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A randomized Clinical Trial comparing embryo quality and clinical pregnancy rate in PCOS patients underwent controlled ovarian stimulation using antagonist protocol with freeze all strategy and triggered for final oocyte maturation by gonadotropin agonist versus human chorionic gonadotropin in IVF cycles

Abstract

Background: The use of Gonadotropin-releasing hormone (GnRH) antagonist protocol rather than the long agonist protocol showed a marked reduction in the incidence of OHSS.

Aim: To compare the effect of triggering oocytes by agonist versus HCG on reduction of risk of OHSS, embryo quality and clinical pregnancy rate.

Patients and methods: A randomized Clinical Trial was conducted at IVF unit in Cairo University Obstetric and Gynecologic hospital.

The patients were divided into two groups, the 1st group received GnRH agonist trigger, the 2nd group received hCG trigger; all embryos were frozen at day 5 and frozen embryos were transferred the next cycle.

Results: There was an obvious reduction in the risk of OHSS in the GnRH agonist triggered group than in the HCG triggered group but with no statistically significant difference.

In the current study, there was no statistically significant difference between the HCG triggered group in comparison to the GnRH agonist triggered group regarding chemical and clinical pregnancy rates.

Conclusion: The use of GnRH triggering for women with PCOS undergoing ICSI cycle with antagonist protocol with freeze all and transfer of frozen embryos in a later cycle has a lower risk of OHSS than using HCG triggering method.

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Wafaa Ramadan,[1] Mahmoud Alalfy,[2] Rania Refaat[3]

[1]Obstetrics and Gynecology Department, Cairo University, Egypt

[2]Reproductive health and family planning Department, National Research Centre, Egypt

[3]Obstetrics and Gynecology Department Misr University for science and technology n6th October city, Egypt

Correspondence: Mahmoud Alalfy, PhD, Reproductive health and family planning department, National Research Centre, Dokki, P.O:12622, Egypt ,Affiliation ID: 60014618 and Consultant OB/Gyn ,Aljazeerah Hospital, Egypt, Tel +201002611058, Email mahmoudalalfy@ymail.com

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Introduction

Women with PCOS undergoing IVF/ICSI treatment are predisposed to developing OHSS due to their high antral follicle count (AFC). The use of Gonadotropin-releasing hormone (GnRH) antagonist protocol rather than the long agonist protocol showed a marked reduction in the incidence of ohss Teede et al.,[1]

With GnRH antagonists becoming more clinically in usage, Gonadotropin-releasing hormone agonist (GnRHa) have gained much interest and has become possible to trigger final oocyte maturation and ovulation as an alternative to human chorionic gonadotropin (hCG) Humaidan et al.,[2]

Although there is a marked decrease in pregnancy rates with GnRH agonist trigger compared with hCG trigger, some researches observe improvements in oocyte capability. Many studies have shown significant improvement in number of mature oocytes, fertilization or both Green et al.,[3]

Traditionally, a dose of 5.000-10.000 IU hCG is given for the final follicular maturation and ovulation as a standard method. HCG a luteinizing hormone (LH) like action .It has a long lutheotrophic influence which rises the possibility of ovarian hyper stimulation syndrome (OHSS). Lately, gonadotropin-releasing hormone agonist (GnRH-a) trigger is tried for the induction of final follicular maturation and ovulation aiming at minimizing the risk of OHSS.[4]

In this study, we assessed the efficacy of GnRH agonist versus hCG for triggering final oocyte maturation in IVF/ICSI PCOS patients undergoing controlled ovarian hyperstimulation (COH), also chemical and clinical pregnancy rate in a GnRH antagonist protocol.

Patients and methods

A randomized Clinical Trial was conducted at IVF unit in Cairo University Obstetric and Gynecologic hospital. started on February 2021 & finished on July 2021 and to ensure that everyone has the chance of participation, after meeting the inclusion criteria the patients

was randomized 1:1 into one of the 2 groups with at least 44 patients per group (Total of 88 Patients) was included in the study.

