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Adding Low Dose hCG to rFSH in GnRH Antagonist ICSI Cycles: A Randomized Controlled Trial

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ABSTRACT

Inhibition of luteinizing hormone (LH) by gonadotropin releasing hormone (GnRH) antagonist may lead to suboptimal response during ovarian stimulation. In addition, several studies suggest that low level of LH is associated with lowered fertilization and implantation rate and increased early pregnancy loss rate. The aim of this study is to study the effect of adding low dose human chorionic gonadotropin (hCG - 200 IU), as an LH supplement, to recombinant follicle stimulating hormone (rFSH) in a GnRH antagonist cycles in women undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment. Sixty-three infertile women undergoing IVF were randomly divided into two groups. One group was stimulated with the conventional stimulation protocol (rFSH alone), while the second group received 200 IU hCG in addition to rFSH in the late follicular phase (hCG + rFSH). Both groups' results including pregnancy rate, total dose of rFSH required, duration of stimulation, endometrial thickness, oocytes and embryos characteristic, serum hormone levels (Testosterone, Estradiol, Progesterone, and LH) and level of epidermal growth factor (EGF) were compared. The results show that pregnancy rate among the group of women who received the low dose hCG was higher than those who did not receive hCG. However, this difference did not reach statistical significance. Furthermore, other cycle outcomes and hormonal values were comparable between the two stimulation protocols.

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KEYWORDS

GnRH antagonist, Late Follicular Phase, Low Dose hCG, Ovarian Stimulation, LH

1. Introduction

Gonadotropin releasing hormone (GnRH) antagonists are now used more than GnRH agonists in the in vitro fertilization (IVF) stimulation protocols (**Efstratios, et al.** [1]). Unlike GnRH agonists which require prolonged period of administration, GnRH antagonists cause immediate suppression of gonadotropin release from the pituitary gland (**Tarlatzis, et al.** [2]). Additional benefits include reduction in the dose of recombinant follicle stimulating hormone (rFSH) required for ovarian stimulation, shorter duration of treatment and reduced rate of Ovarian Hyperstimulation Syndrome (OHSS) (**Griesinger, G.** [3], **Khalaf, et al.** [4]). However, GnRH antagonists cause profound suppression of luteinizing hormone (LH) which occurs when the developing follicle is highly sensitive to LH (**Griesinger, et al.** [5]). It was found that during GnRH antagonist protocol, the levels of serum LH and estradiol were inversely proportional to the dose of GnRH antagonists (**Gardner, et al.** [6]). The two-cell two-gonadotropin theory indicates that both follicle stimulating hormone (FSH) and LH are essential for normal follicle development and steroidogenesis; LH controls the final stages of follicle development, oocyte maturation, ovulation, and support of the corpus luteum; and also stimulates the theca cells to produce androgen, while FSH promotes follicle growth and development and stimulates granulosa cells' aromatase enzyme to convert the androgen produced by the theca cells into oestrogen (**Barbieri, RL** [7], **Hillier, et al.** [8]). Despite the fact that rFSH is the most important gonadotropin, there is a major debate about the importance of adding LH activity to ovarian stimulation protocols used in IVF (**Propst, et al.** [9]). Moreover, the minimum threshold level of endogenous LH necessary for normal folliculogenesis is still not known. However, several studies suggested that the low levels of endogenous LH might lead to suboptimal cycle outcomes (**Urman, et al.** [10]). It was found that the addition of supplementary LH to the GnRH antagonist stimulation, lead to higher fertilization rate (**Acevedo, et al.** [11], **Alviggi, et al.** [12]). Likewise, the addition of LH (in the form of low dose of Human Chorionic

