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Comparison of the Insulin-Like Growth Factor-1/Follicle Stimulating Hormone Ratio in Infertile Women With Diminished Ovarian Reserve

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Abstract

Objectives: This research aims to compare the insulin-like growth factor-1 (IGF-1)/follicle-stimulating hormone (FSH) ratio between infertile women with DOR and those with usual ovarian reserve.

Materials and Methods: This observational longitudinal study was conducted on 80 women scheduled for in vitro fertilization (IVF) in our infertility department. Each participant underwent blood sample testing for the measurement of FSH, anti-Mullerian hormone (AMH), and IGF1 serum levels on the second day of the menstrual cycle. The infertile women were placed into two groups: Group I consisted of infertile women who were diagnosed with DOR according to the Bologna criteria, and group II included women with unexplained infertility and usual ovarian reserve.

Results: The mean IGF-1 level was 113.72±45.37 ng/mL in group I, and 119.37±45.79 ng/mL in Group II, with no significant difference ($P=0.649$). We found a significant positive correlation between AMH levels and IGF-1 ($P=0.005$) and IGF/FSH ratio ($P<0.001$) in DOR (group I) women. In contrast, this correlation was significant only for AMH levels and IGF/FSH ratio ($P=0.002$) in group II. The IGF-1/FSH ratio was significantly less in group I versus group II (14.76±1.28 vs. 28.27±6.30; $P=0.001$). The IGF1/E2 ratio was significantly less in group 1 versus group 2 (5.52±0.98 vs. 11.69±3.2; $P=0.029$).

Conclusions: Our results show that IGF1 and the IGF/FSH ratio are significantly positively correlated with ovarian reserve markers. Hence, this ratio may be used as a screening marker to predict ovarian reserve, independent of age.

Keywords: Ovarian reserve, Assisted reproductive technology, Biomarkers, IGF1, FSH, Infertility

Introduction

Although significant improvements in in vitro fertilization (IVF) outcomes have been achieved (1,2), the failure rate remains noticeable. According to the ESHRE report 2010, only 32.4-33% of IVF cycles are successful (3); this rate is even lower in poor responder women, who are about 10% of women undergoing IVF (4). One of the suggestions to improve assisted reproductive technology (ART) outcomes, especially in poor responders, is individualized ovarian stimulation (5,6), which requires efficient and reliable indicators. An ideal dynamic indicator reflects the effects of pretreatment and adjuvant therapy on the oocyte metabolic environment and can improve ART outcomes (4).

Serum insulin-like growth factor-1 (IGF-1) levels have been recommended as a reliable predictor of IVF cycle success. The liver secretes IGF-1 in response to GH and is essential for enhancing gonadotropin function during follicular development (7). IGF-1 significantly affects the reproductive system, including folliculogenesis, primordial follicle activation, and oocyte maturation (8).

On the other hand, molecular research has shown that IGF-1 and follicle-stimulating hormone (FSH) are part of the same signaling pathway, and that the response of granulosa cells to gonadotropins via FSH and LH receptors is mediated. IGF-1 is an essential regulator of follicle growth and maturation, and its activity is increased by FSH (9,10). GH is best known for its roles in ovarian cell proliferation and differentiation, E2 production, and the regulation of granulosa cell function through IGF-1 (11-13).

Although the IGF-1 and FSH molecular pathways are well established, their relationship with ovarian reserve has not been reported in previous studies (14,15). However, in a study (9), the association between the IGF1/FSH ratio and semen parameters was assessed, and a positive correlation with sperm concentration and testicular size was reported. In addition, men with oligozoospermia had a significantly lower IGF1/FSH ratio.

Hence, we hypothesized that the IGF1/FSH ratio in women with diminished ovarian reserve (DOR) could predict IVF outcomes. If our hypothesis is correct, this ratio can serve as a useful predictor and may explain the positive effects of GH co-treatment in patients with DOR.

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Therefore, this research aims to compare the IGF-1/FSH ratio level in infertile women with DOR versus those whose ovarian reserve was in normal ranges.

Materials and Methods

This observational longitudinal study was conducted on infertile women who were planned for IVF in our infertility department in Yas Hospital Complex, affiliated with Tehran University of Medical Sciences. We consecutively recruited 80 women aged 18 to 40 years with an indication for IVF from November 2024 to August 2025. Exclusion criteria included malignancies and underlying diseases, such as sarcoidosis.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Code: IR.TUMS.MEDICINE.REC.1403.301). After explaining the study aim to all patients, informed consent was obtained from all participants.

