Early luteal phase endocrine profile is affected by the mode of triggering final oocyte maturation and the luteal phase support used in recombinant follicle-stimulating hormone–gonadotropin-releasing hormone antagonist in vitro fertilization cycles

Human M. Fatemi, M.D., Ph.D.,[a] Nikolaos P. Polyzos, M.D., Ph.D.,[a] Inge van Vaerenbergh, M.Sc.,[b] Claire Bourgain, M.D., Ph.D.,[b] Christophe Blockeel, M.D., Ph.D.,[a] Birgit Alsbjerg, M.D.,[c] Evangelos G. Papanikolaou, M.D., Ph.D.,[a] and Peter Humaidan, M.D., M.Sc.[c,d]

[a] Center for Reproductive Medicine and [b] Reproductive Immunology and Implantation Unit, Dutch-Speaking Free University, Brussels, Belgium; [c] Fertility Clinic, Skive Regional Hospital, Skive, and [d] Faculty of Health, Aarhus University, Aarhus, Denmark

Objective: To assess endocrine differences during early luteal phase according to mode of triggering final oocyte maturation with or without luteal phase support (LPS).
Design: A prospective randomized study.
Setting: University center for reproductive medicine.
Patient(s): Four oocyte donors each underwent four consecutive cycles.
Intervention(s): To avoid interpatient variation, each donor underwent the same stimulation regimen. However, different modes of triggering final oocyte maturation and LPS were administered: A) 10,000 IU hCG and standard LPS; B) GnRH agonist (GnRHa; 0.2 mg triptorelin), and 35 hours later 1,500 IU hCG, and standard LPS; C) GnRH agonist (0.2 mg triptorelin) and standard LPS; and D) GnRH agonist (0.2 mg triptorelin) without LPS.
Main Outcome Measure(s): Blood sampling was performed on the day of ovulation trigger, ovulation trigger + 1 day, and ovum pick-up + 5 days. Serum E_2, FSH, LH, and P were measured.
Result(s): The early luteal phase steroid levels following GnRHa trigger and modified luteal phase support (B) were similar to those seen after hCG trigger (A). However, significant differences were seen between groups A and B compared with C and D, as well as between groups C and D.
Conclusion(s): Administration of a single bolus of GnRHa effectively induced LH and FSH surges in oocyte donors stimulated with recombinant FSH and cotreated with a GnRH antagonist. However, gonadotropin and steroid levels differed significantly according to the type of luteal phase support used after GnRHa trigger.
European Community Clinical Trial System (EudraCT) Number: 2009-009429-26. (Fertil Steril® 2013;100:742–7. ©2013 by American Society for Reproductive Medicine.)
Key Words: Progesterone, luteal phase, GnRH antagonist, GnRH agonist trigger, hCG

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/fatemihm-luteal-phase-gnrh-agonist-trigger/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received January 16, 2013; revised May 15, 2013; accepted May 17, 2013; published online June 24, 2013.
H.M.F. has received honoraria as a speaker for Ferring, Merck Serono, Merck, Sharp & Dohme (MSD), IBSA, and Actavis; served as an advisory board member for MSD, received travel grants from Merck Serono, Ferring; and MSD and grants from MSD. N.P.P. has nothing to disclose. I.v.V. received a travel grant from MSD Belgium to present a part of this work at ESHRE, Istanbul, 2012. C.B. has nothing to disclose. C.B. has nothing to disclose. B.A. has nothing to disclose. E.G.P. has received payment for lectures from MSD and Merck Serono. P.H. has received a lecture honorarium from Merck Serono, MSD Denmark, and Nordic Infucare.
Supported by Merck, Sharp & Dohme/Belgium, a subsidiary of Merck & Co.
Reprint requests: Human M. Fatemi, M.D., Ph.D., Department of Reproductive Medicine, Academic Hospital at the Dutch-Speaking Brussels Free University, Laarbeeklaan 101, 1090 Brussels, Belgium (E-mail: hmousavi@uzbrussel.be).

Fertility and Sterility® Vol. 100, No. 3, September 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.05.028

In assisted reproductive technology (ART), a bolus of hCG is usually administered to mimic the midcycle surge of LH activity for final oocyte maturation. Although activating the same receptor, differences exist between LH and hCG, mainly in the half-life of <60 minutes for LH versus >24 hours for hCG (1, 2). Therefore, the prolonged half-life of hCG and the sustained luteotropic activity increases the risk of the ovarian hyperstimulation syndrome (OHSS) in patients with hyperresponse to ovarian stimulation. Moreover, a bolus of hCG provides an LH-like activity only, in contrast to the midcycle surge of FSH as well as LH (3). Finally, recent data have suggested a possible negative impact of a bolus of hCG on oocytes son endometrial receptivity (4).

