DUAL TRIGGER (GNRH AGONIST + HCG) VERSUS HCG TRIGGER in IMPROVING ART OUTCOMES IN POOR RESPONDERS UNDERGOING ANTAGONIST PROTOCOL.

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Running Title

Dual Trigger vs. HCG in Poor Responders

Abstract

Background and aim: Dual triggering, which combines a gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin (HCG), has been suggested to enhance outcomes in poor ovarian responders undergoing infertility treatment. This study aimed to compare the efficacy of dual trigger versus HCG trigger in improving assisted reproductive technology (ART) outcomes in poor responders using a protocol of GnRH antagonist.

Methods: A prospective clinical randomized trial was conducted at Cairo University from June 2020 to March 2021, involving 86 poor responders. The study dual group (n=43) obtained a dual trigger of 5000 units of HCG plus triptorelin 0.2 mg and, whereas the other group (n=43) was given a conventional HCG trigger. Primary outcomes included the number of retrieved oocytes, mature oocytes (MII), obtained embryos, and fertilization rate.

Results: The study group exhibited significantly higher numbers of retrieved oocytes, MII oocytes, fertilization rate, obtained embryos, and embryos transferred compared to the control group (P value < 0.05). Although the implantation rate and chemical pregnancy rate were higher in the study group, the differences were not statistically significant (P value 0.482 and 0.492, respectively).

Conclusion: dual triggering with HCG and GnRH agonist may enhance ovulation triggering and reproductive outcomes in poor responders undergoing antagonist ICSI cycles, leading to increased numbers of retrieved oocytes, MII oocytes, obtained embryos, and fertilization rate. However, the impact on pregnancy and implantation rates was not statistically significant.

Keywords: Poor responders, Dual trigger, Antagonist cycles, ICSI protocols.

Synopsis: This study compares the effectiveness of dual triggering (using both GnRH agonist and HCG) versus HCG triggering alone in improving ART outcomes for poor ovarian responders undergoing treatment with a GnRH antagonist protocol.

Introduction

Since its inception in 1978, in-vitro fertilization then transfer of embryo has revolutionized infertility therapy, offering hope to many couples (1). Controlled ovarian hyperstimulation (COH) is a critical component of IVF success, enabling the retrieval of multiple healthy oocytes (2). However, a significant challenge in IVF treatment is poor ovarian response (POR), particularly among women over 40, whose numbers seeking fertility treatment continue to rise (3). POR is characterized by suboptimal outcomes in oocyte recovery and pregnancy rates despite various stimulation protocols, including the GnRH antagonist protocol, being attempted (4). One promising approach to improving outcomes in poor responders is "dual triggering," which involves combining a gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin (HCG) for triggering ovulation (5,6). Dual triggering aims to optimize oocyte development and has shown benefits in normal and high responders, including improved embryo quality and implantation rates, as well as a decreased hazard of stimulation syndrome of ovaries (7,8). In poor responders, dual triggering has shown promise in improving outcomes, even in cases of repetitive immature oocyte retrieval and empty follicle syndrome (9). The purpose of this study is to investigate the potential advantages of dual triggering with a GnRH-agonist and HCG combination on the number of oocytes that retrieved and rate of clinical pregnancy in women with low fertility response during GnRH-antagonist IVF-ICSI cycles.

Patients and Methods

The goal of this prospective clinical randomized experiment was to evaluate and compare the efficacy of a dual trigger (gonadotropin-releasing hormone agonist in addition to human chorionic gonadotropin) to an HCG trigger in women with low fertility response during GnRH-antagonist cycles. The study was conducted at Cairo University Hospital's IVF Unit from June 2020 to March 2021, after scientific and ethical committee permission. The trial population consisted of 86 women with low fertility response to ovarian hyperstimulation drugs undergoing fertility treatment with a GnRH antagonist regimen, who were split into two groups. The experimental group (n=43) got 5000 units of HCG (choriomon®, IBSA 10000 IU) with triptorelin 0.2 mg (Decapeptyl), whereas the control group (n=43) received the typical HCG trigger dosage (10000 units of HCG (choriomon®, IBSA 10000 IU)). The criteria for inclusion included patients who were not responding well to ovarian hyperstimulation drugs during ICSI using a GnRH antagonist regimen. These patients were classified as poor ovarian responders (POR) based on the Bologna criteria, meaning they had at least two of the following three characteristics: reduced ovarian reserve, poor ovarian response in the preceding cycle, and partner age of ≥40. Acute male factor infertility, age over 45, BMI > 30 kg/m2, PCO, other metabolic diseases, and abnormalities of the uterine cavity were among the exclusion criteria. All patients had office hysteroscopy, laparoscopy, hysterosalpingography, and general examination in the course of the study. Additionally, day three serum sample for FSH, LH, E2, AMH, prolactin, and TSH measures as well as baseline 2D transvaginal ultrasonography (MINDRAY DP-5) were performed. On the second day of the cycle, ovarian stimulation was initiated with a beginning dosage of 300 IU of human menopausal gonadotropin (HMG; Merional ®, IBSA) and increased to 450 IU. Beginning

