Reproductive BioMedicine Online (2012) **24**, 134–141

www.sciencedirect.com
www.rbmonline.com

REVIEW

The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives

Peter Humaidan [a,*], EG Papanikolaou [b], D Kyrou [b], B Alsbjerg [c], NP Polyzos [d], P Devroey [e], Human M Fatemi [e]

[a] *The Fertility Clinic, Odense University Hospital, 5000 Odense, Denmark;* [b] *Assisted Reproduction Unit, 1st OB-GYN Department, Aristotle University of Thessaloniki, Thessaloniki, Greece;* [c] *The Fertility Clinic, Skive Regional Hospital, Skive, Denmark;* [d] *Section of Obstetrics and Gynaecology, Panhellenic Association for Continual Medical Research (PACMeR), Athens, Greece;* [e] *Department of Reproductive Medicine, Academic Hospital at the Dutch-speaking Brussels Free University, Brussels, Belgium*

[*] Corresponding author. *E-mail address:* peter.humaidan@ouh.regionsyddanmark.dk (P Humaidan).

Peter Humaidan is a specialist in reproductive endocrinology, professor and clinical director of the Fertility Clinic at Odense University Hospital, Denmark. He trained at the Sahlgrenska University Hospital, Gothenburg, Sweden, where he also completed a speciality degree in obstetrics and gynaecology. His research interests include reproductive endocrinology, the function of gonadotrophins, sperm chromatin integrity in relation to assisted reproduction and gonadotrophin-releasing hormone-(GnRH) antagonist co-treatment in ovarian stimulation. During recent years, his research has been focused on GnRHa triggering and prevention of ovarian hyperstimulation syndrome. He is a former board member of the Danish Fertility Society.

Abstract In stimulated IVF/intracytoplasmic sperm injection cycles, the luteal phase is disrupted, necessitating luteal-phase supplementation. The most plausible reason behind this is the ovarian multifollicular development obtained after ovarian stimulation, resulting in supraphysiological steroid concentrations and consecutive inhibition of LH secretion by the pituitary via negative feedback at the level of the hypothalamic–pituitary axis. With the introduction of the gonadotrophin-releasing hormone-(GnRH) antagonist, an alternative to human chorionic gonadotrophin triggering of final oocyte maturation is the use of GnRH agonist (GnRHa) which reduces or even prevents ovarian hyperstimulation syndrome (OHSS). Interestingly, the current regimens of luteal support after HCG triggering are not sufficient to secure the early implanting embryo after GnRHa triggering. This review discusses the luteal-phase insufficiency seen after GnRHa triggering and the various trials that have been performed to assess the most optimal luteal support in relation to GnRHa triggering. Although more research is needed, GnRHa triggering is now an alternative to HCG triggering, combining a significant reduction in OHSS with high ongoing pregnancy rates.

KEYWORDS: GnRH agonist, GnRH antagonist, HCG, IVF, luteal phase, ovulation induction

Introduction

With the introduction of gonadotrophins for ovarian stimulation in patients undergoing IVF treatment, it became obvious that the luteal phase of all stimulated IVF cycles was abnormal (Edwards et al., 1980) as compared with 8% of natural cycles (Rosenberg et al., 1980).

The aetiology of the luteal-phase defect in stimulated IVF cycles has been debated for more than three decades.

1472-6483/$ - see front matter
doi:10.1016/j.rbmo.2011.11.001

Initially, it was argued that the removal of large quantities of granulosa cells during oocyte retrieval might negatively impact the function of the corpora lutea, leading to a luteal-phase insufficiency. However, this hypothesis was rejected when it was established that the aspiration of pre-ovulatory oocytes in a natural cycle neither diminished the luteal-phase steroid secretion nor shortened the length of the luteal phase (Kerin et al., 1981).

As steroid-hormone production by the corpus luteum is totally dependent on the pulsatile secretion of LH by the pituitary (Devoto et al., 2000), it was suggested that the prolonged pituitary desensitization following a long gonadotrophin-releasing hormone-(GnRH) agonist (GnRHa) down-regulation to prevent a premature LH rise might result in circulating LH concentrations too low to support the corpora lutea, causing a luteal-phase defect (Smitz et al., 1992a,b). Thus, with the introduction of GnRH antagonists in IVF protocols it was anticipated that luteal-phase supplementation would be unnecessary due to the rapid recovery of the pituitary (within 2 days) after GnRH-antagonist discontinuation (Oberyé et al., 1999). However, subsequent IVF/intracytoplasmic sperm injection (ICSI) studies using GnRH antagonist co-treatment did not confirm this expectation. On the contrary, luteolysis was also induced prematurely after GnRH-antagonist co-treatment, resulting in a significant reduction in the luteal-phase length and a compromised reproductive outcome (Albano et al., 1998; Beckers et al., 2003). Thus, despite the rapid recovery of the pituitary in GnRH-antagonist protocols, luteal-phase supplementation was necessary (Dal Prato and Borini, 2005; Tarlatzis et al., 2006).

Finally, it was proposed that the triggering bolus of human chorionic gonadotrophin (HCG) administered for final oocyte maturation in stimulated cycles could potentially cause a luteal-phase defect by suppressing the LH secretion of the pituitary via a short-loop feedback mechanism (Miyake et al., 1979). However, this theory was questioned after the results of a cohort study, showing that the administration of HCG did not decrease luteal-phase LH concentrations in the natural cycle of normogonadotrophic women (Tavaniotou and Devroey, 2003).

