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Comparison of The Outcome of IVF Cycles Between Poor Ovarian Responders and Unexplained Infertility Patiens

IVF Sonuçlarının Zayıf Over Yanıtı Olan Hastalar ile Açıklanamayan İnfertilite Olan Hastalar Arasında Karşılaştırılması

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Abstract

The aim of this research was Compare of the oucome of IVF cycles in poor ovarian reserve (POR) patients with the unexplained infertility group with normal ovarian reserve. IVF results of 488 patients who applied to the German hospital IVF center between 2012 and 2014 for infertility were retrospectively analyzed. Of these, 292 cases were included in the POR group and 192 cases in the unexplained infertility group. Female age, hormonal parameters, oocyte counts, embryo development levels and clinical pregnancy rates were evaluated. The mean female age, duration of infertility, basal FSH value, duration of ovulation induction, and dose of gonadotropins used were found to be higher, and AMH level, antral follicle count and E2 value on the day of hCG administration were lower in POR cases compared to unexplained infertility cases (p <0.001). Body mass index, basal LH value, basal E2 value were similar in both groups. Sperm parameters did not differ between groups. In the POR group, the number of oocytes collected, the number of mature oocytes, and the number of Grade I and Grade II embryos were significantly lower than the unexplained infertility group (p <0.001). The clinical pregnancy rate was significantly lower in the POR group (19.6%) than in the unexplained infertility group (33.6%) (p <0.01). In Conclusion patients with poor ovarian reserve, the number of mature oocytes, day 3 embryos and clinical pregnancyrate are lower in an IVF cycle compared to patients with normal reserves.

Key words: poor ovarian reserve, unexplained infertility, AMH

Özet

Bu çalışmada, zayıf over yanıtı olan (POR) olgularda IVF uygulaması sonuclarını normal over rezervine sahip acıklanamayan infertilite grubu ile karşılaştırmayı amacladık. 2012-2014 yılları arasında Alman hastanesi IVF merkezine infertilite nedeniyle başvuran 488 hastanın IVF sonucları retrospektif olarak incelendi. Bunlardan 292 olgu zayıf over yanıt grubunda, 192 olgu acıklanamayan infertilite grubunda değerlendirildi. Calışmada kadın yaşı, hormonal parametreler, oosit sayıları, embriyo gelişim duzeyleri ve klinik gebelik oranları değerlendirildi. Bu calışmada POR olgularında ortalama kadın yaşı, infertilite suresi, bazal FSH değeri, ovulasyon induksiyon suresi ve gonadotropin dozu acıklanamayan infertilite vakalarına gore daha yuksek bulundu (p <0.001). AMH duzeyi, antral folikul sayısı ve HCG gununde E2 değeri duşuk bulundu (p <0.001). Vucut kitle indeksi, bazal LH değeri, bazal E2 değeri her iki grupta benzer bulundu. Sperm parametreleri gruplar arasında farklılık gostermedi. POR grubunda toplanan oosit sayısı, olgun oosit sayısı ve Derece I ve Derece II embriyo sayısı acıklanamayan infertilite grubundan anlamlı olarak duşuk bulunmuştur (p <0.001). Klinik gebelik oranı POR grubunda (% 19.6) acıklanamayan infertilite grubuna gore anlamlı derecede duşuktu (% 33.6) (p <0.01). Sonuç olarak IVF uygulamalarında, duşuk yumurtalık rezervi olan hastalarda, olgunlaşmış oosit sayısı, 3. gun kaliteli embriyo sayısı ve klinik gebelik oranı normal rezervleri olan hastalara gore daha duşuktur.

Anahtar kelimeler: zayıf yumurtalık rezervi, açıklanamayan infertilite, AMH

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INTRODUCTION

When medical data are analyzed in terms of infertility source, it has been stated that 30% men, 45% women and 25% unexplained factor are effective (1,2,3). The causes of female-related infertility can be summarized such as ovarian factors, tubal factors, uterine factors, cervical factors (4, 5). The most important parameters in the treatment of reproduction in women due to aging are the primordial follicle reserve, the number and quality of oocytes. While the depletion of the ovarian reserve results in menopause, the decreasing reproductive potential in the pre-menopausal period is primarily related to the number and quality of oocytes (6).

Ovarian insufficiency or poor ovarian response (POR) indicates a decrease in the amount of ovarian follicular pool in women of reproductive age and is one of the important causes of infertility. Low ovarian response (POR) due to decreased follicular reserve in the ovaries results in a low number of oocytes collected during in vitro fertilization-embryo transfer (IVF-ET) process (7). POR affecting a large number of women is seen between 5-18% in the society (8). Studies show that approximately 10% of women undergoing IVF received a poor response to gonadotropin stimulation (9,10). Decreased ovarian reserves are a condition that occurs in women mostly in their late 30s, but it can also be seen in young women. It is believed that there is an accelerated decline in folliculogenesis at the age of 37-38 when the number of follicles falls below 25,000 critical values (11). Today, many tests have been developed to evaluate the ovarian reserve. These are methods such as age, estradiol (E2), inhibin-B, serum basal follicle stimulating hormone (FSH), anti-muller hormone (AMH) levels, and antral follicle count (AFC) and ovarian biopsy. While studies have not been determined exactly what the most reliable test is, AMH has been suggested as one of the most reliable markers (12,13,14). Recently, it has been suggested that serum AMH level correlates significantly with AFC and the number of oocytes collected and is also associated with abortion and fertilization rate in IVF cycles (15).

