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REVIEW

GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis

Lawrence Engmann [a,*], Claudio Benadiva [a], Peter Humaidan [b]

[a] *Department of Obstetrics and Gynecology, Center for Advanced Reproductive Services, University of Connecticut School of Medicine, 2 Batterson Park Road, Farmington, CT, USA;* [b] *The Fertility Clinic, Skive Regional Hospital and Faculty of Health, Aarhus University, Resenvej 25, 7800 Skive, Denmark*

* Corresponding author. *E-mail address:* lengmann@uchc.edu (LL Engmann).

Dr Engmann graduated from the University of Ghana Medical School and completed his residency and fellowship in both England and the USA. He is currently the Director of the Oncofertility Program at the Center of Advanced Reproductive Services and an Assistant Professor in Obstetrics and Gynecology at the University Of Connecticut School Of Medicine, USA. Dr Engmann is a CREST Scholar and has collaborated with the Reproductive Medicine Network on several projects. He has lectured extensively at national and international conferences and authored over 50 peer reviewed publications. His current research interests are the use of GnRH agonist trigger, prevention of ovarian hyperstimulation syndrome and optimization of Controlled Ovarian Stimulation protocols.

Abstract Gonadotrophin releasing hormone agonist (GnRHa) trigger is effective in the induction of oocyte maturation and prevention of ovarian hyperstimulation syndrome during IVF treatment. This trigger concept, however, results in early corpora lutea demise and consequently luteal phase dysfunction and impaired endometrial receptivity. The aim of this strenghths, weaknesses, opportunities and threats analysis was to summarize the progress made over the past 15 years to optimize ongoing pregnancy rates after GnRHa trigger. The advantages and potential drawbacks of this type of triggering are reviewed. The current approach to the management of GnRHa trigger in autologous cycles is based on the peak serum oestradiol level or follicle number and aims at a fresh embryo transfer or a segmentation approach with elective cryopreservation policy. We recommend intensive luteal support with transdermal oestradiol and intramuscular progesterone alone if peak serum oestradiol is 4000 or more pg/ml after GnRHa trigger or dual trigger with GnRHa and HCG 1000 IU if peak serum oestradiol is less than 4000 pg/mL. On the contrary, we recommend HCG 1500 IU 35 h after GnRHa trigger if there are less than 25 follicles, or freeze all oocytes or embryos if there are over 25 follicles.

KEYWORDS: GnRH agonist trigger, IVF, OHSS, pregnancy rates

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Introduction

The administration of HCG to induce final oocyte maturation has been used for decades and has been considered the gold standard during ovarian stimulation for IVF cycles. Recently, however, it has been suggested that the time has come for a paradigm shift in triggering policies (Humaidan and Alsbjerg, 2014; Humaidan and Polyzos, 2014). Although HCG effectively induces oocyte maturation and maintains excellent pregnancy rates during the IVF process, the prolonged half-life of HCG compared with natural LH promotes supraphysiological luteal steroid levels and the development of multiple corpora lutea, resulting in a potential increased risk of ovarian hyperstimulation sndrome (OHSS). Therefore, the use of alternate modalities to induce oocyte maturation to prevent OHSS, such as gonadotrophin releasing hormone agonist (GnRHa) has been the focus of research for years (Engmann et al., 2008; Humaidan et al., 2005, 2010; Itskovitz-Eldor et al., 2000; Kol and Itskovitz-Eldor, 2010; Shapiro et al., 2011a, 2011b).

A single dose of GnRHa induces an endogenous LH and FSH surge similar to that of the natural cycle, sufficiently high enough to successfully induce final oocyte maturation. This modality of triggering was initially advocated in the late 1980s and early 1990s (Emperaire, 1994; Gonen et al., 1990; Itskovitz et al., 1991; Itskovitz-Eldor et al., 1993; Lanzone et al., 1989; Lewit et al., 1996; Segal and Casper, 1992; van der Meer et al., 1993). Soon after the introduction of GnRHa to trigger oocyte maturation during IVF treatment, however, its use was hampered by the introduction of GnRHa for pituitary down-regulation during ovarian stimulation. Subsequently, the introduction of the GnRH antagonist for the prevention of premature LH surge in the late 1990s (Albano et al., 1997; The Ganirelix Dose-Finding Study Group, 1998) rekindled the interest in the use of GnRHa to induce oocyte maturation (Itskovitz-Eldor et al., 2000).

