Aromatase inhibitors (Letrozole) for ovulation induction

2023 TAOG annual meeting

台北榮民總醫院 婦女醫學部

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Disclosure

- No conflicts of interest
- Novartis: “NOT MY BUSINESS!”

Outline

- Overview of Letrozole (LE)
- Letrozole use in ovulation induction
- Letrozole versus laparoscopic ovarian drilling in clomiphene citrate (CC)-resistant PCOS women
- Whether the pre-treatment characteristics had the predictive value for the ovarian response to letrozole
- Letrozole resistance
- Ovulation induction using letrozole combined with other agents (dexamethasone/clomiphene/gonadotropin/metformin)

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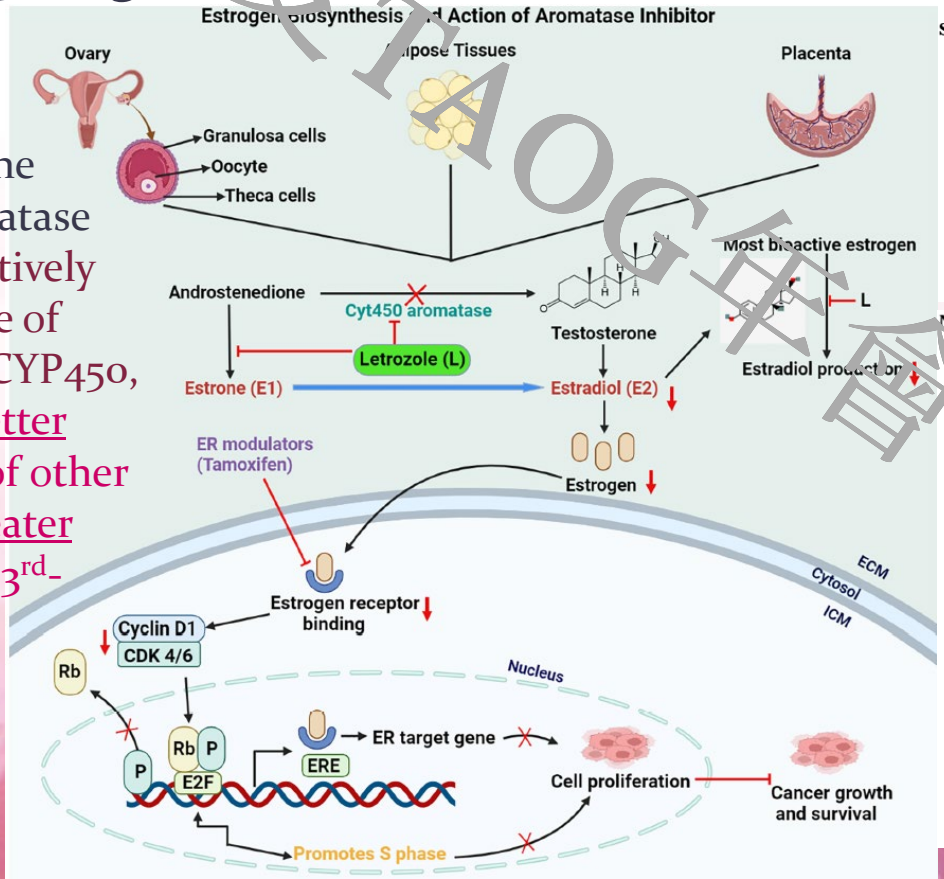
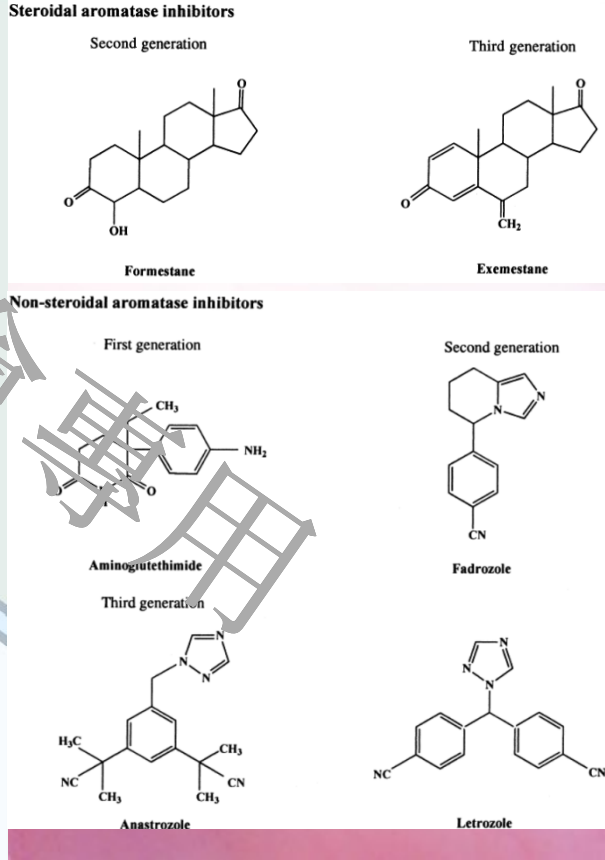
Review article