Following the introduction of the GnRH antagonist protocol, it became possible again in ART to use GnRH agonists (GnRHa) to trigger final oocyte maturation. Thus, an injection of GnRHa will dislocate the GnRH antagonist from the GnRH receptors in the pituitary, eliciting a surge (flare-up) of LH and FSH that effectively induces final oocyte maturation and ovulation (5–7). However, the first large randomized clinical trial reported a very poor reproductive outcome when GnRHa was used to trigger final oocyte maturation (8). The reason for the poor outcome, despite standard luteal phase support (LPS) was interpreted as a severe luteal phase insufficiency caused by low levels of endogenous LH and P (9–12). Subsequently, through a series of trials, efforts were made to overcome the luteal phase insufficiency after GnRHa trigger by supplementing the early luteal phase with LH (13) or LH-like activity in the form of a small bolus (1,500 IU) of hCG administered immediately after oocyte retrieval (9–11). In addition, patients received vaginal micronized P and oral E_2. With this new concept of "modified LPS" after GnRHa trigger, similar delivery rates between hCG triggering and GnRHa triggering were obtained in addition to a reduction in the OHSS rate and the retrieval of more mature oocytes (11).

Because the cause of the previously reported luteal phase defect after GnRHa trigger was thought to be caused mainly by a lack of LH activity (14), the aim of the present study was, among others, to assess the LH levels in the early luteal phase of the groups compared and to verify whether the LH suppression in the GnRHa-triggered group would be more severe compared with the hCG-triggered/supported cycles.

A total of four different protocols were explored. To avoid any interindividual variation, each donor underwent four consecutive oocyte donation cycles within 1 year.

MATERIALS AND METHODS

Patient Population

Four oocyte donors underwent four oocyte donation cycles within 1 year (2010–2011); thus a total of 16 oocyte donation cycles were analyzed. The donors were randomized to different models of final oocyte maturation and LPS. The endometrial gene expression profiles analyzed from this study have previously been published (15). In brief, the inclusion criteria were: presence of at least five antral follicles in each ovary, normal chromosomal analysis, normal serologic findings within 3 months before stimulation, and normal vaginal ultrasound.

The exclusion criteria were: presence of polycystic ovarian syndrome diagnosed according to the revised Rotterdam criteria (16), presence of endometriosis American Fertility Society classification stage >2, age ≥36 years, ultrasonographically verified hydrosalpinges, and presence of any intrauterine contraceptive device and/or oral contraceptive use in the 6 months before initiation of stimulation.

The research project was approved by the local Institutional Review Board and registered in the European Community Clinical Trial System (EudraCT): number 2009-009429-26, protocol number 997 (P06034).

Protocols

After a vaginal ultrasound examination and the confirmation of baseline FSH, LH, P, and E_2 levels, stimulation commenced in the afternoon of day 2 of the cycle with 200 IU recombinant FSH (Puregon; MSD). The FSH dose was fixed until day 5 of the stimulation, after which the FSH dose was adjusted according to the ovarian response. Daily GnRH antagonist cotreatment (0.25 mg Orgalutran; MSD) commenced from the morning of day 5 of stimulation. Final oocyte maturation was induced as soon as three or more follicles reached a size of ≥17 mm. Randomization to one of four protocols through a computer-generated list took place on the day of triggering of final oocyte maturation. Once a patient had been allocated to one protocol, that protocol was automatically deleted from the computer-generated list. Oocyte retrieval was carried out 34 hours later. The gynecologist in charge of the oocyte retrieval was blinded to the treatment allocation.

The same donor underwent four stimulation protocols using different modes of final oocyte maturation and luteal phase support (LPS): A) 10,000 IU hCG and standard LPS; B) GnRHa (0.2 mg triptorelin) followed by 1,500 IU hCG 35 hours after triggering of final oocyte maturation and standard LPS (modified LPS); C) GnRHa (0.2 mg triptorelin) with standard LPS; and D) GnRHa (0.2 mg triptorelin) without any type of LPS.

Luteal Phase Support

The standard LPS for GnRHa-triggered GnRH antagonist cycles consisted of vaginal administration of 600 mg natural micronized P in three separate doses (Utrogestan; Besins-Iscovesco) and 4 mg daily E_2 valerate per os (Progynova; Schering), starting 1 day after oocyte retrieval and continuing until the day of blood sampling, i.e., ovum pick up day + 5 (OPU+5).

Blood Sampling

Blood sampling was performed on 3 days: day of ovulation trigger, ovulation trigger + 1, and OPU+5. Sera were analyzed immediately locally.

Serum LH, FSH, hCG, E_2, and P were assessed by a central laboratory using the automated Elecsys immunoanalyzer (Roche Diagnostics). Intra-assay and interassay coefficients of variation were, respectively, <3% and <4% for LH, <3% and <6% for FSH, <5% and <7% for hCG, <5% and <10% for E_2, and <3% and < 5% for P. The upper limit of P level measured was 60 μg/L.