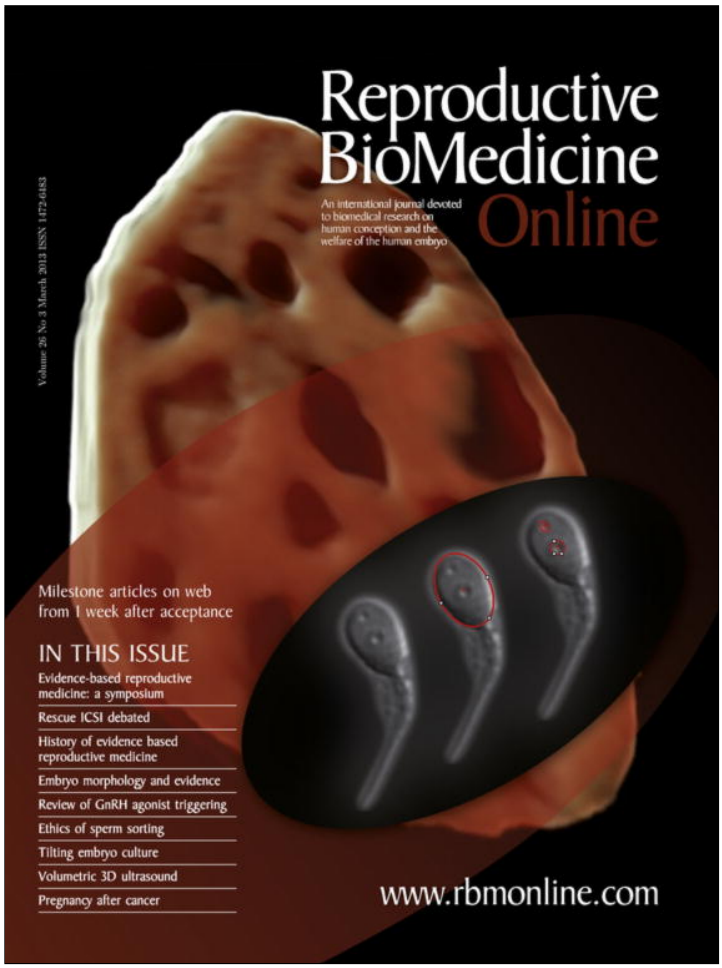

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REVIEW

# GnRH agonist triggering: recent developments

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**Abstract** The concept that a bolus of gonadotrophin-releasing hormone agonist (GnRHa) can replace human chorionic gonadotrophin (HCG) as a trigger of final oocyte maturation was introduced several years ago. Recent developments in the area strengthen this premise. GnRHa trigger offers important advantages, including virtually complete prevention of ovarian hyperstimulation syndrome (OHSS), the introduction of a surge of FSH in addition to the LH surge and finally the possibility to individualize luteal-phase supplementation based on ovarian response to stimulation. We maintain that the automatic HCG triggering concept should be challenged and that the GnRHa trigger is the way to move forward with thoughtful consideration of the needs, safety and comfort of our patients.



**KEYWORDS:** GnRH agonist, FSH surge, LH surge, OHSS, oocyte maturation, ovulation triggering

## Introduction

With the introduction of the gonadotrophin-releasing hormone (GnRH) antagonist protocol and the subsequent possibility of using a bolus of GnRH agonist (GnRHa) for final oocyte maturation and ovarian hyperstimulation syndrome (OHSS) prevention, the authors of this paper founded a special interest group in 2009 'The Copenhagen GnRH Agonist Triggering Workshop Group'. The first meeting was held in Copenhagen, resulting in an extensive review (Humaidan et al., 2011), followed by several publications employing the GnRHa trigger concept. The purpose of most of the subsequent trials was to overcome the luteal-phase insufficiency previously reported post GnRHa trigger – despite supplementation with a standard luteal-phase support. A recent review focused on luteal-phase deficiency after ovarian stimulation in general, emphasizing the luteal phase after GnRHa trigger (Humaidan et al., 2012a). Following this publication, several studies were published on the subject. As the interest in GnRHa trigger is rapidly increasing, this review presents an update on the most recent literature and the continuing controversies regarding GnRHa trigger.

