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Single versus double agonist trigger in antagonist protocol cycles: a multicenter prospective and retrospective study

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Background: The use of GnRH agonist (GnRHa) to induce final oocyte maturation in IVF has become increasingly common due to its proven ability to reduce the incidence of OHSS. It has previously been demonstrated that the LH surge induced by a single bolus of GnRHa at mid-cycle results in a shorter LH surge than in natural cycles. There has been concern, that the GnRHa-induĉed LH surge may not adequately induce maturation of the oocytes. ***Objective***: The aim of this study is to establish if a second dose of GnRHa repeated 12 h following the initial dose optimizes the cycle outcome in terms of ongoing pregnancy rate in women undergoing intracytoplasmic sperm injection (ICSI) cycles using a GnRH-antagonist protocol. ***Methods*:** This prospective and retrospective study included 160 women, they were divided into two groups, group (A) 80 subjects were triggered by a single dose of 0.3 mg GnRH agonist triptorelin subcutaneously 36 h prior to oocyte retrieval. Group (B) 80 subjects were triggered by 2 doses of GnRH agonist triptorelin the first as in group A + a second dose of 0.2 mg 12 h following the 1st dose. 12 h & 24 h post-trigger luteinizing hormone (LH) values were estimated. 25 patients were followed prospectively and the data of 55 patients was collected retrospectively in each group. ***Results***: there was a statistical significant difference between both groups in favor of group (B) as regard ongoing pregnancy rate and implantation rate, but there was no significant statistical difference as regard oocyte maturity rate, clinical pregnancy rate and OHSS occurence. ***Conclusion***: the double dose GnRHa trigger offers better ongoing pregnancy rate than single dose GnRHa trigger but their efficacy is comparable regarding clinical pregnancy rate, oocyte maturity rate and OHSS occurrence.

Keywords: GnRHa trigger, ongoing pregnancy , oocyte maturity, OHSS

Introduction

Since 1999, GnRH antagonists have been used to avoid premature LH surges in females undergoing controlled ovarian stimulation for IVF.(1) Even while GnRH-agonist therapy is very successful, there are many drawbacks. Before pituitary

desensitization occurs, GnRH receptors are first stimulated. Therefore, menopausal symptoms can occasionally develop, 7–14 days are required for proper downregulation, and unless a depot formulation is utilized, daily injections or numerous intranasal treatments are required for 2-4 weeks.(2) However, gonadotropin and steroid hormone secretion are rapidly inhibited by GnRH antagonists, which are competitive inhibitors of endogenous GnRH due to their receptor binding property. This results in a reduction of FSH (follicle stimulating hormone) and LH (luteinizing hormone) secretion in approximately 8 hours after administration, which is a potential advantage over GnRH agonists.To avoid an early LH surge, the GnRH-antagonist protocol starts the GnRH antagonist in the mid-follicular phase and starts the gonadotropins on day 2 of the cycle.(2)

In the periovulatory period, LH surge occurs to complete meiosis I, to cause oocyte cumulus expansion, follicular rupture and lutienization and to promote progesterone production.(3, 4) In the case of ART, final oocyte maturation is a critical step in order to retrieve mature oocytes ready for further laboratory processing.(5) The GnRH antagonist protocol permits the triggering of oocyte maturation by either GnRH agonist or hCG, but the long GnRH agonist protocol requires hCG to do this.(5) The usual criteria for administration of the trigger in GnRH antagonist cycles; when there are at least 1 or 2 leading follicles ≥ 18 mm in diameter or at least 3 follicles ≥ 17 mm in diameter.(6)

GnRH agonist is used for its initial flare effect to induce oocyte final maturation as a substitute to hCG in GnRH antagonist stimulation cycles. When administered, it displaces the GnRH antagonist from the GnRH receptors. A single mid-cyclic bolus of GnRH agonist can be injected subcutaneously (0.2 to 0.5 mg of buserelin, leuprorelin or triptorelin) or administered intra-nasally (200 μg buserelin).(6-11) This single dose causes acute FSH and LH release after 12 and 4 hours respectively and their levels remain high for 24-36 hours.(4, 7)

