Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2021, 11, 1452-1460
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

GnRH-Agonist Trigger versus Human Chorionic Gonadotrophin (HCG) Trigger in Cases of Controlled Ovarian Stimulation; Randomized Controlled Trial

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How to cite this paper: Elmahdy, M. and Elsharkawy, S. (2021) GnRH-Agonist Trigger versus Human Chorionic Gonadotrophin (HCG) Trigger in Cases of Controlled Ovarian Stimulation; Randomized Controlled Trial. *Open Journal of Obstetrics and Gynecology*, **11**, 1452-1460.
https://doi.org/10.4236/ojog.2021.1111135

Received: September 10, 2021
Accepted: November 7, 2021
Published: November 10, 2021

Abstract

Objectives: The aim of the study was to compare the efficacy and safety of GnRH-agonist to the human chorionic gonadotrophin (HCG) trigger in cases of simple ovarian stimulation. Study design: Randomized controlled trial was conducted on 291 women complaining of unexplained infertility visiting Elshatby Maternity University Hospital from February to December 2019. Trial registration unique ID is PACTR202001787868341 (https://www.pactr.org/). Age included from 20 - 43 years. All patients were stimulated by the sequential stimulation protocol using letrozole then FSH injection, when the criteria of ovulation trigger were reached; cases were randomized into two groups using closed envelopes method. Group A (123 cases) GnRh agonist (triptorelin 0.2 IU) subcutaneous injection and Group B (168 cases) HCG 10,000 IU intramuscular injection were used for triggering of ovulation then followed by timed intercourse. Results: Primary outcome was the clinical pregnancy rate while rate of miscarriage and ovarian hyper-stimulation rate were the secondary outcome. Clinical pregnancy rates, in Group A were (21.1%) while it was (31.5%) in another group (P = 0.049). Miscarriage rate was (4.9%) in the first group and (3.6%) in the second group (P = 0.580). Except for one case of moderate ovarian hyper-stimulation syndrome (OHSS) complicated the HCG group, there were no such cases in GnRH group. Conclusion: Triggering final oocyte maturation with HCG was superior to GnRH agonists triggers as regards the clinical pregnancy rate.

Keywords

GnRH Agonist, HCG, Ovulation Trigger, OHSS

1. Introduction

The first oocyte collected for successful *in vitro* fertilization was done by laparoscopy in a natural cycle without any stimulation [1]. Later, to achieve more cost effective cycles, ovulation induction was necessary to harvest more oocytes per cycle, and to control the time for ovulation and oocyte retrieval as a consequence-pituitary down regulation became a must [2].

The down regulation was first done by gonadotrobin-releasing hormone agonists (GnRH), added to the exogenous human chorionic gonadotropin (HCG) as a trigger for final oocyte maturation. Such a combination gave the best control of the cycle but carried the risk for a serious complication called ovarian hyper-stimulation syndrome (OHSS).

OHSS is almost exclusively an iatrogenic complication of supernatural ovulation induction, which is associated mainly with gonadotropin usage and rarely seen with clomiphene citrate or natural ovulation [3].

To decrease the incidence of OHSS, and as a trial to avoid HCG triggering, the first report on using GnRh agonists as a trigger came from Rambam Health Care Campus in 1988 [4]. They used agonists to induce an adequate luteinizing hormone (LH) surge in eight non-suppressed IVF cycles of high risk patients for OHSS [5]. The result appeared to decrease the clinical manifestations of the deadly syndrome, but the technique was not popular worldwide until the last decade of the twentieth century, after the production of GnRH antagonists with proven clinical activity and fewer side effects that can be used for pituitary down regulation instead of the agonists [6] [7], saving them for triggering in high risk patients.

