UDC 618.11-089.85:615.03
SCSTI 76.31.29,76.29.48
DOI: 10.24412/2707-6180-2021-63-4-10

LETROZOLE FOLLOWING LAPAROSCOPIC OVARIAN DRILLING IN CLOMIPHENE RESISTANT POLYCYSTIC OVARY SYNDROME WOMEN

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Citation/
библиографиялық сілтеме/
библиографическая ссылка:

Abdelazim IA. Letrozole Following Laparoscopic Ovarian Drilling in Clomiphene Resistant Polycystic Ovary Syndrome Women. West Kazakhstan Medical Journal. 2021;63(1):4-10. doi: 10.24412/2707-6180-2021-63-4-10

Абдельазим ИА. Кломифенге төзімді аналық безінің поликистозды синдромымен ауыратын әйелдерде аналық бездің лапароскопиялық дриллингінен кейінгі летрозол. West Kazakhstan Medical Journal. 2021;63(1):4-1. doi: 10.24412/2707-6180-2021-63-4-10

Абдельазим ИА. Летрозол после лапароскопического дриллинга яичников у женщин синдромом поликистозных яичников с устойчивостью к кломифену. West Kazakhstan Medical Journal. 2021;63(1):4-10. doi: 10.24412/2707-6180-2021-63-4-10

Letrozole Following Laparoscopic Ovarian Drilling in Clomiphene Resistant Polycystic Ovary Syndrome Women

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Polycystic ovary syndrome (POOS) is the most common endocrine disorder in reproductive age, and it is the commonest cause of anovulatory infertility.
Purpose: to evaluate letrozole for ovulation induction (OI) after laparoscopic ovarian drilling (LOD) in (clomiphene citrate) CC-resistant polycystic ovary syndrome (PCOS) women.
Methods: Two hundred and forty (240) CC-resistant PCOS women were included in this study after LOD and randomized into two groups; 120 CC-resistant PCOS women received letrozole after LOD (letrozole group), and controls (120 women).Women in letrozole group received 2.5 mg of letrozole twice daily for 5 days between 2-5th days of menses for 6 consecutive cycles after LOD, while controls did not receive any OI medications after LOD for 6 months. The ovarian response, and endometrial thickness were monitored in both studied groups using trans-vaginal sonography (TVS). Pregnancy was confirmed by serum β-hCG or visualization of gestational sac after missed period. The collected data were compared in both studied groups to evaluate letrozole for OI after LOD in CC-resistant PCOS women.
Results: The endometrial thickness at the time of human chorionic gonadotropins (hCG) injection was significantly higher in letrozole group compared to controls (7.5 ± 1.7 versus 6.2 ± 1.4 mm), (P=0.01, 95%CI; 0.90, 1.3, 1.69). The ovulation, and clinical pregnancy rates were significantly higher in letrozole group compared to controls (77.5% (93/120), and 60% (72/120) versus 46.7% (56/120) and 35.8% (43/120); respectively), (P=0.01, and 0.02; respectively). While, the miscarriage, multiple pregnancy, and ovarian hyperstimulation syndrome (OHSS) rates were similar with no significant difference between the two studied groups.
Conclusions: The use of letrozole for OI after LOD in CC-resistant PCOS women was associated with significantly higher ovulation, and clinical pregnancy rates.
Keywords: *letrozole, laparoscopic ovarian drilling, LOD, polycystic ovary syndrome, PCOS.*

Кломифенге төзімді аналық безінің поликистозды синдромымен ауыратын әйелдерде аналық бездің лапароскопиялық дриллингінен кейінгі летрозол

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Аналық безінің поликистозды синдромы (PCOS) бұл - репродуктивті жастағы көп кездесетін эндокриндік ауру және ановуляциялық бедеуліктің жиі кездесуінің себебі.
Мақсаты: кломифенге төзімді аналық безінің поликистозды синдромы (АПС) бар әйелдерде аналық бездің лапароскопиялық дриллингінен (АЛД) кейін (кломифен цитраты) овуляцияны индукциялау үшін летрозолды қолдануды бағалау.
Әдістер. Бұл зерттеуге LOD-дан кейін АПС бар екі жүз қырық (240) әйел кірді және екі топқа бөлінді; 120 СС-кломифенге төзімді АПС бар әйелдер АЛД-

