Dual trigger for final follicular maturation in normal responders undergoing ICSI cycles: Randomized controlled trial.

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Abstract

Background: Dual trigger for final oocyte maturation using combination of GnRha and hCG can improve clinical outcomes in high responder IVF-ICSI GnRh antagonist protocol. However this modality is not widely studied in normal responder.

Aim of the work; to investigate whether "dual triggering", combination of GnRha and hCG for final oocyte maturation, improve the live-birth rate for normal responders undergoing ICSI "GnRH-antagonist" cycles.

Patients and Methods: a total 200 infertile women were included in this study, randomized and divided into two equal groups: Group (1): hCG trigger only group; included 100 women who received the hCG trigger alone. Group (II): dual trigger group; included 100 women, who received the dual trigger (GnRha & hCG). All participants were subjected to; full history taking, complete general, abdominal and pelvic examinations and full investigations to confirm criteria of the study.All participants were subjected to controlled ovarian hyper stimulation protocol starting on day 2-3 of the menstrual cycle with a daily administration of recombinant FSH intramuscularly for 5 days, Co administration of the GnRH-ant was initiated at day 6 stimulation and was continued until triggering day. Oocyte retrieval was undertaken guided by transvaginal ultrasonography 34–36 h later. Transfer of fresh embryos was done 3 days after oocyte retrieval. The number of transferred embryos was 1–2 depending on embryo quality and patient age.

Results: Dual triggering in comparison to hCG alone for final oocyte maturation in normal responder, showed a highly statistically significant difference with peak value <0.0001 as regard the number of retrieved oocytes (dual: 12.53 ± 2.27 vs 9.50 ± 1.87 single trigger), Number of MII oocytes retrieved (dual: 8.74 ± 1.46 vs 5.08 ± 1.35 single trigger) number of fertilized oocytes(dual: 6.59 ± 1.61 vs 2.86 ± 0.99 single trigger), implantation rate(dual: 66.7% vs 31.9% single trigger), chemical pregnancy(dual: 68% vs 47% single trigger), clinical pregnancy(dual: 65% vs 44 single trigger), ongoing pregnancy(dual: 38.22% vs 21.47 single trigger) and live birth rate(dual: 49% vs 24% single trigger). No statistically significant difference as regard miscarriage rate between both group (P-value >0.05.)

Conclusion: in terms of the number of mature retrieved oocytes, implantation rate, rates of chemical pregnancy, clinical pregnancy rate, ongoing pregnancy and live birth in normal responders undergoing ICSI using antagonist protocols, a dual-trigger approach with a GnRH agonist and 5000 IU of hCG was found to be significantly superior to an hCG trigger alone.

.**Key words: ICSI, dual triggering, GnRH antagonist, pregnancy rate, normal responder.**

1- Introduction:

Millions couples have received IVF treatment Since the birth of the first IVF conceived baby in 1978, which in broad terms includes controlled ovarian hyperstimulation (COH), in vitro fertilization and embryo transfer**.** [1]

Peak oestrogen (>200 pg/ml) secreted by preovulatory follicles during natural ovulatory cycles triggers the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which causes the pituitary gland to release gonadotropin and cause an increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH). The latter stages of oocyte maturation, meiosis, and luteinization are all induced by the LH surge**.** [2]

The rapidly increasing estradiol levels may cause an untimely LH surge when stimulating the ovaries to produce multifollicular development. Oocyte pick up may fail if it is done too early, when follicles may not have gotten big enough to provide the best quality oocytes, or if it is done too late and goes unnoticed. Progestins, GnRH agonists, and GnRH antagonists are examples of medications that disrupt the GnRH pulse generator's communication to the pituitary, and their usage has significantly increased the effectiveness of ovarian stimulation during IVF/ICSI**.** [3]

hCG can stimulate luteinization of granulosa cells and complete oocyte maturation as the endogenous LH surge. However, as hCG has a longer half-life than endogenous LH, the surge may remain for 48 hours while the biological effect may last for several days. [2]

