

Does the Incorporation of Dual Trigger Improve IVF Outcome When Compared to HCG Trigger in IVF / ICSI Cycles?

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Abstract: Background: Utilization of HCG alone for stimulating oocyte growth was associated with many undesired effects like affecting endometrial receptivity and associated with OHSS. Dual trigger involves administering both GnRH agonists and HCG together. Objectives: To compare the effect of dual trigger with HCG trigger in IVF outcome and to compare the outcome in case of poor responder, normal responder and hyper responders with regard to dual and HCG triggers. Material and methods: The present study was retrospective observational study carried out among sub fertile women who underwent IVF/ICSI cycles in the department of institute of reproductive medicine between 2018 and 2021. The sample size was calculated to be 120 in each group. Data collection was made using secondary data. The data analysis was done using SPSS, independent samples t test and chi square test were applied. Results: Baseline characteristics were found to be similar between the groups. The mean number of expected follicles in the dual trigger group was 10.46 ± 5.91 and that of the HCG trigger group was 9.07 ± 1.51 . The mean number of oocytes retrieved in the dual trigger group was 12.03 ± 7.31 and that of the HCG trigger group was 10.08 ± 5.48 . Number of oocytes retrieved was significantly more in the dual trigger group than in the HCG group. All other parameters with regard to stimulation was similar between the groups. Sub group analysis revealed the parameters to be comparable between the groups. Implantation rate was similar between the groups while clinical pregnancy and live birth rates were more in HCG than in dual trigger group. Conclusion: Dual trigger resulted in a greater number of oocytes retrieved than the HCG trigger. The clinical pregnancy rate and live birth rate were more in HCG trigger than in the dual trigger.

Keywords: HCG trigger, Dual trigger, GnRH agonists, oocytes, clinical pregnancy rate, live births, implantation rates

1. Introduction

Traditionally in both IVF and ICSI following the stimulation of oocyte growth, the next step is to trigger the oocyte so that the oocytes would undergo the final step, the maturation. Following maturation, the oocytes would be retrieved and fertilized. The trigger that will be usually used for maturation was Human Chorionic Gonadotropin (HCG). But HCG for the above purpose was reported to have many undesired effects. Endometrial receptivity was found to be negatively affected by HCG and so was embryo quality (1). Furthermore, HCG was found to have prolonged circulatory half - life leading to a sustained luteotropic effect leading to ovarian hyperstimulation syndrome (OHSS).

In order to overcome the advantages due to HCG triggered oocyte maturation, Gonadotrophin agonists (GnRH agonists) were proposed to be alternate. Unlike HCG, the LH activity of GnRH last for only 24 hours (2). Many studies were done

comparing the outcome of using GnRH agonist in the place of HCG (3) (4) (5). Utilization of GnRH agonists aided in direct manipulation of the luteal phase and one was able to achieve optimal P concentrations mimicking the natural cycle (6). However some studied comparing GnRH agonist with HCG stimulation reported a lesser implantation and clinical pregnancy rates in the former than in the latter. The stimulation due to GnRH agonists resulted in defective corpus luteum was found to be responsible for the lower implantation rates as there was lower P concentration (7). In order to overcome the disadvantages dual trigger method was introduced (8).

Dual trigger involves administering both GnRH agonists and HCG together. It was proposed that such a dual trigger would increase the number of metaphase - II oocytes (9). Dual trigger would also be useful in case of suboptimal response to GnRH agonist for getting adequate number of mature oocytes (10). With this background, the aim of the present study was to compare the effect of dual trigger with

Volume 12 Issue 5, May 2023

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HCG trigger in IVF outcome and to compare the outcome in case of poor responder, normal responder and hyper responders with regard to dual and HCG triggers. Studies with similar objective were not undertaken in the present study setting before. The study would throw a light on the effectiveness of dual trigger in comparison to the usual HCG trigger among the study population.

2. Methodology

The present study was retrospective observational study carried out among sub fertile women who underwent IVF/ICSI cycles in the Institute of reproductive medicine, Madras Medical Mission (MMM) hospital between 2018 and 2021. Women with history of donor oocyte retrieval, uterine abnormalities and primary ovarian insufficiency were excluded from the study. Using the software G power version 3.1.9.4, based on the previous study conducted by Lin MH et al. substituting the mean number of oocytes retrieved between the study and control group (12.36 ± 6.64 and 10.10 ± 4.58), effect size was calculated to be 0.39. The sample size was calculated under "t" test where the statistical test was "mean difference between two independent means". Assuming, tail = two tailed, Effect size = 0.39, α error = 0.05, Power ($1 - \beta$) = 0.95. The sample size was calculated to be 100 in each group, with 20% attrition rate sample size increased to 120 in each group. Ethical clearance for the study was obtained from the institutional ethics committee. Since a retrospective study, most data collected were from secondary source like case sheets.

