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Can elevated levels of basal follicle stimulating hormone predict a decrease in fertility in young women undergoing ART cycles?

Abstract

Background: The determination of ovarian reserve is often measured in normal cycling women through day 3 basal FSH. This determination will help to choose patients who are eligible for starting assisted reproductive technique (ART) cycles. Female age and basal FSH level are independently associated with IVF outcome.

Objective: This study aims' at evaluating the impact of basal FSH level associated with female age on IVF outcome.

Methods: A retrospective study that included 367 patients undergoing ICSI cycles. Basal FSH levels were measured using the same immunoenzymatic method for all patients. The age of women was checked before they were undergoing pituitary desensitization. Patients were divided into 4 groups according to their age and basal FSH levels. Then its correlation with IVF outcome was evaluated.

Results: The increase of FSH levels was associated significantly with reduced oocytes retrieved, and embryos obtained in young women. Nevertheless, there was no significant difference in terms of fertilization or pregnancy rate. Cancellation rates were significantly higher among patients with high day 3 FSH levels compared to patients having normal FSH levels in all age groups. Loss rates were affected by FSH levels among patients < 38 years old. However, they were significantly higher in older patients having elevated day 3 FSH levels. Younger women with high FSH levels produced less but better quality embryos resulting in acceptable pregnancy rate.

Conclusion: Female age is the most important prognostic factor. The basal FSH should be used to identify women who are purveyors of poor response to ART and should not be used to exclude them from fertility treatment.

Keywords: Age, Elevated basal FSH, Ovarian response, IVF, Cancellation, Pregnancy

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Sonia Jellad,[1] Amine Haj Hassine,[2] Mohamed Basly,[2] Lotfi Massoudi,[2] Mounir Chibani,[1] Radhouane Rachdi[2]

[1]Department of sterility exploration and PMA, Military hospital, Tunisia

[2]Department of obstetrics and Gynecology, Military hospital, Tunisia

Correspondence: Sonia Jellad, Department of sterility exploration and PMA, Military hospital– 1008 Montfleury, Tunis, Tunisia, Tel 00216–55–688–788 /00216–98565010, Email jellad_sonia@yahoo.fr

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Abbreviations: ART, Assisted Reproductive Technology; FSH, Follicle Stimulating Hormone; IVF, In Vitro Fertilization; ICSI, Intracytoplasmic Sperm Injection; GnRH, Gonadotropin Releasing Hormone

Introduction

An appropriate clinical evaluation and a proper treatment of women are essential for a positive outcome of assisted reproductive technology (ART) cycles. In order to obtain good results it is necessary to assess ovarian reserve before planning treatment. The determination of ovarian reserve by measuring day 3 basal FSH among normal cycling women is one of the most commonly used tests for predicting success in IVF treatment.[1] Several studies have reported that women with an elevated FSH level have poor response to ovarian stimulation that leads to a lower pregnancy rate in ART regardless their age.[2] However, other authors argued that young age does not protect against the adverse effects of reduced ovarian reserve. They also suggest that an elevated basal FSH is associated with poor quality oocytes leading to reduction in pregnancy rate and in miscarriage rates.[3,4] Recently, some studies have shown that women with higher basal FSH levels especially younger women can still achieve reasonable pregnancy rates with ART.[5–7] Therefore, the question to be raised is whether an elevated basal FSH level should be used as an entrance criterion to discourage patient's access to treatment with ARTs.

This study evaluates the influence of high FSH among women with different age categories undergoing ART cycles on reproductive outcome.

Materials and methods

Study population

This retrospective study offers data analysis of results provided by patients with infertility undergoing ICSI treatment in our centre (376 cycles). Institutional review board approval was not required, because of the retrospective nature of the study. The patients' information included: the age, the duration, type, and etiology of infertility, and the pelvic surgery history. Only the undergoing fresh ICSI cycles were selected. Patients with a history of pelvic surgery, endometrioma larger than 2cm in vaginal ultrasonography, and severe endometriosis at laparoscopy were excluded from this study.

