Age and basal FSH as a predictor of ART outcome

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Abstract

Background: Female age and basal FSH level are independently associated with IVF outcome. They are both related to the same phenomenon, namely ovarian reserve.

Objective: To evaluate the effective role of serum FSH concentration at the start of treatment cycle on ART outcome.

Materials and Methods: A total of 207 women undergoing IVF and ICSI cycles were included in this study. Basal FSH concentrations were measured and the women's ages were calculated before they were undergoing pituitary desensitization and its correlation with ART outcome was evaluated.

Results: Increasing FSH was associated significantly with reduced number of follicles > 15mm, oocytes retrieved, and embryos obtained.

Conclusion: Age is the most important prognostic factor but basal serum FSH can be used to identify women who are very likely to perform poorly in ART, probably because of diminished ovarian reserve.

Key words: Age, ART, Pregnancy outcome, Serum FSH.

Introduction

Assisted reproduction treatments are expensive, time consuming and stressful for patients. It is very important for infertile couples to expect chance of achieving pregnancy before deciding to start assisted reproductive treatment.

Age of the female partner is an important factor related to pregnancy outcome (1, 2). As a woman become older, the ovarian reserve and her ability to have pregnancy decrease both in natural and stimulated cycles (3). In addition, the experiments in in vitro fertilization (IVF) programs show that women of the same age are different with response to ovarian stimulation and some of young women under age 35 have a diminished ovarian reserve and poor IVF outcome. Thus, a useful predictor of ovarian response to ovulation induction is needed.

Measuring day 3 follicle stimulating hormone levels (FSH) often use in IVF units for choosing eligible patients for assisted reproductive techniques (ART) cycles. At the first time, Muasher *et al* described that the cycle day 3 FSH level is one of the most common used tests for predicting success in ART treatment(4). Several studies have reported that women with an elevated FSH level have poor response to ovarian stimulation leading to a lower pregnancy rate in ART, independent of age (5). However, other authors, have stressed that FSH concentration also may be an unreliable indicator of reproductive potential in older women because FSH measurement represents an indirect assessment of ovarian reserve (6, 7).

Female age and basal FSH level are independently associated with IVF outcome. They are both related to the same phenomenon, namely ovarian reserve, which can be defined as the quality and the quantity of the remaining follicle pool (8). The development of diminished ovarian reserve generally reflects the process of follicular depletion and decline in oocyte quality (9-11).

Margarelli *et al* demonstrated that a combination of basal FSH level and age are useful predictors of fertility potential in women older than

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35 years undergoing ovulation induction protocol (12).

The present study is an attempt to assess which parameters of ovarian functional reserve including female age and basal FSH levels will predict the results of ovarian stimulation and ART outcome.

Material and methods

Study population

In this prospective analytic study, 207 women undergoing IVF/ICSI cycles in our unit were chosen between January 2005 to December 2007.The study was retrieved by the Institutional review board at Yazd University of Medical Science. Patient's information included: age, etiology of infertility, reproductive and surgery history. Only the women with first IVF/ICSI cycles were selected.

Patients with the history of pelvic surgery, endometrioma larger than 2 cm in vaginal sonography and patients with severe endometriosis at laparoscopy were excluded from this study.

Patients were divided according to the age in two groups: < 37 and ≥ 37 years old and these two groups according to basal FSH levels were divided in two subgroups: FSH<10 and FSH≥10 mIU/ml and therefore four groups were produced. (group 1: <37 years old and FSH <10, group 2: <37 years old and FSH ≥10, group 3: ≥37 years old and FSH <10, group 4: ≥37 years old and FSH ≥10) .

Number of follicles>15 mm on the day of human chorionic gonadotrophin (hCG) administration, number of oocytes retrieved, number of oocytes fertilized, number of embryos obtained, total dose of gonadotropins required, fertilization rate, cancellation rate and clinical pregnancy rate were compared between these groups. Age was calculated as complete years on the day of starting ovarian stimulation.

All the serum FSH samples were collected on the day 3 of the prior cycle to IVF/ICSI treatment. We used an Immunoenzymometric assay (MONOBIND, INC. Costa Mesa, CA, USA) for quantitative measurement of FSH in serum. The Intra-assay and Interassay coefficient of variation for the FSH level were 4.3% and 6.9% for 5.9mIU/mL respectively.

Stimulation protocol

All patients were stimulated using the long GnRH-a protocol with subcutaneous buserelin (Hoechst , Germany) that was started at a dose of

0.5 CC daily, from the day 21 of previous cycle and the dosage was reduced to 0.25 CC per day when menses was begun .

Ovarian stimulation with gonadotropins was initiated on the second day by hMG (Menogon, Germany), 150 – 375 IU per day consecutively. When at least 3 follicles ≥ 18 mm was observed by vaginal ultrasonography, hCG (Daroupakhsh, Iran) 10.000 IU was administered and transvaginal oocyte retrieval was performed 36 hours after hCG injection. Embryo transfer was performed 2–3 days later. All patients received luteal support, using progesterone in oil 100 mg per day for 14 days.

Pregnancies were established by elevated serum levels of β-subunit of hCG more than50 mIU/mL 14 days after embryos transferred. Clinical pregnancy was defined as the presence of fetal cardiac activity in ultrasonography 3 weeks after embryos transferred. Cancellation rate was defined as the cycles with no ovarian response. The cycles that was resulted to ovum pick – up was defined as a normal cycles.

Statistical analysis

The data were analyzed with Student's t–test, Fisher, s exact test, X^2 test, ROC curve, by using the SPSS version 13. Statistical significance was defined as a value of $p<0.05$.

