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Review article

Combined ovulation triggering with GnRH agonist and hCG in IVF patients

Running title: GnRH-a and hCG triggering

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Abstract

Keywords: combined ovulation triggering, GnRH agonist trigger, hCG-triggering, dual trigger, double trigger

The aim of the review is to analyse the combination of a gonadotrophin releasing hormone (GnRH) agonist with a human chorionic gonadotrophin (hCG) trigger, for final oocyte maturation in in vitro fertilisation (IVF) cycles. The concept being a ‘‘dual trigger’’combines a single dose of the GnRH agonist with a reduced or standard dosage of hCG at the time of triggering. The use of a GnRH agonist with a reduced dose of hCG in high responders demonstrated luteal phase support with improved pregnancy rates, similar to those after conventional hCG and a low risk of ovarian hyperstimulation syndrome. The administration of a GnRH agonist and a standard hCG in normal responders, demonstrated significantly improved live-birth rates and a higher number of embryos of excellent quality, or cryopreserved embryos. The concept of the „double trigger“, represents a combination of a GnRH agonist and a standard hCG, when used 40 and 34 hours prior to ovum pick-up, respectively. The use of the „double trigger“ has been successfully offered in treatment of empty follicle syndrome and in patients with a history of immature oocytes retrieved or with low/poor oocytes yield. Further prospective studies are required to confirm the aforementioned observations prior to clinical implementation.

Introduction

During in vitro fertilisation (IVF) treatment a single bolus of 5,000–10,000 IU human chorionic gonadotrophin (hCG**)** has been routinely used for decades as a substitute for the endogenous luteinizing hormone (LH) surge, to induce luteinization of the granulosa cells, final oocyte maturation and resumption of meiosis prior to oocyte retrieval due to the fact that LH and hCG bind and activate the LH/hCG receptor. However, ovarian hyperstimulation syndrome (OHSS) can appear 3–7 days after hCG triggering, or during early pregnancy, 12–17 days after hCG administration in patients at risk. Therefore the withholding of the ovulation-inducing trigger of hCG with cycle cancellation was used to eliminate the syndrome [1].

Although a single bolus of hCG has long been the gold standard for triggering final oocyte maturation and ovulation, it was later demonstrated by introducing gonadotrophin releasing hormone (GnRH) antagonist protocols with gonadotrophins, that the use of GnRH agonists for final oocyte maturation represents a valuable alternative for classical hCG-triggering. Since the GnRH agonist trigger may allow a more physiological surge of LH and follicle stimulating hormone (FSH) with the shorter duration (approximately 34 hours), it has often been shown to be beneficial in GnRH antagonist protocols for preventing OHSS in patients at risk, when compared with the prolonged elevation of hCG trigger (≥6 days) [2]. Recent evidences from an updated Cochrane review suggest that final oocyte maturation triggering with the GnRH agonist, instead of hCG, in fresh autologous GnRH antagonist IVF cycles, effectively prevents mild, moderate or severe OHSS. However, a lower live birth rate and a higher rate of early miscarriage compared with the conventional hCG triggered cycles have been reported. Therefore, the routine use of a GnRH agonist as the lone trigger for final

oocyte maturation in fresh IVF autologous cycles was discouraged. It was considered that it could be useful for women who choose to avoid fresh transfers, women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation [3]. However, it should be noted that the authors did not recognize that luteal support was the variable responsible for lower pregnancy rates because the luteal phase support differed among studies included in the Cochrane analysis. Therefore, a meaningful comparison between GnRH agonists and the hCG trigger must be confined to outcome measures that are not affected by the luteal support regime used. Although the GnRH agonist trigger is effective for preventing OHSS by inducing quick and reversible luteolysis, the inferior pregnancy outcomes have been attributed to defective luteal phase function and decreased endometrial receptivity. Therefore, modifications of the standard luteal phase support are mandatory to achieve acceptable pregnancy rates similar to that of the hCG trigger after fresh embryo transfer. Recently, several methods have been accepted to improve the luteal phase in IVF cycles triggered with a GnRH agonist including aggressive steroidal luteal support (American approach), or **l**ow-dose hCG (1 500 IU) on the day of oocyte retrieval (European approach), to allow successful fresh embryo transfer. In addition, with the availability of vitrification, segmentation in GnRH agonist-triggered cycles and freezing all oocytes/embryos followed by a frozen transfer in an unstimulated cycle, may be the optimal optimal strategy for eliminating OHSS [4-9].