Similar to other COS regimen components, activation of final follicular maturation has drawn study attention over the past ten years in an effort to raise IVF success rates. [4] It has been shown that the release of endogenous hormones (mostly FSH and LH) necessary for the final follicular maturation, which prevents the

incidence and progression of OHSS, and also trigger the ovulation**.** [5]

The success of (ICSI-ET) is correlated with the trigger drug selected for the controlled ovarian hyperstimulation (COH) procedure. Recent years have seen a lot of interest in the co-administration (hCG) and (GnRH-a), or dual trigger, for ultimate oocyte maturation [6].

Accordingly, it has been demonstrated that the idea of a "dual trigger," which combines one bolus of GnRha with a regular or lower dosage of hCG at the time of triggering, increases the rates of oocyte recovery, oocyte maturation, pregnancy, and live birth. [7] Additionally, the use of dual trigger lowers the necessary dose of hCG, making it more appropriate for women who have ovarian hyperstimulation syndrome risk factors**.** [8]

The aim of this study was to investigate whether "dual triggering" for final oocyte maturation, improve the live-birth rate for normal responders undergoing ICSI "GnRH-antagonist" cycles.

2. Type of study and study population:

Prospective randomized controlled study was conducted at private ICSI centre- Mansoura – Egypt through the period from December 2018 to September 2021and was subjected to approval by the Local Ethics Committee of the Obstetrics and Gynaecology Department, Benha University Hospital, Benha – Egypt.

The study included 200 infertile women from those attended the private ICSI centre and prepared to undergoing ICSI trial using GnRH antagonist protocol

All participants were subjected to; full history taking, complete general, abdominal and pelvic examinations and full investigations to confirm criteria of the study. Eligible patients selected according to the following inclusion and exclusion criteria:

Inclusion Criteria

The inclusion criteria were women:

(i) aged <40 years;
(ii) with a body mass index (BMI) of 20–35 kg/m2;
(iii) Who had a normal response to controlled ovarian stimulation (4–20) retrieved oocyte.

The ovarian response to ovarian stimulation (OS) reflected by the number of oocytes retrieved is a keystone in in vitro fertilization (IVF) cycles and an independent factor in the success of treatment. Although the ideal number of oocytes needed might be a matter of debate, 10–15 follicles is considered to be the optimal response after OS. [9]

Exclusion Criteria

The exclusion criteria were women:

(i) her husband is azoospermia
(ii) Recurrent miscarriage (> 3 previous first trimester miscarriages).
(iii) With >3 attempts IVF / ICSI.
(iv) Presence of endocrine disorder (DM, PCO, hyperprolactinemia or thyroid disorder).
(v) History of empty follicle syndrome.
(vi) Previous cycle required coasting or freeze all or clinical OHSS.

Methods

All participants were subjected to:

Complete history taking:

1. Personal history including: Name, Age, duration of marriage, address. Special habits.
2. Menstrual history: including age of Menarche, date of last menstrual period, dysmenorrhea, menstrual disturbance and related symptoms.
3. Infertility aetiology
4. Parity and mode of delivery
5. Present history: of chronic diseases and medication.
6. Past history of previous attempts IVF and/or ICSI
7. Family history of similar condition

Laboratory evaluation: hormonal profile**;** serum (FSH, LH) in day 2-3 of the cycle, TSH, prolactin and AMH.

Examination: TV ultrasonography was done for; assessment the AFC in day (2-3) of the cycle and showing endometrial thickness, follicullometry from 6th day of cycle and followed up every 2 days till the triggering criteria was achieved (2-3 follicles reached a diameter of 17-20 mm which is considered mature).

