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Original Article

Use of clomiphene or letrozole for treating women with polycystic ovary syndrome related subfertility in Hilla city

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a common endocrino-pathology characterized by oligo-ovulation or an ovulation, signs of androgen excess, and multiple small ovarian cysts. It is thought to be one of the leading causes of female sub-fertility. It has been estimated that PCOS affects 5–10% of females in reproductive age. Its etiology is complex and likely multi-factorial. The aim of this study was to evaluate the therapeutic effect of clomifene citrate (CC) compared to letrozole in the treatment of patients with sub-fertility secondary to PCOS.

Patients and methods: Eighty five sub-fertile married women at reproductive age were involved in this study during their attendance to the Infertility center of Maternity and Pediatrics Teaching Hospital in Hilla city and those referred from hospital in Hilla city, Babylon Province, Iraq. Patients were collected depending on history and physical examination seeking for features of endocrine disorders, clinical signs of hyper-androgensim such as acne and hirsutism. At day two of menstrual cycle measurement of hormones including Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin, Testosterone and Thyroid Stimulating Hormone (TSH), also Fasting blood glucose (FBG) and LH/FSH ratio were done. On day 12 of menstrual cycle ultrasound examination was done trans-vaginally to detect the number and size of follicles. Patients were diagnosed as PCOS when they have at least two out of three of Rotterdam criteria. Then patients were divided into two groups. Group 1 include 45 patients (80 cycles) were treated with CC (50 mg twice daily for 5 days starting from day 2 of menstrual cycle) and group 2 include 40 patients (47 cycles) were treated with letrozole (5 mg daily for 5 days starting from day 2 of menstrual cycle). After treatment the outcome measured (size and number of mature follicles, mono-follicular cycles and endometrial thickness measured at day 12 of menstrual cycle and pregnancy rate) in CC group were compared to those in letrozole group.

Results: The present study found that each of the percentages of cycles responded to the treatment (resulted in mature follicles $\geq$17 mm in size) (70.21% vs 41.25%) and the mean number of mature follicles (1.42 ± 0.66 vs. 1.15 ± 0.44) was significantly higher in letrozole treated group ($p < 0.05$). While the number of mono-follicular cycles (87.87% vs 63.63%) and the mean of endometrial thickness (ET) (9.68 ± 2.73 vs. 8.02 ± 1.24 mm) was significantly higher in CC treated group ($p < 0.05$). Also the pregnancy rate (per cycle) was higher in CC treated group (12.12% vs 9.09%) although there was no significant difference ($p > 0.05$).

Conclusion: Letrozole was the better in comparison to CC in regard to responded cycles and mean number of mature follicles whereas regarding to endometrial thickness, mono-follicular cycles, and pregnancy rate (per cycle), CC was the better.

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1. Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in female, and it is one of the leading causes of sub-fertility in female [1]. Stein and Leventhal were the first who recognize an association between the presence of polycystic ovaries and signs of hirsutism, menstrual disturbances as amenorrhea and obesity [2,3]. According to Rotterdam Workshop Group in 2004, PCOS women must have two out of the following three criteria: (1) oligo-ovulation or anovulation, (2) hyperandrogenism (clinical and/or biochemical), and (3) polycystic ovaries on sonographic examination [4]. Between 5–10% of females aged 18–44

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are affected by PCOS [5] insulin resistance is a central, probably inherited, biochemical abnormality of PCOS, which lead to hyperinsulinemia [6]. While it can be found in up to 50% of women with PCOS [7], both lean and obese women with PCOS are found to be more insulin resistant than non affected weight-matched controls [8]. High levels of insulin in the blood stimulate the enzyme cytochrome P450c 17-α in both ovaries and adrenal gland to produce increased amounts of male hormones [9].