But how does GnRH triggering prevent OHSS? This question can be answered by understanding the difference between HCG and LH (which is produced by GnRH). LH has a short half-life (one hour) when compared to HCG (more than 24 hours). This main difference makes GnRH agonists more physiological triggers but with the disadvantage of luteal phase defects as a consequence of decreased circulating levels of progesterone and estradiol, which are significantly lower than those obtained after HCG triggering. Humaidan *et al.* [8] reported equal results as regards number of retrieved oocytes, fertilization and quality of embryos in patients received HCG and GnRH agonists trigger. But with the latter group, there were poor clinical results as decreased pregnancy rates and increased early abortion rates, mainly due to luteal phase insufficiency.

GnRH triggering stimulates follicle stimulating hormone (FSH) surge in addition to LH, FSH surge in the mid-cycle has a beneficial effect on oocyte maturation. It leads to further expansion of the cumulus cells and release of proteolytic enzymes essential for ovulation [9]. It causes better oocyte recovery and higher fertilization rates when added to HCG in IVF cycles [10]. It also leads to more maturation of the nucleus, the resumption of meiosis and it increases the number of oocytes in Metaphase II [11]. Finally GnRH triggering decreases the immature oocyte syndrome. In this situation, more than 25% of the oocytes re-

trieved after stimulation are immature, despite the proper timing of HCG triggering and oocyte retrieval [12].

GnRH trigger allows for dissociation of the ovulation triggering process and luteal support. In this study we aimed to compare GnRH-agonist trigger versus HCG trigger in cases of controlled ovarian stimulation.

2. Methods and Materials

Study design: This was a randomized controlled study.

Study setting: It was conducted in the period from February to December 2019. All patients were recruited from Elshatby university maternity hospital fertility clinic. Pregnant women were followed up till the end of the first trimester.

Sample size: It included 291 women complaining of infertility and was scheduled for simple ovarian stimulation. The patients were randomized into 2 groups; A and B using a closed envelop method. Sample size calculation was done using Creative Research Systems that offers a free sample size calculator online (http://www.surveysystem.com/sscalc.htm) which was based on last Egyptian census in 2014, which gave us 240 cases as an adequate sample. An informed consent was taken from each participant and the study was accepted by the department ethical committee of faculty of medicine, Alexandria University.

Participants: Inclusion criteria were; women complaining of infertility either primary or secondary for a duration not more than 2 years. They were similar in the sociodemographic characteristics. All women were indicated for controlled ovarian stimulation. The age was between 20 - 43 years, women with regular ovulatory menstrual cycles, normal male factor and normal hystrosalpengiogram (HSG) were included. Exclusion criteria were; previous uterine surgery, evidence of endometrial, uterine or pelvic pathology, medical disorders or regular intake of medications and poor ovarian reserve.

Methods: Included women were subjected to complete history taking with special emphasis on causes and duration of infertility. Complete general examination including weight, height and any sign of endocrinal abnormalities. Basal transvaginal ultrasound (TV-US) scans on day 1 - 3 of the cycle to exclude endometrial abnormality or functional ovarian cyst.

All patients started controlled ovarian stimulation using sequential protocol starting on day 2 of menstruation. They were given oral ovulation induction (letrozole 5 mg daily) for 5 days then FSH daily injections of 75 IU or 150 IU according to BMI and previous response history. The dose modification was done according to each patient response to induction, which was monitored with TV-US starting from day 8 of stimulation.

Upon reaching a follicular size of 18 mm, triggering of ovulation was given; GnRh agonist triptorelin 0.2 IU subcutaneous in cases of group A (123 cases) and HCG 10,000 IU intramuscular in cases of group B (168 cases) followed by timed intercourse 36 hours later. Luteal support was given to both groups and

pregnancy test was done after 14 days of the estimated time of ovulation. Chemical pregnancy was confirmed to be clinical by doing TV-US examination 2 weeks later to detect gestational sac intrauterine.

Our main outcomes were chemical and clinical pregnancy rates, our secondary outcomes were abortion rates and ovarian hyperstimulation (OHSS) rates.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 22. Quantitative data were described using mean and standard deviation error of mean. Comparison between the different studied groups was analyzed using independent T-test. Significance of the obtained results was judged at the 5% level.