In POR cases, the standards determined in the prediction of embryo development with hormone evaluations and other parameters have not been established yet (16) . In this study, IVF results were examined by comparing the outcomes of patients identified as POR with those with unexplained infertility.

MATERIAL AND METHOD

The IVF results of 488 patients who applied to the German hospital IVF Center for infertility between 2012 and 2014 were analyzed by retrospective case control . In order to realize the study, ethical permission number 55 and 14.4.2017 was obtained from the Hospital ethics committee. Women with POR as patient groups and women with normal ovarian reserve who applied for unexplained infertility were considered. In both groups, the intrauterine cavity was found normal after being examined by hysterosalpingogram or hysteroscopy before being programmed. Age of women, hormonal parameters, total oocyte count, mature oocyte count and embryo development levels were evaluated.

Group 1; poor ovarian response (POR): In clinical practice of assisted reproductive technologies, it is evaluated as a part of patients responding to ovulation induction by producing fewer than average number of follicles (16). The POR group was determined according to the ESHRE consensus. The ESHRE consensus describes "poor ovarian response (POR)" when at least two of the following three features are present in women: advanced maternal age (≥40 years) or any risk factor for POR, previous poor ovarian response (with traditional stimulation protocol ≤3 oocytes), and abnormal ovarian reserve test, antral follicle count (AFC) <5-7 follicles or AMH <1.1 ng / ml (16). AMH hormone evaluations were performed as in Table 1 (17).

Group 2; Unexplained infertility (Control Group): If all diagnostic tests performed in the infertility evaluation give normal results, unexplained infertility is diagnosed. In this group, ovarian response to ovarian reserve and ovulation induction was normal in women.

292 patients in the POR patient group and 196 patients in the unexplained infertility patient group were studied. Hormonal findings, ages, body mass indexes, semen analysis, embryo development, number of embryos and clinical pregnancy were recorded. FSH and AMH levels obtained from stimulated cycles were evaluated based on the table below (Table 1) (18,19). Statistical analysis of the study was done using IBM SPSS STATISTICS version 22 program.

Table 1. Evaluation of anti-mullerian hormone values in obtaining oocytes (18,19).	
AMH (ng/dl)	**Clinical value**
>6	Very high
4-6	high
2-4	moderate
<2	low

RESULTS

In this study, the mean female age, duration of infertility, FSH value, duration of ovulation induction and gonadotropin dose were found to be higher in POR cases compared to unexplained infertility cases (p <0.001). AMH level, antral follicle number and E2 value on hCG day were low in POR cases (p <0.001) (Table 2). Body mass index, basal LH value, basal E2 value were similar in both groups. Sperm parameters did not differ between groups (Table 2).The number of oocytes collected, the number of mature oocytes, and the number of Grade I and Grade II embryos were significantly lower in the POR group than in the unexplained infertility group (p <0.001) (Table 3).The clinical pregnancy rate was significantly lower in the POR group (19.6%) than in the unexplained infertile group (33.6%) (p <0.01).

Table 2. Demographic data in infertile cases with poor response and unexplained			
	POR n=292	**Unexplained infertilit (n= 196)**	**P**
Age (years)	39,2±5,4	32,6±4,6	0,001
Duration of infertility	9,0±4,8	6,9±4,7	0,039
Body mass index	27,4±4,1	25,1±4,3	0,112
Antral follicule count	3,61±2,59	9,4±4,1	0,001
Ovulation induction (days)	11,6±4,8	8,9±1,9	0,001
Total Gonadotrophin (IU)	3427,5±1054,9	2718,0±1334,6	0,001
3. rd day FSH (mIU/ml)	11,6±5,2	7,0±2,5	0,001
3. rd day LH (mIU/ml)	5,6±3,6	4,9±2,6	0,059
3. rd day E2 (pg/ml)	49,2±32,0	39,2±25,5	0,600
HCG day E2	510,0±351,8	1173,8±829,4	0,001
AMH (ng/ml)	1,1±0,5	2,9±2,1	0,001
Sperm concentration (mil/ml)	94,1±46,8	88,3±32,8	0.650
Sperm morphology (%)	4,3±4,1	6.2±2,5	0.089
Sperm motility (%)	36,±12,8	39,1±5,8	0,176

Table 3. Oocyte and embryo parameters of poor responders compared to control			
	POR n=292	**Unexplained infertilit (n= 196)**	**P**
The number of oocyte	1,9±1,5	7,9±4,2	0,001
M2 oocyte	1,4±1,1	5,9±3,6	0,001
% of M2 oocyte	88,2±18,4	85,6±21,9	0,203
GV oocyte	0,4±0,5	1,0±1,4	0,005
Fertilization (%)	74,7±23,8	71,3±2,5	0,187
Total grade 1 emb	0,8±0,6	2,5±1,7	0,001
Total grade 2 emb	0,7±0,4	2,6±1,6	0,005
Clinical pregnancy (%)	%19,6	%33,6	0.01

DISCUSSION

In women, unlike men, AMH is not expressed during sex differentiation, but it is first seen in the newborn ovary in granulosa cells of primordial follicles. AMH continues to be expressed in granulosa cells of growing follicles until the recruitment stage, a process controlled by FSH (22). In the mouse ovaries, this selection takes place in the early antral stage and in the human, 4-6 mm sized antral folliIcles (23).

