REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Elevated day 3 follicle-stimulating hormone in younger women: is gonadotropin stimulation/intrauterine insemination a good option?

Irene Souter, MD; Irene Dimitriadis, MD; Lina M. Baltagi, MD; John D. Meeker, ScD; John C. Petrozza, MD

OBJECTIVE: The objective of the study was to determine the fecundity of young women (<35 years) with an elevated day 3 follicle stimulating hormone (FSH) undergoing gonadotropin-stimulation/intrauterine insemination.

STUDY DESIGN: This was a retrospective study. The study was conducted at an academic fertility center. A total of 1396 gonadotropin stimulation/intrauterine insemination cycles from 563 women were stratified by day 3 FSH levels (<10 vs ≥10 U/L) and outcomes were compared. Gonadotropin dose, treatment duration, peak estradiol (E_2), number of preovulatory follicles (total, large, and medium size), E_2/follicle, endometrial thickness, spontaneous abortion, clinical and multiple pregnancy rates were measured.

The statistics included a Student *t* test, a χ^2, regression, and a discrete survival analysis.

RESULTS: An elevated day 3 FSH was found in 10.2% of the women, despite favorable age (31.9 ± 2.5 years). Women with a day 3 FSH of 10 U/L or greater when compared with women with a normal day 3 level required significantly more medication (1058.9 ± 1106.0 vs 632.7 ± 477.5 IU, $P < .0001$) were triggered a day earlier (10.6 ± 2.4 vs 11.5 ± 2.9 days, $P = .0006$) and had E_2 levels (on the day of and the day prior to human chorionic gonadotropin administration) that were significantly higher (529.5 ± 244.3 vs 450.0 ± 244.2 and 359.6 ± 141.7 vs 306.8 ± 160.9 pg/mL, respectively, $P < .05$). Clinical pregnancy rates were comparable among the groups (14.6 vs 14%, respectively, $P > .05$). Spontaneous abortion and multiple pregnancy rates were higher among women with an FSH of 10U/L or greater but not significantly so (27.8% vs 12.0%, 22.2% vs 13.8% for FSH of ≥10 vs FSH < or >10 U/L, $P > .05$).

CONCLUSION: Women younger than 35 years with an elevated day 3 FSH, when treated aggressively with gonadotropins have pregnancy rates comparable with those of women with a normal baseline FSH. To achieve this outcome, they need higher doses of medication to stimulate the production of a larger preovulatory follicular cohort.

Key words: day 3 follicle stimulating hormone, gonadotropins, infertility, intrauterine insemination, ovulation induction

Cite this article as: Souter I, Dimitriadis I, Baltagi LM, et al. Elevated day 3 follicle-stimulating hormone in younger women: is gonadotropin stimulation/intrauterine insemination a good option? Am J Obstet Gynecol 2014;210:xx-xx.

In the setting of infertility, accurate determination of ovarian reserve is extremely important because the information is used by clinicians to determine eligibility and protocols for fertility treatments and to properly counsel couples about the probability of success of the proposed therapies. Several ovarian reserve tests are available and include measurement of day 3 follicle-stimulating hormone (FSH) and estradiol (E_2),[1-4] basal inhibin-B and antimullerian hormone (AMH) levels,[5-7] the clomiphene citrate (CC) challenge test,[2,8-10] and the ultrasonographic evaluation of antral follicle counts (AFC) and ovarian volume.[2,11-13] Despite the plethora of available ovarian response biomarkers and the evidence suggesting that AFC and AMH correlate better with true ovarian reserve (histologically confirmed ovarian primordial follicle number) than day 3 FSH does,[14] the latter is widely available and often used as either the first-line or the only test in ovarian reserve evaluation.

Elevation in basal FSH levels is thought to reflect ovarian aging and is associated, at least in older women undergoing in vitro fertilization (IVF), with poor ovarian response and low pregnancy rates,[4,15,16] with numerous studies also suggesting that decreased ovarian reserve (DOR) is associated with a higher chance of fetal loss[17-22] and chromosomal abnormalities in the conceptus.[23-26]

Because most of the studies evaluating the association between measures of

From the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA (Drs Souter, Dimitriadis, Baltagi, and Petrozza), and Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI (Dr Meeker).

Received Oct. 27, 2013; revised Jan. 15, 2014; accepted Jan. 21, 2014.

J.C.P. is a consultant to Interlace Medical, Framingham, MA, owned by Hologic, Inc, Bedford, MA. The other authors report no conflict of interest.

Presented, in part, at the 64th Annual Scientific Meeting of the American Society for Reproductive Medicine, San Francisco, CA, Nov. 8-12, 2008.

Reprints not available from the authors.