Presently, according to recent research, the most plausible reason for the luteal-phase insufficiency seen after ovarian stimulation is the multifollicular development achieved during the follicular phase, resulting in luteal supraphysiological concentrations of progesterone and oestradiol which directly inhibit the LH secretion by the pituitary via negative feedback actions at the level of the hypothalamic–pituitary axis (Fatemi, 2009; Fauser and Devroey, 2003; Tavaniotou and Devroey, 2003; Tavaniotou et al., 2001). This has been shown to have a dramatic effect on the reproductive outcome (Humaidan et al., 2005, 2010) as LH plays a crucial role during the luteal phase not only for the steroidogenic activity of the corpus luteum (Casper and Yen, 1979), but also for the up-regulation of growth factors (Sugino et al., 2000; Wang et al., 2002) and cytokines (Licht et al., 2001a,b), which are important for implantation. Apart from this, the activation of extragonadal LH receptors, expressed in human endometrium, is thought to enhance and support implantation (Rao, 2001; Tesarik et al., 2003).

Ovarian stimulation and the endometrium

During ovarian stimulation, an endometrial histological advancement has been observed on the day of oocyte retrieval when comparing with the endometrium from the ovulation day in natural cycles (Bourgain et al., 2002; Kolibianakis et al., 2002). The endometrial advancement has mainly been considered to be the result of the exposure of the endometrium to supraphysiological steroid hormones throughout the IVF treatment, independent of the type of GnRH analogue administered during the follicular phase (Bourgain et al., 2002). Importantly, an endometrial advancement exceeding 3 days has been shown to negatively impact the reproductive outcome (Kolibianakis et al., 2002; Ubaldi et al., 1997).

HCG triggering of final oocyte maturation

In the natural cycle, ovulation is induced by the mid-cycle surge of LH (and FSH) from the pituitary, elicited by an increasing late follicular concentration of oestradiol. More than 50 years ago, exogenous HCG (5000–10,000 IU) was successfully introduced as a substitute for the endogenous LH surge to induce final oocyte maturation. Sharing the same α subunit and 81% of the amino-acid residues of the β subunit, LH and HCG bind to the same receptor, the LH/HCG receptor (Kessler et al., 1979). However, due to the significantly longer half-life of HCG, the ovulatory dose will support the corpora lutea for 7–10 days, after which HCG is cleared from circulation (Damewood et al., 1989; Mannaerts et al., 1998); from now on, the corpora lutea will be totally dependent on the endogenous LH secretion by the pituitary or by the HCG production from an implanting embryo. Importantly, the significantly longer half-life of HCG, as compared with LH, leads to a prolonged luteotrophic effect, development of multiple corpora lutea and raised serum concentrations of oestradiol and progesterone throughout the luteal phase (Itskovitz et al., 1991), increasing the risk of ovarian hyperstimulation syndrome (OHSS) (Haning et al., 1985). Not only because of the increased risk of OHSS by triggering final oocyte maturation with HCG but also because of reports on a negative impact of HCG on endometrial receptivity and embryo implantation (Fanchin et al., 2001; Fatemi et al., 2010; Forman et al., 1988; Valbuena et al., 2001), alternative triggering methods have been investigated.

GnRHa triggering of final oocyte maturation

Previously, GnRHa was shown to effectively stimulate ovulation and final oocyte maturation, inducing an initial secretion of LH and FSH (flare-up), similar to that of the natural cycle, prior to down-regulation of the receptor (Gonen et al., 1990; Itskovitz et al., 1991). The GnRHa trigger concept gained some interest in the late 1980s and early 1990s. However, with the introduction of GnRHa for pituitary down-regulation prior to IVF/ICSI treatment (Porter et al., 1984), this concept was clearly not applicable, as the simultaneous use of GnRHa for down-regulation and triggering of final oocyte maturation is not possible.

With the introduction of the GnRH antagonist (Albano et al., 1997; Borm and Mannaerts, 2000; Itskovitz-Eldor et al., 1998), it again became possible to trigger ovulation with a bolus of GnRHa as an alternative to HCG, as GnRHa will displace the GnRH antagonist from the GnRH receptor in the pituitary and elicit a surge of gonadotrophins (LH and FSH). However, there are significant differences between the GnRHa-induced surge of gonadotrophins and that of the natural cycle. Thus, the LH surge of the natural cycle is characterized by three phases, with a total duration of 48 h (Hoff et al., 1983), as compared with the GnRHa-induced LH surge, which consists of two phases with a duration of ~24–36 h (Itskovitz et al., 1991). This leads to a significantly reduced total amount of gonadotrophins being released from the pituitary when GnRHa is used to trigger final oocyte maturation (Gonen et al., 1990; Itskovitz et al., 1991). This *per se* could induce a defective luteal phase (Balasch et al., 1995; Segal and Casper, 1992), necessitating a modification of the standard luteal-phase support commonly used in IVF treatment to secure the reproductive outcome (Humaidan et al., 2010).

The advantage of GnRHa triggering, however, is a significant reduction in or even total elimination of OHSS as compared with HCG triggering (Kol, 2004; Kol and Itskovitz-Eldor, 2000; Orvieto, 2005). Moreover, the retrieval of more metaphase II (MII) oocytes has been reported after GnRHa triggering compared with HCG triggering (Humaidan et al., 2005; Imoedemhe et al., 1991; Oktay et al., 2010). This finding could be the result of the endogenous FSH surge elicited along with the LH surge after GnRHa triggering (Kol and Humaidan, 2010). Although not fully elucidated, the natural mid-cycle surge of FSH has been shown to promote nuclear maturation, i.e. resumption of meiosis, as well as LH receptor formation in the luteinizing granulosa cells – securing the function of the corpus luteum during the following luteal phase (Eppig, 1979; Stickland and Beers, 1976; Yding Andersen, 2002; Yding Andersen et al., 1999; Zelinski-Wooten et al., 1995).

