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Review Article

An Innovative Approach of HCG Trigger with Concurrent 1500 IU HCG and 450 IU FSH Utilization for OHSS Avoidance in High Risk Patients - Is it Superior to Dual Trigger

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Abstract

Numerous studies have illustrated composed of with regards to human chorionic Gonadotropins (HCG) dosage in the canonical/ standard HCG trigger (5000-10,000 IU) used for IVF trigger. However avoidance of ovarian hyperstimulation syndrome (OHSS) OHSS is not avoided. This has been further followed by utilizing 2000, 2500, or 3300 IU of HCG dosage for finding minimum efficacious dosage. Subsequently use of gonadotropin releasing hormone agonist (GnRH) trigger was introduced in view of natural LH/FSH surge trigger. Nevertheless, its disadvantage was we could not use it uniformly like in GnRH agonist downregulated cycles. Recently a randomized double blind controlled, non inferiority trial was introduced by Anaya Y., et al. where 1500 IU HCG with concurrent delivery of 450 IU of FSH was observed to be successful in IVF cycles with parallel utilized contrasting with 5000-10,000 IU also for the final oocyte maturation. They found reduced OHSS in this innovative trial. However a larger study is essential with regards to evaluation of embryo production as well as LBR results Although no cycles cancelled one needs to compare this with the recently introduced Dual trigger (HCG + GnRHa trigger) where they observed superiority of results in with regards to embryo formation as well as pregnancy results. One of the modes that might give reason for the enhancement in pregnancy rate is the escalation of receptivity along with implantation in view of the extra-pituitary actions of the GnRH molecule, which is implicated in endometrial receptivity, embryo implantation, and trophoblast invasion. The expression of HOXA-10, possesses a key part in modulating endometrial receptivity, is diminished in endometrial tissues in antagonist cycles as explained by *Olieviera*., et al.

Keywords: Innovative HCG Trigger; Standard HCG Trigger; OHSS; Dual Trigger

The primary objective of the utilization of injectable medicine for *in vitro* fertilization (IVF) with regards to triggering oocyte competency is the acquisition of a healthy pregnancy [1]. Canonically, a single bolus injection composed of 5000-10,000 IU human chorionic Gonadotropins (HCG), has been done for acquisition of oocytes competence. HCG utilization has been made in the form of a substitute/replacement for the Luteinizing hormone (LH) by binding akin receptors; however with greater affinity, escalated bioactivity in addition to having a substantially greater half -life [2].

The requirement of HCG dosage for acquisition of retrieved competent oocytes has not been established with clarity. Numerous studies have tried finding the minimum efficacious HCG dosage with the idea of avoidance of ovarian hyperstimulation syndrome (OHSS) [3]. Abdalla., *et al*. [4], hypothesized that 5000 IU was the minimum dosage subsequent to the randomized controlled trial (RCT), performed by them; where they observed a considerably lesser laparoscopic oocyte getting retrieved in patients who received triggering with 2000 IU in contrast to 5000 IU as well as

10,000 IU (22.7% vs 4.5% along with 1.9% respectively). Nevertheless, in case oocytes got recovered, they observed no variations in the number of oocytes recovered or fertilization rates implying a patient t particular or follicle particular different dosage threshold. The lesser incidence or lack of a failure of response to 2000, 2500, or3300 IU of HCG dosage in other studies queried the properties of the minimum efficacious dosage reactions, specifically if it might be imperative to attenuate the OHSS risk [3,5]. Furthermore, in a case Report mistakenly1000 IU injections administration of the standard HCG observed that whereas one patient had failure of egg getting retrieved the other one possessed mature oocyte getting retrieved which resulted in an ongoing pregnancy which further validated with regards to the effectiveness of lesser HCG dosage [6].

Despite, the natural LH surge is correlated with a lesser amplitude follicle stimulating hormone (FSH) surge, HCG by itself possesses the capacity of induction of oocyte competence in an IVF program [7]. Apparently in view of there is no requirement of FSH, no clarification exists regarding its precise part in humans. It has been illustrated that FSH possess the capacity of induction of LH receptors expression in granulosa cells, facilitates meiosis getting resumed in addition to cumulus expansion as well as stimulates follicular plasminogen activator in case of animals [8,9]. Animal have further illustrated how a FSH bolus possesses the capacity of ovulation induction despite lack of LH actions [10]. This might be feasible in humans as well; the manner illustrated in a patient going through IVF was inadvertently delivered a big FSH bolus rather than HCG [11]. Further proof that verified the part of FSH surge was revealed subsequent to gonadotropin releasing hormone agonist (GnRH) trigger which results in induction of endogenous FSH as well as LH surge [12]. In contrast to HCG trigger alone GnRH a was correlated with greater oocytes getting retrieved, maturation along with fertilization rates [13]. The improvement of results were accounted by the associated FSH surge that resulted in potentiation. To our misfortune utilization of GnRHa is not feasible for all in view of its incapacity to work in downregulated cycles or patients having hypothalamic impairment.

