Comparison of Letrozole vs Clomiphene Citrate for induction of ovulation in polycystic ovarian syndrome - An Iraqi study

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Abstract
Polycystic ovary syndrome is a common endocrine disorder in young women and manifests as infertility in 55-75%. Clomiphene citrate is still the standard drug for inducing or augmenting ovulation. It is not, however, equally successful in all situations. Metromile is an aromatase inhibitor and is one of the alternative treatments to Clomiphene. This study aims to answer the question (does letrozole add anything to the art of ovulation induction and represent a real alternative to Clomiphene? To compare the effects of letrozole (5 mg) and clomiphene citrate (100 mg) for ovulation induction in women with polycystic ovary syndrome. A prospective randomized trial study was done at Tikrit Teaching Hospital. The study comprised a total of 40 infertile women with polycystic ovary syndrome; Patients were randomized to treatment with 5 mg Of letrozole daily (20 patients) or 100 mg of clomiphene citrate daily (20 patients) for 5 days starting on day 3 Of menses. Timed intercourse was advised 24-36 hours after hCG injection. Then, both groups were followed by sonography every other day from day 10 Of the menstrual cycle for the number and size Of follicles and endometrial thickness were assessed. The study revealed that the C . C group induce ovum with size > 18mm 12 (60%) versus 17 (85%) among Letrzol group, while < 18mm in about 8 C.C group as compared with 3 (15%) in Letrzol group, this relation was statistically not significant. The study revealed that C.C group induce > 1 follicle 8 (40%) versus 2 (10%) among Letrzol group, while I follicle induced in about 6 (30%) in C.C group as compared with 16 (80%) in Letrzol group, this relation was statistically significant. The endometrium thickness was 4-5 mm in 14 (70%) among C.C group, and 17 (85%) in Letrzol group , while uterine thickness was 6-9.5mm in 6 (30%) among C.C group and 3 (15%) among Letrzol group, this relation was statistically not significant, study conclude that Letrozole should be considered as first line drug to get away from clomiphene's unwanted effects like thin endometrium and multi-folliculogenesis.

Keyword: letrozole, endometrium, clomiphene citrate, ovulation, Polycystic ovarian syndrome (PCOS)

AIM OF study: aims at answering the question (does letrozole add anything to the art of ovulation induction and represent a real alternative to Clomiphene? To compare the effects of letrozole (5 mg) and clomiphene citrate (100 mg) ü'r ovulation induction in women with polycystic ovary syndrome.

Introduction Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy, affecting 6% of within of reproductive age [ll. The overall prevalence of PCOS among repxxiuicive age women in the United States (US) was 4% Clomiphene citrate has been the first-line and standard drug treatment for PCOS for the
last 40 years. Early studies proved that up to 80% of anovulatory patients responded well to Clomiphene citrate as assessed by achievement of ovulation, with about half of those who were ovulatory achieving pregnancy. However, approximately 20% of patients required a high dose of Clomiphene citrate (200 mg daily taken for 5 days early in the cycle), which may result from anti-estrogenic activities on the endometrium and cervical mucus. Letrozole was as an alternative to clomiphene citrate as a highly selective aromatase inhibitor that prevents androgen-to-estrogen conversion. This aromatase inhibitor has a short half-life (45 hours); thus it is rapidly eliminated from the body. No adverse effects on estrogen target tissues or downregulation of estrogen receptor (ER) are seen with Letrozole due to this short half-life, unlike Clomiphene citrate [31]. The aim of the aromatase inhibitor was to avoid the peripheral anti-estrogenic effects of Clomiphene citrate, especially thinning of the endometrial lining.

Objectives:

1. The clinical manifestation of patients with PCOS
2. The relationship between medical problems and type of infertility
3. The relationship between pelvic surgery and other surgical problems with infertility
4. To know the distribution of Rotterdam criteria according to type of infertility S. To assess the effect of Clomiphene and Letrozol on induction of ovulation.
5. To assess the effect of Clomiphene and Letrozol on ovum number and size.
6. To assess the effect of Clomiphene and Letrozol on endometrium thickness

2.1. Definition

PCOS is a heterogeneous collection of signs and symptoms that together form a spectrum of disorders with mild presentation in some while in others severe disturbances of reproductive endocrine, and metabolic function. Main recent advance in the agreed definition of PCOS was agreed at the Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Work Shop. Joint ESHRE/ASRM consensus defined PCOS as requiring the presence of two out of the following three criteria

1. Oligo — and or anovulation (that is oligo — amenorrhea or amenorrhoea).
2. Hyperandrogenism, (Clinical features and/or biochemical elevation of testosterone and or).  
3. Poly cystic ovarian assessed by US. Defined as the presence of 12 or more follicles in each ovary (with one ovary being sufficient for diagnosis) measuring 2-9 mm in diameter and/or increased ovarian volume (> 10 Omi).  