Infertility is one of the common problems that face women with PCOS and the FSH and CC are the principal treatments used for anovulating women [10]. Gonadotropins are used to induce ovulation in women with PCOS who do not respond to CC [11]. Also lowering insulin levels by using insulin-sensitising drugs such as biguanides and thiazolidinediones (Tzds) may restore fertility [12]. The laparoscopic ovarian surgery "ovarian drilling" is used to induce ovulation in CC resistance women with anovulatory PCOS [13]. Other option for achieving pregnancy in women with PCOS is to use *in Vitro* Fertilization (IVF) [14].

Clomifene citrate (CC) is a non-steroidal selective estrogen receptor modulator (SERMs). The pharmacological goal of SERMs is to produce beneficial estrogenic action and antagonist activity in other tissues such as endometrium, where estrogenic actions (e.g., carcinogenesis) might be deleterious. CC is approved for the treatment of infertility in anovulatory women [15].

Letrozole is a member of the third generation aromatase inhibitors (AIs) drugs (anastrozole, letrozole and vorozole), an oral non-steroidal agents which have been widely used in the treatment of postmenopausal women with early-stage or advanced, hormone-receptor positive breast cancer [16]. Aromatase converts androstenedione to estrone and testosterone to estradiol. Its activity can be demonstrated in several tissues, including the ovaries, brain, placenta, adipose tissue, muscle, liver, breast and estrogen-dependent breast cancer. Aromatase is expressed in a tissue-specific manner. This enzyme is mainly expressed in the ovaries of premenopausal women. AIs prevent the aromatase from producing estrogens by competitive reversible binding to the heme of its cytochrome P450 unit [17]. Letrozole has been shown to be effective, in inducing ovulation and pregnancy in women with anovulatory PCOS and inadequate CC response [18] and improving ovarian response to FSH in poor responders [19]. Letrozole has less side-effect than CC and gonadatropins such as multiple pregnancies and OHSS [20].

1.1. Aim of the study

Evaluate and compare the therapeutic effect of CC and letrozole in the treatment of infertility in women with PCOS.

2. Patients and methods

2.1. Patients

This prospective clinical trial was conducted during the period from May to August 2011, approved by The Ethics Committee of the Al-Nahrain medical college. Women included in this study were among those who attended the infertility center of maternity and pediatrics teaching hospital and those who referred from outpatient clinics to the hospital in Hilla city, Babylon Province, Iraq. All participants were given informed consent before they were included in this study. They were in reproductive age (18–40 years), all of them had at least 2 out of 3 of Rotterdom criteria. Each one got detailed clinical history, physical examination and typical appearance of polycystic ovaries by ultrasound according to the criteria of Rotterdam consensus meeting 2003. Clinical assessment included menstrual cycle regularity (oligomenorrhea or amenorrhea), body mass index (BMI), type and duration of infertility and presence or absence of hirsutism.

Hormonal studies were performed on day 2 (early follicular phase) of the menstrual cycle. A non heparinized venous blood sample was obtained to measure the circulating concentration of LH, FSH, LH:FSH ratio, total testosterone, Prolactin, TSH and Fasting blood sugar (FBS). BMI was calculated using the equation: weight (kilograms)/height (meters)^2. All patients enrolled in the study fulfilled the following inclusion criteria: (1) diagnosed as PCOS in the presence of at least 2 of Rotterdam criteria, based on Rotterdam consensus meeting (2003). (2) Agreed to participate in the study. (3) Unable to achieve pregnancy in a period of last 12 months or more despite regular unprotected intercourse. (4) Had patent fallopian tubes proved by hysterosalpingography. (5) Evaluation of husband infertility by a specialist doctor revealed no abnormalities in the male side. (6) No history of heart, liver, or kidney disease, and un suspected pregnancy.

The exclusion criteria include: (1) Patient's refusal. (2) History of recent administration of hormonal therapy. (3) Male factor infertility. (4) Patients aged more than 40 years.