Letrozole: Pharmacology, toxicity and potential therapeutic effects

➢Letrozole: 3rd-generation non-steroidal aromatase inhibitor (AI)

Letrozole inhibits the activity of the aromatase enzyme by competitively binding to the heme of cytochrome P450 (CYP450, Aromatase) with better selectivity than AI of other generations and greater potency than other 3rd-generation AI.





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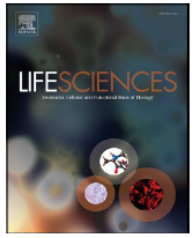

Review article

Letrozole: Pharmacology, toxicity and potential therapeutic effects

Pharmacodynamics :

- With 0.5 to 2.5 mg/day of letrozole, there was <2 % residual activity of aromatase & nearly complete inhibition of the enzyme within 2-3 days.
- The most frequent adverse effects of letrozole include nausea (6–13 %), fatigue (3–6 %), and hot flashes (3–16 %) with a mild to moderate manifestation. The most pronounced adverse effects of prolonged exposure to 2.5 mg/day of letrozole were bone resorption and atherogenic risk due to increased cholesterol levels.

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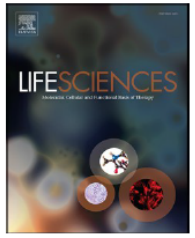


