ART outcome in young women with premature ovarian aging

Meenakshi Dua, Vandana Bhatia, Sonia Malik1, Ved Prakash2

Department of Reproductive Medicine, Senior Consultant, IVF, 1Program Director, 2Head of Embryology, Southend Fertility and IVF Centre, Holy Angels Hospital, Basant Lok, Vasant Vihar, New Delhi, India

ABSTRACT

Background: Young women with signs of ovarian aging are a matter of concern as far as their reproductive performance is concerned. With more women approaching infertility centers with this problem, it becomes necessary to understand what reproductive outcomes are possible in such cases. Female age and basal Follicle stimulating hormone (FSH) level, both are strong independent predictors of In Vitro Fertilization (IVF) outcome.

Objective: To correlate age-related basal FSH with IVF outcome in women with premature ovarian aging in gonadotropins-induced cycles.

Materials and Methods: Between January 2011 and October 2012, a total of 135 women undergoing IVF and ICSI cycles with antagonist protocol were included in this retrospective cohort study. Basal FSH concentrations were measured and the women’s ages were calculated before they were undergoing pituitary desensitization and its correlation with assisted reproduction technique (ART) outcome was evaluated.

Results: Increasing FSH was associated significantly with reduced number of oocytes retrieved, and embryos obtained. Young women with high FSH up to 20 produced less but good quality embryo’s resulting in sound pregnancy rate.

Conclusion: FSH is a quantitative and age is a qualitative measure of ovarian reserve. Both are equally important in predicting IVF outcome. Basal FSH concentration should be restricted to counseling of patients on probability of achieving pregnancy, but should not be used to exclude them from fertility treatment.

Key Words: Assisted reproduction technique, age, high follicle stimulating hormone, premature ovarian aging

INTRODUCTION

Although age predicts loss of reproductive future, some women have enhanced reproductive aging, due to a more rapid than normal depletion of ovarian follicular pool. This condition is known as premature ovarian aging (POA).[1]

Diminished ovarian reserve/POA are found to be associated with:[2]
1. Suboptimal response to ovulation induction.
2. Diminished pregnancy rates after assisted reproduction technique (ART) independent of age.
3. Increased risk of miscarriage.

The present study is to evaluate the impact of high FSH in young women undergoing ART cycle on reproductive outcome.

MATERIALS AND METHODS

Study population

In this retrospective observational study, 135 women undergoing IVF/ICSI cycles at our centre were chosen during January 2011 to October 2012. Patient’s information included: Age, duration, type and cause of infertility, reproductive, and surgery history. Only the women undergoing IVF/ICSI cycles with antagonist protocol were selected. Patients with the history of pelvic surgery, endometrioma larger than 2 cm in vaginal ultrasonography, and patients with severe endometriosis at laparoscopy were excluded from this study. Patients were divided according to the age in two groups: Aged <35 and ≥35 years 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: aged < 35 years and FSH < 10, group 2: aged < 35 years and FSH ≥ 10, group 3: aged ≥ 35 years and FSH < 10, group 4: aged ≥ 35 years and FSH ≥ 10). Number of oocytes retrieved, number of oocytes fertilized, number of embryos obtained, number of A grade embryo’s obtained, total dose of gonadotropins required, fertilization rate, cancellation rate, and clinical pregnancy rate were compared among these groups. Age was calculated as complete years on the day of starting ovarian stimulation. All the serum FSH samples were collected on day 2 of the prior cycle to IVF/ICSI treatment.

**Stimulation protocol**

All patients were stimulated using the short antagonist protocol. Ovarian stimulation with gonadotropins was initiated on the second day by r FSH 150-375 IU per day consecutively. It was changed over to u FSH/Human menopausal gonadotropin depending on patient’s response. Antagonist (Ganirelix) was started on day 5/6 of stimulation, depending on follicular size and endometrial thickness. When at least two follicles ≥18 mm was observed by vaginal ultrasonography, hCG/decapeptyl was administered and transvaginal oocyte retrieval was performed 36 hours after trigger. Embryo transfer was performed 2-5 days later. All patients received luteal support, using progesterone gel or injection per day for 16 days. Pregnancies were established by elevated serum levels of β-subunit of hCG more than 50 mIU/ml, 16 days after embryos are transferred. Cancellation rate was defined as the cycles with no ovarian response. The cycles that resulted to ovum pick-up was defined as a normal cycles.

**Statistical analysis**

The data were analyzed with Student’s t-test and Chi-square test by using the SPSS version 11. Statistical significance was defined as a value of P < 0.05.

### RESULTS

A total of 135 women undergoing IVF/ICSI cycles were studied. Table 1 detail the data on ART performances, pregnancy rates and cancellation rates among the four groups. Mean age was comparable in both groups. Young women with high FSH (group 2) required significantly high dose of gonadotropins for stimulation when compared with group 1 (P < 0.05). Older women, irrespective of FSH levels (groups 3 and 4) required high dose of gonadotropins for stimulation (P > 0.05).

Number of eggs retrieved, fertilized, and embryo formation were significantly less in women with high basal FSH (groups 2 and 4; P < 0.05), however, percentage of A grade embryo’s were similar in all four groups suggesting that young women with high FSH, if embryo’s are formed, will be of good quality. When groups 1 and 3 were compared, it was found that number of eggs retrieved were significantly less, again to emphasize the importance of age in IVF (11.3 ± 6.5 vs 6.9 ± 5.9).

