Dual triggering for final oocyte maturation compared to single triggering in GnRH antagonist (IVF-ICSI) protocols

Original Article

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ABSTRACT

Objective: To investigate whether co-administration of GnRH-a and hCG for final oocyte maturation (dual trigger) would improve number of oocytes retrieved& its quality and eventually IVF/ICSI clinical outcomes compared to single triggers in women with normal ovarian response undergoing (IVF/ICSI) technique using GnRH antagonist protocol of stimulation.

Design: A Retrospective Cohort Study.

Setting: Ain Shams University, maternity hospital, assisted reproductive technology unit (ART unit).

Materials and Methods: A review of medical records of a total 120 patients aged between 20-38 years old, with normal ovarian response who underwent IVF/ICSI using GnRH antagonist protocol of controlled ovarian hyper-stimulation. Patients were grouped into 2 groups, by whether final oocyte maturation was triggered with GnRH agonist plus standard dose of hCG (Group A, dual trigger/study group: n= 60) or hCG alone (Group B, hCG trigger/control group: n= 60).

Main Outcome Variable(s): The main study outcome variable was the Implantation rate. Other analyzed variables included the oocyte number and stage of maturity, the fertilization rate, the clinical pregnancy rate, the incidence of severs OHSS, and embryo transfer cancellation rate**.**

Results: Our study showed statistically significant difference with *p-value <0.05* between study groups as regards to the number of retrieved oocytes (cases: 10.73±2.94 vs. control: 9.33±3.6), number of MII oocyte retrieved (dual trigger: 6.2±2.7 vs. single trigger: 4.6±3.1), and number of fertilized oocyte (dual trigger: 4.03±2.2 vs. single trigger: 3.05±2.5) with higher mean among dual trigger group. In the current study also the dual-trigger group demonstrated a significantly higher percentage as regards to biochemical pregnancy rate (cases: 68.3%vs. 33.3% among controls), implantation rate (cases: 41.3% vs. 21.4% among controls), and clinical pregnancy rate (cases: 58.3% vs. 31.7% among controls) with a statistically significant difference with *p-value <0.05* between study groups. Both groups showed no statistically significant difference as regards to the mean number of transferred embryos (1.9±1.01 in cases vs. 1.7±1.2 in control) and number of frozen embryos (1.33±1.08 in cases vs. 1.1±1.4 in control), or as regards to complications; whether ET cancellation or incidence of sever OHSS.

Conclusion: In conclusion, in terms of the number of mature retrieved oocytes, implantation rate and clinical pregnancy rate in normal responders undergoing IVF/ICSI using antagonist protocols, a dual-trigger approach with a GnRH agonist and the standard dosage of hCG was found to be significantly superior to an hCG trigger alone.

Key Words: Dual triggering, GnRH antagonist, normal responders, oocyte maturation, single triggering.

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INTRODUCTION

Infertility is one of the major medical problems in the world which has led to continuous research and advances in the field of assisted reproductive technology (ART)[1].

Controlled ovarian hyperstimulation (COH) is a fundamental step of in vitro fertilization (IVF) that has been in practice since the 1970s[2].

Over the past two decades, gonadotropin-releasing hormone (GnRH) antagonist protocols have been proposed as a safer and efficacious way for ovarian stimulation[3].

GnRH antagonist protocols have several advantages over the long agonist, including the rapid decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels without flare-up effect, decreased number of days of stimulation and the amount of gonadotropin administered,[4] and statistically significant reduction of ovarian hyperstimulation syndrome (OHSS)[5,6].

Since the pioneering days of in vitro fertilization (IVF), human chorionic gonadotropin (hCG) has been used as a surrogate for the natural mid-cycle luteinizing hormone (LH) surge[7].

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The administration of hCG results in sustained luteotrophic effect and supraphysiological levels of estradiol and progesterone; the sustained luteotrophic effect may contribute to the development of ovarian hyperstimulation syndrome (OHSS)[8].

More than 30 years ago, Nakano *et al*., described that it was possible to trigger an endogenous LH surge sufficient for induction of ovulation with a single injection of a gonadotropin-releasing hormone agonist (GnRH-a). Unfortunately, this finding was soon underestimated, as GnRH-a rapidly became the first line treatment to prevent premature luteinization, which precluded the use of GnRH-a to induce final follicular maturation[9].