After publication of the initial clinical experience from GnRHa trigger during GnRH antagonist co-treatment in IVF cycles (Itskovitz-Eldor et al., 2000), two randomized controlled trials in normal responder patients were published, showing an unacceptably high early pregnancy loss rate, resulting in low live birth rates (Humaidan et al., 2005; Kolibianakis et al., 2005). Subsequently, several prospective randomized and retrospective trials evaluated various protocols after GnRHa trigger to optimize conception rates and prevent or reduce OHSS as well as optimize the luteal phase endocrine profile (Beckers et al., 2003; DiLuigi et al., 2010; Engmann et al., 2008; Fauser et al., 2002; Griffin et al., 2012; Humaidan, 2009; Humaidan et al., 2006, 2010, 2013a, 2013b; Kol et al., 2011; Melo et al., 2009; Papanikolaou et al., 2011; Shapiro et al., 2011a, 2011b). Most of these studies have moved the science forward to the present state of affairs and ensured that patient safety is considered paramount during ovarian stimulation.

The use of GnRHa to induce oocyte maturation during IVF, however, is still not widely accepted and not widely used (Worldwide, 2013). Several reasons may account for the lack of widespread acceptance, including premature Cochrane reviews and meta-analyses with debatable conclusions (Griesinger et al., 2006; Youssef et al., 2011, 2014), reports of bad experiences with its use (Griesinger et al., 2011a, 2011b; Honnma et al., 2011), misconceptions as well as a general resistance to change and adopt a new protocol that may involve some learning curve in its successful usage.

Table 1 Strengths, weaknesses, opportunities and threats analysis of gonadotrophin releasing hormone agonist trigger.

Strengths
Physiological endogenous gonadotrophin surge
Similar pregnancy rates using 'modified luteal support'
Prevention of ovarian hyperstimulation syndrome
Less luteal phase patient discomfort
Improved oocyte yield in immature oocyte syndrome and empty follicle syndrome
Weaknesses
Abnormal luteal phase
Lower 'success rates' without modified luteal phase support
Failure to induce oocyte maturation and empty follicle syndrome in certain case scenarios
More intense luteal supplementation and monitoring
No consensus on GnRHa trigger type or dose
Opportunities
Development of individualized luteal phase regimens
Improved safety for oocyte donors and patients
Ideal protocol for specific clinical scenarios
Improved performance of embryo cryopreservation programmes
Threats
Lack of availability of intramuscular progesterone, HCG dosing, or both, in some countries
Patient characteristics limiting widespread use
Premature Cochrane reviews and meta-analyses
Misconceptions and resistance

We, therefore, aim to summarize the studies that have been published since the first study using GnRHa during GnRH antagonist co-administration (2000–2015), and review the progress that has been made. Moreover, we aim to explore potential reasons for the lack of widespread acceptance of GnRHa trigger and try to offer practical proposals for its safe use to allow more clinicians and patients to experience the advantages of this approach of triggering. We have used the format often applied in the business world, the SWOT (strengths, weaknesses, opportunities and threats) analysis (**Table 1**), which has previously been used in reproductive medicine (Fauser et al., 2010) and other areas of medicine (Ferrer et al., 2009; Pastrana et al., 2015; Willis and Thurston, 2015).

Current state of affairs

The administration of a single bolus of GnRHa for trigger results in early corpora lutea demise and, therefore, a decrease in the release of factors such as vascular endothelial growth factor (VEGF) and prevention of OHSS development (Cerrillo et al., 2009, 2011). The first randomized trials after the initial publication on GnRHa trigger were in normal responder patients, using standard luteal support and showing unacceptably low live birth rates of 4–6% (Humaidan et al., 2005; Kolibianakis et al., 2005). Subsequently, a systematic

meta-analysis and a Cochrane review concluded that GnRHa should not be used routinely for final oocyte maturation in autologous cycles in view of the low pregnancy and live birth rates (Griesinger et al., 2006; Youssef et al., 2011). With the realization that the luteal phase was suboptimal, several approaches were subsequently suggested to improve pregnancy rates, ranging from intensive luteal phase steroid support (Engmann et al., 2006, 2008; Iliodromiti et al., 2013a, 2013b; Imbar et al., 2012), adjuvant low-dose HCG at the time of GnRHa trigger (Griffin et al., 2012; Shapiro et al., 2008, 2011a, 2011b) or at the time of oocyte retrieval (Humaidan, 2009; Humaidan et al., 2010, 2013a, 2013b; Iliodromiti et al., 2013a, 2013b) or during the luteal phase (Castillo et al., 2010; Humaidan et al., 2013a, 2013b) as well as the use of luteal phase recombinant LH administration (Papanikolaou et al., 2011).