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Received/
Келіп түсті/
Поступила:
10.02.2021

Accepted/
Басылымға қабылданды/
Принята к публикации:
12.03.2021

ISSN 2707-6180 (Print)

Published by West Kazakhstan Marat Ospanov Medical University

ден кейін тұрақты летрозол алды (летрозол тобы) және бақылау тобы (120 әйел). Летрозол тобындағы әйелдер 2,5 мг летрозолды күніне екі рет 5 күн ішінде етеккірдің 2-5 күні аралығында АЛД-дан кейінгі 6 цикл ішінде алды, ал бақылау тобы 6 ай бойы АЛД-дан кейін ИО-да ешқандай дәрі қабылдаған жоқ. Аналық бездің реакциясы мен эндометрияның қалыңдығы зерттелген екі топта трансвагинальды сонография (ТВС) арқылы бақыланды. Жүктілік сарысуы β-ХГЧ немесе гестациялық қапты визуализациялау арқылы расталды. Жиналған мәліметтер кломифенге төзімді АПС бар әйелдерде АЛД-дан кейінгі летрозолды бағалау үшін екі топта да салыстырылды.

Нәтижелер. Адамның хорионикалық гонадотропиндерін (HCG) егу кезінде эндометрияның қалыңдығын бақылау (6,2 ± 1,4 мм қарсы 7,5 ± 1,7), (P = 0,01, 95% ДИ; 0,90, 1,3, 1,69) салыстырғанда Летрозол тобында айтарлықтай жоғары болды. Бақылау (77,5% (93/120) және 60% (72/120) салыстырғанда 46,7% (56/120) және 35,8% (43/120); тиісінше), (p = 0,01 және 0,02; тиісінше). Жүктіліктің жиілігі, бірнеше жүктілік және аналық гиперстимуляция синдромы (АГС) ұқсас болғанмен, зерттелген екі топтың арасында айтарлықтай айырмашылық жоқ.

Қорытынды. Кломифенге төзімді АПС бар әйелдерде АЛД-дан кейінгі ОИ емдеу үшін летрозолды қолдану овуляция мен клиникалық жүктіліктің едәуір жоғары деңгейімен байланысты болды.

Негізгі сөздер: *летрозол, аналық бездің лапароскопиялық дриллингі, АЛД, аналық бездің поликистикалық синдромы, АПС.*

Летрозол после лапароскопического дриллинга яичников у женщин синдромом поликистозных яичников с устойчивостью к кломифену

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Синдром поликистозных яичников (СПКЯ) - наиболее частое эндокринное заболевание в репродуктивном возрасте и самая частая причина ановуляторного бесплодия.

Цель: оценить использование летрозола для индукции овуляции (ИО) после лапароскопического дриллинга яичников (ЛДЯ) у (кломифен цитрат) у женщин с синдромом поликистозных яичников (СПКЯ) с устойчивостью к кломифену.

Методы. Двести сорок (240) женщин с СПКЯ были включены в это исследование после LOD и рандомизированы на две группы; 120 CC-устойчивых женщин с СПКЯ с устойчивостью к кломифену получали летрозол после ЛДЯ (группа летрозола) и контрольная группа (120 женщин). Женщины в группе летрозола получали 2,5 мг летрозола два раза в день в течение 5 дней между 2-5 днями менструации в течение 6 последовательных циклов после ЛДЯ, в то время как контрольная группа не получала никаких лекарств при ИО после ЛДЯ в течение 6 месяцев. Реакцию яичников и толщину эндометрия контролировали в обеих исследуемых группах с помощью трансвагинальной сонографии (ТВС). Беременность была подтверждена с помощью сывороточного β-ХГЧ или визуализации гестационного мешка. Собранные данные сравнивали в обеих исследуемых группах для оценки летрозола при ИО после ЛДЯ у женщин с СПКЯ с устойчивостью к кломифену.