Data was collected using a semi structured proforma. The following protocol was followed for oocyte retrieval. The Controlled ovarian stimulation usually gets started on 2nd day of cycle using gonadotrophins (HMG/rFSH) and fixed antagonist protocol with cetrorelix 0.25mg started from day 5 of stimulation until the day of trigger. When > 2 leading follicles reach 18mm, final oocyte maturation was triggered with dual trigger or HCG trigger. Oocyte retrieval done 35 - 36 hours later. Study participants were divided into two groups based on the trigger they received before ovum pickup, the DUAL TRIGGER group and HCG TRIGGER group. Based on the oocytes retrieved, the study participants in each group were subdivided into 3 subgroups based on the number of retrieved oocytes and results will be analyzed. Normal responder (6 to 15 retrieved oocytes), Poor responder (1 - 5 retrieved oocytes) and Hyper responder (>16 retrieved oocytes).

The following variables were recorded in the proforma which included age, body mass index (BMI), cause of infertility, number of oocytes retrieved, number of M2 oocytes retrieved, number of oocytes fertilized, number of embryos obtained and number of embryos transferred.

Number of implantations, clinical pregnancies and live births were also recorded.

2.1 Statistical analysis

The data collected were entered into Microsoft excel 2019 and the master chart was created. The master chart was then loaded onto SPSS version 26 for statistical analysis. The quantitative variables were expressed using mean and standard deviation. The qualitative or categorical variables using frequency and percentages. To compare the quantitative variables between dual trigger and HCG trigger groups, independent samples t test was used. To compare the distribution of categorical variables between dual trigger and HCG trigger groups, Chi square test was applied. For subgroup analysis, for comparing the mean within the responder group between dual trigger and HCG trigger groups, independent samples t test was used. A P value of less than 0.05 was considered to be statistically significant.

3. Results

Participants included into the dual trigger and HCG group were 120, respectively. The mean age among the participants in the dual trigger group was 31.76 ± 4.35 years and that of the HCG group was 31.74 ± 4.11 years. Both the groups were similar with regard to mean age with P value of more than 0.05. The mean BMI among the participants in the dual trigger and HCG trigger groups were 26.34 ± 4.77 Kg/m² and 27.33 ± 3.79 Kg/m², respectively. The mean BMI was found to be similar between the groups. The mean AMH was 3.28 ± 2.34 pg/ml in the dual trigger group and 2.76 ± 2.41 pg/ml in the HCG trigger group. The mean AFC was 15.73 ± 8.15 in the dual trigger group and 14.59 ± 8.22 in the HCG group. Both the mean AMH and AFC were found to be similar between the dual trigger and HCG trigger groups (P value > 0.05).

The mean FSH among the Dual trigger and HCG trigger groups were 5.86 ± 2.31 IU/L and 5.93 ± 2.16 IU/L, respectively. The mean D2 estrogen for the dual trigger group was 34.53 ± 9.28 and for the HCG trigger group was 32.82 ± 11.03 . The mean D2 LH for the dual trigger group was 3.53 ± 1.59 and for the HCG trigger group was 3.88 ± 1.95 . The mean FSH, D2 estrogen and D2 LH groups were similar between dual trigger and HCG trigger groups with P value of more than 0.05. The cause of infertility among the participants in the dual trigger group was tubal factor (29.1%), male factor (25.8%), ovulatory dysfunction (15.8%) and endometriosis (14.1%) and among those in the HCG group, the causes were male factor (28.3%), tubal factor (25%), ovulatory dysfunction (17.5%) and endometriosis (17.5%). The distribution of causes were similar between the groups with P value of more than 0.05 (Table 1).

