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Using Of Human Menopausal Gonadotropin Hormone Versus Oral Ovarian Stimulation Agents In Induction Of Ovulation In Women With Polycystic Ovary Syndrome In Salah Al-Deen Hospital/Tikrit City

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ABSTRACT

Polycystic ovary syndrome is a common cause of an ovulatory infertility. Drugs like Aromatase inhibitors, Human menopausal gonadotropin, used for ovulation induction. The aim of this study was carried out to compare the therapeutic effects of gonadotropin hormone versus oral ovarian stimulating agents. A prospective randomized controlled clinical trial was carried out in the Salahdeen general hospital in Tikrit from 1st Feb-30th August 2020. About 75 PCOs patients enrolled randomly in the study and divided equally into 3 groups as below: Group A treated with (75 IU intramuscular HMG gonadotropin) daily for 5 days starting Day 2 of menstrual cycle. Group B treated with oral clomiphene citrate 100 mg daily for 5 days starting Day 2 of menstrual cycle. Group C treated with oral Letrezole 5 mg daily for 5 days starting Day 2 of menstrual cycle. Multiple mature follicles were obtained commonly by HMG, followed by Letrozole, then Clomiphene, this relation was statistically significant. Endometrial thickness was higher among those treated with HMG (10.5±1.7) than those treated by Clomiphene (9.03±0.9), and then treated by letrozole (8.5±1.2). This is a significant difference in ET value between Clomiphene, letrozole, and HMG. Chemical pregnancy (early pregnancy loss that occurs shortly after implantation may account to 50-75% of all miscarriages) was higher among those treated with HMG (20%), while it was (16%) of those treated with Clomiphene, and (12%) of the Letrozole group, this relation was statistically not significant. In conclusion, HMG had the highest response rate, followed by Letrozole, and Clomiphene. The multiple mature follicles was obtained commonly by HMG, followed by Letrozole, then Clomiphene .

***Keywords*:** Human Menopausal Gonadotropin Hormone, Polycystic Ovary Syndrome, Ovulation induction

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استعمال عقار هرمون الغدد التناسليه المحفزه مقابل عوامل تحفيز المبيض عن طريق الفم في تحريض الاباضة عند النساء المصابات بمتلازمة المبيض المتعدد الكيسات في مستشفى صلاح الدين/مدينة تكريت

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الملخص

الهدف من الدراسة هو إجراء مقارنة بين التأثيرات العلاجية لهرمون الغدد التناسلية مقابل عوامل تحفيز المبيض الفموية كخط أول من أدوية تحريض الإباضة عند النساء المصابات بالعقم المصابات بمتلازمة تكيس المبايض. تم إجراء تجربة إكلينيكية عشوائية خاضعة للرقابة في قسم التوليد وأمراض النساء بمستشفى صلاح الدين العام في مدينة تكريت في الفترة من 1 فبراير إلى 30 أغسطس 2020. تم تسجيل حوالي 75 مريضًا بشكل عشوائي في الدراسة وتم تقسيمهم إلى 3 مجموعات بشكل عشوائي على النحو التالي: المجموعة أ (25 مريضًا) عولجت بـ (75 وحدة دولية من هرمون موجهة الغدد التناسلية العضلي) يوميًا لمدة 5 أيام تبدأ اليوم الثاني من الدورة الشهرية. المجموعة ب (25 مريضًا) عولجت با سترات كلوميفين عن طريق الفم 100 ملغ يوميًا لمدة 5 أيام بدءًا من اليوم الثاني من الدورة الشهرية. المجموعة C (25 مـ ريضًا) عولجت بـ Letrezole عن طريق الفم 5 مجم يوميًا لمدة 5 أيام بدءًا من اليوم الثاني من الدورة الشهرية. تم الحصول على الجريب الناضج المتعدد بشكل شائع بواسطة HMG ، يليه ليترزول ، ثم كلوميفين ، وكانت هذه العلاقة ذات دلالة إحصائية. كان سمك بطانة الرحم أعلى بين أولئك الذين عولجوا بـ HMG (10.5 ± 1.7) من أولئك الذين عولجوا بواسطة كلوميفين (9.03 ± 0.9) ، ثم عولجوا بـ ليترزول (8.5 ± 1.2). هذا فرق كبير (p <0.05) في قيمة ET بين كلوميفين و ليترزول و HMG. كان الحمل الكيميائي أعلى بين أولئك الذين عولجوا بـ HMG (20٪)، بينما كان (16٪) من الذين عولجوا بالكلوميفين، و (12٪) من مجموعة ليتروزول، هذه العلاقة كانت غير معنوية إحصائياً (P> 0.05). والاستنتاج ان لدى HMG أعلى معدل استجابة، يليه ليترزول وكلوميفين تم الحصول على الجريب الناضج المتعدد بشكل شائع بواسطة HMG ، يليه ليترزول ، ثم كلوميفين ،