In recent years, several promising modifications of ovulation triggering using a single bolus of GnRH agonist concomitant with a reduced or standard dosage of hCG have been investigated, attempting to rescue the luteal phase and to further optimise pregnancy outcomes in cycles with GnRH antagonist protocols (dual trigger) [1,10-

13,15-17,19-21]. One of the suggested optional methods is the addition of low-dose (1000 to 2500 IU) hCG rescue on the day of GnRH agonist triggering in high responders at risk of OHSS, which has been shown to be effective in achieving acceptable pregnancy rates similar to those obtained after conventional hCG triggering with a very low risk of the syndrome [1,10-12]. Another strategy for final follicular maturation, the concomitant administration of both a GnRH agonist and a standard bolus of hCG (5000–10,000 IU) in normal responders, demonstrated significantly improved implantation, clinical pregnancy and live-birth rates in GnRH-antagonist IVF cycles [15], or a higher number of embryos of excellent quality and cryopreserved embryos [16]. Furhermore, using a combination of a GnRH agonist and a standard dose of hCG in patients with a previous history of > 25% immature oocytes retrieved, a significantly higher proportion of mature oocytes has been retrieved [17]. Since the percentage of mature oocytes can be increased by prolonging the interval > 36 h between hCG injection and oocyte retrieval [18], it was reported that prolonging the time between ovulation triggering and ovum pickup using a GnRH agonist combined with a standard hCG dose (40 and 34 hours), resulted in successful treatment in a recurrent case of empty follicle syndrome [19]. The aforementioned indication for the effective use of co-administration of a GnRH agonist and a hCG for final oocyte maturation, 40 and 34 hours prior to ovum pickup (double trigger), has been successfully extended as a valuable new tool in the armamentarium for treating patients with low/poor oocytes yield and in cases with a high proportion of immature oocytes [20,21]. The purpose of the review is to analyse current ovulation triggering regimens using co-administration of a GnRH-agonist with different doses of hCG for final oocyte maturation in patients undergoing IVF prior to routine implementation.

Dual trigger

Despite the fact that triggering of ovulation with a GnRH agonist and 1500 IU hCG 35 h later in GnRH antagonist IVF cycles provides a normal luteal phase and pregnancy outcome comparing with a single bolus of 10,000 IU of hCG [22], concomitant administration of a GnRH agonist and the low hCG doses have been introduced as a so-called „dual trigger". The concept of a dual trigger has been investigated for IVF high responders who had significant risk factors for OHSS to aid in oocyte maturation and more sustained support for the corpus luteum. After at least three follicles exceeded 18 mm in fresh autologous GnRH antagonist-regulated cycles with gonadotrophins of IVF, the patients at risk of developing severe OHSS were treated with a combination of leuprolide acetate (4 mg) and hCG (1,000 to 2,500 IU) injections based on a patient's weight (≤33 IU/kg). Acceptable rates of fertilization (62.8%), implantation (47.5%), clinical pregnancy (53.3%), ongoing pregnancy (53.3%), and early pregnancy loss (17.2%), along with the absence of OHSS, have been reported in high responders after triggering final oocyte maturation with a combination of leuprolide acetate and low doses of hCG. The findings of the study suggested that concomitant administration of a GnRH agonist and hCG for final oocyte maturation appears to be effective and safe in terms of the ability to achieve ongoing pregnancies and reduced OHSS risk in patients with significant risk factors for the syndrome [10]. Similar results were confirmed by the same authors after fresh autologous blastocyst transfers in high responders with gonadotrophins and GnRH antagonist cotreatment, compared with the use of a GnRH agonist trigger alone with standard or enhanced luteal support, and a GnRH agonist with concomitant low-dose hCG. The beneficial effect of a dual trigger in patients receiving