Protocol for Ovarian Stimulation

All participants received a fixed GnRH antagonist protocol for COH and they did not receive oral contraceptive pill before the IVF cycle. Ovarian stimulation began on day-2 of the menstrual cycle with recombinant FSH (150–225 IU daily; Gonapure, Mina Pharm pharmacutical, Egypt) intramuscular, IM for 5 consecutive days and continue till day of triggering. The starting dose was determined by patient age, ovarian reserve, BMI, and previous response to COH. Then, the dose of recombinant FSH was adjusted according to follicular growth as monitored by serial transvaginal ultrasound. Co administration of the GnRH-antagonist, cetrorelix (0.25 mg of Cetrotide; Merck Serono, SPA-Italy given SC at 10 a.m. daily) from day 6 stimulation and was continued until the day of triggering **.**

When ≥4 leading follicles had reached 17 mm in diameter, the women were prospectively randomized into two double blinded groups for final oocyte maturation and triggering

according to a computer-generated randomization table.

Group (I) (hCG alone trigger); were triggered by 5000 IU of urinary hCG (choriomon; IBSA pharmaceutical, Switzerland) IM.

Group (II) (dual trigger); were triggered by triptorelin acetate 0.2 mg (**Decapeptyl**, Ferring pharmaceutical, Germany) subcutaneous, SC plus urinary hCG 5000 IU (**choriomon**; IBSA pharmaceutical, Switzerland) IM.

Oocyte retrieval was undertaken using transvaginal ultrasonography 34–36 h later.

Embryo Transfer

Transfer of fresh embryos was done 3 days after oocyte retrieval. The number of transferred embryos was 1–2 depending on embryo quality and patient age.

Luteal Phase Support

Luteal phase Support was comprised progesterone, 400 mg vaginal suppositories, (prontogest, Marcryl pharmaceutical, Egypt) twice a day starting on the day of oocyte retrieval. Serum β-hCG was measured 14 days after embryo transfer, and a value above 5 IU/mL was considered a positive pregnancy. The luteal phase support was continued until the 10th w of gestation.

The primary outcome: clinical pregnancy rate.

- "Clinical pregnancy" was defined as the presence of gestational sacs with foetal heartbeat on US 14 days after a positive pregnancy test.

The secondary outcome: Implantation rate, chemical pregnancy miscarriage rate, ongoing pregnancy and live birth rate.

- The "implantation rate" was defined as the total number of gestational sacs on ultrasound at 6 weeks divided by total number of embryos transferred x 100.
- A Chemical pregnancy was defined as an elevated serum β-hCG level of more than 50 IU/ml with no intrauterine or extrauterine gestational sac detected on vaginal ultrasound.
- Miscarriage refers to the termination of pregnancy before 28 weeks of gestation or fetus that weighs 500 g or less**.**
- Early miscarriage was defined as pregnancy loss that occurs spontaneously before 12 weeks of gestation.
- Early miscarriage rate defined as number early miscarriage dividing by number of clinical pregnancy x 100.
- Ongoing pregnancy was defined as a pregnancy documented by ultrasound at 12 gestational weeks that showed the presence of fetal heartbeat. Ongoing pregnancy rate was defined as the number of ongoing pregnancy divided by the number of embryo transferred for each group.
- The late miscarriage rate was defined as the proportion of pregnancies arresting after 12 weeks and before 28 weeks of gestation dividing on number of ongoing pregnancy x 100.
- The LBR was calculated by dividing the total deliveries of viable infants over 28 gestational weeks by the total number of fresh ET cycles (which is 100 cycles in each group) x 100

Data management and Statistical Analysis

Data management and statistical analysis were done using SPSS version 25 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using Kolmogorov–Smirnov test and direct data visualization methods. According to normality testing, numerical data were summarized as means and standard deviations. Categorical data were summarized as numbers and percentages. Quantitative data were compared between study groups using independent t-test. Categorical data were compared using the Chi-square test. All statistical tests were two-sided. P values less than 0.05 were considered significant.

3. Results:

Table (1): Comparison of demographic characteristics of the two studied groups.