الكلمات الدالة: عقار هرمون الغدد التناسليه المحفزه، متلازمة المبيض المتعدد الكيسات، تحريض الاباضة

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1. Introduction

The therapeutic choices for infertility in PCOS women involve gonadotropins, clomiphene citrate, assisted reproductive technology and laparoscopic ovarian drilling (LOD) [1, 2]. Mutual to all methods is the ovulation induction. Letrozole also play principle parts in induction of ovulation as has been now well explained. [3]. Gonadotropins are utilized as second-line drugs for induction of ovulation following failure of treatment with first-line oral ovulation induction drugs. This composed those females who are resistant to oral drugs or have the undesirable antioestrogenic adverse effects on the endometrium. [4] A prospective, comparative randomized clinical trial was carried out to compare the therapeutic effects of gonadotropin hormone versus oral ovarian stimulating agents as the first line of ovulation induction drugs in infertile women with polycystic ovarian syndrome.

2. Patient and Methods

This is a prospective randomized controlled clinical trial, done in the Department of Obstetrics and Gynecology Salahdeen general hospital in Tikrit city, from 1st Feb. 2020 – 31st August 2020. Patients diagnosed with PCOs depending based on the Rotterdam criteria, in which at least two of the following three criteria were met: oligomenorrhea or amenorrhea, clinical hyperandrogenism and/or hyperandrogenemia, and polycystic ovaries. [5] The luteinizing hormone (LH)/FSH ratio was not taken into account since there is some controversy over its reliability as a diagnostic criterion for PCOS. Participants were enrolled after all eligibility criteria were confirmed and informed consent completed. Randomization occurred during the first 3 days of spontaneous menses or while taking medroxyprogesterone (10 mg/d Provera for 5 days) to induce withdrawal bleeds. About 75 patients enrolled randomly in the study and divided into 3 groups as described below: Group A (25patient) treated with (75 IU intramuscular HMG gonadotropin) daily for 5 days starting Day 2 of menstrual cycle, Group B (25patient) treated with oral clomiphene citrate 100 mg daily for 5 days starting Day 2 of menstrual cycle, Group C (25patient) treated with oral Letrezole 5 mg daily for 5 days starting Day 2 of menstrual cycle. The hCG injection (10000 IU, intramuscular) was given when the leading follicle measured more than 18 mm in diameter. Intercourse was advised to be performed 24–36 h after the hCG injection. Serum hCG concentration was determined 2 weeks after the hCG injection in the absence of menstruation

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for diagnosis of pregnancy. All patients followed for 3 consecutive cycles. The patients were evaluated using TVS, while the patient was in the lithotomy position. At day 12 of the cycle all patient evaluated for endometrial thickness (ET), the number and size of the growing and mature follicles [6]. Good response was achieved when at least one mature follicle becomes 17 mm in diameter and the patients were advised to have timed intercourse every other day, starting at least 24 h after the leading follicular diameter reached 17 mm in size [7]. At day 2 of the cycle evaluation of FSH, LH, E2. Measurement of b-hCG in blood after at least 3 days after missed period. For chemical pregnancy assessment.Outcome Measurements; Number of follicles >17 mm in diameter on the day of hCG, Endometrial thickness on the day of hCG (mm), Pregnancy rate per cycle, mono versus multifollicular rate.