concomitant low-dose hCG (≤33 IU/kg) and leuprolide acetate (4 mg) was evidenced by greater ongoing pregnancy (57.7%) **(p<.001)**, or implantation rates (48.8%) **(p<.001)**, and reduced pregnancy loss rates (23.4%) **(p<.001)**, with the incidence of clinically significant OHSS being 0.5% **(p=.723)**. Similarly, the use of more-aggressive luteal support after the GnRH agonist trigger, was also associated with superior reproductive outcome (50% vs. 37.8% vs. 20%, respectively) when compared with the GnRH agonist alone and standard luteal support (20,6% vs.25.3% vs.58.2%, respectively) **(p<.001)** with no cases of OHSS **(p=.723)** [11]. Since the lower pregnancy rates after the GnRH agonist trigger with peak estradiol (E2) <4,000 pg/mL and intensive luteal support were attributed to the lower LH levels on the day of trigger [23], the use of the dual trigger with GnRH agonist and low-dose hCG compared the reproductive outcome with GnRH agonist trigger alone in high responders with peak E2 <4,000 pg/mL. It appears that the dual trigger with low-dose hCG (1,000 IU) and leuprolide acetate (1 mg) combined with intensive luteal support is an effective strategy with only one case of mild OHSS and a significantly higher live birth rate (52.9% vs. 30.9%) **(p=.03)**, implantation rate (41.9% vs. 22.1%) **(p<.01)** and clinical pregnancy rate (58.8% vs. 36.8%) **(p=.03)** compared with the GnRH agonist trigger group [12].

Aiming to improve oocyte and embryo quality and the consequent IVF outcome in cycles treated with a GnRH antagonist protocol, the concomitant administration of both the GnRH agonist and a standard bolus of hCG (5000–10,000 IU) prior to oocyte retrieval have been introduced as a new strategy for final follicular maturation in normal responders in a limited number of studies [13,15-17]. In the first ever prospective randomised study on dual triggering the administration of triptorelin (0.2 mg) at the time of hCG administration in GnRH antagonist IVF cycles significantly improved

ongoing pregnancy rates compared with the use of the hCG (5000 IU) trigger alone (36.1% vs. 22.3%, respectively) **(p=.046)**. It was suggested that the GnRH antagonist used in IVF cycles binds to endometrial GnRH receptors, provoking events that putatively interfere with implantation. However, the use of a preovulatory GnRH agonist may overcome this putative interference by displacing the bound GnRH antagonist from the endometrial GnRH receptor, thus enabling proper post-receptor actions for improvements in implantation. Another possible explanation for improved results in GnRH agonist triggered cycles is the induction of an FSH surge in addition to the LH surge which has been postulated to be instrumental in resumption of some of the oocyte's meiotic processes, conferring some advantages to developing embryos [13]. Similar observations about the beneficial effects of GnRH agonists resulting in higher rates of implantation and ongoing pregnancy after IVF in GnRH antagonist cycles were demonstrated in a later meta-analysis following the administration of a single dose of GnRH agonist in the luteal phase. The possible mechanisms responsible for the effects of the GnRH agonist luteal action may be a direct beneficial effect on the embryos or uterine tissue. Nevertheless, it seems premature to recommend the use of the GnRH agonist in the luteal phase until further randomised controlled trials are provided [14]. In the light of these preliminary results further investigations regarding the efficacy of dual triggering have investigated whether a single dose of GnRH agonist with a standard dosage of hCG could improve live-birth rates for normal responders in GnRH antagonist IVF cycles. A retrospective cohort study a total of 376 normal responders who had undergone IVF using a GnRH antagonist protocol with either a standard dosage of recombinant hCG trigger (250 mcg), or the dual trigger (0.2 mg of triptorelin and 250 mcg of recombinant hCG). The dual trigger group demonstrated a statistically

significant increase in the number of oocytes retrieved (**12.4 vs.10.1**) **(p<.01)**, matured oocytes (**10.5 vs. 8.1**) **(p<.01),** and the number of embryos cryopreserved **(1.9 vs.1.6**) **(p<.01)**, with the consequent significant increase in implantation (29.6% vs. 18.4%) **(p<.001)**, clinical pregnancy (50.7% vs. 40.1%) **(p=.047)** and live-birth (41.3% vs. 30.4%) **(p=.042)** rates, compared with the hCG trigger group [15]. In a subsequent prospective randomised controlled trial of 120 normal responders using recombinant FSH with GnRH antagonists, the IVF outcome following either, 5000 IU of hCG trigger or a combination of GnRH agonist plus 5000 IU of hCG concomitantly, the role of the GnRH agonist induced FSH surge on the number of metaphase II (MII) oocytes and hormonal profiles was investigated. There was no difference reported in the number of mature oocytes obtained between the groups, however in the group with dual triggering a significant increase of morphologically excellent embryos accompanied by a significant increase in the number of patients with cryopreserved supernumerary embryos was observed. The number of patients who received at least one embryo of excellent quality (45 out of 61 patients or 73.8%), and the number of cryopreserved embryos (33 out 61 or 54.1%) were significantly higher following the dual trigger **(p<.001 and p<.04)** compared with the group with hCG triggering alone (28 out of 59 patients or 47.5% vs. 21 out of 59 or 35.6%, respectively). The mean number of MII oocytes in the hCG triggered group was 9.2 compared with 10.3 in the hCG-GnRH agonist group and there was no statistically significant difference in the number of cumulus oocyte complexes. The hormonal curves showed a significantly higher level of LH and FSH immediately after triggering in the combination group with no difference in the E2 and progesterone levels in the luteal phase. However, the pregnancy rate in the dual triggering group was lower than that obtained in the group triggered by hCG