Having a short half-life compared to hCG, it can decrease the risk of OHSS in high risk patients due to the reversible and rapid luteolysis and lower levels of VEGF.(4, 7, 10) GnRH agonist trigger use also decreases the risk of ovarian torsion in case of OHSS and has comparable ongoing pregnancy rate (OPR), pregnancy loss rate and live birth rate (LBR).(8, 12) It has been suggested that using GnRH agonist trigger instead of hCG would result in lower rates of pregnancy and live births due to its shorter half-life, which causes early luteolysis. Consequently, various strategies for luteal phase support (LPS) have been developed to counteract these unfavorable outcomes, such as dual triggering, luteal coasting, adding hCG or estrogen to standard progesterone doses, or to freeze all embryos for transfer in a later cycle.(8, 13, 14)

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Compared to the endogenous LH surge during a natural cycle, the gonadotropin response that occurs after a GnRHa trigger lasts much shorter.(15-17)This could lead to a suboptimal response. Therefore, one dose of GnRHa may not be able to induce an LH surge above the threshold level and for a threshold duration (like the physiological surge) that is required for optimal oocyte maturation, especially in women with PCOS who have neuroendocrine abnormalities. Another dosage of GnRHa, given twelve hours after the first dose, optimizes the cycle outcome regarding oocyte maturity because one dose of GnRHa may not be adequate to provide an adequate response.(18)

The aim of this study was to see if ongoing pregnancy rate & oocyte maturity improve by a repeat dose of GnRHa or not.

Patients & methods

This study is a prospective and retrospective study performed at multiple private ART centers including (Life clinic, Al Madina fertility center, Agial fertility center, Dar elkhosoba fertility center) and the same protocol should have been applied in all centers.

Sample size:

Sample size was calculated by staff members of the high institute of public health, Alexandria University. A total hypothesized sample size of 160 eligible women undergoing ICSI using GnRH antagonist protocol (80 per group) is needed to compare between both types of ovulation triggering methods (single GnRH dose & double GnRH dose)with an assumption of obtaining an effect size of 10%, with 0.05 probability of type I error and power of 80% using Chi-square test.

Participants:

The study was conducted on 160 women undergoing ICSI using GnRH antagonist protocol. They were divided into 2 groups (80 per group) according to the mode of ovulation triggering.

Group A: 80 subjects triggered by single dose of GnRH agonist (0.3 mg triptorelin)

Group B: 80 subjects triggered by double dose of GnRH agonist (0.3mg + 0.2 mg triptorelin)

Inclusion & exclusion criteria:

- We included women aged less than 40 years with a spontaneous normal menstrual cycle and a normal uterine cavity & with body mass index (BMI) < 35 & should be average responders with AMH level above 1.2 ng/ml.

- Women with comorbidities including hypertension , diabetes mellitus & other endocrinopathies, also women with communicating hydrosalpinx , uterine abnormalities (even if corrected) , poor responders , women with polycystic ovarian syndrome & cases with surgically retrieved sperms were excluded from the study.

Before enrollment in the study, all patients were subjected to routine medical evaluation to make sure of presence of inclusion criteria and absence of exclusion criteria. All included women undergone a fixed GnRH antagonist protocol of COH. COS was initiated on the second day of the menstrual cycle by administration of (FSH and HMG) daily for 5 days. Follow up visit was done after 5 days to assess the serum E2, the endometrial thickness and the size and number of the growing follicles. GnRH antagonist; cetrorelix acetate 0.25 mg (cetrotide; Merck Serono) was given daily starting on stimulation day 6- regardless of the size of the dominant follicles by subcutaneous route "fixed antagonist protocol" to suppress endogenous luteinizing hormone. Follow up was done repeatedly every two days with ultrasonography and E2 analysis and the doses of FSH and HMG were adjusted according to the individual response of each patient till the 3 or more follicles reached 18 mm in size, then the GnRH agonist trigger was given. At the day of triggering, number of follicles and the number of oocytes expected to be retrieved were documented.

Two main groups were created depending on the trigger protocol used:

Group A: 80 subjects were triggered by a single dose of 0.3 mg GnRH agonist triptorelin (3 ampoules of Decapeptyl 0.1 mg; Ferring or Triptofem 0.1 mg; Marckyrl Pharma Gmbh) subcutaneously, 36 h prior to oocyte retrieval. 25 patients were followed prospectively and the data of 55 patients was collected retrospectively.

Group B: 80 subjects were triggered by 2 doses of GnRH agonist triptorelin the first as in group A 0.3 mg (3 ampoules of Decapeptyl 0.1 mg; Ferring or Triptofem 0.1 mg; Marckyrl Pharma Gmbh) subcutaneously 36 h prior to oocyte retrieval + a second dose of 0.2 mg 12 h following the 1st dose (24 h before oocyte retrieval). 12 h & 24 h post-trigger, luteinizing hormone (LH), progesterone (P4) values were estimated. 25 patients were followed prospectively and the data of 55 patients was collected retrospectively.

