

Comparison between the Effect of GnRH Agonist and HCG Injection on the Luteal Phase Support in Patient Undergoing IUI

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Abstract

Intrauterine insemination is amongst the foremost recommended procedures to reinforce the probability of pregnancy in couples with infertility. The success rate of this system depends on numerous factors, one among which is that the quality of the luteal phase which could be due to insufficient production of progesterone.

To study the impact of luteal phase GnRH agonist versus HCG supplementation on pregnancy rates in females undergoing intrauterine insemination.

This study was performed on random 40 infertile couples. Basal hormones measurement of FSH, LH, E2 and progesterone was done before undergoing ovarian stimulation by letrozole or clomiphene citrate. In the mid cycle transvaginal ultrasound was done to measure the dominate follicle/ s and endometrial thickness (ET). Assessment of progesterone and E2 was done on the trigger day. Triggering of ovulation was done by the HCG injection (5000IU). IUI for all females included in the study then they were divided into two groups of 20. Group A were supplemented with GnRH agonist injections (0.1 mg) on day 9,10,11,12 post IUI plus progesterone suppositories 400 mg for 14 days while group B were supplemented with HCG injections 1500IU on day 1, 4, 7 post IUI plus progesterone suppositories 400 mg for 14 days. Then Progesterone level was re measured at day 21 of the cycle. Chemical pregnancy rate was done and recorded.

The hormonal levels showed no significant difference in baseline serum FSH, LH and estradiol (E2) ($P > 0.05$); however, there was significant difference in mean serum baseline progesterone between protocol groups ($p = 0.024$); additionally, there was no significant difference in mean serum estradiol (E2) and progesterone at day 12 ($p > 0.05$), but the difference in mean serum progesterone at day 21 was highly significant ($p < 0.001$); its level was highest in group B than A. The pregnancy rate of infertile women in group A (who used GnRH as supportive to luteal phase) was higher (40.0 %). Conclusions:

Luteal phase support by GnRH injection (Decapeptyl 0.1mg) significantly increased pregnancy rate in infertile females undergoing intrauterine insemination compared to HCG injection (1500IU) in spite of significant elevation in progesterone hormone at 21the day in HCG group.

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Introduction

The first-line treatment during ART procedure is intrauterine insemination (IUI), in which the sperms pass through the cervical to increase the number of sperm around the egg¹.

IUI is a simple and non-invasive procedure with a reasonable success rate. It is fit to couple compliance (low drop-out rate) and a very low risk for complications such².

One among the factors of intrauterine insemination (IUI) failure is secretory phase deficiency (LPD) that could be related to insufficient production of progesterone, which is important for embryo implantation and maintenance of an early pregnancy².

The endometrium, which lines the uterus is ready for implantation of the embryo, this

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process starts within the proliferative phase and extends throughout the luteal phase (from ovulation until menstruation).³ The luteal phase ends at the onset of subsequent menstruation and typically lasts 12 to 16 days, during the luteal phase, the endocrine gland undergoes morphological and biochemical changes referred to as 'luteinization'.⁴ Under the influence of LH, specific cells called granulosa cells produce progesterone.

After implantation, trophoblastic tissue of the placenta secretes human chorionic gonadotropin (hCG), which acts on the ovary. HCG maintains and stimulates the endocrine gland (the remnant of the follicle) to supply estradiol and progesterone, this is important in maintaining the pregnancy until the placenta takes over steroid production at approximately seven weeks of gestation.⁵

Progesterone prepares the endometrium for pregnancy by stimulating proliferation in response to human chorionic gonadotropin (hCG) produced by the endocrine gland within the secretory phase of the cycle. In assisted reproduction techniques (ART), progesterone and/or hCG levels are low, therefore the secretory phase is supported with progesterone, hCG or gonadotropin releasing hormone (GnRH) agonists to enhance implantation and pregnancy.⁶

In IUI there are several agents for ovulation induction (OI) that stimulate the expansion of follicles which may end with multifollicular development with higher steroid serum concentrations, compared with natural cycles.⁷ It's assumed that supraphysiologic serum steroid concentrations might adversely affect LH secretion via feedback mechanisms, which successively leads to premature luteolysis and defective progesterone secretion.⁸ Thought that LH levels are lowered by high steroid levels which are high due to the multiple corpora lutea, which produce more steroids than are produced during a natural cycle. This causes feedback on the pituitary and lowers LH levels, through this way, the secretory phase is shortened (known as premature luteolysis), and chances of pregnancy are reduced.¹

Materials and methods

This prospective comparative study was done randomly on patients their infertility duration ranges 2-15 years with both primary and secondary infertility. The females age range from 18-40 years with BMI 18.5-45kg/m². The tubal patency was documented by HSG and normal male partners regarding their seminal fluid analysis. Females with uterine congenital anomaly or their partners diagnosed as oligoasthenotertozoospermia were excluded from the study. Polycystic ovarian syndrome in group treated with HCG hormone as supportive secretory phase were excluded to prevent OHSS.