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## Physiology

LH homology, an extended half life and an easy manufacturing process turned human chorionic gonadotrophin (HCG) into an excellent molecule to be used for triggering of final oocyte maturation and ovulation during assisted reproduction treatment. Typically, one bolus of urinary HCG (5000–10,000 units) or recombinant HCG (250 μg) is administered approximately 36 h before oocyte retrieval in IVF cycles.

Unlike the physiological mid-cycle surge of LH and FSH, terminating 48 h after its onset, the HCG-mediated LH activity spans several days into the luteal phase. This supra-physiological LH activity stimulates the multiple corpora lutea, leading to high serum progesterone and oestradiol concentrations, which in turn decrease the endogenous LH secretion by the pituitary (Fauser and Devroey, 2003). As the HCG administered for final oocyte maturation covers the luteal phase for a total of 8–10 days, all luteal actions of LH – among those the up-regulation of VEGF and FGF2 and cytokines (LIF) necessary for implantation to successfully take place – will be covered by the exogenous HCG, and after this period gradually by the HCG produced by the implanting embryo (Humaidan et al., 2012a).

GnRH antagonist co-treatment during ovarian stimulation allows ovulation to be induced with a bolus of GnRHa, as GnRHa displaces the GnRH antagonist in the pituitary, activating the GnRH receptor, resulting in a surge of gonadotrophins (flare-up), similar to that of the natural midcycle surge of gonadotrophins. However, significant differences exist between the GnRHa-induced surge 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 surge of gonadotrophins, which consists of two phases only, with 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). Thus, the combined effect of ovarian stimulation and GnRHa trigger dramatically reduces the endogenous LH concentration during the early luteal phase (Humaidan, 2009), necessitating a modification of the standard luteal-phase support to secure the reproductive outcome (Humaidan et al., 2009, 2010).

At present, there is no commercial product that fully imitates the mid-cycle surge of gonadotrophins. An effort to introduce recombinant LH as a trigger was published in 1998 by the European Recombinant LH Study Group; however, it did not result in a commercial preparation due to the high dose of recombinant LH needed for trigger.

## Dual trigger

'Dual trigger' is the concept in which the benefits of a bolus of a GnRHa in terms of release of endogenous LH and FSH from the pituitary are combined with the long acting LH activity of a small bolus of HCG, covering the early luteal-phase LH deficiency, previously described after GnRHa trigger (Shapiro et al., 2008). The dual trigger protocol is usually followed by a standard luteal-phase support. Shapiro et al. (2011) retrospectively reported the effect of dual trigger in high-risk OHSS patients, mainly patients with a polycystic ovaries-like ultrasonography pattern and polycystic ovary syndrome (PCOS) patients. A total of 182 patients was treated according to this protocol, receiving on the day of triggering final oocyte maturation 4 mg leuprolide acetate as well as a mean of 1428 IU HCG for trigger. Patients had a mean of 28 follicles on the day of trigger and a mean of 20 oocytes were retrieved. After blastocyst transfer, an ongoing pregnancy rate of 58% per transfer was obtained. One patient (1/182) in this high-risk group of patients developed late-onset OHSS.