2.2. Treated groups

Eighty five married women at reproductive age, who had PCOS (based on Rotterdam consensus meeting 2003), were included in this study, two-month washout period was used to eliminate the effect of any post-treatment [21]. In women who were amenorrhoeic, withdrawal bleeding was induced by using 10 mg of dydrogesterone oral tablets (Duphaston Solvay pharmaceuticals B.V., Holland) daily for 10 days [22]. Women included in this study were classified into two groups as follows:

A. Clomifene citrate group (45 women, 80 cycles) received 50 mg of CC oral tablets (Clomid; Patheon France S.A) twice daily from day 2 of the menses for 5 days [23]. The project of the present study was including the administration of CC for 3 successive cycles but due to poor compliance, CC had been received only by 10 patients for 3 successive cycles while 15 patients received CC for 2 cycles and 20 patients received CC for one cycle.
B. Letrozole group (40 women, 47 cycles) received 5 mg of letrozole oral tablets (Femara; Novartis pharma AG, Basel, Switzerland) daily from day 2 of the menses for 5 days [23,24]. The project of the present study was including administration of letrozole for 3 successive cycles but due to poor compliance, letrozole had been received only by 2 patients for 3 successive cycles while 3 patients received letrozole for 2 cycles and 35 patients received CC for one cycle.

The primary outcome measured in these treated groups were the number and size of the growing and mature follicles and endometrial thickness (ET) by monitoring with transvaginal ultrasound (TVU) at day 12 of the menstrual cycle [22]. 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 [24]. The secondary outcome measure was the occurrence of pregnancy. Chemical pregnancy was assessed by measurement of β-hCG in blood after at least 3 days after missed period and clinical pregnancy by detection of fetal heart beat on sonography at 6–7 weeks of gestation [25]. Miscarriage rates could not be determined in all groups because follow up had been lost [26].

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2.3. Statistical analysis

SPSS version 17.0 was used for the statistical analysis. ANOVA, chi-square and Fisher exact tests were used when appropriate. P-values less than 0.05 were considered as statistically significant [27].

3. Results

3.1. Number and percentage of cycles responded to the treatment with clomifene and letrozole

Table 1 shows the response of cycles to employed therapy with either clomifene or letrozole achieved at day 12 of menstrual cycle.

3.2. Mean number and mean size of mature follicles ≥17 mm post treatment with Clomifene and letrozole

Table 2 shows mean number and mean size of mature follicles ≥17 mm per cycle measured at day 12 of menstrual cycle post treatment with CC and letrozole. There was no significant difference ($p > 0.05$) among size of follicles, while significant difference ($p < 0.05$) was found among mean number of mature follicles post treatment with CC and letrozole.

3.3. Number of mature follicle ≥17 mm per cycle post treatment with clomifene and letrozole

Table 3 shows number of cycles resulted in mature follicles ≥17 mm and number of mature follicles ≥17 mm per cycle post treatment with CC and letrozole. There was a significant difference ($p < 0.05$) between CC and letrozole, which mean that the two drugs are not homogenous in respect to the number of mature follicles ≥17 mm per cycle.

Table 1
Number and percentage of cycles responded to the treatment with clomifene and letrozole.

Treatment groups	No. (%) of cycles	
	Total	[a]Responded
C	80	33 (41.25%)
L	47	33 (70.21%)

C = Clomifene, L = Letrozole.
[a] Resulted in one or more mature follicles ≥17 mm.

Table 2
Mean number and mean size of follicle ≥17 mm post treatment with clomifene and letrozole.

Treatment groups	Mature follicle ≥17 mm (Mean ± SD)	
	No.	Size
C	1.15 ± 0.44	19.82 ± 2.94
L	[a]1.42 ± 0.66	20.57 ± 2.74

C = Clomifene, L = Letrozole.
[a] The mean difference is significant ($p < 0.05$).

Table 4
Means of ET value post treatment with clomifene and letrozole.

Treatment Groups	C	L
ET mean ± SD (mm)	[a]9.62 ± 2.66	8.02 ± 1.24
ET range (mm)	4.6–13	6–10.2

C = Clomifene, L = Letrozole.
[a] The mean difference is significant ($p < 0.05$).