For all infertile females enrolled within the study the hormonal analysis was done on day two of the cycle, including FSH, LH, Estradiol (E2) and progesterone. Measurement of hormones at 21th day of cycle to detect secretory phase defect. For ovarian stimulation Letrozole 2.5 mg tab was given twice daily from day 3 of cycle for five days. Recombinant FSH ampules 75 IU /S.C was given once daily from day 5 of the cycle. Maturity of the follicles was monitored by serial transvaginal ultrasound examinations to assess follicle number, size and endometrial thickness.⁹ The dimensions of dominant follicle should be between 17-25 mm.¹⁰

Injection of 250 microgram/ 6500 IU solution of recombinant hCG was given when a minimum of one follicle reach 17 mm.¹¹ Females were prepared and IUI was done 34-36 hour post trigger with HCG. The female partner was inseminated by gently inserting the loaded IUI catheter into the uterine cavity. The sperm preparation (0.3-0.5ml sperm suspension) was gently inserted into the cavity.¹²

Luteal phase support:

Post IUI luteal phase support done by progesterone suppositories to all females for 14 days. The females included within the study were divided into two groups according to treatment received during luteal phase:

1-Group A: Twenty females were treated by intramuscular injections of GnRH agonist 0.1 mg at days 9,10,11,12 post IUI plus 400mg progesterone suppositories for 14 days.

2- Group B: Twenty females were treated by intramuscular injections of HCG 1500 mg was at day 1,4,7 post IUI plus 400mg progesterone suppositories for 14 days. Measurement of progesterone level at 21th day was done. Chemical pregnancy test results were recorded.

Statistical analysis:

The collected data was statistically analyzed by statistical package for social sciences (SPSS) version 23.0. By applying appropriate statistical procedure data were presented as mean ±SD. The groups were compared by the student’s paired t-test, and chi square test. The degree of association between continuous variables were calculated by person’s correlated coefficient(r). The level of significance was taken at *p* value <0.05.

Results

Characteristic	Protocol A n = 20	Protocol B n = 20	<i>p</i>
Age (years)			
Mean ±SD	30.70 ±8.21	30.05 ±7.13	0.933 NS
< 35, n (%)	15 (75.0 %)	12 (60.0 %)	0.583 NS
> 35, n (%)	5 (25.0 %)	8 (40.0 %)	
BMI (kg/m²)			
Mean ±SD	27.40 ±4.55	29.11 ±6.33	0.667 NS
Type of infertility			
Primary, n (%)	13 (65.0 %)	9 (45.0 %)	0.344 NS
Secondary, n (%)	7 (35.0 %)	11 (55.0 %)	
Previous ART			
Previous 1 IUI, n (%)	4 (20.0 %)	1 (5.0 %)	0.062 NS
Previous 2 IUI, n (%)	0 (0.0 %)	4 (20.0 %)	
Previous 1 IVF, n (%)	0 (0.0 %)	1 (5.0 %)	0.401 NS
Previous 2 IVF, n (%)	0 (0.0 %)	0 (0.0 %)	
Previous endometriosis, n (%)	1 (5.0 %)	0 (0.0 %)	0.362 NS
Cycle			
Regular, n (%)	16 (80.0 %)	15 (75.0 %)	0.911 NS
Irregular, n (%)	4 (20.0 %)	5 (25.0 %)	

Table 1. Demographic characteristics of women categorized according to type of luteal phase support protocol.

n: number of cases; *SD*: standard deviation; **BMI**: body mass index; **ART**: assisted reproductive technologies; **IUI**: intrauterine insemination; **IVF**: in vitro fertilization; **NS**: not significant at *P*> 0.05.

Categorizing infertile women according to type of luteal phase support protocol:

The infertile females enrolled in the present study were divided according to luteal phase supported into two groups: Women in the first group (group A) were treated with injections of GnRH Agonist (Decapeptyl 0.1 mg) at days 9,

10, 11 and 12 post IUI. Women in the second group (group B) received supplement with injections of (hCG) day 1, 4, 7 post IUI.

Demographic characteristics of women categorized according to type of luteal phase support protocol

Demographic characteristics of women categorized according to type of luteal phase support protocol were shown in table (1). There was no significant difference in mean age or body mass index, type of infertility, previous ART cycles and menstrual cycle regularity percentage between two protocol groups (*P*> 0.05).