Oocyte retrieval was performed by ultrasound-guided vaginal follicle aspiration under a strictly aseptic technique 36 hours after giving the trigger. In all subjects, ICSI was performed according to the standard operating procedure. The fertilization was assessed 18 h following ICSI by the appearance of two pronuclei. All patients undergone fresh embryo transfer with the transfer of 2 blastocysts.

Luteal phase support was continued until the day of serum β-hCG assessment (14 days after embryo transfer) through administration of 400 mg of natural progesterone (Prontogest 400 mg pessary; Marcyrl) twice daily per vagina with or without 100 mg intramuscular progesterone (Prontogest 100mg amp; Marcyrl) once daily. Beta human chorionic gonadotropin (β-hCG) was measured 14 days after embryo transfer for evaluating chemical pregnancy. Clinical pregnancy was confirmed by transvaginal ultrasound at two weeks later. Then, luteal support was continued through administration of 400 mg of natural progesterone (Prontogest 400 mg pessary; Marcyrl) twice daily per vagina until the 10th weeks of gestation. Patients were followed to confirm ongoing pregnancy at 20th weeks of gestation.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The **Kolmogorov-Smirnov** test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were

1- Chi-square test

For categorical variables, to compare between different groups.

2- Fisher's Exact

Correction for chi-square when more than 20% of the cells have expected count less than 5.

3- Student t-test

For normally distributed quantitative variables, to compare between two studied groups

4- Mann Whitney test

For abnormally distributed quantitative variables, to compare between two studied groups.

Results

A total of 160 women attending multiple private ART centers were divided into two groups 80 women were subjected to single GnRH agonist trigger after GnRH antagonist Protocol for ICSI (group A) and 80 women were subjected to 2 doses of

GnRH agonist trigger; the first as in group A 0.3 mg + a second dose of 0.2 mg 12 h following the 1st dose after GnRH antagonist Protocol for ICSI (group B). 25 patients in each group were followed prospectively and the data of 55 patients in each group was collected retrospectively. Table (1) demonstrates the main study results. There were no drop out of patients during the study. The mean age for patient in group (A) was 29.10 ± 4.63 years vs 28.75 ± 5.05 years in group (B) with no significant statistical difference. According to gravidity 62.5% were nulli-gravida & 37.5% were multi-gravida in group A & in group B 71.3% were nulli-gravida while 28.7% were multi-gravida & there was no statistical significant difference between the 2 groups. The mean duration of infertility in group (A) was (5.10 ± 2.92 years), while in group (B) was (4.59 ± 3.05 years). There was no statistical significant difference between both groups.

In group (A) the mean number of oocytes retrieved was 28.76 ± 10.80 , while for group (B) it was 27.25 ± 10.18. There was no statistical significant difference between both groups regarding the number of oocytes retrieved (p=0.324). The mean of oocyte maturity rate in group (A) was (77.0 ± 14.0 %) & for group (B) it was (80.0 ± 15.0%). There was no statistical significant difference between the two groups regarding the oocyte maturity rate (p=0.117).

In group (A) the mean implantation rate was (41.25 ± 36.26 %) & in group (B) the mean implantation rate was (53.13 ± 36.75 %). There was statistical significant difference between the two groups regarding the implantation rate (p=0.042). As regarding Clinical pregnancy rate in group (A) the clinical pregnancy rate was 63.8% while in group (B) it was 76.3% & there was no statistical significant difference between the two groups regarding clinical pregnancy rate (p=0.084). Regarding ongoing pregnancy rate, group (A) showed ongoing pregnancy rate of 41.3% while in group (B) it was 68.8% & there was a statistical significant difference between both groups (p=≤ 0.001). Both groups showed very low incidence of OHSS. As in group A there was only three cases of late mild OHSS (3.8%) & in group B there was two cases of late mild OHSS (2.5%) and one case of late moderate OHSS (1.3%). There was no statistical significant difference between both groups regarding OHSS (p=1).

The mean serum LH level 12 hours post trigger was 55.96 ± 5.53 IU/L for group A, while it was 58.18 ± 7.81 IU/L for group B & there was no statistical significant difference between both groups (p= 0.059). As regarding the mean serum LH level 24 hours post trigger, In group A it was 18.02 ± 2.39 IU/L ,while for group B it was 24.46 ± 3.03 IU/L & there was a statistical significant difference between both groups (p=≤ 0.001).