The required sample size has been calculated using PASS 11 software. The study conducted on infertile women "primary or secondary infertility" undergoing ICSI cycle using GnRH antagonist protocol.

The patients were divided into two groups, the 1st group received GnRH agonist trigger, the 2nd group received hCG trigger; all embryos were frozen at day 5 and transferred the next cycle .The Inclusion criteria includes: PCOS patients according to Rotterdam criteria Female age between 20 and 40 years. Primary or secondary infertility. Body mass index (BMI) between 18 and 40 kg/m2. The Exclusion criteria includes male factor of infertility Ovarian endometriosis, Ovarian cysts before induction Known uncontrolled endocrinal abnormalities (like hypo or hyperthyroidism) Duration of induction more than 16 days. Last E2 level before trigger more than 3500 pg/ml, Day 3 embryo transfer.

ICSI cycle

Ovarian stimulation: Stimulation was started day 2 or 3 of cycle using highly purified FSH (Fostimon™) 150:300 IU once daily. Fixed antagonist protocol was used on the 6th day of ovarian stimulation GnRH antagonist in the form of Cetrotide™ 0.25mg introduced till the end of stimulation. 1st U/S was done on day 6 on FSH stimulation then every other day until at least 3 of the follicles reach a size of 18-22ml then the trigger was given. The cycle cancelled if the responding follicles are less than 3 follicles. Last E2 before trigger recorded on the day of trigger before triggering.

Triggering method: was either GnRH agonist trigger or hCG trigger. The 1st group received GnRH agonist trigger in the form of Triptofem™ 0.2 mg SC. The 2nd group received hCG trigger in the form of Choriomon™ 5000 .TVUS guided vaginal oocyte retrieval was done 34:36 hours after triggering. On the same day of oocyte retrieval, husband's semen also collected. Intracytoplasmic sperm injection was performed. Patients with day 3 embryo transfer was excluded from the study.

At Day 5: All embryos were assessed for quality (good, fair, poor) and frozen in day 5 and embryo transfer (ET) was done next cycle.

All blastocysts were assessed by embryologists who used the grading system designated by Gardner and Schoolcraft.[5]

The laboratory is certified and all embryologists are examined and graded yearly on their performance.

All embryo grading is reviewed in real-time by one of 2 senior embryologists for verification and consistency.

SART grade good was assigned for inner cell mass (ICM) grade A and trophectoderm (TE) grade A or B (AA or AB blastocysts).

SART grade fair was assigned for ICM grade B and TE grade A, B or C (BB, BC, or BA blastocysts).SART grade poor was assigned for any ICM grade C (CC or CB blastocysts). Patient return after 5 days after oocyte retrieval for evaluation of indices of OHSS.

Endometrial preparation for FET

Estradiol valerate in the form of cycloprogenova™ (white tablet only) was started on day 2 or 3 of cycle with oral dose 4 mg divided on 2 doses in addition to Aspocid 75mg once daily with folic acid 500 mcg once daily. U/S was done on day 9 or 10 of cycle to assess endometrial thickness, then every other day until endometrial thickness of 8 mm or more is reached and when endometrial thickness reaches 8mm or more FET was planned. Progesterone in the form of prontogest™ 400 mg vaginal suppository twice daily, Two to Four Day 5 Embryos was transferred.

Assessment of patients for chemical and clinical pregnancy and ohss.

Chemical pregnancy: quantitative serum B-hCG was done 15 days after ET and repeated after 48 hours. Clinical pregnancy for positive B-hCG: one month after ET (6 weeks GA), U/S was done to detect number of Gestational sacs and Fetal cardiac pulsation.

Results

No significant difference between the studied groups regarding base line characteristics (Table 1).

Table 2 show that No significant difference between the studied groups regarding stimulation characteristics (Tables 3–5).

