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# Factors influencing the ovarian response in intracytoplasmic sperm injection (ICSI)

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## Abstract

**Background:** Ovarian response to gonadotropin stimulation can predict the success rate of Assisted Reproductive Technology. The purpose of this study was not only to determine the ovarian response rate in patients on whom intracytoplasmic sperm injection (ICSI) did not successfully work but also to assess the influence of factors on ovarian response.

**Methods:** In a retrospective study, the medical records of 220 women undergoing their first cycle of ICSI from March 2012 to October 2016 were thoroughly examined. Special attention was paid to ovarian response with regards to age, body mass index, the history of menstrual cycle, the type of infertility, the duration of infertility, and the cause of infertility with respect to measures of women's hormones. The ovarian response expressing the number of mature MII oocytes after oocyte retrieval was regarded as "poor response" representing a yield of 1–4 oocytes, and "appropriate response" representing a yield of 5 or more oocytes.

**Results:** Out of 220 infertile women, 45 subjects (20.5%) had poor response, 175 subjects (79.5%) had appropriate response to ovulation stimulation with gonadotropin. The results of indicated that lower female age (p=0.005) and lower female FSH (p=0.006) were consistent with appropriate ovarian response. After adjusting the variables, the age (age <30 years) (OR= 2.45, 95% CI= 1.19-5.07) and the female FSH (FSH <30 years) (OR= 2.59, 95% CI= 1.16-5.71) were found to be associated with an appropriate ovarian response.

**Conclusion:** It can be concluded that entering the first cycle of ICSI with FSH test and considering the age of women seem to be acceptable strategies.

**Keywords:** Reproductive Sterility, Ovarian Cycle, Intracytoplasmic Sperm Injection

## Introduction

As estimated by the World Health Organization, the global rate of infertility is presumably about 8-12% (1). It is estimated that almost 9% of couples are affected by infertility around the world, and about 50-60% of them seek treatment (2). In the same vein, the rate of infertility appears to be about 15.5% in Babol, Iran (3). It is widely believed that the success rate of Assisted Reproductive Technology (4) for infertile couples depends on many factors such as the

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selection of an appropriate protocol, the proper implementation of ovarian stimulation, the proper ovarian response to hormonal stimulation, and the sufficient number of oocytes (5). Failure to respond adequately to standard protocols and the application of adequate follicles is called 'poor ovarian response'. This can result in decreased oocyte production, cycle cancellation and, overall, it is associated with a significantly diminished probability of pregnancy (6). It is worth noting that poor ovarian response to gonadotrophin can remain a problem in assisted reproductive techniques (ART). According to the results of previous studies, a number of factors such as genetic factors, the women's FSH- receptor genotype (7), the advanced age of the patients (8, 9), and high body mass index may be associated with poor ovarian response (10). In addition, women's factors, the choice of drugs for ovarian stimulation may play a significant role in poor ovarian response. Despite the numerous technological developments to improve the quality of ART, the rate of fertility (40%) is still low (1). It is also vital to define the impact of factors on ovarian response in intracytoplasmic sperm injection (ICSI) cycles. Therefore, we strove not only to determine the ovarian response rate in patients on whom ICSI did not successfully work but also to assess the influence of factors on ovarian response.

## Materials and Methods

In this retrospective study, the medical records of 220 women undergoing their first cycle of ICSI (Intra Cytoplasmic Sperm Injection) were thoroughly reviewed. The study was conducted with its focus on medical records from March 2012 to October 2016 at Omid Fertility Center. Patients on whom common infertility treatments and ICSI using fresh embryos did not successfully work were included in the study. The exclusion criteria included such factors as the age of over 45, the need for surrogacy and egg or embryo donation, frozen embryo transfer, and sperm collection through testicular biopsy. Ethics approval for this study was obtained from the local research ethics committee, and all women were requested for consents for all clinical procedures. There was also a checklist including various pieces of information in patients' records such as age, body mass index, the history of menstrual cycle, the type of infertility, the duration of infertility, the cause of infertility, the day-3 estradiol, the days of stimulation, and the total dose of

**Table 1.** The demographic and clinical characteristics of patients participating in ICSI treatment by ovarian response (n=220).