There are currently several schools of thought regarding the use of GnRHa trigger in autologous IVF cycles: the first approach is based on the peak serum oestradiol level or follicle number, and aims at a fresh embryo transfer either using an intensive luteal phase steroid support or low dose HCG at the time of trigger (dual trigger) or at the time of oocyte retrieval (Engmann and Benadiva, 2010, 2012; Griffin et al., 2012; Humaidan, 2012; Humaidan et al., 2015). In the second, segmentation approach, stimulation and embryo transfer are disconnected. Therefore, an elective cryopreservation policy followed by embryo transfer in a subsequent frozen thawed cycle has been proposed to circumvent the abnormal luteal phase seen after GnRHa trigger without the need for modification of the luteal phase support (Devroey et al., 2011; Garcia-Velasco, 2012; Griesinger et al., 2010, 2011a, 2011b).

Interestingly, GnRHa trigger in oocyte donors is less controversial and currently more widely used in view of the excellent pregnancy rates reported in recipients, and the clear advantage of OHSS prevention (Acevedo et al., 2006; Bodri et al., 2010, 2011; Melo et al., 2009).

Strengths

More physiological endogenous gonadotrophin surge

The endogenous gonadotrophin surge released after the administration of a single bolus of GnRHa is considered more physiological than HCG trigger as LH as well as FSH are released, inducing a surge similar to that of the natural mid-cycle surge of gonadotrophins. Although the specific function of the mid-cycle FSH surge has not been completely elucidated, and its role may not be completely essential, some studies have shown that it may have an effect on the resumption of oocyte meiosis and oocyte maturation, expansion and dispersion of the oocyte cumulus complex, and establishment of adequate complements of LH receptors on granulosa cells (Eppig, 1979; Yanagishita et al., 1981; Yding Andersen, 2002; Zelinski-Wooten et al., 1995).

In fact, previous studies have shown a higher proportion of mature oocytes after GnRHa trigger compared with HCG (Humaidan et al., 2005, 2011; Oktay et al., 2010; Reddy et al., 2014), although other studies have not confirmed this (Acevedo et al., 2006; Bodri et al., 2011; Engmann et al., 2008; Melo et al., 2009). The use of a dual trigger, however, i.e. the combination of a standard dose HCG with a bolus of GnRHa, has been shown to improve the number, proportion of mature oocytes, or both, in normal responders (Lin et al., 2013), and specifically in cases of immature oocyte syndrome (Castillo et al., 2012; Griffin et al., 2012), which could be potentially attributed to the combined LH and FSH surge induced by the GnRHa trigger.

Similar pregnancy rates using 'modified' luteal support

Modified luteal support consisting of intensive steroidal support or adjuvant low-dose HCG (**Table 2**) has been advocated to circumvent the abnormal corpora luteal function induced by the administration of a bolus of GnRHa. The use of intensive steroidal support in the form of intramuscular progesterone and transdermal oestradiol and luteal phase serum oestradiol and progesterone monitoring to maintain levels of 200 pg/ml and 20 ng/ml, respectively, have been shown to have similar pregnancy rates compared with HCG trigger (Engmann et al., 2006, 2008; Iliodromiti et al., 2013a, 2013b; Imbar et al., 2012).

Moreover, several clinical trials have also shown excellent pregnancy rates with the use of low-dose HCG 1500 IU at the time of oocyte retrieval after GnRHa trigger in both normal and high responders (Humaidan, 2009; Humaidan et al., 2006, 2010, 2013a, 2013b; Iliodromiti et al., 2013a, 2013b; Radesic and Tremellen, 2011).

Finally, the use of dual trigger with low-dose HCG 1000 IU and GnRHa with intensive luteal phase steroid support results in optimal pregnancy rates in high responders with peak serum oestradiol less than 4000 pg/ml (Griffin et al., 2012; Shapiro et al., 2008, 2011a, 2011b). Adjuvant low-dose HCG, however, should be used with caution and should take the number of follicles at the time of trigger into account to reduce the risk of OHSS (Bodri, 2013; Seyhan et al., 2013).

Table 2 Luteal phase support protocols after gonadotrophin releasing hormone agonist trigger.

Protocol	*Indication*
Intensive luteal support	Peak serum oestradiol ≥4000 pg/ml
Dual trigger with GnRHa and HCG 1000 IU	Peak serum oestradiol <4000 pg/ml
GnRHa trigger and HCG 1500 IU 35 h later	<25 follicles
Freeze all oocytes or embryos	≥25 follicles

GnRHa, gonadotrophin releasing hormone agonist.

Prevention of OHSS

Without question, one of the major benefits of GnRHa trigger is the prevention of OHSS. The administration of GnRHa induces a short LH surge duration of only 24–36 h (Itskovitz et al., 1991) resulting in defective corpora lutea formation. Hence, the defective corpus luteum formation or early corpus luteum demise results in the decrease in release of vasoactive peptides such as VEGF (Cerrillo et al., 2009, 2011), which *per se* prevent OHSS development (Bodri et al., 2011; Engmann et al., 2008; Humaidan et al., 2011). In fact, the mid-luteal ovarian volume is significantly reduced after GnRHa trigger compared with HCG trigger (Babayof et al., 2006; Engmann et al., 2008; Garcia-Velasco et al., 2010). Similarly, less fluid is found in the cul de sac in the mid-luteal phase after GnRHa trigger (Garcia-Velasco et al., 2010).

