Prognosis following in vitro fertilization-embryo transfer (IVF-ET) in patients with elevated day 2 or 3 serum follicle stimulating hormone (FSH) is better in younger vs older patients

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Summary

Purpose: To determine if younger women with increased day 2 or 3 serum follicle stimulating hormone (FSH) levels have a better prognosis than older women with similar FSH elevations.

Methods: Retrospective comparison of in vitro fertilization (IVF) outcome from cycles from 1/1/97 to 9/30/99 according to serum FSH ≤ 12 vs > 12 and age ≤ 38 or > 38. Only cycles where follicular phase leuprolide acetate was used were included.

Results: Age group ≤ 38 - clinical pregnancy rate (PR)/transfer was 32% with lower FSH vs 28.6% with higher FSH. The respective PRs for the older group were 30.3% and 5.5%.

Conclusions: Oocyte quality as evidenced by PRs following IVF-ET seems to be better in younger vs older patients despite increased basal serum FSH levels.

Key words: Age; Serum FSH; In vitro fertilization.

Introduction

Pregnancy rates (PRs) in women with elevated serum follicle stimulating hormone (FSH) levels during the early follicular phase are notoriously poor following in vitro fertilization-embryo transfer (IVF-ET) even in women with fairly regular menses [1-6]. In fact, there are data suggesting that if the early follicular phase FSH level is elevated in one cycle, then subsequent PRs are poor in subsequent cycles even if the FSH level is normal in those cycles [7]. A similar poor prognosis is ascribed to women whose day 3 FSH is in the normal range related to stimulation of a dominant follicle with suppression of FSH by high serum estradiol (E2) levels during the early follicular phase [7]. The reason for poor PRs may be related both to paucity and poor quality of oocytes retrieved [1-5, 7-9]. Thus, most patients are advised to use donated oocytes under these circumstances.

A previous study of euestrogenic women with elevated serum FSH levels during the early follicular phase found that without the use of IVF or gamete intrafallopian transfer, PRs varied according to age [10]. Women age 39 or younger had a 6-month clinical PR of 46% and a viable PR of 35% compared to 10.5% and 5%, respectively, for women 40 or older despite similar early follicular phase serum FSH levels [10]. The study presented herein attempted to evaluate whether the same trend would be found following IVF-ET.

Materials and Methods

All patients (n=692) who initiated an IVF cycle using the follicular phase leuprolide acetate (LA)/gonadotropin protocol between 1/1/97 and 9/30/99 were included in this study. At our center, this protocol is used primarily for older women or women with a history of poor ovarian response.

In the protocol women are required to have a baseline ultrasound and serum levels of E2, progesterone (P), luteinizing hormone (LH), and FSH drawn on day 2 of their cycle. After the testing, LA is administered beginning on day 2 of the cycle in dosages varying from .05 to 0.5 mg daily (.75 mg = 0.15 cc/day) and continued daily until the day of human chorionic gonadotropin (hCG). Gonadotropins were administered beginning on day 5 of the cycle and adjusted as needed; 10,000 U hCG were administered when two or more follicles reached a mean diameter > 18 mm.

Oocyte retrieval was scheduled 36 hours after hCG. Following IVF, embryos were transferred three days after the retrieval.

In the event of elevated E2 levels (> 4000 pg/mL) or poor endometrial development (thickness < 9 mm and/or homogeneous hyperechogenic echo pattern), ET was deferred and all embryos were cryopreserved [11, 12].

Patients were stratified by age into two groups: those ≤ 38 years old and those older than 38. Within each age group, patients were stratified by serum FSH levels on day 2 of the cycle into two groups: those with FSH levels ≤ 12 mIU/mL and those with FSH > 12 mIU/mL. Several FSH assays were used depending on the patient's medical insurance. All assays had an upper bound on the normal range < 12.9 mIU/mL.

The mean number of oocytes retrieved, embryos available per patient and fertilization rates were compared by age and FSH level. The main outcome measures were clinical PR per ET (sonographic evidence of a gestational sac in the uterus), implantation rates (number of gestational sacs per embryos

transferred) and viable PRs per transfer (viable fetus at end of first trimester). Statistical analysis included independent t-test, analysis of variance and chi-square analysis as indicated. A p value of .05 was used to determine significance.

Results

The ages in the first group ranged from 21 to 38 years old with a mean of 34.0±3.1 years. The mean age in the older group was 41.2±2.1 years; the age ranged from 38.1 to 48 years. Ninety-two cycles were canceled prior to oocyte retrieval. Seventy-three (79.3%) were due to poor ovarian response to stimulation, while the other 19 were canceled for other reasons (e.g., the patient ovulated or by patient request). The cancellation rates were similar within the FSH groups when compared by age but were higher for women with elevated FSH (Table 1).

The response to ovarian stimulation was compared for 600 women who underwent ovarian stimulation and oocyte retrieval. The number of oocytes retrieved, embryos available, number of canceled cycles, and failure to fertilize are seen in Table 2.