3.4. Endometrial thickness (ET) post treatment with clomifene and letrozole

Table 4 shows means value of ET measured in day 12 of menstrual cycle in the cycles responded to the treatment with CC and letrozole. Statistical analysis showed significant difference ($p < 0.05$) in ET value between CC and letrozole.

3.5. Pregnancy rate (per cycle) in clomifene and letrozole groups

There was no significant difference ($p > 0.05$) between the pregnancy rates per cycles in CC and letrozole groups (12.12% vs 9.09%). Two pregnancies had occurred among women who had received letrozole for one cycle and one pregnancy had occurred among women who had received letrozole for two cycles.

One pregnancy had occurred among women who had received CC for one cycle, one pregnancy occurred among women who received CC for two cycles and two pregnancies had occurred successively in the same woman who had received CC for two cycles.

Note: Regarding the occurrence of miscarriage, up to our knowledge two miscarriages among the four pregnancies that were occurred in CC group had occurred in the same women who had received CC for two cycles. One miscarriage and one full term delivery had occurred among the three pregnancies that were occurred in letrozole group.

4. Discussion

Regarding Clomifene citrate, morphometric analysis of the endometrium from women with CC-treated cycles revealed abnormal endometrial development as demonstrated by a reduction in glandular density and an increase in the number of vacuolated cells [28]. In the present study the percentage of the responded cycles (41.25%) after treatment with CC disagrees with that of Shamdeen and Mohammad [29] study in which only (27%) cycles were responded to 200 mg CC daily for 5 days given to overweight PCOS infertile women who failed to respond to 150 mg CC, and this may explain the low number of responded cycles in our study as the CC treated women were overweight (BMI is 29.3 ± 4.3), moreover Legro et al. [2] found that indication of CC in women with PCOS and anovulation, has certain limitations in patients with BMI > 30 and advanced age. Also it disagrees with Badawy et al. [30], Atay et al. [31] and Bayar et al. [32] studies in which ovulatory cycles

Table 3
Distribution of cycles according to the number of mature follicles in each cycle post treated with clomifene and letrozole.

Treatment groups	Cycles with mature follicles according to the no. of MF in a cycle no. (%)				
	With 1 MF	With 2 MF	With 3 MF	With 4 MF	Total cycles
C	[a]29 (87.87)	3(9.67)	1(3.22)	0 (0)	33
L	21(63.63)	11(33.33)	0(0)	1(3.03)	33

C = Clomifene, L = Letrozole, MF = mature follicles.
[a] The mean difference is significant ($p < 0.05$).

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were (70.9%), (63.6%) and (74.7%) respectively. The low percentage of responded cycles in CC group (41.25%) may be related to the use of different brand of CC by the above studies or it may be explained by the presence of CC resistance that may affects (20–25%) of PCOS women [33].

The mean no. of mature follicles ≥17 mm in CC treated group (1.15 ± 0.44) is in agreement with that found by Bayar et al. [32] study in which it was (1), and it is comparable to that found by Sohrabvand et al. [34] study which was (1.8), while it disagrees with that found by Atay et al. [31] and Badawy et al. [30] studies in which the mean no. of mature follicles were (2.4) and (3.1) respectively. In the present study one mature follicle (monofollicular cycles), two mature follicles and three mature follicles had developed in (87.87%), (9.67%) and (3.22%) cycles treated with CC. This result indicates that monofollicular cycles was higher in CC than in letrozole treated cycles which disagrees with the previous studies [35,36].

In the present study the ET measured at day 12 of menstrual cycle after treatment with CC (9.68 ± 2.73 mm), is in agreement with ET measured by Davar et al. [26] and Badawy et al. [30] at the day of hCG administration which were (9.3 ± 0.9 mm.) and (9.2 mm) respectively, while it disagrees with ET measured by Sohrabvand et al. [34] and Atay et al. [31] at day of hCG injection which were (5.5 ± 2.8 mm) and (5.2 mm) respectively. However Kolibianakis et al. [37] found that ET is not necessarily predictive of pregnancy in CC-stimulated cycles.