3. Results

The analysis of 75 patient with PCOs aged from (20-39) years, show that primary infertility found among 44 (58.7%), while secondary was 31(41.3%). Seventeen (22.7%) women of them with hirsutism's, 11 (14.7 %) with acne, 63 (84%) of all women in the study with oligomenorrhea. The mean hormonal level that measured at 2nd day of menstrual cycle was LH (10.38±0.2), FSH (6.3±0.4), and E2 (33.9±1.1). The mean age of the patient was (32.5±3.1), (33.1±2.7),(31.8±2.9), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05). The mean LH level was (10.8±1.8),(11.5±2.3),(10.3±1.5), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05). The mean FSH level was (5.6±1.2),(6.1±0.9),(5.4±2.1), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05). The mean E2 level was (33.9±4.6), (34.5±3.3), (35.6±2.5), among Clomiphene, Letrozole, and HMG respectively, this relation was statistically not significant(P value> 0.05) as shown in table 1.

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Table 1. Distribution of Clinical Characteristics among Study Groups

	Clomiphene (Group A)	Letrozole (Group B)	HMG (Group C)	P value
	Mean±SD	Mean±SD	Mean±SD	
Age	32.5±3.1	33.1±2.7	31.8±2.9	>0.05 NS
LH (IU/ml)	10.8±1.8	11.5±2.3	10.3±1.5	>0.05 NS
FSH (IU/ml)	5.6±1.2	6.1±0.9	5.4±2.1	>0.05 NS
E2(pg/ml)	33.9±4.6	34.5±3.3	35.6±2.5	>0.05 NS

(ANOVA test for: age df=2, F=0.26, P=0. 7, LH df=2, f=2.5, FSH Df=2, f=1.4, p=0.2, p=0.09, E2 Df=2, f=1.5, p=0.2,)

Clomiphene group consist of 25 patient (the complete cycle number was 59 cycle) 13 patient received treatment for 3 cycles, 8 received for 2 cycles, and 4 received clomiphene for 1 cycle. Letrozole group consist of 25 patient (the complete cycle number was 49 cycle) 7 received Letrozole for 3 cycles, 10 patient for 2 cycles, and 8 patient for 1 cycle. HMG group were 25 patient (the complete cycle number was 42 cycle) 4 received HMG for 3 cycles, 9 patient for 2 cycles, and 12 patient for 1 cycle. Table 2 show the respondent rate of different study group. The respondent rate is defined as cycle with one or more mature follicles ≥17 mm. HMG had the highest response rate 36(85.7%), followed by Letrozole 32(65.3%), and Clomiphene 24 (40.7%).

Table 2. Number and percentage of cycles responded to the treatment with clomiphene, letrozole and HMG.

Study Groups	Mature Follicle		Total No. of Cycles
	Yes	No	
Clomiphene	24	35	59
	40.70%	59.30%	100.00%
Letrozole	32	17	49
	65.30%	34.70%	100.00%
HMG	36	6	42
	85.70%	14.30%	100.00%
Total	92	58	150
	61.30%	38.70%	100.00%

X2=21.5,df=2, P value< 0.05 Significant *HMG (gonadotropin)

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Regarding number of follicles measured ≥ 17 mm per cycle after treatment, the table 3 shows that after Clomiphene treatment single mature follicle was obtained in 21(87.5%) of the cycles, and ≥2 mature follicles obtained in 3 (12.5%) of the cycles. after Letrozole treatment single mature follicle was obtained in 21(65.6%) of the cycles, and ≥2 mature follicles obtained in 11(34.4%)of the cycles. after HMG treatment single mature follicle was obtained in 20(55.6%) of the cycles, and ≥2 mature follicles obtained in 16(44.4%)of the cycles. From this figure the multiple mature follicles was obtained commonly by HMG, followed by Letrozole, then Clomiphene, this relation was statistically significant as shown in table 3.

Table 3. The Distribution Of Study Group Cycles According to Number of Follicle ≥17 Mm Post Treatment With Clomiphene, Letrozole And HMG.

Study Groups	NO. of Follicle ≥17 Mm		Total
	Single Mature Follicle	≥2 Mature Follicle	
Clomiphene	21	3	24
	87.50%	12.50%	100.00%
Letrozole	21	11	32
	65.60%	34.40%	100.00%
HMG	20	16	36
	55.60%	44.40%	100.00%
Total	62	30	92
	67.40%	32.60%	100.00%

X2=6.8,df=2, P value< 0.05 Significant

Endometrial thickness (ET) was higher among those treated with HMG (10.5±1.7) than those treated by Clomiphene (9.03±0.9), and then treated by Letrozole (8.5±1.2). This is a significant difference ($p < 0.05$) in ET value between Clomiphene, Letrozole, and HMG, as shown in table 4.

