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.

Ultrasound Assessment

Ultrasound was performed on day 6 of stimulation and then as necessary to ensure that final oocyte maturation was triggered as soon as the patient had at least three follicles measuring ≥17 mm.

Statistical Methods

Mean values and SDs were calculated for FSH, LH, E_2, and P on the day of ovulation triggering, ovulation triggering + 1 and OPU+5. Normality of the distribution was assessed with the Shapiro-Wilk test. Mean hormonal values were compared with a one-way analysis of variance analysis or Kruskal-Wallis test based on the normality of the distribution, with a level of significance at 0.05. For pairwise comparisons of non-normally distributed values, we used the Mann-Whitney *U* test, which yields results identical to the Kruskal-Wallis test for two independent samples. When multiple comparisons were performed, Bonferroni correction for multiple comparisons was used to test differences between protocols. All analyses were performed in SPSS 20.0 statistical software.

RESULTS

Early Luteal Phase Endocrine Profile

First sampling on the day of ovulation trigger. The endocrine profile (E_2, P, LH, and FSH) did not differ between all protocols compared during the first sampling (Supplemental Table 1, available online at fertstert.org).

Second sampling on ovulation trigger + 1. The endocrine profiles (E_2, P, LH, and FSH) measured during the second sample were similar in all GnRHa-triggered cycles (i.e., groups B, C, and D). The hCG-triggered group (A) had similar E_2 (P=.844) and P (P=.087) levels (Figs. 1 and 4; Supplemental Table 1) compared with all GnRHa-triggered groups (B, C, and D). FSH values were significantly lower in hCG-triggered cycles (A), 9.3 ± 2.7 IU/L, compared with GnRHa-triggered cycles without LPS (D), 25.4 ± 4.2 IU/L (P=.003), and GnRHa-triggered cycles with conventional LPS (C), 24.3 ± 0.9 IU/L (P<.0001). Although serum FSH levels were higher in GnRHa trigger + modified LPS (B), 17.1 ± 10.2 IU/L compared with hCG trigger, the difference did not reach statistical significance (P=.074) (Fig. 2; Supplemental Table 1).

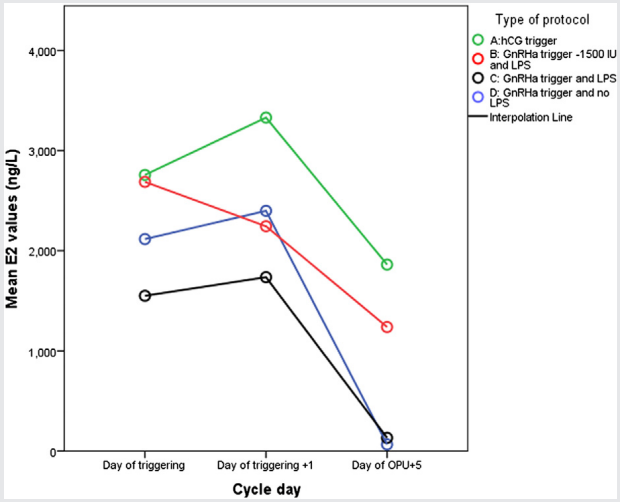
LH levels differed between the hCG-triggered group (A) and all GnRHa-triggered groups (B, C, and D). Group A had statistically significantly lower LH levels, 2.2 ± 2.0 IU/L, compared with cycles with GnRHa trigger and modified LPS (B), 27.4 ± 22.7 IU/L (P=.011), GnRHa trigger without LPS (D), 56.2 ± 23.4 IU/L (P=.001), and GnRHa trigger with conventional LPS (C), 43.8 ± 9.8 IU/L (P<.0001; Fig. 3; Supplemental Table 1).

