The serum follicle-stimulating hormone-to-luteinizing hormone ratio at the start of stimulation with gonadotropins after pituitary down-regulation is inversely correlated with a mature oocyte yield and can predict "low responders"

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Objective: The aim of this study was to investigate the relationship of serum FSH and LH levels at the commencement of stimulation to ovarian follicular development in women undergoing pituitary down-regulation and controlled ovarian hyperstimulation with gonadotropins in IVF or intracytoplasmic sperm injection (ICSI) cycles.
Design: Retrospective analysis.
Setting: An IVF program in a tertiary medical center.
Patient(s): A total of 245 women proven to be pituitary down-regulated by their serum E_2 levels.
Intervention(s): Patients treated with a GnRH agonist and FSH and hMG underwent assisted reproductive technique (ART).
Main Outcome Measure(s): Mature oocyte yield, pregnancy rate (PR), and live birth rate.
Result(s): The serum FSH levels and the FSH-to-LH ratio at the commencement of gonadotropin stimulation were inversely correlated to the number of mature oocytes ($r = -0.193$ and $r = -0.224$, respectively). When assessed with receiver-operating characteristic (ROC) analysis, there was statistically significant ability for the FSH/LH ratio to differentiate between the "poor response" cycles (with mature oocyte yield ≤ 4) and the normal response cycles. Using the cutoff value derived from ROC analysis, cycles with the FSH-to-LH ratio ≥ 3 produced less mature oocytes (8.25 vs. 11.74), lower peak E_2 levels (1,975.3 pg/mL vs. 3,324.8 pg/mL), and higher percentage of poor ovarian response cycles (32.5% vs. 14.3%).
Conclusion(s): The serum FSH-to-LH ratio at the start of gonadotropin stimulation after pituitary down-regulation provided a practical method for early prediction of mature oocyte yield. (Fertil Steril® 2005;83:883–8. ©2005 by American Society for Reproductive Medicine.)

Key Words: Down-regulation, FSH, FSH-to-LH ratio, LH, oocyte yield, poor ovarian response

The outcome of assisted reproductive technique (ART) is strongly dependent on ovarian responsiveness during controlled ovarian hyperstimulation (COH). An optimal COH provides a higher number of mature oocytes available for ART procedures and thus provides a greater possibility to select higher quality embryos for embryo transfers. Conversely, for those patients defined as poor responders, an inadequate number of mature oocytes provides a lesser opportunity to select high quality embryos for transferring and thus results in poorer pregnancy outcomes (1). Accordingly, a variety of parameters, namely, the day 3 basal serum concentrations of FSH, E_2, LH, and the FSH-to-LH ratio have shown an ability to predict the response to ovarian stimulation (2–7).

Regarded as standard treatment protocols during COH in ART, GnRH agonists (GnRH-a) are widely applied because of their effective blockade of the positive E_2 feedback to the pituitary, so as to prevent the untimely exposure of the developing follicles to an LH surge and therefore to P. Because the responsiveness of the ovary to gonadotropin stimulation differs from cycle to cycle depending on the intensity of pituitary down-regulation, those day 3 basal

Received May 25, 2004; revised and accepted October 6, 2004.
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parameters before the actual stimulation cycle seem to not exactly reflect the cycle-specific hormonal profiles during COH after pituitary down-regulation with GnRH-a. However, only exiguous studies emphasized the predictive value of gonadotropin concentrations after pituitary desensitization with GnRH-a. It was advocated by some researchers that higher serum FSH and E_2 concentrations after pituitary down-regulation were associated with lower mature oocyte yield (3, 8); however, other investigators found that a higher FSH-to-LH ratio after pituitary desensitization was related to poor ovarian response (9).

In previous studies, although the relationship between ovarian response and serum gonadotropin levels after pituitary desensitization were demonstrated, the threshold values were not established for recommendation of good or poor ovarian response. To answer this question, we performed an analysis of the prospectively collected serum FSH and LH concentrations after pituitary down-regulation with a statistical method using receiver-operating characteristic (ROC) curve analysis, which is not only capable of testing the significance of the parameters, but also provides a cutoff value to distinguish between the poorer and normal response cycles.

