Defining the "sweet spot" for administered luteinizing hormone-to-follicle-stimulating hormone gonadotropin ratios during ovarian stimulation to protect against a clinically significant late follicular increase in progesterone: an analysis of 10,280 first in vitro fertilization cycles

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Objective: To determine whether different ratios of administered LH-to-FSH influence the risk of clinically relevant late follicular P elevations and whether there is an optimal range of LH-to-FSH to mitigate this risk.
Design: Retrospective cohort.
Setting: Private academic center.
Patient(s): A total of 10,280 patients undergoing their first IVF cycle.
Intervention(s): None.
Main Outcome Measure(s): The ratio of exogenous LH-to-FSH throughout stimulation and association with absolute serum P level $\geq$1.5 ng/mL on the day of hCG administration.
Result(s): Stimulations using no administered LH (N = 718) had the highest risk of P elevation $\geq$1.5 ng/mL (relative risk [RR] = 2.0; 95% confidence interval [CI] 1.8–2.2). The lowest risk of P increase occurred with an LH-to-FSH ratio of 0.30:0.60 (20%; N = 4,732). In contrast, ratios <0.30, reflecting proportionally less administered LH (N = 4,847) were at increased risk for premature P elevation (32%, RR = 1.6; 95% CI 1.5–1.7) as were ratios >0.60 (23%, RR 1.1; 95% CI 1.0–1.3). This pattern of lowest risk in the 0.30–0.60 range held true for cycles characterized by low, normal, and high response. When performing a logistic regression to control for multiple confounding variables this relationship persisted.

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Conclusion(s): Absent or inadequate LH dosing is associated with a risk for a late follicular elevation in P sufficient to induce suboptimal outcomes. A total LH-to-FSH ratio of 0.30:0.60 was associated with the lowest risk of P elevation. Optimization of this parameter should be considered when making gonadotropin dosing decisions. (Fertil Steril® 2014;102:1312–7. ©2014 by American Society for Reproductive Medicine.)

Key Words: Gonadotropins, late follicular increase in progesterone, exogenous LH, exogenous FSH, stimulation

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The hormonal milieu, which accompanies a supraphysiologic response to controlled ovarian hyperstimulation (COH), has been associated with impaired endometrial receptivity. Much of this diminution has been attributed to significant increases in circulating E_2 concentrations; however, other changes that accompany superovulation may also impact endometrial receptivity. One such factor may be subtle increases in P levels during the late follicular phase (1, 2). These P elevations are important as they prognosticate suboptimal clinical outcomes (3–5).

Early literature describing these elevations assumed that they were part of the spectrum of early and excessive LH effect on the maturing follicles. As such, they were termed premature luteinization (6, 7). There are two potential sources of LH, either exogenous from injectable gonadotropins or endogenous from the pituitary. Given the near universal practice of administering a GnRH agonist or a GnRH antagonist during stimulation, premature LH surges should be uncommon and pointed to exogenous LH as a possible causative agent.

More recently, studies have compared the prevalence of premature P elevations in patients receiving pure FSH stimulations to those receiving hMG alone (8, 9). Given that the hMG group received pharmacologic levels of LH stimulation, it might seem intuitive that they would have had a higher prevalence of premature P elevations. In fact, those women receiving hMG had a lower risk. This suggests that a relationship between LH and premature P elevations is complex and may not be wholly attributed to excessive stimulation.

These data suggest that optimizing the effect of LH during COH may be dependent on both the level of exogenous LH and FSH that are administered (10–12). The impact of different administered LH-to-FSH ratios during stimulation have not been studied in detail. To that end, this study seeks to determine whether different ratios of LH:FSH activity in stimulation protocols impact the risk for premature P elevation and whether those differences also apply to different ovarian response groups.

MATERIALS AND METHODS

Population

In this retrospective cohort study, all patients attempting conception through IVF from October 1999 to May 2013 were reviewed. Patients undergoing their first IVF cycle in this program and whose superovulation protocol used either GnRH agonist down-regulation or a GnRH antagonist were selected for further study. Patients using microdose GnRH agonist flare protocols were excluded, as there was no mechanism to quantify the contribution of endogenous LH release on the overall level of LH stimulation. Patient characteristics and demographic information were recorded. Response to stimulation was measured by the number of mature metaphase II oocytes obtained after vaginal oocyte retrieval. This retrospective analysis of data was Institutional Review Board approved by Western Institutional Review Board, protocol 20021333.

Study Design

The purpose of this study was to determine whether variations in the relative amounts of exogenous LH and FSH impact the risk for significant P elevations before the administration of hCG to induce final oocyte maturation. The ratio of exogenous LH to FSH was calculated based on the total dose of each medication administered throughout the cycle. Starting dosages and protocol were selected by the primary physician in relation to patient characteristics, such as age, ovarian reserve, and prior history, but were also guided by insurance restrictions. Overall medication dosages maintained a relatively constant ratio throughout the stimulation as per practice standards. Although doses infrequently changed throughout the cycle, this metric was believed to be the most reflective of total LH exposure. Serum levels of LH and FSH were not routinely measured during cycles.

The quantity of FSH was expressed in international units and was based on total FSH dose without regard to whether it was from a pure FSH preparation (recombinant or purified), an hMG preparation, or a combination of the two. The quantity of LH was also expressed in international units when using hMG or recombinant LH. One ampule of hMG was considered to have 75 IU of LH activity. In the case of low dose hCG administration, 10 IU was designated to be equivalent to 75 IU of LH. Starting and total doses of exogenous LH and FSH were recorded for each included cycle. The LH-to-FSH ratio was calculated by simply dividing the total LH dose by the total FSH dose administered. Serum P levels were measured throughout the cycle, and the P level on the day of hCG administration was also documented to assess for clinically significant late follicular P elevations.

Assay

Serum P was determined using the Immulite 2000 immunoassay system (Siemens). The interassay coefficient of variation