The pregnancy rate per cycle in CC group (12.12%) is comparable to that found by Al-Fozan et al. [38], Atay et al. [31], Bayar et al. [32], Sohrabvand et al. [34] and Badawy et al. [30] studies, which were (8.9%), (9.1%), (7.4%), (7%) and (17.9%) respectively, while it disagrees with that found by Batukan et al. [39], Eijkemans et al. [40] and Davar et al. [26] studies, which were (4.2%), (22%) and (1%) respectively.

According to the result of our study the use of CC alone for treatment of PCOS related infertility is insufficient and it should be combined with other infertility medication such as metformin as shown by a meta-analysis of randomized clinical trials which found that metformin plus CC superior to CC plus placebo for ovulation induction [41].

For women given Letrezole as an ovulation inducing agent been claimed to have several advantages including, rapid clearance from the body so less likely to have antiestrogenic effect on endometrium and cervical mucus quality resulting in high pregnancy rate, monofollicular ovulation resulting in lesser chance of ovarian hyperstimulation syndrome (OHSS) and multiple gestation, no accumulation of the medicine or its metabolite [36,42]. AIs have been proposed as both first and secondary treatment for ovulation induction in women with PCOS especially after CC failure [43], and also for unexplained infertility [44]. In our study regarding the number of the responded cycles after treatment with letrozole (70.21%), it is in agreement with that found by Mitwally and Casper [19], Bayar et al. [32], and Badawy et al. [30,22] studies in which the ovulatory cycles were (75%), (65. 7%), (67.5%) and (62%) respectively after treatment with 2.5 mg daily letrozole. While it disagrees with that found by Davar and Aflatoonian [25], Elnashar et al. [45] and Nupur et al. [24] studies in which ovulation rates were (5%), (54.6%) and (35.2%) respectively among cycles treated with 2.5 mg daily letrozole, on the other hand our study showed less percentage of responded cycles than that were obtained by Al-Omari et al. [46] and Atay et al. [31] studies in which ovulation rates were (84.4%) and (82.4%) respectively among cycles treated with 2.5 mg daily letrozole.

In regard to the number of cycles responded to CC and letrozole treatment (41.25% and 70.21% respectively) our results are in agreement with Atay et al. [31], Bayar et al. [32], Sohrabvand et al. [34] and Badawy et al. [30] studies in which the overall effects of letrozole in comparison to CC in PCOS women were insignificant. In our study the mean no. of mature follicles (≥17 mm) in letrozole treated group (1.42 ± 0.66) is in agreement with that found by Nupur et al. [24] study in which the mean no. of mature follicles was (1.30 ± 0.2) after treatment with 2.5 mg letrozole twice daily (5 mg/day), also it is in agreement with that found by Al-Omari et al. [46], Atay et al. [31], Elnashar et al. [45], Bayar et al. [7] and Sohrabvand et al. [34] studies in which the mean no. of mature follicles were (1.7), (1.2), (1.2), (1) and (1.9) respectively after treatment with letrozole 2.5 mg daily. While it disagrees with that found by Mitwally and Casper [19] and Badawy et al. [22] studies in which mean no. of mature follicles were (2.1) and (2.3) respectively after treatment with letrozole 2.5 mg daily.