Variables		*Dual trigger* *No. = 100*	*Single trigger* *No. = 100*	*P-value*	*Sig.*
Age (year)	Range	21 - 34	23 - 34	**0.810**	**NS**
	Median [IQR]	28 [5]	28 [5]		
	Mean ± SD	27.52 ± 2.70	27.61 ± 2.58		
BMI	Range	21 – 34	20 – 33	**0.477**	**NS**
	Median [IQR]	28.5 [4]	29 [5]		
	Mean ± SD	28.02 ± 3.22	28.34 ± 3.13		

Table (1) illustrates that there is no statistically significant difference with peak value >0.05 between the two groups as regard age and BMI which indicate proper matching between groups.

Table (2): Comparison of infertility characteristics between the two studied groups

Variables		**Dual trigger** **No. = 100**	**Single trigger** **No. = 100**	**P-value**	**Sig.**
Type of Infertility	1ry	54 (54%)	56 (56%)	**0.776***	**NS**
	2ry	46 (46%)	44 (44%)		
Infertility Duration (years)	Range	2 – 6	1.5 – 6	**0.683•**	**NS**
	Median [IQR]	3 [2]	3 [2]		
	Mean ± SD	3.24 ± 1.00	3.30 ± 1.07		
Cause of Infertility	Male factor	8 (8%)	8 (8%)	**0.612**	**NS**
	Tubal factor	34 (34%)	42 (42%)		
	Endometriosis	24 (24%)	20 (20%)		
	Ovulation defect	16 (16%)	12 (12%)		
	combined	8 (8%)	12 (12%)		
	Unexplained	10 (10%)	6 (6%)		

Table (2) illustrates that there is no statistically significant difference with peak value >0.05 between the two groups as regard the infertility (type, duration and cause) which indicate proper matching between groups.

Table (3): Comparison of hormonal profile and antral follicle count (AFC) between the two studied groups.

Variables		**Dual trigger** **No. = 100**	**Single trigger** **No. = 100**	**P-value**	**Sig.**
AFC	Range	6 - 12	5 - 12	**0.121**	**NS**
	Mean ± SD	9.68 ± 1.66	9.30 ± 1.78		
Basal FSH miu/ml	Range	3.13 – 7.5	3.13 – 7.5	**0.175**	**NS**
	Mean ± SD	5.85 ± 1.18	5.61 ± 1.31		
Basal LH miu/ml	Range	2.2 – 6.5	2.2 – 6.5	**0.145**	**NS**
	Mean ± SD	4.84 ± 1.19	4.60 ± 1.30		
AMH ng/ml	Range	1.10 – 3.20	1.10 – 3.20	**0.266**	**NS**
	Mean ± SD	1.69 ± 0.59	1.78 ± 0.55		
TSH	Range	1.3 – 4.3	1.2 - 4	**0.528**	**NS**
	Mean ± SD	2.57 ± 0.64	2.63 ± 60		
Prolactin	Range	8.9 - 15	10.8 -15	**0.895**	**NS**
	Mean ± SD	12.04 ± 1.75	12.08 ± 1.75		

Table (3) illustrates that there is no statistically significant with peak value >0.05 between the two groups as regard hormonal profile (FSH, LH, TSH, prolactin and AMH) and antral follicle count (AFC) which indicate proper matching between groups.

Table (4): Comparison of ovarian stimulation characteristics between the two studied groups.

Variables		Dual trigger No. = 100	Single trigger No. = 100	P-value	Sig.
Duration of stimulation (d)	Range	9-13	10-12	0.173	NS
	Mean ± SD	11±1	11±49		
Number of retrieved oocytes	Range	8 - 17	6 - 15	<0.0001	HS
	Mean ± SD	12.53 ± 2.27	9.50 ± 1.87		
Number of MII oocytes	Range	5 - 12	3 – 9	<0.0001	HS
	Mean ± SD	8.74 ±1.64	5.08 ± 1.35		
Number of fertilized oocytes	Range	3 - 9	1 - 5	<0.0001	HS
	Mean ± SD	6.59 ±1.61	2.86 ± 0.99		
Number of transferred embryos	Range	1-2	1-2	0.661	NS
	Mean ± SD	1.65 ± 0.48	1.62 ± 0.49		

Table (4) illustrates that there is a highly statistically significant difference with peak value <0.0001 between the two groups as regard number of retrieved oocytes, Number of MII oocytes and number of fertilized oocytes with higher mean among dual trigger group than single trigger group.

