Luteal phase supplementation after gonadotropin-releasing hormone agonist trigger in fresh embryo transfer: the American versus European approaches

Peter Humaidan, M.D.,[a] Lawrence Engmann, M.D.,[b] and Claudio Benadiva, M.D.[b]

[a] Fertility Clinic, Skive Regional Hospital, and Faculty of Health, Aarhus University, Aarhus, Denmark; and [b] Center for Advanced Reproductive Services, Department of Obstetrics and Gynecology, University of Connecticut School of Medicine, Farmington, Connecticut

The challenges in attaining an adequate luteal phase after GnRH agonist (GnRHa) trigger to induce final oocyte maturation have resulted in different approaches focused on rescuing the luteal phase insufficiency so that a fresh transfer can be carried out without jeopardizing IVF outcomes. Over the years, two different concepts have emerged: intensive luteal support with aggressive exogenous administration of E_2 and P; and low-dose hCG rescue in the form of a small dose of hCG either on the day of oocyte retrieva or on the day of GnRHa trigger (the so called "dual trigger"). Both approaches have been shown to be effective in achieving pregnancy rates similar to those obtained after conventional hCG trigger and resulting in a very low risk of ovarian hyperstimulation syndrome (OHSS). Although the idea of freezing all embryos after GnRHa trigger and transferring them in a subsequent frozen-thawed cycle has been gaining momentum, a fresh transfer leading to the live birth of a healthy child is currently considered to be the goal of IVF treatment. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)

Key Words: GnRHa trigger, dual GnRHa trigger, OHSS, luteal phase support, low-dose hCG supplementation

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/humaidanp-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.

Ovarian hyperstimulation syndrome (OHSS) is a dangerous and potentially life threatening complication of controlled ovarian stimulation (COS). Considering that ovarian stimulation is performed on healthy uncompromised infertility patients and in healthy oocyte donors, every effort should be made to prevent or eliminate this complication. Although it has been generally assumed that OHSS is an inevitable and possibly unavoidable complication of COS, it is now largely accepted that GnRH agonist (GnRHa) administration to induce final oocyte maturation is effective in the prevention of OHSS (1–3). The administration of a single dose of GnRHa results in defective corpus luteum (CL) function with resultant decrease in the release of vasoactive peptides, such as vascular endothelial growth factor, that may potentially prevent OHSS (4). This is due to the shorter half-life of the endogenous LH surge which results in defective CL function and also subsequent pituitary suppression leading to early luteolysis (5). In addition, the supraphysiologic levels of E_2 and P after COS directly inhibit LH secretion from the pituitary by means of negative feedback actions on the hypothalamic-pituitary axis (6–8). Importantly, LH plays a significant role during the luteal phase, not only for CL function, but also for the upregulation of growth factors and cytokines involved in early implantation (9–11). The amount of LH needed to support CL function and early implantation is currently unknown, so LH levels can not be used for monitoring the luteal phase.

One of the associated consequences of defective CL function is significantly

Received November 25, 2014; revised January 13, 2015; accepted January 22, 2015.
P.H. reports unrestricted research grants from Ferring and MSD and honoraria for speaking from MSD and Merck Serono. L.E. has nothing to disclose. C.B. has nothing to disclose.
Reprint requests: Claudio Benadiva, M.D., Clinical Professor, Center for Advanced Reproductive Services, Department of Obstetrics and Gynecology, 2 Batterson Park Rd., Farmington, Connecticut 06032 (E-mail: Benadiva@uchc.edu).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.01.034

lower luteal levels of serum E_2 and P, resulting in a potential detrimental effect on endometrial receptivity (12). The mean duration of the nonsupplemented luteal phase after GnRHa trigger in oocyte donors may be as short as 4 days, compared with 13 days after hCG trigger, suggesting a markedly defective CL function (13). Even with intramuscular (IM) P supplementation in the luteal phase, significantly lower luteal-phase serum P as well as E_2 levels have been reported (14, 15). It is therefore critical that strategies to improve the luteal-phase steroidal profile and endometrial receptivity are optimized to maintain adequate live birth rates without increasing the risk of OHSS development.