Several randomized and retrospective studies in autologous high responders and oocyte donors previously reported the total elimination of OHSS after GnRHa trigger (Babayof et al., 2006; Bodri et al., 2011; DiLuigi et al., 2010; Engmann et al., 2008; Humaidan et al., 2011; Kol and Muchtar, 2005). In a randomized study involving high responders, such as women with polycystic ovary syndrome, no patient developed moderate or severe OHSS compared with 31% after HCG trigger and fresh transfer (Engmann et al., 2008). Similar findings were reported by Babayof et al. (2006) in women with polycystic ovary syndrome. Kol and Muchtar (2005) reported no OHSS development in six women with mean serum oestradiol levels of 6322 pg/ml and 20 oocytes retrieved. Moreover, no cases of OHSS were reported in a study consisting of 61 high responders with mean peak serum oestradiol levels above 4824 pg/ml who had an average of 26 oocytes retrieved (DiLuigi et al., 2010).

In recent years, however, cases of OHSS occurring after GnRHa trigger and a 'freeze all' policy have been reported (Fatemi et al., 2014; Gurbuz et al., 2014; Ling et al., 2014), raising concerns that GnRHa trigger may not totally eliminate OHSS in all patient categories as either GnRH, FSH or LH receptor mutations in these patients might explain the occurrence of OHSS. Moreover, specific patient characteristics, which have not yet been elucidated, may play an important role. It is, therefore, important that, although GnRHa may be effective in reducing the risk of OHSS, caution is exercised and efforts made to use mild ovarian simulation protocols, especially in high-risk patients.

Less patient discomfort

Multiple follicular development and a significant increase in ovarian volume and fluid retention after HCG trigger may predispose the patent to significant abdominal discomfort, bloating and pain in the luteal phase. On the contrary, GnRHa trigger results in reduced ovarian volumes (Engmann et al., 2008), less fluid in the cul de sac (Garcia-Velasco et al., 2010) and onset of early menses (Bodri et al., 2009), which result in less abdominal discomfort and bloating after GnRHa trigger and hence an improved quality of life. In a study consisting of 39 oocyte donors, no patients complained of abdominal discomfort 1 week after GnRHa trigger compared with 42% after HCG trigger (Cerrillo et al., 2009). This, therefore, makes GnRHa trigger the protocol of choice for oocyte donors and women undergoing an elective cryopreservation cycle.

Improved oocyte yield in immature oocyte syndrome and empty follicle syndrome

Immature oocyte syndrome is characterized by the retrieval of more than 25% immature oocytes (Bar-Ami et al., 1994), and the exact incidence and cause is currently unknown. The dual surge of FSH and LH seen after GnRHa trigger may be beneficial in improving oocyte maturation because the FSH surge may have a role in the induction of oocyte maturation and has been shown to induce ovulation independent of the LH surge in animals (Zelinski-Wooten et al., 1998).

GnRHa trigger has been used alone for successful induction of oocyte maturation in a patient with a previous history of empty follicle syndrome (EFS) (Lok et al., 2003). Moreover, Castillo et al. (2013) described a case of a successful pregnancy after the use of a dual trigger of GnRHa and standard dose of HCG in a patient who previously had repetitive immature oocytes and EFS (Castillo et al., 2013). Finally, Griffin et al. (2014) evaluated 27 patients who had immature oocytes in a previous cycle triggered with HCG, and showed a higher proportion of mature oocytes and higher fertilization rates after a dual trigger of GnRHa and a standard dose of HCG (Griffin et al., 2014).

Weaknesses

Abnormal luteal phase

The cause of the abnormal luteal phase after GnRHa trigger is currently not completely understood. It has, however, been shown that administration of GnRHa to induce oocyte maturation results in a defective corpus luteum formation, early demise of the corpus luteum, or both. This is because the administration of GnRHa induces a rise of LH lasting only 24–36 h (Itskovitz et al., 1991), with subsequent pituitary desensitization and withdrawal of LH support for the development and function of the corpora lutea. Although an LH surge of around 18–24 h duration will induce oocyte maturation, it will not be of sufficient duration to induce adequate corpora luteum formation (Chandrasekher et al., 1991; Zelinski-Wooten et al., 1991, 1992).