Third sampling on OPU + 5. E_2 values were similar between hCG-triggered cycles (A) and GnRHa-triggered cycles with modified LPS (B): 1,862 ± 1,105 ng/L versus 1,238 ± 733 ng/L, respectively (P=1.00). In contrast, E_2 levels were significantly lower in GnRHa-triggered cycles with standard LPS (C), 132 ± 83 ng/L compared with hCG trigger (A) and GnRHa trigger with modified LPS (B): *P* values <.0001 and .001, respectively. GnRHa trigger without LPS (D) resulted in significantly lower E_2 levels, 66 ± 51 ng/L compared with both hCG (A) and GnRHa trigger with modified LPS (B): *P* values .001 and 0.011, respectively (Fig. 1).

Serum FSH levels were significantly lower in hCG-triggered cycles (A), 1.1 ± 0.2 IU/L, compared with GnRHa trigger without LPS (D), 2.2 ± 0.4 IU/L (P=.002) and GnRHa trigger with standard LPS (C), 1.6 ± 0.4 IU/L (P=.006), but not compared with GnRHa trigger with modified LPS (B), 1.3 ± 0.3 IU/L (P=.984; Fig. 2, Supplemental Table 1).

Moreover, LH levels were similar between hCG trigger (A) and GnRHa trigger with modified LPS (B): 0.3 ± 0.2 IU/L versus 0.1 ± 0 IU/L (P=1.00). In contrast, GnRHa trigger with modified LPS (B) resulted in a significantly lower LH level, 0.1 ± 0 IU/L, compared with GnRHa trigger with

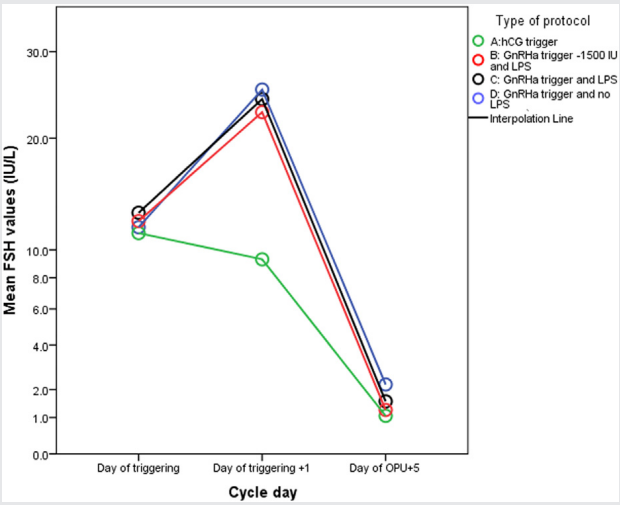
FIGURE 1



Mean E_2 values of the four protocols. GnRHa = GnRH agonist; LPS = luteal phase support.

Fatemi. Endocrine profile of early luteal phase. Fertil Steril 2013.

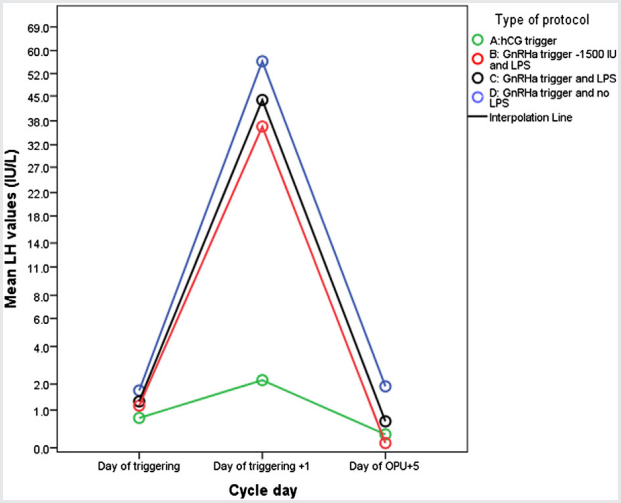
FIGURE 2



Mean FSH values of the four protocols. Abbreviations as in Figure 1.

Fatemi. Endocrine profile of early luteal phase. Fertil Steril 2013.