When the third generation GnRH antagonist was introduced into the market for the use in ovarian stimulation protocols during the 1990's, it became possible to trigger final oocyte maturation and ovulation with a single bolus of a GnRH-a as an alternative to hCG[10].

Though some studies have suggested an increase in the percentage of mature oocytes retrieved when triggered with GnRH-a compared with hCG[11], it has been found that triggering ovulation with GnRH agonist leads to a suboptimal luteal phase[12].

"Dual trigger" was first defined as the concept of a combination of GnRH agonist and a low-dose hCG in GnRH antagonist cycles for triggering final oocyte maturation and prevention of Ovarian Hyperstimulation syndrome (OHSS),[13].

Lin *et al*. conducted a retrospective study, consisted of normal responders undergoing IVF with GnRH antagonist protocol and showed significant improvement in total number of retrieved oocytes and number of mature (MII) oocytes, also rates of embryo implantation, clinical pregnancy, ongoing pregnancy and live birth when dual trigger regimen was used[14].

Lu *et al*. also presented a retrospective data analysis of medical records where final oocyte maturation was triggered using a GnRH-a alone (Decapeptyl 0.1–0.2 mg) or in combination with hCG (1,000, 2,000, or 5,000 IU), and concluded that using a dual trigger with a low dose of hCG (1,000 IU) as an adjuvant to GnRH-a to induce final oocyte maturation significantly improved the oocytes retrieval rate of suboptimal responders[15].

AIM OF THE STUDY

The objective of the present study is to compare between single trigger with standard dose of hCG alone and dual triggering with the combination of GnRH agonist and hCG in IVF/ICSI cycles in improving the number of oocytes retrieved and oocyte quality.

PATIENTS AND METHODS

A review of medical records from February 1st 2020, through February 28th 2022, of all IVF-ICSI cycles with a GnRH-antagonist protocol conducted at ART unit of Ain Shams University, maternity hospital.

The study protocol was approved by the Research Ethics Committee (REC), Ob/Gyn department, Faculty of Medicine, Ain Shams University.

A total of 120 patients using GnRH antagonist protocol of controlled ovarian hyper-stimulation were included and divided into 2 groups for final analysis (Group A, dual trigger/study group: n= 60 and Group B, hCG trigger/ control group: n= 60).

Study Participants:

The study was conducted on infertile women attending Ain Shams University assisted reproductive technology unit; fulfilling the criteria and investigations eligible for IVF/ICSI.

Recruitment to the study was done at the day of trigger. At our hospital during the COVID-19 pandemic, all patients had obligatory PCR testing for COVID-19 before any operative intervention, and who had +ve results; operative interventions were cancelled.

To be noted, our study included 120 patients, 4 of them were cancelled after recruitment from the study (2 in the study group; after the day of OPU and 2 in the control group just before the day of ET) due to their +ve PCR results.

All the prepared embryos for transfer were cultured to the blastocyst stage and cryopreserved.

The study included patients with ages between 20 and 38 years old, undergoing IVF/ICSI trial using GnRH antagonist protocol of controlled ovarian hyper-stimulation, with expected normal ovarian response, which is defined as: Antral follicle count (AFC) between 3-8 for each ovary, Serum anti-mullerian hormone (AMH) level of 1.0-4.0 ng/mL on cycle day 3 and Serum estradiol (E2) level on the day of triggering between 500-4000 pg/mL).

While patients with body mass index, BMI≤18 or ≥25 kg/m2, or undergoing IVF/ICSI trial using GnRH agonist or minimal stimulation protocols, or occult ovarian failure "defined as day-3 follicle stimulating hormone (FSH) concentration of ≥10 IU/L or serum anti-mullerian hormone (AMH) level of ≤ 1.0 ng/mL", or either poor response to controlled ovarian hyper-stimulation (COH) "defined as a serum estradiol (E2) level less than 500 pg/mL on the day of triggering or as the number of retrieved oocytes≤3",

or high ovarian response "defined as an E2 level greater than 4,000 pg/mL on the day of triggering or as the number of retrieved oocytes ≥20", or the presence of endocrine disorders as (diabetes mellitus, hyper-prolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome, or polycystic ovary syndrome) or the presence of uterine anomaly confirmed by either hystero-salpingography or hysteroscopy were all excluded from the study.