Patients were divided according to their age in two groups: aged <38 and ≥ 38 years. These two groups were divided in two subgroups: FSH < 9.6 IU/L and FSH ≥ 9.6IU/L. Therefore, four groups were produced (according to their basal FSH levels as follows:

a. group1: aged < 38 and FSH < 9.6;

b. group2: aged < 38 and FSH ≥ 9.6;

c. group3: aged ≥ 38 and FSH < 9.6;

d. group4: aged ≥ 38 and FSH ≥ 9.6)

The age of patients was calculated starting from the day ovarian stimulation begun. All the serum FSH samples were collected on the day 2 or 3 of the prior cycle to ICSI treatment.

In vitro fertilization outcome variables included: patients' age, baseline FSH, number of oocytes retrieved, number of mature oocytes, number of embryos obtained, number of top embryos, total dose gonadotropins required, fertilization rate, cancellation rate, clinical pregnancy rate, implantation rate, and loss rates. All variables were compared between these groups.

Serum FSH level test

The concentration of FSH serum was measured using an immunoenzymatic assay (Abbot AxSYM® FSH, Abbott laboratories, IL USA). The analytical sensitivity of the assay was calculated to be better than 0.05 mIU/ml. Analytical sensitivity is defined as the concentration at 2SDs from the AXSYM® FSH level 0(0.00mIU/ml), and represents the lowest measurable concentration of FSH that can be distinguished from zero. The specificity of the assay was determined by studying the cross–reactivity of LH, thyroid–stimulating hormone (TSH) and HCG. The percentage cross–reactivity was calculated and was shown to be 0.2% for LH, 1.2% for TSH and 0.009% for HCG. The inter and intra assay coefficients of variation were 2.1% and 2.8%, respectively. The cutoff level for FSH used in this study was provided by calculating the 95% confidence interval (CI) of the study population that did not undergo cancellation. The 95% CI was 1.8–9.6IU/l. Thus 9.6IU/l was selected as the threshold between normal and elevated FSH levels.

Treatment protocol

All women underwent FSH stimulation and pituitary suppression with an agonist protocol (short or long). For the long protocol, the GnRH agonist (decapeptil 3mg LP/sc one day) was administered in the midluteal phase of the previous menstrual cycle. After pituitary desensitization patients were stimulated with recombinant FSH (gonal F, sereno®) at doses of 150–375 IU per day. For the short protocol, the GnRH agonist decapeptyl 0.1mg daily in concomitance with r–FSH100–375 IU per day starting from the second day was injected. When at least 3 follicles reached pre – ovulatory size (18–20mm); 10000 IU of hCG or recombinant hCG (Ovitrelle® 250 µg) was administered. Oocytes were aspirated using transvaginal ultrasound guidance 34–36 hours after hCG administration. Embryos transfer was performed on day 2 or 3 using a soft catheter with transabdominal ultrasound guidance. All patients received progesterone (utrogestan® 400mg) as supplement throughout the luteal phase. Pregnancies were established by elevated serum levels of β subunit of hCG more than 50 mIU/ml fourteen days after embryos were transferred. Clinical pregnancy was defined as the presence of fetal cardiac activity in ultrasonography three weeks after embryos transfer. Pregnancy loss was defined by the lack of embryonic growth or development after the visualization of a gestational sac by transvaginal ultrasound. Cancellation rate was defined as the cycles with no ovarian response. The cycles that resulted to ovum pick–up were defined as normal cycles.

Statistical analysis

The data were analyzed with studentstest,Fisherstest,Fishers exact test, x^2 test, and ROC curve using the SPSS version13.0. Statistical significance was defined as a value of $p < 0.05$.