Gonadotropin (hCG)) has been found to promote both follicular growth and oocyte development, and hence lower ampules of rFSH required for ovarian stimulation (**Van Horne, et al.** [13]). Nevertheless, other studies showed no significance in the addition of hCG to the GnRH antagonist standard protocol results (**Filicori, et al.** [14], **Serafini, et al.** [15]). Although both regimens are being used nowadays, the controversy of whether hCG should be added to the protocol or not is still standing. Here, we aim to test the hypothesis that the addition of LH supplements in the form of low dose hCG during GnRH antagonist cycle is beneficial. The primary outcome was to compare the pregnancy rate between two protocols. Other factors including the number of oocytes collected, number of MII oocytes, number of good quality embryos, endometrial thickness, fertilization rate and the required rFSH dose, were all compared between the two study groups and considered as secondary outcomes. Epidermal growth factor and hormones (estradiol, progesterone, androgen, and LH) were compared between the groups as well.

2. Materials and Methods

The target subjects for this study were female patients attending the High Institute for Infertility Diagnosis and Assisted Reproduction Technologies in Al Nahrain University; who were presented for intracytoplasmic sperm injection (ICSI) treatment. Approval for the study was provided by the Local Medical Ethical Committee. All participating individuals signed an informed written consent. The study included 63 women who were selected according to a pre-set inclusion criteria that included; standard indication for ICSI, age between 20 to 40 years old, perceived infertility of more than one year, level of early follicular phase FSH was < 10 mIU/mL, and level of Estradiol was < 60 pg/mL. Excluded cases were women with obesity (having body mass index (BMI) > 30), ovarian or uterine pathologies, or endocrine disorders. Besides, any woman with history of poor response to previous IVF cycles or history of OHSS had been eliminated from the study (**Ferraretti, et al.** [16]). Patients were randomly divided into two groups. One group was given hCG (200

IU at the late follicular phase) in addition to rFSH while the other group did not receive hCG and were stimulated with rFSH alone. All participants first underwent full clinical assessment including medical history, general physical examination, pelvic and transvaginal ultrasound examination, BMI calculation, and hormonal assays at day two of the menstrual cycle. Male partners' seminal fluid was also examined.

2.1. ICSI Protocol

Participants went through the GnRH antagonist protocol, as shown in **Figure 1**. Patients in both groups received 150-300 IU of r-FSH (Gonal-F® Serono Laboratories, Germany) subcutaneously starting on day 2 or 3 of the menstrual cycle. When at least two follicles reached 13 mm in size, GnRH antagonist (Cetrotide® Serono Laboratories, Inc.) was administered at a dose of 0.25 mg daily until the ovulation trigger day. The initial starting rFSH dose was based on individual's clinical conditions (age, BMI, antral follicle count (AFC)) and previous ovarian response to stimulation. Dose was then adjusted according to patients' response monitored by ultrasound and serum E2 levels. The study group were also given 200 IU daily subcutaneous (SC) injections of hCG (Diclair® HP-hCG, Germany) starting with the Cetrotide® administration. While the control group did not receive the hCG. Pelvic ultrasound examination was carried out to assess the ovaries and endometrial thickness in response to stimulation. Blood samples were collected on the day of ovulation trigger and on day of oocyte pickup (OPU). Afterward, when at least two follicles reached 18 mm, all the previously mentioned drugs were stopped and ovulatory dose of hCG (Ovitrelle®, Germany) was given to all patients at a single dose of 2 ampoules of 250 µg subcutaneously. Oocyte's pick-up was undertaken 34-36 hours later and ICSI was performed with the husband's sperm. Three to five days later, embryo transfer was performed and luteal support was started.

2.2. Hormonal Analysis

Baseline hormone levels were measured at the early follicular phase (day 2 or 3 of the menstrual cycle) which was achieved using

enzyme linked fluorescent assay (ELFA) technique, via TOSOH analysis equipment. Hormonal assays (LH, progesterone, estradiol, testosterone and epidermal growth factor) were also performed on serum samples collected on the day of ovulation trigger and OPU for patients in the hCG group, while patients in the non-hCG group had their serum checked only on the day of OPU.