3. Results

This current study was a randomized control study conducted on 291 patients that were recruited from El-Shatby fertility clinic from February to December 2019. The patients were allocated in two groups A (123 women) and B (168 women). There were no dropped patients from the recruited patients during the study. The two studied groups were compared as regards the clinical pregnancy rates, abortion rates and ovarian hyperstimulation (OHSS) rates.

As regards age of the patients, in control group, the age of the patients ranged between 21 - 41 years with a mean of 30.89 ± 5.93, and in study group the age of the patients ranged between 20 - 43 years with a mean of 29.85 ± 5.10 with no statistically significant difference between the two studied groups as shown in Table 1.

Regarding clinical pregnancy rates, in group A (GnRH group) 26 cases (21.1%) were clinically pregnant (confirmed to be clinical by doing TV-US examination 2 weeks after the chemical testing to detect gestational sac intrauterine), while in the other group (HCG group) 53 cases (31.5%) were clinically pregnant which were statistically significant (P = 0.049), in favor to the HCG group as shown in Table 2.

According to our secondary outcomes, the abortion rates were 6 cases (4.9%) in the first group and 6 cases (3.6%) in the second group, which had no statistical significance (P = 0.580) as shown in Table 2 except for one case of moderate OHSS complicated the HCG group, there were no such cases in GnRH group.

Table 1. Comparison between the two studied groups according to age.

Age	Group A (n = 123)	Group B (n = 168)	Test of sig.	P
Min. - Max.	20.0 - 43.0	21.0 - 41.0		
Mean ± SD.	29.85 ± 5.10	30.89 ± 5.93	T = 0.689	0.494
Median (IQR)	30.0 (26.5 - 32.0)	31.0 (26.0 - 36.0)		

t: Student t-test; P: P value for comparing between the studied groups.

Table 2. Comparison between the two studied groups according to pregnancy and abortion.

	GnRH (group A) (n = 123)	HCG (group B) (n = 168)	□□	p
Pregnancy				
Negative	97 (78.9%)	115 (68.5%)	3.890*	0.049*
Positive	26 (21.1%)	53 (31.5%)		
Abortion				
Negative	117 (95.1%)	162 (96.4%)	0.307	0.580
Positive	6 (4.9%)	6 (3.6%)		

χ^2: Chi square test; P: P value for comparing between the two groups; *: Statistically significant at P ≤ 0.05.

4. Discussion

Using the simple ovarian stimulation protocol has the advantage of absence of down regulation of pituitary gland. It freed our hands to trigger ovulation with GnRH agonists. After injection of a single bolus of GnRH agonist, activation of the receptor, producing a flare-up of gonadotrophins (LH and FSH), which adequately stimulate the final oocyte maturation and ovulation occurs.

Triggering with GnRH agonist simultaneously induce a mid-cycle FSH surge that is similar to what happens in a natural ovulatory cycle. Animal studies have showed the importance of FSH in up regulating of (LH) receptor sites in granulosa cells [13]. This expression of LH receptors is essential for luteinzation of granulosa cells with the aid of for the pre-ovulatory LH surge [13]. FSH also has important for resumption of oocyte meiosis and the expansion of cumulus cells [14].

There is a difference between the LH surges that results from triggering with GnRH agonists compared to that of the natural cycle. In the natural cycle, the LH surge has a total duration of around 48 hours in three phases. While GnRH agonist triggering, the surge consists of two phases, and a duration of 24 - 36 hours only, which lead to a much lower amount of LH released [8]. This short half-life of the pituitary hormone will induce rapid and irreversible luteolysis, and reducing the risk of OHSS to minimum [15]. Notably, the expression of inhibin β and vascular endothelial growth factor (VEGF) were found to be less in the granulosa cells retrieved from patients with GnRH agonist triggering than those from patients with hCG triggering, which may be another factor that lowers OHSS rate in those women [16].