| | **Poor** (N=45) N (%) | **Appropriate** (N=175) N (%) | $\chi^2$ p value |
|---|---|---|---|
| Age (years) | | | |
| <30 | 16(35.6) | 103(58.9) | 0.005 |
| ≥30 | 29(64.4) | 72(41.1) | |
| BMI (kg/m$^2$) | | | |
| <25 | 10(22.2) | 27(15.4) | 0.277 |
| ≥25 | 35(77.8) | 148(84.6) | |
| History of menstrual cycle | | | |
| Regular | 35(77.8) | 128(73.1) | 0.527 |
| Irregular | 10(22.2) | 47(26.9) | |
| Type of sub fertility | | | 0.535 |
| Primary | 33(73.3) | 136(77.7) | |
| Secondary | 12(26.7) | 39(22.3) | |
| Causes of infertility | | | |
| Male | 24(53.3) | 104(59.4) | 0.347 |
| Female | 19(42.2) | 56(32) | |
| Unexplained | 2(4.4) | 15(8.6) | |
| Duration of sub fertility (month) | | | |
| <24 | 6(13.3) | 39(22.3) | 0.184 |
| ≥24 | 39(86.7) | 136(77.7) | |



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gonadotropins. The checklist also included parameters such as the concentration of baseline cycle day-3 follicle-stimulating hormone (FSH), estradiol, luteinizing hormone (LH), thyroid stimulating hormone (TSH), and prolactin (Prl).

The women were subdivided into two subgroups based on the yield of the number of mature MII oocytes after oocyte retrieval: "poor responses" represented a yield of 1–4 oocytes and "appropriate responses" a yield of 5 or more oocytes.

Based on the literature, day-3 FSH, day-3 estradiol, the number of days of stimulation, and the total dose of gonadotropins were considered as possible confounders associated with ovarian responses.

The stimulation protocol: ovarian hyper-stimulation was performed through the injection of gonadotropin-releasing hormone (GnRH) agonist (Buserelin acetate: super fact, Aventis, Germany) of down regulation of pituitary gland started from the middle of previous luteal cycle (long protocol), or GnRH was received from the first day of menstruation (short protocol). Gonadotrophin was injected following a vaginal ultrasound on the second day of the cycle. In addition, the ovaries were checked for cysts, and the womb were also checked for uterine myoma or any structural disorders. H*uman menopausal gonadotropin* (HMG) was injected 2-3 ampoules per day, and the dose was set based on the number and size of follicles. When a follicle became 18-20 mm, the ovulation stimulation was stopped and H*uman Chorionic Gonadotropin* (HCG) (IVF-CR, LG Life Sciences Korea) was injected. After 34-36 h, the follicles were suctioned and evacuated through ultrasound under anesthesia. ICSI was then applied to the oocytes.

***Statistical analysis***

Data were analyzed by SPSS-20, using chi-square, independent t-test, and logistic regression. The significance level was considered to be lower than 0.05.

## Results

In this study, 220 medical records were examined. The demographic and clinical characteristics of the women are summarized in Table 1. The mean age of women was 30.0±5.4 years, and the mean body mass index was 27.7±3.2, while the mean infertility duration was 63.8±5 months. Considering the number of mature MII oocytes after oocyte retrieval of mature ovarian follicles, out of all women, 45 subjects (20.5%) had poor response, and 175 subjects (79.5%) had

**Table 2.** Adjusted OR* from multiple logistic regression models for the association of characteristics of patients participating with "appropriate ovarian response", [odds ratio (OR) and confidence interval (CI) (n=220)

| | **Crud OR** (95% CI) | **Adjusted OR** (95% CI) |
|---|---|---|
| Age (years) | | |
| <30 | 2.59 (1.31, 5.12) | 2.45(1.19, 5.07) |
| ≥30 | 1.00 | 1.00 |
| BMI (kg/m$^2$) | | |
| <25 | 0.63(0.28, 1.44) | 0.45(0.18,1.11) |
| ≥25 | 1.00 | 1.00 |
| History of Menstrual cycle | | |
| Regular | 078(0.36, 1.70) | 1.21(0.50, 2.91) |
| Irregular | 1.00 | 1.00 |
| Type of sub fertility | | |
| Primary | 1.27(0.60, 2.69) | 1.15(0.49, 2.71) |
| Secondary | 1.00 | 1.00 |
| Causes of infertility | | |
| Male | 0.59(0.12, 2.70) | 0.84(0.16, 4.30) |
| Female | 0.39(0.82, 1.88) | 0.54(0.10, 2.80) |
| Unexplained | 1.00 | 1.00 |
| Duration of sub fertility (month) | | |
| ≤24 | 1.86(0.73, 4.73) | 1.86(0.70, 4.98) |
| >24 | 1.00 | 1.00 |

