Serum Progesterone Is Lower in Ovarian Stimulation With Highly Purified HMG Compared to Recombinant FSH Owing to a Different Regulation of Follicular Steroidogenesis: A Randomized Controlled Trial

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ABSTRACT

Serum progesterone levels following ovarian stimulation (OS) are associated with the cycle result in terms of ongoing pregnancy and live birth rate, with levels above a certain threshold associated with poorer results. An increase in progesterone is positively associated with the ovarian response and the FSH dose administered during OS; however, this mechanism is not well understood. It has been observed that progesterone levels after stimulation are higher when recombinant FSH (r-FSH) is used for OS compared with highly purified HMG (hp-HMG). Whether this differential response to gonadotropins is due to greater folliculogenesis or differential steroidogenesis when using r-FSH is unknown.

This parallel, single-center, open-label, prospective randomized study aimed to determine if the use of hp-HMG leads to lower serum progesterone in the follicular phase compared with r-FSH cycles through a different regulation of follicular steroidogenesis in women undergoing OS for oocyte donation. Women aged 18–35 years with a body mass index (BMI) <25 kg/m^2, regular menstrual cycle, normal ovarian reserve (AMH 10–30 pMol/L), and a normal karyotype undergoing OS for oocyte donation were randomized to r-FSH or hp-HMG. Transvaginal ultrasound and blood sampling were performed for ovarian response monitoring on days 1, 4, 6, and 8 of stimulation and on the day of trigger. Follicular volume was calculated using ultrasound measurement, and the total follicle volume was the sum of all individual volumes recorded. The largest follicle was aspirated for follicular fluid analysis, and hormone measurements were conducted in serum and follicular fluid.

A total of 112 patients were randomized (56 per group), 111 underwent OS, and 104 completed treatment (52 per group). Subjects in both group has comparable age, BMI, AMH levels, total dose of gonadotropins, length of stimulation, total follicular volume, and oocyte yield. No differences were observed in serum FSH and LH between groups. Serum progesterone on the day of trigger was 0.45 ± 0.26 in the hp-HMG group compared with 0.74 ± 0.52 in the r-FSH group ($P = 0.001$), and this difference was also significant on day 6 and 8 of stimulation. The progesterone:pregnenolone ratio was increased in the r-FSH group on stimulation day 8 and the day of trigger ($P = 0.019$). Serum androstenedione on the day of trigger was 3.0 ± 1.4 in the hp-HMG group compared with 2.4 ± 1.1 in the r-FSH group ($P = 0.015$), and this difference was also significant on day 8 of stimulation. The androstenedione:pregnenolone ratio was significantly higher in the hp-HMG group on stimulation days 6 and 8 and triggering. Polynomial interpolation analysis showed the total exposure to each hormone across the follicular phase was higher for progesterone in the r-FSH group ($P = 0.016$), specifically from day 6 to triggering ($P = 0.006$) but not in the first half of stimulation ($P = 0.782$). Follicular fluid levels of FSH, LH, E2, DHEA, androstenedione, and testosterone were significantly higher in the hp-HMG than in the r-FSH group.

The results of this study reveal different endocrine profiles across the follicular phase based on the use of r-FSH or hp-HMG. The androstenedione pathway was enhanced by hp-HMG, leading to lower serum progesterone at the end of the cycle, whereas r-FSH promoted the conversion of pregnenolone to progesterone causing higher follicular phase progesterone levels.

EDITORIAL COMMENT

(Ovarian stimulation is the cornerstone of assisted reproduction, in that it enables retrieval of multiple, meiotically competent oocytes, to overcome the inherent inefficiency of human

reproduction. Ovarian stimulation, however, increases not only circulating estradiol, but also progesterone levels, with concomitant reduction in pregnancy rates, presumably via detrimental effects on endometrial receptivity. Elevation of progesterone is proportional to ovarian response and FSH dose during OS, but the mechanism underlying this relationship remains poorly understood. Intriguingly, stimulation with r-FSH produces higher progesterone levels compared with hp-HMG. This r-FSH effect could be mediated via increased folliculogenesis and/or differential steroidogenesis. This study tested the hypothesis that hp-HMG leads to lower serum progesterone in the follicular phase compared with r-FSH through differential regulation of follicular steroidogenesis. Oocyte donors 18–35 years old with a BMI <25 kg/m^2, regular menstrual cycles, and normal ovarian reserve were randomized to OS with r-FSH or hp-HMG. Transvaginal ultrasound and blood sampling were performed on days 1, 4, 6, and 8 of stimulation and on day of trigger. Follicular volume was calculated using ultrasound measurement, and total follicle volume measured. The largest follicle was aspirated for follicular fluid analysis, and hormones measured in serum and follicular fluid. One hundred twelve subjects were randomized, 111 underwent OS, and 104 completed the study. No differences were observed in serum FSH and LH between groups. Serum progesterone levels on day of trigger (0.45 ± 0.26 in the hp-HMG group vs 0.74 ± 0.52 in the r-FSH group), as well as on days 6 and 8 of stimulation differed significantly between the groups. R-FSH stimulation increased the progesterone:pregnenolone ratio by stimulation day 8 and day of trigger. hp-HMG increased serum androstenedione on day of trigger (3.0 ± 1.4 vs 2.4 ± 1.1) and on day 8. The androstenedione:pregnenolone ratio was significantly higher in the hp-HMG group on stimulation days 6 and 8 and trigger. Polynomial interpolation analysis showed the total exposure to each hormone across the follicular phase was higher for progesterone in the r-FSH group (P = 0.016), specifically from day 6 to trigger (P = 0.006) but not in the first half of stimulation (P = 0.782). Follicular fluid levels of FSH, LH, E2, DHEA, androstenedione, and testosterone were significantly higher in the hp-HMG than in the r-FSH group. This study reports superior endocrine profiles across the follicular phase with hp-HMG versus rFSH stimulation. Hp-hMG's enhancement of the androstenedione pathway produces lower serum progesterone toward cycle end, whereas r-FSH increases follicular phase progesterone levels by promoting conversion of pregnenolone to progesterone. This study provides a plausible mechanism to explain the improved outcomes associated with OS using hp-HMG.—DK)