Результаты. толщина эндометрия во время инъекции хорионических гонадотропинов человека (ХГЧ) была значительно выше в группе летрозола по сравнению с контролем (7,5 ± 1,7 против 6,2 ± 1,4 мм), (P = 0,01, 95% ДИ; 0,90, 1,3, 1,69). Частота овуляции и клинической беременности была значительно выше в группе летрозола по сравнению с контрольной (77,5% (93/120) и 60% (72/120) по сравнению с 46,7% (56/120) и 35,8% (43/120); соответственно), (P = 0,01 и 0,02; соответственно). В то время как частота выкидышей, многоплодной беременности и синдром гиперстимуляции яичников (СГЯ) был аналогичным, без существенной разницы между двумя исследуемыми группами.

Заключение. Использование летрозола для лечения ОИ после ЛДЯ у женщин с СПКЯ с устойчивостью к кломифену было связано со значительно более высокими показателями овуляции и клинической беременности.

Ключевые слова: *летрозол, лапароскопический дриллинг яичников, ЛДЯ, синдром поликистозных яичников, СПКЯ.*

Introduction

Polycystic ovary syndrome (POOS) is the most common endocrine disorder in reproductive age with high prevalence rate up to 17-20% [1]. PCOS is the commonest cause of anovulatory infertility [2].

Traditionally, clomiphene citrate (CC) is the first choice for ovulation induction (OI) in PCOS women since

it is safe, effective, and of low-cost [3].

About 20-25% of PCOS women have CC-resistance which can be attributed to the antiestrogenic effect of CC on the endometrium, and cervical mucus [4].

In addition, CC has long half-life (2 weeks), and depletes estrogen receptors, which leads to 18% pregnancy rate despite high ovulation rate [5].

Currently, the most common treatment options for CC-resistant PCOS are laparoscopic ovarian drilling (LOD), and/or gonadotropins. Because of the high sensitivity of the ovaries in PCOS women to exogenous gonadotropins, OI with human menopausal gonadotropin (hMG) or pure follicle-stimulating hormone (FSH) is associated with multi-follicular growth, which expose PCOS women to risks of multiple pregnancy, and ovarian hyperstimulation syndrome (OHSS) [6].In addition, gonadotropins are expensive, represents a financial burden to the infertile couple, and their use for OI entails extensive monitoring [6].

LOD was introduced in 1984, as an effective, and safe therapeutic option for CC-resistant PCOS women. It is as effective as gonadotropins in terms of clinical pregnancy, and live birth rates with additional advantage of spontaneous mono-follicular growth, which minimize the risks of OHSS, and multiple pregnancies [7]. Moreover, LOD provides a good opportunity for PCOS women to explore their pelvis for other potential causes of infertility which could be treated at the same time[8]. However, 20-30% of anovulatory PCOS women fail to respond after LOD, and 45% of PCOS women remained anovulatory after LOD [9-10].

Letrozole is selective aromatase inhibitors (AI), it decreases estrogen production without affecting estrogen receptors, reduces the feedback on hypothalamus, and pituitary, and stimulates FSH release. It avoids the unwanted anti-estrogenic side effects of CC on the endometrium, and cervical mucus [11]. Furthermore, letrozole has short half-life of 45 hrs compared to CC [12]. The multiple pregnancy, and OHSS risks are low following use of letrozole for OI [5,8].

Previous studies showed that the use of letrozole for OI gave promising results [13-14], and the use of letrozole for OI in CC-resistant PCOS women was associated with high ovulation rate [15]. The randomized trials reported higher ovulation, and pregnancy rates after using letrozole for OI in PCOS women[16-17]. Therefore, this study designed to evaluate letrozole for OI after LOD in CC-resistant PCOS women.

Methods

Two hundred and forty (240) CC-resistant PCOS women were included in this prospective randomized comparative study after LOD which was conducted at Ain Shams University, Cairo, Egypt from March 2018 till March 2020 after informed consent in accordance with the Declaration of Helsinki.