Results

A totality of 367 infertile couples underwent ICSI cycles were studied. The distribution of patients according to age and FSH levels is shown in Table 1. The overall, clinical pregnancy rate per treatment cycles was 23.1% in age group of < 38 and 8.6% in age group of ≥ 38 years old. The average cancellation rate was 0.9% in age group of < 38 vs. 18.7% in age group of ≥ 38 years. (Table 2) details the data on ART performances, clinical pregnancy rates and cancellation rates among the four groups. Younger women with high FSH (group2) required high doses of gonadotropins compared with group1 ($p < 0.05$). However, this was not available for older women. Cancellation rates were significantly higher in patients with an elevated day 3 FSH compared to patients with normal FSH levels in all age groups ($p < 0.0001$). The data showed that younger women with higher FSH levels were significantly associated with less numbers of oocytes retrieved ($p < 0.0001$), less numbers of mature oocytes ($p < 0.0001$), and less numbers of embryos obtained ($p < 0.05$). Fertilization rates were not significantly different when we compare patients with normal FSH to others with elevated FSH in all age groups. We found a significant decrease of average of embryos available for transfer in younger patients with higher FSH (groups2 vs. 1). Nevertheless; this number was not significantly different among older women (group3 and 4). Clinical pregnancy rates were not significantly different between patients with a normal and patients with an elevated day 3 FSH in all age groups. Younger women with high FSH, had good quality embryos and had clinically sound pregnancy rate 33.3 %($p > 0.05$), even though they had produced fewer embryos for transfer.

Table 1 Distribution of patients according to age category and FSH level

Age Group	Number of Patients with Normal FSH(<9.6IU/L)	Mean(±SD) FSH(IU/l)	Number of patients with high FSH(≥9.6IU/l)	Mean(± SD) FSH(IU/l)	Total Number of Patients
<38 years	147	5.4±1.6	31	12.3±3.9	176
≥38 years	124	6.4±1.69	74	13.9 ±4.95	198

FSH: Follicle Stimulating Hormone.

Table 2 Ovarian stimulation cycles characteristics of patients

Variables	Age <38 Years			Age ≥38 Years		
	FSH < 9.6IU/L Group1(N=147)	FSH ≥ 9.6IU/L) Group2(N=31)	P value	FSH < 9.6IU/L Group3(N=124)	FSH ≥ 9.6IU/L) Group4(N=74)	P value
Mean Age	31.8±3.6	32.7±4.2	–	39.9±2	41.3±2.3	–
Total Dose of Gonadotropins used (Ampouls 75mg)	26.2±7.8	30.4±8.2	<0.05	27.4±9.2	24.9±9	NS

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Table Continued...

Variables	Age <38 Years FSH < 9.6IU/L Group1(N=147)	FSH ≥ 9.6IU/L) Group2(N=31)	P value	Age ≥38 Years FSH < 9.6IU/L Group3(N=124)	FSH ≥ 9.6IU/L) Group4(N=74)	P value
Duration of Stimulation	11.1±1	11.2±1	NS	11±0.9	10.9±0.7	NS
No of Oocytes Retrieved	11.3±7.3	5.4±5.2	<0.0001	5.6±4.4	5.6±4.5	NS
No of Oocytes Matures	5.6	3.1	>0.001	3.5	2.4	<0.05
Fertilization Rate (%)	53.6	47	NS	57.7	60.5	NS
No of Embryos Obtained	3.8	2.8	<0.001	2.4	1.5	<0.05
No of Top Embryos	2.2	2.1	NS	1.3	1.12	NS
No of Embryos Transferred	2.1±1.2	1.2±1.2	<0.0001	1.5±1.1	1.8±1.5	NS
Cancellation Rate (%)	0.4	6.9	<0.0001	6.4	35.1	NS
Clinical (%) Pregnancy Rate	23.6	33.3	NS	14	48	>0.01
Pregnancy Loss Rate (%)	3	6.5	NS	14	48	<0.01

FSH: Follicle Stimulating Hormone/ No: number.

Discussion

Many studies demonstrated that an elevated level of basal FSH affects both ovarian quality and quantity.[3] This marker is superior to age in predicting results.[3,8,9] However, younger women with high FSH levels may not respond in the same way as older women with high FSH.[10] We have retrospectively analyzed our IVF patients who had normal day 3 FSH, and compared their outcomes to those of IVF patients with an elevated day 3 FSH.