While there is no statistically significant difference with peak value >0.05 between both groups as regard number of transferred embryos.

Table (5): Comparison of pregnancy outcome between the two studied groups

Variables		Dual trigger No. = 100	Single trigger No. = 100	P-value	Sig.
Implantation rate		105/157 (66.7%)	52/163 (31.9%)	**<0.0001**	**HS**
Chemical Pregnancy rate		68/100 (68%)	47/100 (47%)	**0.003**	**HS**
Clinical Pregnancy rate		65/100 (65%)	44/100 (44%)	**0.003**	**HS**
Gestational sacs	**Single**	25	36		
	twin	40	8		
	Total sacs	105	52		
Early Abortion rate		5/65 = 8%	9/ 44 = 20.5%	**0.051**	**NS**
Ongoing Pregnancy rate		60/157 (38.22%)	35/163 (21.47%)	**0.001**	**HS**
Late abortion rate		11/60 (18.33%)	11/35 (31.42%)	**0.144**	**NS**
Live birth rate per women		49/100 (49%)	24/100 (24%)	**0.0002**	**HS**

Table (5) illustrates that:

There is a highly statistically significant difference with peak value <0.001 between the two studied groups as regard implantation rate (dual: 66.7% vs 31.9% in single trigger), chemical pregnancy rate (dual: 68% vs 47% in single trigger), clinical pregnancy rate (dual: 65% vs 44% single trigger), ongoing pregnancy(dual: 60% vs 35% in single trigger) and LBR(dual: 49% vs 24% in single trigger).

The early and late abortion rate showed no significant difference between the two groups, with a P-value of >0.05.With higher abortion number in single trigger

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4. Discussion

Since the question of whether dual-trigger improves oocyte maturation and pregnancy outcomes has been raised in the past few years, numerous studies have been conducted, but as of today there are still no conclusive results, therefore This study aimed to further explore any beneficial effect of adding GnRha to hCG (dual trigger) on oocyte yield and live-birth rate in normal responder women.

This study was conducted on 200 infertile women after applying the inclusion and exclusion criteria at private IVF-ICSI centers. Women were randomly divided into two equal groups for final oocyte maturation triggering as follows:

Group I (control group): One-hundred women received 5000 IU hCG alone **(single trigger group)**.

Group II (study group): One-hundred women received 5000 IU hCG plus GnRHa (0.2 mg of triptorelin) **(dual trigger group)**.

The results of this study suggest that the use of a dual trigger for triggering final oocyte maturation may be more effective in improving pregnancy outcomes compared to the use of a single trigger in infertile women underwent ICSI trial using gonadotropin – releasing hormone antagonist protocol and is normal responder.

Regarding the demographic characteristics among the two groups in this study; mean age in dual trigger group was 27.52 ± 2.70 year and 27.61 ± 2.58 year in single trigger group. Mean BMI in dual trigger group was 28.02 ± 3.22 and 28.34 ± 3.13 in single trigger group. No significant differences were noted between both groups regarding age (P-value = 0.810) and BMI (P-value = 0.477) **(Table 1).** Which indicate proper matching between groups.

[10] was in the same line with our study as mean age was 30.5 ± 4.1y in hCG triggering group and 30.0 ± 3.6 y in Dual triggering group , mean BMI was 23.5 ± 5.1 in hCG triggering group and 23.8 ± 4.6 in Dual triggering group. Analysis of the covariates, age, body mass index (BMI) did not demonstrate any differences between the compared groups.