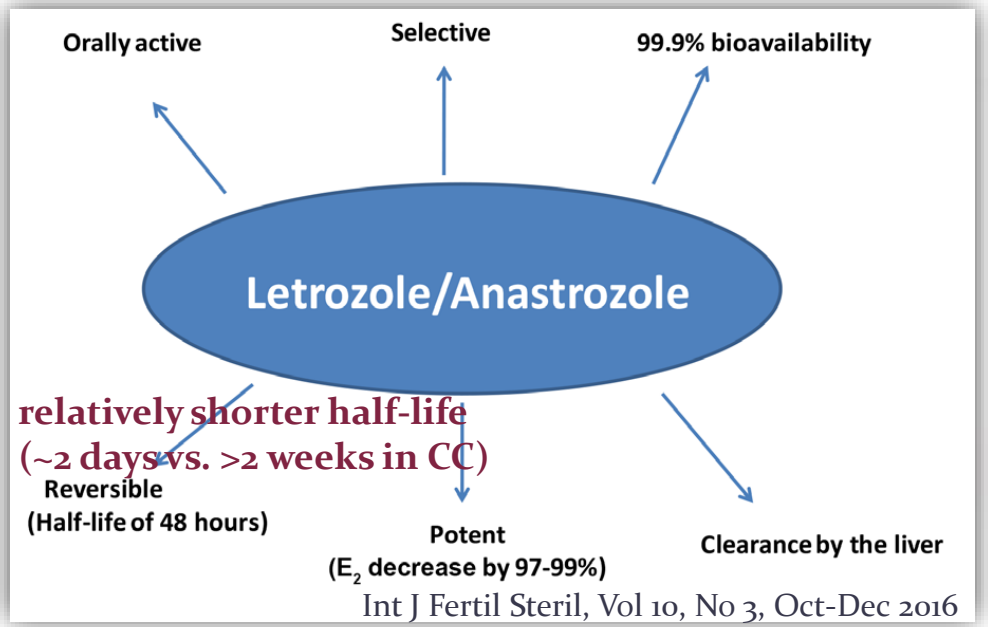
Review article

Letrozole: Pharmacology, toxicity and potential therapeutic effects

Pharmacokinetics :

- Nearly 60 % is weakly bound to the plasma proteins, mainly albumin.
- The vital elimination pathway was hepatic oxidative metabolism (biotransformation of letrozole to an inactive carbinol metabolite), accompanied by glucuronidation and succeeding renal excretion.
- Absence of continuous accumulation

- Orally administered: absorbed from the GI tract (no first-pass elimination) and is not influenced by either the food consumed or fasting status.
- Rapidly absorbed (within an hour) with complete bioavailability of about 99.9 %, and has a half-life of approximately 48 h (much less than Clomiphene).



Int J Fertil Steril, Vol 10, No 3, Oct-Dec 2016

- The pharmacokinetic profile of post-menopausal women with breast cancer : administered with a single dose of 2.5 mg of letrozole
  → The plasma concentration attained maximum within a median time of 2 h
- Age did not influence the pharmacokinetic parameters of the drug & unaffected by patients with renal impairment (data from post-menopausal women between 50 and 70 years under letrozole treatment).
- Pharmacokinetic parameters of the drug were affected in patients with liver cirrhosis or severe liver damage resulting in the reduction of their recommended dose range by 50 %.