Evidence of defective corpus luteum formation and function has been demonstrated by previous studies showing a significantly reduced mid-luteal phase ovarian volume (Engmann et al., 2008; Garcia-Velasco et al., 2010), low levels of serum markers of corpus luteum function in the non-supplemented (Beckers et al., 2003) as well as the supplemented luteal phase (Engmann et al., 2008; Fauser et al., 2002; Nevo et al., 2003) and shorter duration of the luteal phase (Acevedo et al., 2006; Beckers et al., 2003; Garcia-Velasco et al., 2010; Hernandez et al., 2009). The consequences of an abnormal luteal phase include impaired endometrial receptivity and implantation rates.

Lower 'success' rates

Early studies reported lower pregnancy rates after GnRHa trigger when a standard luteal phase support, only, was used

after fresh transfer (Humaidan et al., 2005; Kolibianakis et al., 2005). An adverse effect of GnRHa on oocyte or embryo quality and implantation potential was previously suggested as the reason for the lower pregnancy rates; however, several studies have actually shown excellent oocyte maturation rates (Acevedo et al., 2006; Engmann et al., 2008; Melo et al., 2009) and good-quality embryos (Acevedo et al., 2006; Hernandez et al., 2009) as well as optimal numbers of supernumerary embryos available for cryopreservation (Engmann et al., 2008). Moreover, excellent pregnancy rates have been reported in oocyte recipients who received embryos from GnRHa triggered oocyte donor cycles (Acevedo et al., 2006; Bodri et al., 2011; Melo et al., 2009) and in women who underwent frozen embryo transfer where the oocytes originated from fresh GnRHa triggered cycles (Eldar-Geva et al., 2007; Griesinger et al., 2011a, 2011b; Herrero et al., 2011). These pieces of evidence have clearly excluded any possible adverse effect of GnRHa on oocyte and embryo quality.

The reasons for the reported lower pregnancy rates after GnRHa trigger have now been clearly attributed to low circulating early luteal LH levels, impairing corpus luteum function, endometrial receptivity and implantation (Beckers et al., 2003; Chandrasekher et al., 1991; Engmann and Benadiva, 2010; Humaidan et al., 2012a, 2012b, 2012c). A standard luteal phase support similar to that used after HCG trigger has been shown to result in significantly lower pregnancy rates after GnRHa trigger (Humaidan et al., 2005; Kolibianakis et al., 2005). Altered endometrial gene expression after GnRHa trigger may account for the low pregnancy rates with the use of standard luteal support (Bermejo et al., 2014; Humaidan et al., 2012a, 2012b, 2012c). Therefore, it is now widely accepted that some form of modified luteal phase support involving either an intensive luteal phase steroidal support or low-dose HCG supplementation is required to circumvent the abnormal luteal phase after GnRHa trigger (Engmann and Benadiva, 2010; Engmann et al., 2008; Griffin et al., 2012; Humaidan, 2009; Humaidan et al., 2006, 2013a, 2013b; Iliodromiti et al., 2013a, 2013b; Imbar et al., 2012; Kol et al., 2015a, 2015b; Shapiro et al., 2011a, 2011b).

Failure to induce oocyte maturation and empty follicle syndrome

The efficacy of GnRHa to induce optimal oocyte maturation has been questioned in some circles in view of reports of failed oocyte maturation (Griesinger et al., 2011a, 2011b; Honnma et al., 2011). This concern has contributed to the lack of universal adoption of this approach of trigger. The risk of EFS after GnRHa trigger has been reported to be between 1.4% (Kummer et al., 2013) and 3.5% (Castillo et al., 2012), which is similar to the incidence after HCG trigger of 0.1-2% (Ben-Shlomo et al., 1991; Zegers-Hochschild et al., 1995; Quintans et al., 1998; Mesen et al., 2011; Baum et al., 2012).

The factors that contribute to failed GnRHa trigger have been extensively reviewed by different studies and may be similar to those of failed HCG trigger (Castillo et al., 2012; Chen et al., 2012; Kummer et al., 2013; Shapiro et al., 2011a, 2011b). Kummer et al. (2013) evaluated 508 cycles using GnRHa trigger and showed that all the cases of EFS could be attributed to a failure of induction of an optimal endogenous LH surge or progesterone rise after GnRHa trigger. Appropriate selection of patients is important, and those with hypothalamic dysfunction are not candidates for GnRHa trigger as they may not reliably respond to GnRHa administration. It has also been proposed that prolonged use of oral contraceptive pill may result in a lack of response to GnRHa trigger, although there is currently no evidence to support this.