The patients were placed into two groups: Group I consisted of infertile women who were diagnosed with DOR according to the Bologna criteria (16), and group II included women with usual ovarian reserve who were planned for IVF in our department. Each participant underwent blood sample testing for the measurement of Follicle FSH, anti-Mullerian hormone (AMH), and IGF1 serum levels on the second day of the menstrual cycle. Patients were fasting for at least 9 hours, and all blood samples were assessed in our hospital laboratory.

Information, including age and lab test results (AMH, FSH, IGF-1, and estradiol (E) 2), was collected for all women. FSH and estradiol (E2) were measured using an immunoanalytical method with ELISA. Immunoassay ELISA measured AMH and IGF-1.

Sample Size

Using G*Power software, with a medium effect size of 0.15, an α level of 0.05, and a statistical power of 85%, the required sample size was estimated to be 80.

Data Analysis

All data were evaluated using descriptive statistics, including mean, standard deviation, and relative frequency. The normality of the data was assessed using the Kolmogorov-Smirnov test. For data analysis, the independent t-test was used for data with a parametric distribution, and the Mann-Whitney U test was used for data with a nonparametric distribution. Pearson's correlation coefficient was used to assess relationships between variables. All analyses were performed using the Statistical Package for the Social Sciences software (SPSS, version 26.0 for Windows; SPSS Inc., Chicago, IL). A P value of < 0.05 was considered statistically significant.

Results

A total of 80 subjects were enrolled in the study. The patients were placed into two groups: 51 women in group I consisted of infertile women who were diagnosed with DOR, and 29 women in group II included women with usual ovarian reserve. The mean age was 39.43 ± 6.70 years in group I and 32.21 ± 6.27 years in group II; the difference between the groups was statistically significant ($P < 0.001$).

The mean AMH level was 0.42 ± 0.04 ng/mL in group I, and 1.70 ± 0.07 ng/mL in group II, with a significant difference ($P < 0.001$). The mean FSH level was 11.14 ± 1.64 IU/L in group I and 7.81 ± 2.56 IU/L in group II, with a significant difference ($P < 0.001$). In addition, the mean IGF-1 level was 113.72 ± 45.37 ng/mL in group I, and 119.37 ± 45.79 ng/mL in group II, with no significant difference ($P = 0.649$) (Table 1).

We find a positive, significant correlation between AMH levels and IGF-1 ($P = 0.005$) and IGF/FSH ratio ($P < 0.001$) in DOR (group I) women. In contrast, this correlation was observed only for AMH levels and the IGF /FSH ratio ($P = 0.002$) in group II (Table 2).

The IGF-1/FSH ratio was significantly less in group I versus group II (14.76 ± 1.28 vs. 28.27 ± 6.30; $P = 0.001$). The IGF1/E2 ratio was significantly less in group 1 versus group 2 (5.52 ± 0.98 vs. 11.69 ± 3.2; $P = 0.029$) (Figure 1).

Discussion

This study evaluated the correlation between the IGF-1/FSH ratio and ovarian reserve markers. In our study population, there was a significant difference regarding the mean age and AMH level between the two groups, as expected. However, there were no significant differences regarding IGF-1 between the DOR and control groups.

Consistent with our findings, Duzok et al (14) reported

Table 1. Basal Hormone Levels of Patients With Infertility

Variables	Group I (n=51)	Group II (n=29)	*P* value
Age	39.43±6.7	32.20±6.27	<0.001
Anti-Mullerian hormone	0.42±0.04	1.70±0.07	<0.001
FSH	11.14±1.64	7.81±2.56	<0.001
IGF-1	113.72±45.37	119.37±45.79	0.649
E2	49.64±6.46	32.23±5.56	0.037
IGF-1/FSH	14.76±1.28	28.27±6.30	0.001
IGF-1/E2	5.52±0.98	11.69±3.2	0.029

FSH: follicle-stimulating hormone, IGF-1: insulin-like growth factor-1, E: estradiol.

Table 2. Correlation Analysis of Variables Between AMH Levels in All Groups

Variables	Group I (n=51)		Group II (n=29)	
	r	*P* value	*r*	*P* value
Age	-0.644	<0.001	-0.167	0.385
FSH	-0.382	0.006	-0.057	0.771
IGF-1	0.387	0.005	0.221	0.249
E2	-0.185	0.241	0.093	0.630
IGF/FSH	0.580	<0.001	0.548	0.002
IGF/E2	0.180	0.254	0.140	0.470

FSH: follicle-stimulating hormone, IGF-1: insulin-like growth factor-1, E: estradiol.

that DOR patients have significantly higher age and lower AMH, whereas this difference was not significant for GH. Their analysis showed no relationship between GH and ovarian reserve markers, including AFC and AMH.

