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GnRH agonist trigger *vs.* HCG trigger for tinal oocyte maturation in GnRH antagonist protocol ICSI cycles: A randomized controlled trial

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SUMMARY

Background: Infertility is common and the global burden remains high over years. With the explosive increase *In Vitro* Fertilization (IVF) cycles worldwide, the morbidity and mortality associated with Ovarian Hyper Stimulation Syndrome (OHSS) cannot be ignored. Clinicians all over the world are moving toward newer modifications to eliminate its occurrence.
Objective: To compare the effectiveness of GnRHa versus HCG trigger to reduce OHSS.
Patients and methods: 200 women who underwent ICSI at Ain Shams university hospital IVF center and other private center using GNRH long antagonist protocol; were randomly divided into two equal groups 1st group 100 cases received agonist trigger with cycle segmentation and the other group 100 cases received Human Chorionic Gonadotropin (HCG) as trigger.
Results: There was a high statistically significant difference between GnRHa and HCG groups as regard OHSS rate, with higher percentage of cases among HCG group (3% *vs.* 20%). p-value was <0.001.
Conclusion: Using GnRHa trigger has the advantage over HCG trigger regarding OHSS rate with lower incidence of OHSS rate among GnRHa group.

Keywords: Infertility; IVF OHSS; ICSI; HCG; GnRHa

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INTRODUCTION

The infertility burden remains high over the years. The National Institute for health and Care Excellence (NICE) recommends *In-Vitro* Fertilization (IVF) as the definitive treatment for prolonged unresolved infertility [1]. The success of IVF depends in part on obtaining a sufficient number of eggs to create high quality embryos for uterine transfer without exposing patients to the risks of excessive ovarian stimulation [2].

An exaggerated response to ovarian stimulation can lead to Ovarian Hyper Stimulation Syndrome (OHSS). The severe form of OHSS is a potentially life threatening complication in about 2%-6% of IVF cycles. It is associated with some sequels, including; massive ovarian enlargement, shift of protein rich fluid from intravascular to third space (thoracic and abdominal cavities), liver dysfunction, electrolyte imbalance and rarely mortality [3].

For a long time exogenous hCG has been used to trigger final oocyte maturation because its similar to LH biologically. As GnRH antagonists protocol for ovulation induction becomes more frequently used, it was observed that the incidence of severe OHSS was significantly lower than in agonist protocol. Another advantage of this protocol in high risk patients is using GnRHa as a trigger which has gained much interest as a trigger for final oocyte maturation and ovulation [4].

In this study we aimed to compare the effectiveness of the GnRH agonist trigger versus the HCG trigger to reduce OHSS and also to compare them regarding oocyte maturation rate, fertilization rate and chemical and clinical pregnancy rates.

MATERIALS AND METHODS

This is a prospective randomized controlled trial. The study was approved by the research ethical committee, faculty of medicine, Ain Shams University (FMASUMS 342/2019). It was retrospectively registered in the pan African clinical trial registry.

The trial was conducted in Ain Shams university maternity hospital and private IVF center from October 2019 to September 2020. All patients were accurately informed about the steps of the study. Written informed consent was taken from all patients after fully explaining the study procedure and its suspected success rate and hazards.

Eligibility criteria

Patients inclusion criteria: Age ranged from 18-40 years, primary or secondary infertility, BMI between 18 Kg/m²-40 Kg/

m² and baseline FSH and LH below 12 IU/L.

Exclusion criteria: Included those women with ovarian endometriosis, ovarian cyst before induction, or AMH ≥ 10 ng/ml.

The primary outcome: OHSS (Ovarian Hyperstimulation Syndrome) frequency with different grades.

Secondary outcomes were oocyte maturation rate, fertilization rate, chemical pregnancy rate and clinical pregnancy rate.

Sample size calculation: Results from a previous study showed that the OHSS rate in the GnRH agonist trigger group was 0%, while for the HCG group, it was 16%.

Based on this, the required sample size has been calculated using PASS 11 software. It was estimated that a sample size of 41 women in each group (total 82) will achieve a power of 90% to detect statistically significant differences between the two groups regarding OHSS rate with (α error) 0.05 [5].

The 200 patients were randomized into two groups, each 100 patients. The 1st group (GnRHa group n=100); triggering of ovulation by triptoreline acetate 0.2 mg subcutaneous (Decapeptyl; Ferring). The 2nd group (HCG group n=100) triggering of ovulation by HCG 10000IU intramuscular (Choriomon, IBSA).

