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EFFECT OF ADMINISTRATION OF SINGLE DOSE GNRH AGONIST IN LUTEAL PHASE ON CLINICAL PREGNANCY OF FRESH ICSI CYCLES

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Abstract

Background: Outcome in assisted reproductive technique (ART) treatment. However, with great effort to improve this outcome is still limited. In fact, among cases transferred with one or more embryos, less than one-third results in a live birth. Adequate luteal phase support is one of the satisfactory solutions to improve implantation and pregnancy rates because luteal phase in fresh cycles is deficient. It is well established that following ovarian stimulation is an insufficient luteal phase. LH concentrations are low during the luteal phase due to negative feedback on pituitary gland of supra-physiological serum levels of steroids which are secreted by multiple corpora lutea. LH plays an important role to sustain corpus luteum function in addition to enhance angiogenic factors, growth factors, and cytokines that may help the implantation. Inhibit LH release results in premature luteolysis or significant reduction in the luteal phase length. GnRH agonist has been reported debatably to support the luteal phase. On the one hand, it is believed that GnRH-antagonist with a suitable dose may retain its stimulatory effect to reserve LH production to support the luteal phase. Moreover, GnRH-agonist may have a direct effect on embryos for successful implantation.

Objective: To explore whether the addition of a mid-luteal bolus of GnRHa improves the clinical pregnancy rate in fresh ICSI cycle.

Patients and methods: A prospective randomized comparative study was implemented on 80 infertile women. Those patients were categorized into two groups: (40) patients as study group received GnRh-agonist (Decapeptil 0.1 mg), in addition to standard luteal phase support (LPS) in leutel phase, three day after embryo transfer ET (day three embryo development, grade one), to increase the pregnancy rate in IVF; and their control group (40) received standard luteal phase support only.

Results: There was no significant difference in the general characteristics of the patients in both groups (the study group and the control group) such as age, weight, type of infertility (primary or secondary), cause of infertility, and duration of infertility. There is an increase in clinical pregnancy rate in study group that received GnRha hormone 3 days after the embryo transfer, in addition to the standard luteal phase support (LPS) in secretory phase of the fresh ICSI cycles than the control group which received (LPS) only in secretory phase, although no statistical evidence was reached ($p > 0.05$).

Conclusion: There is evidence that GnRH agonist administration in luteal phase improve the clinical pregnancy rate in fresh ICSI cycle, but not reach statically significance. Larger sample size studies and a meta-analysis are required to establish the role of GnRHa in the luteal phase of ICSI cycle.

Keywords: *luteal phase support, GnRh-agonist, LH, clinical pregnancy.*

Introduction

One of the major problems faced couples during their life is the problem of infertility. Infertility problems signify challenge for reproductive medicine. The worldwide prevalence of infertility is reported to be 10%-15% [(1)]. According to updated international glossary on infertility and fertility care, sterility is defined as "a disease characterized by the failure to establish a clinical pregnancy after 12 months of even, unprotected sexual intercourse or due to damage of a person's capacity to reproduce either as an individual or with his/her partner" [(2)]. Management of infertility includes sterility counselling, medical and or surgical treatment of fundamental cause, fertility medications, and assisted reproductive technologies (ARTs) [(3)]. Assisted reproductive technologies (ART) is defined as all interventions that contain the *in vitro* handling of both human oocytes and sperm or of embryos for the reason of reproduction. This contains *in vitro* fertilization (IVF) and embryo transfer (ET), intracytoplasmic sperm injection (ICSI), embryo biopsy, preimplantation genetic diagnosis (PGD), assisted hatching, gamete intrafallopian transfer, zygote intrafallopian transfer, gamete and embryo cryopreservation, semen, oocyte and embryo donation [(4)]. Despite the significant developments in ART that have overwhelmed many underlying causes of infertility, pregnancy outcome rates remain comparatively low [(5)]. IVF defined as "a series of procedures that involves extracorporeal fertilization of gametes. It contains conventional *in vitro* insemination and ICSI" [(2)]. The success of IVF is determined by positive harvest in a sequence of IVF stages, including controlled ovarian stimulation (COS), ovum pick-up (OPU), insemination, embryo transfer, and implantation [(6)]. In assisted reproductive technique (ART) therapy, successful implantation is a must-have result. Despite great efforts to change, this result remains minimal. In fact, only about a third of cases involving one or more embryos result in a live birth [(7)]. Since the luteal phase in fresh cycles is inadequate, adequate luteal phase support is one of the appropriate solutions to increase implantation and pregnancy rates [(8)]. It is well established that there is an inadequate luteal period after ovarian stimulation [(9)]. Because of supra-physiological serum levels of steroids secreted by several corpora lutea, LH concentrations are poor during the luteal process due to negative feedback on the pituitary gland. LH is essential for maintaining corpus luteum function and enhancing angiogenic factors, growth factors, and cytokines that can help with implantation [(10)]. LH inhibition causes premature luteolysis or a major shortening of the luteal process [(9)]. As a result, fertility treatment with new cycles necessitates more luteal support. GnRH agonist (GnRHa) has been shown to help with the luteal process. On the one hand, it is thought that GnRHa, given at the right dosage, can maintain its stimulatory effect, allowing LH development to continue during the luteal process [(11)]. GnRHa can also have a direct effect on early embryos, enhancing implantation. Some early meta-analyses identified a positive impact of mid-luteal GnRHa administration [(12)].