alone, despite the fact that the number of good quality embryos was significantly lower in the hCG-only triggered group. Although the reason for this discrepancy is still unclear, a possible explanation could be a negative effect on the endometrial receptivity, induced by the higher LH levels and the additional FSH surge. Further research with the cryopreserved embryos is required to elaborate whether pregnancy rates are indeed lower after the combined triggering, despite the improvement of embryo quality, since the frozen/thawed cycles are not affected by the potential negative effect of the dual triggering on the endometrium [16]. Following the successful use of a dual trigger with a GnRH agonist and a standard dose of hCG in a patient with repetitive immature oocytes and empty follicle syndrome [24], in a later retrospective cohort study the percentage of mature oocytes retrieved in patients with a previous history of >25% immature oocytes retrieved has been evaluated with the use of the dual trigger. It was hypothesised that the endogenous LH and FSH released by the GnRH agonist bolus, in addition to the hCG, would result in a larger proportion of mature oocytes in patients with a history of poor oocyte maturation after the hCG trigger alone. All patients in the study used the intracytoplasmic sperm injection (ICSI) technique for fertilization, so that the oocyte maturation could be assessed. The proportion of mature oocytes retrieved was significantly higher in patients using a GnRH antagonist controlled ovarian stimulation protocol with recombinant FSH who were triggered with a combination of 1 mg leuprolide acetate plus 5,000–10,000 IU hCG compared with the subject's previous cycle who were triggered only with the same dose of hCG (75.0% vs. 38.5%, respectively) **(p<.01).** However, despite the fact that with a combination of GnRH agonist and hCG the percentage of mature oocytes signficantly improved, the implantation, clinical and ongoing pregnancy rates for the dual trigger were

disappointing (11.8%, 26.1% and 17.4%, respectively) which may be due to an underlying oocyte dysfunction in folliculogenesis [17].

Double trigger

Since the prolonged luteinization to oocyte retrieval increased the production of oocytes of fully expanded cumulus, which may reflect oocyte maturation, it was assumed that the subsequent proportion of oocytes proceeding to fertilisation and cleavage also increased. Therefore, in a meta-analysis of 5 randomised controlled trials the time interval between hCG priming and oocyte retrieval has been evaluated to determine whether a prolonged hCG-to-oocyte retrieval interval is beneficial to IVF outcome. The results of the study suggested that the percentage of mature oocytes can be increased by prolonging the interval between hCG priming and ovum pick-up (> 36h), despite the fact that the fertilisation rate, implantation rate and pregnancy rate do not differ significantly between oocyte retrieval <36 h or > 36h after hCG injection and oocyte retrieval [18]. By using the advantages and beneficial effects of the prolongation of the time between standard hCG triggering prior to ovum pick-upcohort and GnRH agonists in a preliminary historical study, the co-administration of the GnRH agonist and hCG for final oocyte maturation (40 to 34 h prior to ovum pick-up) has been implemented successfully as a new treatment modalitity (double trigger) for treatment in a recurrent case of empty follicle syndrome. It was assumed that by prolonging the time between ovulation triggering and ovum pick-up with the GnRH agonist trigger and the consequent induction of an FSH surge, the „double trigger" could overcome any existing impairments in granulosa cell function, oocyte meiotic maturation, or cumulus expansion. Although it was impossible to differentiate which of the two strategies