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2014.01.031

ovarian reserve and reproductive outcomes have been performed in older patients undergoing aggressive assisted reproduction technology treatments, it is difficult to counsel younger women with elevated basal FSH levels about their appropriate treatment options and expected success rates. Furthermore, basal FSH levels predict more accurately the size of the remaining oocyte pool and not necessarily its quality (the latter declines as age advances and biological damage to the oocyte accumulates).[27-32] This potentially accounts for the more favorable reproductive outcome of younger poor responders compared with that of their older counterparts.[33-34]

The purpose of the present study was to evaluate the prognostic significance of elevated day 3 FSH levels on the outcome of gonadotropin stimulation (GS)/intrauterine insemination (IUI) cycles in women younger than 35 years. GS/IUI cycles with normal basal FSH levels (<10 U/L) were compared with cycles characterized by elevated FSH levels (≥10 U/L). Thus, we sought to provide the treating physicians with a tool to properly counsel younger patients (with elevated basal FSH levels) regarding less aggressive treatment options such as GS/IUI.

Materials and Methods

The study was approved by the Massachusetts General Hospital Institutional Review Board. All IUI cycles (January 2004 through July 2010) from women younger than 35 years were retrospectively reviewed, and 1396 GS/IUI cycles were identified and further analyzed. Of these, 143 cycles were from women with a basal FSH of 10 U/L or greater.

At the time of treatment initiation, all participants had completed a standard infertility work-up (as described elsewhere).[35] Recombinant FSH or human menopausal gonadotropins was started on the third day after a spontaneous or a progesterone-induced menstrual bleed. Response to gonadotropins was monitored and dose adjusted, as needed. Ovulation was triggered with recombinant human chorionic gonadotropin (hCG; Ovidrel; Serono, Norwell, MA), and 35-36 hours later, the IUI was performed.

Once stimulation started, cycles were cancelled either for overresponse (more than 5 preovulatory follicles) or for no response. Pregnancy was defined as clinical when at least 1 gestational sac was visualized on ultrasound 3-4 weeks after the IUI.

Outcome measures included the following: total gonadotropin dose, duration of gonadotropin stimulation, peak E_2, number of preovulatory follicles (total, large [≥15 mm], and medium size [13-15 mm]), E_2 per follicle produced, spontaneous abortion (SAB), and clinical and multiple pregnancy rates.

Statistics

Means or geometric means between groups were compared using a Student *t* test or 1-way analysis of variance as appropriate for continuous variables, and χ^2, and Fisher exact tests were used to compare categorical data. Multivariable models for associations between day 3 FSH and the outcomes of interest, adjusted for age and body mass index (BMI), were constructed.

For continuous outcomes, linear mixed-effects models were used to account for correlations between cycles within patient. Several variables (gonadotropin dose, peak E_2 variables, and peak E_2 variables divided by number of follicles) were skewed and transformed by the natural logarithm prior to inclusion in the models. The association of elevated day 3 FSH on the number of large, medium, and total follicles was assessed using generalized estimating equations (GEE) poisson regression models. A logistic GEE model was used to model whether a pregnancy was achieved as well as the odds of a multiple pregnancy or SAB.

Finally, because a live birth occurred only a maximum of 1 time per patient, a discrete survival model that adjusted for the cycle was used to calculate odds ratios for achieving a live birth in relation to elevated day 3 FSH.[36] Values of $P < .05$ were considered statistically significant.

Results

During the study period, 2681 insemination cycles were performed. In 1396 cycles, gonadotropins were used either alone (n = 1391) or in combination with CC (n = 5). Five hundred and two women (89.2%) with a basal FSH less than 10 U/L contributed 1253 cycles (89.8%) and 61 women (10.8%) with an FSH of 10 U/L or greater contributed 143 cycles (10.2%). Overall, GS/IUI cycles represented 57% and 71.8% of the insemination cycles performed among women with normal and elevated basal FSH levels, respectively ($P = .0001$).

Table 1 summarizes the demographic characteristics stratified by the day 3 FSH. The mean age, day 3 FSH, and BMI of the study participants were 31.9 ± 2.5 years, 7.3 ± 2.7 U/L, and 23.7 ± 4.4 kg/m^2, respectively. The age distribution was as follows: 235, 293, and 868 cycles were from women younger than 30 years, 30 years or less to 32 years or less, and between 32 years or less and 35 years or less, respectively.

Women with an elevated day 3 FSH were slightly older than the ones with a normal day 3 value (Table 1) and were less likely to have received CC in the past (14.7 vs 49.1%, respectively, $P < .01$). The most common infertility diagnosis among the former group was DOR, followed by combined factors, and idiopathic infertility, whereas in the latter, the most prevalent diagnosis was idiopathic infertility, followed by male and combined factors ($P < .01$ for all comparisons, Table 1).

Women with a day 3 FSH of 10 U/L or greater required significantly more medication and were triggered a day earlier than women with normal day 3 levels. E_2 on the day of and the day prior to hCG trigger was significantly higher in women with an elevated day 3 FSH (Table 2).

On average, women with a normal day 3 FSH produced 1.8 ± 0.95 total follicles per cycle, and those with an elevated FSH produced 2.1 ± 0.96 follicles ($P = .0004$). The percentage of patients who developed 1 follicle only in response to gonadotropins was significantly higher in the normal FSH group with significantly more patients in the high FSH group producing 2-3 follicles (46.9 vs 33.6%; $P = .003$, and 45.2 vs 59.2%; $P = .002$, respectively).

Using a GEE model adjusted for age and BMI, we noted that women with an