GnRHa triggering and the luteal phase

During the natural cycle, the frequency of pulsatile LH release from the pituitary changes across the luteal phase, correlating significantly with progesterone concentrations (Filicori et al., 1986). Not only does LH play a crucial role for the steroidogenic activity of the corpus luteum, but also for the up-regulation of growth factors, such as vascular endothelial growth factor A, fibroblast growth factor 2, cytokines involved in implantation and stimulation of extragonadal LH receptors (Casper and Yen, 1979; Licht et al., 2001a,b; Rao, 2001; Sugino et al., 2000; Tesarik et al., 2003; Wang et al., 2002), all factors important for normal implantation and early neovascularization.

Extragonadal LH receptors have been localized to the endometrium, indicating that the endometrium is a target organ for LH (Reshef et al., 1990; Ziecik et al., 1992). Unlike previous suggestions that LH can only indirectly affect the endometrium through ovarian steroid-hormone production (de Ziegler et al., 1991), recent studies have linked exposure to LH to regulatory changes pertinent to the morphological and functional proliferation and differentiation of endometrial glands and stroma, mainly via activation of the adenylate cyclase and phospholipase C pathways and via an increase in the local synthesis of steroid hormones (Ku et al., 2002; Licht et al., 2001a,b; Shemesh et al., 2001). Thus, withdrawal of or reduction in circulating LH during the luteal phase leads to luteolysis and implantation failure (Duffy et al., 1999).

As previously described, GnRHa triggering *per se* leads to a significantly reduced total amount of gonadotrophins (LH and FSH) released from the pituitary. In addition, after ovarian stimulation the supraphysiological luteal steroid concentration directly inhibits the LH secretion from the pituitary via negative feedback actions at the level of the hypothalamic–pituitary axis (Fatemi, 2009; Fauser and Devroey, 2003; Tavaniotou and Devroey, 2003; Tavaniotou et al., 2001). This combined effect of ovarian stimulation and GnRHa triggering on LH concentrations was clearly seen in a recent randomized controlled trial comparing HCG triggering to GnRHa triggering (Humaidan et al., 2005). Thus, in the GnRHa group, the endogenous mid-luteal LH concentration was reduced by 75% compared with the natural cycle (1.5 IU/l versus 6 IU/l) and the study had to be discontinued due to an extremely high early pregnancy loss rate, despite supplementation with a standard luteal-phase support including vaginal progesterone as well as oestradiol (Humaidan et al., 2005).

Following this study, the question to ask was: why was standard luteal-phase support not sufficient to secure the early implanting embryo after GnRHa triggering, although it resembled that generally used after HCG triggering and in successful oocyte recipient and frozen–thaw cycles? In this context, it is important to recollect that during the process of implantation the embryo actively secretes HCG, which is detectable in maternal serum as early as 8 days after ovulation (Bonduelle et al., 1988). However, due to the absence of direct vascular communication, the secretion of HCG into the maternal circulation is initially limited (Nepomnaschy et al., 2008). This means that in HCG-induced stimulation cycles, the actions of LH will be covered by the bolus of HCG and after this period gradually by the HCG produced by the implanting embryo. However, after GnRHa triggering, the combined effect of ovarian stimulation and GnRHa triggering reduces the endogenous LH concentration dramatically (Humaidan, 2009). Furthermore, although the patient is supplemented with luteal progesterone and oestradiol, the reduction in endogenous LH will have a negative impact on normal implantation – leading to early pregnancy loss. In contrast, in the early to mid-luteal phase of oocyte recipient and frozen–thaw cycles, the luteal-phase steroid concentration (oestradiol and progesterone) is physiologically comparable with that of the natural cycle and thus, no reduction in luteal LH is seen (Lewin et al., 2002).

In conclusion, the most plausible reason for the luteal-phase defect seen in stimulated GnRH antagonist cycles triggered with a GnRHa seems to be a lack of endogenous LH activity during the early to mid-luteal phase, which necessitates a modification of the standard luteal-phase supplementation currently used after HCG triggering to secure the reproductive outcome.

GnRHa triggering and modified luteal-phase support

HCG bolus

Following the first disappointing trials after GnRHa triggering, a number of studies were performed in normoresponding as well as hyper-responding patients to explore the possibility of rescuing the luteal phase with a small supplementary bolus of LH-like activity in the form of 1500 IU HCG (Humaidan et al., 2006, 2010; Humaidan, 2009). The results of the first study confirmed the LH deficiency theory, as the luteal phase after GnRHa triggering was normalized not only in terms of mid-luteal serum progesterone concentrations, but also in terms of good clinical pregnancy rates if a bolus of 1500 IU HCG was administered 35 h after the triggering dose of GnRHa, i.e. after oocyte retrieval (Humaidan et al., 2006).