yielded the desired outcome, it seems that combining hCG with GnRH agonist and prolonging the interval between ovulation triggering and ovum pick-up resulted in the aspiration of mature oocytes, pregnancy and delivery [19]. With the aim of evaluating whether the double trigger improves the number of oocytes retrieved in patients with a low (<50%) number of oocytes retrieved per number of preovulatory follicles, a preliminary cohort historical study compared the stimulation characteristics of 8 IVF cycles, which included the double trigger to the patients' previous IVF attempt, triggered with hCG-only. The results suggested that patients who received the double trigger had a significantly higher number of oocytes retrieved (**7.0 vs. 2.3**) **(p<.02),** number of 2PN (**6.0 vs. 1.7**) **(p<.002),** number of embryos transferred (**2.2 vs. 0.8**) **(p<.002),** and significantly higher proportions of the number of oocytes retrieved to the number of follicles >10 mm (**80.3 vs. 18.5**) **(p<.001),** and >14 mm in diameter (**118.0 vs. 23.7**) **(p<.01)** on day of hCG administration, compared with the hCG-only trigger. Therefore, the "double trigger" was suggested as a valuable new tool in the armamentarium for treating patients with low/poor oocytes yield, despite an apparently normal follicular development and E2 levels, and in the presence of optimal hCG levels on the day of ovum pick-up. Nevertheless, additional larger prospective studies are required to confirm these findings in this and other situations, prior to its routine use [20]. Finally, a recent cohort historical study further extended the aforementioned indications to the co-administration of a GnRH agonist and hCG for final oocyte maturation, 40 and 34 h prior to oocyte retrieval, evaluating whether the double trigger might improve the proportions of MII oocytes in patients with low proportion of mature oocytes (<66%) per number of oocytes retrieved. The stimulation characteristics of 12 IVF cycles were compared, which include the cycle with the double trigger to the same

patients' previous IVF attempt, triggered with hCG-only. Patients who received the double trigger, had a significantly higher number of mature oocytes - MII (6.5 vs. 3.6) **(p<.008),** number of embryos transferred (2.4 vs. 1.1) **(p<.03),** a significantly higher proportion of MII oocytes per number of oocytes retrieved (69.7% vs. 47.1%) **(p<.03)** and a higher number of top quality embryos (3.1 vs. 1) **(p<.02),** compared with their hCG-only trigger. There was six pregnancies achieved the in study group (50%) and none in the control group. The beneficial effects of the double trigger in respect to an improvement in oocyte maturation and pregnancy rates achieved may be explained by the additional prolongation of the time between ovulation triggering and ovum pick-up. Since the co-administration of a GnRH-agonist and hCG for final oocyte maturation, 40 and 34 h prior to ovum pick-up, improves IVF outcome in patients with high proportion of immature oocytes, the double trigger is suggested as a valuable tool in the armamentarium for treating patients with low proportions of mature oocytes, despite normal follicular development and optimal hCG levels on the day of ooocyte retrieval. However, further large prospective studies are required to confirm the aforementioned recommendation prior to its clinical use [21].

Conclusions

The concept of the ‘‘dual trigger’’combines the concomitant use of a single dose of GnRH agonist with a reduced or standard dosage of hCG at the time of triggering. The administration of GnRH-agonist with a reduced dose of hCG (1000 to 2500 IU) in high responders at risk of OHSS has been demonstrated to rescue the luteal phase resulting in improved pregnancy rates as compared to a GnRH trigger alone, similar to those obtained after conventional hCG trigger and with a very low risk of the syndrome. The

use of both a GnRH agonist and a standard bolus of hCG (5000–10,000 IU) in normal responders, demonstrated significantly improved implantation, clinical pregnancy, and live-birth rates, or a higher number of embryos of excellent quality and cryopreserved embryos and therefore may be offered simultaneously to the standard hCG trigger dose.

A modification of the „dual trigger", the so called „double trigger" which consists of the administration of a GnRH agonist and a standard dose of hCG for final oocyte maturation, 40 and 34h prior to oocyte retrieval, respectively, differs from the „dual trigger" by the additional prolongation of the time between ovulation triggering and ovum pick-up. Since the use of the „double trigger" has been successfully extended in treatment of empty follicle syndrome and in patients with a previous history of higher proportion of immature oocytes retrieved, or low/poor oocytes yield, it may be utilised in the improvement of abnormal final follicular maturation. Nevertheless, further prospective, randomised controlled studies are required to confirm the beneficial role of dual/double triggers prior to clinical implementation.

Declaration of Interest: The authors report no declarations of interest.

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