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Editorial

A Brief History of GnRH Agonist Trigger and Directions for Future Research

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The first report of ovulation trigger by a gonadotropin releasing hormone agonist (GnRHa) predates development of human in vitro fertilization[1]. Gonen and Casper [2] were the first to use GnRHa trigger in human IVF. They randomized 18 women, who underwent ovarian stimulation without pituitary suppression to receive GnRHa or human chorionic gonadotropin (hCG) as the trigger to induce final follicular maturation. They reported similar numbers of oocytes collected, fertilization rate, embryo quality and pregnancy rates. However, pituitary suppression with GnRHa in order to prevent ovulation prior to egg retrieval (ER) soon became the norm and GnRHa as a trigger remained in oblivion until the introduction of gonadotropin releasing hormone antagonists (GnRHant) into IVF practice.

Early on it was realized that GnRHa triggering could be a means of preventing ovarian hyperstimulation syndrome (OHSS) in GnRHant cycles [3]. Firstly, the luteinizing hormone (LH) surge induced by GnRHa trigger lasts even shorter than the endogenous LH surge in a natural cycle, and secondly half-life of LH is very much shorter than that of hCG [4,5]. These two characteristics serve to decrease the luteinizing stimulus to the granulosa cells, limiting the production of vascular endothelial growth factor, which leads to increased vascular permeability, the hallmark of OHSS [6-8]. However, limited luteinisation was found to be associated with significantly decreased estradiol and progesterone production during the luteal phase[4]. In a rat model, GnRHa trigger was associated with decreased size and number of corpora lutea, decreased expression of steroidogenic enzymes as well as decreased expression of molecules playing role in formation and stabilization of new vessels, such as angiopoietin [9]. Recently, a study in humans confirmed these findings, i.e. altered gene expression in both mural granulosa cells and cumulus cells following GnRHa trigger. Among several differentially expressed genes were decreased angiopoietin expression in mural granulosa cells and decreased steroidogenic enzyme expression in cumulus cells. It is noteworthy that GnRHa trigger was associated with increased LH receptor expression in cumulus cells [10].

Initial clinical trials conducted before 2005, confirmed Gonen and Casper's findings of similar oocyte yield and embryo quality following GnRHa trigger. However significantly decreased pregnancy rates accompanied by a significantly higher rate of pregnancy loss compared to conventional hCG trigger was alarming [4,11,12]. Although Fauser et al's. [4] finding of decreased estradiol and progesterone production following GnRHa trigger suggested the presence of a luteal phase defect, it was also possible to isolate effect of GnRHa trigger on oocytes/embryos and luteal phase/endometrium by using oocyte donor-recipient or cryopreservation cycles. In a randomized trial Acevedo et al. [13] demonstrated similar implantation and pregnancy rates in oocyte recipients from donors triggered with hCG or GnRHa. Two uncontrolled case series of oocyte and embryo freezing following GnRHa trigger reported cryosurvival, implantation and pregnancy rates within expected range of hCG trigger.Altogether these data provided convincing evidence for a severely defective luteal phase impacting on birth rates following GnRHa trigger [14,15].

Initial studies of rescuing luteal phase by administering high doses of exogenous progesterone and estrogen yielded contradictory results. While Engmann et al. [16] retrospectively reported 56% live birth rate with "intensive luteal support" involving active monitoring of serum levels of estradiol and progesterone, Babayoff et al. [17] prematurely terminated their RCT due to unacceptably high early pregnancy loss rate in the GnRHa trigger + intensive luteal phase support (LPS) arm. An important difference between the two studies was starting time of LPS. Engmann et al. [16] started LPS the evening of ER; Babayoff et al. [17] delayed it for 48 hours. Although starting time of LPS does not seem to effect clinical outcome in hCG triggered cycles, later findings suggest early start LPS is associated with better outcome following GnRHa trigger. Indeed, Engmann et al. [16] in a RCT including 66 women with polycystic ovaries/ovarian syndrome reported 53% ongoing pregnancy rate following GnRHa trigger and intensive LPS started right after ER, similar to 48% achieved in controls triggered with hCG [18]. However, it was later realized that high endogenous LH levels was an important factor contributing to the observed success of intensive LPS [19]. The magnitude of the LH peak induced with GnRHa bolus, which seems related with early follicular phase serum LH levels, was found a determinant of pregnancy rates following GnRHa trigger and intensive LPS [20]. Overall, intensive LPS can be a viable option for women with PCOS, the very same patients who comprise the highest risk group for OHSS following hCG injection.

Rescuing the luteal phase with a small dose of hCG after GnRHa trigger was explored as another option. Humaidan et al. [11] conducted a series of randomized controlled trials (RCTs) suggesting equivalent ongoing pregnancy rates with GnRHa trigger followed by 1,500 IU hCG injection 35 hours later and LPS with vaginal progesterone and oral estradiol [21-23]. Not only luteal phase serum estradiol and progesterone levels were similar to hCG trigger with this method, but ongoing pregnancy rates were also statistically similar to hCG trigger, despite a trend towards lower rates with GnRHa + 1,500 hCG (Figure 1). The success of hCG rescue in maintaining pregnancy rates were confirmed in several uncontrolled case series, and it was suggested that severe early OHSS could be successfully prevented with this method [24,25]. However, several reports of severe early OHSS following GnRHa trigger with or even without any hCG rescue proved it an elusive goal to completely prevent OHSS [26-28]. Therefore, it seems prudent to totally avoid hCG support in women with high ovarian response, however precise markers of such ovarian reserve and threshold levels remain to be determined. The incidence of empty follicle syndrome seem similar with the hCG trigger, initial studies of obstetric and