## Modified luteal-phase support post GnRH agonist trigger with HCG

The basic premise behind this approach is to dissociate the ovulation trigger from the luteal support. While a bolus of GnRHa is responsible for an endogenous surge of LH and FSH, a low dose(s) of HCG after oocyte aspiration will replace the actions of early luteal LH to sustain implantation and luteal ovarian steroidogenesis. This approach was previously reported prospectively by Humaidan et al. (2006, 2010) and Humaidan (2009) in normo-responding as well as hyper-responding patients, proving that low-dose luteal HCG normalizes the reproductive outcome post GnRHa trigger. Moreover, similar results were recently reported by Radesic and Tremellen (2011) who retrospectively analysed 71 consecutive high-risk OHSS cases, treated according to the protocol suggested by Humaidan et al. (2010). Forty-five per cent of patients were PCOS patients and the mean anti-Müllerian hormone concentration was 48 pmol/l. A high risk of developing OHSS was defined as the presence of at least 14 follicles $\geq$12 mm on the day of triggering final oocyte maturation. All patients were triggered with a bolus of GnRHa (leuprolide acetate, 2 mg), followed by 1500 IU HCG administered subcutaneously, after the oocyte retrieval. A mean of 17 oocytes were retrieved and all 71 patients received a single embryo transfer, which resulted in a clinical pregnancy rate of 52% per transfer and a miscarriage rate of 8%. One patient developed late-onset severe OHSS, requiring 7 days of hospitalization.

Interestingly, a total of two injections of 1500 IU HCG – on the day of oocyte retrieval and 4 days later – in low-risk OHSS patients (less than 12 follicles $>$12 mm) rescued the luteal phase and the reproductive outcome to a degree that no additional luteal-phase support was needed (Kol et al., 2011). This novel, simple and patient-friendly approach assures robust luteal activity as well as avoids lengthy luteal-phase treatment in the low-risk OHSS patient.

## Modified luteal-phase support post GnRH agonist trigger: intensive luteal oestradiol and progesterone

Babayof et al. (2006) were the first to report the use of intensive oestradiol and progesterone for luteal support in high-risk OHSS patients post GnRHa trigger. The reproductive outcome of this trial was disappointingly low. Subsequently, Engmann et al. (2008) used a similar approach in high-risk OHSS patients ($n$ = 33) post GnRHa trigger,

reporting the prevention of OHSS while maintaining good pregnancy rates. In contrast, the OHSS rate in the HCG trigger control group ($n = 32$) was 30%. These findings were recently supported by Imbar et al. (2012) in an observational trial in high-risk OHSS patients comparing the outcome of fresh transfer ($n = 70$) after GnRHa trigger and an intensive luteal-phase support with oestradiol and progesterone, based on Engmann et al. (2008), versus frozen–thawed embryo transfer cycles ($n = 40$). The authors reported a live birth rate of 27% after fresh transfer. Finally, Orvieto (2012) published a report including a cohort of 67 high-risk OHSS patients treated during the period 2010–2011, who after GnRHa trigger received an intensive luteal-phase support with oestradiol and progesterone, similar to the one reported by Engmann et al. (2008). However, despite the intensive luteal support, implantation and pregnancy rates remained disappointingly low – comparable to results previously published after GnRHa trigger without intensive luteal support (Orvieto et al., 2006). This finding was commented by Benadiva and Engmann (2012) in a Letter to the Editor with updated recommendations for handling of the luteal phase after GnRHa trigger. Thus, according to their most recent publication (Griffin et al., 2012) patients should be stratified according to their oestradiol concentration on the day of triggering final oocyte maturation. In patients with oestradiol concentrations >4000 pg/ml, the authors adhere to the previously published protocol of intensive luteal-phase support, only (Engmann et al., 2008). In patients with oestradiol concentrations <4000 pg/ml a dual trigger is used (GnRHa + 1000 IU HCG) in combination with intensive luteal-phase support.

## OHSS

A recent report by ESHRE (de Mouzon et al., 2012) clearly reveals that OHSS is still one of the major complications of ovarian stimulation for IVF. A diagnosis of OHSS was reported in 26 of the 33 countries. In total, 2470 cases of OHSS were recorded in 2007, corresponding to an OHSS occurrence of 0.7% in all stimulated cycles (0.8% in 2006). A wide variation in the occurrence of OHSS was reported: UK (1.3%) and Russia (1.8%) having the highest rates, and Germany and Spain the lowest (0.3%). However, the issue of OHSS reporting still seems to be a 'grey zone' with major under-reporting.