Randomization was done using a computer generated random sequence in a ratio of 1:1. Allocation concealment was achieved by using sealed opaque sequentially numbered envelopes from 1 to 200. After randomization, each patient number was written on a piece of paper and underneath the name was the drug assigned to the patient. Each piece of paper was put in one envelope. The envelopes were opened at the time of triggering ovulation.

Study intervention

All patients in this study were subjected to full medical, gynecological and surgical history taking. General, local, and ultrasound examinations were performed for all 200 patients. The ICSI cycle was done using antagonist protocol for ovarian stimulation in which the patients had a starting daily dose of 150 IU of recombinant FSH (Gonal F; Merk), and then from day 7 of the cycle, 0.25 mg of Cetrorelix (Cetrotide; Merk) was also injected daily till the last day of rFSH injection. The dose of Gonal F was individually adjusted from day 7 according to E2 levels and size of follicles by transvaginal ultrasound performed every other day until at least 3 of the follicles reach a volume of 18 ml-24 ml, then the trigger was given. Ovum Picks Up (OPU) was done for both groups under general anesthesia 34-36 hours following the trigger. Then patients in the HCG group underwent embryo transfer in the same cycle except for the patients who develop OHSS (were postponed to another subsequent cycle). At the same time, for the GnRHa group, all embryos were frozen. Embryo transfer was postponed to another subsequent cycle to avoid the effect of GnRHa on endometrial receptivity and to give patients the best chance for pregnancy.

Follow Up: Patients were informed to report any symptoms suggestive of OHSS (abdominal distention and discomfort, nausea, vomiting and/or diarrhea, breathing difficulties, or decrease in urine output). If any of them were reported, patients were clinically assessed and an ultrasound was done for assessment of the ovarian size and presence of free pelvic or intra-abdominal fluid collection to diagnose OHSS and to assess its degree; (mild or moderate/severe), it was diagnosed as a mild form if symptoms were pain or discomfort in the abdomen, nausea or vomiting with the ovarian size of 5 cm or less by ultrasound. The moderate OHSS was the same as mild in addition to sonographic ascites or ovarian size reaching 8 cm. The severe form has clinical ascites, hydrothorax, or developing dyspnea, while the critical form is associated with impaired LFT or KFT, oliguria and evidence of venous thromboembolism or respiratory distress syndrome [6].

Assessment for OHSS in the GnRH group was done 7 days after OPU, while OHSS in the HCG group was done on the day of planned ET.

Statistical analysis: The collected data were revised, coded, tabulated and studies statistical package for social science (IBM corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The tests used were student's t-test (for numeric parametric variables), Mann-Whitney's U test, Fisher exact test (for numeric non-parametric variables) and *chi-squared* test (for categorical variables). P value <0.05 was considered significant.

RESULTS

Between October 2019 and September 2020, 200 women were recruited for the study. It shows patients allocation and follow-up. No patients were lost after allocation, as all patients were anxious to complete their cycles.

Demographic and baseline information is provided in **Tab. 1.** Group 1 (GNRHa group) and group 2 (HCG group). There were no statistically significant differences between both groups regarding age, Body Mass Index (BMI), FSH, and period of induction.

Tab. 1. Comparison between the 2 groups as regard Age, hormonal profile and period of induction.

	Group				P	Sig.
	GnRHa		HCG			
	Mean	± SD	Mean	± SD		
Age in years	28.6	4.2	29.3	5.2	0.269*	NS
BMI Kg/m²	27.7	4.8	27.5	4.8	0.795*	NS
FSH (IU)	6.9	1.7	7.3	2.1	0.127*	NS
AMH (ng/ml)	3.7	1.8	2.3	1.4	0.001*	HS
Period of induction in days	12.8	1.3	12.8	1.3	0.205*	NS
Last E2 (pg/ml)	5490.9	1792.2	2688.3	961.6	0.001*	HS
*Student t test						

Tab. 2. shows that there was a highly statistically significant difference between the two groups as regard (cumulus oophorus retrieved, M II, blastocysts) in favor of the GnRH group.

Tab. 2. Comparison between the 2 groups as regard the characteristics of retrieved ovum.