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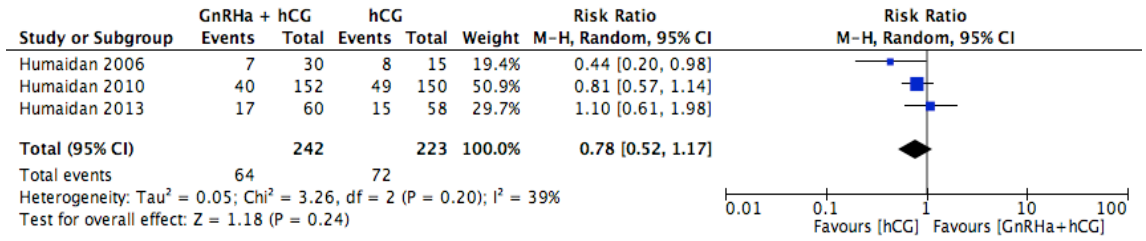

Figure 1: Pooled results of randomized controlled trials comparing GnRHa trigger + 1,500 IU hCG and conventional hCG trigger. Ongoing pregnancy rates.

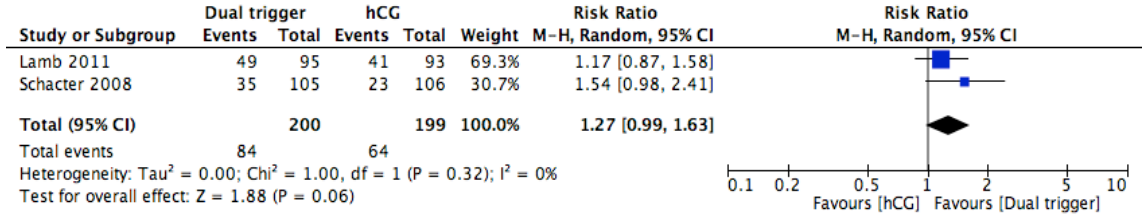

Figure 2: Pooled results of randomized controlled studies comparing hCG and dual trigger including FSH activity. Ongoing pregnancy rates.

neonatal outcome following GnRHa trigger are reassuring, except one study reporting increased risk of ectopic pregnancy, a finding which needs to be confirmed in other series [20,29-31].

The FSH surge induced by GnRHa trigger attracts attention with its resemblance to the natural cycle. Although it can be an epiphenomenon, it is suggested that this short exposure of granulosa cells to FSH can enhance oocyte competence and improve clinical outcome. One possible mechanism is by increasing LH receptor expression, which has already been demonstrated in the above mentioned gene expression study [10]. However, whether increased LH receptor expression is beneficial for the oocyte is controversial, as Maman et al. [32] reported a higher LH receptor expression in oocytes that failed to fertilize normally. Regardless, there are several studies investigating whether dual trigger with simultaneous administration of GnRHa and hCG improves clinical outcome compared to hCG triggering alone. Griffin et al. [33] retrospectively reported significantly increased live birth rates with dual trigger despite similar numbers of oocytes being collected following hCG alone. In a RCT involving 211 patients stimulated with a GnRH ant protocol, Schachter et al. [34] reported similar number of oocytes collected and fertilization rate with dual trigger and hCG trigger. However, despite clinically significant trends in implantation (17%vs 21%, p = 0.34) and ongoing pregnancy rates (22%vs 36%, p = 0.07) favoring dual trigger, differences were short of statistical significance. Lamb et al. [35] investigated effect of FSH on the day of trigger with a different design. One hundred eighty-eight patients undergoing IVF with the long luteal GnRH agonist protocol were randomized to receive 10,000 IU hCG+ 450 IU FSH or 10,000 IU hCG + placebo as ovulation trigger. While, the number of oocytes collected were similar in both arms, a significantly higher proportion of them were mature (70%vs 57%, p = 0.04), and fertilization rate were significantly higher (63%vs 55%, p = 0.01) in the FSH dual-trigger group. Similar to Schachter et al. [34] study, the increment in ongoing pregnancy or live birth rates with co-trigger was short of statistical significance (52%vs 44%, p = 0.3). When the results are pooled the beneficial effect of FSH surge is at the verge of significance (Figure 2). Therefore dual-trigger seems a possibly beneficial practice, which should be further investigated in RCTs.

Another setting where GnRHa triggering could prove useful is oocyte collection cycles for the purpose of fertility preservation in patients with hormone sensitive tumors, such as breast cancer. The rapid decline in serum estradiol and progesterone levels following GnRHa trigger limits tumor exposure to these hormones [36]. Clearly, GnRHa trigger should be the norm in fertility preservation cycles, as it does not affect oocyte yield or quality.

In conclusion, GnRHa trigger enables collection of similar number of oocytes with conventional hCG trigger. It is the best available ovulation trigger for women under risk of OHSS and fertility preservation cycle. The decision to proceed with a fresh or frozen transfer should be individualized, as well as the method of luteal phase rescue in fresh transfers. We need more studies to determine thresholds of ovarian response, e.g. serum estradiol level, number of follicles and oocytes, which would determine whether any LH activity, in the form of hCG or otherwise, should be added and a fresh transfer done. Effectiveness and safety of active management of luteal phase with monitoring of serum estradiol and progesterone levels, and adjusting luteal support accordingly should be explored. There's an urgent need for properly designed RCTs evaluating dual-trigger.

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