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Comparison of Human Chorionic Gonadotropin(hCG) and Gonadotropin Releasing Hormone(GnRH) Agonist Trigger in ART

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Abstract

Study Objective: Human chorionic gonadotropin (hCG) injection is used for the final follicular maturation and ovulation, during In Vitro Fertilization (IVF) cycles. hCG has the same effect of luteinizing hormone (LH) with long half-life. Injection hCG 5000-10000 IU is used as a standard method but it also has increased risk of developing ovarian hyper stimulation syndrome (OHSS). Injection Gonadotropin-releasing hormone agonist (GnRH-a) is used for the induction of final follicular maturation and ovulation .GnRH-a is mainly used for triggering with the aim of reducing the OHSS risk. In this study, we compared the benefits, problems, and triggering complications of injection hCG and injection GnRH-a.

Methods and Materials: The hospital based prospective study consisted of two groups A (hCG trigger) and B(GnRH agonist trigger), each group with 200 cases.

Results: There is no OHSS in the GnRH agonist trigger group. No difference was observed in other parameters in both groups.

Conclusion: GnRH agonists triggering is recommended in all cases with the risk of developing OHSS

Key Words: Gonadotropin-Releasing Hormone, Human Chorionic Gonadotropin, IVF/ICSI cycles

Introduction

Human Chorionic Gonadotropin (hCG) injection is generally used and is considered as standard trigger for final maturation of oocyte during ovulation induction. It is also known as “the hormone of pregnancy” as it has a crucial role in human reproduction. Assisted reproductive technology (ART) is a technique for infertility treatment[1]. This technology includes Intrauterine Insemination (IUI), In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI). The procedures are based on ovulation timing, retrieval of oocytes, insemination and fertilization of oocytes in in vitro environment [1].

In Assisted Reproduction technology (ART) hCG has been used to mimic Luteinizing Hormone (LH)-surge for late follicular phase and to induce final maturation and ovulation[2]. hCG has similar structural and biological activity as LH and share the same receptor, LH/CGR. The binding affinity of hCG is stronger than LH [3]. Also, the half life of hCG is 36 hours while of LH is 10-12 hours which makes hCG more efficient trigger. Injection hCG 5000-10,000 IU is given around the 12th day of simulation or(once the size of at least three follicles are around 18mm), 36 hours before oocyte retrieval intramuscularly or subcutaneously during controlled ovarian stimulation (COS). The objective of COS is to produce multiple follicles and synchronize maturation of oocytes to enhance the success rate of ART. However, hCG is associated with a higher risk of developing ovarian hyperstimulation syndrome (OHSS) and premature luteinizing hormone (LH) surge[4]. OHSS is a potentially life-threatening, but preventable iatrogenic complication of ART treatment. It can occur during either the luteal phase (early-onset OHSS) or early pregnancy (late-onset OHSS). OHSS clinical manifestation could be mild, moderate or severe. It is a life-threatening complication which occurs due to increased capillary membrane permeability as a result of production of angiotensin and vascular endothelial growth factor (VEGF) [5]. This effect is known as angiogenic factors which stimulate accumulation of third-space fluid leading to depletion of intravascular volume. It is this fluid shift from the intravascular to the interstitial spaces which results in ascites, pleural effusion, hypotension, oliguria secondary to acute renal failure, thromboembolism, and in

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cases of severe intravascular volume depletion, multiple organ failure. An increase in ovarian size and the presence of numerous luteal cysts can lead to adnexal torsion during the early stages of OHSS.

According to studies, serum VEGF is a marker and correlate with the clinical severity of OHSS, suggesting that hCG induces the release of VEGF, which, together with other contributing cytokines, is responsible for the signs and symptoms of OHSS [6].

Gonadotropin hormone-releasing hormone (GnRH) is the key regulator of the reproductive axis. Its pulsatile secretion determines the pattern of secretion of the gonadotropins follicle stimulating hormone and luteinising hormone, which then regulate both the endocrine function and gamete maturation in the gonads [7]. In the mid-cycle, in the presence of high levels of estrogen and low increased levels of progesterone, sudden surge of gonadotropins especially LH takes place which induces ovulation after 36-40 hrs .