Importantly, OHSS may have a lethal outcome. The UK-based 'Confidential Enquiry into Maternal and Child Health' organization has reported four OHSS-related deaths during the years 2003–2005 (VIIth report, 2007), which translates into about three OHSS-related deaths per 100,000 assisted reproduction cycles in the UK. Data from the Netherlands (Braat et al., 2010) reported a similar incidence. Importantly, all OHSS-related deaths in the latter report were seen after HCG trigger of final oocyte maturation, following the implementation of a 'freeze-all' strategy for OHSS prevention.

## OHSS and GnRHa trigger

Virtually complete elimination of OHSS is one of the major benefits of GnRHa trigger. The mechanism behind this phenomenon is the luteolysis induced by a bolus of GnRHa caused by the short half-life of endogenous LH as compared with HCG. Once the endogenous HCG production from the trophoblast reaches measurable serum concentrations around day 8 after ovulation (Bonduelle et al., 1988), it is too late to rescue the corpora luteae, which results in virtual elimination of the late-onset pregnancy-associated OHSS (Humaidan et al., 2012a,b). Taken together, the combination of GnRH antagonist co-treatment and GnRHa trigger is the tool by which the concept of a future OHSS-free clinic could become a reality (Devroey et al., 2011; Kol, 2004).

So far, only one case of severe, early onset OHSS after GnRHa trigger was reported in the English literature (Griesinger et al., 2011). This case, therefore, merits closer scrutiny. A 30-year-old patient with PCOS and male factor infertility underwent her first stimulated cycle. The oestradiol concentration on the GnRHa trigger day was 47,877 pmol/l (13,041 pg/ml) and 13 oocytes were retrieved. Following oocyte retrieval the patient was hospitalized with abdominal distension, enlarged ovaries and lower abdominal pain. She received low molecular weight heparin, cabergoline (0.5 mg/day) and i.v. infusion therapy, including albumin. Due to a drastic decrease of the haemoglobin concentration to 4.9 mmol/L (8 g/dl), the patient received blood transfusion 2 days post oocyte retrieval. Importantly, the haematocrit concentration was 0.41 on the GnRHa trigger day, 0.37 on the oocyte retrieval day and <0.35 post blood transfusion. Three to four days post trigger, 3.9 litres of 'blood-stained ascites' were drained, indicative of a subacute intraperitoneal haemorrhage – a well-known complication of vaginal ultrasound-guided oocyte retrieval; unfortunately, in the conclusions of the abstract, this was described as '... a single case of a severe early onset OHSS', even though this diagnosis was clearly not supported by the clinical details since the hallmark of OHSS is haemo-concentration.

## Cochrane reviews and GnRHa trigger

A recent Cochrane review comparing GnRHa versus HCG for triggering of final oocyte maturation in IVF concluded that GnRHa as a trigger of final oocyte maturation should not be routinely used due to the significantly lower live birth rate (Youssef et al., 2011). Moreover, the section on implications for research stated: 'In view of the poor reproductive outcomes following oocyte triggering with GnRH agonist we believe there is no indication for further research with GnRH agonists for oocyte triggering in ART in fresh autologous cycles'. This conclusion was unprecedented and obviously too premature, based on an analysis compiling data from some of the initial clinical trials, reporting a very poor reproductive outcome, with newer trials in which modifications of the luteal-phase support resulted in pregnancy rates comparable to those seen after HCG trigger – and with a reduction in the OHSS rate. Thus, apples were compared with oranges. This issue was thoroughly addressed in debates questioning not only the performance of meta-analyses during the development of new concepts, but also the role of meta-analyses as a whole in the field of reproductive medicine (Humaidan and Polyzos, 2012; Humaidan et al., 2012b).

## Predictive factors and how to handle patients at risk of OHSS

Predicting OHSS is difficult; there are, however, predictive factors which need to be taken into consideration when choosing the type of GnRH analogue, the FSH dose and the duration of stimulation as well as the choice of trigger method. Predictive factors for OHSS may be divided into primary and secondary risk factors. The most important primary risk factors are: high anti-Müllerian hormone, high antral follicle count, PCOS, isolated PCOS characteristics and a previous history of OHSS. In contrast, an important secondary risk factor is the number of follicles >11 mm on the day of trigger, and a threshold of more than 14 follicles >11 mm has previously been shown to predict 87% of severe OHSS cases (Papanikolaou et al., 2006). Once a decision to use GnRHa trigger has been made, there are now several clinical options.