*Potential confounders used in day-3 FSH, day-3 estradiol, number of days of stimulation, and total dose of gonadotropins



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**Table 3.** Adjusted OR* from multiple logistic regression models for the association of hormonal status of patients participating with "appropriate ovarian response", [odds ratio (OR) and confidence interval (CI) (n=220)

| | Crud OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| TSH ( mIU /mL) | | |
| <2.5 | 1.64(0.84, 3.17) | 1.80(0.88, 3.66) |
| ≥2.5 | 1.00 | 1.00 |
| LH ( mIU /mL) | | |
| <8 | 0.41(0.09, 1.82) | 0.39(0.06, 1.55) |
| ≥8 | 1.00 | 1.00 |
| FSH (mIU /mL) | | |
| <7 | 2.72(1.32, 5.61) | 2.59(1.16, 5.71) |
| ≥7 | 1.00 | 1.00 |
| Prolactin (ngr/dL) | | |
| <25 | 0.95(0.48, 1.88) | 0.87(0.41, 1.85) |
| ≥25 | 1.00 | 1.00 |

*Potential confounders used in day-3 FSH, day-3 estradiol, number of days of stimulation, and total dose of gonadotropins.

appropriate response to ovulation stimulation with gonadotropin. The lower female age (p=0.005) and the lower female FSH (p=0.006) were consistent with the appropriate ovarian response. The body mass index, the history of menstrual cycle, the type of fertility, the causes of infertility, and the duration of infertility did not differ significantly between the two groups.

Table 2 shows the odd ratios (ORs) of appropriate ovarian response using univariate and multiple logistic regression models with the likelihood of 95% CI in women on whom ICSI did not successfully work. After adjusting the day-3 FSH, the day-3 estradiol, the number of days of stimulation, and the total dose of gonadotropins, the age (age <30 years) (OR= 2.45, 95% CI= 1.19-5.07) was found to be all associated with appropriate ovarian responses.

Furthermore, the adjusted logistic regression model showed that there was an increased chance of appropriate ovarian response with FSH (FSH <7 mIU /mL) (OR= 2.59, 95% CI= 1.16-5.71) in patients on whom ICSI did not successfully work. On the other hand, the results indicated that the concentration of TSH, LH, and Prl had no effect on ovarian responses (Table 3).

## Discussion

It is generally believed that the poor ovarian response could reduce the chance of fertilization success in IVF/ICSI (11, 12). The data used in this study demonstrated a strong association between women under the age of 30 and appropriate ovarian response. This result seems to be consistent with those of other studies suggesting that aging would have a negative impact on oocyte retrieval (13-15).

A second interesting finding is the influence of baseline female FSH on ovarian response. In this study, the average baseline FSH in women with appropriate ovarian response was lower than the poor response. These results are consistent with those of other reports (13, 14, 16), one of which (17) showed that young women with high FSH levels and old women with low FSH levels would still have the chance of giving birth.

Similar to the present findings, Chuang (18) showed that FSH level was beneficial as it provided couples with consultations before undergoing IVF, although it is not a proper predictor for IVF. There is no universally accepted cut-off value to identify a poor response. A wide range in threshold values, up to 25 IU/L, has been used to define abnormal levels of basal FSH. In regularly cycling women, FSH can predict a poor response adequately only at very high levels, and it will consequently be helpful only to a small number of women as a screening test for counseling purposes (19). It is also thought that the usefulness of basal FSH in a general sub-fertile population or elevated levels in young, regularly cycling women is unclear (4).

One of the limitations of this study was the Müllerian hormone level, which was not tested in our samples; therefore, we were not able to exclude the subjects with diminished ovarian reserve. Hence, the results of this study showed that the age of the women and day-3 FSH were associated with ovarian response. Second, in this study, all patients went through long GnRH agonist protocol, whereas the routine use is GnRH antagonist protocol, which makes the results less generalizable.

In conclusion, the present study proved that there were no useful predicting clinical tests to evaluate the ovarian reserve accurately. Since the precision of predicting fertilization is limited, entering the first cycle of ICSI without any previous tests seems to be an acceptable strategy in individuals with inadequate ovarian responses, especially those with maximized ovarian stimulation. To increase the appropriate ovarian responses in ICSI, more emphasis should be placed on the age of women as well as the female FSH.

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## Conflict of interest

The authors have no competing interests.

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