Comparison of hormonal characteristics between women categorized according to type of luteal phase support protocol

The hormonal characteristics of women categorized according to type of luteal phase support protocol were shown in table (2). There was no significant difference in baseline serum FSH, LH and estradiol (E₂) (*P*> 0.05); however, there was significant difference in mean day 2 serum progesterone between two protocol groups (*p*= 0.02). In addition, there was no significant difference in mean serum estradiol (E₂) and progesterone at day 12 (*P*> 0.05), but the difference in mean serum progesterone at day 21 was highly significant (*P*< 0.001); its level was highest in B followed by group A as shown in figure (1).

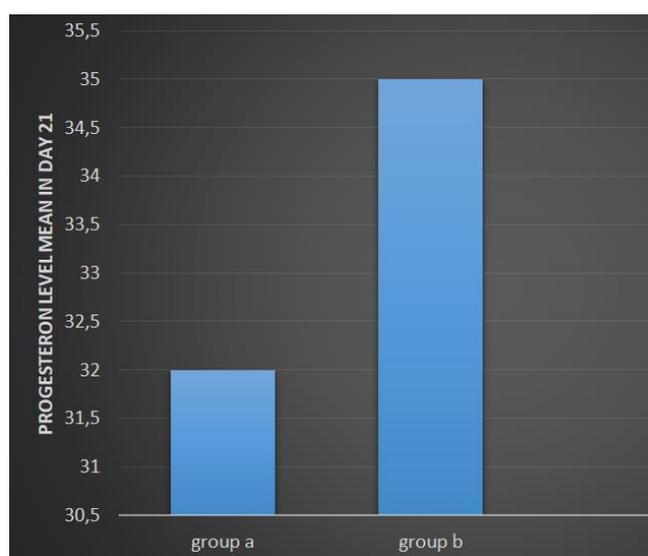


Figure 1: Bar chart showing mean serum progesterone concentration of infertile women at day 21 according to type of protocol.

Characteristic	Protocol A n = 20	Protocol B n = 20	P
Baseline serum FSH (day 2)			
Mean ±SD	6.13 ±2.11	7.59 ±2.63	0.080
Baseline serum LH (day 2)			
Mean ±SD	5.07 ±1.58	6.36 ±2.35	0.112
Baseline serum (E ₂) (day 2)			
Mean ±SD	59.09 ±30.45	60.19 ±28.40	0.689
Baseline serum Progesterone (day 2)			
Mean ±SD	1.26 ±0.68	1.25 ±0.59	0.024
E ₂ at day 12			
Mean ±SD	282.16 ±101.17	262.67 ±48.75	0.593
Progesterone at day 12			
Mean ±SD	2.33 ±1.00	2.66 ±0.66	0.189
Progesterone at day 21			
Mean ±SD	26.72 ±6.63	35.34 ±9.51	< 0.001

Table 2. Hormonal characteristics of women categorized according to type of luteal phase support protocol.

n: number of cases; SD: standard deviation; NS: not significant at $P > 0.05$; HS: highly significant at $P \leq 0.01$; S: significant at $P \leq 0.05$; Capital letters indicate level of significance following LSD multiple comparison test so that similar letters denote no significant difference whereas, different letters denote significant difference.

Pregnancy rate of women categorized according to type of luteal phase support protocol

The Pregnancy rate of women categorized according to type of luteal phase support protocol was shown in table (3). The pregnancy rate of group A was the higher (40.0 %) and it significantly different from that of group B which was 20% only ($P = 0.002$).

Pregnancy test	Protocol A n = 20	Protocol B n = 20	P
Positive	8 (40.0 %)	0 (0.0 %)	0.002
Negative	12 (60.0 %)	20 (100.0 %)	

Table 3. Pregnancy outcome of women categorized according to type of luteal phase support protocol.

n: number of cases; HS: highly significant; Capitals letters indicate significance following Chi-square test between 2 groups.

Discussion

During gonadotropin-stimulated cycles luteal phase has been shown to be 20 percent shorter (11 days in average) as inferred from available observational researches. The reduction in luteal phase time can be returned back to normal by mid-luteal administration of human chorionic gonadotropin (hCG), and the

mid-luteal level of progesterone in women receiving luteal phase support is higher than that of women who receive no luteal phase support in a significant manner.¹³ It has been hypothesized that the reduction in steroid levels was associated with negative drawback on pregnancy outcome and therefore luteal phase support, by giving hCG or progesterone, has been shown to be essential to overcome this problem.¹³ The utilization of "gonadotropin releasing hormone agonists (GnRHa)" in assisted reproduction technology (ART) has been shown to affect adversely the production of progesterone, at time of luteal phase that is essential for success of the embryo implantation.¹³

As of late, there is no accepted consensus about the agent of choice and the exact timing of giving such an agent, in spite of the substantial information dealing with agents and timing utilized for luteal phase support at time of assisted reproductive technologies.^{14,15}

In the current study, a design was adopted to compare two methods of luteal phase support in a sample of Iraqi women undergoing ART. Women in the first group (group A) received supplement with injections of GnRH Agonist (Decapeptyl 0.1 mg) at days 9, 10, 11 and 12 post IUI. Women in the second group (group B) received supplement with injections of (hCG) day 1, 4, 7 post IUI, all women participating in the current study were given micronized progesterone as a post IUI luteal phase support for 14 days.

