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Abstract title:

Follicular steroidogenesis in GnRH antagonist ovarian stimulation cycles with r-FSH vs. hp-HMG. A randomized controlled trial

E. Bosch Aparicio¹, P. Alamá¹, J.L. Romero¹, M. Mari¹, E. Labarta¹.

¹IVI-RMA, Human Reproduction, Valencia, Spain.

Study question:

Does ovarian stimulation with hp-HMG protect from elevated Progesterone in the follicular phase compared to r-FSH cycles through a different follicular steroidogenesis?

Summary answer:

Hp-HMG enhanced the Δ_4 pathway from Pregnenolone to Androgens, while r-FSH promoted the conversion of Pregnenolone to Progesterone leading to higher follicular phase serum Progesterone

What is known already:

Elevated Progesterone in the follicular phase has been related to lower clinical outcome in fresh IVF cycles. Progesterone levels are positively correlated to ovarian response, and some studies have shown that when r-FSH alone is used for ovarian stimulation, serum P levels the day of triggering are higher than when hp-HMG is given. Whether this is due to a lower ovarian response in hp-HMG cycles or to a different follicular steroidogenesis between both ovarian stimulation regimens has not been well characterized

Study design, size, duration:

Randomized controlled trial including 110 oocyte donors undergoing ovarian stimulation with GnRH antagonists and 225 IU/day of rFSH (n=56) or hp-HMG (n=54) in a University affiliated private infertility clinic. Subjects were recruited between October 2016 and June 2018

Participants/materials, setting, methods:

Women aged 18 to 35, with a regular menstrual cycle (25-35 days) and normal ovarian reserve (AMH=10-30 pMol/L) undergoing ovarian stimulation for oocyte donation. Serum FSH, LH, Estradiol, Estrone, Progesterone, Pregnenolone, 17-OH-Progesterone, Androstenedione, Dehydroepiandrosterone, and Testosterone, were determined on stimulation days 1, 4, 6, 8 and triggering and in follicular fluid. Samples were frozen at -20°C until determination. Total exposures across the follicular phase were compared by polynomial extrapolation

Main results and the role of chance:

Subjects of both groups were comparable for age, body mass index and AMH levels. Ovarian response was also similar: 17.5 ± 7.9 vs. 16.5 ± 7.5 oocytes with r-FSH and hp-HMG respectively ($p=0.49$) Serum P (ng/mL) the day of trigger was 0.46 ± 0.27 in the hp-HMG group vs. 0.68 ± 0.50 in the r-FSH group ($p=0.010$). Differences were also significant on stimulation days 6 and 8. The Pregnenolone:Progesterone ratio was significantly increased in the r-FSH group from stimulation day 8 to the day of trigger ($p=0.019$). Serum Androstenedione (ng/mL) the day of trigger was 3.0 ± 1.4 in the hp-HMG group vs. 2.4 ± 1.1 in the r-FSH group ($p=0.015$). Differences were also significant on stimulation day 8. The Pregnenolone:Androstenedione ratio was significantly higher in the hp-HMG group ($p=0.012$). There were no other significant differences between both groups for any other hormones in any stimulation day. Follicular fluid E2, FSH, LH, Dehydroepiandrosterone, Androstenedione and Testosterone were significantly higher in the hp-HMG group. No differences were observed for Progesterone, Estrone, 17-OH Progesterone and Pregnenolone. The multivariable regression analysis showed that ovarian stimulation with r-FSH remained as a significant factor for elevated serum P on stimulation day 8 and triggering after adjusting for age, ovarian response and body mass index

Limitations, reasons for caution:

All women included in the study were young, non infertile, had a normal body mass index and a good ovarian reserve. Findings might be different in other patients' subpopulations

Wider implications of the findings:

The findings of the present study suggest that stimulation with hp-HMG may prevent for Progesterone elevation at the end of the follicular phase because of a different follicular steroidogenesis, regardless of ovarian response. This should be considered particularly in high responders if a fresh embryo transfer is planned

Trial registration number:

NCT02738580

Keywords:

Progesterone

Ovarian stimulation