Participants were randomized using computer generated program into two groups; 120 CC-resistant PCOS women received letrozole for OI after LOD (letrozole group (120 women)), and controls (120 women, who did not receive any OI after LOD).

Inclusion criteria include women between 20-35 years, primary or secondary infertility, with at least one patent fallopian tube, and normal uterine cavity (confirmed by hysterosalpingography, and/or sonohysterography), and normal semen analysis of their spouses according to WHO cut-off points [18].

Exclusion criteria include causes of infertility other than anovulation, previous history of ovarian surgery or exposure to cytotoxic drugs or pelvic irradiation or pelvic inflammatory disease, bilateral tubal block, endometriosis, abnormal uterine cavity, abnormal spouse's semen analysis, endocrine disorders (thyroid, Cushing syndrome, adult-onset adrenal hyperplasia), medical disorders (diabetes, hypertension, hyperlipidaemia), and smokers.

The diagnosis of PCOS was based on the presence of ≥2 criteria of Rotterdam ESHRE/ASRM, after exclusion of endocrine disorders and other causes of hyperandrogenism [19].

Rotterdam ESHRE/ASRM criteria include1). Oligo/anovulation (oligo/amenorrhea), 2). Clinical/biochemical evidence of hyperandrogenism, and 3). Appearance of polycystic ovaries by trans-vaginal sonography (TVS) [19].

CC-resistance was defined as failure to achieve ovulation after 3 consecutive cycles of using CC 150 mg/day for 5 days started between 2-5th days of spontaneous menses or progesterone withdrawal bleeding [5,20].

Participants underwent LOD under general anesthesia using monopolar electrocautery (diathermy), where 3-5 punctures technique each for 4 sec at 40 W were done in each ovary [7]. The LOD, was followed by methylene blue dye test to check the tubal patency.

Collected data after LOD include age, body mass index (BMI), duration of infertility, and type of infertility (primary, secondary).

Before OI, the participants` uterus, and ovaries were evaluated using TVS, followed by day 2-3 hormonal profile including follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and prolactin.

Women in letrozole group received 2.5 mg of letrozole twice daily for 5 days between 2-5th days of spontaneous menses or progesterone withdrawal bleeding for 6 consecutive cycles after LOD [5], while controls did not receive any OI medications after LOD for 6 months.

The ovarian response, and endometrial thickness were monitored in both studied groups using TVS started from the 9th day of menses, and thereafter according to follicular growth (usually every other day). When at least one follicle ≥18 mm in diameter detected by TVS, 10,000 IU human chorionic gonadotropin (hCG) was given intramuscularly (only for letrozole group), and timed intercourse was advised. TVS was repeated 48 hrs after hCG injection to determine the follicular rupture (ovulation), and endometrial thickness.

The diagnosis of ovulation was based on signs of follicular rupture by TVS, and mid-luteal progesterone (≥10 ng/ml day 21 progesterone).

Clinical pregnancy defined after visualization of gestational sac by TVS after missed period, while miscarriage defined as pregnancy loss before 24 thweeks`.

Primary outcome measures the ovulation, and clinical pregnancy rates. Secondary outcome measures endometrial thickness, miscarriage, multiple pregnancy, and OHSS rates.

Sample size: the required sample size was calculated using G Power software version 3.17 for sample size calculation, setting α -error probability at 0.05, power (1-β error probability) at 0.95%, and effective sample size (w) at 0.5. An effective sample size ≥220 women in two groups (study group, and controls) was needed to produce a statistically acceptable figure.

Statistical analysis

Collected data were statistically analyzed using Statistical Package for Social Sciences (SPSS): computer software version 20 (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number (n) and percentage (%). Chi-square test (x2), and Student t test were used for analysis of qualitative, and quantitative variables, respectively.

Results

Two hundred and forty (240) CC-resistant PCOS women were included in this prospective comparative study after LOD and randomized into two groups; 120 CC-resistant PCOS women received letrozole for OI after LOD (letrozole group (120 women)), and controls (120 women, who did not receive any OI medications after LOD).