Other possible reasons for failed GnRHa trigger, including administration error and variability in the in-vivo biological activity of some batches of commercially available GnRHa cannot be ruled out. Although there is no clear serum LH or progesterone cut-off level to predict the retrieval of an optimal number of mature oocytes, all cases of failed trigger occurred in patients with post-trigger LH less than 15 IU/l (Kummer et al., 2013). Therefore, monitoring of serum LH 12 h after trigger may serve as a warning sign for a failed endogenous LH surge and additional steps could be taken to re-trigger with HCG (Honnma et al., 2011; Kummer et al., 2013).

More intense luteal supplementation and monitoring

In view of the abnormal luteal phase, intensive supplementation with steroids including both oestradiol and progesterone (Engmann et al., 2008; Iliodromiti et al., 2013a, 2013b; Imbar et al., 2012; Shapiro et al., 2011a, 2011b) or low-dose HCG supplementation (Castillo et al., 2010; Humaidan et al., 2010, 2013a, 2013b; Iliodromiti et al., 2013a, 2013b; Radesic and Tremellen, 2011) in the luteal phase is essential to maintain optimal conception rates. It has been debated whether luteal phase oestradiol supplementation is necessary after GnRHa trigger. The intensive luteal phase support used after GnRHa trigger is based on the premise that the corpus luteum is dysfunctional. Therefore, the design of the luteal phase protocol was initially derived from protocols used for oocyte recipient cycles where there are no functional corpora lutea, and which have always included both oestradol and progesterone supplementation. Several of the studies that used protocols without oestradiol supplementation after GnRHa trigger have resulted in low pregnancy rates (Fauser et al., 2002; Kolibianakis et al., 2005). Studies have also showed that monitoring of steroid levels in the luteal phase may be essential in maintaining optimal conception rates (Engmann et al., 2008; Shapiro et al., 2011a, 2011b). This may involve regular clinic visits for serum monitoring as well as the use of intramuscular injections, which may be painful and place an undue burden on patients compared with HCG triggering.

No consensus for GnRHa trigger dose

Although, several studies have been published over the past 2 decades evaluating the use of GnRHa for trigger of oocyte maturation, to the best of our knowledge, only one study has compared the efficacy and doses of different types of GnRHa currently in use (Parneix et al., 2001). Several different doses and regimens of GnRHa have been used without prior dose-finding studies to determine the optimal dose required for induction of oocyte maturation and prevention of OHSS that will exert minimal detrimental effect on the luteal phase. It

is plausible that the use of different types and dosages may account for the differences in efficacy of GnRHa trigger as well as its effects on pregnancy rates and risk of OHSS development.

Single doses of leuprolide acetate (Engmann et al., 2008; Fauser et al., 2002; Oktay et al., 2010; Shapiro et al., 2007), as well as two doses, have been previously used (Parneix et al., 2001). No consensus has been reached on the dosage required for optimal induction of oocyte maturation and several different dosages have been used for leuprolide acetate ranging from 0.5 mg (Fauser et al., 2002), 1 mg (Engmann et al., 2008; Ling et al., 2014; Oktay et al., 2010), 1.5 mg (Castillo et al., 2010), 2 mg (Radesic and Tremellen, 2011) to 4 mg (Shapiro et al., 2011a, 2011b). The dose of triptorelin has been most consistent, and almost all studies have used 0.2 mg (Babayof et al., 2006; Beckers et al., 2003; Fauser et al., 2002; Imbar et al., 2012; Itskovitz-Eldor et al., 2000; Kolibianakis et al., 2005). Two dose-finding studies have been published to date using buserelin (Buckett et al., 1998) and triptorelin (Ngoc Lan Vuong et al., 2015). It has been shown that the most effective minimum dose of buserelin to consistently induce the gonadotrophin surge and oocyte maturation was 0.5 mg, and this is the dose that has been used in previous studies (Humaidan et al., 2013a, 2013b). A recent randomized controlled trial explored three different doses of triptorelin (0.2, 0.3 and 0.4 mg) in oocyte donors, and reported no differences in number of metaphase II oocytes, fertilization rates, embryo development and pregnancy rates in the recipients between the different doses used (Ngoc Lan Vuong et al., 2015).

Opportunities

Development of individualized luteal phase regimens

The use of GnRHa trigger in IVF for the first time allows the separation of the induction of final oocyte maturation from the luteal phase, which opens an opportunity for a 'tailored' approach to the luteal phase support, taking into account the ovarian response to stimulation of each individual patient (**Table 2**) (Beckers et al., 2003; Humaidan et al., 2013a, 2013b; Kol et al., 2011).

