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A compression between oocytes trigger by Human chorionic gonadotropin and Gonadotropin Releasing Hormone Agonist regarding number of mature oocytes, fertilization rates and embryos quality

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Abstract:

Background: Ovarian hyperstimulation syndrome (OHSS) is one of the most serious iatrogenic complications of ovulation induction in assisted reproductive treatments. The patients who are most at risk of developing it are young females with a PCOS and women with a high sensitivity and ovarian response to gonadotropins. and is associated with significant morbidity and rare mortality. The appearance of the GnRH antagonist opened an alternative route to the exclusive use of hCG in IVF cycles, since it allowed inducing ovulation with the GnRH agonist instead of hCG and thus avoiding OHSS.

Objective: To determine the differences between trigger by Human chorionic gonadotropin and Gonadotropin releasing hormone agonist regarding number of mature oocytes ,fertilization rates and embryos quality.

Patients and method: A retrospective cohort study carried in the Fertility center- AL Sadder Medical city- AL Najaf Iraq, in the period from Jan 1, 2019 to the end of Dec. 2019. 40 patients were enrolled in the current study within the age between 20-35 years old.

Results: Oligospermia is the major cause of the infertility in Decapeptyl group, while oligoasthenospermia in the hCG group and no significant association regarding the cause of infertility. Pregnancy rate in this study were found in 4/20 (25%) in Decapeptyl group, while inhCG group were found in 7/20 (35.0%) of the patients. **Conclusion:** hCG were better than GnRH agonists for use as a trigger final oocyte maturation in the antagonist protocol

Keyword: Trigger, hCG, GnRH agonist, oocyte maturation

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Introduction:

Gonadotropin RH antagonist is a drug that produces inhibition of the production of androgens and estrogens. GnRH analogs produce an initial phase of stimulation, and their continued administration

lead to downregulation of gonadotropin-releasing hormone receptors, which result in decreasing the release of gonadotropins (FSH and LH), which determines, in turn, an inhibition of the synthesis of androgens and estrogens. [1]

GnRH analogs are used to treat endometriosis, precocious puberty, infertility, uterine fibroid anemia (along with iron supplements), breast cancer and prostate cancer and before intrauterine surgery. GnRH antagonists inhibit the release of gonadotropins. They used to treat infertility with assisted reproduction techniques. [2]

Assisted reproductive technology (ART) consisting in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI) are grounded on the exact timing of ovulation, pick-up of the oocyte in the time before ovulation and then fertilization of oocyte were done.[3]

The use of protocols with GnRH antagonists (GnRH-a) has allowed inducing ovulatory discharge (OD) and final oocyte maturation by administering GnRH-a. This concept is based on the property of the agonist to produce a sudden increase and for a short time the levels of endogenous gonadotropins (flare *up* effect) in a more physiological approach than hCG to induce the final ova maturation [4]. An important advantage with respect to the use of GnRH in OD is that it significantly decreases the risk of OHSS due to its luteolytic effect [4-6].

Oocyte maturation is the final process of differentiation of the immature ovum prior to fertilization, both in the natural ovarian cycle and in assisted reproduction treatments. In the in vitro fertilization (IVF) cycles, there are two hormones that can trigger the activation of intracellular signals that induce oocyte maturation: HCG and LH released by a bolus of Gonadotropin releasing hormone agonist. (GnRH agonist). [7]

GnRH agonist in oocyte donation

Oocyte donation is a treatment that has been carried out for more than 20 years and is a good alternative in patients with repeated IVF failures, decreased ovarian reserve or quality, menopause or increased risk of transmission of genetic diseases. [8]

Before the appearance of the antagonists in the market, there was only the possibility of maturing the oocytes with hCG, which caused in some donors, various degrees of ovarian hyperstimulation, or in other occasions, the cancellation of the cycle before reaching its completion to avoid such hyperstimulation. [9]

Currently, in many assisted reproduction centers, for safety and proven efficacy, ovulation is only induced to donors with a GnRH analog when the protocol selected is with an antagonist. The first work published in this regard was in 2006 by Acevedo B. et al, the number of donors studied was small (60 patients), in half of them ovulation was induced with hCG and in another half an analogue of GnRh (0.2 mg of triptorelin) was used for this purpose. It was shown that there were no significant differences in the number of oocytes recovered in metaphase II, the percentage of fertilization, pregnancy and implantation by transfer between oocyte recipients whose embryos came from donors in

which the final maturation of the ovule was triggered with hCG, with respect to who received an analogue of GnRh. Therefore, it can be deduced that the GnRH analog produces intense luteolysis in the donor's ovary, but its embryos have no compromised implantation capacity in the uterus of the recipient woman. [10]