In this study, there is no statistically significant difference with peak value >0.05 between the two groups as regard mean infertility type; 1^{ry} infertility (dual: 54 (54%) versus 56 (56%) single trigger group, 2^{ry}infertity (dual: 46 (46%) vs 44 (44%) single trigger group, duration; (dual: 3.24 ± 1.00 vs 3.30 ± 1.07 single trigger group, and infertility factor; male factor is 8% in group I and 8% in group II, ovarian cause is 12% in group I and 16% in group II, tubal cause is 42% in group I and 34% in group II, endometriosis cause is 20% in group I and 24% in group II, while Unexplained cause is 6% in group I and 10% in group II and combined cause is 12% in group I and 8% in group II. which indicate proper matching between groups **(table 2)**.

This agree with **[11]**, as their results showed that there were no significant differences regarding the infertility type and duration for both groups, The infertility duration for the dual trigger group was 4.17y compared to 4.49y for the hCG group. **[12][-13]** found no significance differences regarding infertility duration and type for both groups. **[14]** Found no significant difference between the two study groups regarding type, cause and duration of infertility.

[15] 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 this study as regard hormonal profile, no significant differences noted between both groups regarding mean baseline FSH (5.61 ± 1.31 mIU/L in group I and 5.85 ± 1.18 mIU/L in group II) (P-value = 0.175) and LH (4.60 ±1.30 IU/L in group I and 4.84 ±1.19 IU/L in group II) (P-value = 0.145), mean TSH (group I: 2.63 ± 60 vs 2.57 ± 0.64 in group II) and mean prolactin (group I: 12.08 ± 1.75 vs 12.04 ± 1.75in group II. There is no statistically significant difference between the two groups as regard mean antral follicle count (dual: 9.68 ± 1.66 vs 9.30 ± 1.78 in single trigger group) peak value (0.121) which indicate proper matching between groups **(table 3).**

This in line with **[14]** and **[16]** who found no significant difference between the two study groups regarding hormonal profile and AFC.

As regards to the ovarian stimulation outcomes, our study showed that there was a highly statistically significant difference with p-value <0.001 between the study groups as regards number of oocyte retrieved (dual trigger: 12.53±2.27 vs. single trigger: 9.50±1.87), number of MII oocyte retrieved (dual trigger: 8.74±1.64 vs. single trigger: 5.08±1.35) and number of fertilized oocyte (dual trigger: 6.59±1.61 vs. single trigger: 2.86±0.99) with higher mean among dual trigger group. While there is no statistically significant difference with peak value >0.05 between both groups as regard duration of stimulation and number of transferred embryo **(Table 4).**

This agree with **[11-17]** who found that the number of total oocytes, the number of MII oocytes and the number of fertilized oocytes were all significantly higher with the dual trigger protocol compared to hCG-only trigger

and no significant difference was observed regarding mean duration of stimulation.

On the other hand, [18] in their RCT, which included 120 patients, they reported no differences in the number of oocytes retrieved, MII oocytes, and fertilized oocytes between the dual trigger group and the hCG group.

The diversity in oocyte outcomes may be caused by irregularities in the technique utilized , triggering drugs (nature, dose, timing of administration), the inclusion of subjects; as we include only normal responder other include (poor responder or high responder or all), or the small sample size in the majority of research and heterogeneity of the infertile population.

in this study as regards to the pregnancy outcomes; a highly statistically significant difference with peak value <0.001 was found between the two studied groups as regard implantation rate, biochemical pregnancy, clinical pregnancy rates, ongoing pregnancy, and live birth rate (dual: 66.7% vs 31.9% in single trigger), (dual: 68% vs 47% in single trigger), (dual: 65% vs 44% in single trigger), (dual: 60% vs 35% in single trigger), (dual: 49% vs 24% in single trigger) respectively with higher percentage among the dual trigger group. On the other hand; the early and late miscarriage rate show no significant difference between the two groups (P-value of >0.05). With higher abortion in single trigger. While the early and late abortion rate show no significant difference between the two groups, with a P-value of >0.05.With higher abortion in single trigger **(Table 5).**

These results actually came in agreement with [2] 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.