Table 1 Baseline characteristics among the studied groups

Items	measure	GnRHa N=44	HCG N=44	P-value
Age (years)	Mean±SD	28.82±4.79	28.73±4.76	0.929
BMI (Kg/m^2)	Mean±SD	25.73±6.46	24.48±5.56	0.333
AMH (ng/ml)	Mean±SD	4.983±2.3621	5.0593±3.2427	0.899
FSH (mIU/ml)	Mean±SD	7.2057±2.0409	7.2534±2.0086	0.912
LH (mIU/ml)	Mean±SD	9.0095±2.8539	8.6811±3.2896	0.618

Table 2 Stimulation characteristics among the studied groups

Items	Measure	GnRHa N=44	HCG N=44	p-value
Fostimon™ dose (IU)	Mean±SD	216.48±24.8	216.48±33.21	1
Endometrial thickness at trigger (mm)	Mean±SD	9.6±1.666	9.6±1.706	1
Duration (days)	Mean±SD	11.64±1.08	11.98±1.17	0.159
E2 before trigger (pg/mL)	Mean±SD	2807.05±461.82	2754.02±515.98	0.529

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Table 3 Oocyte number and maturity among the studied groups

Items	Measure	GnRHa N=44	HCG N=44	P –value
Oocyte retrived	Mean±SD	16.27±5.28	15.52±5.85	0.529
GV	Mean±SD	2.82±2.4	2.82±2.54	1
EZ	Mean±SD	0.27±0.82	0.27±0.76	1
M1	Mean±SD	2.07±2.4	2.25±2.16	0.709
M2	Mean±SD	10.95±3.85	10.43±3.62	0.513

Table 4 Embryo number and quality among the studied groups

ITEMS	Measure	GnRHa N=44	HCG N=44	P –value
Embryo number	Mean±SD	7.25±2.4	6.64±2.43	0.237
Good embryos	Mean±SD	3.64±1.28	3.5±1.17	0.603
Fair embryos	Mean±SD	2.82±1.26	2.73±1.4	0.75
Poor embryos	Mean±SD	0.89±1.13	0.5±0.95	0.085
Embryos transferred number	Mean±SD	2.77±0.52	2.77±0.48	1

Table 5 OHSS among the studied groups

OHSS	GnRHa N=44	HCG N=44	p-value
POSITIVE	3	10	0.068
negative	41	34	
Chemical	GnRHa	HCG	p-value
Pregnancy	N=44	N=44	
POSITIVE	14	13	1
negative	30	31	
Clinical	GnRHa	HCG	p-value
Pregnancy	N=44	N=44	
POSITIVE	10	11	1
negative	34	33	

Discussion

HCG causes endogenous mid-cycle LH surge in IVF cycles for follicular maturation, as it has similarities with LH . but, it has a long lasting luteotropic effect that raises the risk of OHSS in PCOS and in hyper-responders. GnRHa recently considered as an alternative trigger, due to its initial flare action, releasing endogenous gonadotrophins from the pituitary but it has a short-lasting LH surge (24-36 h), so , it result in rapid luteolysis, with a rapid fall in steroid hormones and vascular endothelial growth factor (VEGF), the cytokine primarily blamable for OHSS. So, reduces the OHSS risk, but with a possibility of compromised cycle outcomes and decreased pregnancy rates.[6]

Review articles revealed that fertility outcome in triggering by GnRH agonist is alike that after hCG trigger. So, it is suggested that GnRH-a trigger is an appropriate method for ladies at risk of OHSS and also oocyte donors.[4]

Freezing all oocytes or embryos with triggering by GnRH and transfer of embryos in a later cycle is suggested and is known as segmentation of IVF cycle.[7,8]

In the current study, there was no statistically significant difference between GnRH agonist and HCG triggering regarding the number of oocytes.