Our study found that the mean no. of mature follicles was significantly higher in letrozole than in CC group (1.42 vs 1.15), which is in agreement with Mitwally et al. [35] study. Also it is in agreement with Al-Fozan et al. [38] study in women undergoing ovulation induction and intrauterine insemination (IUI) after treatment with CC and letrozole (7.5 mg daily) although significant difference was not found, and it is comparable to Bayar et al. [32] study (1 vs 1) in which letrozole dose was 2.5 mg daily. While it disagrees with studies achieved by the following; Fisher et al. [18] who found no significant difference in the number of follicles between CC and letrozole stimulated cycles, Fatemi et al. [47] who found that significantly more follicles ≥17 mm were developed in CC than in letrozole (2.5 mg daily) treated patients among those who were undergoing IUI, Jee et al. [48] who found that letrozole (2.5 mg daily) associated with gonadotrophins resulted in a significantly lower number of mature follicles when compared with CC combined with human menopausal gonadotrophin (hMG), Atay et al. [31] who found that the mean no. of mature follicles was (1.2 vs 2.4) after treatment with letrozole (2.5 mg daily) and CC (100 mg daily) respectively, and with Badawy et al. [30] who found that the mean no. of mature follicles was (2.3 vs 3.1) after treatment with letrozole (5 mg daily) and CC (100 mg daily) respectively.

The significant differences in the mean no. of mature follicles between CC and letrozole groups (1.15 ± 0.44 vs 1.42 ± 0.66) may be attributed to the dose of letrozole (5 mg daily) used in this study which may be high, this explanation goes with [38] who had use 7.5 mg letrozole daily, the letrozole high dose may result in an amplified effect that may lead to accumulation of high amount of intrafollicular androgen [49], which in turn augment follicular FSH receptor expression thus, it promotes follicular growth and estrogen biosynthesis indirectly by amplifying FSH effects [50].

In the present study the number of cycles resulted in one mature follicle (monofollicular cycles) in letrozole after treated was higher than those resulted in two mature follicles (63.6% vs 33.3%); this result agrees with Atay et al. [31] and Bayar et al. [32] who found that the monofollicular cycles was high in letrozole treated women, also it is comparable to that found by Elnashar et al. [45] study in which (79%) cycles developed one mature follicle and (21%) cycles developed two mature follicles. This limitation in the number of mature follicles might decrease the risk of multiple pregnancy and OHSS [46]. In the present study, letrozole caused only (3.4%) cycles to develop four mature follicles, which may be occurred due to low estrogen production and accumulation of intraovarian androgen because of aromatase inhibition that may lead to growth of one or more ovarian follicles by increasing follicular sensitivity to FSH or deceasing estrogen production [34].

According to the result of our study and although the mean no. of mature follicles ≥17 mm was significantly higher in letrozole group in comparison to CC group (1.42 vs 1.15), treatment with letrozole does not need intensive monitoring. This result is in agreement with Casper who demonstrated that the major advantage of AIs for ovulation induction in women with PCOS is mono-ovulation [51].

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In this study the percentage of monofollicular cycles was higher in CC than in letrozole group and this disagrees with that found by Atay et al. [31] and Bayar et al. [32] studies in which the percentage of monofollicular cycles was higher in letrozole than in CC treated women, this disagreement may be attributed to discrepancy between numbers of patients and cycles which in turn affects the cumulative effect of CC or it may be attributed to the cap between total numbers of the included cycles in both groups of our study which was higher in CC group (80 vs 47) while their numbers in Atay et al. [31] and Bayar et al. [32] studies were very near (55 vs 51 and 95 vs 99 respectively).