Ovarian Stimulation Protocol:

All patients began controlled ovarian hyper-stimulation on day 2-3 of the menstrual cycle with a starting daily administration of human menopausal gonadotropin hMG (Menogon 75IU, Ferring Pharmaceutical,Ltd, Germany), or highly purified hMG (Menopur 75IU, Ferring Pharmaceutical, Ltd, UK, or Merional 150IU, IBSA Pharmaceutical, Switzerland), or highly purified FSH (Fostimon 150IU, IBSA Pharmaceutical, Switzerland) or with recombinant FSH rFSH (Gonapure 150IU, Mina Pharm pharmaceuticals, Egypt) intramuscularly for 4–5 days, and continued until the day of final oocyte maturation injection.

The starting dosage was determined according to patient age, AFC, BMI, serum FSH on day 2–3, and previous ovarian response to COH. The dose was adjusted on the basis of serum estradiol and follicular growth, and monitored by serial trans-vaginal ultrasound.

After at least one follicle had reached 14 mm in diameter, or on reaching the number of ten follicles, patients also began subcutaneous injection of GnRH antagonist, cetrorelix (Cetrotide; Merck Serono, S.P.A-Italy) at a dosage of 0.25 mg per day along with the HMG/FSH. GnRH antagonist administration was continued until the trigger day for final oocyte maturation.

When at least two leading follicles reached 18 mm in diameter, final oocyte maturation was triggered by either (the recruitment point): Group A, by single dose of hCG 5,000 IU (Choriomon, IBSA Pharmaceutical, Switzerland) plus 0.2 mg of triptorelin acetate (Decapeptyl, Ferring Pharmaceuticals, Germany), or Group B, by standard dose of hCG 10,000 IU (Choriomon, IBSA Pharmaceutical, Switzerland) alone.

These dose adjustments were planned to achieve the induction of an endogenous LH surge that would coincide with the LH-like effect of the standard hCG administration 34–36 hours before oocyte retrieval.

Serum LH, E2 and progesterone levels were assessed the day after trigger to ensure adequate LH surge response and hCG absorption. Oocyte retrieval was done under general anesthetic. Oocyte retrieval and embryos transfer procedures were performed only by the senior supervisor. All embryo transfers were performed 72 hours after oocyte retrieval. The remaining viable embryos were cultured to the blastocyst stage and were cryopreserved.

Luteal Phase Support and Confirmation of Pregnancy:

The luteal phase support included daily vaginal supplementation of progesterone 400mg (Cyclogest, Actavis pharmaceutical, UK) starting on the day of oocyte retrieval.

Serum β-hCG was measured 14 days after embryo transfer, and a value above 5 IU/mL considered being a positive pregnancy. The luteal support was continued until the 10th week of gestation after the establishment of luteal-placental shift for all positive pregnancies.

Outcome Variables:

The study main outcome variable was the Implantation rate, defined as the number of gestational sacs on ultrasound at 6 weeks divided by total number of embryos transferred x 100.

Other analyzed variables included the oocyte number and stage of maturity, the fertilization rate defined as the percentage of transformation of micro injected oocyte into two pronuclie, the clinical pregnancy rate, the incidence of sever OHSS, and embryo transfer cancellation rate.

Clinical pregnancy was defined as viable pregnancy when there is evidence of gestational sac with fetal heart beat by trans-vaginal ultrasound between the 5th to 6th weeks of gestation.

Embryo transfer cancellation, defined as discontinuation of embryo transfer due to fertilization failure or embryonic cleavage arrest.

STATISTICAL ANALYSIS

Data collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis performed using the Statistical Package of Social Science (SPSS) software version 22 in windows 7 (SPSS Inc., Chicago, IL, USA). Simple descriptive analysis in the form of numbers and percentages of qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion of quantitative parametric data. Quantitative data included in the study first tested for normality by One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests selected.

