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ORIGINAL ARTICLE

Evaluation of Dual Trigger Versus Higher Dose hCG Trigger in Antagonist Protocol for Patients with Low Number of Oocytes Retrieved Per Number of Follicles

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Abstract

Background: **Controlled ovarian hyper stimulation is a critical step in the process of *in vitro* fertilization and embryo transfer because it ensures the absorption of a large number of oocytes that are of sufficient quality to be fertilized. This condition's source, mechanism, and/or pathophysiology are still unknown, unpredictable, and unpreventable, despite the years of clinical experience that have been accumulated.**

Aim and objectives: **To assess the efficiency of utilizing a dual trigger as opposed to a higher dosage of human chorionic gonadotropin (hCG) as a trigger in an antagonist protocol for the purpose of improving the number of up taken eggs/number of follicles that are greater than 17 mm in diameter on the day of the trigger in individuals who have a previous history of a low egg number of up taken eggs/number of follicles.**

Patients and methods: **The International Islamic Center for Population Studies and Research Assisted Reproductive Technology Unit (IICPSR) of Al-Azhar University in Egypt and the Egyptian *in vitro* fertilization and embryo transfer Center in Maadi collaborated on the conduct of this prospective clinical trial. Two hundred (200) eligible women were selected from the infertility outpatient clinic of the ART unit. They were randomized by sealed envelope into two groups. Group (1) involved one hundred women who were triggered by an extra 5000 IU higher dose of hCG than that of the previous trial. While group (2) involved one hundred women who were triggered by dual trigger (5000 iu hCG and two ampoules of decapeptile 0.1).**

Result: **Dual trigger can dramatically enhance the number of retrieved oocytes, the number of MII oocytes and the number of top quality embryos (TQE) for individuals who have a low number of egg uptakes relative to the number of follicles. ($P = 0.001$, 0.010, and 0.04, respectively).**

Conclusion: **The cumulative pregnancy rate, which is calculated from the clinical pregnancy rate after frozen embryo transfer, appears to rise when a dual trigger is employed.**

Keywords: Antagonist protocol, Dual trigger, Human chorionic gonadotropin trigger, Oocytes retrieved

1. Introduction

Controlled ovarian hyper stimulation ensures the absorption of many high-quality oocytes for embryo transfer and *in vitro* fertilization.[1] Human chorionic gonadotropin (hCG) is given towards the end of ovarian stimulation to replicate the LH surge and promote egg maturation and cell division. This practice is followed to raise the odds of having a healthy baby.[2]

The ratio of the number of eggs up taken to the number of follicles larger than 17 mm in diameter on the day of trigger is less than or equal to 50%, which is a circumstance that occurs often in normal responders. In this case, the number of eggs up taken is lower than the number of follicles that are present.[3]

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Despite years of clinical experience, the cause, mechanism, and/or pathophysiology of this condition is still unpreventable, unpredictable and unknown.[4]

2. Patients and methods

This is a multi-centered prospective comparative randomized clinical trial that was conducted on 200 women from the time period between December 2017 to March 2023 at: IICPSR Al-Azhar University, Egypt and The Egyptian IVF and ET center, Maadi, Cairo, Egypt.

All cases with 1^{ry} female infertility had undergone a previous IVF/ICSI trial in our IVF units IICPSR and Egyptian IVF and ET Center during one to two year period. Those 200 women had history of low number of up taken eggs per number of follicles despite normal level of E2 and response to controlled ovarian hyper stimulation.

Those patients were previously stimulated with the GnRH-Antagonist COH protocol (Multi-Dose-Flexible) and had a single urinary hCG trigger (5000 IU-10 000 IU), 36 h before the ovum pick up (OPU).

In this trial, all patients are be stimulated again with the GnRH-Antagonist COH protocol (Multi-Dose-Flexible) and will be subdivided into two groups according to type of trigger by a sealed envelope after informed written consent: Group (1) included 100 women who were triggered by an extra 5000 IU higher dose of hCG than that of the previous trial. Group (2) included 100 women who were triggered by dual trigger (5000 iu hCG and two ampoules of decapeptile 0.1 SC). hCG trigger is given when the largest follicle is greater than 17 mm in diameter by trans vaginal ultrasound assessment (TVUS).

2.1. Ethical approval

The Assisted Reproductive Technology Unit of the Department of Obstetrics and Gynecology at the Faculty of Medicine at Al-Azhar University has approved this procedure. Al-Azhar University's Medical School has a Research Ethics Committee.

3. Results

Table 1.

The fertilization rate, measured by the ratio of 2 PN produced to oocytes injected, was same across the two groups. In the dual trigger group, there were more successful fertilizations, more MII oocytes, and more top quality embryos (TQE) (Table 2).

Implantation rate 'the number of gestational sacs seen divided by the number of embryos transferred' (WHO-ICMART glossary 2009).

Implantation rate and multiple pregnancy rates did not get affected by the change in trigger among two groups (Table 3).

Table 1. Retrieval and fertilization characteristics.

	Human chorionic gonadotropin group (Mean ± SD)	Dual group (Mean ± SD)	*P*- value
Retrieved Oocyte	9.87 (4.79)	12.1 (7.868)	0.001 Sig
Number of MII Oocytes	9.41 (4)	12.08 (6.758)	0.010 Sig
Number of Top Quality Embryo	4.29 (2.66)	5.77 (3.79)	0.04 Sig
Fertilization Rate	73.7%	77.01%	0.442 NS

Table 2. Implantation rate on both groups.