Subsequently, the results of the pilot study were confirmed in a large randomized controlled trial, including a total of 302 patients. The study reported a non-significant difference in live-birth rates between HCG and GnRHa triggering when the patients in the GnRHa group were supplemented with 1500 IU HCG 35 h after the triggering bolus of GnRHa (Humaidan et al., 2010). Importantly, one-third of patients in both study groups had at least 13 follicles $\geq$11 mm on the day of ovulation induction — a cut-off level suggested to predict 87% of severe OHSS cases (Papanikolaou et al., 2006). However, no OHSS case was seen in the group of patients who had GnRHa to trigger final oocyte maturation, as compared with 2% in the HCG group (Humaidan et al., 2010).

To test the safety of the GnRHa trigger/1500 IU HCG protocol in hyper-responding patients ($\geq$25 follicles $\geq$11 mm on the day of ovulation induction), a proof-of-concept study was conducted. All patients underwent embryo transfer after the retrieval of a mean of 21.5 oocytes, resulting in a live-birth rate of 50%. One patient developed moderate late-onset OHSS that did not require hospitalization (Humaidan et al., 2006).

Following the same line, Shapiro et al. (2008) in a retrospective analysis in OHSS risk patients (20 oocytes retrieved) reported a high ongoing pregnancy rate and no OHSS by the use of so-called dual trigger; i.e. patients received final oocyte maturation with leuprolide acetate (4 mg) as well as HCG (1000—2500 IU), followed by luteal-phase supplementation with oestradiol and progesterone.

In conclusion, one bolus of HCG administered either at the time of triggering (dual trigger) or after oocyte retrieval rescues the luteal phase after GnRHa triggering, resulting in a reproductive outcome comparable with that of HCG triggering. At the same time, the risk of OHSS seems to be decreased, even in the OHSS high-risk patient.

Intensive luteal-phase support with oestradiol and progesterone

The concept of overcoming the luteal-phase insufficiency seen after GnRHa triggering with intensive luteal support of oestradiol and progesterone was described in 30 OHSS high-risk patients by Engmann et al. (2008). The authors used intramuscular progesterone and oestradiol patches as well as oral oestradiol and reported a high ongoing clinical pregnancy rate. Importantly no OHSS case was seen in this group of high-risk patients. Although initial results were promising in terms of the reproductive outcome and the total elimination of OHSS in a group of patients with polycystic ovaries/polycystic ovary syndrome (PCOS), the findings need to be confirmed in a larger group of high-risk patients. An important question is whether this concept also applies to the normogonadotrophic patient, as serum LH concentrations are significantly increased (30—90%) in the PCOS patient during the follicular and luteal phases, as compared with the normogonadotrophic patient due to an increase in the LH pulse frequency and amplitude elicited by the GnRH pulse generator (McCartney et al., 2002). This, in combination with a decreased sensitivity of the GnRH pulse generator to inhibition by ovarian steroids — in particular progesterone — leaves the PCOS patient with a significantly higher LH concentration during the luteal phase as compared with the normogonadotrophic patient (McCartney et al., 2002).

Importantly, the findings of Engmann et al. (2008) are contrasted by a previous study (Babayof et al., 2006), in which a group of OHSS high-risk patients were treated with a similar luteal-phase support, with a disappointingly low ongoing pregnancy rate of 6% and a high early pregnancy loss rate (80%). However, recently Shapiro et al. (2011), in a retrospective analysis of 24 blastocyst transfers, using intensive luteal-phase support with oestradiol and progesterone, confirmed the previous findings of Engmann et al. (2008).

Recombinant LH

In a proof-of-concept study (Papanikolaou et al., 2011) patients were randomized to either GnRHa or HCG triggering. In the GnRHa group, the luteal phase was supported with six alternate doses of 300 IU recombinant LH after GnRHa triggering in addition to vaginal progesterone. All patients underwent elective single blastocyst transfer, resulting in a good ongoing clinical pregnancy rate. No OHSS case was reported. Due to the significantly shorter half-life of recombinant LH as compared with HCG, this concept is interesting, as its use might even further reduce the risk of developing OHSS. However, a large randomized controlled trial is necessary to draw conclusions.

GnRHa

An alternative method to increase the endogenous LH concentrations during the luteal phase of IVF/ICSI patients was explored in a pilot study by Pirard et al. (2006), using daily intranasal administration of GnRHa during the luteal phase after triggering of final oocyte maturation with GnRHa without any exogenous progesterone supplementation. Five IVF patients treated with intranasal administration of 100 μg GnRHa t.i.d. obtained progesterone concentrations and a reproductive outcome comparable with that of the HCG-induced group. However, the administration of GnRHa during a potential early pregnancy is controversial and was disputed after the publication of the paper (Lambalk and

Homburg, 2006). Larger prospective trials are needed to prove the efficacy and safety of this procedure.

Future perspectives

Clomiphene citrate

Clomiphene citrate is a selective oestrogen receptor modulator and ovulation-inducing agent used for the initial treatment of a large majority of anovulatory infertile women (Cantineau et al., 2007). A direct endometrial adverse effect of clomiphene citrate administered during the follicular phase has been presumed, and interference with the oestrogen receptor-mediated endometrial oestrogen receptor and progesterone receptor induction has been implicated as plausible mechanisms for the negative impact (Dickey and Holtkamp, 1996).

In contrast, Maruncic and Casper (1987) evaluated whether the administration of clomiphene citrate during the luteal phase would have an impact on LH secretion. The authors demonstrated an increase in luteal LH pulsatility after the administration of clomiphene citrate. Moreover, it was postulated that the finding could be explained by a decrease in endogenous opioid activity caused by clomiphene citrate. Importantly, the increase in LH pulse frequency following clomiphene citrate administration resulted in a significant increase in serum oestradiol and progesterone concentrations and prolongation of the luteal phase (Maruncic and Casper, 1987). Based on this knowledge, it needs to be determined whether administration of clomiphene citrate after the initial GnRHa trigger in GnRH antagonist stimulation cycles increases endogenous LH concentrations sufficiently to rescue the luteal phase without compromising implantation.