- For quantitative parametric data:

 Independent samples t-test was used to compare quantitative measures between two independent groups

- For quantitative non parametric data

 The Mann-Whitney test used to compare two independent groups.

- For qualitative data

 Chi square test used to compare between two of more than two qualitative groups.

 The *P-value< 0.05* was considered as statistical significance.

RESULTS

The two studied groups were matched for age and BMI. The groups did not significantly differ with regard to the baseline characteristics such as age, BMI, type, cause, and duration of infertility in patients of both the groups (Table 1and 2) pectively.

Table 1: Comparison of demographic characteristics differences of study groups.

Variables	Cases (N=60)		Control (N=60)		P-value	Sig.
	Mean	SD	Mean	SD		
Age (years)	28.38	5.06	29.98	5.2	0.9	NS
BMI (kg/m^2)	21.88	2.2	22.48	2.3	0.15	NS

Table 2: Comparison of infertility characters in different study groups:

Variables	Cases (N=60)		Control (N=60)		P-value	Sig.
	No.	**%**	**No.**	**%**		
			Type of infertility			
1 ry	25	41.7%	35	58.3%	0.1	NS
2 ry	35	58.3%	25	41.7%		
Cause of infertility						
Male	21	35%	28	46.7%	0.4	NS
Female	17	28.3%	18	30%		
Mixed	4	6.7%	2	3.3%		
Unexplained	18	30%	12	20%		
Infertility duration						
Mean ± SD	3.45 ± 1.9		4.26 ± 2.6		0.1	NS

The basal hormonal FSH, LH, E2,TSH, Prolactin, and AMH, also the AFC, the type and the mean dosage of Gonadotropins injection used did not show a statistical difference between the two study groups (Table 3 and 4).

Table 3: Comparison of hormonal profile and AFC in different study groups:

Variables	Cases (N=60)	Control (N=60)	*P-value*	Sig.
	mean ± SD	mean ± SD		
AFC	10.43 ± 2.98	10.43 ± 3.01	0.99	NS
Baseline FSH	6.67 ± 2.1	6.93 ± 2.37	0.35	NS
Baseline LH	4.58 ±2.03	4.78 ± 2.3	0.61	NS
Baseline E2	57.4 ± 13.2	52.6 ± 17.2	0.08	NS
Baseline TSH	2.18 ± 0.96	2.09 ± 0.89	0.54	NS
Baseline Prolactine	12.76 ± 4.9	12.22 ± 5.4	0.56	NS
AMH	1.94 ± 6.36	2.07 ± 7.48	0.29	NS

Table 4: Comparison of type and dose of Gonadotropins injection in different study groups:

Type of injection	Cases (N=60)		Control (N=60)		*P-value*	Sig.
	No.	%	No.	%		
HMG	8	13.3%	6	10%	0.68	NS
Highly purified HMG	16	26.7%	15	25%		
Highly purified FSH	17	28.3%	23	38.3%		
Recombinant FSH	19	31.7%	16	26.7%		
Dose of injection						
Mean ± SD	49.7 ± 9.4		49.3 ± 17.9		0.9	NS

Our study showed that there was a statistically significant difference with *p-value <0.05* between study groups as regards number oocyte retrieved (dual trigger: 10.73±2.94 vs. single trigger: 9.33±3.6), Number of MII oocyte retrieved (dual trigger: 6.2±2.7 vs. single trigger: 4.6±3.1) and Number of fertilized oocyte (dual trigger: 4.03±2.2 vs. single trigger: 3.05±2.5) with higher mean among dual trigger group. On the other hand, there was no statistically significant difference with *p-value >0.05* as regards other variables (number of embryos transferred and number of cryopreserved embryos) between dual trigger and single trigger groups (Table 5).