FIGURE 3



Mean LH values of the four protocols. Abbreviations as in Figure 1.

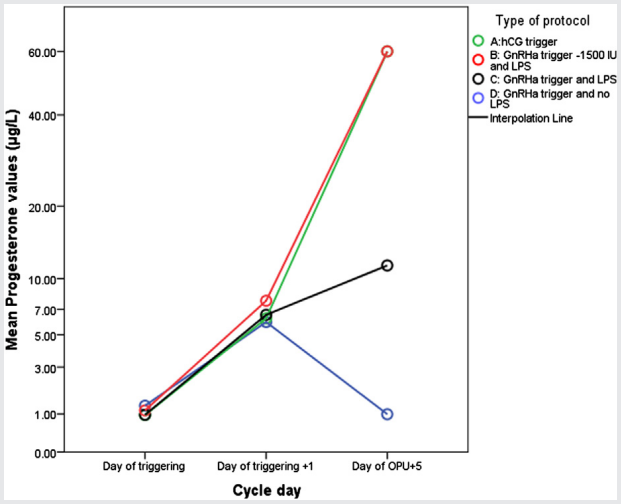
Fatemi. Endocrine profile of early luteal phase. Fertil Steril 2013.

standard LPS (C), 0.7 ± 0.7 IU/L (P=.024) and without LPS (D), 1.9 ± 0.8 IU/L (P=.001; Fig. 3, Supplemental Table 1).

P values were high in hCG-triggered cycles (A) and GnRHa-triggered cycles with modified LPS (B): 60 ± 0 μg/L and 60 ± 0 μg/L, respectively (P=1.00). In contrast, GnRH trigger without LPS (D) induced significantly lower P levels, 0.99 ± 0.61 μg/L, compared with hCG-triggered cycles (A), 60 ± 0 μg/L (P<.0001), and GnRHa trigger with modified LPS (B), 60 ± 0 μg/L (P<.0001). In addition, P levels were significantly lower in GnRHa-triggered cycles with standard LPS (C), 11.49 ± 3.17 μg/L, compared with hCG-triggered cycles (A), 60 ± 0 μg/L (P=.001), and GnRHa-triggered cycles with modified LPS (B), 60 ± 0 μg/L (P<.0001). Finally, P levels did not differ significantly between groups C and D: 11.49 ± 3.17 μg/L versus 0.99 ± 0.61 μg/L (P=1.00; Fig. 4; Supplemental Table 1).

Taken together, there were no significant differences in all GnRHa trigger protocols (groups B, C, and D) until the third measurement on OPU+5.

FIGURE 4



Mean P values of the four protocols. Abbreviations as in Figure 1.

Fatemi. Endocrine profile of early luteal phase. Fertil Steril 2013.

DISCUSSION

This study performed in an oocyte donor model revealed significant differences in the early luteal phase endocrine profile according to the mode of triggering final oocyte maturation and LPS administered. The hypothesis that LH suppression in the GnRHa-triggered group would be more severe compared with the hCG-triggered/supported cycles was rejected.

The four donors each underwent four consecutive stimulation cycles, using the same protocol for stimulation but different protocols for triggering of final oocyte maturation and LPS, mimicking the conditions previously described in randomized controlled trials: A) 10,000 IU hCG to trigger final oocyte maturation followed by standard LPS; B) GnRHa trigger followed by modified LPS (11); C) GnRHa trigger followed by standard LPS (8); and D) GnRHa trigger without LPS (17). Whereas groups A and B were similar in early luteal phase serum steroid levels (P and E_2) throughout the measurements, significant differences were seen between groups A and B compared with C and D, as well as between groups C and D.

Importantly, the intervals between stimulation cycles were 2–3 months. Therefore, a possible carryover effect from a previous stimulation can be excluded, because on the day of final oocyte maturation all of the measured variables were similar and significant differences were observed only during the luteal phase.