	Group										P	Sig.
	GnRHa					HCG						
	Mean	± SD	Median	IQR‡		Mean	± SD	Median	IQR‡			
Cumulus retrieved	20.9	7.56	20	15.5	25	13.94	6.85	13.5	9	17	0.001*	HS
Number M II	16.3	6.45	16	12	20.5	10.78	5.12	10	7	13.5	0.001*	HS
% of M II	78.39	15.11	81.6	67.3	89.7	78.28	13.52	80	71	87.5	0.76*	NS
Number 2PN	13.27	5.99	13	9.5	17	8.02	4.3	7.5	5	10	0.001*	HS
% of 2PN	80.17	15.73	83.7	73.9	90.9	73.66	18.29	75	63.4	87.5	0.006*	HS
Number of blastocysts	6.86	4.15	7	4	9	4.06	3.36	3	1	6	0.001*	HS
% of blastocysts	50.03	21.79	50.9	40	65	44.54	30.04	45	21.1	67.9	0.165*	NS
‡inter quartile range												
*Mann whitney test												

Tab. 3. shows a high statistically significant difference between GnRHa and HCG groups regarding the rate of OHSS, with no difference between the two groups regarding the degree of severity of OHSS. A high statistically significant difference was found between the two groups as regard biochemical and clinical pregnancy, with a higher percentage of cases among the GnRH group. However, no statistically significant difference was found between GnRH and HCG groups as regards the number of sacs and miscarriage rate.

Comparison between cases with frozen embryo transfer in both groups (all cases (100 cases) in GnRHa group and (20 cases with OHSS in HCG group where embryo transfer was postponed due to OHSS revealed no statistically significant difference between the two groups regarding biochemical and clinical pregnancy (79% *vs.* 90%), (70% *vs.* 85%).

Tab. 3. Comparison between two groups as regard OHSS rate, chemical, clinical pregnancy rates, number of sacs, miscarriage rate.

		Group				P	Sig.
		GnRH		HCG			
		N	%	N	%		
OHSS rate		3	3.00%	20	20.00%	0.001*	HS
OHSS Grade	Mild	2	66.70%	17	85.20%	0.47**	NS
	Moderate/ severe	1	33.30%	3	15.80%		
Chemical pregnancy rate		79	79.00%	63	63.00%	0.013*	S
Clinical pregnancy rate		70	70.00%	56	56.00%	0.04*	S
Number of sacs	One	46	65.70%	30	53.60%	0.166*	NS
	Two	24	34.30%	26	46.40%		
Miscarriage rate (biochemical only and/or abortion)		9	9.00%	7	7.00%	0.602*	NS
Chi-square tests							
**Fisher's exact test							

Tab. 4. shows the relation between PCO and OHSS among studied groups; where there was a 1.4 fold increased risk in the PCO with occur OHSS in the GnRH group but the insignificant association with (P=0.684), there was a 4.26 fold increased risk in the PCO with occur OHSS in HCG group, but the insignificant association with (P=0.134).

Tab. 4. Relation between PCO and OHSS among study group.

		OHSS				Total		Relative risk		
		No		Yes						
		No.	%	No.	%	No.	%	RR	C.I.95%	p-value
	GnRH agonist group	97		3		100				
	Non PCO	74	76.30%	2	66.70%	76	76.00%	1.41	0.27-7.24	0.684
	PCO	23	23.70%	1	33.30%	24	24.00%			
	HCG group	81		19		100				
	Non PCO	79	97.50%	17	89.50%	96	96.00%	4.26	0.64-28.37	0.134
	PCO	2	2.50%	2	10.50%	4	4.00%			
	Total study	178		22		200				
	Non PCO	153	86.00%	19	86.40%	172	86.00%	0.97	0.32-2.95	0.959
	PCO	25	14.00%	3	13.60%	28	14.00%			

DISCUSSION

OHSS is potentially life threatening, especially in its severe form, and is considered the most serious iatrogenic complication of (ART) [6]. GnRH antagonist protocols have been associated with lower OHSS and allow usage of GnRHa as a trigger in high risk patients.

Interpretation of our results and their comparison to similar studies

The current study showed that using GnRHa as a trigger significantly reduces OHSS and increases the number of MII oocytes retrieved, the number of blastocysts and both biochemical and clinical pregnancy rates. In contrast, the number of sacs or miscarriage rate didn't significantly differ between groups [7].

The current study's result agrees with Reddy, et al. where oocyte maturation was triggered with GnRHa (n=46) or hCG (n=83). There was one case of mild or moderate OHSS in the GnRHa group compared to 12 in the hCG group (2.1% *vs.* 14.4%, p=0.032).

In concordance, similar results were obtained from a randomized study by Babay OF, et al., for patients at risk of OHSS. Twenty eight patients with PCO, undergoing controlled ovarian hyper stimulation with FSH and GnRH antagonist for IVF embryo transfer treatment, were randomized to trigger final oocyte maturation with GnRH agonist (GnRH agonist group, n=15) or HCG (HCG group, n=13). They reported 31% OHSS in the hCG group versus 0% in the GnRHa trigger group [8].