Although there is no relation between ovarian reserve and GH, previous randomized controlled trials have shown that administering adjuvant GH during the IVF cycle results in higher oocyte retrieval and pregnancy rates in poor responders (16). This hypothesis was proposed that GH might affect ovarian reserve via IGF-1 (17).

In this regard, Gleicher et al (15) reported that women with IGF-1 levels below the 25th percentile had lower IVF success rates. In our study, we did not follow women to evaluate their ART outcomes. Still, we found a positive, significant correlation between AMH levels and IGF1 in DOR women, and a positive, significant correlation between AMH and the IGF/FSH ratio in both study groups.

In another study, the relationship between IGF-1 concentrations and ovarian reserve parameters was investigated in 30 infertile individuals. This study reported that FSH, AMH, and IGF-1 can be used to assess women's ovarian age and reserve (18). Furthermore, IGF-1 and FSH may act with each other for follicle selection at the pre-hierarchical follicular phase (19).

On the other hand, evidence indicates that IGF-1 concentration on the second day of the menstrual cycle is inversely associated with the ovarian response. In this regard, serum IGF-1 levels were significantly higher in poor responders than in regular responders, which may be due to follicular resistance to IGF-1 (4). Ligand-dependent receptor internalization has been proposed as a possible mechanism of resistance to IGF-1 (20).

As in the relation between the IGF-1/FSH ratio and women's ovarian reserve, as confirmed by Cannarella et al (9), there was a positive correlation between the IGF-1/FSH ratio and sperm concentration, total sperm count, and volume. It may be due to the same molecular pathway as that of IGF1 and FSH. IGF1, which is present in the follicular fluid, acts in combination with FSH, increasing granulosa cell proliferation and aromatase activity and inhibiting follicle apoptosis. Treatment with IGF1 is so expensive. Therefore, GH administration has been used steadily to increase IGF1 levels in patients with poor ovarian response. In addition, a meta-analysis showed an increase in clinical pregnancy rates with the addition of GH to FSH in poor ovarian responders (21,22). However, the beneficial effects of GH on oocyte and embryo quality may also apply to women with normal ovarian response (23).

Limitations and Strengths

Our study has some limitations and strengths. We did not follow up with our patients to assess their ART outcomes.

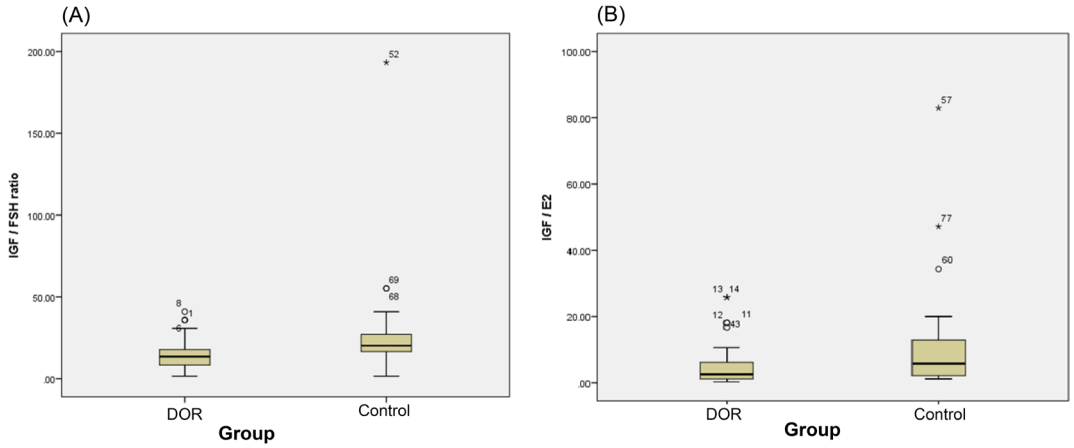

Figure 1. IGF1/FSH (A) and IGF1/E2 (B) ratio in Group 1 and Group 2. FSH: follicle-stimulating hormone, IGF-1: insulin-like growth factor-1, E: estradiol.

The other limitations were the lack of age-matching between groups and the failure to measure and compare follicular fluid GH with plasma GH levels. However, the study's prospective design and execution at a referral infertility center were our strengths.

Conclusions

Our results show that IGF1 and the IGF/FSH ratio are significantly positively correlated with ovarian reserve markers. Hence, this ratio may be used as a screening marker to predict ovarian reserve, independent of age.

Authors' Contribution

Conceptualization: Firoozeh Akbari Asbagh, Mahbod Ebrahimi, Fatemeh Davari-Tanha.
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Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The study proposal was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Code: IR.TUMS.MEDICINE.REC.1403.301). All participants signed a written informed consent form before entering the study.

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