Opioid antagonists

Endogenously produced opiates participate in the endocrine events leading to low LH secretion during the luteal phase through an inhibition of the hypothalamic LH releasing factor. Several studies published decades ago demonstrated that short-term infusion of the specific opiate receptor antagonist naloxone leads to a marked increase in LH release during the luteal phase. However, sustained administration of naloxone did not have any impact on LH secretion during the luteal phase (Rossmanith et al., 1998). Future studies should explore this concept to increase the endogenous LH production in the luteal phase of GnRH antagonist stimulation cycles triggered by GnRHa. Importantly, safety issues concerning the use of opioid antagonists during a potential early pregnancy need to be addressed.

Conclusions

The luteal phase in all stimulated IVF cycles is disrupted. However, GnRHa triggering possesses advantages over HCG triggering in terms of an almost complete elimination of OHSS, the retrieval of more mature oocytes (Humaidan et al., 2005, 2010; Imoedemhe et al., 1991; Kol, 2004; Kol and Itskovitz-Eldor, 2000; Oktay et al., 2010; Orvieto, 2005), less luteal distension and discomfort for the patient (Garcia-Velasco et al., 2010) and luteal-phase steroid concentrations closer to those of the natural cycle. The luteal-phase insufficiency previously reported after GnRHa triggering can now be resolved with modifications of the luteal support. Importantly, GnRHa triggering paves the way for the exogenous progesterone-free luteal support, and thus the introduction of a novel, simple and patient-friendly protocol (Kol et al., 2011).

Future trials should explore the most optimal luteal support after GnRHa triggering in order to further increase the implantation rate in fresh transfer IVF cycles. Moreover, comparisons should be made regarding the cumulative pregnancy rate in GnRHa-triggered cycles with fresh versus frozen transfer: a freeze-all policy would eliminate the risk of OHSS. However, this concept demands not only access to optimal cryopreservation programmes and efficient endometrial priming programmes for transfer of frozen embryos, but also a radical change of mind in patients and clinicians.

References

Albano, C., Smitz, J., Camus, M., Riethmüller-Winzen, H., Van Steirteghem, A., Devroey, P., 1997. Comparison of different doses of gonadotropin-releasing hormone antagonist Cetrorelix during controlled ovarian hyperstimulation. Fertil. Steril. 67, 917–922.

Albano, C., Grimbizis, G., Smitz, J., Riethmuller-Winzen, H., Reissmann, T., Van Steirteghem, A., Devroey, P., 1998. The luteal phase of nonsupplemented cycles after ovarian superovulation with human menopausal gonadotropin and the gonadotropin-releasing hormone antagonist Cetrorelix. Fertil. Steril. 70, 357–359.

Babayof, R., Margalioth, E.J., Huleihel, M., Amash, A., Zylber-Haran, E., Gal, M., Brooks, B., Mimoni, T., Eldar-Geva, T., 2006. Serum Inhibin A, VEGF and TNFα levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. Hum. Reprod. 21, 1260–1265.

Balasch, J., Fabregues, F., Tur, R., Creus, M., Casamitjana, R., Peñarrubia, J., Barri, P.N., Vanrell, J.A., 1995. Further characterization of the luteal phase inadequacy after gonadotrophin-releasing hormone agonist-induced ovulation in gonadotrophin-stimulated cycles. Hum. Reprod. 10, 1377–1381.

Beckers, N.G., Macklon, N.S., Eijkemans, M.J., Ludwig, M., Felberbaum, R.E., Diedrich, K., Bustion, S., Loumaye, E., Fauser, B.C., 2003. Non supplemented 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. 88, 4186–4192.

Bonduelle, M.L., Dodd, R., Liebaers, I., Van Steirteghem, A., Williamson, R., Akhurst, R., 1988. Chorionic gonadotrophin-beta mRNA, a trophoblast marker, is expressed in human 8-cell embryos derived from tripronucleate zygotes. Hum. Reprod. 3, 909–914.

Borm, G., Mannaerts, B., 2000. Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. The European Orgalutran Study Group. Hum. Reprod. 15, 1490–1498.

Bourgain, C., Ubaldi, F., Tavaniotou, A., Smitz, J., Van Steirteghem, A.C., Devroey, P., 2002. Endometrial hormone receptors and proliferation index in the periovulatory phase of stimulated embryo transfer cycles in comparison with natural cycles and relation to clinical pregnancy outcome. Fertil. Steril. 78, 237–244.

Cantineau, A.E., Cohlen, B.J., Heineman, M.J., 2007. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst. Rev. 18, CD005356.

Casper, R.F., Yen, S.S., 1979. Induction of luteolysis in the human with a long-acting analog of luteinizing hormone-releasing factor. Science 205, 408–410.

Dal Prato, L., Borini, A., 2005. Use of antagonists in ovarian stimulation protocols. Reprod. Biomed. Online 10, 330–338.

Damewood, M.D., Shen, W., Zacur, H.A., Schlaff, W.D., Rock, J.A., Wallach, E.E., 1989. Disappearance of exogenously administered human chorionic gonadotropin. Fertil. Steril. 52, 398–400.