on the seventh day after HMG stimulation, a daily dose from cetrerelix (cetrotide) 0.25 mg was administered. Ultrasound was used to track the ovarian response until at least two of the leading follicles had grown to a diameter of 18 mm. Either 10000 HCG units (choriomon ®, IBSA 10000 IU) for the control group or 5000 HCG units (choriomon ®, IBSA 5000 IU) + 0.2 mg of triptorelin (Decapeptyl) for the study group caused the last stages of oocyte maturation. 34 to 36 hours after triggering, oocyte retrieval was carried out under transvaginal ultrasound supervision. On days two or three following fertilization, a fresh embryo transfer was carried out, and luteal phase support taken as a daily progesterone 100 mg IM as well as a micronized progesterone 400 mg vaginally. Serum pregnancy hormoen β-HCG was assessed 14 days following extraction of oocyte, and for all successful pregnancies, luteal support persisted until the tenth week of gestation. Both groups' data included the number of oocytes obtained, MII oocytes, acquired embryos, rate of fertilization, rate of implantation, rate of chemical pregnancy, as well as rate of clinical pregnancy.

By calculating the mean number of oocytes obtained, the sample size was determined. The mean number of oocytes obtained in dual trigger was around 7± 4.6, whereas in HCG trigger it was roughly 2.3± 2.5, as described in a recent publication by Haas et al. (10). Using the student t-test test for independent samples, to reject the null hypothesis with 80% power at the $\alpha = 0.05$ level, we established a minimum sample size of 10 individuals per group. MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used to calculate the sample size.

Statistical analysis

IBM SPSS Statistics version 24 (IBM Corp, Armonk, NY) was used for data collection, tabulation, as well as analysis. Numerical data that was regularly distributed was displayed as mean and standard deviation, whereas skewed data was shown as median and interquartile interval. Numbers and percentages were utilized to represent qualitative data. The unpaired t test was employed to compare normally numerical distributed data. The Mann-Whitney test was utilized to compare nonparametric skewed data. When comparing categorical data, the chi-squared test or, if applicable, Exact Fisher test were employed. A P value < 0.05 indicates statistically significant value.

Results

This prospective clinical randomized experiment involved 86 women with low fertility response to be managed with ovarian stimulation therapy during IVF-ICSI utilizing a GnRH antagonist therapy protocol. The patients were splitted equally into two groups: the study group, consisting of 43 patients who received triptorelin 0.2 mg (Decapeptyl) in plus 5000 units of HCG (choriomon ®, IBSA 10000 IU), and the other group, comprising 43 patients who received the standard HCG trigger dosage. Table 1 showed that there were no significant differences in age, BMI, duration of infertility, primary or secondary infertility, or causes of infertility (anovulation, male factor, unexplained) between the demographic characteristics of the two groups. These findings indicate that the groups were well-matched at the outset of the study. The ultrasonography characteristics and hormonal profiles of each group of patients are detailed in Table 2. Both groups exhibited similar hormonal and ultrasonography profiles, as evidenced by the lack of significant differences in AMH, basal FSH, basal E2, basal LH, AFC, or endometrial thickness at trigger. Table 3 presents the total dose of gonadotropins used and the duration of stimulation for patients in both groups. Similar ovarian stimulation outcomes were suggested by the lack of significant differences in total gonadotropin

dosage and stimulation duration between the groups. When comparing the dual trigger group to the HCG trigger group, the latter showed significantly fewer follicles, retrieved oocytes, M II oocytes, obtained embryos, and transferred embryos in terms of cycle stimulation results, as seen in Table 4. Furthermore, in the dual trigger group, the rate of fertilization was significantly higher. However, there were no significant differences in implantation rate, chemical pregnancy rate, or clinical pregnancy rate between the two groups. Overall, the data suggest that the use of dual trigger (a combination of GnRH agonist and HCG) in poor responders undergoing IVF-ICSI cycles led to improved cycle stimulation outcomes, including a higher number of retrieved oocytes, M II oocytes, obtained embryos, transferred embryos, and fertilization rate. Comparisons between the dual trigger and HCG trigger groups showed no significant differences in implantation rate, chemical pregnancy rate, or clinical pregnancy rate.