GnRH agonist to prevent the development of OHSS

OHSS is one of the most serious iatrogenic complications of ovulation induction in assisted reproductive treatments. The patients who are most at risk of developing it are young females with a PCOS and women with a high sensitivity and ovarian response to gonadotropins.[11] The incidence of severe OHSS is less than 1% and is associated with significant morbidity and rare mortality.[12]

Although the pathogenesis of ovarian hyperstimulation is not fully known, it is known that there is a notable increase in vascular permeability due to an increase in VEGF (vascular endothelial growth factor), hCG-dependent, both in blood and follicular fluid.[13] In this context, the use during the luteal phase of albumin, cabergoline[14] or the prolongation of the GnRH agonist has been proposed, but with none of them a significant difference is obtained regarding the incidence and intensity of the clinical manifestations. [15] The appearance of the GnRH antagonist opened an alternative route to the exclusive use of hCG in IVF cycles, since it allowed inducing ovulation with the GnRH agonist instead of hCG and thus avoiding OHSS. In 2000, Itskovitz-Eldor published the first study where the administration of the GnRH agonist was proposed to induce oocyte maturation with LH as a mechanism to reduce the risk of hyperstimulationin IVF antagonist cycles.[4]

Therefore, it happened, since after the administration of the agonist there is a severe luteolysis in which there is a significant decrease in the concentration of steroids and peptides responsible for hyperstimulation. However, this strategy, which is good to avoid hyperstimulation, significantly worsens the percentage of embryonic implantation compared to the use of hCG.[16]

Several meta-analyses have confirmed this finding and conclude that the administration of GnRH agonist to induce ovulation is associated with a significant reduction in the probability of achieving clinical pregnancy. [17-19]The cause may be due to the fact that the low levels of endogenous circulating LH do not reach sufficient concentration to maintain the activity of the corpus luteum, to the inhibition in the expression of cytokines, to growth factors involved in the implantation, to the affectation of the endometrial function or by a direct effect of GnRH-a on granulosa cells and the oocyte.[17] Another possibility is that the embryos from oocytes matured with GnRH-a would have an impact on their implantation capacity. [20]

Protocols thatuse the Gonadotropin Releasing Hormone agonist (GnRH-a) in Assisted Reproduction Techniques

Traditionally the classic ovarian stimulation protocol has been known as the long protocol with GnRH agonists, with good results for a long time.With the emergence of GnRH antagonists, new possibilities were opened in controlled ovarian stimulation protocols in females at risk of suffering from OHSS or

donors.[21] The utility of a GnRH bolus in ovulation induction has already been described decades ago in ovulation induction treatments.Thus, a concept is introduced in which, within a protocol with GnRH antagonists, a bolus of GnRH agonist is used to induce the final ova maturation and trigger ovulation.[22] The protocol can be administered in a single dose or in a multiple dose, the latter being the most widely used.Ovarian stimulation begins on the 2nd or 3rd day of menstruation and, from the sixth day or since the follicle is 14 mm or more, it starts with 0.25 mg of GnRH antagonists.The control is done through the ultrasound monitoring of the patient until the time of ovulatory discharge with a bolus of GnRH agonists.0.3 mL triptorelin or 0.2 mL of leuporelin was administered.In this case and, since pregnancy rates are significantly lower than in fresh transfer, vitrification of the embryos obtained is recommended.

In the multicenter randomized study by *Fauser* and others, they compare the effect of two types of GnRH-agonists (Triptorelin and Leuporelin) with hCG, under a controlled ovarian stimulation with recombinant FSH and antagonist GnRH and a luteal support based on vaginal progesterone.

Humaidan P study describes that a bolus of GnRH agonist as a final inducer of ovulation and oocyte maturation seems to be effective in normoresponding patients included in an IVF cycle.[23]

Final maturation induction

The final maturation induction of the oocyte is a method usually carried as a part of ovarian hyperstimulation controlled to create fully developed of the oocyte and resulted of optimal pregnancies chances, basically it is a luteinizing hormone wave replacement whose effects include final maturation in natural menstrual cycles.Human chorionic gonadotropin and GnRH agonists is the main medications that used final maturation induction. In the cycles followed by oocyte donation, the risk of OHSS were decreased when using GnRH agonists instead of HCG.[24]

Aim of the study:

To determine the differences betweentrigger by human chorionic gonadotropin and gonadotropin releasing hormone agonist regarding number of mature oocytes ,fertilization rates and embryos quality.

