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Effect of Age on Pregnancy Outcome without Assisted Reproductive Technology in Women with Elevated Early Follicular Phase Serum Follicle-Stimulating Hormone Levels

Key Words

Age, pregnancy outcome
Elevated serum follicle-stimulating
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Fecundity
Incipient ovarian failure
Non-IVF treatment

Abstract

There are data suggesting that patients with elevated early follicular phase serum follicle-stimulating hormone (FSH) levels have a poor fertility outcome. This has been attributed to a high rate of aneuploidy in the oocytes. It is not clear whether the spindle defects leading to nondisjunction are related to the high FSH levels or the age of the oocyte. The study presented herein retrospectively evaluated 6-month pregnancy rates in women with elevated early follicular phase serum FSH levels according to age. Only cases without in vitro fertilization were used, since the elevated FSH levels were deemed likely to interfere with multiple egg recruitment needed for assisted reproductive technology. The 6-month clinical and ongoing pregnancy rates were significantly higher in the women <40 years of age (46.1 and 34.6%, respectively) than in those aged 40 or older (10.5 and 5.3%). These data suggest that women with elevated follicular-phase serum FSH levels have a better fertility prognosis when they are younger.

Introduction

The age-related decline for fecundity in women seems to accelerate between 35 and 40 years, and the pregnancy rate (PR) almost reaches zero by 45 years [1]. The main contributing factor to the decreased fecundity is probably an oocyte factor especially related to aneuploidy [2]; in addition, a relative reversible uterine senescence may also contribute [3-5].

Elevated serum follicle-stimulating hormone (FSH) levels during the early follicular phase have been associated with fewer oocytes retrieved and lower PRs following in vitro fertilization (IVF) [6-9]. The older patient has a smaller cohort of follicles recruited each cycle and thus is

more apt to have a higher serum FSH level during the early follicular phase. Similarly, a younger patient with incipient ovarian failure will have a higher serum FSH level during the early follicular phase and will not adequately respond to ovarian stimulation.

The women over 40 years of age may have had a natural selection process where the oocytes recruited during her previous cycles may have had the best quality. Therefore, the 40-year-old and older women may be more likely to have a higher proportion of oocytes that have nondisjunction of the chromosomes during the meiotic process. However, in younger patients with decreased ovarian reserve, it is not clear whether the oocytes go through an accelerated process of atresia similar to the natural meno-

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pause or whether some pathological destructive process leads to an indiscriminatory reduction in the 'best' and 'worst' immature oocytes. Contrasting to IVF where multiple oocytes are needed to be retrieved to have adequate success, the normal *in vivo* process usually only promotes one dominant follicle each cycle, no matter how many primary follicles were selected for that cycle's cohort.

The study presented herein compared 6-month pregnancy and spontaneous abortion (SAB) rates and PRs per cycle in younger versus older menstruating patients with decreased ovarian reserve as manifested by elevated serum FSH levels during the follicular phase. Higher PR and lower SAB rates in the younger group would suggest better-quality oocytes despite the apparent paucity of follicles.

Patients and Methods

Female patients presenting for treatment from November 1993 to April 1995 with at least 1-year infertility history were prospectively enrolled in the study, if their serum FSH levels obtained during the early follicular phase were >12 mIU/ml. This cutoff level had been previously determined to predict a decrease in ovarian reserve using the Boehringer Mannheim enzyme-linked immunosorbent assay for serum FSH [10]. Couples were excluded if there was a male factor problem (motile density $<10 \times 10^6$ /ml, motility $<30\%$). Bilateral tubal patency was required by hysterosalpingography. They were followed for six cycles of treatment.

A total of 45 consecutive female subjects were included in the study. The women were divided into two groups: group 1 <40 ($n = 26$) and group 2 ≥ 40 ($n = 19$) years of age.

All patients received oral micronized progesterone (P) supplementation during the luteal phase with 50 mg four times daily for those <40 and 100 mg four times/day for those ≥ 40 years old to partially compensate for the uterine need of extra P at the older age [3]. Thirty-two women were treated with follicle maturation drugs, such as gonadotropin therapy or clomiphene citrate, because they did not attain a mature follicle of 18–24 mm average diameter by sonography and a serum estradiol level >200 pg/ml without these drugs.