From 1970s to 1990s several researches were carried out on stimulation of gonadotrophin and oocyte maturation of oocytes. According to Nakano et al. in 1973, it was demonstrated that 600ug GnRH for 6 hours followed by 400 ug SC can lead to Ovulation. Some other studies were carried out using similar dose or more GnRH agonist dose in the mid-cycle for gonadotropin surge stimulation. This helped to release LH/FSH naturally and shorter duration of increasing LH which avoids OHSS[9].

GnRH-a decreases significantly the risk of OHSS and gradually is used in most clinics to induce final oocyte maturation in patients with the risk of OHSS (22). Although a few cases of OHSS following GnRH-a trigger can be seen in the literature, in general using GnRH-a trigger, almost declines the risk of OHSS as a complication of ovarian stimulation by gonadotropins and its incidence is less common than hCG trigger[10]. Recent modifications of luteal phase after GnRH-a trigger make it possible to transfer embryo in the same cycle for many women at the risk of OHSS and provide a good outcome [7, 8].

Materials and Methods

The hospital based prospective study was carried out at Safal Fertility Foundation & Bansal Hospital. The study was conducted over the period from1st January 2014 to 31st December 2019. The total number of study participants included in the study was 400. The patients who were undergoing IVF/ICSI cycles were included in this study.

Both types of patients, with self oocytes and donor oocytes were included in the study. In this study, two groups were formed. Group A included 200 patients with hCG trigger and Group B included 200 patients with GnRH agonist trigger.

For both the groups, baseline sonography performed for antral follicle count & size. Stimulation protocol started by administration of Inj.Gonadotropin daily .The dose of gonadotrophin was calculated based on the BMI, AMH and AFC of the patient. Gonadotropin dosage varied according to the ovarian response to stimulation. Approximately after the 6th or 7th day of gonadotropin injection or when follicular size reached 14 mm, subcutaneous administration of the GnRH antagonist started. In both groups, routine monitoring of patients via trans-vaginal sonography (TVS) done in both the groups.

The trigger was given when the size of follicles had reached size 17 to 18 mm and at around 12th day of stimulation, Inj. hCG/GnRH agonist administered. At 34 to 35 hours post inj.hCG, Oocyte retrieval performed.

Result

Two hundred women underwent IVF cycle using GnRHa trigger, and 200 women had hCG trigger. The ongoing pregnancy rate and clinical pregnancy rate per embryo transfer were similar between the groups (Table 1). The clinical pregnancy rate were non-significantly higher with GnRHa trigger compared with hCG trigger, mainly because of higher rate of freezing all the embryos in the GnRH agonist trigger group (26.4% versus 8.9%; P = 0.04).

In cycles undergoing embryo transfer, the live birth rate and ongoing pregnancy rate was 43.4% in the GnRHa group and 32.7% in the hCG group. One case of severe early onset OHSS occurred with hCG (3.9%) and none occurred with GnRHa trigger, which did not reach statistical significance. No incidence of secondary OHSS (late-onset or pregnancy-associated) occurred in either group.

The normality of data was checked. The continuous and categorical variables were compared by t-test and Fisher's exact or chi-squared tests, respectively. $P < 0.05$ was statistically significant and an odds ratio was expressed with 95% confidence interval.

Mean number of oocytes retrieved and embryos created were similar in the two groups (Table 1). No difference was found in the mean number of mature (metaphase II) eggs between the groups when ICSI was carried out (Table 1). The fertilization rates were 53.5% and 54.9% and implantation rates were 30.2% and 28.9% with GnRHa and hCG trigger, respectively.

Among women aged younger than 37 years on their first treatment cycle, the embryo quality was suitable for SET in 40.5% of GnRHa trigger cycles and 16.7% of hCG trigger cycle. Between the variables, only total gonadotropin dose was directly related to days of stimulation, based on a linear regression model.

Discussion

GnRH agonist for final maturation of oocytes in GnRH antagonist protocol has emerged to be the most effective method for prevention of OHSS. With the development in the medicinal field, all clinicians prefer "OHSS free clinic" [11]. GnRH agonist proved to be promising for the same. A single small dose of hCG immediately after oocyte retrieval has been found to result in excellent clinical pregnancy and ongoing pregnancy rates, with only rare occurrences of severe OHSS in uncontrolled retrospective studies conducted in women at high-risk of OHSS [12].