Method:

A retrospective cohort study carried in the Fertility center- AL Sadder Medical city- AL Najaf Iraq, in the period from Jan 1, 2019 to the end of Dec. 2019. 40 patients were enrolled in the current study within the age between 20-35 years old. women were analyzed and then divided into 2 groups each one with (20) patients, first group (group A) using GnRH agonist(Decapeptyl) and group B using hCG. Stimulation of the ovary was started with FSH from day 2 or 3 of the cycle and sustaineduntilthe day of ovulation induction, and by using ultrasound scanning the monitoring of cycles were done.When the leading follicle measured14 mm diameter, patients administer the GnRH antagonist. Then after 2 follicles at least reached the diameter of 18mm the trigger of final oocyte by administering 0.2 mg Decapeptyl for case group ,and 10.000 IU ofHCG for control group. Oocyte pick-up was achieved 35 h and 30 min after triggering. ICSIwere done in all patients. On the 2nd or 3rd the Embryos were

evaluated, and up to embryos were transferred. For luteal phase support, all patients received micronized progesterone vaginally. Biochemical pregnancy was detected by measuring β-hCG levels on Day 12 after embryo transfer. All the data was recorded in medical record.

Ethical concept: all respondents signed a written informed paper after we informed them about the purpose of the study and all this information with confidentiality.

Statistical analysis:

Data entered by the researcher by use of computerized statistical software; Statistical Package of the Social Sciences (SPSS) version 23. Descriptive statistics are presented in the form (mean ± standard deviation). One-way ANOVA analysis was used to compare more than two means. In all statistical analyzes, the significance level (p-value) was set at ≤ 0.05 and the result was presented in tables and / or graphs.

Results

Forty patients were included in the current study; Decapeptyl triggered half of them and the other half-triggered by HCG. The mean age of the group A was (28.1±5.47) years and group B was (28.9±5.3) years and with no significant differences found. BMI of the group A was (23.2±1.7) and (24.0±1.48) for group B with no difference. Oligospermia is the major cause of the infertility in-group A, while oligoasthenospermia in the group B and no significant association were found regarding the cause of infertility between the studied groups (table 1 and figure 1).

Table1: Patients characteristics.

Domain	Trigger by Decapeptyl (group A) (n=20)	Triger by HCG (group B) (n=20)	P Value
Age mean±SD	28.1±5.47	28.9±5.3	0.6
BMI	23.2±1.7	24.0±1.48	0.1

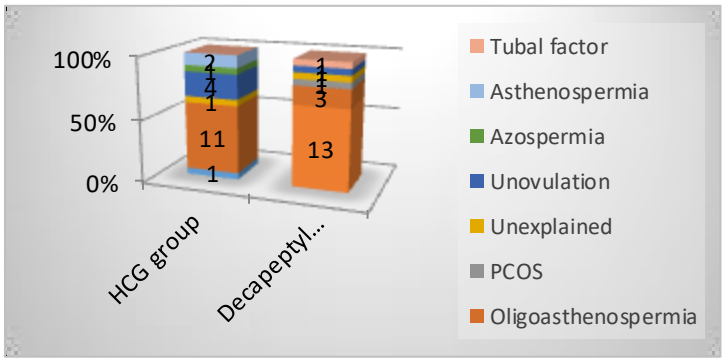

Figure 1: Patients characteristics depending on HCG and Decapepeptyl

Table 2 show that there is significant highly increase in number of follicles and estradiolin-group A than that in group B. no difference were found between the studied groups among the endometrial thickness at day of trigger.

Table 2: At day of trigger

Domain	Triger by Decapeptyl	Triger by HCG	P value
No. of follicles ≥ 15-17 mm	7.05±3.5	4.3±3.3	0.01
No of follicles ≥ 18 mm	11.25±6.2	6.75±2.5	0.004
Estradiole at triggerpg\ml	2776.4±615.5	1928.4±851.2	<0.001
Endometrial thickness at day of trigger	10.725±1.32	10.375±1.07	0.3

After the trigger by both decapeptyl and HCG we found that there is highly significant increase in: number of oocytes collected, MII oocytes, fertilized oocytes, cleaved embryo, transferred embryos, and number of frozen embryo in group A that triggered by decapeptyl than group B that triggered by HCG. While number of embryo in grade V were associated with group B (table 3).

Table 3: Different variables after the trigger.