Serum FSH and luteinizing hormone (LH) levels were measured by an enzyme-linked immunosorbent assay (Boehringer Mannheim, Indianapolis, Ind., USA). They were obtained on day 3 of the menstrual cycle. The normal range for FSH for this assay is 3–12 mIU/ml, and intra- and interassay coefficients of variation are 1.8 and 4.3% respectively. The normal range for LH for this assay is 1.6–7.9 mIU/ml, and intra- and interassay coefficients of variation are 4.2 and 8.5%, respectively.

Chi-square analysis was used to compare pregnancy outcomes per patient and per cycle between the two groups. The Mantel-Haenszel test was utilized to assess the PRs by use of follicle-maturing drugs. A *t* test was used to compare the mean values and the Mann-Whitney U test to compare the median early follicular phase serum FSH and LH levels. A *p* value of 0.05 was considered statistically significant.

Results

The mean (\pm SD) baseline serum FSH level in the younger group was 18.9 ± 8.3 versus 20.8 ± 9.3 mIU/ml in the older group ($p > 0.05$, *t* test). The median levels were 16 (range 13–43) versus 17 (range 17–40) mIU/ml; $p > 0.05$, Mann-Whitney U test). The mean baseline LH and respective medians did not demonstrate any significant differences either [7.4 ± 4.9 vs. 9.8 ± 5.7 and 6.0 (2–22) vs. 8.5 (2–22) mIU/ml].

The mean duration of infertility was 2.3 ± 2.2 years for the younger group versus 2.6 ± 1.9 years for the older group ($p > 0.05$, *t* test). The medians (and ranges) were also similar with 1.5 (1–10) versus 2 (1–7) years ($p > 0.05$, Mann-Whitney U test).

The 26 younger patients had 119 treatment cycles during the 6-month period versus 107 for the 19 in the older group. The proportion of cycles in the younger group where a follicle-maturing drug was not taken was 58.8 ($n = 70$) versus 71% ($n = 76$) in the older group ($p > 0.05$, chi-square analysis). Furthermore, there were no differences in the type of follicle-maturing drugs used during the different cycles according to age. The breakdown found the use of clomiphene citrate, human menopausal gonadotropin, or pure FSH in 18.5 ($n = 22$), 21.0 ($n = 25$), and 1.7% ($n = 2$), respectively, in the younger group versus 14.0 ($n = 15$), 15 ($n = 16$), and 0% in the older group ($p > 0.05$, chi-square analysis). Thus, there were no significant differences in any of the parameters of baseline serum gonadotropin levels, length of infertility, or use of follicle-maturing drugs.

The 6-month clinical and ongoing PRs were significantly higher in the younger group (46.1 and 34.6%, respectively) versus the older group (10.5 and 5.3%, respectively; $p < 0.05$, chi-square) as seen in table 1. Similarly, the clinical and ongoing PRs per cycle were significantly higher in the younger versus older group ($p < 0.05$, chi-square), as seen in table 1. Though the SAB rates were twice as high in the older versus younger group (50% or 1/2 vs. 25% or 3/12), the sample size was too small to demonstrate statistical significance.

A comparison of PRs by age and use of follicle-maturing drugs demonstrated a significant difference in the response to treatment by age ($p < 0.05$, Mantel-Haenszel chi-square). In the younger women, there was a higher 6-month PR per patient in those treated with follicle-maturing drugs (55.0% or 11/20) versus those that were not (16.7% or 1/6), while in the older group, the PR was similar irrespective of treatment: 8.3% (1/12) with treatment versus 14.3% (1/7) without treatment. The PR per cycle

Table 1. Comparison of PRs according to age in women with elevated basal FSH levels

	Group 1 (<40 years)		Group 2 (≥ 40 years)	
	6-month	cycle	6-month	cycle
Clinical-PR	46.1% (12/26) ^a	10.1% (12/119) ^b	10.5% (2/19) ^a	1.9% (2/107) ^b
Ongoing PR	34.6 (9/26) ^a	7.6% (9/119) ^b	5.3% (1/19) ^a	0.9% (1/107) ^b

^a p < 0.05 (chi-square); ^b p < 0.05 (chi-square).

according to the use of follicle-maturing drugs was 13.6% (3/22) with clomiphene citrate, 20% (5/25) for human menopausal gonadotropin, and 50% (1/2) for pure FSH for the younger group. Comparable values for the older group were 0% for clomiphene and 6.3% (1/16) for human menopausal gonadotropin.