The reason for the luteal phase insufficiency seen after controlled ovarian stimulation seems to be the multifollicular development achieved during the follicular phase, resulting in supraphysiological luteal levels of P and E_2 which inhibit LH secretion by the pituitary via negative feedback actions at the level of the hypothalamic-pituitary axis (17–21). Endogenous LH—and endogenous or exogenous LH activity (hCG)—plays a crucial role during the luteal phase, not only for the function, growth, and maintenance of the corpus luteum (22), but also for the up-regulation of growth factors (23, 24) and cytokines, e.g., leukemia inhibitory factor (LIF), important for implantation (25). During the natural cycle, endogenous luteal LH levels are sufficiently high to secure these functions (21). In contrast, after ovarian stimulation for IVF, early luteal LH levels are significantly lower. However, the early luteal actions of LH would be covered by the bolus of hCG (5,000–10,000 IU) routinely used for triggering final oocyte maturation. Later, hCG gradually produced by the implanting embryo, detectable in maternal serum as early as the 8th day after ovulation (26), would cover the LH deficit. It is during this "overlapping" period that LPS with P is mandatory after ovarian stimulation for IVF to sustain an early pregnancy (14).

Induction of final oocyte maturation with a bolus of GnRHa in patients undergoing ovarian stimulation for IVF could be considered to be more physiologic, because the elicited surge mimics the natural cycle surge of gonadotropins, consisting of an FSH as well as an LH surge.

Beckers et al. (17) explored the endocrine profiles and reproductive outcome of the nonsupplemented luteal phase in IVF patients cotreated with a GnRH antagonist phase after ovulation trigger with either hCG, LH, or GnRHa. Low pregnancy rates (overall 7.5%) were seen in all groups, and it was concluded that the nonsupplemented luteal phase was insufficient regardless of the mode of triggering final oocyte maturation, though the luteal phase was less disturbed in hCG triggered patients. The early luteal endocrine profile of group D in the present study corroborates the profile reported by Beckers et al. (17) with high FSH and LH levels on day of trigger + 1—indicative of the surge elicited by the bolus of GnRHa—and low P and E_2 levels on OPU+5.

It is interesting that at OPU+5, LH levels were significantly higher in groups C and D than in groups A and B (Fig. 3). The most plausible reason for the severely suppressed LH levels observed in groups A and B seem to be the supraphysiological luteal steroid level—mainly P—induced by the ovarian stimulation with exogenous gonadotropins and hCG trigger for final oocyte maturation exerting a negative feedback on the hypothalamic-pituitary axis level, leading to a reduction in LH secretion by the pituitary (27–29). Filicori et al. (28) clearly demonstrated that to maintain a constant steroid production, it is crucial to have a certain amplitude and frequency of LH during the luteal phase.

As observed in the present trial and previously by Fauser et al. (30), in GnRHa-triggered antagonist cycles without hCG for LPS, the luteal phase steroid levels are closer to the physiologic range compared with hCG-triggered cycles. Thus, the LH levels in groups C and D were significantly less suppressed compared with groups A and B. The question remains of why the significantly higher LH levels in groups C and D were not sufficient to stimulate the multiple corpora lutea to produce the needed steroids to rescue the luteal phase?

In a normal menstrual cycle, the midcycle LH and FSH surge, lasting 48 hours, is a complex and carefully orchestrated event elicited in the late follicular phase by persistently elevated estrogen concentrations in combination with a small but distinct rise in P (3). The spontaneous LH surge of the natural menstrual cycle is characterized by a short ascending phase of ~14 hours, a peak plateau of 20 hours, and a descending phase of 20 hours (6).

However, the profile of the GnRHa-induced LH surge in gonadotropin-stimulated cycles is significantly different from the average physiologic preovulatory gonadotropin surge. The GnRHa-induced LH surge has been described to be similar in magnitude to the natural LH surge but the ascending phase is significantly reduced, i.e., to <4 hours (6). Increasing the GnRHa dose or repeated administration fail to increase the LH/FSH surge in gonadotropin-stimulated cycles (31).