Discussion

The concept of replacing hormone of human chorionic gonadotropin with a gonadotropin-releasing hormone agonist to initiate the last growth of oocyte was first proposed by Gonen et al. over two decades ago but did not gain a lot of attention until the clinical application of GnRH antagonist regimens for IVF(11). The golden goal of GnRH-agonist in triggering was to reduce the hazard of excess stimulation of ovaries through GnRH-antagonist of IVF cycles. Surprisingly, no cases of OHSS were recorded in a series of clinical randomized experiments involving high ovarian responders or normal ovarian responders undergoing fresh IVF treatment and transfer of embryo with GnRH-agonist triggering (12). Previous studies have predominantly focused on high and normal responders, with limited investigation into low responders. Dual triggering was developed as a strategy to address the limitations of GnRH-agonist triggering, which was initially implemented to reduce OHSS risk but was associated with inferior pregnancy outcomes, likely due to compromised endometrial receptivity and altered luteal phase function (13). Compared to traditional HCG-triggered cycles, GnRH-agonist triggering has been linked to significantly lower implantation rates and higher miscarriage rates, despite effectively mitigating the risk of OHSS (14). The adverse pregnancy outcomes associated with GnRH-agonist triggering have been credited to impaired Luteal phase efficiency and decreased susceptibility of endometrium. A new Cochrane article discouraged the widespread of GnRH agonists utilization as the most effective trigger for last growth of oocyte in new IVF cycles due to the substantial decrease in rate of ongoing pregnancy and rate of live birth compared to traditional HCG triggers (15). To address these challenges, the concept of a "double trigger utilization," which consisting of a single GnRH-agonist bolus with a reduced dose of HCG hormone at triggering, has been searched in IVF cycles with high ovarian responders. The inclusion of HCG preserved healthy luteal function while significantly reducing the risk of OHSS associated with GnRH-agonist triggering. Studies in high responders have shown that utilizing a dual trigger significantly improves ongoing pregnancy and live birth rates without significantly increasing the hazard of OHSS (16). To improve the likelihood of pregnancy in GnRH-antagonist phases, just one administration of GnRH agonist added to the typical HCG amount for oocyte development has been tested in normal respondents who are not at high danger for OHSS. Whereas statistics on the number of live babies born were not available, research on double triggering in regular responders found considerably higher continued conception rates among the investigated group in comparison to the other group that obtained just the hormone HCG triggering. (17). The "double trigger" approach has also shown promise in treating empty follicle

syndrome (EFS) in patients with a history of low or poor oocyte yield or immature oocytes obtained (18). A study report showen a successful conception obtained with a double trigger in a patient with EFS. Following two unsuccessful oocyte retrievals, a dual trigger of GnRH agonist and HCG resulted in 11 oocytes retrieved in the third IVF cycle, leading to the transfer of two blastocysts and a live birth. The modification of the treatment regimen with dual triggering yielded a favorable outcome (19). Further research is warranted to evaluate the efficacy of dual triggering in improving rate of baby born lived for women with low fertility response in GnRH-antagonist regimen of IVF-ICSI treatment. Our research goaled to investigate the potential of double triggering for last growth of oocyte, which includes mixing only one injection of GnRH agonist with a standard amount of HCG, in improving rate of babies born live for women with low ovarian response in regimen of GnRH-antagonist of IVF-ICSI therapy. In our search, 86 poor responders undergoing IVF-ICSI with a regimen of GnRH antagonist were split into two sections: the study double trigger group obtained 10,000 units of HCG with triptorelin 0.2 mg, while the other group obtained the standard HCG injection. Our results showed that the study double trigger group had a significantly higher mean number of collected follicles, M II follicles, embryos obtained, and transferred embryos compared to the other group, aligning with previous research demonstrating improved cycle outcomes with double triggering (10,20,21).