	Human chorionic gonadotropin group (n = 100)	Dual group (n = 100)	*P*- value
Implantation rate	%16	%19	0.731 NS
Multiple pregnancy rate	7 (10%)	8 (8%)	0.642 NS

Table 3. Clinical pregnancy rate (CPR) in both groups.

	Human chorionic gonadotropin group (n = 100)	Dual group (n = 100)	*P*- value
Clinical pregnancy			
Fresh cycle	34/100 (34%)	39/100 (39%)	0.621 NS
Frozen cycle	7/20 (35%)	14/29 (48.27%)	0.03 Sig
Cumulative pregnancy rate per transfer cycle	41/120 (34.16%)	53/129 (41.08%)	0.04 Sig

Table 4. Cryopreserved Embryos in both groups.

	Human chorionic gonadotropin group	Dual group	*P*- value
Number of cases with cryopreserved embryo	40	51	0.04 Sig
Total number cryopreserved embryo	141	189	0.02 Sig

Generally, There was no distinction in the percentage of clinical pregnancies among the two categories. The cumulative pregnancy rate was also greater in the dual category, which may be because to the increased pregnancy rate in frozen cycles (Table 4).

Higher numbers of embryos were cryopreserved in the dual group.

4. Discussion

The present research is a prospective, multi-center, randomized clinical trial assessing the efficiency of utilizing a dual trigger to that of a greater dose of hCG trigger in people with a modest egg uptake relative to the number of follicles (normal responders).

Intra cytoplasmic sperm injection (ICSI) is now an established method for treating female infertility. Follicle stimulating hormone (FSH) is now being extensively used to stimulate both ovaries. Antagonist protocol is now most commonly used protocol in IVF centers all over the world. This may be attributed to its flexibility in trigger higher safety profile and clinical pregnancy rates.

Pharmaceutical market provides us now with two types of hCG: Urinary derived hCG (u-hCG), and Recombinant human hCG. Mostly, one to two ampoules of hCG (5000–10 000) are injected to trigger both ovaries 36 h before OPU.

The increase in use of Gn-RH antagonist protocols nowadays enabled the usage of agonist trigger and dual trigger for final oocyte maturation process.[5] The release of gonadotropin hormones is mirrored by the agonist trigger. It will cause an increase in both FSH and LH levels.[5]

In our study we found that there was no significant distinction in starting dose of gonadotrophins, total dose and number of stimulation days, the endometrial thickness and or pattern at the day of trigger and E2 level at the day of trigger among both groups.

In the present research, we demonstrated that in persons who had a poor egg uptake in comparison to the amount of follicles, the application of a dual trigger resulted in a substantial rise in the number of eggs that were retrieved, the number of MII oocytes, the total quality embryos, and the total amount of embryos that were frozen. ($P = 0.001$, 0.010, and 0.04 correspondingly).

The clinical pregnancy rate, the rate of multiple pregnancies, and the incidence of miscarriage are similar across the two groups. In the dual category, the clinical pregnancy rate in frozen cycles as well as the cumulative pregnancy rate were greater than in the higher dose hCG category.

The results of[6,7] supported our results in which they have found that The utilization of a dual trigger led to a rise in both the total number of eggs obtained and the total number of MII oocytes. They suggested that normal responders employ the usage of a dual trigger.

Moreover[8,9] have found that There was no distinction in the total number of up taken eggs, the fertilization rate, TQE, or the frozen embryos when dual trigger was utilized.

Our study together with[9] found that clinical pregnancy rate, and twin pregnancy rate and miscarriage rate is comparable in the two groups. In 2018 a study was held by[9] noticed the same results too.

In 2009,[6] found that the implantation rate, the clinical pregnancy rate, and the live birth rate all improved when dual trigger was employed. They hypothesized that this could be attributable to an agonist trigger, which play several functions in improving endometrial receptivity and implantation window.

In a retrospective study held by[10] they showed that the MII oocyte count, TQE rate, and pregnancy rate all went up in the dual trigger group. In our prospective investigation, we employed hCG extracted from urine, whereas they utilized recombinant hCG.

Also,[11] concluded that Dual trigger is able to prevent severe OHSS while maintaining an extraordinary rate of high-quality embryos in GnRH-antagonist-responsive individuals.

In contrast,[6] concluded that an antagonist down-regulating approach utilizing GnRH-a and a standard amount of hCG can significantly enhance clinical pregnancy rate, live birth rate, and fertilization rate in poor responders when utilized in conjunction with *in vitro* fertilization and *in-vitro* surgical insemination (IVF–ICSI) cycles. The results of the research involved the number of mature and

immature oocytes, the rate of fertilization, the implantation rate, the fertilization rate, clinical pregnancy after fresh and frozen cycles, and the miscarriage rates. This research had a number of strengths, involving the fact that it was a prospective randomized clinical research, that it had a sufficient sample size, and that it was dispersed in both the Egyptian IVF and ET Center Maadi and the IICPSR Azhar university.

4.1. Conclusion

In clinically fresh cycles, there is not a substantial distinction among the two groups. In contrast, Both the cumulative pregnancy rate and the rate of clinical pregnancy following frozen embryo transfer were greater in the dual group. This was the case for both of these measures. In contrast to prior ICSI research and/or greater doses of hCG trigger, it appears that the use of a GnRh agonist in conjunction with urinary hCG trigger may improve the number of uptaken eggs per follicle, the number of MII oocytes, and the number of TQE.

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Conflicts of interest

There are no competing interests that need to be disclosed by the authors.

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