By utilization of combination of acknowledged outcomes of FSH having actions of potentiation of LH with its minimal dosage (for instance 1000-2000 IU) displayed maturation of oocytes Lamb., *et al.* [14], generated an alternate trigger comprising of 1500 IU HCG with addition of 450 IU of FSH to get over the risks as well as restrictions correlated with canonical HCG as well as GnRHa trigger [4-7,14]. This FSH dosage was dependent on a study which illustrated that comparative post trigger serum quantities subsequent to a natural surge [7,14]. Anaya Y., *et al.* [15], retrospectively contrasted this alternate trigger with other triggers (3300 IU HCG, GnRHa, GnRHa+1500 IU HCG) whose utilization was done inpatients having risk of OHSS formation, as well as their observations pointed to diminished OHSS risk along with akin IVF results [15].

The aim of the current study by Anaya Y., *et al.* [16], was to confirm their previous observations in a setting of a randomized controlled trial for estimation of 1500 IU HCG with concurrent delivery of 450 IU of FSH actually results in oocytes competence in contrast to standard HCG trigger (for instance 5000-10,000 IU) utilized in IVF. The alternate trigger will be clinically believed to be non inferior to standard HCG trigger in case it is minimum 80% as efficient with regards to oocytes competence induction. Their selection of non inferiority was dependent on United States FDA recommendations regarding that probable safety treatment need to possess a minimum of 80%-85% equal effectiveness in the form of standard of care to illustrate enough advantageous action as a safer alternate treatment [17].

Hence they performed a randomized double blind controlled, non inferiority trial in women amongst 18-41 yrs who were going through IVF, were having an antral follicle count ≥ 8, body mass index (BMI) ≤30 kg/m^2 along with no history of cancellation of ≥2 IVF cycles in view of poor response got recruited. Those having serum oestradiol levels > 5000 pg/ml on the triggering day were excluded in view of > OHSS risk. Those who took part got randomized for receipt of an alternate trigger of 1500 IU HCG with concurrent delivery of 450 IU of FSH/standard HCG trigger dosage (5000-10,000 IU) for the final oocyte maturation. Their primary outcomes obtained comprised of full competent percentage which by definitions was the possibility of 2 pronuclei from the oocytes recovered. The alternate trigger would be believed to be non inferior to standard HCG trigger in case a -1 sided 95% confidence interval (CI) of the relative risk (RR) was not <0.8. Secondary outcomes obtained were io oocytes retrieved, as well as maturation, Intracytoplasmic sperm injection (ICSI), fertilization rates, quality of embryos, pregnancy rates in addition to serum follicular hormone quantities. Secondary outcomes obtained were contrasted by utilization of 2-sided superiority test. Assessment of outcomes obtained were carried out by intention to treat as well as per protocol. Out of total of 105 women going through IVF got randomized from May

2015-June 2018. The primary outcomes probability was 0.59 with alternate trigger along with 0.65 with standard HCG trigger, having a RR of 0.91 alternative as well as their observations pointed to comprised probability probably with alternate trigger in addition to 1 sided 95% CI of 0.83. non inferiority of the alternate trigger got illustrated. Live birth rates (LBR) from every fresh transfers in alternate trigger group vis a vis standard HCG trigger group were 46.9 vs 46.4% (RR, 1.01; 95% CI, 0.62-1.62) respectively. LBR every randomized patient taking part was 48.1% in the alternate trigger group vis a vis standard HCG trigger vis a vis standard HCG trigger (RR, 0.73; 95% CI, 0.48-1.11). No failure of retrieval was observed in patients taking part.