Table 5: Comparison of intervention outcomes in different study groups:

Variables	Cases (N=60)	Control (N=60)	*P-value*	Sig.
	mean ± SD	mean ± SD		
Number of oocyte retrieved	10.73 ± 2.94	9.33 ± 3.6	0.02	S
Number of MII oocyte retrieved	6.2 ± 2.7	4.6 ± 3.1	0.002	HS
Number of fertilized oocyte	4.03 ± 2.2	3.05 ± 2.5	0.01	S
Number of embryos transferred	1.9 ± 1.01	1.7 ± 1.2	0.48	NS
Number of cryopreserved embryos	1.33 ± 1.08	1.1 ± 1.4	0.08	NS

Also our study showed that there was a statistically high significant difference with *p-value <0.05* between study groups as regards biochemical pregnancy rate (cases: 68.3%vs. 33.3% among controls), clinical pregnancy rate (cases: 58.3% vs. 31.7% among controls), and implantation rate (cases: 41.3% vs. 21.4% among controls), with higher percentage among the dual trigger group of study, but no statistical difference between the study groups as regards the abortion rate with *p-value >0.05* (cases: 14.6% vs. 5% among controls) (Table 6).

Table 6: Comparison of outcomes in different study groups:

Outcomes		Cases (N=60)		Control (N=60)		*p-value*	Sig.
		No.	%	**No.**	%		
Biochemical pregnancy							
Positive		41	68.3%	20	33.3%	0.001	HS
Negative		12	20%	27	45%		
Complication		7	11.7%	13	21.7%		
Clinical pregnancy							
Abortion rate (%)		6	14.6% (6/41)	1	5% (1/20)	0.4	NS
Pregnancy	Single	22	58.3% (35/60)	15	31.7% (19/60)	0.003	HS
	Twin	13		4			
Implantation rate							
Implantation rate		41.3% (48/116)		21.4% (23/107)		0.02	S

In our current study, there were 20 patients had their ET cancelled. Nine out of 13 patients of the control group were due to failed fertilization, one was due to oocyte degeneration and 2 had their ET cycle cancelled due to +ve COVID-19 PCR. Where 7 patients in the study group had their ET cycle cancelled, 3 of them was due to arrest of cleavage, 2 was due to failed fertilization and 2 was due to +ve COVID-19 PCR. One patient had severe OHSS, but she did not require hospitalization, and none occurred in the dual trigger group. Statistically, there was no significant difference with *p-value >0.05* between study groups as regards to complications (Table 7).

Table 7: Comparison of complications in different study groups:

Variables	Cases (N=7)		Control (N=13)		*P-value*	Sig.
	No.	%	No.	%		
ET cancellation	7	11.7% (7/60)	12	20% (12/60)	0.2	NS
Sever OHSS	0	0%	1	1.7% (1/60)	0.3	NS

DISCUSSION

Numbers of retrospective cohort studies[16,17,18], and few numbers of randomized controlled studies[19,20] have investigated whether dual triggering of final oocyte maturation with a gonadotropin-releasing hormone agonist (GnRH-a) and standard dose of human chorionic gonadotropin (hCG) can improve clinical outcomes for normal ovarian, subnormal and poor responders in GnRH antagonist cycles, however it's still debated between researchers who found significant improvement of the outcomes of IVF/ICSI cycles and those who didn't find a significant improvement[21,22].

A total 120 patients were recruited in the current study, where their medical records were reviewed, and divided into two groups, each group consisted of 60 patients according to the type of trigger used, where the study group received the dual trigger, and the control group received the standard dose hCG trigger alone for final oocyte maturation in a trial of improving number of oocytes retrieved& its quality and eventually IVF/ICSI clinical outcomes compared to single triggers in women with normal ovarian response undergoing (IVF/ICSI) technique.

In the present study, the baseline characteristics and demographics showed no statistically significant difference between the study and control groups (Table 1), with *p-value>0.05* regarding mean age (y) (28.38 ± 5.06 vs. 29.98 ± 5.2 respectively), and body mass index (BMI) (kg/m^2) (21.88 ± 2.2 vs. 22.48 ± 2.4 respectively); which agreed with all of the studies done before like Lin *et al*., (2013), where mean age (y) (34.81 ± 3.70 vs. 34.68 ± 3.44 respectively), and body mass index (BMI) (kg/m^2) (22.2 ± 5.4 vs. 22.0 ± 3.1 respectively) were comparable between the study and control groups respectively.