### Fresh transfer and low-dose HCG supplementation to secure the reproductive outcome

This concept has until now resulted in a non-significant difference in delivery rates and a significant reduction in OHSS rate in the high-risk OHSS patient. The concept was recently used in a prospective randomized trial including a total of 118 high-risk OHSS patients (14–25 follicles) with no OHSS development in the GnRHa triggered group versus 3% in the HCG-triggered group (Humaidan et al., submitted for publication). Above 25 follicles, we recommend either a 'freeze-all' policy or intensive luteal-phase support with oestradiol and progesterone.

### Fresh transfer and intensive luteal support

Fresh transfer in combination with a dual trigger (1000 IU HCG) and luteal support with oestradiol and progesterone in patients with oestradiol concentrations <4000 pg/ml on trigger day (Benadiva and Engmann, 2012; Engmann et al., 2008; Griffin et al., 2012; Imbar et al., 2012).

### Freeze-all policy

The use of GnRHa trigger will prevent OHSS even in extreme cases if a freeze-all policy is adopted (Devroey et al., 2011). With the current improvement in cryo-technology, an excellent OHSS risk-free cumulative pregnancy rate has previously been reported (Griesinger et al., 2011).

## GnRH agonist trigger: side-benefits

GnRHa trigger is the trigger method of choice for the oocyte donor due to several advantages over HCG trigger, among those: virtual elimination of OHSS, a reduced luteal ovarian volume leading to diminished abdominal distension and pain, and a short interval until withdrawal bleeding occurs; factors that substantially decrease the treatment burden of the oocyte donor (Cerrillo et al., 2009; Hernández et al., 2009). Moreover, GnRHa trigger should be considered in situations like repeated IVF failure, empty follicle syndrome and repeated retrieval of immature oocytes as a subset of patients may require the FSH surge — in addition to the LH surge — to promote final oocyte maturation (Kol and Humaidan, 2010).

## Conclusion

The fast development during the last 2 years underscores our initial statement that GnRHa is a viable alternative to HCG for triggering of final oocyte maturation. GnRHa trigger is safer, patient friendly and offers several physiological advantages over HCG trigger. Although the most optimal luteal-phase support after GnRHa trigger is still being explored, the time has come to question the automatic HCG trigger concept and to move forward with thoughtful consideration of the needs and comfort of patients, specifically in terms of OHSS prevention.

## References

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 TNFalpha 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.

Benadiva, C., Engmann, L., 2012. Intensive luteal phase support after GnRH agonist trigger: it does help. Reprod. Biomed. Online 25, 329–330.

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.

Braat, D.D., Schutte, J.M., Bernardus, R.E., Mooij, T.M., van Leeuwen, F.E., 2010. Maternal death related to IVF in the Netherlands 1984–2008. Hum. Reprod. 25, 1782–1786.

Cerrillo, M., Rodríguez, S., Mayoral, M., Pacheco, A., Martínez-Salazar, J., Garcia-Velasco, J.A., 2009. Differential regulation of VEGF after final oocyte maturation with GnRH agonist versus hCG: a rationale for OHSS reduction. Fertil. Steril. 91 (Suppl. 4), 1526–1528.

Confidential Enquiry into Maternal and Child Health, 2007. Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003–2005. VIIth report.

de Mouzon, J., Goossens, V., Bhattacharya, S., Castilla, J.A., Ferraretti, A.P., Korsak, V., Kupka, M., Nygren, K.G., Andersen, A.N., 2012. Assisted reproductive technology in Europe, 2007: results generated from European registers by ESHRE. Hum. Reprod. 27, 954–966.

Devroey, P., Polyzos, N.P., Blockeel, C., 2011. An OHSS-free clinic by segmentation of IVF treatment. Hum. Reprod. 26, 2593–2597.