Essentially, the Rotterdam criteria added two phenotypes of women with PCOS.

Women with normal menstrual periods and normal fertility, but who have androgen excess and women with oligomenorrhoea and polycystic ovaries on ultrasound, but normal androgen excess.

This definition was, however, not to be applied to women on the oral contraceptive pill as it changes the ovarian morphology. It was also suggested that in the presence of dominant follicle (>10mm) or corpus luteum, the scan was to be repeated in the next cycle.

Prevalence

The polycystic ovarian syndrome is a common endocrinopathy, affecting approximately 5-10% of women of reproductive age.

Genetics of polycystic ovary syndrome

Polycystic ovary syndrome has long been noted to have a familial component. Genetic analysis has been hampered by lack of universal definition for PCOS, most of the criteria, used for diagnosing PCOS, are continuous traits, such as degree of hirsutism. Level of circulating androgens extent of menstrual irregularity and ovarian volume and morphology. To perform genetic analysis, these continuous variables have to be transformed into nominal variables.

Family studies, have revealed that about 50% of first degree relatives have (PCOS suggesting a dominant mode of inheritance, commonly, first degree male appear more likely to have the metabolic syndrome. As hyperandrogenism is a key feature of PCOS, it is logical to explore the critical steps in steroid genesis and potential enzyme dysfunction, some studies have found an abnormality with the cholesterol side — chain cleavage (CYP11A), which is a rate limiting step in steroidogenesis.

It has also been hypothesized, that polymorphisms in the insulin receptor (INSR) gene that induce mild changes in insulin, receptor function, may contribute to the development of PCOS. As it is unlikely that a major mutation, is present given the wide variability of insulin resistance in women with (PCOS).
Hypersecretion of androgens by the stromal theca cells of the (PCOS) leads to the cardinal clinical manifestation of the syndrome, hyper androgenism, and is also one of the mechanisms where by follicular growth is inhibited with the resultant excess of immature follicles, Hypersecretion of luteinizing hormone (LH) by the pituitary — a result of both disordered ovarian — pituitary feedback and exaggerated pulses of GNRH from the hypothalamus stimulates testosterone secretion by the ovary.

The pathophysiology of (PCOS)

Furthermore, insulin is a potent stimulus for androgen secretion by the ovary, which by way of different receptor for insulin does not exhibit insulin resistance Insulin therefore amplifies the affect of (LEI) and additionally magnifies the degree of hyper androgenism by suppressing liver production Of the main carrier protein, sex hormone binding globulin (SHBG), thus elevating the free androgen index. It is a combination of genetic abnormalities combined with enviromenal factor, such as nutrition and body weight, which then affect exptvssion of the syndrome.

Clinical feature

i- Menstrual irregularity:
Anovulation is usually chronic in (PCOS) and is associated with infertility and dysfunctional bleeding such as oligomenorrhea or amenorrhea. Periods of regular menses are possible. Some women who report normal menses may be anovulatory. The menstrual irregularity Of (PCOS) patient typically begins of menarche and although amenorrhea may occur, the usual presentation is oligomenorrhea. The proportion of (PCOS) patients with regular menses is thought to increase with age, reaching about 7% at 39-41 years.

2. Reproductive abnormalities:

Diagnosis of (PCOS)
Infertility is the presenting problem for about 40% (PCOS) patient. If pregnancy is achieved, other reproductive problem such as miscarriage, The relationship between (PCOS) and miscarriage is complex, (PCOS) is not predictive of miscarriage. But patient who miscarry have higher plasma level of androgen than women with ongoing pregnancies, miscarriage rate in (PCOS) is about 30% Of all pregnancies which is double the rate for early miscarriage in normal women. Higher levels of LH and androgen have been regarded as a cause for poor reproductive history. The unfavorable endocrine environment to which ovarian follicles arc exposed could be at least partly responsible for alow percentage Of pregnancies, because it affect oocyte quality and luteal phase, efficiency however oocytes Of women with (PCOS) are nearly always normal and when removed from their unfavorable environment, have a similar fertilization percentage too oocytes of normal women.