Although, serum oestradiol on the day of trigger has been shown to be predictive of reproductive success after GnRHa trigger (Kummer et al., 2011), another study did not confirm this finding (Iliodromiti et al., 2013a, 2013b), which may be explained by differences in patient characteristics and laboratory assays. Moreover, it has been suggested that intensive luteal phase supplementation alone may be sufficient for patients with serum oestradiol greater than 4000 pg/ml in view of the optimal pregnancy rates (Kummer et al., 2011). In contrast, low-dose HCG supplementation, such as the dual trigger with low-dose HCG, may be required in women with peak oestradiol levels below 4000 pg/ml (Griffin et al., 2012). It has also been shown that women with less than 25 follicles would benefit from adjuvant administration of 1500 IU of HCG at time of oocyte retrieval, whereas those with over 25 follicles may benefit from a freeze all strategy (Humaidan et al., 2013a, 2013b, 2015). Others, however, have recommended freezing all embryos in women with 18 or more follicles measuring 10–14 mm in diameter to prevent development of OHSS (Seyhan et al., 2013).

Other forms of low-dose HCG regimens in the luteal phase have been tried, although this approach may lead to a higher risk of OHSS (Castillo et al., 2010). Recently a randomized GnRHa trigger study showed that a very low dose of daily HCG administration (125 IU) effectively rescued the corpus luteum function and secured good clinical pregnancy rates. Importantly, no other luteal phase support was used, and this study further introduces the concept of the exogenous progesterone free luteal phase in assisted reproduction techniques (Elbaek et al., 2014). Kol et al. (2015a, 2015b) recently introduced the concept of 'luteal coasting' after GnRHa trigger, which suggested that the luteal phase rescue HCG bolus of 1500 IU is administered only when serum progesterone levels drop significantly. Interestingly, no other luteal support was given in that study (Kol et al., 2015a, 2015b).

Improved safety for oocyte donors

Oocyte donors are usually young healthy women, donating oocytes for altruistic reasons and it behoves all clinicians to make the process safe and seamless. Overwhelming evidence shows that GnRHa trigger is effective in inducing optimal oocyte maturation and preventing OHSS development in oocyte donors as well as maintaining excellent pregnancy rates in the recipients (Acevedo et al., 2006; Bodri et al., 2011; Galindo et al., 2009; Hernandez et al., 2009; Melo et al., 2009). The reduction in luteal phase ovarian volume and fluid in the cul de sac (Garcia-Velasco et al., 2010) results in less abdominal discomfort and bloating and a better quality of life. Taking these facts into consideration, GnRHa should be the first line trigger concept in oocyte donors.

Ideal protocol for specific clinical situations

All patients undergoing elective cryopreservation of all oocytes or embryos are ideal candidates for GnRHa trigger as there will be no concerns about the luteal phase. These include patients undergoing fertility preservation for medical or social reasons and those undergoing preimplantation genetic screening or diagnosis, with a plan for trophectoderm biopsy and a 'freeze all' for subsequent transfer. Other specific clinical situations for 'freeze all' are cycles with a premature progesterone elevation.

The use of GnRHa trigger for oocyte and embryo cryopreservation in cancer patients undergoing fertility preservation is ideal because it significantly reduces luteal circulating oestradiol levels in patients with oestradiol receptor positive breast cancer (Oktay et al., 2010; Reddy et al., 2014), thereby reducing the risk of exposure to high oestradiol levels. Moreover, it allows a quick resolution to a normal baseline status, preventing a potential delay in initiating chemotherapy (Oktay et al., 2010).

Recently, trophectoderm biopsy with elective cryopreservation of all embryos and subsequent transfer in a natural cycle has been advocated as the modality of choice for patients undergoing preimplantation genetic screening or diagnosis (Schoolcraft and Katz-Jaffe, 2013; Schoolcraft et al.,

2010, 2011). Trophectoderm biopsy offers several advantages over blastomere biopsy (Schoolcraft et al., 2010; Scott et al., 2013) and, importantly, in most cases the biopsy results may not be available for a day 5 or 6 transfer.

Premature serum progesterone elevation has been associated with lower pregnancy rates in some studies (Bosch et al., 2010; Huang et al., 2012a, 2012b), and it has been proposed that elective oocyte and embryo cryopreservation will allow transfer in a subsequent non-stimulated cycle to optimize conception rates (Shapiro et al., 2010). The use of GnRHa trigger in such situations prevents the development of OHSS, and will allow a quick return of menses to enable a frozen embryo transfer cycle within a short period of time.

Finally, the use of GnRHa trigger allows a second ovarian stimulation shortly after the initial oocyte retrieval in poor responders, optimizing the number of oocytes retrieved during the same menstrual cycle (Kuang et al., 2014).