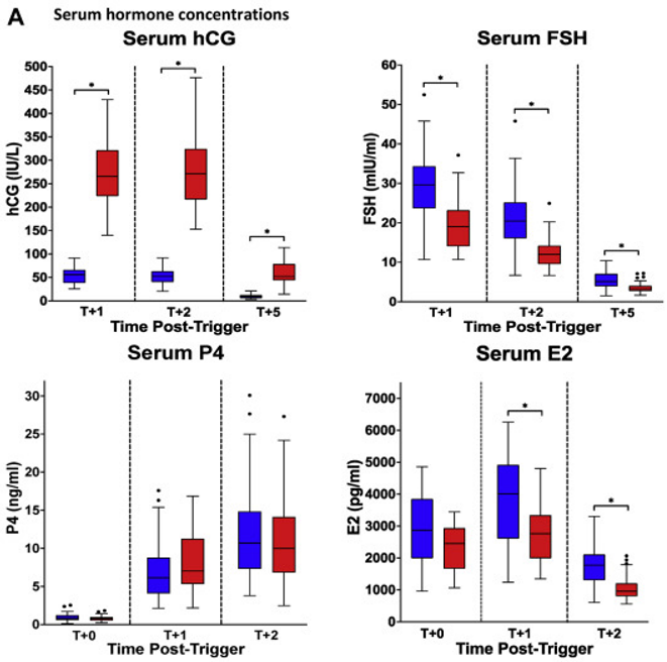

Figure 1: Courtesy ref no-16-Hormone concentrations stratified by alternative trigger (1,500 IU hCG plus 450 IU FSH) vs. standard hCG trigger. Note: Only comparison to 10,000 IU hCG trigger are presented; however, outcomes were similar when compared to 5,000 IU hCG. Values are expressed using whisker-box plots. Significant difference between pairwise comparisons are identified by an asterisk (∗). IU = international units, hCG = human chorionic gonadotropin; FSH = follicle-stimulating hormone; P4 = progesterone; E2 = estradiol; VEGF = vascular endothelial growth factor; T+1 = 12 hours after trigger; T+2 = at retrieval; T+5 = 5 days after trigger.

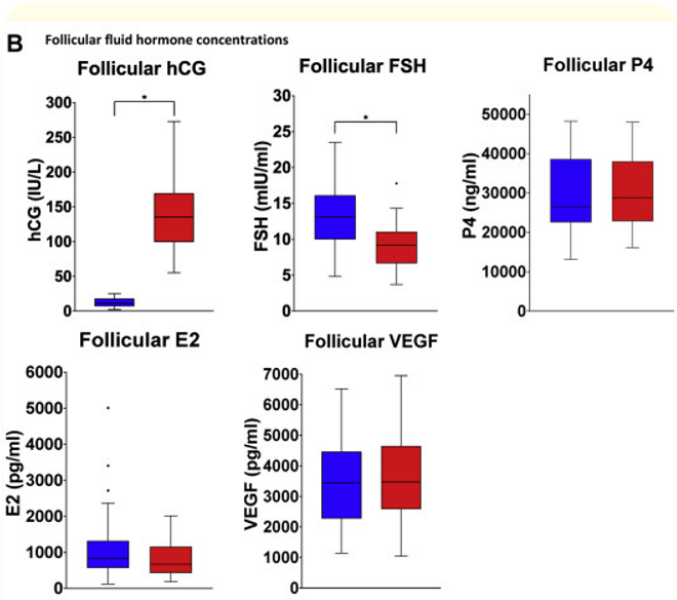

Figure 2: Courtesy ref no-16 - Hormone concentrations stratified by alternative trigger (1,500 IU hCG plus 450 IU FSH) vs. standard hCG trigger. Note: Only comparison to 10,000 IU hCG trigger are presented; however, outcomes were similar when compared to 5,000 IU hCG. Values are expressed using whisker-box plots. Significant difference between pairwise comparisons are identified by an asterisk (∗). IU = international units, hCG = human chorionic gonadotropin; FSH = follicle-stimulating hormone; P4 = progesterone; E2 = estradiol; VEGF = vascular endothelial growth factor; T+1 = 12 hours after trigger; T+2 = at retrieval; T+5 = 5 days after trigger.

Conclusions

Hence the conclusions drawn by Anaya Y., *et al.* [16], was that triggering with utilization of 1500 IU HCG in addition to 450 IU of FSH facilitated non inferior oocyte competence in contrast to a standard HCG triggering dosage. However a larger study is essential with regards to evaluation of embryo production as well as LBR results [16]. Gonzalez- Gonzalez V., *et al.* [18] performed a systematic review and meta-analysis recently with regards to dual Trigger (HCG + GnRHa trigger) where they observed superiority of results in with regards to embryo formation as well as pregnancy results**.** One of the modes that might give reason for the enhancement in pregnancy rate is the escalation of receptivity along with implantation in view of the extra-pituitary actions of the GnRH

molecule, which is implicated in endometrial receptivity, embryo implantation, and trophoblast invasion. The expression of HOXA-10, possesses a key part in modulating endometrial receptivity, is diminished in endometrial tissues in antagonist cycles as explained by Olieviera., *et al*. [19].

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