Tan, et al., performed a retrospective study that included 333 hyper-responders, defined as >15 oocytes retrieved, who underwent segmented IVF cycles using either GnRHa (n=216) or hCG (n=117) as a trigger. There was a statistically significant difference in the rate of OHSS, which was higher in the HCG group (10.8 *vs.* 2.1%, p=0.0009) and a greater proportion of moderate severity cases (6.9 *vs.* 0.8%, p=0.038; noted in the hCG trigger group [9].

In another systematic review and meta-analysis done by Youssef, et al. they got similar results that there was a statistically significant difference in favor of GnRH agonist regarding the incidence of OHSS in fresh autologous (OR: 0.06; 95% CI: 0.01–0.33 and donor cycles respectively (OR: 0.06; 95% CI: 0.01–0.27).

To assess the effect of GnRHa alone on pregnancy outcome, we removed the effect of fresh *vs.* frozen embryo transfer from the equation. We compared cases with frozen embryo transfer in both groups (all cases (100 cases) in the GnRHa group) and (20 cases with OHSS in the HCG group, where embryo transfer was postponed due to OHSS).

We found no statistically significant difference between the two groups regarding biochemical and clinical pregnancy (79% *vs.* 90%), (70% *vs.* 85%) respectively. Similarly, there was no statistically significant difference between GnRH and HCG groups regarding the miscarriage rate (9% *vs.* 5%).

Similar results were also found in a study by Makhijani, et al., comparing pregnancy outcomes from frozen embryo transfer in GnRHa and HCG; they found that there was no statistically significant difference in CPR (69.0% (100/145) *vs.* 72.0% (85/118); p=0.68) between the GnRHa and hCG trigger groups respectively [10,11].

However, the current study disagreed with Engmann L, et al., who found no statistically significant difference between GnRH agonist and HCG, with only one case out of 23 patients in the HCG group developing OHSS and no cases in GnRH agonist group (n=23) [12].

Also, in a meta-analysis done by Haahr, et al., a total of five studies met the selection criteria comprising a total of 859 patients. The OHSS rates in the GnRHa and hCG groups were 0.9 and 1.7%, respectively and the corresponding OR was 0.48 (95% CI 0.15, 1.60, I2=0%). Although not statistically significant, a lower OHSS rate was observed in the GnRHa trigger group [13].

A study done by Tan, et al., demonstrated a slightly higher but not statistically significant average number of total oocytes (21.9 *vs.* 18.4, p=3.48) and MII oocytes (17.6 *vs.* 14.6, p=1.5) were retrieved in the GnRHa trigger group compared to hCG trigger group, while the fertilization and blastulation rates were similar between the two trigger groups which are not matching our results.

Clinical implications of our study

We are recommending using GnRHa as a trigger rather than an HCG trigger; although it is more expensive, it is safer in lowering the incidence of OHSS, which is a life-threatening complication, especially in patients with PCOS.

CONCLUSION

Our study concluded that using GnRha as a trigger lowers the OHSS rate, increases the number of MII oocytes retrieved, and increases both chemical and clinical pregnancy rates.

RECOMMENDATIONS FOR FUTURE RESEARCH

Further studies are needed to find appropriate luteal phase support to allow embryo transfer at the same cycle after using GnRHa as a trigger.

STRENGTHS AND LIMITATIONS OF OUR STUDY

The advantages of the current study are that it is a randomized controlled trial carried out on an adequate number of cases and it was carried out in 2 centers (decreasing the publication bias), while limitations are that it was not selectively done on high risk patients for OHSS like PCO patients, although subgroup analysis for PCOS patients was done in this study and another limitation is that not all patients had embryo transfer at same cycle; where in HCG group 20 women had frozen embryo transfer and the rest 80 women had embryo transfer in the same cycle of induction, while in GnRHa group all women had frozen embryo transfer.

ETHICS APPROVAL

Study approved by Research Ethical Committee, faculty of medicine, Ain Shams university.

CONSENT FOR PUBLICATION

Non applicable.

AVAILABILITY AND DATA MATERIAL

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. After approval of Ain Shams university hospital.

COMPETING INTERESTS

The authors report there are no competing interests to declare

AUTHORS CONTRIBUTIONS

All authors jointly contributed to conception and design of the study.

Abdel Hamid AS: Design of the study, helped in review of literature, revision of results and data analysis, writing the manuscript and submission.

Mostafa MH: Design of the study, revision of review of literature and revision of manuscript, performing ICSI for patients,

Alameldin M: Obtaining ethical committee approval, reviewed the literature, shared in collection of data.

Snosi MS: Design of the study, registration of trial, helped in review of literature, helping in ICSI steps, antenatal care for patients who got pregnant, revision of results and data analysis and contributed in writing the manuscript.

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