In this present study, more cycles progressed to blastocyst in the GnRHa trigger group compared with those in the hCG trigger group (71.4% versus 43.8%; $P = 0.06$). Based on the study, it can be assumed that in GnRH a trigger the quality and maturation of oocytes is improved which

Table 1. Comparison of IVF-ICSI outcomes and risks between GnRH agonist and hCG trigger.

Parameters	GnRH agonist trigger	hCG trigger	P or OR (CI)
	n = 200	n = 200	
Oocytes retrieved [a]	12.91± 10.5	13± 9.3	NS
Mature (metaphase II) oocytes [a]	7.95± 8.2	8.3± 8.6	NS
Embryos [a]	6.5± 5.7	7.1± 5.2	NS
Fertilization rate *n* (%)	53.5	54.9	NS
Implantation rate *n* (%)	30.2	28.9	NS
OHSS [b]	0	35	*P* = 0.04
Freeze all embryos [b]	all	6.7	
Ongoing pregnancy rates			
Per embryo transfer [c]	40.5	34.5	NS
Clinical Pregnancy rate			
Multiple pregnancy per embryo transfer [c]	9.3	10.2	NS
Abortion per embryo transfer- total [c]	10.5	8.6	NS

NS, not statistically significant.
a Mean ± 2 standard deviation, t-test for comparison.
b Number (percentage).
c Number out of the sub-group total (percentage), Fisher's/$\chi 2$ for comparison.

is associated to increases in pregnancy outcomes [13].The hypothesis behind it can be FSH surge alongside the LH surge after GnRHa trigger and an enhanced endometrial receptivity owing to a direct effect on the endometrium at receptor and post-receptor level [14].

Concern has been expressed that administration of hCG for LPS, while improving treatment outcome, may also increase the risk of OHSS. The only RCT that similarly compared GnRHa and hCG trigger, excluded the cycles with more than 25 follicles wider than 10 mm at the end of stimulation to prevent OHSS, and reported no incidence of severe OHSS in the agonist trigger arm even though a bolus of 1500 IU hCG was administered in the luteal phase[15]. This policy was based on the evidence that the numbers of recruited follicles could predict the occurrence of OHSS[17].

GnRH agonist trigger has a negative impact on luteal function and endometrial receptivity. LH surge duration is shorter in GnRH agonist compare to natural LH surge and leads to luteal phase deficiency [16]. The spontaneous LH surge is defined by a short ascending phase (14 hours), a peak phase (14 hours), and a descending phase (20 hours) while the GnRHa induced LH surge consisted of two phases: a short ascending limb (>4 hours) and a long descending limb (>20 hours) [6,21].

The shortened surge may be responsible for accelerated degradation of the corpus luteum and a decrease in progesterone and E2 in cycles triggered by GnRHa versus hCG [18]. It is important to note that our patients did receive progesterone 400 mg twice per day for luteal support [17] .A meta-analysis, which found progesterone luteal support to be beneficial in patients undergoing ovulation induction with gonadotropins in IUI cycles, did recommend vaginal progesterone due to low cost and side effect profile. However, all included studies were triggered with hCG [11]. Significantly lower implantation rates, CPR, and a higher rate of early pregnancy loss have been documented in antagonist IVF cycles triggered with GnRHa versus hCG despite luteal support with oral E2 and vaginal progesterone [19]. A randomized controlled trial (RCT) did report similar ongoing pregnancy rates to hCG trigger when patients who were administered GnRHa trigger received low-dose hCG at the time of oocyte retrieval in addition to oral E2 and intramuscular progesterone in the luteal phase [20].

Conclusion

In the present study, no statistically significant difference was observed in the pregnancy rates and reproductive outcome with GnRH agonist trigger and hCG trigger. The effects of GnRH trigger and hCG on the maturation of oocytes are similar. GnRH trigger is more suitable for patients at risk of OHSS. This study shows 0% OHSS to patients triggered with GnRH agonist. In this study, intensive LPS method could not be effective in all patients with luteal phase deficiency, in despite of acceptable outcomes. At present the most appropriate method for LPS after GnRH-a triggering is unknown and further studies are needed.

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