Ongoing pregnancy rates in intrauterine insemination are affected by late follicular-phase progesterone levels

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Objective: To determine the relationship between serum P levels on the day of hCG administration and ongoing pregnancy rates.
Design: Retrospective study.
Setting: University-affiliated private IVF.
Patient(s): A total of 2,458 couples undergoing IUI.
Intervention(s): Ovarian stimulation with human recombinant FSH.
Main Outcome Measure(s): Ongoing pregnancy and miscarriage rates.
Result(s): Progesterone concentrations were significantly higher given that the E_2 concentration increased. Ongoing pregnancy rates were significantly decreased in women with P levels higher than 1.1 ng/mL; similar results were obtained in relation to miscarriage rates.
Conclusion(s): Significant differences in ongoing pregnancy rates when P levels were elevated on the day of hCG administration may help clinicians to counsel patients about the reduced success rates with IUI and manage the timing of insemination to optimize implantation. (Fertil Steril® 2015;104:879–83. ©2015 by American Society for Reproductive Medicine.)
Key Words: Progesterone levels, intrauterine insemination, ongoing pregnancy

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Progesterone plays a critical role in the process of implantation by inducing significant changes in endometrial morphology that are prerequisites for embryo attachment and invasion. Endometrial receptivity results from a series of molecular events triggered by P after estrogen priming (1). Nevertheless, the mid-cycle LH surge during the reproductive cycle is an intriguing endocrinologic phenomenon; although increased P levels have historically been associated with LH in the context of premature LH surges, some studies indicate that elevated P may be due to exposure to high doses of FSH (2–4). Patients with high E_2 concentrations also have significantly higher P concentrations (5–7); this association suggests that at least one of the mechanisms causing increased P levels during the follicular phase is linked to the ovarian response during ovarian stimulation.

Intrauterine insemination combined with ovarian stimulation has become one of the first treatments for infertility, although the results in terms of pregnancy rates are somewhat limited and quite variable, ranging from 10% to 25% (8). One reason for such low pregnancy rates may be premature peaks in the LH surge within an assisted reproduction treatment, with subsequent follicle luteinization at the end of ovarian stimulation (9). Premature LH surges occur in 25%–30% of stimulated IUI cycles (10) and may theoretically interfere with timing of the IUI or results in cancellation and more treatment failures.

The influence of prematurely increased P levels in stimulated IUI cycles has not has not been well studied,

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but this information could be useful for matching the timing of insemination with the window of implantation. The purpose of this study was to determine whether the P level on the day of hCG administration affects the clinical outcomes during IUI. Specifically, the primary objective was to determine the relationship between serum P levels on the day of hCG administration and ongoing pregnancy rates. As a secondary objective, we also tried, when appropriate, to establish a serum P threshold in this specific set of patients that would define circulating P levels that were detrimental to cycle outcomes.

MATERIALS AND METHODS

Study Population and Design

A total of 2,458 couples undergoing IUI from January 2012 to August 2013 were included in this large, noninterventional, retrospective, multicenter cohort study of patients undergoing routine clinical examinations and procedures. These women received treatment at one of the 11 private clinics belonging to the IVI group in Spain. All procedures were approved by an institutional review board (MAD-AR-03-2015-01) in IVI Madrid and complied with Spanish law governing assisted reproductive technologies (14/2006). Only the first IUI treatment was included in the study.

All patients began recombinant FSH on cycle day 3 after confirming ovarian quiescence by transvaginal ultrasound. Starting doses ranged between 50 and 100 IU/d and were calculated according to the number of antral follicles, age of the patient, and patient's body mass index. Dose adjustments were performed according to ovarian response, which was monitored by vaginal scans and E_2 determinations. Final oocyte maturation was achieved by the administration of 250 μg of recombinant hCG (Ovitrelle, Merck-Serono) when at least one follicle reached 17 mm in mean diameter; only one IUI was scheduled approximately 36 hours after recombinant hCG administration.

Procedures in patients with three or more follicle $\geq$16 mm in mean diameter were cancelled. Similarly, if no dominant follicle was observed after two consecutive scans, the woman's procedure was also cancelled.

A serum β-hCG analysis was performed 12 days after IUI, and clinical pregnancy was confirmed when a gestational sac with a fetal heart beat was visible by ultrasound determination.

Hormonal Measurements

Blood samples were analyzed for circulating E_2 and P levels on the day of hCG administration. Serum samples were analyzed by chemiluminescence with the Architect analyzer (Abbot Diagnostics). The analytical sensitivity of the E_2 assay was $\leq$10 pg/mL, with a coefficient of variation of $\leq$7%. The analytical sensitivity of the P assay was 0.1 ng/mL, with a coefficient of variation of $\leq$7%.

Statistical Analysis

To describe the probability distributions of pregnancy and ongoing pregnancy rates, P concentrations were converted from continuous variables to categorical variable by dividing them into groups based on their percentiles. By using this procedure, we avoided bias by assuming that any relationship between serum P level and clinical outcome may be linear. Next, patients were separated into percentiles (p25, p50, p75, and p90), then subdivided into five distinct groups according to their serum P levels on the day of hCG administration, as follows: 0.1–0.20 ng/mL (p25, n = 619); 0.21–0.30 ng/mL (p25–p50, n = 474); 0.31–0.60 ng/mL (p50–p75, n = 681); 0.61–1.10 ng/mL (p75–p90, n = 430); and >1.11 ng/mL (>p90, n = 254).

The odds ratio (OR) of all the variables generated on pregnancy was expressed in terms of 95% confidence intervals (CIs). We performed a multivariate logistic regression to quantify the effect of different variables (P, age, days of stimulation, doses of FSH, number of mature follicles, and sperm characteristics) on pregnancy. Furthermore, a receiver operating characteristic curve was used to test the predictive value of the variable "progesterone level" included in the model with respect to ongoing pregnancy rate. Receiver operating characteristic curve analysis provides values for the area under the curve (AUC) that are between 0.5 and 1.0, and can be interpreted as measurement of the global classification ability of the model.

Finally, values were expressed as means with SDs. One-way analysis of variance for continuous variables and the χ^2 test for categorical data were used for data analysis. Statistical analysis was performed with the Statistical Package for Social Sciences, version 19.0 (SPPS), and $P<.05$ was considered statistically significant.

RESULTS

Overall Results

A total of 2,458 women undergoing IUI, with either their partner's or a donor's sperm, were included in this study. The clinical characteristics of the study population are presented in Table 1.

Steroid Levels and Clinical Outcomes

Progesterone concentrations became significantly higher as the E_2 concentration increased, with statistically significant differences between the lowest and the highest percentiles. These differences were in accordance with the significant differences observed in the total number of both follicles ($P<.001$) and mature follicles ($P<.001$; Table 2).

Regarding clinical outcomes, we also observed significant differences in ongoing pregnancy ($P<.001$) rates in patients with P levels >1.1 ng/mL (Fig. 1). To rule out that the poor results obtained with P >1.1 ng/mL were associated with a low ovarian response, we analyzed the subsequent IVF cycles of the 254 patients with highly reduced clinical outcomes with IUI, if any, and found that the doses administered (1,780 $\pm$ 30 IU) and the number of oocytes retrieved (9.6 $\pm$ 2) were within normal ranges.

The adjusted OR associated with the effect of different variables on the pregnancy rate showed that only P concentration was statistically significant (OR 0.545, 95% CI