3. Statistical Analysis

In this prospective randomized controlled trial, statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) and Microsoft Office Excel 2010. Normality was tested in data sets before the utilization of chi-square and student t-test. P-value was set to <0.05.

4. Results

4.1. Pregnancy Rate

The pregnancy rate among the two groups is shown in **Table 1**. Percentage of pregnancy among patients in the hCG group was higher than in the non-hCG group (37 % vs 16 %, respectively). However, this difference was non-significant statistically speaking (p=0.06).

4.2. Hormones' Profile

Serum levels of LH, progesterone, oestrogen, testosterone, and epidermal growth factor were measured on the day of OPU and compared between the two study groups, as shown in **Table 2**. Although not statistically significant, the level of E2 was higher in patients who received hCG as compared to those who did not. Serum levels of all other hormones were almost comparable between the two groups of patients.

4.3. Ovarian Stimulation Characteristics

The duration of stimulation and the total required dose of rFSH were similar between the two study groups. The average endometrial thickness, measured on the day of ovulation trigger and the day of OPU, among patients who received hCG was higher than those who did not, but this difference did not reach statistical significance, as shown in **Table 3**.

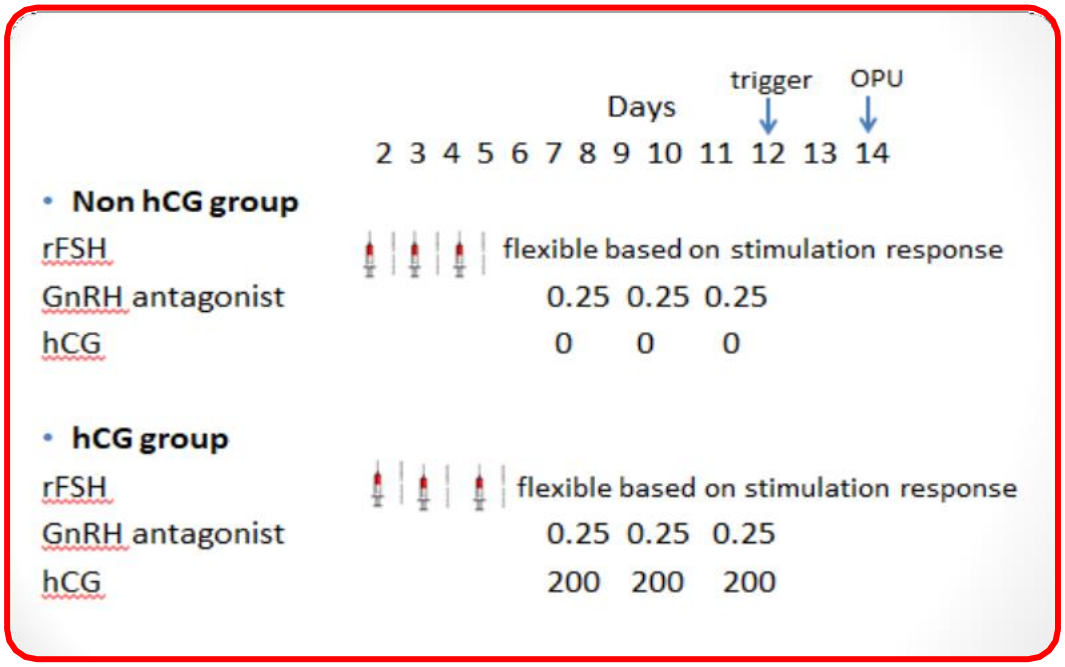

Figure (1): Stimulation protocols using the conventional GnRH antagonist protocol

Table (1): Pregnancy Rate among the study groups

	hCG + rFSH (n=27)	rFSH alone (n=36)	Total	P value
Positive PT	10	6	16	0.06
Negative PT	17	30	47	
Pregnancy rate	37 %	16%	25%	