3. Hyperandrogeism Hirsutism is the presence of terminal (coarse) hairs in females in a male — like pattern, affecting between 5% of women. Hirsutism has asignificant negative impact on psychological development and is usually asign Of an underlying endocrine abnormality — namely, androgen excess. Acne affects 15-25% Of (PCOS) patients although it is unclear whether the prevalence Of acne is significantly increased in those patients. Over that observed in the general population patients have normal secondary sexual characteristic do not exhibit signs Of virilization such as clitromegaly or voice deepening.
What causes polycystic ovary syndrome?

Although the exact cause is not known, polycystic ovary syndrome (PCOS) involves interactions of hormonal abnormalities, some of which are self-perpetuating. The result: hyperandrogenism, anovulation, infertility.

Gonadotropin-releasing hormone (GnRH) stimulates release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

LH is increased, stimulating androgen production.

Follicle-stimulating hormone (FSH) may be low, inhibiting production of estradiol in favor of testosterone and estrone.

Dehydroepiandrosterone sulfate (DHEA) is converted to androstenedione and testosterone.

Androstenedione → Testosterone

Estrogen

Insulin promotes hyperandrogenism (and perhaps vice versa).

Estrogen controls LH release.
Gonadotrophins

In patients with (PCOS) gonadotrophins abnormalities include elevated levels of LH. elevated (LWFSH) ratio, increase LH pulse frequency and elevated diurnal rhythm of LH secretion. The ratio of LH to FSH is greater than as tested on day 3 of the menstrual cycle. The pattern is not very specific and was present in less than (50%) in one study.

2. 2- Progesterin:
Prognosis levels are usually normal although they may slightly elevated in small fraction of patients.

Imaging studies:
Tonard and colleagues nxxlified the definition of (PCO) by adding of (212) follicles measuring (2-9 mm) in diameter (mean of both follicle). they also strengthened the hypothesis that the intra — ovarian hyrrandrogenism promotes excessive early follicular growth and that further progression cannot proceed normally because of hyperinsulinism and/or other metabolic influence linked to obesity. Battaglia et al. reported a higher uterine artery pulsatility index (PI) in women with (PCOS) and a decreased resistance index (RI) within the ovarian Stroma in (PCOS) (suggestive of increased downstream resistance) and a positive correlation with LH levels, capillary area increases after the LH surge, causing blood flow attributed to vasodilatation and resulting in now cektion with Doppler ultrasound. mechanism responsible for these haemodynamic changes in (PCOS) is not known, but it may be significant that stromal blood flow in (PCOS) has been attributed to increased Concentrations of serum vascular endothelial growth factor.

7. Management
Medical treatment of PCOS is tailored to the patient's goals. Broadly, these may be considered under four categories:

- Lowering of insulin resistance levels
- Restoration of fertility
- Treatment of hirsutism or acne
- Restoration of regular menstruation, and prevention of endometrial hyperplasia and endometrial cancer

In each of these areas, there is considerable debate as to the optimal treatment.

One of the major reasons for this is the lack of large scale clinical trials comparing different treatments. Smaller trials tend to be less reliable and hence may produce conflicting results. General interventions that help to reduce weight or insulin resistance can be beneficial for all these aims, because they address what is believed to be the underlying cause, As PCOS appears to cause significant emotional distress, appropriate support may be useful.

Diet
Where PCOS is associated with overweight or obesity, successful weight loss is the most effective method of restoring normal ovulation. menstruation, but many women find it very difficult to achieve and sustain significant weight loss. A scientific review in 2013 found similar decreases in weight and body composition and improvements in pregnancy rate, menstrual regularity, ovulation, hyperandrogenism, insulin resistance, lipids and quality of life to occur with weight loss independent of diet composition. Still, a in which a significant part of total carbohydrates are obtained from fruit, vegetables and whole grain sources, has resulted in increased menstrual regularity than a macronutrient-matched healthy diet. may play some role in the development of the so treatment of any such deficiency is indicated.