Zhou *et al*.[18] conducted a study comparing dual trigger with combination of GnRH agonist and hCG versus hCG alone trigger for oocyte maturation in normal ovarian responders; where there was no statistically significant difference between the study groups as regards infertility characters in terms of the percentage of the cause of infertility whether male factor (cases; 9.8% vs. control; 5.9%), female factor (cases;63.4% vs. control; 50.5%), mixed (cases; 12.5% vs. control; 25.7%) or unexplained infertility (cases;5.4% vs. control; 2.0%), or infertility duration; with mean between the study group and control was (4.55± 3.23 vs. 5.92± 4.34 respectively).

In the current study, there was no statistically significant difference with *p-value >0.05* between both study groups as regards to infertility characters (Table 2) in terms of [type of infertility; where the percentage between the study and control groups was (41.7% vs. 58.3% respectively) in primary type and (58.3% vs. 41.7% respectively) in secondary type, cause of infertility; with percentage related to male factor (35% in cases vs. 46.7% in controls), female factor (28.3% in cases vs. 30% in controls), mixed (6.7% in cases vs. 3.3% in controls) or unexplained infertility with percentage of (30% in cases vs. 20% in controls), or infertility duration; with mean (cases; 3.45± 1.9 vs. control; 4.26± 2.6), which indicated proper matching between groups.

To exclude any hormonal disturbance factor that may affect the purpose of the study, it was essential to study the hormonal profile of both study groups with special emphasis on FSH, LH, Estradiol, TSH, AMH and Prolactin levels which all showed no statistically significant differences between study groups (Table 3); with *p-value >0.05*, where the mean FSH among cases was (6.67±2.1), while in control group was (6.93±2.37). Mean LH among cases was (4.58±2.03), while in control group was (4.78±2.3). Mean TSH among cases was (2.18±0.96), while in control group was (2.09±0.89). Mean Estradiol among cases was (57.4±13.2), while in control group was (52.6±17.2). Mean AMH among cases was (1.94±6.36), while in control group was (2.07±7.48), and mean Prolactin among cases was (12.76±4.9), while it was (12.22±5.4) in control group.

Also, there was no statistically significant difference with *p-value >0.05* between study groups as regards mean antral follicle count (AFC) (Table 3) (10.43±2.98 in study

group vs. 10.43±3.01 in control group) or COH variables (Table 4) such as: type of gonadotropins used for injection, where percentage of HMG was (13.3% in cases vs. 10% in control), percentage of Highly purified HMG was (26.7% in cases vs. 25% in control), Highly purified FSH was (28.3% in cases vs. 38.3% in control) and Recombinant FSH was (31.7% in cases vs. 26.7% in control), or mean total dose of gonadotropins used (49.7±9.4 in study group vs. 49.3±17.9 in control group), which all actually agreed with previous studies of Lin *et al*., Griffin *et al*., and Zhou *et al*.

In a previous prospective randomized study[19], 221 normal responder patients were randomized either to receive hCG or dual trigger for final oocyte maturation. There was no statistical difference between the study and control groups as regards to the number of oocytes retrieved (9.9±7.8 vs. 7.9±11.1 respectively). However; as regards to our present study, the results showed statistically high significant difference with *p-value <0.05* between study groups (Table 5) as regards to the number of retrieved oocytes (cases: 10.73±2.94 vs. control: 9.33±3.6).

Also in the current study, the number of MII retrieved oocytes (cases: 6.2 ± 2.7 vs. control: 4.6 ± 3.1, *p-value=0.002*), and number of fertilized oocytes (cases: 4.03 ± 2.2 vs. control: 3.05 ± 2.5, *p-value=0.01*) showed statistical significant difference with *p-value <0.05* with higher mean in the dual group which came in agreement with Hass *et al*. (2020), who conducted a prospective, randomized, double-blinded clinical trial on 155 normal responder patients either to receive hCG or dual trigger for final oocyte maturation where there was statistical difference between the study and control groups as regards to the number of MII retrieved oocytes (cases:10.3 vs. controls:8.6, *p-value=0.009*), and number of 2 pronuclie (cases:7.8 vs. control: 6.3, *p-value=0.007*) with higher significance among the dual trigger group (Table 5).