Improved performance of embryo cryopreservation programmes

Given that the vitrification technique has improved the efficiency and outcome of oocyte or embryo cryopreservation programmes (Kolibianakis et al., 2009), some investigators recommended a 'freeze all' policy for all IVF patients (Barnhart, 2014; Shapiro et al., 2014a, 2014b; Weinerman and Mainigi, 2014). This concept has also been suggested after GnRHa trigger in view of concerns about the abnormal luteal phase (Atkinson et al., 2014; Devroey et al., 2011; Garcia-Velasco, 2012; Griesinger et al., 2010, 2011a, 2011b; Herrero et al., 2011; Manzanares et al., 2010). It is, therefore, essential that a highly successful oocyte and embryo cryopreservation programme is in place in all centres for this approach to be successful and widely accepted.

Threats

Lack of availability of intramuscular progesterone in some countries and HCG dosing

Some investigators have suggested that intensive luteal support using intramuscular progesterone and serum monitoring during the luteal phase is crucial for the success of GnRHa trigger. The use of intramuscular progesterone is not available in all countries, making it difficult to replicate the success that has been demonstrated by others (Engmann et al., 2008; Imbar et al., 2012; Shapiro et al., 2011a, 2011b). It has also been argued that the intramuscular progesterone is too painful and may not be acceptable to patients and, therefore, several physicians may be reluctant to recommend its use. Although severe allergic reactions to intramuscular progesterone in sesame oil have been described (Bouckaert et al., 2004; Khan et al., 2008), these adverse reactions are rare and the use of intramuscular progesterone in olive oil may prevent these complications. Regarding the use of one or more small boluses of HCG during the luteal phase, there is still a need for fine-tuning the dose as well as the upper cut-off level of follicles at which a 'freeze all' policy should be adopted in order to avoid OHSS (Humaidan et al., 2013a, 2013b).

Patient characteristics limiting widespread use

Certain patient groups are not candidates for the use of GnRHa to trigger oocyte maturation, which obviously limits its widespread use (Kummer et al., 2013). Therefore, patients with hypothalamic amenorrhoea or dysfunction are not candidates for GnRHa trigger. Moreover, patients who have been on long-term oral contraceptive pills may be suppressed to a degree that they may not respond to GnRHa trigger. Finally, most centres in the world still routinely use the long GnRHa pituitary down-regulation protocol as a first-line protocol, which hampers the use of GnRHa trigger.

Premature Cochrane reviews and meta-analyses

Cochrane reviews are widely recognized as a quality source of evidence-based medicine (Humaidan and Polyzos, 2012). Although they provide useful information for daily clinical practice, premature publications of Cochrane reviews and meta-analyses, including limited numbers of heterogeneous studies performed during the development of new concepts, can be harmful and may draw inappropriate conclusions (Humaidan et al., 2012a, 2012b, 2012c; Kol et al., 2015a, 2015b).

Misconceptions and clinical resistance

The use of HCG to trigger oocyte maturation is well established, and pregnancy rates are excellent. Clinicians are, therefore, comfortable using this concept. The use of GnRHa trigger, however, requires changes in daily routine clinical practice in to manage and monitor the luteal phase, which might create clinical resistance as it might not be considered simple enough for the busy clinician to be comfortable with its routine use.

Therefore, in a recent worldwide survey, it was shown that GnRHa trigger is used in 5.2% to 36.1% of cases, only (Worldwide, 2013).

Moreover, previous early reports of lower conception rates lead to misconceptions that have been difficult to change over the years. Importantly, pressure is placed on the clinician to achieve the highest success rates as services offered by many reproductive centres are financially driven. Finally, as OHSS is still not reported as a complication of assisted reproduction techniques in most countries, until now there has been less incentive to adopt the GnRHa trigger concept.

Proposed directions for future research in the development of GnRHa trigger protocols

More studies are needed to evaluate the optimal dose of different types of GnRHa required to achieve optimal oocyte maturation and prevent OHSS without significant aberration of the luteal phase. Further research studies are required to compare the different types of GnRHa available to determine if there are differential effects in the luteal phase and pregnancy rates as well as prevention of OHSS (**Table 3**). It is important to further elucidate the underlying pathophysiology of the abnormal luteal phase after GnRHa trigger. This

Table 3 Proposed directions for future research.

Explore optimal dose of GnRHa for trigger
Explore differential effects of different types of GnRHa on luteal phase and pregnancy
Explore underlying pathophysiology of the abnormal luteal phase
Refine luteal phase supplementation protocols to allow fresh transfers
Identify patients at risk of failed GnRHa trigger
Reporting clinic success rates to include ovarian hyperstimulation syndrome

GnRHa, gonadotrophin releasing hormone agonist.

will help refine luteal phase supplementation protocols to allow fresh embryo transfers and to improve pregnancy rates without increasing the risk of OHSS. More extensive studies are also required to identify patients who may not respond to GnRHa trigger or who will be at risk for a suboptimal LH response. Finally, new ways of reporting success rates to include OHSS should be generally instituted to encourage physicians to use protocols that are safe for the patient.

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