

# HCG: Is it the Best Choice for Ovulation Triggering?

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**Abstract:** With the increasing use of gonadotropin releasing hormone antagonist protocols, it has become an option to trigger ovulation with gonadotropin releasing hormone agonist which has several advantages over human chorionic gonadotropin triggering; among those an elimination or reduction in ovarian hyperstimulation syndrome, and a reduction in luteal phase discomfort. Thus, this paper questions the automated use of human chorionic gonadotropin for triggering of ovulation in assisted reproductive technologies.

**Keywords:** GnRH agonist, GnRH antagonist, hCG, *in vitro* fertilization, LH, OHSS.

## HUMAN CHORIONIC GONADOTROPIN VS. LH

Human chorionic gonadotropin (hCG) has been the universal trigger of final oocyte maturation for decades in assisted reproductive technologies (ART) due to structural and biological similarities with LH as both molecules bind to the same receptor, the LH/hCG receptor [1]. Importantly, however, the half-life of hCG is significantly longer than that of and LH, > 24 h *versus* 60 min [2, 3], facilitating ovarian hyperstimulation syndrome (OHSS) due to the sustained luteotropic activity and the production of vascular permeability mediators [4, 5]. Moreover, even if bona-fide OHSS is not diagnosed, luteal ovarian over-stimulation is a significant source of physical discomfort during the luteal phase, increasing the treatment burden of the patient [6]. Interestingly, it has previously been reported that patients experience physical discomfort throughout the IVF treatment; however, even more discomfort is reported during the luteal phase compared with the stimulation phase [7]. Finally, a “standard” bolus of hCG has been shown to induce a significant histological advancement of the endometrium, which could negatively affect the receptivity [8]. This finding is in line with a recent prospective randomized trial, demonstrating the superiority of a spontaneous LH surge versus an hCG-induced surge in natural cycle frozen embryo transfer cycles. The authors hypothesized that the administration of hCG in the late follicular phase might negatively affect endometrial receptivity by inducing endometrial events which would occur several days later after an endogenous LH surge [9].

Taken together, the ovulatory bolus of hCG increases the physical discomfort of the patient during the luteal phase, increases the risk of OHSS and might hamper implantation.

The consented doses of hCG administered vary between 5,000 and 10,000 IU when urinary hCG is used and 6,500 IU (250 microgram) when recombinant hCG is used. Although hCG has been the drug of choice to trigger final oocyte maturation until now, we believe that the time has now come to question this practice.

The most natural compound with which to trigger final oocyte maturation and with an expected low incidence of OHSS would have been LH. Thus, when recombinant LH (rLH) was introduced, a clinical trial was performed to explore the efficacy of rLH to trigger ovulation in a long GnRHa down-regulation protocol. Doses differing between 5,000 IU and 30,000 IU were explored. However, apart from the significant increase in cost of treatment, a low implantation rate was seen after only one bolus of rLH to trigger ovulation; moreover, a disappointingly high OHSS rate (12%) was reported [10, 11].

## GnRHa TRIGGERING IN ANTAGONIST ART CYCLES

Following the introduction of GnRH antagonists for IVF/ICSI treatment, it became an option again to trigger final oocyte maturation with a GnRHa. This procedure has recently successfully been applied and is now the recommended protocol in oocyte donation cycles due to its many advantages: first and foremost a total elimination of OHSS in the donor, despite the retrieval of a considerable number of good quality mature oocytes, less discomfort in the “luteal phase” i.e. the days following oocyte aspiration, withdrawal bleeding within 4-6 days after triggering and finally and importantly, high pregnancy rates in the recipients [12-15].

In the initial randomized controlled IVF trials with transfer of the patients own embryos in a “fresh” cycle, however, the reproductive outcome was disappointingly low due to an unacceptably high early pregnancy loss rate [16, 17]. This finding was interpreted as an “insufficient luteal phase” after GnRHa triggering caused by low luteal LH

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levels. Following this study, a model for luteal phase rescue with exogenous LH activity administration (1500 IU hCG, significantly lower than the trigger dose) after GnRHa triggering was explored in a pilot study [18], reporting a comparable reproductive outcome after GnRHa triggering compared to hCG triggering. Subsequently the concept of luteal phase rescue with LH activity after GnRHa triggering has been confirmed in trials using either hCG or rLH for rescue [19-23]. A preliminary study [20] found a non-significant reduction of 7% in live birth rate with the use of GnRHa trigger compared to hCG. However, in a recent multicenter study including more than 100 patients in each group, this difference has disappeared, and we now see a non-significant higher ongoing pregnancy rate of 4% in favor of GnRHa trigger with the use of "tailored luteal phase support" (unpublished data). Thus GnRHa triggering is now a valid alternative to hCG triggering [24]. A Chochrane review by Youssef *et al.*, [25] concluded that GnRH agonists as a final oocyte maturation trigger in fresh autologous cycles should not be routinely used due to the associated significantly lower live birth rate, ongoing pregnancy rate. However, the review included studies that differ significantly in the mode of luteal support, and therefore, is meaningless from the clinical perspective. A full account of this flawed and biased review was published by Humaidan *et al.* [26].

## GnRHa TRIGGERING AND FRIENDLY IVF PROTOCOLS

"Friendly IVF" is *the theme* in recent years. Significant efforts have been made to make IVF a simple, "friendly" procedure. The medical industry identified the issue as a new market. An example is the long acting FSH, a product designed to reduce the number of injections during the stimulation phase, thereby alleviating the physical and emotional burden of the patient. Furthermore, clomiphene-based minimal stimulation or natural cycle IVF protocols in conjunction with GnRHa triggering have been proposed as valid alternatives to standard conventional IVF [27-29]. Interestingly, however, up till now, no commercial product or prospective trial targeted the luteal phase, which is a major source of patient discomfort.

Is it possible to implement a "friendly" luteal phase in ART? Yes, however, only if the hCG triggering property is dissociated from its luteal supportive property.

In this aspect, we believe that GnRHa triggering, followed by luteal LH activity support will be the future concept of triggering final oocyte maturation, significantly reducing or eliminating OHSS [12-14, 19, 30-33], significantly decreasing subjective luteal phase discomfort [6, 31] and increasing the number of MII oocytes [17, 20, 34, 35]. A recent "proof-of-concept" study explored the possibility of GnRHa trigger in IVF patients, with hCG-based luteal support [36]. The study suggests that two boluses of 1500 IU hCG revert the luteolysis after a GnRHa trigger in the normo-responder patient. Importantly, no additional luteal support is needed. We therefore assume that progesterone-based luteal phase support (continuing well into the first trimester if pregnancy is achieved) will not be needed, once adequate LH-activity-based support is achieved (i.e. 2 hCG boluses). This will also decrease the overall cost of luteal

support. This concept is further supported by Engmann *et al.*, [37] who showed that granulosa/luteal cells obtained 2 days after GnRH agonist trigger are viable, and have the capacity to respond to hCG by increasing progesterone secretion.

In summary, GnRHa triggering is more patient friendly and offers several physiological advantages over hCG triggering. The time has now come to question the automated hCG triggering concept and move forward with thoughtful consideration of the needs and comfort of our patients.

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## CONFLICT OF INTEREST

None declared.

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