Table 1: Baseline characteristics between the dual trigger and HCG groups

Variables		Dual trigger group (n=120)	HCG group (n=120)	pvalue
Age (in years)		31.76 ± 4.35	31.74 ± 4.11	0.976
BMI (kg/m ²)		26.34 ± 4.77	27.33 ± 3.79	0.076
AMH (pg/ml)		3.28 ± 2.34	2.76 ± 2.41	0.093
AFC (numbers)		15.73 ± 8.15	14.59 ± 8.22	0.278
FSH (IU/ml)		5.86 ± 2.31	5.93 ± 2.16	0.815
D2 Estrogen		34.53 ± 9.28	32.82 ± 11.03	0.197
D2 LH		3.53 ± 1.59	3.88 ± 1.95	0.125
Cause of infertility	Male factor	31 (25.8)	34 (28.3)	0.896
	Tubalfactor	35 (29.1)	30 (25)	
	Ovulatory dysfunction	19 (15.8)	21 (17.5)	
	Endometriosis	17 (14.1)	21 (17.5)	
	Unexplained	10 (8.3)	7 (5.8)	
	Combined	8 (6.6)	7 (5.8)	

The mean LH on day of trigger in the dual trigger group and HCG trigger group was 1.88 ± 1.19 and 1.66 ± 1.40, respectively. The mean E2 on day of trigger in the dual trigger group was 4189.22 ± 2738.99 and for the HCG trigger group, it was 3527.10 ± 2641.91. The mean ET on trigger day was 9.32 ± 1.80 and 9.06 ± 1.51 for the dual trigger and HCG trigger groups, respectively. All the three factors, LH, E2 and ET on trigger day were found to be similar between the groups with P value of more than 0.05. The mean number of expected follicles in the dual trigger group was 10.46 ± 5.91 and that of the HCG trigger group was 9.07 ± 1.51. The mean number of expected follicles were significantly more in the dual trigger group than in the HCG group with P value of less than 0.05. The mean number of oocytes retrieved in the dual trigger group was 12.03 ± 7.31 and that of the HCG trigger group was 10.08 ±

5.48. The number of oocytes retrieved was more in the dual trigger group than in the HCG trigger. The number of M2 oocytes retrieved in the dual trigger group was 9.24 ± 5.62 and that of HCG trigger group was 8.32 ± 4.75. The number of oocytes fertilised was 7.67 ± 4.55 for the dual trigger group and 7.42 ± 4.81 for the HCG trigger group. The mean number of top - quality embryos were 7.42 ± 4.81 in the dual trigger group and 6.98 ± 4.27 in the HCG group. The mean number of embryos transferred were 2.67 ± 0.96 and 2.89 ± 0.84 in the dual trigger and HCG trigger group, respectively. The mean number of M2 oocytes, mean number of oocytes fertilized, mean number of top - quality embryos and the mean number for embryos transferred were similar between the Dual trigger and HCG groups with P value of more than 0.05 (Table 2).

Table 2: Comparison of characteristics of stimulation between the groups

Variables	Dual trigger group (n=120)	HCG group (n=120)	P value
LH on day of trigger (mIU/ml)	1.88 ± 1.19	1.66 ± 1.40	0.192
E2 on day of trigger (pg/ml)	4189.22 ± 2738.99	3527.10 ± 2641.91	0.058
ET on trigger day (mm)	9.32 ± 1.80	9.06 ± 1.51	0.215
No of expected follicles on trigger day	10.46 ± 5.91	9.07 ± 4.32	0.040*
No of oocytes retrieved	12.03 ± 7.31	10.08 ± 5.48	0.021*
No of M2 oocytes	9.24 ± 5.62	8.32 ± 4.75	0.170
No of oocytes fertilized	7.67 ± 4.55	7.42 ± 4.81	0.528
No of top - quality embryos	7.42 ± 4.81	6.98 ± 4.27	0.462
No of embryos transferred	2.67 ± 0.96	2.89 ± 0.84	0.056

* p Value of <0.05 is statistically significant.

38.3% participants in the dual trigger group had successful implantation and in the HCG group the proportion was 50%. The implantation rate was similar between both the trigger groups with P value of more than 0.05. 30% in the dual trigger group and 48.3% in the HCG trigger group were clinically pregnant. Clinical pregnancy rate was significantly more in the HCG group than in the dual trigger group with P value of less than 0.05. The percentage of live birth in the dual trigger group was 21.7% and in the HCG trigger group it was 35.8%. The proportion of live births were significantly more in the HCG group than in the dual trigger group with P value of less than 0.05 (Table 3).