Results

In total 207 women undergoing IVF/ICSI cycles were studied. Overall, clinical pregnancy rate per treatment cycles was 23.3% in age group of < 37 and 2.9% in age group of ≥37 years old and cancellation rate was 2.9% in age group of <37 and 8.05% in age group of ≥37 years old.

Table I detail the data on ART performances, clinical pregnancy rates and cancellation rates among the four groups. When the effects of FSH on cycle parameters and pregnancy outcome were compared in the same age groups (group 1 vs. 2, 3 vs. 4), the data showed that women with higher FSH levels were significantly associated with less number of follicles >15 mm on the day of hCG administration, less number of oocytes retrieved, less number of oocytes fertilized and less number of embryos obtained ($p<0.05$).

On the other hand more required total gonadotropin doses were only observed between the age groups of <37 years old (group 1 vs. group 2) ($p<0.05$), but not in the age group of ≥37 years old (group 3 vs. group 4) ($p>0.05$). In age groups

of < 37 and ≥ 37 years old, cancellation rates were increased with increasing FSH (p>0.05). There was no significant correlation between fertilization rate and serum FSH in both groups of women < 37 and ≥ 37 years old. All of pregnancies occurred in age groups of <37 years and only one pregnancy occurred in groups of ≥37 years (p> 0.05).

Table I. Basic ovarian stimulation cycle characteristics of patients.

variables	Age < 37			Age ≥ 37		
	FSH<10 Group1(n=147)	FSH≥10 Group 2 (n=25)	p- value	FSH<10 Group 3(n=14)	FSH≥10 Group 4 (n=21)	p-value
Gonadotropin used (Ampouls)	22.76±6.72	26.28±6.81	0.017	35.93±12.21	35.05±6.54	0.783
No. of follicles >15mm	11.25±5.15	4.5±3.31	0.000	5.79±3.35	2.52±1.88	0.002
No. of oocytes retrieved	7.55±4.51	2.14±1.95	0.000	3.85±3.33	0.88±0.92	0.001
No. of oocytes fertilized	5.01±3.46	1.45±0.94	0.000	3.55±3.01	0.69±0.87	0.001
No, of embryos obtained	4.97±3.53	1.45±0.94	0.000	3.50±2.87	0.69±0.87	0.001
Fertilization rate (%)	67.48±24.17	78.39±22.97	0.097	80.47±20.39	70.00±30.16	0.559
Cancellation rate (%)	2.0	8.0	0.154	7.1	9.5	>0.05
Clinical pregnancy rate (%)	23.8 (35/147)	20 (5/25)	0.677	0 (0/14)	4.8 (1/21)	0.407

Discussion

Assisted reproduction cycles have revolutionized the treatment of infertility and they are being increasingly used. A woman's age is considered as a prognostic factor when assisted reproduction treatment is proposed to infertile couples. A marked decline in success rates is observed at 35-37 years old patients (13-15). Because pituitary FSH secretion increases with declining ovarian reserve, day 3 serum FSH concentrations are being routinely used in most ART programs and they have been found to be a better predictor of ART outcome than age (14,15).

In our study, women <37 years old had different ART performances. Those with basal FSH <10 mIU/ml (group 1) had the best ART outcome among all groups. According to the present data, women < 37 years old with elevated basal FSH (group 2), can still have a favorable ART outcome (as reflected by pregnancy rate) despite poorer ART performances (as reflected by the number of retrieved oocytes, fertilized oocytes and embryos obtained). The possible explanation might be that patients < 37 years old with FSH ≥ 10 have a decreased remaining follicles pool, but the quality of their remaining follicles is not diminished. Thus, basal FSH is a good predictor of the size of the remaining follicles pool. Elevated basal FSH levels are indicative of diminished ovarian reserve, and women with increased basal FSH levels frequently have decreased oocytes retrieved in IVF program (1). In women ≥37 years old, the ART performances correlated significantly with FSH levels, which was reflected by the number of follicles > 15mm on the day of hCG, the number of retrieved oocytes , number of fertilized oocytes and the number of embryos obtained . Our study

showed that women ≥ 37 years old and FSH ≥ 10 (group 4) had the poorest ART performances. The reason for such poor results is related to an aging population of oocytes of poor quality and a gradual depletion of the follicle pool. Therefore this group of patients should be carefully counseled on their low chances of conception when undergoing ART treatments. With increasing age, ovarian reserve diminishes and spontaneous fecundity rate as well as success rates in IVF programs decline. The age – related decrease in fertility is due primarily to oocyte senescence rather than to poor endometrial receptivity, as suggested by the observation of high pregnancy outcome in oocyte donation programs (16).

In IVF programs, older women produce less oocytes (17) and have lower implantation rate (18), thus reflecting both the smaller size and the impaired quality of their follicles pool. In women <37 years old the total dose of gonadotropins required increased significantly with increasing FSH (group 1 vs. 2).

It means that depleted follicular pool required higher dose of gonadotropin for ovarian stimulation. In women ≥37 years old, the total dose of gonadotropins did not correlate significantly with serum FSH (group 3 vs. 4), it means that older women have small size follicular pool and impaired quality of this follicular pool, these aging follicles do not respond to even high doses of gonadotropins. Cancellation rate in both women <37 and ≥37 years old increased with increasing FSH and pregnancy rate decreased with increasing FSH, the difference was not significant because of the small sample size. As we had exclusion criteria, only limited cases were recruited. Only one pregnancy occurred in group 4 (women ≥ 37 and FSH ≥10).

In conclusion, age is the most important prognostic factor, but basal serum FSH can be used to identify women who are very likely to perform poorly in ART, probably because of diminished ovarian reserve. Measuring basal serum FSH should be regarded before starting the cycle.

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