Embryo transfer was canceled if no embryos were available and sometimes deferred with embryos cryopreserved, if a maximum of only two embryos were available. Also deferment of ET occurred if the patients had poor endometrial development (thickness < 9 mm and/or homogeneous hyperechogenic echo pattern), or elevated E2 levels. The proportion of canceled cycles in each group is presented in Table 2. The percentage of transfers canceled due to poor fertilization or lack of sufficient embryos (≤ 2), was 18.8% in the younger group with normal FSH, 100% in the younger group with elevated FSH, 51.7% in the older group with normal FSH and 85.7% in the older group with elevated FSH.

The outcome of the fresh ET following oocyte retrieval is presented in Table 3. The clinical PR/transfer was similar for women with FSH < 12 mIU/mL irrespective of age (32.0% vs 30.3%). In younger women, the PR transfer did not differ by FSH level (32.0% vs 28.6%). In the older women, the PR was reduced if FSH levels were elevated (303.% vs 5.5%). Similar results were found for viable PRs and implantation rates (Table 3).

The mean sera FSH levels did not differ between different age groups, i.e., the FSH was 6.1±2.8 (age ≤ 38) vs 6.3±2.8 mIU/mL (age > 38) for those with serum FSH ≤ 12 and was 19.4±8.7 vs 16.9±5.5 mIU/mL, respectively, for the group with FSH > 12 mIU/mL.

Discussion

It has been estimated that in the general population the decline in fecundity accelerates between 35 and 40 years of age and approaches zero by age 45 [13]. When evaluating birth rates and implantation rates following IVF, one study concluded that embryo implanting ability and survival declined by more than two-thirds after 40 years and in younger women with reduced ovarian capacity [14]. Hull *et al.* found only a small reduction in the mean number of embryos transferred in women older than 40

Table 1. — *Comparison of number of initiated cycles canceled prior to oocyte retrieval.*

	Age ≤ 38 years	Age > 38 years
FSH ≤ 12 mIU/mL	12.3% (31/252)	10.3% (38/369)
FSH > 12 mIU/mL	36.0% (9/25)	30.4% (14/46)

Table 2. — *Comparison of response to ovarian stimulation by FSH level and age*.*

	Age ≤ 38 years	Age > 38 years
Baseline serum FSH ≤ 12 mIU/mL	(n = 221)	(n = 331)
No. of oocytes retrieved	11.9±8.9 (0-49) 10	7.6±5.7 (0-46) 6
Fertilization rate	62.1±24.7 (0-100) 62.5	68.1±28.5 (0-100) 63.6
No. of embryos available	7.3±5.7 (0-31) 6	5.3±4.7 (0-37) 4
Canceled transfers	65 (29.0%)	120 (36.1%)
Zero oocytes retrieved	2	1
Zero % fertilization	9	17
Only 1-2 embryos available	17	54
Poor lining or high E2	39	58
Baseline serum FSH > 12 mIU/mL	(n = 16)	(n = 32)
No. of oocytes retrieved	7.2±6.3 (1-20) 5	5.6±5.5 (0-23) 4
Fertilization rate	76.0±21.4 (50-100) 66.7	59.8±29.2 (0-100) 52.1
No. of embryos available	4.5±3.4 (1-11) 3	3.5±4.0 (0-17) 2
Canceled transfers	2 (12.5%)	14 (43.7%)
Zero oocytes retrieved	0	1
Zero % fertilization	0	2
Only 1-2 embryos available	2	9
Poor lining or high E2	0	2

*Data presented as mean ± standard deviation (range) median.

Table 3. — *Comparison of IVF-ET outcome by FSH level and age.*

	Age ≤ 38 years	Age > 38 years
Baseline serum FSH ≤ 12 mIU/mL		
N° of embryos transferred	3.3±1.1	3.6±1.4
Clinical PR	32.0% (50/156)	30.3% (64/211)
Implantation rate	10.1% (53/525)	8.3% (63/754)
Viable PRs	27.6% (43/156)	21.8% (46/211)
Baseline serum FSH > 12 mIU/mL		
N° of embryos transferred	2.9±1.2	2.9±1.4
Clinical PR	28.6% (4/14)	5.5% (1/18)*
Implantation rate	10.0% (4/40)	1.9% (1/53)*
Viable PRs	21.4% (3/14)	5.5% (1/18)*

*p<.05, comparing pregnancy groups by FSH in age group >38.

years but there was a significant progressive reduction in pregnancy and birth rates per transfer with advancing age and implantation and achievement of a live neonate [14].

The main point of this study is that the same trend with FSH and age was seen with patients having IVF as was seen in patients not using assisted-reproductive technologies [10] and that is that PRs are significantly higher in patients with elevated FSH who are younger vs older patients. We tried to control for stimulation protocol by eliminating patients taking the luteal phase LA/gonadotropin protocol. In so doing we may have biased the selection for patients who were potential poor candidates despite their normal FSH level. Comparable PRs for all patients age 38 and under during the same time period as this study was 47% irrespective of early follicular phase serum FSH. Thus conclusions that no significant differences are found in PRs in younger women even if the baseline FSH was increased or not may be somewhat misleading.

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