MATERIALS AND METHODS

Subjects

The study group consisted of 245 consecutive infertile women, undergoing COH for IVF or intracytoplasmic sperm injection (ICSI) programs between September 1998 and August 2002 at the Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taiwan. Institutional Review Board approval (931004/401) was obtained for retrospective review of the relevant charts.

All patients registered for IVF or ICSI were included in this study, except for those with the following conditions: [1] infertility attributed to endocrine abnormalities such as hyperprolactinemia, polycystic ovarian syndrome (PCOS), and absence of ovarian function; [2] age more than 41 years; [3] previous COH with documented poor response resulting in a mature oocyte yield $\leq$4; [4] occult ovarian failure with day 3 basal FSH concentration $>$10 IU/L; [5] using stimulation protocols other than GnRH-a pituitary desensitization; and [6] inadequate data for analysis.

Treatment Protocols

In all cycles, ovarian stimulations were carried out with FSH and hMG after pituitary down-regulation with GnRH-a according to the protocol previously reported (10). The pituitary suppression was achieved by subcutaneous injection of leuprolide acetate (LA; Lupron, Takeda Chemical Industries, Osaka, Japan) 0.5 mg daily, which was reduced to 0.25 mg after the down-regulation was achieved, starting in the midluteal phase of the preceding cycle. When the serum E_2 concentration of $<$50 pg/mL was confirmed on day 3 of the cycle, ovarian stimulation was started with an administration of 150 IU FSH (Metrodin, Serono, Aubonne, Switzerland) and 150 IU hMG (Pergonal, Serono) IM per day, lasting for 6 days. Gonadotropin dosage was adjusted accordingly by monitoring the follicular size using transvaginal ultrasound after gonadotropin treatment for 6 days.

Human chorionic gonadotropin (10,000 IU, IM; Profasi, Serono) was given to trigger ovulation when two leading follicles reached a mean diameter of 18 mm. Oocytes were retrieved transvaginally 34–35 hours after hCG administration. The evaluation of the oocyte maturity was in accordance with the criteria established by Veeck (11). Routine sperm preparation and IVF/ICSI and embryo cultures were performed as in protocols previously described (12). Approximately 3–5 embryos were transferred 2–3 days after oocyte retrieval.

Blood Samples and Hormone Assays

Blood samples for FSH and LH were routinely collected at the commencement of stimulation with gonadotropin after the pituitary suppression was proven by E_2 levels. The FSH, LH, and E_2 serum concentrations were measured using the chemiluminescent immunoassay (IMMULITE FSH, LH and Estradiol, Diagnostic Products Corporation, Los Angeles, CA). The inter- and intra-assay coefficients of variation were, respectively, 6.6% and 3.0% for LH, 6.3% and 2.5% for FSH, and 6.7% and 4.3% for E_2. The lower levels of sensitivity were as follows: LH = 0.05 IU/L, FSH = 0.1 IU/L, and E_2 = 20 pg/mL.

Statistical Methods

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS v 11.0 for Windows, Chicago, IL). Statistical significance was assessed using the Student's t test and χ^2 test as appropriate. At $P<.05$, the difference was considered to be statistically significant.

Regression analysis was assessed for the relationship between serum concentrations of gonadotropins and the oocyte yields. Using the Pearson's correlation coefficient, the relationship between two variables was expressed.

The serum concentrations of FSH and LH, and the FSH-to-LH ratio, attained between normal responders and poor responders were evaluated with ROC analysis. The criterion for determining a poor response was a yield of mature oocytes that was less than or equal to four (13). By plotting sensitivity and 1-specificity, the ROC curve was constructed to examine the predictive power of the serum gonadotropin concentrations for poor ovarian response and to define the cutoff value (14, 15). The ability of the hormonal concentrations to discriminate between the normal and poor responders was expressed by the area under the ROC curve (ROC–AUC).