Domain	Trigger by Decapeptyl	Trigger by HCG	P value
No. of oocytes retrieved	14.15±6.98	8.45±3.8	0.002
No. of MII oocytes	11.2±6.5	6.7±3.3	0.008
No. of fertilized oocytes	6.8±3.9	4.45±2.01	0.02
No. of cleaved embryos	6.2±3.9	3.9±1.99	0.02
Embryo grade I	3.7±2.6	2.65±2.05	0.1
Embryo grade II	1.9±1.7	0.95±1.05	0.1
Embryo grade III	0.6±1.046	0.25±0.55	0.19
Embryo grade IV	0.0	0.0	-
Embryo grade V	0.0	2.75±1.37	<0.001
No. of transferred embryos	1.9±1.48	0.8±1.36	0.01
No. of frozen embryo	3.4±3.67	0.8±0.13	0.003

As shown in figure 2 the pregnancy rate in this study were found in 4/20 (25%) in-group A, while in-group B were found in 7/20 (35.0%) of the patients.

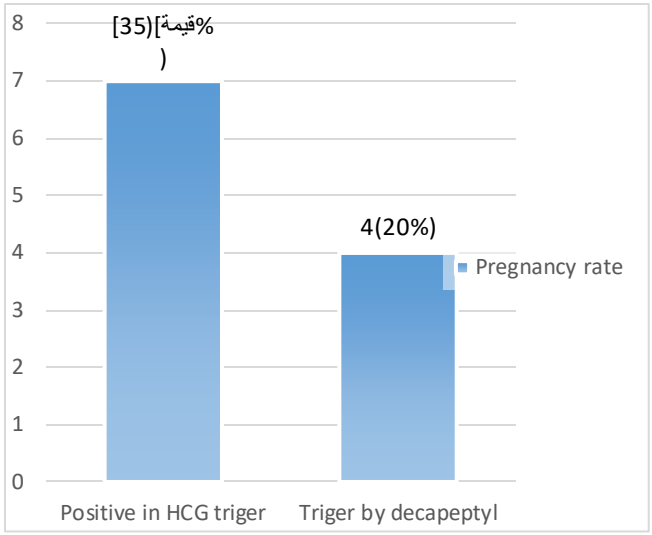

Figure 2: Pregnancy rate in studied group

Discussion:

Humaidan P, believed that ovarian stimulation with GnRH antagonist protocol and then followed by GnRH-a trigger is appropriate protocol for donors.[23] All oocyte donors are in the risk of initial OHSS. Oocyte donors are frequently females in young age group, with good ovarian reserve to products oocytes in a large number, so the opportunity of OHSS in these isn't assessed less than normal. The benefits of using GnRH-a trigger in these groups of patients included in the study to reduce the ovarian volume, reduce of lower abdominal distension and a short period of the luteal phase.[25,26]

The current study revealed that there is no case of OHSS in both groups of the study, while in a study concluded by Permana A et al, when one case of OHSS in HCG group found in his study.[27]Kol S et al study mentioned thatone foremost benefit of the trigger by GnRH agonists could reduce the incidence rate of OHSS. [28]

In a clinical trial carried by Humaidan P et al, included 118 subjects when average of 14 oocytes were taken from the women found that OHSS was stated to be 3% in group of HCG trigger and no cases were found in group triggered by GnRH-a. [29]

Alike studies were achieved byRadesic B and lliodromiti et al, in which a high level of OPR and low levels of miscarriage were found in GnRH-a trigger group, resulting in both studies for delayed OHSS 1.4% and 0.72%, respectively.[30,31]

Pregnancy rate in the current study was (35%) in HCG group, which is more than that in Decapeptyl group when it represents (25%). Which is less than that found byPermana A et al,when the pregnancy rate was (67.72% in GnRH agonist and 61.32% in hCG group)[27]

Kol S, and Humaidan P. mentioned that LH and FSH surge in normal cycle, and its surge more supportive in oocyte maturation process when compared with the LH surge only in the use of hCG to trigger ovulation.[28, 29]

In many studies carried previously mentioned that when they used of GnRH-a in the final oocyte maturation this will give a results similar or better than that from usinghCG trigger.[2] The trigger by GnRH-a in addition to its stimulate LH it will also stimulate the follicular stimulating hormone surge. In a study done by Lamb et al found that better oocyte recovery with higher rate of fertilization in IVF when they adding a dose of FSH compared to the results when using HCG trigger only. [32]

Conclusion:HCG were better than GnRH agonists for use as a trigger final oocyte maturation in the antagonist protocol.

No conflicts of interest

Self-funding source

Ethical clearance: from the Ministry of health and Environment/ scientific committee.

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