In age groups of <35 and ≥35 years old, cancellation rates were increased with increasing FSH (P > 0.05). Pregnancy rate was highest in group 1 (40.6%) and lowest in group 4 (11.1%). Young women with high FSH, though had fewer embryos for transfer, but had good quality A grade (76.9%) embryo’s and had clinically sound pregnancy rate (30.8%).

### DISCUSSION

Rising FSH levels with age are well known markers of poor ovarian reserve. These are the patients who are declined

| Variables                  | Age<35 | P value | Age>35 |
|----------------------------|--------|---------|--------|
|                            | FSH<10 | FSH>10  |        |
|                            | Group I (n=64) | Group II (n=17) |        |
| Age                        | 29.8±2.6 | 30.4±2.5 | 0.45*  |
| Basal FSH                  | 6.3±1.6 | 13.8±3.4 | 0.001* |
| Total dose of gonadotropins used | 2481.2±778 | 3639.7±1380 | 0.001* |
| Duration of stimulation    | 10.03±1.6 | 10.09±1.4 | 0.9*   |
| No. of eggs retrieved      | 11.3±6.5 | 3.8±3.9  | 0.001* |
| No. of eggs fertilized     | 8.47±4.5 | 3.85±1.7  | 0.001* |
| No. of embryo’s formed     | 7.7±4.6 | 3.15±1.7  | 0.001* |
| Percentage of “A” grade embryo’s | 56 (87.5%) | 10 (76.9%) | 0.79** |
| Day of transfer            | 3.02±1.16 | 2.6±0.6  | 0.2*   |
| Cancellation rate          | 1 (1.6%)  | 4 (23.5%) | 0.007**|
| Pregnancy rate             | 26 (40.6%) | 4 (30.8%) | 0.08** |

*P<0.05 is significant. *Independent student t test, **chi-square test, FSH: Follicle stimulating hormone
from IVF treatment and offered donor eggs repeatedly. Young women with high FSH may not behave same as old women with high FSH.[1]

In our study, we found that younger women (age < 35 years) [Table 1] did better over relatively older women. Pregnancy rate was significantly higher in younger women (groups 1 and 2) when compared with relatively older women (groups 3 and 4) ($P < 0.05$). It is comparable to the study by Karizadeh et al., in 2009.[3] In this prospective analytical study of 207 women undergoing IVF/ICSI cycles, found a pregnancy rate of just 4.3% in women aged >37 years, compared with 23% and 20% in younger women.

Age is a well known factor to predict reproductive outcome. It suggests about quality of eggs.[4] Basal FSH levels are 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.[5] We did notice this difference in our study. Younger women with high FSH required significantly higher dose of gonadotropins for stimulation ($P – 0.001$), significantly lower number of retrieved oocytes, number of fertilized oocytes and the number of embryos obtained ($P – 0.001$) [Table 1].

Our study showed that women aged ≥ 35 years and FSH ≥ 10 (group 4) had the poorest ART performances. Results are comparable to the study by Karimzadeh et al.[1] 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 oocytes senescence rather than to poor endometrial receptivity, as suggested by the observation of high pregnancy outcome in oocytes donation programs.[6] In IVF programs, older women produce less oocyte and have lower implantation rate, thus reflecting both the smaller size and the impaired quality of their follicles pool.[7]

Cancellation rate was significantly high in groups 2 and 4 (23.5% and 21.6%, respectively), which reemphasizes the importance of high FSH in IVF cycles.

In summary, basal FSH levels have proved helpful in predicting pregnancy potential in ART, largely through their ability to predict the quantity of eggs, which can be induced to grow. The quality of those eggs seems better predicted by the age of the women, and both factors are important. In women past age 35, current success rates are low overall, even in those whose good ovarian reserve make many eggs; at this age, quantity does not make up for quality.

By contrast, young women with limited ovarian reserve can have good success rates despite their limited cohort of eggs, because the eggs themselves are of high potential; here quality matters more than quantity.

We suggest that while counseling a patient for donor eggs, always keep patients age in mind. Younger women in spite of high FSH tend to produce few good quality eggs, which can lead to good quality embryos and thus good pregnancy rates.

REFERENCES

1. Gleicher N, Weghofer A, Barad DH. Defining ovarian reserve to better understand ovarian ageing. Reprod Biol Endocrinol 2011;9:23.
2. Toner JP. Age = egg quality, FSH level = egg quantity. Fertil Steril 2003;79:491.
3. Karimzadeh M, Ghandi S Age and basal FSH as a predictor of ART outcome. Iran J Reprod Med Vol 7. 2009. p. 19-22.
4. Erdem A, Erdem M, Biberoglu K, Hayit O, Arslan M, Gursoy R. Age-related changes in ovarian volume, antral follicle counts and basal FSH in women with normal reproductive health. J Reprod Med 2002;47:835-9.
5. Toner JP. Modest follicle-stimulating hormone elevations in younger women: Warn but don’t disqualify. Fertil Steril 2004;81:1493-5.
6. van Rooij IA, Bancsi LF, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. Women older than 40 years of age and those with elevated follicle-stimulating hormone levels differ in poor response rate and embryo quality in in vitro fertilization. Fertil Steril 2003;79:482-8.
7. van Rooij IA, De Jong E, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. The limited value of follicle-stimulating hormone as a test for ovarian reserve. Fertil Steril 2004;81:1496-7.

How to cite this article: Dua M, Bhatia V, Malik S, Prakash V. ART outcome in young women with premature ovarian aging. J Mid-life Health 2013;4:230-2.

Source of Support: Nil, Conflict of Interest: None declared.