Methods

This prospective comparative study was done on eighty infertile females who were undergoing intracytoplasmic sperm injection (ICSI) at the infertility center of High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/ Reproductive Physiology / Al-Nahrain University / Baghdad/ Iraq, during the period from November 2018 until September 2020 regardless to the presence or absence of previous Assisted Reproductive Technologies (ART) trials. A written informed consent was obtained from each participant. The morphological assessment of the oocytes aspirated from the ovaries of infertile females and their resulting embryos was done in the ICSI laboratory of the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies. The measurement of serum hormones was done using miniVIDAS in a private laboratory.

The study design, sample size, and selection criteria

The present study enrolled 80 infertile females undergoing ICSI cycles with an age range of 23 to 40 years and an infertility duration ranging from 4 years to 13 years. Women with both primary and secondary types of infertility were included. Some women have experienced IVF/ICSI cycles before while others have not. A number of enrolled women

were complaining of polycystic ovarian syndrome (PCOS), other women had blockage of fallopian tube. A number of couples had male factor infertility or combined causes or unexplained infertility.
The study was designed to be a comparative prospective study.
The selected 80 women are randomly divided into two groups:

1. **Study group:** 40 women undergo antagonist protocol with human chorionic gonadotrophin (HCG) trigger, received single dose of GnRHa (Decapeptil 0.1 mg) on day 6 after ova pick-up (OPU), in addition to standard luteal phase sport (LPS).
2. **Control group:** 40 women undergo antagonist protocol with human chorionic gonadotrophin (HCG) trigger received standard luteal phase support only (LPS).

Inclusion criteria: Infertile women 23-40 years old, Females underwent antagonist protocol with hCG trigger, Infertile females with normal ovarian reserve documented by AMH that should be at least within the satisfactory or normal ovarian reserve, AFC, FSH and E_2, Couples with unexplained infertility, Male factor infertility except those with non-obstructive azoospermia, patients with patent or non-patent tubes, but no uterine pathology.

The parameters measures:

1. The effect of GnRh agonist on ICSI.
2. The biochemical pregnancy rate in the study group. The biochemical pregnancy is diagnosed when HCG level >50IU 14 days or more after embryo transfer with no visible gestational sac on ultrasound examination.
3. The clinical pregnancy rate in the study group. The clinical pregnancy is diagnosed when one or more gestational sac with detection of fetal heart in sonography 5-6 weeks.

Results

There was no significant difference in the general characteristics of the patients in both groups (the study group and the control group) such as age, weight, type of infertility (primary or secondary), cause of infertility, and duration of infertility. Also there was no significant difference in total oocytes number, mean metaphase II oocytes %, mean metaphase I %, mean germinal vesicle oocyte %, mean cleavage rate, mean grade I embryo %, mean grade II embryos %, mean serum hormones level pre and post ova pickup between both groups (study and control group) ($p > 0.05$). There is an increase in clinical pregnancy in study group that received GnRha hormone 3 days after the embryo transfer, in addition to the standard luteal phase support (LPS) in secretory phase of the fresh ICSI cycles than the control group which received luteal phase support (LPS) only in secretory phase, although no statistical evidence was reached ($p> 0.05$).