De Ziegler, D., Cornel, C., Bergeron, C., Hazout, A., Bouchard, P., Frydman, R., 1991. Controlled preparation of the endometrium with exogenous estradiol and progesterone in women having functioning ovaries. Fertil. Steril. 56, 851–855.

Devoto, L., Vega, M., Kohen, P., Castro, A., Castro, O., Christenson, L.K., Carvallo, P., Strauss 3rd, J.F., 2000. Endocrine and paracrine–autocrine regulation of the human corpus luteum during the mid-luteal phase. J. Reprod. Fertil., 13–20.

Dickey, R.P., Holtkamp, D.E., 1996. Development, pharmacology and clinical experience with clomiphene citrate. Hum. Reprod. Update 2, 483–550.

Duffy, D.M., Stewart, D.R., Stouffer, R.L., 1999. Titrating luteinizing hormone replacement to sustain the structure and function of the corpus luteum after gonadotropin-releasing hormone antagonist treatment in rhesus monkeys. J. Clin. Endocrinol. Metab. 84, 342–349.

Edwards, R.G., Steptoe, P.C., Purdy, J.M., 1980. Establishing full-term human pregnancies using cleaving embryos grown in vitro. Br. J. Obstet. Gynaecol. 87, 737–756.

Engmann, L., DiLuigi, A., Schmidt, D., Nulsen, J., Maier, D., Benadiva, C., 2008. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomised controlled study. Fertil. Steril. 89, 84–91.

Eppig, J.J., 1979. FSH stimulates hyaluronic acid synthesis by oocyte–cumulus complexes from mouse preovulatory follicle. Nature 281, 483–484.

Fanchin, R., Peltier, E., Frydman, R., de Ziegler, D., 2001. Human chorionic gonadotropin: does it affect human endometrial morphology in vivo? Semin. Reprod. Med. 19, 31–35.

Fatemi, H.M., 2009. The luteal phase after 3 decades of IVF: what do we know? Reprod. Biomed. Online 19, 4331.

Fatemi, H.M., Kyrou, D., Bourgain, C., Van den Abbeel, E., Griesinger, G., Devroey, P., 2010. Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to human chorionic gonadotropin-induced natural cycle. Fertil. Steril. 94, 2054–2058.

Fauser, B.C., Devroey, P., 2003. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol. Metab. 14, 236–242.

Filicori, M., Santoro, N., Merriam, G.R., Crowley Jr., W.F., 1986. Characterization of the physiological pattern of episodic gonadotropin secretion throughout the human menstrual cycle. J. Clin. Endocrinol. Metab. 62, 1136–1144.

Forman, R., Fries, N., Testart, J., Belaisch-Allart, J., Hazout, A., Frydman, R., 1988. Evidence for an adverse effect of elevated serum estradiol concentrations on embryo implantation. Fertil. Steril. 49, 118–122.

Garcia-Velasco, J.A., Motta, L., López, A., Mayoral, M., Cerrillo, M., Pacheco, A., 2010. Low-dose human chorionic gonadotropin versus estradiol/progesterone luteal phase support in gonadotropin-releasing hormone agonist-triggered assisted reproductive technique cycles: understanding a new approach. Fertil. Steril. 94, 2820–2823.

Gonen, Y., Balakier, H., Powell, W., Casper, R.F., 1990. Use of GnRH agonist to trigger follicular maturation for in vitro fertilization. J. Clin. Endocrinol. Metab. 71, 918–922.

Haning Jr., R.V., Strawn, E.Y., Nolten, W.E., 1985. Pathophysiology of the ovarian hyperstimulation syndrome. Obstet. Gynecol. 66, 220–224.

Hoff, J.D., Quigley, M.E., Yen, S.S., 1983. Hormonal dynamics at midcycle: a reevaluation. J. Clin. Endocrinol. Metab. 57, 792–796.

Humaidan, P., Bredkjaer, H.E., Bungum, L., Bungum, M., Grøndahl, M.L., Westergaard, L., Andersen, C.Y., 2005. GnRH agonist (Buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomised study. Hum. Reprod. 20, 1213–1220.

Humaidan, P., Bungum, L., Bungum, M., Andersen, C.Y., 2006. 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 13, 173–178.

Humaidan, P., Bredkjaer, H.E., Westergaard, L.G., Andersen, C.Y., 2010. 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. 93, 847–854.

Humaidan, P., 2009. Luteal phase rescue in high-risk OHSS patients by GnRHa triggering in combination with low-dose HCG: a pilot study. Reprod. Biomed. Online 18, 630–634.

Imoedemhe, D.A., Sigue, A.B., Pacpaco, E.L., Olazo, A.B., 1991. Stimulation of endogenous surge of luteinizing hormone with gonadotropin-releasing hormone analog after ovarian stimulation for in vitro fertilization. Fertil. Steril. 55, 328–332.

Itskovitz, J., Boldes, R., Levron, J., Erlik, Y., Kahana, L., Brandes, J.M., 1991. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. Fertil. Steril. 56, 213–220.

Itskovitz-Eldor, J., Kol, S., Mannaerts, B., Bennink, H.C., 1998. First established pregnancy after controlled ovarian hyperstimulation with recombinant follicle stimulating hormone and the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462). Hum. Reprod. 13, 294–295.

Kerin, J.F., Broom, T.J., Ralph, M.M., Edmonds, D.K., Warnes, G.M., Jeffrey, R., Crocker, J.M., Godfrey, B., Cox, L.W., Seamark, R.F., Matthews, C.D., 1981. Human luteal phase function following oocyte aspiration from the immediately preovular graafian follicle of spontaneous ovular cycles. Br. J. Obstet. Gynaecol. 88, 1021–1028.