The early degeneration of the corpus leutum decreases the progesterone levels in luteal phase below the limit which is essential for optimal embryo implantation. Therefore, GnRH agonist triggering without accurate luteal phase support causes a decrease in pregnancy rate and high rate of pregnancy loss [17].

Our current study was conducted on 291 patients that were allocated ran-

domly in two study groups, A and B. Our results revealed a clinical pregnancy rates 21.1% (26 cases) in the GnRH group, while in the HCG group 31.5% (53 cases) were clinically pregnant which were statistically significant (P = 0.049), in favor to the HCG group. According to our secondary outcomes, the abortion rates had no statistical significance between the two groups (P = 0.580). Except for one case of moderate OHSS complicated the HCG group, there were no such cases in GnRH group.

In a similar study, M. Le *et al.*, randomized 169 women, 90 were to hCG trigger and 79 to GnRH agonist triggering. Similar to our study results, their Clinical pregnancy rate was higher in the hCG trigger group (30.0%) versus the GnRH agonist trigger group (13.9%) (P $\frac{1}{4}$ 0.01; OR 0.37 95% CI $\frac{1}{4}$ 0.17 - 0.84). They concluded that "Ovulation trigger with hCG was associated with significantly increased clinical pregnancy rates in patients undergoing ovulation induction with IUI in comparison to GnRH agonist trigger. Given the low risk of OHSS in patients undergoing ovulation induction, hCG trigger may be more beneficial for pregnancy outcomes in ovulation induction cycles" [18].

The decreased clinical pregnancy rate with the GnRH triggering is mainly due to luteal phase defects associated with this approach. To overcome this problem, there are two protocols for supporting luteal phase after GnRH-a trigger has become common in recent years: the European versus the American protocols. In the American protocol the use of exogenous steroids with low dose adjuvant of hCG in selected cases is applied, while in the Europe, the use of endogenous steroid production by the corpus leutum is done through complementary exogenous hCG. Both approaches have succeeded in increasing fertility outcomes in patients at high risk of OHSS [19] [20] [21] [22].

In 2015, a review analyzed and discuss the published studies relating to the different methods of GnRH agonist combined with hCG trigger for final follicular maturation, one bolus of 1500 IU hCG, concomitant, 35 h or 5 days after the triggering bolus of GnRHa, were all demonstrated to rescue the luteal phase and resulted in increased reproductive results in patients at risk to develop severe OHSS, as compared to GnRHa trigger alone. Due to the observed comparable or even better oocyte\embryos quality following GnRHa trigger when compared to hCG trigger, GnRHa and hCG may be offered simultaneously 34 - 37 h prior to oocyte retrieval (dual trigger) or 40 h and 34 h prior to oocyte retrieval, respectively (double trigger) in patients with abnormal final follicular maturation [23]. Limitations of this study were the small sample size, the cumulative pregnancy rate wasn't the main outcome and the wide range of the age group. While the strong point was that it is randomized controlled trial dealing with a simple point that can be faced in the daily practice for infertility specialist.

5. Conclusion

Triggering final oocyte maturation with HCG is superior to GnRH agonists triggers as regards the clinical pregnancy rate. Denoting the rare risk of OHSS

occurrence in simple ovarian induction cycles, we recommend the use of HCG in such cases to eliminate the luteal phase defect problems associated with the GnRH triggers.

Declaration

This study was approved from the **Ethics committee**, Faculty of Medicine, Alexandria University. Number: 0304336 date: 17/6/2019.

This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

Trial registration unique ID: PACTR202001787868341 (http://www.pactr.org/).

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Funds: personal.

Authors' Contributions

All authors contributed equally to the study: Data collection, study design, clinical treatments, follow-ups, Data integration and approved the final manuscript.

Acknowledgements

Gynecology Outpatient Clinic staff, Elshatby University Hospital for their assistance.

Conflicts of Interest

The authors declare that they have no competing interests.

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