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Table 4. The Mean Endometrial Thickness at Day 12 of the Cycle Among Study Groups

Study Group	Endometrial Thickness Mean±SD
Clomiphene	9.03±0.9
Letrozole	8.5±1.2
HMG	10.5±1.7

Df=2, F=15.7, P value =<0.001 significant

Chemical pregnancy was higher among those treated with HMG 5(20%), while it was 4(16%) of those treated with Clomiphene, and 3(12%) of the Letrozole group, this relation was statistically not significant (X2=0.6, df=2, P value> 0.05).

4. Discussion

The current study revealed that the analysis of 75 patient with PCOs aged from (20-39) years, show that primary infertility found among (58.7%), while secondary was (41.3%). About (22.7%) of them with hirsutism, (14.7%) with acne, (84%) of all women in the study with oligomenorrhea. Alhindawi Zena found that the mean age of women (25.8 ± 5.9 SD (ranging between 18-47 years old), and (22.6%) women of them with hirsutism, (15.1%) with acne, (23.6%) with acne and hirsutism, (86.8%) of all women in the study with oligomenorrhea while (13.2%) of them with amenorrhea. (71.7%) of women with infertility. [8]

The mean age of patients in this study were (32.5±3.1), (33.1±2.7),(31.8±2.9), among Clomiphene, Letrozole, and HMG respectively, this higher from what found by Eleawi HR found that PCOs cause of infertility had a significantly higher frequency (55%) among women aged 20-29 years (P=0.0001). [9] Eleawi HR found that There was higher frequency of primary infertility (74%) among the PCOs infertility group with a higher percentage of <5 years was more in PCOS infertility group .

In current study about 17 (22.7%) with hirsutism, 11 (14.7 %) with acne, 63. This figure was higher than what reported by Eleawi HR found that the signs and symptoms in cases of PCOS

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was as follows; Hirsutism 83%, Acne 67%, [9] In current study about (84%) with oligomenorrhea this was lower than Eleawi HR Oligomenorrhea 62%. [9]. This difference may be related to cultural differences, dietary and physical activity rate difference.

In current study there were elevated level of LH 10.38±0.2, this goes with Eleawi HR found that a higher frequency of increased Prolactine level & LH level in the PCOS cases than other causes group, while there was increased level of FSH in other causes group than the PCOS group. And with Deliwala K J. et al 95% of women were having increased LH:FSH ratio. [10]

The elevated LH level is due to the fact that androgens are the main source of hyperandrogenemia in PCOS. Hyperandrogenemia has both a direct effect on the ovarian alterations and, an increasing effect on pituitary LH pulse frequency and amplitude with relative low FSH secretion. Further, adrenal androgens contribute to PCOS androgen excess. Insulin resistance with compensatory hyperinsulinemia enhances ovarian androgen production as well as, decreases production of SHBG in the liver, and both increase the pool of bioavailable androgens. PCOS is also associated with increased muscle sympathetic nerve activity that is related to high testosterone, insulin resistance, and obesity. Eleawi HR found that LH level increased in 91% of cases, FSH level normal in 86% of cases, Prolactin level increased in 53%. [9]

Regarding number of follicles measured ≥ 17 mm per cycle after treatment, this study revealed that after Clomiphene treatment single mature follicle was obtained in (87.5%) of the cycles, and ≥2 mature follicles obtained in (12.5%)of the cycles. And after Letrozole treatment single mature follicle was obtained in (65.6%) of the cycles, and ≥2 mature follicles obtained in (34.4%) of the cycles. And after HMG treatment single mature follicle was obtained in (55.6%) of the cycles, and ≥2 mature follicles obtained in (44.4%) of the cycles. In the current study the multiple mature follicle was obtained more frequently commonly by HMG, followed by Letrozole, then Clomiphene, in a statistically significant manner. This result agree with Al-Shaikh S F.M.H et al [11] who found that letrezle produce multiple mature follicles more than CC (36.3%), (12.89%) respectively and with . also agree with M.F. Mitwally et al [12] and R.F. Casper,and M.F.M. Mitwally [13] But results disagree with Jiang and He study who found that letrozole was associated with less mature follicle count in each cycle. There was also no significant difference between pregnancy rates .