Kessler, M.J., Reddy, M.S., Shah, R.H., Bahl, O.P., 1979. Structure of N-glycosidic carbohydrate units of human chorionic gonadotropin. J. Biol. Chem. 254, 7901–7908.

Kol, S., 2004. Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome. Fertil. Steril. 81, 1–5.

Kol, S., Humaidan, P., 2010. LH (as HCG) and FSH surges for final oocyte maturation: sometimes it takes two to tango? Reprod. Biomed. Online 21, 590–592.

Kol, S., Humaidan, P., Itskovitz-Eldor, J., 2011. GnRH agonist ovulation trigger and hCG-based, progesterone-free luteal support: a proof of concept study. Hum. Reprod. 26, 2874–2877.

Kol, S., Itskovitz-Eldor, J., 2000. Severe OHSS: yes there is a strategy to prevent it! Hum. Reprod. 15, 2266–2267.

Kolibianakis, E., Bourgain, C., Albano, C., Osmanagaoglu, K., Smitz, J., Van Steirteghem, A., Devroey, P., 2002. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pick-up. Fertil. Steril. 78, 1025–1029.

Ku, S.Y., Choi, Y.M., Suh, C.S., Kim, S.H., Kim, J.G., Moon, S.Y., Lee, J.Y., 2002. Effect of gonadotropins on human endometrial stromal cell proliferation in vitro. Arch. Gynecol. Obstet. 266, 223–228.

Lambalk, C.B., Homburg, R., 2006. GnRH agonist for luteal support in IVF? Setting the balance between enthusiasm and caution. Hum. Reprod. 21, 2580–2582.

Lewin, A., Pisov, G., Turgeman, R., Fatum, M., Shufaro, Y., Simon, A., Laufer, N., Revel, A., Reubinoff, B., Safran, A., 2002. Simplified artificial endometrial preparation, using oral estradiol and novel vaginal progesterone tablets: a prospective randomized study. Gynecol. Endocrinol. 16, 131–136.

Licht, P., Russu, V., Wildt, L., 2001a. On the role of human chorionic gonadotropin (hCG) in the embryo-endometrial microenvironment: implications for differentiation and implantation. Semin. Reprod. Med. 19, 37–47.

Licht, P., Russu, V., Lehmeyer, S., Wildt, L., 2001b. Molecular aspects of direct LH/hCG effects on human endometrium – lessons from intrauterine microdialysis in the human female in vivo. Reprod. Biol. 1, 10–19.

Mannaerts, B.M., Geurts, T.B., Odink, J., 1998. A randomized three-way crossover study in healthy pituitary-suppressed women to compare the bioavailability of human chorionic gonadotrophin (Pregnyl) after intramuscular and subcutaneous administration. Hum. Reprod. 13, 1461–1464.

Maruncic, M., Casper, R.F., 1987. The effect of luteal phase estrogen antagonism on luteinizing hormone pulsatility and luteal function in women. J. Clin. Endocrinol. Metab. 64, 148–152.

McCartney, C.R., Eagleson, C.A., Marshall, J.C., 2002. Regulation of gonadotropin secretion: implications for polycystic ovary syndrome. Semin. Reprod. Med. 20, 317–326.

Miyake, A., Aono, T., Kinugasa, T., Tanizawa, O., Kurachi, K., 1979. Suppression of serum levels of luteinizing hormone by short- and long-loop negative feedback in ovariectomized women. J. Endocrinol. 80, 353–356.

Nepomnaschy, P.A., Weinberg, C.R., Wilcox, A.J., Baird, D.D., 2008. Urinary hCG patterns during the week following implantation. Hum. Reprod. 23, 271–277.

Oberyé, J.J., Mannaerts, B.M., Kleijn, H.J., Timmer, C.J., 1999. Pharmacokinetic and pharmacodynamic characteristics of ganirelix (Antagon/Orgalutran): Part I. Absolute bioavailability of 0.25 mg of ganirelix after a single subcutaneous injection in healthy female volunteers. Fertil. Steril. 72, 1001–1005.

Oktay, K., Türkçüoğlu, I., Rodriguez-Wallberg, K.A., 2010. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod. Biomed. Online 20, 783–788.

Orvieto, R., 2005. Can we eliminate ovarian hyperstimulation syndrome? Hum. Reprod. 20, 320–322.

Papanikolaou, E.G., Pozzobon, C., Kolibianakis, E.M., Camus, M., Tournaye, H., Fatemi, H., Van Steirteghem, A., Devroey, P., 2006. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil. Steril. 85, 112–120.

Papanikolaou, E.G., Verpoest, W., Fatemi, H., Tarlatzis, B., Devroey, P., Tournaye, H., 2011. 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. 95, 1174–1177.

Pirard, C., Donnez, J., Loumaye, E., 2006. GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study. Hum. Reprod. 21, 1894–1900.

Porter, R.N., Smith, W., Craft, I.L., Abdulwahid, N.A., Jacobs, H.S., 1984. Induction of ovulation for in-vitro fertilisation using buserelin and gonadotropins. Lancet 2, 1284–1285.

Rao, C.V., 2001. Multiple novel roles of luteinizing hormone. Fertil. Steril. 76, 1097–1100.