Table (2): Serum hormone levels measured on the day of OPU

	hCG + rFSH (n=27)	rFSH alone (n=36)	P value
LH (IU/L)	4.65 ± 1.25	5.03 ± 1.84	0.11
Progesterone (ng/ml)	5.63 ± 4.18	7.39 ± 4.07	0.22
Oestrogen (pg/ml)	1671.1 ± 953.5	1108.68 ± 941.87	0.21
Testosterone (pg/ml)	1.03 ± 0.51	0.68 ± 0.49	0.14
EGF (pg/ml)	47.66 ± 22.62	74.48 ± 34.86	0.24

n: number of patients, PT: Pregnancy Test, hCG: human Chorionic Gonadotropin, rFSH: recombinant Follicle stimulating hormone. Mean ± SD, EGF: Epidermal Growth Factor.

Table (3): Ovarian stimulation characteristics

	hCG + rFSH (n=27)	rFSH alone (n=36)	P value
rFSH dose (IU)	1273.66 ± 236.46	1322 ± 331	0.47
Duration of stimulation (days)	8.46 ± 1.37	8.3 ± 1.4	0.55
ET (mm) day of trigger	10.22 ± 1.67	9.21 ± 1.2	0.57
ET (mm) day of oocyte pick-up	10.81 ± 1.55	10.03 ± 1.11	0.56

mm: millimeter

Table (4): Cycle outcomes of all patients in the study

	hCG + rFSH (n=27)	rFSH alone n: 36	P value
No. of oocytes collected	11.32 ± 4.96	12.73 ± 6.19	0.34
No. of mature oocytes	7.07 ± 2.82	7.61 ± 3.09	0.31
Number of fertilized oocytes	5.1 ± 2.64	5.5 ± 2.88	0.78
Fertilization rate per retrieved oocyte	73% ± 23.27	71% ± 22.45	0.7
Number of good quality embryo	2.57 ± 1.79	2.71 ± 1.72	0.83
No. of transferred embryos	3 ± 0.94	2.73 ± 1.15	0.63

4.4. Cycle Outcomes

The two groups had almost similar cycle outcomes which included the number of oocytes collected, number of MII oocytes, fertilization rate, number of good embryos and number of transferred embryos, as shown in **Table 4**.

5. Discussion

Nowadays, controlled ovarian stimulation for IVF uses different protocols according to the kind of GnRH analogues (agonist or antagonist) and the gonadotropins (**Bosch and Ezcurra** [17]). With regard to gonadotropins, although it is clear that LH plays a crucial role in the natural ovarian cycle, its role in controlled ovarian stimulation and the value of adding it to rFSH is still controversial. Some studies reported that adding LH to the ovarian stimulation protocols is of benefit in only special group of patients like older women and those with history of poor ovarian response in previous cycle (**Mochtar, et al.** [18]), while others suggested that adding LH to rFSH during controlled ovarian stimulation has no value (**Kolibianakis, et al.** [20]). Both hCG and LH have α and β subunits in their structure; the α subunit is similar, while the β subunit is different due to the different glycosylation pattern, which in turn results in different affinity for the LH/hCG receptors and different half-life between the two agents (**Cole, LA** [21]). Other studies preferred to add low dose hCG to provide LH activity because of the cost effectiveness and the fact that hCG is able to provide the biological activity of LH at very low doses (**Van Horne, et al.** [22]). In ovarian stimulation protocol, it has been shown that the lowest serum level of LH was reached in the late follicular phase as a result of inhibition by the GnRH analogue. In natural cycle, at this stage of folliculogenesis the granulosa cells LH receptors increase in the mature follicle as it becomes more dependent on LH than FSH. As a result, it has been proposed that the most appropriate time for adding LH/hCG to the stimulation protocol would be the late follicular phase (**Filicori, et al.** [23]). We aim here to study the effect of adding 200 IU hCG to rFSH during the late follicular phase in a GnRH antagonist ICSI cycles. This protocol was compared with women of the same age

group who were treated with rFSH alone regimen during GnRH antagonist ICSI cycles.