A.G. Mukherjee et al. *Life Sciences 310 (2022) 121074*

台北榮民總醫院
婦女醫學部

Outline

- Overview of Letrozole (LE)
- Letrozole use in ovulation induction
  : vs CC/ vs NC/ fetal risk/ hormone parameters/ start timing
- Letrozole versus laparoscopic ovarian drilling in clomiphene citrate (CC)-resistant PCOS women
- Whether the pre-treatment characteristics had the predictive value for the ovarian response to letrozole
- Letrozole resistance
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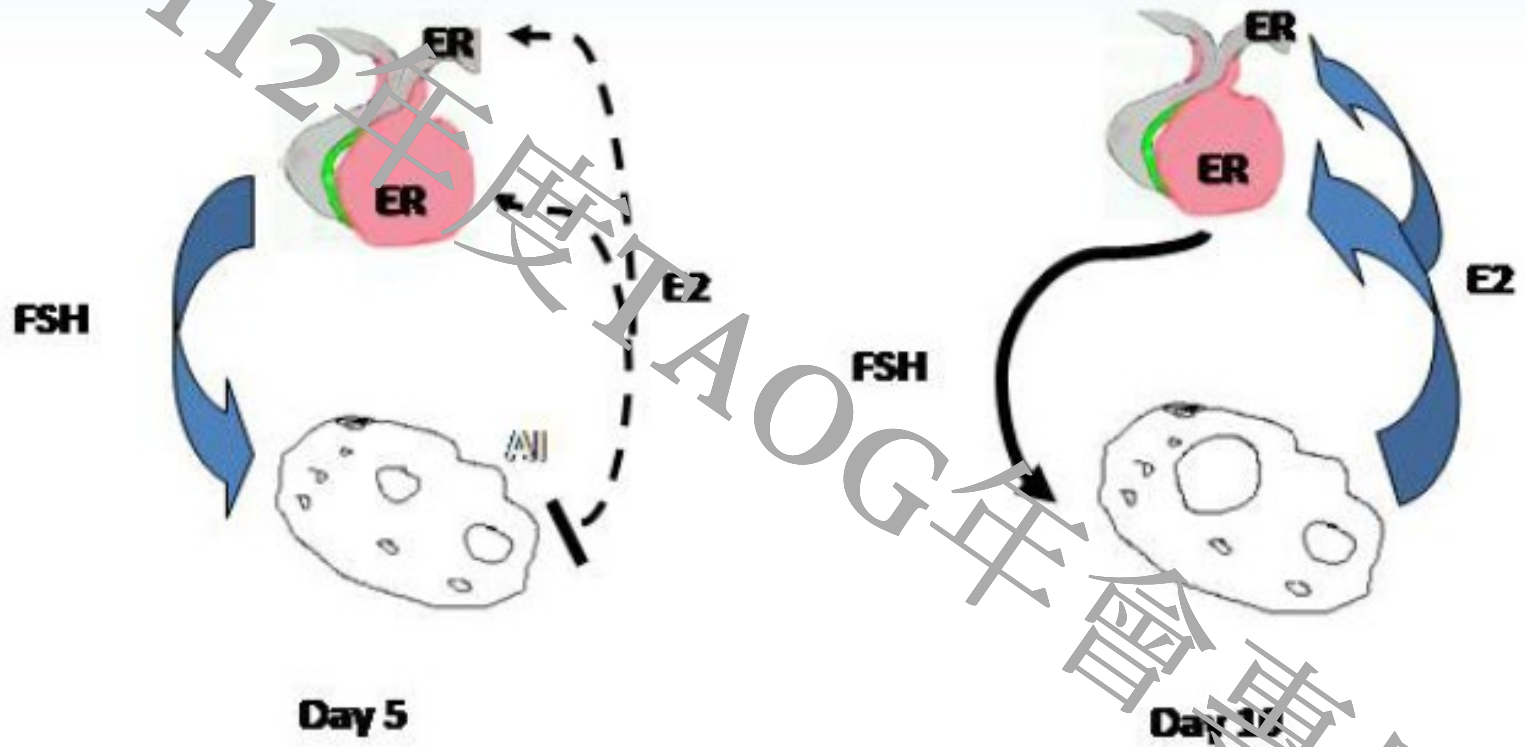
Aromatase Inhibitor Treatment

(AI) for 5 days in early follicular phase



Day 10: E2↑& the effect of AI↓ --As AIs do not affect ER centrally➔normal negative feedback on FSH secretion & follicles less than dominant follicle size undergo atresia ➔monofollicular ovulation in most cases.

vs CC: Owing to the long tissue retention—Day 10: continues to be ER depletion centrally and increased E2 secretion from the ovary➔ not capable of normal negative feedback on FSH➔ multiple dominant follicle growth & multi-ovulation.

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OVULATION INDUCTION

Fertil Steril 2001; 75: 305–309

LE vs CC

Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate

Mohamed F. M. Mitwally, M.D., and Robert F. Casper, M.D.

Division of Reproductive Sciences, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, and the Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada

12 PCOS pt & 10 ovulatory pt:
CC failure of ovulation (10 cycles) or
ovulation with EM thickness ≤0.5 cm (23 cycles)

→ ≥2M washout → Letrozole 2.5 mg/d from MC days 3 to 7

hCG 10,000 IU trigger ovulation when ≥ 1 mature follicle (≥ 2.0 cm)➔timed intercourse or

Characteristics of letrozole and CC treatment cycles in anovulatory patients with PCOS.