2.8 Medications
Reducing insulin resistance by improving insulin sensitivity through medications such as metformin.

Although metformin is not licensed for use in PCOS, the United Kingdom's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin when other therapy has failed to produce results. However subsequent reviews in 2008 and 2009 have noted that randomised control trials have in general not shown the promise suggested by the early observational studies.
Not all women with PCOS have difficulty becoming pregnant. For those who do, anovulation or infrequent ovulation is a common cause. Other factors include changed levels of gonadotropins, hyperandrogenemia and hyperinsulinemia. Like women without women with PCOS who are ovulating may be infertile due to other causes, such as tubal blockages due to a histot of sexually transmitted diseases. For overweight, anovulatory women with PCOS, weight loss and diet adjustments, especially to reduce the intake of simple carbohydrates, are associated with resumption of natural ovulation.

For those who aner weigh loss still are anovulatory Or for anovulatory lean women, then the ovulation-inducing medications clomiphene citrate and FSH are the principal treatments used to promote ovulation. Previously, the anti diabetes medication metformin was recommended treatment for anovulation, but it appears less effective than clomiphene.

For patients who do not respond to clomiphene, diet und lifestyle modification, there are options available including assisted reproductive technology procedures such as controlled ovarian hyperstimulation with folliclestimulating hormone (FSH) injections followed by in vitro fertilisation (IVF).

Though surgery is not commonly perfonne, the polycystic ovaries can be treated with a laparoscopic procedure called "ovarian drilling" (puncture of 4—10 small follicles with electrocautery, laser, or biopsy needles), which often results in either resumption of spontaneous ovulations or ovulations after adjuvant treatment with clomiphene or FSH (Ovarian wedge resection is no longer used as much due to complications such as and the presence of frequently effective medications.) There are, however, concerns about the long-term effects Of ovarian drilling on ovarian function.

2. 11 Hirsutism and acne.

When appropriate (e.g. in women Of child-bearing age who require contraception), a standard contraceptive pill is frequently effective in reducing hirsutism. A common choice of contraceptive pill is One that contains cyproterone acetate; in the UK the available brands are Diane/ Diane. Cyproterone acetate is a progestogen with anti-androgen effects that block the action Of male hormones that believed to Contribute to acne and the growth Of unwanted facial and body hair. On the other hand, progestogens such as norgestrel and levonorgestrel should be avoided due to their androgenic effects.

Other drugs with anti-androgen effects include and spironolactone which can give some improvement in hirsutism. Spironolactone is probably the most-commonly used drug in the US. Metformin can reduce hirsutism, perhaps by reducing insulin resistance, and is often used if there are other features such as insulin resistance, diabetes or obesity that should also benefit from metformin. Ef lomithine (Vaniqa) ig a drug which is applied to the skin in cream form, and acts directly on the hair follicles to inhibit hair growth, It is usually applied to the face. Medications that reduce acne by indirect hormonal effects also include ergot dopamine agonists such as bromocriptine 5-alpha reductase inhibitors (such as finasteride and dutasteride) may also be used; they work by blocking the conversion Of testosterone to dihydrotestosterone (the latter Of which is responsible for most hair growth alterations and androgenic acne).

Although these agents have shown significant efficacy in Clinical trials (for oral contraceptives. in Of individuals), the reduction in hair growth may not be enough to eliminate the social embarrassment Of hirsutism, or the inconvenience Of plucking or shaving. Individuals in their response to different therapies. It is usually worth trying Other drug treatments if one does not work, but drug treatments do not work well for all individuals. For removal Of facial hairs. electrolysis or loser neatlnentg are — at least for some — faster and more efficient alternatives than the above mentioned medical therapies.


If fertility is not the primary aim, then menstruation can usually be regulated with a contraceptive pill. The purpose of regulating menstruation is essentially for the woman's convenience, and perhaps her sense Of well-being; there is no medical requirement for regular periods, so long as they sufficiently often. If a regular menstrual cycle is not desired, then therapy for an irregular cycle is not necessarily required.

Most experts say that if a menstrual bleed occurs at least every three months, then the endometrium (womb lining) is being shed sufficiently often to prevent an increased risk of endometrial abnormalities or cancer. If menstruation occurs less often or not at all, some form of progestogen replacement is
recommended. An alternative is oral progestogen taken at intervals (e.g. every three months) to induce a predictable menstrual bleeding.

2.13 Prognosis

Women with PCOS are at risk for the following:

- Endomyometriosis and endometriosis gangrenous (thickening of the uterine lining) are possible, due to overaccumulation of uterine lining, and also lack of progesterone resulting in prolonged stimulation of uterine cells by estrogen. (20)

- Insulin resistance is increased. Women with PCOS had an elevated prevalence of insulin resistance and type II diabetes, even when controlling for BMI. PCOS also makes a woman, particularly if obese, prone to particularly if obese and/or during pregnancy.