Discussion

These data demonstrate that younger infertile women with elevations in early follicular phase serum FSH levels have a better prognosis for achieving pregnancies than older patients with comparable serum FSH levels.

Success with IVF requires multiple oocytes to be retrieved in order to achieve reasonable success. A high basal FSH level usually indicates a paucity of follicles, and thus the conclusions reached by Toner et al. [11] that the FSH level was a better predictor than age for IVF outcome variables are understandable. Another study from the same institution [12] found that if the basal serum FSH level was elevated in a given cycle, then PRs are poor in subsequent IVF cycles, even if the basal FSH level is now normal. Thus, Toner et al. [11] hypothesized 'that the remaining oocytes in this circumstance are of relatively poor quality even in cycles that are endocrinologically normal.' Based on this hypothesis many clinicians have told younger patients with a high basal serum FSH level that their chance of success is poor and that they should proceed directly to a donor oocyte program. However, the data presented herein suggest that a recommendation of donor oocytes is premature in the younger group.

Our results are more consistent with the hypothesis that although the younger versus older patients with elevated basal sera FSH levels may have a similar paucity of recruited follicles per cycle, the quality of the oocytes remaining in the younger group, as manifested by a much higher PR, is superior to the older group. The older patient going through a natural menopause may have recruited the best follicles first, leaving behind for the fifth

decade the poorest-quality oocytes. Possibly for a majority of the younger patients, diminished ovarian reserve may be more related to some ovarian destructive process that indiscriminately damages good- and poor-quality follicles, leaving at least some good oocytes available for ovulation.

These data thus encourage the need for a matched control study comparing PRs in women <40 years with or without increased basal serum FSH levels with the hypothesis that there may be two mechanisms involved in causing decreased ovarian reserve in the younger patient: a destructive process leading to fewer oocytes in reserve but a normal distribution of good- versus poor-quality oocytes and in other circumstances an acceleration of the normal process of atresia as seen in the women ≥ 40 years of age, thus leaving predominantly poor-quality oocytes.

For women ≥ 40 years of age, Pearlstone et al. [13] demonstrated that PRs are low following ovulation induction and that SAB rates are high, but that the prognosis was worse if the FSH was very high (≥ 25 mIU/ml). It is difficult to compare the results presented herein with those of Pearlstone et al. [13], since different FSH assays were used, and we chose the FSH level to compare based on a level previously shown to predict decreased ovarian reserve [10], whereas Pearlstone et al. [13] used graphic analysis to choose their cutoff value. Nevertheless, the group with the highest PR in Pearlstone's study (the group <44 with serum FSH <25) had only a 5.2% clinical PR and a 1.9% viable PR compared to 10.5 and 5.3% rates, respectively, in the series presented herein in women with increased FSH levels. Perhaps the difference in success may be partially explained by the aggressive use of P beginning during the luteal phase in our patients versus no P therapy for the patients of Pearlstone et al. [13].

The decision not to use a follicle-maturing drug if criteria for a mature follicle were attained was based on previous studies finding superior PRs with P supplementation during the luteal phase rather than follicle-maturing drugs [14]. Since there was a significantly higher PR in the younger group taking follicle-maturing drugs, it is possible

that the previous conclusions do not apply to women with elevated basal serum FSH levels. Alternatively, it is possible that this group requires a higher dose of P during the luteal phase similar to the older patient [3]. However, another possible explanation is that the route of P administration in the previous study [14] was by vaginal suppository as compared with oral micronized P used in the study presented herein. Possibly, oral P is less effective related to its rapid hepatic metabolism and poor bioavailability [15]; there are data suggesting that the vaginal route of administration leads to the highest concentration of P in the endometrium, even when compared to intramuscular P [16]. Nevertheless, it may well be that patients who are clearly anovulatory are more apt to have that

problem exclusively, whereas patients with more subtle ovulatory problems may have a greater tendency to have other occult infertility factors leading to lowered PRs.