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 randomized controlled study. Fertil. Steril. 89, 84–91.

European Recombinant LH Study Group, 1998. Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in LH- and FSH-deficient anovulatory women: a

dose-finding study. The European Recombinant Human LH Study Group. J. Clin. Endocrinol. Metab. 83, 1507—1514.

Fauser, B.C., Devroey, P., 2003. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol. Metab. 4, 236—242.

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

Griesinger, G., Schultz, L., Bauer, T., Broessner, A., Frambach, T., Kissler, S., 2011. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a 'freeze-all' strategy: a prospective multicentric study. Fertil. Steril. 95, 2029—2033.

Griffin, D., Benadiva, C., Kummer, N., Budinetz, T., Nulsen, J., Engmann, L., 2012. Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders. Fertil. Steril. 97, 1316—1320.

Hernández, E.R., Gómez-Palomares, J.L., Ricciarelli, E., 2009. No room for cancellation, coasting, or ovarian hyperstimulation syndrome in oocyte donation cycles. Fertil. Steril. 91 (Suppl. 4), 1358—1361.

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., 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.

Humaidan, P., Polyzos, N.P., 2012. (Meta)analyze this: systematic reviews might lose credibility. Nat. Med. 18, 1321.

Humaidan, P., Bungum, L., Bungum, M., Yding Andersen, C., 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., Ejdrup Bredkjaer, H., Westergaard, L.G., Yding Andersen, C., 2010. 1500 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., Kol, S., Papanikolaou, E.G.on behalf of the 'The Copenhagen GnRH Agonist Triggering Workshop Group', 2011. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum. Reprod. Update 17, 510—524.

Humaidan, P., Papanikolaou, E.G., Kyrou, D., Alsbjerg, B., Polyzos, N.P., Devroey, P., Fatemi, H.M., 2012a. The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. Reprod. Biomed. Online 24, 134—141.

Humaidan, P., Kol, S., Engmann, L., Benadiva, C., Papanikolaou, E.G., Andersen, C.Y., 2012b. Should Cochrane reviews be performed during the development of new concepts? Hum. Reprod. 27, 6—8.

Humaidan, P., Alsbjerg, B., Mikkelsen, A.L., Elbaek, H., Erb, K., Papanikolaou, E.G., Andersen, C.Y., submitted for publication. GnRHa trigger and luteal phase hCG support according to ovarian response to stimulation in IVF patients - A prospective randomized controlled multi-centre study. Hum. Reprod.

Imbar, T., Kol, S., Lossos, F., Bdolah, Y., Hurwitz, A., Haimov-Kochman, R., 2012. Reproductive outcome of fresh or frozen-thawed embryo transfer is similar in high-risk patients for ovarian hyperstimulation syndrome using GnRH agonist for final oocyte maturation and intensive luteal support. Hum. Reprod. 27, 753—759.

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.

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.

Orvieto, R., 2012. Intensive luteal-phase support with oestradiol and progesterone after GnRH-agonist triggering: does it help? Reprod. Biomed. Online 24, 680—681.

Orvieto, R., Rabinson, J., Meltzer, S., Zohav, E., Anteby, E., Homburg, R., 2006. Substituting HCG with GnRH agonist to trigger final follicular maturation — a retrospective comparison of three different ovarian stimulation protocols. Reprod. Biomed. Online 13, 198—201.

Papanikolaou, E.G., Pozzobon, C., Kolibianakis, E.M., Camus, M., Tournaye, H., Fatemi, H.M., 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.

Radesic, B., Tremellen, K., 2011. Oocyte maturation employing a GnRH agonist in combination with low-dose hCG luteal rescue minimizes the severity of ovarian hyperstimulation syndrome while maintaining excellent pregnancy rates. Hum. Reprod. 26, 3437—3442.

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.

Youssef, M.A., Van der Veen, F., Al-Inany, H.G., Griesinger, G., Mochtar, M.H., Aboulfoutouh, I., Khattab, S.M., van Wely, M., 2011. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database Syst. Rev., CD008046.

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