There was no significant difference between the two studied groups regarding the maternal age, body mass index (BMI), duration of infertility, type of infertility, and ovarian volume. In addition, there was no significant difference between the two studied groups regarding the mean FSH, LH, FSH/LH ratio, TSH, and prolactin. Table 1

The endometrial thickness at the time of hCG injection was significantly higher in letrozole group compared to controls (7.5 ± 1.7 versus 6.2 ± 1.4 mm), (P=0.01, 95%CI; 0.90, 1.3, 1.69). The ovulation, and clinical pregnancy rates were significantly higher in letrozole group compared to controls (77.5% (93/120), and 60% (72/120) versus 46.7% (56/120) and 35.8% (43/120); respectively), (P= 0.01, and 0.02; respectively). While, the miscarriage, multiple pregnancy, and OHSS rates were similar with no significant difference between the two studied groups. Table 2

Discussion

Although, CC is the first choice for OI in PCOS women [3]. About 20-25% of PCOS women have CC-resistance which can be attributed to the antiestrogenic effect of CC on the endometrium, and cervical mucus [4].

Currently, the most common treatment options for CC-resistant PCOS are laparoscopic ovarian drilling (LOD), and/or gonadotropins. The use of gonadotropins for OI usually associated with multi-follicular growth, which expose PCOS women to risks of multiple pregnancy, and OHSS [6].

Letrozole is selective aromatase inhibitors (AI), it decreases estrogen production without affecting estrogen receptors, reduces the feedback on hypothalamus, and pituitary, and stimulates FSH release. Letrozole has short half-life of 45 hrs compared to CC [12], and the multiple

Table 1: Demographic data, and baseline criteria of the studied women.

Variables	Letrozole group (120 Women)	Controls (120 Women)	*P* value (95% CI)
Maternal age (Years)	27.8 ± 3.5	28.3 ± 3.2	0.09 (-1.3,-0.5, 0.34)
BMI (Kg/m^2)	25.2 ± 2.4	24.8 ± 2.7	0.8 (-0.25, 0.4, 1.05)
Duration of infertility (Years)	2.9 ± 0.47	2.7 ± 0.52	0.8 (0.07, 0.2, 0.33)
Type of infertility			
▪ Primary infertility	113 (94.17%)	116 (96.7%)	0.8
▪ Secondary infertility	7 (5.83%)	4 (3.3%)	0.3
Ovarian volume (Cm^3)	13.3 ± 1.32	12.5 ± 1.45	0.8 (0.45, 0.8, 1.15)
FSH (mIU/ml	5.32 ± 0.29	5.28 ± 0.27	0.2 (-0.03, 0.04, 0.11)
LH (mIU/ml)	13.1 ± 1.24	12.9 ± 1.20	0.3 (-0.11, 0.2, 0.51)
LH/FSH ratio	2.46 ± 0.23	2.42 ± 0.25	0.8 (-0.02, 0.04, 0.10)
TSH (mIU/ml)	2.95 ± 2.10	3.12 ± 1.88	0.1 (-0.67,-0.17, 0.34)
Prolactin (mIU/ml)	344 ± 36.15	292 ± 32.35	0.1 (43.27, 52, 60.73)

**BMI: Body mass index. Chi-square test (X2) used for analysis when data presented as number and percentage (%).*

CI: Confidence interval. Data presented as mean ± SD (standard deviation), and number and percentage (%).

FSH: Follicle stimulating hormone. LH: Luteinizing hormone.

Student t test used for analysis when data presented as mean ± SD.

TSH: Thyroid stimulating hormone

Table 2: Reproductive outcome of the two studied groups

Variables	Letrozole group (120 Women)	Controls (120 Women)	*P* value (95% CI)
Endometrial thickness at hCG injection (mm)	7.5 ± 1.7	6.2 ± 1.4	0.01* (0.90, 1.3, 1.69)
Ovulation rate	93 (77.5%)	56 (46.7%)	0.01*
Clinical pregnancy rate	72 (60%)	43 (35.8%)	0.02*
Miscarriage rate	3 (2.5%)	2 (1.66%)	0.6
Multiple pregnancy rate	2 (1.66%)	1 (0.83%)	0.5
OHSS	0 (0%)	0 (0%)	1.0

**: Significant difference. Chi-square test (X2) used for analysis when data presented as number and percentage (%).*
CI: Confidence interval. Data presented as mean ± SD (standard deviation), and number and percentage (%).
hCG: Human chorionic gonadotropin. Student t test used for analysis when data presented as mean ± SD.
OHSS: Ovarian hyperstimulation syndrome

pregnancy, and OHSS risks are low following the use of letrozole for OI [5,8]. Therefore, this study designed to evaluate letrozole for OI after LOD in CC-resistant PCOS women.