5.1. Pregnancy Rate

The results indicate that pregnancy rate improved by the addition of low dose hCG to ovarian stimulation protocol, although no significant difference was identified. This is consistent with the results of a pervious study which showed that the addition of low dose hCG to stimulation protocols did not have significant beneficial effect on pregnancy rate (**Aghahosseini, et al. [24]**). Moreover, data from previous research reported that the addition of low dose hCG has no significant beneficial effect in an unselected group of patients (**Humaidan, et al.** [22]). The latter study showed a significant improvement in pregnancy rate associated with the addition of LH to the stimulation protocol in women older than 35 years. Hence, including only young patients in this study could be the cause why pregnancy rate was not significantly improved by the addition of low dose hCG. Moreover, some research started low dose hCG simultaneously with rFSH (**Propst, et al.** [9], **Van Horne, et al.** [13]), while in the current study, hCG was given in the late follicular phase.

5.2. Required Dose of rFSH and Duration of Stimulation

The total dose of rFSH required for ovarian stimulation was comparable between the two study groups. Similarly, the duration of stimulation was almost the same. This is in contrast to what had been reported that adding low dose of hCG was associated with less total dose of rFSH and shorter duration of stimulation (**Filicori, et al.** [23], **Serafini, et al.** [15]). However, in the previous studies, rFSH was reduced to 75 IU at the start of hCH administration, whereas in this study, rFSH dose after adding hCG was kept the same.

5.3. Serum Concentration of Estradiol

Serum level of E2 measured on the day of ovulation trigger and the day of OPU was higher in the hCG group than in the non hCG group. Although this difference did not reach statistical significance, it is consistent with

previous data (**Gomaa, et al.** [24]). Low dose hCG could be the reason behind the rise in serum estradiol concentration. hCG stimulates theca cells androgen production which in turn form the substrate for oestrogen production by the granulosa cells. This direct relation between LH/hCG and the rise in serum estradiol has been confirmed in other studies (**Levi-Setti, et al.** [25], **Tarlatzis, et al.** [26]). Moreover, it has been noted that low serum LH level leads to low serum E2 concentration, impaired follicle development and poor reproductive outcomes (**Lahoud, et al.** [27], **O'Dea, et al.** [28]).

5.4. Other Serum Hormones and Epidermal Growth Factor (EGF)

There was no significant difference in the level of testosterone, LH, or progesterone between the two study groups. Similarly, the level of EGF was comparable between the two study groups. This means that adding LH activity in the form of low dose hCG had no significant effect on any of these hormones measured on the day of OPU.

5.5. Endometrial Thickness (ET)

Adding low dose of hCG to rFSH was not associated with significant increase in the average endometrial thickness both on the day of hCG trigger and pick-up. Tesarik et al. reported that adding hCG to the stimulation protocol increased the endometrial thickness by an average of 1.5 mm compared to the group who did not receive hCG (**Tesarik, et al.** [29]). However, it is worth mentioning that this inconsistency could be due to several reasons: the different patients' population, dissimilar interval and dose of hCG, different rate of endometrial growth and also the accuracy of ultrasound measurement.

5.6. Cycle Outcome

There was no significant difference in the number of oocytes collected from patients in the two groups. Similarly, the number of mature oocytes (MII), fertilization rate and number of good quality embryos were almost the same between the two groups. This finding

agrees with the findings from other studies (**Serafini, et al.** [15]).

6. Conclusions

In GnRH antagonist protocol, adding low dose of hCG to rFSH in the late stages of follicular development is associated with higher pregnancy rate compared to the rFSH-alone, the difference almost reaches statistical significance (p=0.06). On the other hand, the duration of stimulation, total dose of rFSH required for stimulation, hormonal profile, endometrial thickness and other oocytes and embryo characteristics were comparable between the two regimens.

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Author Contribution

Al-Masoody, FF, performed the study, examined and reviewed results, and manuscript writing with the help and supervision of Al-Obaidi, MT.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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