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The researchers revealed that Letrozole was as efficient as clomiphene in induction of ovulation in PCOS cases. [14] Accordingly, Casper reported that Letrozole is as effective as clomiphene and requires lesser monitors because of lower rate of complications. [15] The results of this study disagree with those of Badawy et al [16] who didn't found any advantage to the utilization of Letrozole over Clomiphene citrate as a first-line treatment for ovulation induction in PCOS patients. [16] The difference in results may be due to difference in study methodology, sample size, and largely difference in study subject characteristics. Shi S, et al [17] found that Letrozole-induced ovulation can obtain ovulation rate and pregnancy rate similar to gonadotropin, but reduce the risk associated with treatment. It can be utilized as an efficient ovulation choice for patients with PCOS who are resistant to clomiphene .

But Shi S, et al found that the multiple pregnancy rates in HMG group was significantly higher than that in the letrozole group, and the difference was statistically significant (P.05). Shi S, et al found that there was ovarian hyperstimulation syndrome in the letrozole group; the incidence of ovarian hyperstimulation syndrome in the HMG group was 12.5%. [17]

Endometrial thickness (ET) was higher among those treated with HMG (10.5±1.7) than those treated by Clomiphene (9.03±0.9), and then those treated by letrozole (8.5±1.2) in a statistically difference ($p < 0.05$) in ET value between Clomiphene, letrozole, and HMG. Regarding Clomiphene versus Letrozole, the current study agree with Al-Shaikh et al [11] , were the ET in CC was (9.68 ± 2.73 mm), and among letrizole group was (8.02 ± 1.24), and with Davar et al. [18] and Badawy et al. [19] which were (9.3 ± 0.9 mm.) and (9.2 mm) respectively, disagree with Al-Fozan et al who didn't found difference in endometrial thickness between the two groups [20] . This may be explained by the fact of that CC has an antiestrogenic effect and has a negative effect on endometrial thickness, which is believed to have a negative effect on pregnancy despite high ovulation. [21]

Shi S, et al found that there was no significant difference in the endometrial thickness between the 2 groups on the day of HCG injection [(9.1±0.2) mm versus (10.7±1.6) mm. The incidence of ovarian cysts was lower than that of HMG group. [17] In the current study, chemical pregnancy was higher among those treated with HMG (20%), while it was (16%) of those treated with Clomiphene, and (12%) of the Letrozole group. In Letrozole group, chemical pregnancy rate was (12%). This agree with that found by Elnashar et al. [22] , Also it is comparable to Al-Shaikh et al [23] , Al-Fozan et al [20] , Bayar et al. [24] and

Gregoriou et al. [25] which were (11.5%) %), (9.1%), (9.09%) and (8.9%) respectively. Only in Nupur et al. [7] study the ovulation was spontaneous.

The current study disagrees with Polyzos et al who reported that the rate of pregnancy was equal in both letrizol and CC and there was no variations in terms of pregnancy with increasing the dose. [26] . Additionally, although the rate of pregnancy reported in the letrozole group was slightly higher than that in the clomiphene group, in some patients, patients tended to utilize cheaper agent because of letrozole cost. According to the results of this research, these two medicines are not superior to each other and can be chosen based on cost, patient tolerance, and side effects. Abtahi SH et al have reported that clomiphene and metformin can be considered as the first line of treatment for infertility [27].

The current study agrees with Weiss NS et al (RR 1.24, 95% CI 1.05 to 1.46) that Gonadotrophins resulted in more live births than continued clomiphene citrate. Shi S, et al found that there was no significant difference in the number of ovulation cycles between Letrozole and human menopausal gonadotropin (53.6% versus 64.7%, P>.05). [17] Ganesh et al carried out a comparing the efficacy of letrozole, CC with recombinant FSH, and recombinant FSH alone in the treatment of CC-resistant PCOS patients with Letrozole 5 mg/d, obtaining ovulation rate 79.3% (295/372), the cycle pregnancy rate was 23.39% (87/372), The ovulation rate was better in the Letrozole group than in the CC recombinant FSH, but in the single-use recombinant FSH group. Ganesh et al found that there was no significant difference in the rate of pregnancy and rate abortion rate between the 2 groups. [28]

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