The mechanisms of action of letrozole, and LOD in PCOS women are different. The mechanism of LOD action is not fully understood, and several mechanisms were suggested. The reduction of inhibin production following LOD with subsequent increase in FSH secretion, and recruitment of new cohort follicles was suggested as one theory. Drainage of androgens, and inhibin from the ovary may inhibit excess collagen formation in the ovarian cortex with subsequent softening of ovarian tunica that facilitate ovulation was suggested as another theory [21].

The inadequate response after LOD in some PCOS women can be explained by the amount of ovarian tissue destruction during LOD, which may be not enough to produce its desired effect and/or by the severity of PCOS in some women [22]. Hyperprolactinemia may be a possible cause of anovulation in PCOS women after LOD [10].

Depletion of estrogen receptors, cumulative effect, and long half-life are major drawbacks of CC. While letrozole reduces circulating, and local estrogens that releases the hypothalamo-pituitary axis from the negative feedback of estrogens with subsequent restoration of normal gonadotropin surges, mono-follicular growth, and ovulation [23].

In addition, letrozole increases the intra-ovarian androgens, which increases the ovarian follicular sensitivity to FSH [23]

Moreover, letrozole improves endometrial thickness, and cervical mucus which leads to higher pregnancy rates [24].

In this study, the endometrial thickness at the time of hCG injection was significantly higher in letrozole group compared to controls (7.5 ± 1.7 versus 6.2 ± 1.4 mm), (P=0.01). The ovulation, and clinical pregnancy rates were significantly higher in letrozole group compared to controls (77.5% (93/120), and 60% (72/120) versus 46.7% (56/120) and 35.8% (43/120); respectively), (P= 0.01, and 0.02; respectively).

Liu et al, reported that letrozole had a superior effect in treating CC-resistant PCOS women compared to LOD, and the endometrium was significantly thicker in letrozole group compared to LOD group in the day of hCG injection, which may improve the uterine angiogenesis, and subsequent implantation [25].

Furthermore, on the day of hCG injection, the ovulation was better synchronized with endometrial development in letrozole group, compared to LOD group [25].

Legro et al, reported that the high pregnancy rates with letrozole was associated with elevated mid-luteal serum progesterone levels [16].

Parsanezhad et al,reported that normal ovulation was restored in 52.8% of PCOS women after LOD [10].

Fernandez et al,comprehensive review found that 20-64% of PCOS women who did not respond to CC restore their fertility after LOD [26].

Induction of ovulation in CC-resistant PCOS women by two different modalities (letrozole, and LOD) could explain the high ovulation, and pregnancy rates in this study than using one of the two modalities alone.

In this study, the miscarriage, multiple pregnancy, and OHSS rates were similar with no significant difference between the two studied groups.

Abu Hashim et al, found that there was no significant difference between letrozole, and LOD regarding ovulation, pregnancy, miscarriage, and live birth rates [27].

Huang et al, reported that the mono-follicular development, and singleton pregnancy rates were significantly higher in PCOS-women after OI using letrozole compared to CC [28].

In addition, Roque et al, meta-analysis showed no significant difference between letrozole, and CC regarding the multiple pregnancy rate [29].

Franik et al, systemic review foundletrozole improves live birth, and pregnancy rates in anovulatory PCOS-women compared to CC [30].

Franik et al, also found that OHSS, miscarriage, and multiple pregnancy rates were similar after OI using either letrozole or CC [30]. In addition, the risk of fetal/neonatal anomalies did not increase when letrozole used for OI compared to CC [16].