As has been established in primates as well as in humans, the duration of the LH/FSH surge is critical to a normal luteal function (32, 33). A relatively short LH surge results in normal oocyte maturation and ovulation, but the luteal phase length is reduced significantly, implying that luteal support is required under these conditions. An LH increment of too short a duration prevents the granulosa cells from completing luteinization, leading to a corpus luteum with impaired secretory function and a shortened lifespan (31).

Humaidan et al. (8) used standard LPS after GnRHa trigger under the hypothesis that the LPS would solve the problems previously encountered by Beckers et al. (17). However, the study had to be closed early because of an extremely low ongoing pregnancy rate. The set-up of that study was used in the present study group C, showing the initial flare-up effect of the GnRHa trigger regarding FSH and LH levels followed by very low E_2, FSH, and LH levels on OPU+5 similar to those seen without standard LPS (group D). On that same day, the P levels were significantly higher than without supplementation (11 ng/mL). However, this P level accounted for the exogenous micronized P supplementation only, known to be ~11.9 ng/mL after a dosage of 600 mg/d (34), indicative of a complete corpus luteum insufficiency.

In a follow-up, study Humaidan et al. (11) used so-called modified LPS after GnRHa trigger, including a small bolus of LH activity (1,500 IU hCG) administered on OPU to cover the early luteal LH insufficiency. Patients also received standard LPS. That protocol was used in group B of the present study, showing now a significant increase in E_2 levels on OPU+5 as well as P levels similar to those seen after trigger with 10,000 IU hCG (group A). From a clinical point of view, the protocol resulted in delivery rates similar to those seen after hCG trigger (11), confirming that the luteal phase insufficiency caused by GnRHa trigger alone or followed by standard LPS was caused by low luteal LH levels.

Finally, group A represents the criterion standard trigger with 10,000 IU hCG, resulting in low luteal LH and FSH levels (day of trigger + 1) due to a negative feedback action on the pituitary caused by the prolonged LH-like activity induced by a bolus of 10,000 IU hCG with high E_2 and P levels. This negative feedback effect is still visible on OPU+5, mainly owing to increasing P levels. Therefore, although LH levels are very low, that has no negative impact, because hCG covers for the LH deficiency and secures the function of the corpus luteum and growth factors and cytokines involved in early implantation.

Interestingly, the findings of the present study correlate with the findings of a recent paper exploring the endometrial gene expression pattern in relation to different trigger and luteal phase protocols (15). Significant differences in endometrial gene expression were seen related to type of ovulation trigger and LPS. However, the gene expression after GnRHa trigger followed by modified LPS (group B) was similar to that of hCG trigger (group A).

In conclusion, gonadotropin and steroid levels differed significantly between groups according to the mode of trigger and LPS administered. To rescue the luteal phase, it is crucial to have a certain amplitude and frequency of LH secretion during ovulation and the luteal phase. In this study, significantly higher luteal phase LH values were measured in the GnRHa-triggered cycles without hCG administration for LPS, which might be a reason to reconsider and question the etiology of the luteal phase defect seen in all stimulated and triggered IVF cycles. Thus, effects on the dynamics of the pituitary-ovarian axis during ovulation and the luteal

phase require further evaluation, and future studies should focus on mimicking natural ovulation to possibly attempt to correct the luteal phase defect seen after controlled ovarian stimulation.

Acknowledgments: The authors thank Mrs. Andrea de Brabander and Mrs. Elsie Nullens for their excellent help during all phases of this study.