On the other hand, there was no statistically significant difference with *p-value >0.05* as regards other variables; the mean number of embryos transferred (1.9 ± 1.01 in cases vs. 1.7± 1.2 in control) and number of cryopreserved embryos (1.33±1.08 in cases vs. 1.1 ± 1.4 in control) between dual trigger and single trigger groups (Table 5).

In terms of the main present study outcomes, the dual-trigger group demonstrated a significantly higher percentage as regards to biochemical pregnancy rate (cases: 68.3% vs. 33.3% among controls), implantation rate (cases: 41.3% vs. 21.4% among controls), and clinical pregnancy rate (cases: 58.3% vs. 31.7% among controls), with a statistically significant difference with *p-value <0.05* between study groups. The difference in abortion rate between the two groups was not statistically significant (Table 6).

These results actually came in agreement with Hass *et al*. (2020) study, where their results showed statistically significant improvement in the implantation rate (22.8% vs. 43.7%), and the clinical pregnancy rate (37.3% vs. 56.8%) with significantly higher percentages in the dual trigger group.

Conversely, Şükür *et al*.,[22] conducted a retrospective cohort study in a total 214 normal responders who underwent ICSI trial following a cycle down-regulated by a GnRH antagonist protocol. The biochemical pregnancy rate (33.9% in cases vs. 36.5% in control), and clinical pregnancy rate (33.9% in cases vs. 30.6% in control) were similar among both study groups.

Also Eser *et al*.,[21] conducted a case-control study of a total 109 ICSI cycles "in poor responders" where a dual trigger was used for final oocyte maturation compared with hCG trigger, where they reported no statistically significant difference between ICSI outcomes as regards to biochemical pregnancy rate (in cases 16% vs. 12.1% in control), Clinical pregnancy rate (4% in cases vs. 12.1% in control), and implantation rate (3.2% in cases vs. 9.3% in control).

Statistically, there was no significant difference with *p-value >0.05* between study groups as regards to complications. In our current study, there were 20 patients had their ET cancelled. Nine out of 13 patients of the control group were due to failed fertilization, one was due to oocyte degeneration and 2 had their ET cycle cancelled due to +ve COVID-19 PCR. Where 7 patients in the study group had their ET cycle cancelled, 3 of them was due to arrest of cleavage, 2 was due to failed fertilization and 2 was due to +ve COVID-19 PCR. One patient had severe OHSS, but she did not require hospitalization, and none occurred in the dual trigger group (Table 7).

Controversy, Wafa *et al*. (2019)[23], performed a randomized controlled trial at the International Islamic Center for Population Studies and Research of Al-Azhar University Assisted Reproduction Unit, to compare rates of ovarian hyperstimulation syndrome (OHSS) and the pregnancy outcome after using gonadotropin-releasing hormone agonists (GnRH-a) alone and GnRH-a in combination with low-dose human chorionic gonadotropin (hCG) as dual trigger for final oocyte maturation, where a total of 150 infertile high responder women at risk of ovarian hyperstimulation syndrome (OHSS) underwent ICSI. There were 6 case of OHSS developed with dual trigger group (Group II) (3 were mild early OHSS, 2 were moderate early OHSS and one case was severe late OHSS). In contrast, there was only one case of severe late OHSS seen in (Group I) so the incidence of OHSS was higher after dual trigger than GnRHa trigger but with no statistically significance as they described (8.0% vs 1.33%, *p >0.05*).

One of the weaknesses of the present study is that we did not include a third arm of patients who were triggered with GnRH agonist alone. If we had added the third arm, we would have been able to test whether it was the administration of GnRH agonist or the co-administration of GnRH agonist and hCG that improved the outcome as demonstrated in the study.

CONCOLUSION

In conclusion, in terms of the number of mature retrieved oocytes, implantation rate and clinical pregnancy rate in normal responders undergoing IVF/ICSI using antagonist protocols, a dual-trigger approach with a GnRH agonist and the standard dosage of hCG was found to be significantly superior to an hCG trigger alone.

The results we presented here are another proof-of-concept that suggests a possible paradigm shift in ovulation triggering agents in GnRH antagonist cycles.

CONFLICT OF INTEREST

There are no conflicts of interests.

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