- Depression with anxiety disorders.

- Dyslipidemia — cholesterol and triglycerides. Patients show decreased removal of atherosclerosis inducing remnants, seemingly independent of insulin resistance.

- Cardiovascular disease with a meta-analysis estimating a 2-fold risk of arterial disease for women with PCOS relative to women without PCOS independent of BMI. Strokes, weight gain, miscarriage, sleep apnea, autoimmune thyroiditis, non-alcoholic fatty liver disease, acanthosis nigricans.

Early diagnosis and treatment may reduce the risk of some of these, such as type 2 diabetes and heart disease.

2.14 Clomifene (INN) or elomipbene.

Is a (SERM) that increases production of gonadotropins by inhibiting negative feedback of estrogen on gonadotropin release, leading to up-regulation of the hypothalamic-pituitary-gonadal axis. This synthetic drug comes supplied as white, round tablets in 50 mg strength only. It has become the most widely prescribed of all fertility drugs. It is used in the form of its citrate to induce 2.15 Use in female infertility

It is used mainly in female infertility, in turn mainly as ovulation induction to oligoovulation or anovulation such as in infertility in polycystic ovary syndrome, as well as being used for ovarian hyperstimulation, such as part of an in vitro fertilization procedure.

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2.16 Mode of action

Clomifene inhibits estrogen receptors in hypothalamus inhibiting negative feedback of estrogen on gonadotropin release, leading to up-regulation of the hypothalamic-pituitary-gonadal axis. Zuclomifene, a more active isomer, stays bound for long periods of time. Non-Steroid. In normal physiologic female hormonal cycling, at 7 days post ovulation, high levels of 

- progesterone produced from the corpus luteum inhibit beta-hCG, at the hypothalamus and of estrogen anterior pituitary. If fertilization does not occur in the post-ovulation period the corpus luteum disintegrates due to a lack of beta-hCG. This would normally be produced by the embryo in the effort of maintaining progesterone and estrogen levels during pregnancy.

Therapeutically, clomifene is given early in the menstrual cycle. It is typically prescribed beginning on day 3 and continuing for 5 days. By that time, FSH level is rising steadily, causing development of a few follicles. Follicles in turn produce the estrogen, which circulates in serum. In the presence of clomifene, the body perceives a low level of estrogen, similar to day 22 in the previous cycle.
2.22 Adverse effects

The most common side effects are sweating, hot flashes, arthrulgia (joint pain), and Generally, side effects include signs and symptoms Of hypoestrogenism. is concern that term use may lead to osteoporosis(45) which is in certain patient populations such as post-menopausal women or osteoporotics, bisphosphonates may also bc prescribed

2.23 Interactions

Letrozole inhibits the liver enzyme and to a lesser extent CYP2C19, but no relevant interactions with drugs like cimetidine und warfarin have been observed(46)

2.24 Comparison with tamoxifen

Tamoxifen is also used to treat hormonally-responsive breast cancer, but it does so by interfering with the estrogen receptor. However, letrozole is effective only in post-menopausal women, in whom estrogen is produced predominantly in peripheral tissues (i.e. in adipose tissue, like that Of the breast) and a number of sites in the brain(48). In pre-menopausal women. the main source of estrogen is from the ovaries not the peripheral tissues, and letrozole is ineffective. In the BIG 1—98 Study, of post-menopausal women with hormonally-responsive breast cancer, letrozole reduced the recurrence of cancer, but did not change survival rate, compared to tamoxifen.(51)(49)

In 2012, an Indian parliamentary committee said that the drug controller office colluded with letrozoWs makers to approve the drug for infertility in India and also stated that letrozole•s for infertility was illegal however, such off-label uses are legal in many countries such as the US and

The anti-estrogen action Of letrozole has been shown to be useful in pretreatment for termination of pregnancy, in combination with misoprostol. It can be used in place of mifepristone, which is expensive and unavaiable in many countries.(51)

2.20 Mechanism Of action

Estrogens are produced by the conversion of androgens through the activity of the ammatase enzyme. Estrogens then bind to an estrogen receptor, which causes cells to divide. Letrozole prevents the aromatase from producing estrogens by comFtitive, reversible binding to the heme of its cytochrome 11450 unit. The action is specific. and letrozole not reduce production of mineralo- or corticosteroids.