Table 3: Comparison of implantation and clinical pregnancy rate between the groups

Variables		Dual trigger group (n=120)		HCG group (n=120)		P value
		N	%	N	%	
Implantation	Yes	46	38.3	60	50	0.069
	No	74	61.7	60	50	
Clinical pregnancy	Yes	36	30	58	48.3	0.004*
	No	84	70	62	51.7	
Live birth	Yes	26	21.7	43	35.8	0.015*
	No	94	78.3	77	64.2	

*Statistically significant

Among the participants in the dual trigger group, 22 (18.3%) were categorised as poor responders, 66 (55%) as normal responders and 32 (26.7%) as hyper responders. Among those in the HCG group, 25 (20.8%) were categorised as

poor responders, 72 (60%) were categorised as normal responders and 23 (19.2%) as hyper responders. Both the groups were similar with regard to the categories of responders with P value of more than 0.05 (Fig 1).

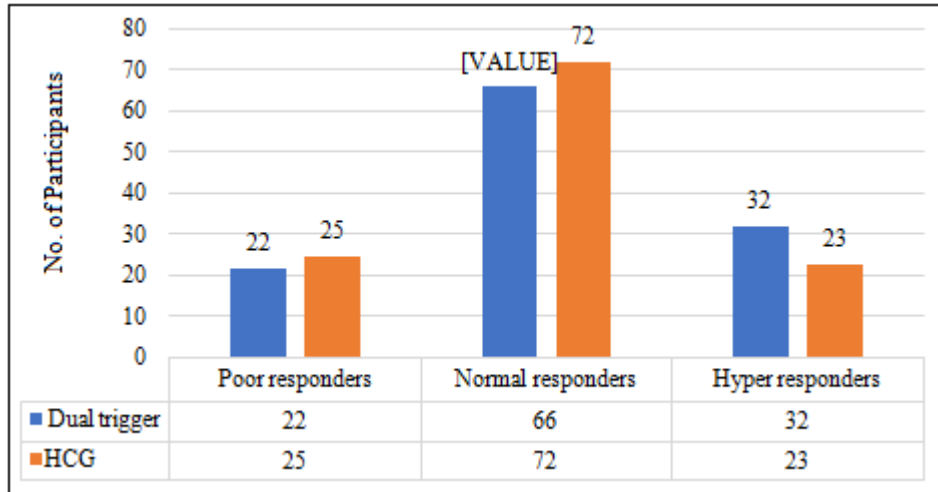


Figure 1: Bar chart showing comparison of responders between the groups

On comparing within each subgroup, there is no statistical significance with a p value of 0.382.

Within the poor responders, the mean number of M2 oocytes was 2.64 ± 1.32 and 3.24 ± 1.20 for the dual trigger and HCG groups, respectively. The mean number of oocytes fertilized was 2.50 ± 1.40 and 3.12 ± 1.33 for dual trigger and HCG groups, respectively. The mean number of top - quality embryos retrieved for the dual trigger group was 2.23

± 1.23 and for the HCG group was 2.64 ± 1.18 . The mean number of embryos transferred was 2.09 ± 1.01 in the dual trigger group and 2.64 ± 1.11 in the HCG group. The number of M2 oocytes, number of oocytes fertilized, number of top - quality embryos and number of embryos transferred were similar between the dual trigger and HCG groups with P value of more than 0.05. Similar pattern was found among the normal responders and hyper responders too (Table 4).

Table 4: Comparison of characteristics of stimulation among different categories of responders between dual trigger and HCG groups – A sub group analysis

Responders	Characteristics of stimulation	Dual trigger group (n=120)	HCG group (n=120)	P value
Poor	No of M2 oocytes	2.64 ± 1.32	3.24 ± 1.20	0.109
	No of oocytes fertilized	2.50 ± 1.40	3.12 ± 1.33	0.128
	No of top - quality embryos	2.23 ± 1.23	2.64 ± 1.18	0.248
	No of embryos transferred	2.09 ± 1.01	2.64 ± 1.11	0.086
Normal	No of M2 oocytes	7.82 ± 2.72	7.86 ± 2.79	0.927
	No of oocytes fertilized	6.98 ± 3.11	7.01 ± 2.48	0.952
	No of top - quality embryos	6.41 ± 2.94	6.44 ± 2.43	0.939
	No of embryos transferred	2.62 ± 0.94	3.00 ± 0.76	0.01*
Hyper	No of M2 oocytes	16.72 ± 3.39	15.26 ± 3.86	0.144
	No of oocytes fertilized	14.09 ± 3.72	14.65 ± 3.82	0.590
	No of top - quality embryos	13.06 ± 3.94	13.39 ± 3.59	0.753
	No of embryos transferred	3.16 ± 0.72	2.83 ± 0.71	0.100