Variable	Mean value for letrozole treatment (± SD)	Mean value for CC treatment (± SD)	*P* value	Range for letrozole treatment	Range for CC treatment	Median for letrozole treatment	Median for CC treatment
Day of hCG administration	14.2 ± 2.1	14.8 ± 2.7	NS	12–18	11–19	14	14
Endometrial thickness (cm) on day of hCG	0.81 ± 0.14	0.62 ± 0.25	<.01	0.7–1.1	0.3–1.2	0.8	0.6
Follicles >1.5 cm on day of hCG	2.1 ± 0.93	1.9 ± 1.6	NS	1–4	1–5	2	2
E_2 (pmol/L) on day of hCG	962 ± 654	1,638 ± 1,406	<.01	344–2,347	178–5,210	84[illegible]	1,174
E_2 per mature follicle (pmol/L)	444 ± 256	830 ± 279	<.01	172–786	278–1,174	347	917
LH on day of hCG (IU/L)	22 ± 22	19 ± 14	NS	6–66	5.6–43	9.6	10.1

÷4為 pg/mL

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Characteristics of letrozole and CC treatment cycles in ovulatory patients.

Variable	Mean value for letrozole treatment (± SD)	Mean value for CC treatment (± SD)	*P* value	Range for letrozole treatment	Range for CC treatment	Median for letrozole treatment	Median for CC treatment
Day of hCG administration	11.6 ± 2.6	10.5 ± 1.6	NS	8–16	8–13	12	10
Endometrial thickness (cm) on day of hCG	0.89 ± 0.12	0.5 ± 0.1	<.001	0.7–1.1	0.3–0.6	0.9	0.5
Follicles >1.5 cm on day of hCG	2.3 ± 0.8	2.5 ± 1	NS	1–4	1–5	2	2
E_2 (pmol/L) on day of hCG	719 ± 411	3,003 ± 1,422	<.001	357–1,674	559–6,782	548	2,756
E_2 per mature follicle (pmol/L)	344 ± 217	1,366 ± 683	<.001	136–837	280–2,755	257	1,378
LH on day of hCG (IU/L)	17 ± 14	13 ± 7	NS	3.6–40	3–29	8	12.7

÷4為 pg/mL

LE vs NC

Letrozole 5.0 mg/d from MC day 3~7

Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients

Patient(s): Eight ovulatory infertile patient candidates for ovarian superovulation.
Intervention(s): Subjects were monitored in one control cycle. In the next cycle, they received letrozole 5.0 mg daily on days 3 through 7 after menses.
Main Outcome Measure(s): Number of ovulatory follicles; dominant follicle diameter; endometrial thickness; hormonal profile of FSH, LH, E_2, A, T, and P; endometrial histological dating; and pinopode formation assessed by scanning electron microscopy.
Result(s): Cycles stimulated with letrozole resulted in more ovulatory follicles than did natural cycles (mean ± SD 2.0 ± 0.9 vs. 1.0 ± 0.0), which attained a greater preovulatory diameter (mean ± SD 23.8 ± 2.7 vs. 19.3 ± 2.1 mm), with similar endometrial thickness at midcycle compared with spontaneous cycles. Endocrine profile of medicated cycles was characterized on day 7 by increased levels of LH (5.9 ± 0.8 vs. 3.5 ± 0.4 IU/mL), reduced E_2 (98.4 ± 11.4 vs. 161.5 ± 14.7 pmol/L), and elevated androgens. Preovulatory and midsecretory E_2 were similar to spontaneous cycle, and P levels during midluteal phase were significantly elevated (44.2 ± 4.6 vs. 27.7 ± 4.6 pmol/L). Endometrial morphology during the implantation window in letrozole-stimulated cycles was characterized by in-phase histological dating and pinopode expression on scanning electron microscopy.
Conclusion(s): Letrozole induces moderate ovarian hyperstimulation in ovulatory infertile patients with E_2 levels similar to spontaneous cycles and higher midluteal P, leading to both abnormal endometrial histology and development of pinopodes, considered to be relevant markers of endometrial receptivity. (Fertil Steril® 2005;83:

Variable	Mean value for natural cycle (± SD)	Mean value for letrozole cycle (± SD)	P value
Ovulatory follicles	1.0 ± 0.0	2.0 ± 0.9	.02
Greatest follicle diameter (mm)	19.3 ± 2.1	23.8 ± 2.7	.01
Greatest endometrial thickness (mm)	12.1 ± 1.7	12.3 ± 2.3	.815
Ovulatory day	13.9 ± 2.7	14.0 ± 1.4	.199

Variable	Mean value for natural cycle (± SD)		Mean value for letrozole cycle (± SD)	P value
Day 7 FSH (IU/mL)	4.6 ± 0.7		4.9 ± 0.6	.63
Day 7 LH (IU/mL)	3.5 ± 0.4		5.9 ± 0.8	.003
Day 7 E_2 (pmol/L)	161.5 ± 14.7		98.4 ± 11.4	.002
Preovulatory E_2 (pmol/L)	427.2 ± 40.7		430.8 ± 48.8	.93
Preovulatory E_2/mature follicle (pmol/L)	427.2 ± 40.7	>	252.5 ± 49.9	.018
Day 7 A (nmol/L)	7.36 ± 1.36		8.58 ± 1.5	.016
Day 7 T (nmol/L)	1.28 ± 0.17	<	1.63 ± 0.21	.006
Postovulatory day + 7 Progesterone (pmol/L)	27.7 ± 4.6		44.2 ± 4.6	.008

E2: pmol/L÷4為pg/mL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

LE vs CC

Legro et al. **N Engl J Med 2014;371:119-29.**

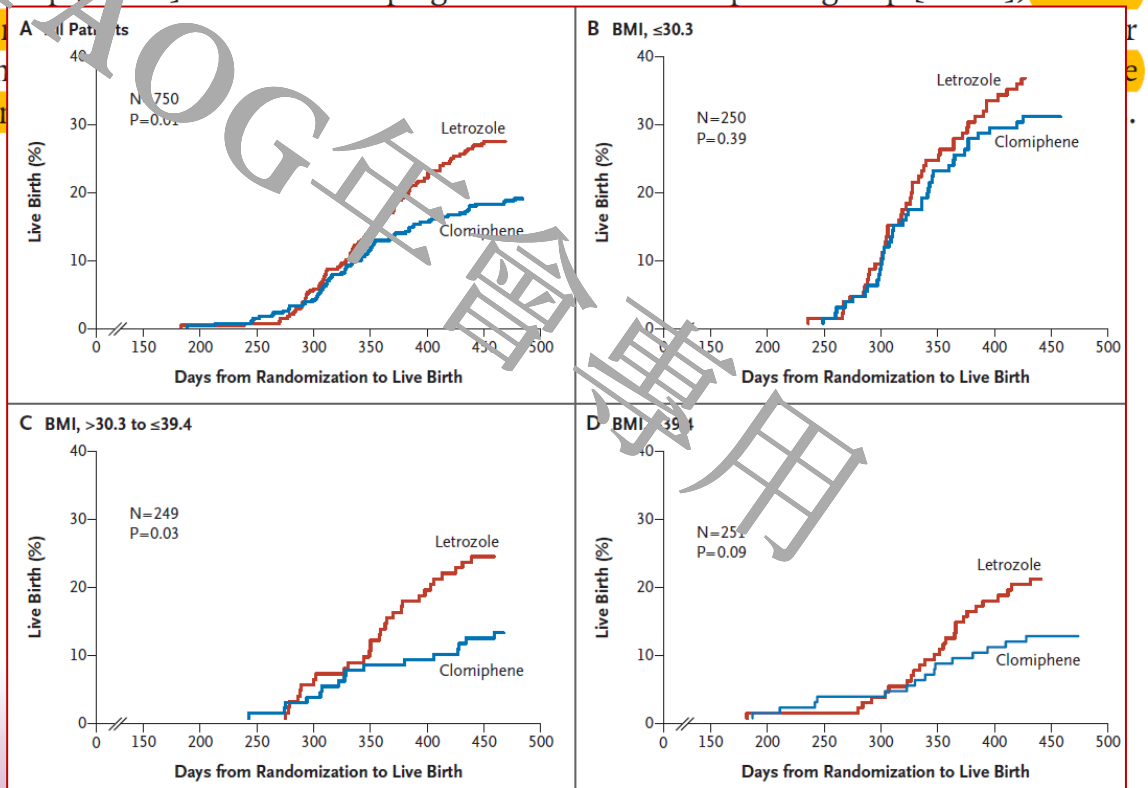
Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