2.21 Contraindications

Letrozole is contraindicated in women having a pre-menopausal hormonal status, during pregnancy and lactation.(50) Letrozole is approved by the united states food and drug administration (FDA) for the treatment Of local or metastatic breast cancer that is hormone receptor positive or has unknown receptor status in postmenopausal women.(45)

Off-label uses Letrozole bas used for ovarian stimulation by fertility doctors since 2001 it has fewer side-effects than clomiphene (Clomid) and less chance of multiple gestation. A Canadian study presented at the American Society of Reproductive Medicine 2005 Conference suggests that letrozole may increase the risk of birth defects A more detailed ovulation induction follow-up study found that letrozole, compared with a control group of clomiphene, had significantly lower congenital malformations and chromosomal abnormalities at an Overall rate of 2.4% (1.2% major malformations) compared with clomiphene 4.8% (3.0% major malformation Despite this, India banned the usage of letrozole in 2011, potential risks to infants.(47)

Infrequent adverse effects of patients) include: abnormal uterine bleeding, nausea, and/or vomiting. Rare adverse effects of patients) include: reversible AløeggiA and/or

In comparison to treatment with purified FSH, the rate of ovarian hyperstimulation syndrome is low when using clomifene. Clomifene can lead to multiple ovulation, hence increasing the chance of Of births instead of the normal — and Ej21pE; some parents-to-be then opt for to reduce number of fetuses. Overall, clomifene citrate has not been round to cause a significant increase in the risk of overion cancer except in women who remain nylligtavid after treatment.(33)
History: Clomifene has been used since the 1960s. It was first used to treat cases of oligomenorrhea. When it was realized that women undergoing treatment had higher than expected pregnancy rates, it was then applied to treatment of anovulation.

**Letrozole** is an oral non-steroidal aromatase inhibitor for the treatment of hormonally responsive breast cancer after surgery. Uses FDA-approved use. Since estrogen can no longer effectively exert negative feedback on the hypothalamus, GnRH secretion becomes more rapidly pulsatile, which results in increased pituitary gonadotropin (FSH, LH) release. (It should be noted that more rapid, lower amplitude pulses of GORH lead to increased LH/FSH secretion, while more irregular, larger amplitude pulses of GORH leads to a decrease in the ratio of LH/FSH.) Increased FSH level causes growth of more ovarian follicles, and subsequently rupture of follicles resulting in ovulation occurs most often 6-7 days after a course of clomifene.

2. Chemistry

Clomifene is a mixture of two isomers, enclomifene (E. clomifene) and zucloifene (Z-clomifene).
Most experts say that if a menstrual bleed occurs at least every three months, then the endometrium (womb lining) is being shed sufficiently often to prevent an increased risk of endometrial abnormalities or cancer. If menstruation occurs less often or not at all, some form of progestogen replacement is recommended. An alternative is oral progestogen taken at intervals (e.g., every three months) to induce a predictable menstrual bleeding.

2.12 Menstrual irregularity and endometrial hyperplasia

If fertility is not the primary aim, then menstruation can usually be regulated with a contraceptive pill. The purpose of regulating menstruation is essentially for the woman's convenience, and perhaps her sense of well-being; there is no medical requirement for regular periods, so long as they sufficiently often. If a regular menstrual cycle is not desired, then therapy for an irregular cycle is not necessarily required. Though surgery is not commonly performed, the polycystic ovaries can be treated with a laparoscopic procedure called "ovarian drilling" (puncture of 4—10 small follicles with electrocautery, laser, or biopsy needles), which often results in either resumption of spontaneous ovulations or ovulations after adjuvant treatment with clomiphene or FSH (Ovarian wedge resection is no longer used as much due to complications such as and the presence of frequently effective medications.) There are, however, concerns about the long-term effects of ovarian drilling on ovarian function.

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Patients and Method

The study comprised 40 women with PCOS among those attending the Outpatient Clinic in Tikrit Teaching Hospitals, in the period from February - June 2014. The diagnosis of PCOS was based on the Revised consensus diagnostic criteria for PCOS patients age range between 20-43 years old and their main presentation is infertility. All women and their partners had normal semen analysis parameters according to the modified criteria of the World Health Organization. All patients had normal serum prolactin, thyroid stimulating hormone (TSH) and 17-OH progesterone.

Withdrawal bleeding was achieved using 10-mg levonorgestrel tablets for 10 days before stimulation. Patients then were randomly allocated into two treatment groups: letrozole group (20 patients) and CC group (20 patients).