The ongoing PRs were sufficient following simple correction of ovulatory defects and other minor infertility problems that it seems reasonable to recommend to the younger group with elevated basal FSH levels to try for a 6-month trial period more conservative therapy allowing them to conceive with their own gametes. In contrast, the older patients with elevated basal serum FSH levels should be presented the dismal statistics found in this study to see if these data might influence them to choose the donor oocyte program initially.

References

- 1 Hull MGR, Fleming CF, Hughes AO, McDermott A: The age-related decline in female fecundity: A quantitative controlled study of implanting capacity and survival of individual embryos after in vitro fertilization. *Fertil Steril* 1996;65:783-790.
- 2 Munne S, Alikani M, Tomkin G, Grifo J, Cohen J: Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. *Fertil Steril* 1995; 64:382-391.
- 3 Meldrum DR: Female reproductive aging - ovarian and uterine factors. *Fertil Steril* 1993; 59:1-5.
- 4 Check JH, Askari HA, Fisher C, Vanaman L: The use of a shared donor oocyte program to evaluate the effect of uterine senescence. *Fertil Steril* 1994;61:252-256.
- 5 Yaron Y, Botchan A, Amit A, Kogosowski A, Yovel I, Lessing JB: Endometrial receptivity: The age-related decline in pregnancy rates and the effect of ovarian function. *Fertil Steril* 1993;60:314-318.
- 6 Muasher SJ, Oehninger S, Simonetti S, Matta J, Ellis LM, Liu-H-C, Jones GS, Rosenwaks Z: The value of basal and/or stimulated serum gonadotropin levels in prediction of stimulation response and in vitro fertilization outcome. *Fertil Steril* 1988;50:298-307.
- 7 Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z: Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. *Fertil Steril* 1989;51:651-654.
- 8 Fenichel P, Grimaldi M, Olivero J-F, Donzeau M, Gillet J-Y, Harter M: Predictive value of hormonal profiles before stimulation for in vitro fertilization. *Fertil Steril* 1989;51:845-849.
- 9 Tanbo T, Dale PO, Abyholm T, Stokke KT: Follicle-stimulating hormone as a prognostic indicator in clomiphene citrate/human menopausal gonadotropin-stimulated cycles for in vitro fertilization. *Hum Reprod* 1989;4:647-650.
- 10 Check JH, Nazari A, Kuhn R, Lauer C: Relationship of early follicular phase sera FSH and LH levels as measured by a radioimmunoassay and an enzyme-linked immunosorbent assay to number of oocytes retrieved. *Clin Exp Obstet Gynecol* 1996;23:83-86.
- 11 Toner JP, Philput CB, Jones GS, Muasher SJ: Basal follicle-stimulating hormone level is a better predictor of in vitro fertilization performance than age. *Fertil Steril* 1991;55:784-791.
- 12 Scott RT Jr, Hofmann GE, Oehninger S, Muasher SJ: Intercycle variability of day 3 follicle-stimulating hormone levels and its effect on stimulation quality in in vitro fertilization. *Fertil Steril* 1990;54:297-302.
- 13 Pearlstone AC, Fournet N, Gambone JC, Pang SC, Buyalos R: Ovulation induction in women age 40 and older: The importance of basal follicle-stimulating hormone level and chronological age. *Fertil Steril* 1992;58:674-679.
- 14 Check JH, Nowroozi K, Wu CH, Adelson HG, Lauer C: Ovulation inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. *Int J Fertil* 1988;33:252-256.
- 15 Maxson WS, Hargrove JT: Bioavailability of oral micronized progesterone. *Fertil Steril* 1985;44:622-626.
- 16 Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmouh L, Sauer MV: Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: A comparative study. *Fertil Steril* 1994;62:485-490.