyon oranları ve gebelik oranları da benzerdi (p>0.05).
Sonuç: Bizim sonuçlarımız, mikrodoz ve antagonist rejimlerin zayıf yanıt veren kadınlarda IVF-ICSI sonucu üzerinde benzer etkiye sahip olduğunu göstermiştir.

Anahtar kelimeler: antagonist rejim; gebelik; ın vitro fertilizasyon; mikrodoz protokol; zayıf yanıt veren

ABSTRACT

Purpose: In this study, we aimed to compare the effects of microdose and antagonist regimens on IVF-ICSI outcome.
Materials and Methods: The study was conducted at the Maltepe University Medical Faculty Training and Research Hospital IVF Clinic during the period of 2018 and 2022. The files of the patients were reviewed retrospectively and age, duration of infertility, basal FSH level, body mass index, antral follicle number (AFC), antimullerian hormon (AMH) level, retrieved oocyte number, metaphase 2 oocyte number, fertilization and pregnancy rates were evaluated. The patients in Group 1 (n=124) were treated by using gonadotropin releasing hormone (GnRH) microdose protocol and in Group 2 (n=136) were treated by using antagonist protocol.
Results: There was no significant difference between the groups in terms of the characteristics of the patients such as age, infertility duration, basal FSH level body mass index, AFC and AMH level (p>0.05). The retrieved oocyte number, metaphase 2 oocyte number, fertilization rates and pregnancy rates were also similar (p>0.05).
Conclusion: Our results demonstrated that microdose and antagonist regimens have similar effect in poor reponder women on IVF-ICSI outcome.

Keywords: antagonist regimen; ın vitro fertilization; microdose protocol; poor responder; pregnancy

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[1] Kırşehir Ahi Evran Üniversitesi Tıp Fakültesi, Histoloji ve Embriyoloji AD, Kırşehir, Türkiye.
[2] Maltepe Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum AD, İstanbul, Türkiye.
Corresponding Author: Özlem Kara, Kırşehir Ahi Evran Üniversitesi Tıp Fakültesi, Histoloji ve Embriyoloji AD, Kırşehir, Türkiye.
e-mail: ozlemozturk34@hotmail.com

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INTRODUCTION

While infertility is defined as the inability to achieve pregnancy despite regular and unprotected sexual intercourse for 1 year or longer, this period is limited to 6 months over the age of 35.[1] Causes of infertility include ovulatory dysfunctions, tubal and peritoneal pathologies, male factor, and unexplained infertility.[2] Ovarian reserve reflects the number of oocytes, thus reproductive capacity, of a woman of reproductive age. Despite the innovations in IVF-ICSI technology, the age of the woman and the decreased ovarian reserve (DOR) are the most important factors affecting the success of the treatment.[3] The reasons for a lower pregnancy rate in DOR patients are less oocyte pick up due to reduced ovarian reserve and reduced oocyte quality.[4] de Placido et al suggested that increasing the dose of gonadotropin may increase the number of oocytes retrieved and thus the fertilization and pregnancy rates. However, increasing the gonadotropin dose after a certain dose does not improve the results.[5] Detection of decreased ovarian reserve in an infertile woman indicates a reduced chance of pregnancy and ovulation induction in such a patient should be individualized and optimized.[6] There is still debate about the ideal ovulation induction protocol in DOR patients. Demirol et al. reported that microose regime was better than antagonist regime in poor responder patients. They yielded a significantly higher mean number of mature oocytes and higher implantation rate in microdose group.[7] However, other studies claimed that antagonist protocol was associated with more retrieved oocytes.[8,9] Therefore, we hypothesized that a clinical study comparing microdose and antagonist protocols on the success of IVF in the patients with poor ovarian reserve. The aim of this study was to compare the efficacy of microdose and antagonist regimens on IVF-ICSI outcome in the patients with DOR.

MATERIALS and METHODS

In this retrospective study, infertile patients who applied to Maltepe University Medical Faculty Hospitals IVF Center between 2018 and 2022 were screened. The women with diminished ovarian reserve (DOR) were selected. The approval date and number of the ethics committee document obtained from Kırşehir Ahi Evran University Clinical Research Ethics Committee are 24.01.2023 and 2023-02/18.

Patients with serum follicle stimulating hormone (FSH) level >15iu/l and having antral follicle count <4 on the 2nd day of their menstruation or having AMH level <1.0 ng/ml were included in the study. Patients who underwent testicular sperm extraction (TESE) were not included in the study. Standard IVF-ICSI procedure was applied to all patients.