The study was approved by the hospital research ethics committee, and all participants gave informed consent before inclusion in the trial. Patients in the letrozole group had 5 mg or letrozole (Novartis Pharma Services, Basel, Switzerland) daily for 5 days starting on day 3 of menses (20 patients); patients in the CC group had 100 mg of CC daily starting day 3 of the menses for 5 days (20 patients).

All patients were monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on the days 10, 12, and 14 of the cycle.

Statistical Analysis

Data were statistically analyzed using SPSS computer package SpSS, version 18. Chi X^2 square test used for testing the proportional relations between variables of two study groups. Unpaired Student test used to compare means of numerical variables, was regarded as statistically significant.
RESULTS

Table 1 the sample distribution according to state of medical problems

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<th>Type of Infertility</th>
<th>Medical problems</th>
<th>No medical problem previously</th>
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<tr>
<td></td>
<td>H.T. No</td>
<td>percent</td>
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<tr>
<td>Primary</td>
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<tr>
<td>Secondary</td>
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<td>0</td>
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<td>Both</td>
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<td>25</td>
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Χ²=5.91, df=6, P> 0.05 NS
Table 2 the sample distribution according to state of surgical problems

<table>
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<th>Type of Infertility</th>
<th>Surgical Problems</th>
<th>No</th>
<th>Percent</th>
<th>No</th>
<th>Percent</th>
<th>No</th>
<th>Percent</th>
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<tbody>
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<td>9</td>
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<td>26</td>
<td>100.0</td>
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</tbody>
</table>

X²=2.136, df=4, P>0.05 NS

Figure 1 shows that the presenting symptom was infertility in about 31(77.5%) of the sample followed by hirsuitism 2(5%), and hirsuitism and infertility 2(5%), and hirsuitism and infertility and obesity 2(5%).

Figure 1 the main presenting symptoms of study group
Table 3 the sample distribution according to type of infertility and Rotterdam criteria

<table>
<thead>
<tr>
<th>Type of Infertility</th>
<th>Rotterdam criteria</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&amp;2</td>
<td>1&amp;3</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>1ry</td>
<td>7</td>
<td>53.9</td>
</tr>
<tr>
<td>2ndry</td>
<td>6</td>
<td>46.1</td>
</tr>
<tr>
<td>Both</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>100</td>
</tr>
</tbody>
</table>

1-Oligo and/or amenorrhea, 2-U/s picture of poly cystic ovary, 12 or more follicles measuring 2-9mm in diameter, and/or increased ovarian volume (≥ 10 cm3), 3-hyperandrogenism (clinical feature and/or biochemical elevation of testosterone), X2=6.422, df=6, P>0.05 NS
Table 4 the sample distribution according to type of infertility and type of treatment received

<table>
<thead>
<tr>
<th>Type of Infertility</th>
<th>C.C group N=20</th>
<th>L** group 2</th>
<th>P value()</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>percent</td>
<td>No</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26.4±3.55</td>
<td>27.72±3.334</td>
<td>&gt;0.05 NS (t=1.212)</td>
</tr>
<tr>
<td>BMI(Kg/m2)</td>
<td>24.31±1.3</td>
<td>24.43±1.21</td>
<td>&gt;0.05 NS (t=2.5)</td>
</tr>
<tr>
<td>1ry</td>
<td>13</td>
<td>65</td>
<td>14</td>
</tr>
<tr>
<td>2ndry</td>
<td>6</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Both</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100</td>
<td>20</td>
</tr>
</tbody>
</table>

*clomiphene citrate, **Letrozol

Table 5 the sample distribution according to type of treatment received and effect on ovulation induction

<table>
<thead>
<tr>
<th>No. of follicles</th>
<th>C.C</th>
<th>L</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>percent</td>
<td>No</td>
</tr>
<tr>
<td>1 follicle</td>
<td>6</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>&gt;1 follicle</td>
<td>8</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>no response</td>
<td>6</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100</td>
<td>20</td>
</tr>
</tbody>
</table>

X²=10.145, df=2, P<0.05 S

Table 6 show that the C.C group induce ovum with size > 18mm 12 (60%) versus 17 (85%) among Letrozol group, while < 18mm in about 8 (40%) in C.C group as compared with 3 (15%) in Letrozol group, this relation was statistically not significant.