This study found the endometrial thickness at the time of hCG was significantly higher in letrozole group compared to controls. In addition, the use of letrozole for OI after LOD in CC-resistant PCOS women was associated with significantly higher ovulation, and clinical pregnancy rates.

Women refused to participate and/or give consent was the only limitation faced during this study. Future studies are needed to confirm the use of letrozole for OI in CC-resistant PCOS women.

Conclusions

The use of letrozole for OI after LOD in CC-resistant PCOS women was associated with significantly higher ovulation, and clinical pregnancy rates.

References:

1. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012;27(10):3067–73. doi: 10.1093/humrep/des232. [PubMed]
2. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007;356(6):551–66. doi: 10.1056/NEJMoa063971. [PubMed]
3. Yousefi B, Rahbar E. Clomiphene citrate impairs the endometrial CD98 expression in ovariectomized and non-ovariectomized rats:Role of HCG. Int J Reprod Biomed (Yazd) 2019;17(6):385–394. doi:10.18502/ijrm.v17i6.4809. [PubMed]
4. Homburg R. Clomiphene citrate--end of an era? A mini-review. Hum Reprod. 2005;20(8):2043–51. doi: 10.1093/humrep/dei042. [PubMed]
5. Sakar MN, Oglak SC. Letrozole is superior to clomiphene citrate in ovulation induction in patients with polycystic ovary syndrome. Pak J Med Sci. 2020;36(7):1460–1465. doi: 10.12669/pjms.36.7.3345. [PubMed]
6. Lunenfeld B, Bilger W, Longobardi S, Alam V, D'Hooghe T, Sunkara SK. The Development of Gonadotropins for Clinical Use in the Treatment of Infertility. Front Endocrinol (Lausanne). 2019; 10:429. doi: 10.3389/fendo.2019.00429. [PubMed]
7. Abu Hashim H, Al-Inany H, De Vos M, Tournaye H. Three decades after Gjönnaess's laparoscopic ovarian drilling for treatment of PCOS; what do we know? An evidence-based approach. Arch Gynecol Obstet. 2013;288(2):409–22. doi: 10.1007/s00404-013-2808-x. [PubMed]
8. Yanamandra NK, Gundabattula SR. Outcome of ovarian drilling in women with polycystic ovary syndrome. J Clin Diagn Res. 2015;9(2):01–3. doi: 10.7860/JCDR/2015/8001.5586. [PubMed]
9. Toman AK, Muhi FA. Predicting Factors for The Efficacy of Laparoscopic Ovarian Drilling for Ovulation Induction in Polycystic Ovary Disease. Medical Journal of Babylon. 2014;11 (3):599–605. [Google Scholar]
10. Parsanezhad ME, Alborzi S, Zolghadri J, Parsa-Nezhad M, Keshavarzi G, Omrani GR, et al. Hyperprolactinemia after laparoscopic ovarian drilling: an unknown phenomenon. Reprod Biol Endocrinol. 2005; 3:31. doi: 10.1186/1477-7827-3-31. [PubMed]
11. Casper RF. Aromatase inhibitors in ovarian stimulation. J Steroid Biochem Mol Biol. 2007;106(1-5):71–5. doi: 10.1016/j.jsbmb.2007.05.025. [PubMed]
12. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014 Feb 24;(2):CD010287. doi: 10.1002/14651858.CD010287.pub2. Update in: Cochrane Database Syst Rev. 2018 May 24;5:CD010287. [PubMed]
13. Oğlak SC, Sakar MN, Özçelik Otçu SM, Ege S, Obut M, Kahveci B, et al. Comparion of the efficacy of letrozole and gonadotropin combination versus gonadotropin alone in intrauterine insemination cycles in patients with unexplained infertility. Eastern J Med. 2020;25(3):427–433. doi:10.5505/ejm.2020.24993. [Google Scholar]
14. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril. 2006;85(2):277–84. doi: 10.1016/j.fertnstert.2005.05.078. [PubMed]
15. Abdellah MS. Reproductive outcome after letrozole versus laparoscopic ovarian drilling for clomiphene-resistant polycystic ovary syndrome. Int J Gynaecol Obstet. 2011;113(3):218–21. doi: 10.1016/j.ijgo.2010.11.026. [PubMed]
16. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014;371(2):119-29. doi: 10.1056/NEJMoa1313517. Erratum in: N Engl J Med. 2014;317(15):1465. [PubMed]
17. Palomba S. Aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab. 2015;100(5):1742-7. doi: 10.1210/jc.2014-4235. [PubMed]
18. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231–45. doi: 10.1093/humupd/dmp048. [PubMed]
19. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41–7. doi: 10.1093/humrep/deh098. [PubMed]
20. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. Cochrane Database Syst Rev. 2009;(4):CD002249. doi: 10.1002/14651858.CD002249.pub4. Update in: Cochrane Database Syst Rev. 2016 Dec 15;12:CD002249. [PubMed]
21. Yu Q, Hu S, Wang Y, Cheng G, Xia W, Zhu C. Letrozole versus laparoscopic ovarian drilling in clomiphene citrate-resistant women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2019;17(1):17. doi: 10.1186/s12958-019-0461-3. [PubMed]
22. Amer SA, Li TC, Cooke ID. Repeated laparoscopic ovarian diathermy is effective in women with anovulatory infertility due to polycystic ovary syndrome. Fertil Steril. 2003;79(5):1211–5. doi: 10.1016/s0015-0282(02)04960-9. [PubMed
23. Kar S. Current evidence supporting "letrozole" for ovulation induction. J Hum Reprod Sci. 2013;6(2):93–8. doi: 10.4103/0974-1208.117166. [PubMed]
24. Legro RS, Kunselman AR, Brzyski RG, Casson PR, Diamond MP, Schlaff WD, et al. The Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial: rationale and design of a double-blind randomized trial of clomiphene citrate and letrozole for the treatment of infertility in women with polycystic ovary syndrome. Contemp Clin Trials. 2012;33(3):470–81. doi: 10.1016/j.cct.2011.12.005. [PubMed]
25. Liu W, Dong S, Li Y, Shi L, Zhou W, Liu Y, et al. Randomized controlled trial comparing letrozole with laparoscopic ovarian drilling in women with clomiphene citrate-resistant polycystic ovary syndrome. Exp Ther Med. 2015;10(4):1297–1302. doi: 10.3892/etm.2015.2690. [PubMed]
26. Fernandez H, Morin-Surruca M, Torre A, Faivre E, Deffieux X, Gervaise A. Ovarian drilling for surgical treatment of polycystic ovarian syndrome: a comprehensive review. Reprod Biomed Online. 2011;22(6):556–68. doi: 10.1016/j.rbmo.2011.03.013. [PubMed]
27. Abu Hashim H, Mashaly AM, Badawy A. Letrozole versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Arch Gynecol Obstet. 2010;282(5):567–71. doi: 10.1007/s00404-010-1566-2. [PubMed]
28. Huang S, Du X, Wang R, Li R, Wang H, Luo L, et al. Ovulation induction and intrauterine insemination in infertile women with polycystic ovary syndrome: A comparison of drugs. Eur J Obstet Gynecol Reprod Biol. 2018;231:117-121. doi:10.1016/j.ejogrb.2018.08.002. [PubMed]
29. Roque M, Tostes AC, Valle M, Sampaio M, Geber S. Letrozole versus clomiphene citrate in polycystic ovary syndrome: systematic review and meta-analysis. Gynecol Endocrinol. 2015;31(12):917–921. doi:10.3109/09513590.2015.1096337. [PubMed]
30. Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018;5(5):CD010287. doi: 10.1002/14651858.CD010287.pub3. [PubMed]

Ethical considerations: The study was approved by the ethical committee of the Obstetrics and Gynecology department, and informed consent taken from the studied woman in accordance with the Declaration of Helsinki.

Acknowledgments:Author is grateful to women agreed and gave consent to participate in this study.

Conflict of interest: Authors declare no conflict of interests in relation to this study.

Financial Disclosure: Nil