A number of previous studies have compared the effect of hCG to that of progesterone as a luteal phase support in ART. A common belief among specialists deal with fertility is that the drug of choice for luteal phase, in contrary to current study finding, is hCG.¹⁶

luteal phase support (LPS) were contrasted in terms of efficacy and safety, including, hCG on the day of embryo transfer (ET) in combination with daily vaginal progesterone, three times hCG or vaginal progesterone only and results pointed out to that luteal phase support using progesterone alone resulted in the same viable clinical pregnancy rate as hCG, with the advantage of patients' comfort as there were more suffering towards the termination of the luteal phase in women receiving hCG only or an additional injection of hCG, in comparison to women receiving progesterone alone groups.¹⁷

In a study enrolling a total of 456 patients, the patients were categorized into two subsets according to type of luteal phase support: in the first group received single-dose triptorelin acetate 0.1 mg on the sixth day following the oocyte pick-up. In the second group, hCG 1500 IU was given on day 4, 7 and 10 after the oocyte pick-up. The clinical pregnancy rate was slightly higher in the GnRHa group, but this difference was not statistically significant.¹⁸ Indeed, these results support the findings of the current study that the use of GnRH resulted in a clinically beneficial effect of higher pregnancy rate; however, in terms of statistics this rise in pregnancy rate is not significant. These findings are also consistent with the findings of other previous reports.¹⁹

Kyrou *et al.*, in 2011 did a recent meta-analysis on the influence of luteal single-dose GnRHa on ART outcomes. They have conducted a search up of literature until December 2010 using computerized software. Six randomized controlled trials were analyzed out of the 38 studies yielded. The conclusion of the authors was that the administration of GnRHa during the luteal phase improves rates of live birth. Martins *et al.*, in 2015 also performed a meta-analysis and documented the value of GnRHa at time of luteal phase for women experiencing ARTs. In one study, luteal phase support with decapeptyl resulted in a higher implantation rate (24.5% vs. 17.0%, $p = 0.023$), a greater clinical pregnancy rate (49.0%, $n = 72$ vs. 33.3%, $n = 31$, $p = 0.023$) and a greater live birth rate (41.5%, $n = 61$ vs. 28.0%, $n = 26$, $p = 0.039$). Nonetheless, the control group did not receive progesterone or hCG for purpose of comparison.²⁰ In another study, when GnRH agonist was administered subcutaneously at the time of implantation there was no significant rise in clinical or ongoing pregnancy.²¹

The exact way by which GnRH agonist acts is not clear; however, there are two suggestions, the first is that GnRH agonist supports the corpus luteum function by enhancing secretion of LH by the pituitary gland and the second is that GnRH agonist stimulates the endometrium through GnRH receptors.²²

It has been found that the administration of the GnRHa continuously in the luteal phase may cause sustained down-regulated state of the GnRH receptors in organs of reproduction leading to ineffectiveness of GnRHa in improving the pregnancy rate in addition previous

researches evaluated the effect of continuous administration of GnRHa in the luteal phase on the outcome of ART cycles, and found that the pregnancy rate was not affected by duration of GnRHa administration.^{23,24}

In another study, the results suggested that, administration of 0.1 mg of Decapeptil 6 days after oocyte retrieval, in addition to routine luteal phase support using progesterone, in women with previous history of 2 or more ART failures caused a significant rise in implantation and pregnancy rates following ART cycles after ovarian stimulation with GnRH antagonist protocol.²⁵

There exist two systematic reviews showing that administration of a luteal phase single-dose GnRH agonist may significantly improve ART outcomes. The meta-analysis, conducted by Kyrou, Kolibianakis *et al.* showed a positive effect of GnRHa on improving clinical pregnancy rate and live birth rate in both agonist and antagonist protocols. Kung, Chen *et al.* Confirmed in their study that a subgroup of patients with basal FSH >8 mIU/mL or mature oocytes ≤ 3 would benefit from luteal phase single-dose decapeptyl administration.^{26,27}

Conclusions

Luteal phase support by GnRH injection (Decapeptyl 0.1mg) significantly increase pregnancy rate in infertile females undergoing intrauterine insemination compared to HCG injection (1500IU) in spite significant elevation in progesterone hormone at 21the day on HCG group.

Declaration of Interest

The authors report no conflict of interest.

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