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Table (1): Main study results

Parameter	Group (A) 80 women	Group (B) 80 women	p value
Age (mean) years	29.10 ± 4.63	28.75 ± 5.05	0.648
Gravidity			
Nulligravida	50 (62.5%)	57 (71.3%)	0.240
Multigravida	30 (37.5%)	23 (28.7%)	
Duration of infertility (mean) years	(5.10 ± 2.92)	(4.59 ± 3.05)	0.131
No. of oocytes retrieved	28.76 ± 10.80	27.25 ± 10.18	0.324
Oocyte maturity rate (%)	77.0 ± 14.0%	80.0 ± 15.0%	0.117
Implantation rate (%)	41.25 ± 36.26%	53.13 ± 36.75%	0.042*
Clinical pregnancy rate	51/80 (63.8%)	61/80 (76.3%)	0.084
Ongoing pregnancy rate	33/80 (41.3%)	55/80 (68.8%)	<0.001*
OHSS	3 (3.8%)	3 (3.8%)	1.00
Post trigger serum LH			
12 hours	55.96 ± 5.53	58.18 ± 7.81	0.059
24 hours	18.02 ± 2.39	24.46 ± 3.03	<0.001*

Discussion

A conventional assisted reproductive technology (ART) cycle is divided into four steps: controlled ovarian stimulation (COS), oocyte retrieval and fertilization in vitro, embryo transfer, and luteal phase support. The ultimate objective of ART is the delivery of a healthy singleton at term. Given the psychological and economic burden

of ART on couples, this goal should be met in the shortest time, with the least interventions and cost.(19, 20)

Even while GnRH-agonist therapy is very successful, there are many disadvantages. Before pituitary desensitization happens, GnRH receptors are first stimulated. Therefore, menopausal symptoms can sometimes develop, 7–14 days are required for adequate downregulation, and unless a depot formulation is used, daily injections or numerous intranasal treatments are needed for 2-4 weeks.(2)

However, gonadotropin and steroid hormone secretion are rapidly inhibited by GnRH antagonists, which are competitive inhibitors of endogenous GnRH due to their receptor binding property. This results in a reduction of FSH (follicle stimulating hormone) and LH (luteinizing hormone) secretion in approximately 8 hours after administration, which is a potential advantage over GnRH agonists.

To avoid an early LH surge, the GnRH-antagonist protocol starts the GnRH antagonist in the mid-follicular phase and starts the gonadotropins on day 2 of the cycle.(2)

In the periovulatory period, LH surge occurs to complete meiosis I, to cause oocyte cumulus expansion, follicular rupture and lutienization and to promote progesterone production.(3, 4)

In the case of ART, final oocyte maturation is a critical step in order to retrieve mature oocytes ready for further laboratory processing.(5) The GnRH antagonist protocol permits the triggering of oocyte maturation by either GnRH agonist or hCG, but the long GnRH agonist protocol requires hCG to do this.(5)

HCG binds to LH receptors with greater affinity and has a longer half-life. The half-life of LH is less than 60 minutes while that of hCG is more than 24 hours.(4, 5, 9, 10, 21)

Unfortunately, it raises the risk of OHSS as it activates the VEGF (vascular endothelial growth factor) pathway, increases capillary permeability and has a prolonged luteotrophic effect owing to its longer half-life and the supraphysiological steroid levels detected in the luteal phase due to the evolution and maintenance of multiple corpora lutea.(4-7, 9)

GnRH agonist is used for its initial flare effect to induce oocyte final maturation as a substitute to hCG in GnRH antagonist stimulation cycles. When administered, it displaces the GnRH antagonist from the GnRH receptors. A single mid-cyclic bolus of GnRH agonist can be injected subcutaneously (0.2 to 0.5 mg of buserelin, leuprorelin or triptorelin) or administered intra-nasally (200 μg buserelin).(6-11)

Having a short half-life compared to hCG, it can decrease the risk of OHSS in high risk patients due to the reversible and rapid luteolysis and lower levels of VEGF.(4, 7, 10)

It has been suggested that using GnRH agonist trigger instead of hCG would result in lower rates of pregnancy and live births due to its shorter half-life, which causes early luteolysis. Consequently, various strategies for luteal phase support (LPS) have been developed to counteract these unfavorable outcomes, such as dual triggering, luteal coasting, adding hCG or estrogen to standard progesterone doses, or to freeze all embryos for transfer in a later cycle.(8, 13, 14)

Compared to the endogenous LH surge during a natural cycle, the gonadotropin response that occurs after a GnRHa trigger lasts much shorter.(15-17)This could lead to a suboptimal response. Therefore, one dose of GnRHa may not be able to induce an LH surge above the threshold level and for a threshold duration (like the physiological surge) that is required for optimal oocyte maturation, especially in women with PCOS who have neuroendocrine abnormalities.