Discussion

Luteal phase defect has been a well-known problem in ART. Many studies have proposed the positive effect of GnRH agonist as standard luteal phase support (LPS). This study was designed to be a comparative prospective study, which investigated the effect of single dose of gonadotropin releasing hormone antagonist GnRHa (Decapeptil 0.1 mg) on day 6 after ova pick-up or day 3 after embryo transfer in addition to LPS support on the outcome of ICSI in infertile women undergo antagonist protocol with HCG trigger. One merit of current study is that the study population consisted of infertile patients aged not more than 40 years old, with regular menstrual cycle and with both ovaries present and normal uterus plus no history of chronic disease. In this study show no significant difference in demographic features (age, BMI, duration, type and causes of infertility) between the study and control group, all findings were comparable between the two groups to assure statistical matching and reduce any variations that may affect the outcome of the study. Indeed, the substantial bulk of data are present in infertility literature discussing the role of age, duration, type, and cause of infertility in association with pregnancy outcome following ICSI cycles.

Positive pregnancy and clinical pregnancy rate

Positive pregnancy rate diagnosed when HCG level > 50 IU 14 days or more after embryo transfer with or without visible gestational sac on ultrasound examination [(13)]. In the current study, although there was slightly higher positive pregnancy rate in the

study group [17 (42.5 %)] in comparison to the control group [13 (32.5 %)]. But the result failed to reach statistical significant (*P* = 0.356). This result was in agreement with previous studies like [14]. Clinical pregnancy was defined as a positive serum β-HCG test with ultrasound evidence of a gestational sac and fetal heart beat at 5 weeks after oocyte pick-up while clinical pregnancy rate was defined as a positive serum β-HCG test with ultrasound evidence of a gestational sac and fetal heart beat at 5 weeks after oocyte pick-up divided by the number of embryos transferred [13]. In the current study, although clinical pregnancy rate in the study group [12 (30 %)] was higher than control group [5 (12.5 %)], but the difference was not significant (P = 0.056). On the basis of our results, it is possible that administration of GnRHa in the luteal phase may improve clinical pregnancy rate. It may be argued that delaying the GnRHa injection to day 6 in the luteal phase may be the reason for not improving the pregnancy rate [15]. Several studies have reached similar conclusions. Ata study (large randomized double blind study) found clinical pregnancy rate were similar in GnRH agonist (Single 0.1 mg triptorelin administration 6 days after ICSI) and placebo groups following ovarian stimulation with the long GnRH agonist protocol [15]. The continuous administration of the GnRHa in the luteal phase will continue the down regulated state of the GnRH receptors in the reproductive organs (i.e. GnRH receptor in the endometrium is saturated) which may cause ineffectiveness of GnRHa in improving the pregnancy rate, whereas adding GnRHa to a GnRH antagonist cycle may show different results [16]. Bellver study (a randomized controlled trial) detected no significant difference in clinical pregnancy rate and ongoing pregnancy per randomized patient in GnRH agonist (triptorelin) group administered at the time of implantation and control group [17]. Inamdar and Majumdar study (prospective randomized controlled study) found no significant difference in clinical pregnancy and ongoing pregnancies rates between the GnRHa group (three daily doses of Lupride 1 mg subcutaneously administered 6 days after oocyte retrieval) and placebo groups in cycles stimulated with the long GnRH agonist protocol [16]. Yildiz study (a randomized clinical trial) reported the clinical pregnancy and the ongoing pregnancy rates were similar in among the groups A (received one Leuprolide acetate injection 3 days after embryo transfer), B (received two Leuprolide acetate injection 3 and 6 days after embryo transfer) and control group that received only the routine luteal phase support following controlled ovarian stimulation with long luteal GnRH agonist protocol, the difference was not significant among the groups [18].

Conclusions

In conclusion, the addition of a mid-luteal single dose GnRH-agonist (Decapeptil 0.1 mg / triptorelin) on day 6 after ova pickup or three days after embryo transfer (Day three embryo, grade one, one or more embryo transfer), in addition to standard luteal phase support (LPS) improved the clinical pregnancy rate of fresh ICSI cycles in the infertile women undergo antagonist protocol, with hCG trigger put it is statically not significant. Larger sample size studies and a meta-analysis are required to establish the role of GnRHa in the luteal phase of ICSI cycle.

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Table 1-1: Comparison of demographic features between study and control groups

Parameters	Control group	Study group	*p* value
Age (years) (Mean ± SD)	30.78 ± 4.35	29.2 ± 4.03	0.097 ₸
BMI (kg/m²) (Mean ± SD)	28.49 ± 2.51	27.43 ± 1.98	0.076 ₸
Duration of infertility (years) (Mean ± SD)	3.12 ± 1.85	2.26 ± 1.71	0.087 ₸
Type of infertility	Primary 20 Secondary 20	Primary 20 Secondary 20	1.00 ¥
Causes of infertility			
Male factor (MF)	13 (32.5%)	9 (22.5%)	0.484 ¥
Ovulatory disorders	10 (25 %)	14 (35%)	
Tubal factor	10 (25%)	7 (17.5%)	
Unexplained	7 (17.5%)	10 (25%)	

SD: Standard deviation; BMI: Body mass Index; ₸: Independent sample t test; ¥: Chi square.