A recent meta analysis showed that the cumulative live birth rate was higher after transfer of frozen-thawed embryos produced by GnRHa-triggered cycles in comparison to hCG trigger. So, in IVF cycles for PCOS women, a trigger by HCG should be substituted by a trigger by GnRHa with vitrification of all embryos followed by frozen embryo transfer.[6]

In the current study, there was no statistically significant difference between GnRH agonist and HCG triggering regarding the quality of oocytes.

GnRH agonist causes FSH and LH surge that resembles normal physiology that helps separation of oocyte from the wall of follicle and formation of receptors for LH in the luteinizing cells and making an open gap junction in between cumulus cells and oocyte helping cumulus expansion and maturation of oocyte.[9–12]

In the present study, there was no statistically significant difference between HCG triggering group and GnRH triggering group as regard the total number of embryos.

A recent meta analysis concluded that there was a statistically significant higher clinical pregnancy rate after the transfer of embryos obtained from the GnRHa group in comparison to that from the HCG group in frozen-thawed cycles, that might be linked to a higher number of oocytes retrieved, greater maturity, better fertilization, greater number of high quality embryos and a higher number of blastocysts gained in the GnRHa group in comparison to the HCG group.[13]

Moreover, in the present study, there was no statistically significant difference between HCG triggering group and GnRH agonist triggering group as regard the quality of embryos nor the number of transferred embryos.

A recent research was made to evaluate the Triggering with GnRH agonist and documented that triggering with GnRH agonist has a comparable ICSI outcome to hCG as regard quality of oocytes and

Citation: Ramadan W, Alalfy M, Refaat R. A randomized Clinical Trial comparing embryo quality and clinical pregnancy rate in PCOS patients underwent controlled ovarian stimulation using antagonist protocol with freeze all strategy and triggered for final oocyte maturation by gonadotropin agonist versus human chorionic gonadotropin in IVF cycles. *Obstet Gynecol Int J.* 2021;12(5):279–282. DOI: 10.15406/ogij.2021.12.00592

embryos. Whereas pregnancy rate was significantly worse with GnRH agonist that denotes that GnRH agonist may have undersirable effect on receptivity of endometrium with decreased implantation rate.[14]

Notably , there was an obvious reduction in the risk of OHSS in the GnRH agonist triggered group than in the HCG triggered group but with no statistically significant difference.

The negative effect of GnRH agonist on pregnancy rate may result from the fact that GnRH agonist trigger, which is unlike to hCG trigger, decreases LH level, so the amount of LH becomes insufficient for maintaining the function of the corpus luteum (Shapiro & Andersen, 2015).[14]

A recent study made by Kai Lun Hu 2021 showed that dual triggering with GnRH agonist and HCG is accompanied by elevated live birth rate in comparison to hCG trigger alone.[15]

In the current study, there was no statistically significant difference between the HCG triggered group in comparison to the GnRH agonist triggered group regarding chemical and clinical pregnancy rates.

A recent systematic review and meta analysis made by Zhang Y et, al 2021 comparing dual trigger versus GnRH agonist trigger alone versus HCG trigger alone, they revealed that the dual trigger was accompanied with a significantly larger number of oocytes retrieved , MII oocytes and fertilized oocytes in comparison to HCG trigger. But there was no significant difference between the groups as regard pregnancy rate. The GnRHa-alone trigger had no better clinical outcome than the HCG. None of the three interventions increased the OHSS risk in f normal responders.[16]

Limitations of the study

We thought that the small sample size of the study could be a limiting factor , with the need for follow up of the live birth rate , so future researches with a larger sample size and with monitoring of live birth rate is needed for reach more solid conclusion regarding the chemical , clinical and live birth rates between the 2 triggering methods.

Conclusion

The use of GnRH agonist for women with PCOS undergoing ICSI cycle with antagonist protocol with freeze all and transfer of frozen embryos in a later cycle has a lower risk of OHSS than using HCG triggering method.

Orcid number - Mahmoud Alalfy 0000-0002-8429-6376.

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Conflicts of interest

Authors have nothing to declare.

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