The initial experience of using GnRHa to trigger final oocyte maturation resulted in very disappointing results. A number of early studies reported significantly higher miscarriage rates and lower ongoing pregnancy rates after GnRHa trigger (16, 17). In 2006, a very early meta-analysis including three randomized clinical trials (RCTs) showed a significantly lower chance of pregnancy and higher risk of miscarriage, which resulted in two trials being prematurely discontinued (18). It became clear that the use of standard luteal phase support after GnRHa trigger is inadequate and almost invariably results in lower conception rates. The authors of the initial meta-analysis, therefore, prematurely suggested that GnRHa to trigger final oocyte maturation should not be recommended for clinical use. Likewise, a recent updated Cochrane review on GnRHa trigger (19) reached the same general conclusion that GnRHa trigger is associated with a lower ongoing pregnancy rate compared with conventional hCG trigger. Unfortunately, data were compiled from studies that were not comparable due to different luteal phase protocols being used. The Cochrane analysis therefore missed the fact that it is the luteal support that is the variable that affects the pregnancy rate and not the use of the GnRHa trigger for final oocyte maturation (20).

In searching for an optimal luteal phase protocol, Engmann et al. hypothesized that using a modified intensive hormonal replacement regimen similar to the one used for agonadal oocyte donor recipients would overcome the CL dysfunction and result in adequate implantation rates (15). Around the same time, Humaidan et al. explored the use of low-dose hCG to rescue the luteal phase, also with very favorable results (21). In view of the more encouraging results obtained with these new approaches, a consensus was beginning to emerge that the time had arrived to reconsider the use of GnRHa for triggering of final oocyte maturation (22). An international group of experts met in Denmark in November 2009 to evaluate the existing evidence on the use of GnRHa to trigger final oocyte maturation. The members of the Copenhagen GnRH Agonist Triggering Workshop Group agreed that the time had come for a paradigm shift in the ovulation triggering concept in ART. The discussions and expert opinions of the group were reported in a consensus paper published in 2011, setting the foundation for future research developments and continuing international collaboration in this area of investigation (23).

In the present article, we summarize the current status of the different approaches available for the management of the luteal phase after GnRHa trigger.

INTENSIVE LUTEAL SUPPORT (THE "AMERICAN" APPROACH)

Optimal luteal-phase steroidal supplementation after GnRHa is important because of the vast amount of evidence in the literature regarding the abnormal luteal phase steroid profile (12, 14). Several studies have attempted to supplement the luteal phase after GnRHa trigger with the use of luteal phase support similar to that used after hCG trigger, with disappointing results.

Fauser et al. (14) utilized only IM P (50 mg) as luteal support for $\geq$2 weeks and obtained an ongoing pregnancy rate of 18% and 20% for patients triggered with triptorelin or leuprolide, respectively. All the patients in the study by Humaidan et al. (16) received micronized P vaginally and oral E_2 daily starting on the day after oocyte retrieval and continued until the day of pregnancy test, obtaining a clinical pregnancy rate of only 6%. These poor results may have been attributed to the premature discontinuation of the hormonal supplementation (24). In the study by Kolibianakis et al. (17), one of the participant centers used micronized vaginal P (600 mg in three separate doses) and oral E_2 (4 mg/d) from the day after oocyte retrieval until 7 weeks of gestation, achieving an ongoing pregnancy rate of 5.6%. The other center in the study used only vaginal and IM P, without E_2 support, until 7 weeks' gestation and reported an ongoing pregnancy rate of 2.9%. The trial was prematurely discontinued owing to the low ongoing pregnancy rates.

Adopting the approach that regular supplementation is suboptimal, in a randomized controlled trial our group used intensive luteal phase support and monitoring of serum steroid levels after GnRHa trigger with an excellent ongoing pregnancy rate of 53.3% (2). All of the patients received 50 mg IM P daily starting the evening after oocyte retrieval and continued until ~10 weeks' gestation. In addition, they received three 0.1-mg E_2 transdermal patches every other day starting on the day after oocyte retrieval. Serum E_2 and P were measured on the day of embryo transfer, 1 week after oocyte retrieval, and weekly thereafter. The dose of transdermal E_2 patches was increased, if necessary, to a maximum of four 0.1-mg patches every other day, and/or addition of oral micronized E_2 to maintain the serum E_2 level $>$200 pg/mL. The IM P dose was also increased, if necessary, to a maximum of 75 mg daily and/or addition of micronized vaginal P to maintain serum P level $>$20 ng/mL.

The ideal type of luteal phase support after GnRH agonist is still under investigation, however it is evident that some form of aggressive steroidal support and serum monitoring with appropriate dose adjustment is essential. The ideal route of P administration after COS is still debatable (25, 26), although it is likely that the IM route will be preferable after GnRHa trigger because of the abnormal luteal phase and the need for adequate supplementation and monitoring. Although the evidence for E_2 supplementation after hCG trigger in IVF treatment is weak (25, 27, 28), it may be required after GnRHa trigger because of the defective CL function. Additionally, the route of E_2 administration may be important in correcting the abnormal luteal phase, and it is possible that the use of transdermal E_2 patches may be