REFERENCES

1. Yen SS, Llerena O, Little B, Pearson OH. Disappearance rates of endogenous luteinizing hormone and chorionic gonadotropin in man. J Clin Endocrinol Metab 1968;28:1763–7.
2. Damewood MD, Shen W, Zacur HA, Schlaff WD, Rock JA, Wallach EE. Disappearance of exogenously administered human chorionic gonadotropin. Fertil Steril 1989;52:398–400.
3. Hoff JD, Quigley ME, Yen SS. Hormonal dynamics at midcycle: a reevaluation. J Clin Endocrinol Metab 1983;57:792–6.
4. Evans J, Salamonsen LA. Too much of a good thing? Experimental evidence suggests prolonged exposure to hCG is detrimental to endometrial receptivity. Hum Reprod 2013;28:1610–9.
5. Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. J Clin Endocrinol Metab 1990;71:918–22.
6. Itskovitz J, Boldes R, Levron J, Erlik Y, Kahana L, Brandes JM. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. Fertil Steril 1991;56:213–20.
7. Yding AC, Westergaard LG, Figenschau Y, Bertheussen K, Forsdahl F. Endocrine composition of follicular fluid comparing human chorionic gonadotrophin to a gonadotrophin-releasing hormone agonist for ovulation induction. Hum Reprod 1993;8:840–3.
8. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grondahl ML, Westergaard L, et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod 2005;20:1213–20.
9. Humaidan P, Bungum L, Bungum M, Yding AC. Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. Reprod Biomed Online 2006;13:173–8.
10. Humaidan P. Luteal phase rescue in high-risk OHSS patients by GnRHa triggering in combination with low-dose HCG: a pilot study. Reprod Biomed Online 2009;18:630–4.
11. Humaidan P, Ejdrup BH, Westergaard LG, Yding AC. 1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study. Fertil Steril 2010;93:847–54.
12. Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum Reprod Update 2011;17:510–24.
13. Papanikolaou EG, Verpoest W, Fatemi H, Tarlatzis B, Devroey P, Tournaye H. A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study. Fertil Steril 2011;95:1174–7.
14. Humaidan P, Papanikolaou EG, Kyrou D, Alsbjerg B, Polyzos NP, Devroey P, et al. The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. Reprod Biomed Online 2012;24:134–41.
15. Humaidan P, Van Vaerenbergh I, Bourgain C, Alsbjerg B, Blockeel C, Schuit F, et al. Endometrial gene expression in the early luteal phase is impacted by mode of triggering final oocyte maturation in recFSH stimulated and GnRH antagonist co-treated IVF cycles. Hum Reprod 2012;27:3259–72.
16. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
17. Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, et al. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 2003;88:4186–92.
18. Fatemi HM. The luteal phase after 3 decades of IVF: what do we know? Reprod Biomed Online 2009;19(Suppl 4):4331.
19. Fauser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab 2003;14:236–42.
20. Tavaniotou A, Devroey P. Effect of human chorionic gonadotropin on luteal luteinizing hormone concentrations in natural cycles. Fertil Steril 2003;80:654–5.
21. Tavaniotou A, Albano C, Smitz J, Devroey P. Comparison of LH concentrations in the early and mid-luteal phase in IVF cycles after treatment with HMG alone or in association with the GnRH antagonist Cetrorelix. Hum Reprod 2001;16:663–7.
22. Casper RF, Yen SS. Induction of luteolysis in the human with a long-acting analog of luteinizing hormone-releasing factor. Science 1979;205:408–10.
23. Sugino N, Kashida S, Takiguchi S, Karube A, Kato H. Expression of vascular endothelial growth factor and its receptors in the human corpus luteum during the menstrual cycle and in early pregnancy. J Clin Endocrinol Metab 2000;85:3919–24.
24. Wang XF, Xing FQ, Chen SL. Interleukin-1beta expression on ovarian granulosa cells and its clinical implication in women undergoing in vitro fertilization. Di Yi Jun Yi Da Xue Xue Bao 2002;22:934–6.
25. Licht P, Russu V, Lehmeyer S, Wildt L. Molecular aspects of direct LH/hCG effects on human endometrium—lessons from intrauterine microdialysis in the human female in vivo. Reprod Biol 2001;1:10–9.
26. Bonduelle ML, Dodd R, Liebaers I, Van SA, Williamson R, Akhurst R. Chorionic gonadotrophin-beta mRNA, a trophoblast marker, is expressed in human 8-cell embryos derived from tripronucleate zygotes. Hum Reprod 1988;3:909–14.
27. Fatemi HM, Popovic-Todorovic B, Donoso P, Papanikolaou E, Smitz J, Devroey P. Luteal phase oestradiol suppression by letrozole: a pilot study in oocyte donors. Reprod Biomed Online 2008;17:307–11.
28. Filicori M, Butler JP, Crowley WF Jr. Neuroendocrine regulation of the corpus luteum in the human. Evidence for pulsatile progesterone secretion. J Clin Invest 1984;73:1638–47.
29. Fatemi HM, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P. An update of luteal phase support in stimulated IVF cycles. Hum Reprod Update 2007;13:581–90.
30. Fauser BC, de Jong D, Olivennes F, Wramsby H, Tay C, Itskovitz-Eldor J, et al. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. J Clin Endocrinol Metab 2002;87:709–15.
31. Emperaire JC, Parneix I, Ruffie A. Luteal phase defects following agonist-triggered ovulation: a patient-dependent response. Reprod Biomed Online 2004;9:22–7.
32. Zelinski-Wooten MB, Hutchison JS, Chandrasekher YA, Wolf DP, Stouffer RL. Administration of human luteinizing hormone (hLH) to macaques after follicular development: further titration of LH surge requirements for ovulatory changes in primate follicles. J Clin Endocrinol Metab 1992;75:502–7.
33. Cohlen BJ, te Velde ER, Scheffer G, van Kooij RJ, Maria de Brouwer CP, van Zonneveld P. The pattern of the luteinizing hormone surge in spontaneous cycles is related to the probability of conception. Fertil Steril 1993;60:413–7.
34. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmoush L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril 1994;62:485–90.