Another dosage of GnRHa, given twelve hours after the first dose, optimizes the cycle outcome regarding oocyte maturity because one dose of GnRHa may not be adequate to provide an adequate response.(18)

The aim of this study is to establish if a second dose of GnRHa repeated 12 h following the initial dose optimizes the cycle outcome in terms of ongoing pregnancy rate, oocyte maturity rate, clinical pregnancy, LH levels , progesterone levels & OHSS occurrence in women undergoing intracytoplasmic sperm injection (ICSI) cycles using a GnRH-antagonist protocol.

In the current study the ongoing pregnancy rate of group B was higher than group A & was statistically significant (p=≤ 0.001). The oocyte maturity rate in group B was higher than group A but wasn`t statistically significant (P=0.117). The implantation rate in group B was higher than group A & was statistically significant (P=0.042). The clinical pregnancy rate was higher in group B than in group A but wasn`t statistically significant (P= 0.084). The miscarriage rate was higher in group A than in group B & was statistically significant (P=≤ 0.001). Post trigger serum LH (24hours) was higher in group B than in group A & was statistically significant (P = ≤0.001).

This agrees with the work of Aflatoonian et al. (2020)(22) where the results of their study showed higher oocyte maturity rate in the double dose group than in single dose group (80% vs 79%) but it wasn`t statistically significant (p=0.89). Also, post trigger LH (12hr) levels didn`t show a statistically significant difference between both groups (p=0.96). OHSS occurrence didn`t show a statistically significant difference

between both groups (p= 0.72) & this agrees with our study (p= 1.00). But opposing our study was the 24 hour post trigger LH where there was no statistical significant difference between both groups (P= 0.94)

The difference between the results of this study & our study may be due to several factors as lower sample size (120 patients) with high dropout rate, also patients in this study had PCOS, also different doses of GnRH agonist were used the single dose was 0.2 mg & the second dose was 0.1 mg. Additionally, we used fixed antagonist protocol, while in this study they used flexible antagonist protocol.

Our work agrees with the study done by Deepika et al. (2018)(18) regarding the clinical pregnancy rate where the double dose group showed higher clinical pregnancy rate compared with the single dose group (58% vs 44%) but there was no statistical significant difference between both groups (P= 0.15). Also, this study agrees with our work regarding the post trigger LH level (12h) where there was no statistical significant difference between both groups (P= 0.615), this is the same with post trigger progesterone level (12h) where there was no statistical significant difference between the 2 groups (P= 0.328). Regarding OHSS, our study agrees with this study where there was no statistical significant difference between both groups. But this study disagrees with our study regarding oocyte maturity rate where there was a statistical significant difference between both groups in favor of double dose group (85% vs 72.7%) (P= <0.001). It also disagrees with our work regarding implantation rate where there was no statistical significant difference between the 2 groups (P= 0.28).

The difference between the results of this study & our study may be due to several factors as lower sample size (100 patients), also patients in this study had PCOS, also different doses of GnRH agonist were used the single dose was 0.2 mg & the second dose was 0.1 mg. Additionally, we used fixed antagonist protocol, while in this study they used flexible antagonist protocol. Also, in this study all embryos were cryopreserved & both cleavage stage embryos & blastocysts were transferred later. Also the scope of this study didn`t include ongoing pregnancy rate.

Conclusion: The double dose GnRHa trigger offers better ongoing pregnancy rate than single dose GnRHa trigger but their efficacy is comparable regarding clinical pregnancy rate, oocyte maturity rate and OHSS occurrence. In the light of such results, the double dose GnRH agonist trigger offers better outcome compared to single dose GnRH agonist trigger with a minimal increase in cost & burden on treated couples. It is worth further studying on a large scale of patients in a randomized controlled trial and with other outcomes as livebirth rate.

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Conflict of Interest: The authors declare that they have no competing interests.

Ethics Approval: Approval was obtained from the ethics committee of Faculty of medicine, Alexandria University in 2022. Approval number was 0201640 .

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Consent to Participate: Informed consent was obtained from all participants included in the study.

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