Conclusion

According to our research, in patients who are poor responders enduring antagonist ICSI cycles, dual stimulation of ovulation with using HCG hormone plus a GnRH agonist injection may increase the number of oocytes obtained, MII oocytes, embryos acquired, and transplanted embryos. Although there seems to be a correlation between dual trigger and increased frequencies of implantation and pregnancy, the findings lacked statistical significance.

Acknowledgments

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Table 1: demographic data of patients of both groups

Variable	Dual trigger (N =40)	HCG trigger (N=41)	P value
Age (year)[a]	41.6 ± 1.6	41.39 ± 1.8	0.942*
BMI (kg/m²)[a]	25.10 ± 2.5	26.35 ± 3.6	0.546*
Duration of infertility (year)[a]	4.87± 2.3	4.92± 2.28	0.919*
Type of infertility[b] • **1ry** • **2ry**	 29 (67.4%) 14 (32.6%)	 30 (69.7%) 13 (30.3%)	0.816#
Causes of infertility[b] • **Anovulation** • **Male factor** • **Unexplained**	 37 (86%) 4 (9.3%) 2 (4.7%)	 36 (83.7%) 4 (9.3%) 3 (7%)	0.898#

[a]Values (continuous quantitative data) are given as mean±SD.

[b]Values Qualitative (categorical) data are given as numbers (percentage).

Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of all study cases.

*t-test was used for normally distributed continuous quantitative data

#Chi-square test was used for qualitative (categorical) data

P value <0.05 significant

Table 2: Hormonal profile and ultrasound features among patients of both groups

Variable	Dual trigger (N =40)	HCG trigger (N=41)	P value*
AMH (ng/ml)	1 ± 0.1	1.1 ± 0.1	0.852
Basal FSH (IU/L)	12.3 ± 1.6	12.2 ± 1.6	0.855
Basal E2 (pg/ml)	59.5 ± 9	61 ± 8.8	0.450
Basal LH (IU/L)	4.7 ± 0.62	4.75 ± 0.7	0.770
AFC	4.5 ± 0.7	4.4 ± 0.7	0.631
Endometrial thickness on trigger	10.3 ± 1.1	10.1 ± 1.0	0.426

All Values (continuous quantitative data) are given as mean±SD.

Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of all study cases.

*t-test was used for normally distributed continuous quantitative data

P value <0.05 significant

Table (3): total dose of gonadotropins used for ovarian stimulation and stimulation duration in patients of both groups.

Variable	Dual trigger (N =40)	HCG trigger (N=41)	P value*
Total dose of GN	378.41±64.6	375±63.38	0.805
Stimulation duration	12.5±0.8	12.7±0.9	0.279

Values (continuous quantitative data) are given as mean±SD.

Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of all study cases.

*t-test was used for normally distributed continuous quantitative data

P value <0.05 significant

Table (4): cycle stimulation outcomes in patients of both groups.

Variable	Dual trigger (N =40)	HCG trigger (N=41)	P value
Number of follicles[a]	7.15±0.69	7±0.75	0.358*
Number of retrieved oocytes[a]	6.2 ± 1.2	5.6 ± 1.1	0.008*
Number of M II oocytes[a]	4.3 ± 1.1	3.6 ± 1.0	0.003*
Number of embryos obtained[a]	3 ± 1	2.2 ± 0.7	0.0001*
Number of embryos transferred[a]	2.5 ± 0.8	1.9 ± 0.5	0.0001*
Fertilization rate %[a]	69.5 ± 14.9	59.8 ± 14.3	0.003*
Implantation rate %	13.1 ± 6.5	12.3 ± 3.7	0.485*
Chemical pregnancy rate %[b] **Yes** **No**	15 (34.8%) 28 (65.2%)	12 (28%) 31 (72%)	0.485#
clinical pregnancy rate %[b] **yes** **no**	10 (23.25%) 33 (76.75%)	8 (18.6%) 35 (81.4%)	0.596#

[a]Values (continuous quantitative data) are given as mean±SD.

[b]Values Qualitative (categorical) data are given as numbers (percentage).

Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of all study cases.

*t-test was used for normally distributed continuous quantitative data

#Chi-square test was used for qualitative (categorical) data

P value <0.05 significant

CONSORT 2010 Flow Diagram