Table 6 the sample distribution according to type of treatment received and size of follicle

<table>
<thead>
<tr>
<th>size of ovum</th>
<th>C.C</th>
<th>L</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>percent</td>
<td>No</td>
</tr>
<tr>
<td>&gt;18 mm</td>
<td>12</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>&lt;18 mm</td>
<td>8</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100</td>
<td>20</td>
</tr>
</tbody>
</table>

X²=3.135, df=1, P> 0.05 NS
Discussion

Most common treatable cause of infertility is anovulation. For last 40 years, the first line of treatment for women having anovulatory infertility was clomiphene citrate. Unfortunately, despite high rates of ovulation, pregnancy rates per cycle remain relatively low Both thin endometrium and nontrilaminar pattern of the endometrium at midcycle are associated with low pregnancy rates and early pregnancy loss For women who experienced these adverse effects with clomiphene citrate, the next option is induction of ovulation with gonadotropin which increases both cost and risk to the woman. Alternatively, letrozole a potent aromatase inhibitor with excellent oral bioavailability and relatively short half-life is used for ovulation induction. The study reveal that C.C group induce > 1 follicle 8 (40%) versus 2 (10%) among Letrzol group, while I follicle induced in about 6(30%) in C.C group as compared with 16 (80%) in Letrzol group, this relation was statistically significant. This agree with what seen by Usama M Fouda, Ahmed M Sayed that the extended letromle regimen had a superior efficacy as compared with clomiphene citrate in patients of unexplained infertility undergoing superovulation and LUI. (52) And also agree with Badawy et al who stated that In a recent study, Badawy et al reported that the extended letrozole regimen (2.5 mg/day from cycle day 1 to10) resulted in higher pregnancy rate compared with short high dose letrozole regimen (5 mg/day for 5 days) in clomipheneresistant women with polycystic ovary syndrome. (53)

During the past decade, letrozole (aromatase inhibitor approved by FDA for the treatment of postmenopausal women with breast cancer) has been successfully used for induction of ovulation in anovulatory patients with polycystic ovary syndrome (PCOS) and for augmentation of ovulation in ovulatory women [54]. In contrast to clomiphene citrate, letrozole is rapidly eliminated from the body and does not deplete estrogen receptors and therefore has no adverse effect on endometrium or endocervix. (55)

In our study we noted that women who had endometrial thickness Of 5mm with clomiphene citrate responded well with 2.5mg Of Letrozole and showed an increase in endometrial thickness up to 8mm. The numbers Of follicles developed per cycle by using clomiphene citrate was higher so it increases the chances Of ovarian hyperstimulation syndrome and multiple pregnancy , this results may be due to increase resistance to the clomiphene citrate in polycystic ovary syndrome.. This agree with the study that the endometrial thickness was significantly greater in the extended letrozole group. The results Of Our study are in agree with the results of Metwally and Casper and Sh Tehrani-Nejad et al (56). On the other hand, other studies revealed that the endometrial thickness was comparable in patients treated with letrozole or clomiphene citrate (57). In only one study, the endometrial thickness was significantly greater in the group Of patients treated with clomiphene citrate (57).
Conclusions
1. 1.75% of those with HT had primary infertility.
2. 100% of those with DM have primary infertility.
3. 60% of women with pelvic surgery had secondary infertility in comparison to 66.7% of those with surgical problems with 2ndary infertility.
4. Presenting symptom of PCOS patient was infertility in about 773% follow by hirsutism and infertility. While Obesity alone and irregular cycle, obesity and hirsutism (2.5%) for one.
5. The distribution of Rotterdam criteria according to type of infertility, in which of those patient that had I & 2 of
6. Rotterdam criteria 53.9%
7. C.C group induce > 1 follicle 8(40%)versus 10% among Letrozol group. while 1 follicle induced in about 30% in C.C group as compared with 16 (80%) in Letrozol group.
8. The C.C group induce ovum with size > 18mm 12 (60%) versus 17 (85%) among Letrozol group, while < 18mm in at.X1ut 8 40% CC group as compared with 3 (15%) in Letrozol group.

RECOMMENDATIONS
1. It is advisable to use Letrozole as ovulation inducing agent in those patient with clomiphene resistant PCOS.
2. Continue more detailed research in this field concerning the different items,
3. Taking in account taking larger sample size and followed for longer duration, testing the teratogenic effect of both drugs.

REFERENCES
4.Di Marcantonio T. (2008) Controva•sy around the Definition of PCOS continues. Endrocrine today, April. comngndQGLinology/endocrinology/reproduction-

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