This agree with other studies which show that the dual trigger has a higher implantation and pregnancy rates than hCG alone trigger. [19] ***and*** [20]**).**

Similar results were obtained by [14], they performed RCT study on160 women. They were divided equally into two groups: group I received 10 000 units of hCG plus 0.2 mg of triptorelin while group II received 10 000 units of hCG only for triggering of ovulation. Dual triggering was associated with significantly higher chemical (25% vs 11.3%, P=0.039) and clinical (22.5% vs 8.8%, P=0.028) pregnancy rates in women with dual triggering compared with those with single triggering.

In line to our study, several studies have indicated that dual trigger treatment may be associated with increased clinical pregnancy and live birth rates compared with the hCG trigger alone [19-21]**).** Also a previous meta-analysis including four randomized trials, showed that dual trigger significantly improved clinical pregnancy rate compared with hCG trigger [22]**.**

In concordance, similar results were found in RCT by [18], RCT, which included 120 patients, they reported a higher implantation rate, clinical pregnancy rate and live birth rate in the dual trigger group.

Conversely, [23] 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.

In opposite to our study [16] and [2] found that there was no significant difference in implantation rates despite higher numbers and rates in the dual trigger group.

On the contrary to our study, [24] performed retrospective cohort study with 856 women who underwent IVF, were classified into 3 groups (1 - hCG, 2 - GnRH agonist, 3 - dual trigger) did not observe a difference in the number of abortions when comparing the three groups**.**

Unlike to our study [16-15-25]**,** came to the conclusion that there was no discernible change in implantation rates between dual trigger group and hCG group.

In opposite of our study [15] found no differences in live birth rates between both groups. [13] Showed that a dual trigger was not superior to hCG-alone trigger for normal responders in GnRH-antagonist cycles in terms of the live-birth rate.

In opposite to our study [26] conducted RCT with 126 normal responders revealed that there was no discernible difference in the clinical pregnancy rate between two groups. Also [15] examined the results from 325 normal responders in a recent retrospective study; 224 were in the dual group compared to 101 were in the hCG group. The researchers discovered no differences in clinical pregnancy rates.

A retrospective cohort study involving 856 women who underwent IVF and were divided into three groups—one receiving hCG, one receiving a GnRH agonist, and one receiving a dual trigger—found no difference between the three groups' as regard rates of abortions [24] **.**

[13] had contradictory results with our findings. They found that the miscarriage rate was higher in the dual-trigger group than that in the hCG-only group, but this difference was not significant

No significant difference in the ongoing pregnancy rate between groups according to a prior meta-analysis that included four randomized trials [22].

In general the divergence between the results of the present study and those reported by the different authors previously mentioned might be attributed to many variables that can influence the outcome such as: ovarian reserve, stimulation protocol, sample size, inclusion criteria, type and dose of used drugs, triggering time, ultrasound machine resolution and oocyte access during oocyte retrieval, number of MII oocyte, quality of IVF labs, embryo quality and age (morula or blastocyst), different mode of embryo transfer (fresh or frozen transfers), endometrial receptivity, patient cooperation during stimulation time and skills of the clinicians.

According to the results from this study, dual triggering with GnRH-agonist and (5000IU) HCG can be an effective alternative to hCG trigger alone, as it results in better cycle outcome for normal responders, the choice of the trigger method is paramount to achieving greater Outcome in GnRH-antagonist cycles. Hence in near future, it may be the recommended mode of trigger for normal responders

5. Conclusion*:*

Dual triggering could be a good alternative to the standard single HCG triggering in normal responder, undergoing an antagonist IVF-treatment cycle as regard pregnancy outcomes.

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