The effect of antimullerian hormone (AMH) related to ovarian reserve has been studied for a long time. In a study by Visser et al., It shows that serum AMH levels decrease in pre-menopausal women with age (24). In addition, AMH serum levels show a significant correlation with the number of antral follicles, thus suggesting that AMH levels reflect the size of the primordial follicle pool. Evaluation of the ovarian reserve is particularly important in the IVF clinic, where AMH has been found useful as predictive of poor response. Studies have confirmed the use of serum AMH levels as markers for the quantitative aspect of the ovarian reserve (25). In other studies, the effect of female age on IVF results was evaluated. Hu et al. reported a statistically significant decrease in the success rate with age (26). Since basal FSH, AMH, and antral follicle number (AFS) change with age, negative relationships are generally shown with assisted reproductive technology results (26). In a study by Broer et al. reported that AMH is at least as effective as antral follicle count in predicting poor ovarian response and pregnancy (25). Many researchers have tried to determine a differential value to predict AMH's pregnancy success and failure (28,29). In our study, it was observed that the mean age of the patients with weak responses was statistically significantly higher compared to the control, and the AMH values were significantly lower in this group.

The maturation of the human follicle can be divided into four stages: primary follicle, secondary follicle, and mature follicle, regardless of a natural cycle or stimulated ovulation cycle. AMH secreted from granulosa cells in this process, rising FSH hormones act in the growth process of oocyte. It has been shown that with aging, morphology of oocyte and zona pellucida changes and the number of good quality embryos decreases (30). Studies have suggested that FSH is not a good predictor of ovarian reserve and response (31). Some studies have shown that FSH is better than the female age in estimating the number of oocytes taken (32). Galey-Fontaine et al. compared the pregnancy rates of poor responders according to basal FSH level in their study (31). The analysis, which included 163 participants with normal or high basal FSH levels, showed a significant decrease in pregnancy rates of women with high baseline FSH compared to those with normal FSH. The results of this study confirmed with our study. In our study, it was observed that the total gonadotropin dose was significantly higher and the treatment period was longer in the poor responder patient group. In addition, the fertilization rate and body mass index did not differ between the groups. However, Tanriverdi et al. in their study, the average female infertility period and total gonadotropin dose did not differ significantly between the two groups (33). However, there was a significant difference between the mean values between AMH and FSH and serum estradiol on the day of HCG injection in 2 groups. In addition, the total number of oocytes differed significantly between the 2 groups. However, the fertilization rate (fertilized oocytes / ICSI oocyte count), percentage of good embryos (grade 1 embryo + grade 2 embryos / total embryos number), and oocyte maturation rate (M2 oocyte count / total oocyte count) did not differ significantly between the groups (33). In our study, the number of developing embryos was found to be lower compared to those with normal ovarian reserve. The classification criteria for patients with poor responses reported in the literature are baseline FSH levels, the number of aspirated oocytes, the woman's age and the E2 level measured on the day of HCG (34,35). Most studies have emphasized that age and depleted ovarian egg reserves are the main factors that cause a weak ovarian response, and the age-related decrease in ovarian function causes a decrease in the number of follicles available for stimulation. Several studies have emphasized that AMH can be a strong indicator in determining the ovarian response. In their studies, Irez and Sahmay found a close relationship between serum AMH value and oocyte count (19,35). On the other hand, in the study of La Marca et al., there was no significant difference between the ages of the good and poor responders, even if those who responded well were older, they did not correlate with the negative relationship between the ovarian response to female aging in this induction (12). In our study, the female age was found to be high in the weak response group. This result is also in conformity with the rule of decreasing ovarian reserve with age (36). Two separate patient data meta-analyzes related to poor and over-response prediction were published by Broer et al in 2014 (37). With this study, it has been determined that AMH is useful in pre-

dicting ovarian hyperstimulation and also a valuable test to be used in evaluating ovarian response. Changing the doses of gonadotropin, which are frequently applied in poor responders during ovarian stimulation treatment, has failed to provide a clinical benefit (37).

CONCLUSION

In patients with poor ovarian reserve, the number of mature oocytes, day 3 embryos and clinical pregnancy rate are lower in an IVF cycle compared to patients with normal reserves. Even in cases of higher gonadotropin use in patients with a weak ovarian reserve, low oocyte maturation has been observed that high gonadotropin therapy is not beneficial. It was also understood that low AMH and high FSH levels had negative effects on oocyte maturation.

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