Our study shows that younger women < 38 years old provide better results than older women. Pregnancy rate is significantly higher among younger women when compared with older women > 38 years old. Patients with basal FSH < 9.6IU/l (group 1) have the best ART outcome among all groups despite having a higher pregnancy rate in group2 (33.3% versus 23.6% in group1; $p > 0.05$). This is comparable to Karimzadeh & Ghandhi[7] prospective analytical study of 207 women undergoing IVF/ICSI cycles who found a pregnancy rate of just 4.3% in women aged > 37 years, compared to 23% and 20% among younger women.

According to the previously presented data, women < 38 years old with elevated basal FSH (group2) can still have a favorable ART outcome as reflected by pregnancy rate despite poorer numbers of oocytes retrieved, fertilized and embryos obtained. This result can be explained by the decreased remaining follicles pool without diminuting their quality. Thereby, Female age is a well known factor related to reproductive outcome.[11,12] It reflects on the quality of oocytes. Basal FSH is a good predictor of the remaining follicles pool. Elevated basal FSH levels are indicative of diminished ovarian reserve and women with higher basal FSH levels have frequently decreased oocytes retrieved in IVF program.[11] In addition, the required dose of gonadotropins have increased significantly when increasing FSH among younger women (group1 vs. group 2; $p < 0.05$). This means that depleted follicular pool requires higher doses of gonadotropins for ovarian stimulation.

Overall, the number of embryos available for transfer was lower for younger patients with a high basal FSH level , and thus, the number of embryos to choose from and the number of embryos transferred were lower in that group. This results nonetheless in an accepted pregnancy rate. This fact implies that elevated basal FSH is associated with low ovarian reserve, but is not linked to poor oocyte quality and early embryo quality. This finding is illustrated in several other studies including Karimzadeh & Ghandhi[7] and Meenakshi et al.[13]

For women ≥ 38 years old, no significant difference is noted regarding the number of retrieved oocytes and fertilized oocytes in group3 vs group4. However, there is a decrease in the number of matures oocytes and embryos obtained with an increased FSH. For these patients, the total dose of gonadotropins did not correlate significantly with FSH levels (group3 vs 4). This means that older women have small size follicular pool with impaired quality. The aging follicles do not respond to even high doses of gonadotropins. Our study shows that women aged ≥ 38 years with FSH ≥ 9.6IU/l (group4), provide 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. Our results are in accordance to those by Karimzadeh & Ghandhi.[7] 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.[5,14] 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.[15]

The cancellation rate among both women < 38 and ≥ 38 years old, increases with the increase of FSH. It was significantly higher in groups2 and 4(6.9% and 35.1%, respectively), which highlights the importance of high FSH in IVF cycles.

We note that the fertilization rate is affected neither by the level of FSH nor by women's age. The miscarriage rate, however, is affected by age but not by the FSH level. It does significantly increase with increased age. This increased miscarriage rate in older women is therefore associated with age–related changes in chromosomes structure of the oocytes and thereby, high FSH does not reflect ageing oocytes.

Conclusion

Age is the most important prognostic factor and tends to better predict the oocyte quality. Basal FSH levels have proved helpful in predicting pregnancy potential in ART, largely through their ability to predict the quantity of oocytes. They should be used as additional information to counsel patients appropriately regarding the realistic chance of conception as well as aiding the clinician in determining the appropriate dose of gonadotropins. Current success rates among women aged ≥ 38 years are low even in among those with good ovarian reserve. At this age, quantity does not make up for quality. However, younger women with limited ovarian reserve can have good success rate despite their limited oocyte cohort and here quality matters more than quantity. We also believe that these women should

be granted the opportunity to undergo an IVF cycle as they should also be informed that they have a high risk of cycle cancellation due to low oocyte production.

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None.

Conflicts of interest

None.

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