SUPPLEMENTAL TABLE 1

Endocrine profile.

	Group A (10,000 IU hCG)	Group B (GnRHa + 1,500 IU hCG + LPS)	Group C (GnRHa + LPS)	Group D (GnRHa)
Day of trigger				
E_2 (ng/L)	2,757 ± 2,473	2,687 ± 1,473	1,550 ± 524	2,116 ± 1,787
FSH (IU/L)	11.3 ± 3.2	12.3 ± 4.2	12.9 ± 3.8	11.8 ± 2.7
LH (IU/L)	0.75 ± 0.87	1.15 ± 0.99	1.30 ± 1.81	1.73 ± 2.53
P (μg/L)	0.97 ± 0.52	1.12 ± 0.53	0.98 ± 0.41	1.29 ± 0.81
Day of trigger + 1				
E_2 (ng/L)	3,329 ± 2,790	1,684 ± 1,568	1,736 ± 529	2,399 ± 1,873
FSH (IU/L)	9.3 ± 2.7	17.1 ± 10.2	24.3 ± 0.9[a]	25.4 ± 4.2[a]
LH (IU/L)	2.18 ± 2.02	27.38 ± 22.71[a]	43.83 ± 9.79[a]	56.15 ± 23.4[a]
P (μg/L)	6.25 ± 1.63	5.83 ± 3.59	6.54 ± 1.14	5.96 ± 2.64
Day of ovum pickup + 5				
E_2 (ng/L)	1,862 ± 1,105	1,238 ± 733	132 ± 83[a]	66 ± 51[a]
FSH (IU/L)	1.1 ± 0.2	1.3 ± 0.3	1.6 ± 0.4[a]	2.2 ± 0.4[a]
LH (IU/L)	0.30 ± 0.23	0.10 ± 0	0.65 ± 0.68	1.90 ± 0.78
P (μg/L)	60 ± 0	60 ± 0	11.49 ± 3.17[a]	0.99 ± 0.61[a]

Note: GnRHa = GnRH agonist; LPS = luteal phase support.
[a] $P < .05$ compared with group A.

Fatemi. Endocrine profile of early luteal phase. Fertil Steril 2013.