Reshef, E., Lei, Z.M., Rao, C.V., Pridham, D.D., Chegini, N., Luborsky, J.L., 1990. The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua. J. Clin. Endocrinol. Metab. 70, 421–430.

Rosenberg, S.M., Luciano, A.A., Riddick, D.H., 1980. The luteal phase defect: the relative frequency of, and encouraging response to, treatment with vaginal progesterone. Fertil. Steril. 34, 17–20.

Rossmanith, W.G., Monn, M., Benz, R., 1998. Effects of chronic opioid antagonism on gonadotrophin and ovarian sex steroid secretion during the luteal phase. Clin. Endocrinol. 49, 343–351.

Segal, S., Casper, R.F., 1992. Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in in vitro fertilization. Fertil. Steril. 57, 1254–1258.

Shapiro, B.S., Daneshmand, S.T., Garner, F.C., Aguirre, M., Thomas, S., 2008. Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of in vitro fertilization. Fertil. Steril. 90, 231–233.

Shapiro, B.S., Daneshmand, S.T., Garner, F.C., Aguirre, M., Hudson, C., 2011. Comparison of 'triggers' using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. Fertil. Steril. 95, 2715–2717.

Shemesh, M., Mizrachi, D., Gurevich, M., Shore, L.S., Reed, J., Chang, S.M., Thatcher, W.W., Fields, M.J., 2001. Expression of functional luteinizing hormone (LH) receptor and its messenger ribonucleic acid in bovine endometrium: LH augmentation of cAMP and inositol phosphate in vitro and human chorionic gonadotropin (hCG) augmentation of peripheral prostaglandin in vivo. Reprod. Biol. 1, 13–32.

Smitz, J., Devroey, P., Faguer, B., Bourgain, C., Camus, M., Van Steirteghem, A.C., 1992a. A randomized prospective study comparing supplementation of the luteal phase and early pregnancy by natural progesterone administered by intramuscular or vaginal route. Rev. Fr. Gynecol. Obstet. 87, 507–516.

Smitz, J., Erard, P., Camus, M., Devroey, P., Tournaye, H., Wisanto, A., Van Steirteghem, A.C., 1992b. Pituitary gonadotrophin secretory capacity during the luteal phase in superovulation using GnRH-agonists and HMG in a desensitization or flare-up protocol. Hum. Reprod. 7, 1225–1229.

Stickland, S., Beers, W., 1976. Studies on the role of plasminogen activator in ovulation. In vitro response of granulosa cells to gonadotrophins, cyclic nucleotides and prostaglandins. J. Biol. Chem. 251, 5694–5702.

Sugino, N., Kaskida, S., Takiguchi, S., Karube, A., Kato, H., 2000. 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. 85, 3919–3924.

Tarlatzis, B.C., Fauser, B.C., Kolibianakis, E.M., Diedrich, K., Rombauts, L., Devroey, P., 2006. GnRH antagonists in ovarian stimulation for IVF. Hum. Reprod. Update 12, 333–340.

Tavaniotou, A., Devroey, P., 2003. Effect of human chorionic gonadotropin on luteal luteinizing hormone concentrations in natural cycles. Fertil. Steril. 80, 654–655.

Tavaniotou, A., Albano, C., Smitz, J., Devroey, P., 2001. 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. 16, 663–667.

Tesarik, J., Hazout, A., Mendoza, C., 2003. Luteinizing hormone affects uterine receptivity independently of ovarian function. Reprod. Biomed. Online 7, 59—64.

Ubaldi, F., Bourgain, C., Tournaye, H., Smitz, J., Van Steirteghem, A., Devroey, P., 1997. Endometrial evaluation by aspiration biopsy on the day of oocyte retrieval in the embryo transfer cycles in patients with serum progesterone rise during the follicular phase. Fertil. Steril. 67, 521—526.

Valbuena, D., Martin, J., de Pablo, J.L., Remohí, J., Pellicer, A., Simón, C., 2001. Increasing levels of estradiol are deleterious to embryonic implantation because they directly affect the embryo. Fertil. Steril. 76, 962—968.

Wang, T.H., Horng, S.G., Chang, C.L., Wu, H.M., Tsai, Y.J., Wang, H.S., Soong, Y.K., 2002. Human chorionic gonadotropin-induced hyperstimulation syndrome is associated with up-regulation of vascular endothelial growth factor. J. Clin. Endocrinol. Metab. 87, 3300—3308.

Yding Andersen, C., 2002. Effect of FSH and its different isoforms on maturation of oocytes from pre-ovulatory follicles. Reprod. Biomed. Online 5, 232—239.

Yding Andersen, C., Leonardsen, L., Ulloa-Aguirre, A., Barrios-De-Tomasi, J., Moore, L., Byskov, A.G., 1999. FSH-induced resumption of meiosis in mouse oocytes: effect of different isoforms. Mol. Hum. Reprod. 5, 726—731.

Zelinski-Wooten, M.B., Hutchison, J.S., Hess, D.L., Wolf, D.P., Stouffer, R.L., 1995. Follicle stimulating hormone alone supports follicle growth and oocyte development in gonadotrophin-releasing hormone antagonist-treated monkeys. Hum. Reprod. 10, 1658—1666.

Ziecik, A.J., Derecka-Reszka, K., Rzucidło, S.J., 1992. Extragonadal gonadotropin receptors, their distribution and function. J. Physiol. Pharmacol. 43, 33—49.

Declaration: The authors report no financial or commercial conflicts of interest.

Received 10 September 2011; refereed 3 October 2011; accepted 2 November 2011.