The ET measured at day 12 of menstrual cycle after treatment with letrozole (8.02 ± 1.24 mm) is in agreement with ET value measured at the time of hCG administration after treatment with letrozole by Mitwally and Casper [19], Al-Omari et al. [46], Atay et al. [31], Bayar et al. [32], Elnashar et al. [45], Badawy et al. [30,22] and Nupur et al. [24] in which ET was (8.1 mm), (8.4 mm), (8.2 mm), (8 mm), (10.2 mm), (8.1 mm), (9.1 ± 0.2 mm.) and (10.1 ± 0.3 mm.) respectively, also it is in agreement with (8.2 ± 1.3 mm) measured by Sohrabvand et al. [34] in PCOS CC-resistant women who were treated with a combination of letrozole and meftormin compared to those treated with a combination of CC and metformin (5.5 mm), also it is in agreement with (10.3 ± 1.02 mm) measured by Davar et al. [26] in CC-resistance PCOS patients undergoing IUI after treatment with metformin-letrozole combination in comparison to metformin–CC combination. Our study showed that ET measured at day 12 of menstrual cycle was significantly greater in CC than in letrozole treated groups (9.7 ± 2.7 mm vs 8.0 ± 1.2 mm), this result is in agreement with Badawy et al. [30] study in which ET at the day of hCG administration was significantly greater in patients received CC than in patients received letrozole (9.2 mm vs 8.1 mm), the greater ET in CC group in comparison to letrozole group may be as had explained by Badawy et al. [30] attributed to the high level of estrogen per each follicle which is positively correlated with the development and growth of endometrium.

Although AIs appear to have less anti-estrogenic effect on the endometrium [36], the evidence on endometrial effects is conflicting and most studies show equivalence with CC [38,30,32]. Some studies showed that ET at mid-cycle was similar in letrozole and CC treated groups [18,47].

The pregnancy rate per cycle in letrozole group in our study (9.09%) is in agreement with that found by Al-Fozan et al. [38], Bayar et al. [32] and Gregoriou et al. [52] which were (11.5%), (9.1%) and (8.9%) respectively, although hCG was not used to trigger ovulation in our study while it was used by the above mentioned studies. Also it is comparable to that found by Elnashar et al. [45], Badawy et al. [22] and Nupur et al. [24] studies in which pregnancy/cycle were (13.6%), (12.2%) and (14.2%) respectively; only in Nupur et al. [24] study the ovulation was spontaneous (not induced by hCG). The current study disagrees with that found by Davar and Aflatoonian [25] and Davar et al. [26] studies in which pregnancy/cycle were (0%) and (5%) respectively despite the use of hCG to induce ovulation, also it disagrees with that found by Metawie [53], Mitwally and Casper [19], Al-Omari et al. [46], Atay et al. [31], Sohrabvand et al. [34], Badawy et al. [30] and Begum et al. [54] in which pregnancy/cycle were (17.5%), (25%), (18.8%), (21.6%), (19%), (15.1%) and (40.3%) respectively, although hCG had been used to induce ovulation by the above mentioned studies. In the present study the low pregnancy rate per cycle in letrozole group (9.09%) despite high percentage of the responded cycles (70.21%) indicates that letrozole used alone for treatment of PCOS related infertility was not sufficient and the use of hCG may be necessary.

In order to enhance its activity, letrozole should be combined with another medication of infertility like low dose of FSH as found by Healey et al. [55], Mitwally and Casper [56], Garcia-Velasco et al. [49] and Badawy et al. [30] studies in which rate of pregnancy per cycle were (21.6%), (22.2%), (22.4%) and (19%) respectively, letrozole combined low-dose gonadotropins therapy offers a higher rate of ovulation, monofollicular development, with a significantly lower risk of OHSS [57] or it combined with metformin as in Sohrabvand et al. [34] study in which pregnancy rate per cycle was (19%). Result of our study in regard to rate of pregnancy per cycle after treatment with letrozole and CC goes with that found by Atay et al. [31], Bayar et al. [32], Sohrabvand et al. [34] and Badawy et al. [30] in which significant differences in pregnancy per cycle between letrozole and CC in PCOS women were not found.

Another study showed that letrozole was not significantly superior to CC in the following variables: ovulatory cycles, pregnancy rates per cycle and per patient [58].

5. Conclusions

Letrozole (5 mg/day) was better than CC (100 mg/day) in regard to the responded cycles but it resulted in significantly unfavorable mean number of mature follicles (≥17 mm) in comparison to CC, whereas regarding to ET (at day 12 of cycle), monofollicular cycles, and pregnancy/cycle, CC had a better effect.

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