*Statistically significant

4. Discussion

Dual trigger involves administering both GnRH agonists and HCG together. Dual trigger administered 35 to 36 hours before oocyte retrieval. It was proposed that such a dual trigger would increase the number of metaphase - II oocytes (9) . The objective of the present study was to compare the effect of dual trigger versus HCG trigger in IVF outcome and to compare the outcome in case of poor responder, normal responder and hyper responders with regard to dual and HCG triggers. The retrospective observational carried out at the Institute of reproductive medicine, Madras Medical Mission (MMM) between 2018 and 2021. Total of 240 participants were included into the study of which 120

received dual trigger and 120 received HCG trigger. The baseline characteristics like mean age, mean BMI and the distribution of cause of infertility were found to be similar between the groups. The mean AMH, AFC, FSH, D2 estrogen and D2 LH were also found to be similar between those who had received dual trigger and HCG trigger, respectively.

4.1 Characteristics of stimulation between the groups

With regard to the characteristics of stimulation between the groups, LH, E2 and ET on the trigger day were found to be statistically similar between the groups. The mean number of expected follicles on trigger day was found to be

significantly more in the dual trigger group than in the HCG group. The number of oocytes retrieved was also significantly more in the dual trigger group than in the HCG group. Similar results were obtained by systematic review where they reported number of oocytes collected was more in the dual trigger group than in the HCG group (11). Haas et al (2020) also reported a similar result of higher oocytes in the dual trigger than the HCG trigger (12).

The other parameters like number of M2 oocytes, number of oocytes fertilized, number of top - quality embryos and number of embryos transferred were similar between dual trigger and HCG trigger in the present study. With regard to each category of responders too, the present study found that the characteristic of stimulation like number of M2 oocytes, number of fertilized oocytes, number of top - quality embryos and number of embryos were found to be similar between dual trigger and HCG groups. Ding et al also reported a similar observation of no difference in the quantity of oocytes retrieved, mature oocyte, oocytes fertilized and the good quality embryos between dual trigger and HCG alone trigger (13). Mahajan et al and Dong et al also reported a similar comparable result for the above parameter between both the triggers (14) (15), possibly due to smaller sample size.

4.2 Comparison of outcome between the groups

The implantation rate was found to be similar on both the groups. The clinical pregnancy rate was found to be significantly higher in the HCG group than in the dual trigger group. The clinical pregnancy rate was 18.3% higher in the HCG group in comparison to the dual trigger group. The live birth rate was also significantly higher in the HCG group than in the dual trigger group with the difference of 14.1%. Zhou et al in their study reported similar ongoing pregnancy and live birth rates in both dual trigger and HCG group in the circumstances of both fresh embryo transfer and frozen embryo transfer (16). The reduced pregnancy rate could be because of GnRH agonist, GnRHa trigger is associated with corpus luteum dysfunction leading to luteal phase insufficiency with an increased rate of miscarriages and a decreased pregnancy rate.

Chan et al reported similar ongoing pregnancy rate between the dual trigger and HCG trigger groups (17). Gurbuz et al reported comparable implantation rate and clinical pregnancy rate between the dual trigger and HCG groups (18). Similar results were also obtained by Albeitawi et al (19), Decler et al (20) and Dong et al (15).

5. Strength and Limitation of the study

The strength of the study is its retrospective nature documenting the effect of the both the type of triggers for a period of three years. Comparison of outcome is based on the response to controlled ovarian stimulation. Patient characteristics and cause of IVF/ICSI were comparable in both the groups and are similar. Also all ICSI procedures were done in a same centre by the same embryologist team.

One of the limitations of the study could be its external validity as the study documented the cases treated at one center only.

6. Conclusion

Dual trigger resulted in a greater number of oocytes than the HCG trigger. The remaining factors studied with regard to stimulation were similar between the triggers. Though the implantation rate was similar between the group, the clinical pregnancy rate and live birth rate were more in HCG trigger than in the dual trigger.

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