Table 1-2: Comparison of pregnancy outcome between control & study groups

Parameter	Control group (N.)(%)	Study group (N.)(%)	*p* value
Positive pregnancy	13 (32.5%)	17 (42.5 %)	0.356 ¥
Clinical pregnancy	5 (12.5 %)	12 (30 %)	0.056 ¥

¥: Chi square.

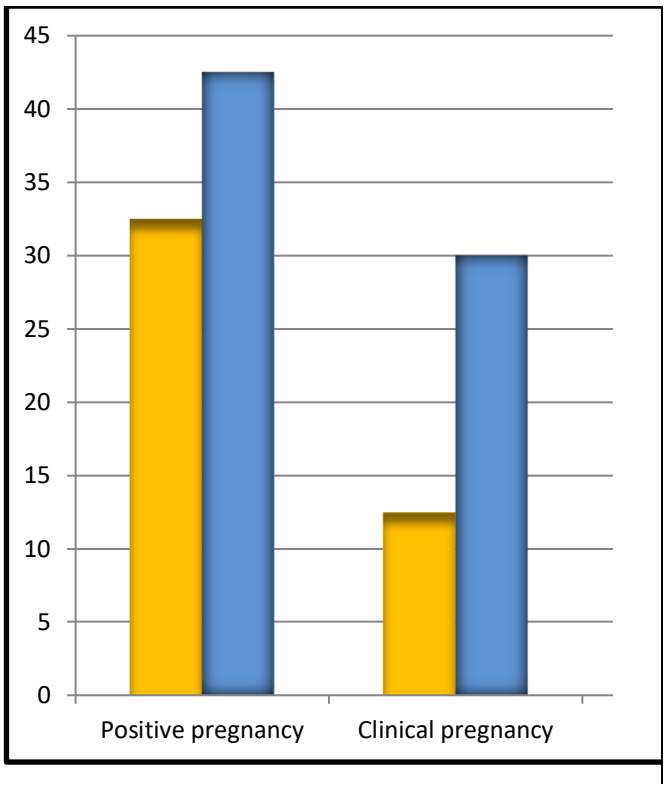

Figure 1-1: Comparison of pregnancy outcome between control & study groups

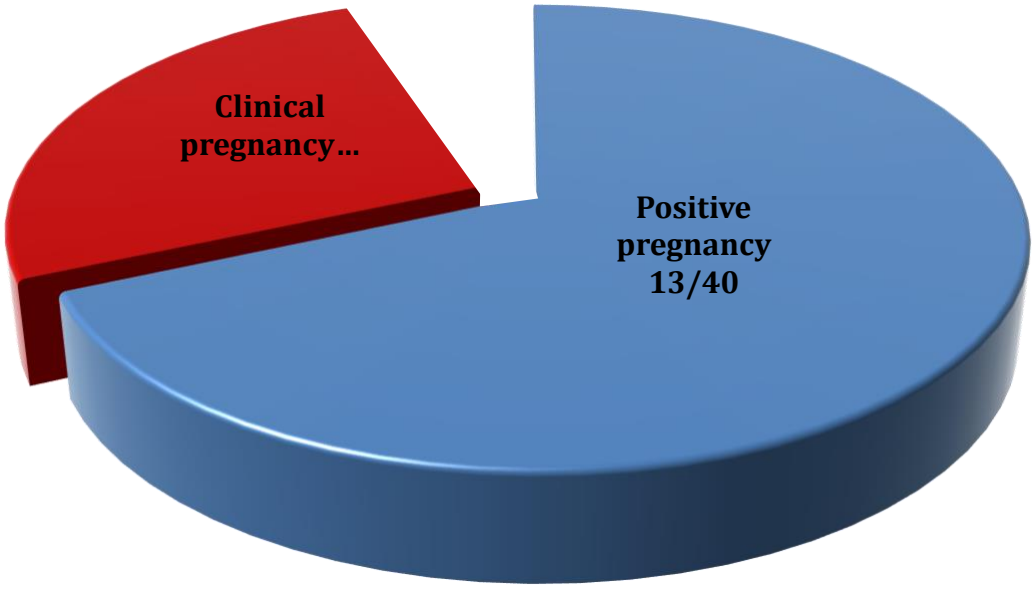

Figure 1-2: Comparison of pregnancy outcome in control group