Agonist or antagonist protocol treatments were applied to the patients according to the clinician's preference. Leuprolid acetate (Lucrin ® daily 0.25 mg Abbott, USA) at a dose of 0.1mg/day was started on the 2nd day of the cycle in patients who underwent microdose protocol and continued at the same dose until the day of hCG. On the 3rd day of menstruation, urinary FSH (HP u FSH, Fostimon HP ® 150 IBSA, Switzerland) 225 iu and recombinant FSH (r FSH, Gonal-F® 150 Merck-Serono, Switzerland) 225 iu, a total of 450 iu of FSH was started. The dose is adjusted individually according to the previous therapy, body mass index (BMI) and age of the patients. The microdose protocol was used as previously described.[10] In patients treated with the antagonist protocol, Cetrorelix (Cetrotide 0.25 Merck-Serono, Switzerland) was used for pituitary suppression. The flexible regimen was preferred and Cetrorelix was started on the 6th or 7th day of the menstrual cycle. Antagonist regimen was performed as stated by Kara et al.[11] Follicles were monitored with serum E2 level and serial ultrasonographic measurements. When the leading follicle reached a diameter of 16 mm, hCG (Pregnyl ® 5000 iu x 2, Schering-Plough, USA) was administered. 36 hours after hCG administration, follicular fluid aspiration was performed under the guidance of transvaginal ultrasonography. After the collected oocytes were incubated in the incubator for 2-4 hours, hyaluronidase (Vitrolife, Sweden AB, Kungsbacka, Sweden) was applied for the denudation process. Embryos were divided into groups as type 1, 2, 3 and 4 according to the number of blastomeres, blastomere appearance and fragmentation rate. Embryos were transferred on day 3 or 5 following oocyte pickup (OPU). Vaginal progesterone (Crinone 8% vaginal gel ® Merck-Serono, Switzerland) started on the day of oocyte retrieval for luteal phase support until the 12 th week of pregnancy. Clinical pregnancy was diagnosed by β hCG measurement after the transfer and the detection of gestational sac in transvaginal ultrasonography.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 17.00 (SPSS Inc., Chicago) was used for statistical analysis. Chi-square test for categorical variables and t test for continuous variables were used. Results were evaluated as mean±standard deviation. A p value of <0.05 was considered significant.

RESULTS

A total of 260 infertile women were included in the study. 124 patients were in the microdose group and 136 patients were in the antagonist group. When both groups were evaluated in terms of demographic parameters such as age, infertility duration, basal FSH level, antral follicle count, antimullerian hormone level and body mass index, no statistically significant difference was found (Table 1).

Fertilization rate was 62.0% and 67.4% in microdose and antagonist groups, respectively. Retrieved oocyte number, metaphase 2 oocyte number, fertilization rate, and pregnancy rate were similar in microdose group and antagonist group (p>0.05) (Table 2).

Table 1. Patient characteristics.

	Microdose Group (n=124)	Antagonist Group (n=136)	p
Age (years)	30.4±2.3	29.6±2.0	0.75
Duration of infertility (years)	6.3±0.8	5.7±0.6	0.54
Basal FSH (iu/L)	11.0±1.7	12.6±1.5	0.21
Antral follicle count	3.3±0.4	3.5±0.8	0.19
Antimullerian hormone (ng/ml)	1.1±0.2	1.2±0.2	0.68
Body mass index (kg/m2)	27.4±2.3	25.8±2.6	0.11

FSH, follicle-stimulating hormone. Data are expressed as mean standard deviation.

Table 2. Comparison of in vitro fertilization-intracytoplasmic sperm injection outcome between the microdose group and the antagonist group.

	Microdose Group (n=124)	Antagonist Group (n=136)	p
Retrieved oocyte number	3.1±0.2	3.6±0.7	0.09
Metaphase 2 oocyte number	1.8±0.2	2.2±0.3	0.14
Fertilization rate (%)	62.0	67.4	0.27
Pregnancy rate (%)	27.5	29.1	0.32

Data are expressed as mean standard deviation.

DISCUSSION

We aimed to investigate the effect of microdose protocol and antagonist regimen on IVF-ICSI outcome. Despite the appropriate treatment regimen in patients with reduced follicle reserve, the response is not very good. In those DOR patients, the response to gonadotrophins is limited. Thus, different interventions and stimulation protocols were tried or the dosage of gonadotrophins was increased in DOR patients.[12] Unfortunately, IVF-ICSI success has not increased at the same rate. In our study, we compared patients with low ovarian reserve, for whom we tried the microdose protocol and antagonist regimen. Our findings have been demonstrated that there was no significant difference between microdose and antagonist protocols in relation with the outcome of the IVF-ICSI.[13]

Although there is conflicting data about the stimulation methods, microdose and antagonist protocols are believed the best treatment modalities in poor responders.[14] The microdose protocol was firstly described by Scott et al 30 years ago. The retrieved oocyte number, and pregnancy rates were found to be increased with microdose regimen.[15] Surrey et al reported that microdose protocol enhanced the IVF outcome. They thought that microdose protocol might lead to an increase in the levels of endogenous FSH.[16] Therefore, we planned to administer the microdose protocol to patients in one arm of the study.

Nikolettos et al reported that antagonist protocol seems to be a novel method due to short stimulation period and low gonadotrophin dosages in patients having poor ovarian reserve.[17] Similar results were obtained in the study performed by Mahutte et al.[18] They claimed that GnRH antagonists could shorter the duration of stimulation and lower the amount of gonadotrophins. Therefore, we planned antagonist treatment for the patients in the other arm of our study.

Akman et al reported that serum E_2 level and retrieved oocyte number was higher in the patients performed microdose protocol than the women treated with antagonists.[19]

However, IVF results in both groups were similar, pregnancy rates were the same. Similar to previous studies, we did not find any difference between the microdose protocol and the antagonist regimen in terms of IVF-ICSI success. Retrieved oocyte number, metaphase 2 oocyte number, fertilization rate, and pregnancy rate were similar in microdose group and antagonist group.

The most important reasons limiting the study are the small number of cases and the retrospective nature of the study. Large randomized trials are required to compare both stimulation protocols in DOR patients.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Approval for this study was received from Kırşehir Ahi Evran University Non-Interventional Research Ethics Committee (dated 24.01.2023 and numbered 2023-02/18).

Authors' Contributions

Concept/Design: ÖK. Data Collection and/or Pro-cessing: ÖK, İD. Data analysis and interpretation: İD. Literature Search: ÖK. Draft-ing manuscript: ÖK. Critical revision of manuscript: ÖK, İD. Supervisor: ÖK.

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