either clomiphene citrate (50 mg daily) or letrozole (2.5 mg daily) in a 1:1 ratio in permuted blocks of two, four, or six, beginning on cycle day 3 for 5 days and for up to five menstrual cycles. The dose was increased in subsequent cycles in both treatment groups in cases of nonresponse (progesterone level during the midluteal phase, <3 ng per milliliter) or a poor ovulatory response (progesterone levels indicative of ovulation but with values clustering just above the cutoff point [see the Supplementary Appendix]), noted in 2% of 2777 treatment cycles. The maximum daily dose of clomiphene was 150 mg (three pills), and the maximum daily dose of letrozole was 7.5 mg (three pills), both

About 15% of patients may fail to ovulate after receiving letrozole

RESULTS

Women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5%] vs. 72 of 376 [19.1%], P=0.007; rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group (P=0.65). The cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], P<0.001). There were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin



GYNECOLOGICAL ENDOCRINOLOGY
2019, VOL. 35, NO. 10, 862–865
https://doi.org/10.1080/09513590.2019.1612358

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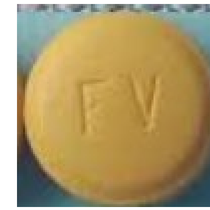
LE vs CC

ENDOMETRIAL RECEPTIVITY OF CLOMIPHENE CITRATE VERSUS LETROZOLE IN PCOS: A RANDOMIZED CONTROLLED STUDY



Comparison of endometrial receptivity of clomiphene citrate versus letrozole in women with polycystic ovary syndrome: a randomized controlled study

ABSTRACT
The aim of the study was to compare the effect of clomiphene citrate (CC) and letrozole on endometrial receptivity for ovulation induction in women with polycystic ovary syndrome (PCOS). A randomized controlled study included 160 patients diagnosed with PCOS, out of which 80 patients received 50 mg of CC and 80 patients received 2.5 mg of letrozole for successful ovulation inductio
pattern, the blood flow of uterine artery and subendometrial region, endome
tion index were measured. The ratio of multilayered endometrial pattern in
cantly increased on the day of human chorionic gonadotropin (hCG) admin
group (77.5% vs. 55.0%). The volume, vascularization index (VI), flow index
index (VFI) of endometrium on the day of hCG administration and 7–9 days
group were significantly increased. The biochemical pregnancy rate, clinical p
pregnancy rate in letrozole group were significantly increased compared w
22.5% vs. 21.3%, 13.8%, 10.0%, respectively). Letrozole increased pregnancy
rial receptivity compared with CC in patients with PCOS.

subjects were randomly assigned to the CC group or letrozole group using computer-generated random numbers. One hundred and nineteen patients with PCOS were given CC at a small dose of 50 mg/day on cycle days 3–7 (1 cycle), 80 patients with successful ovulation were assigned to the CC group. One hundred and twenty patients were given 2.5 mg/day of letrozole (1 cycle), among them 80 patients with successful ovulation were assigned to the letrozole group (Figure 1).

vascularity index (VI): vascular density

flow index (FI): blood flow

vascularization flow index (VFI): tissue perfusion

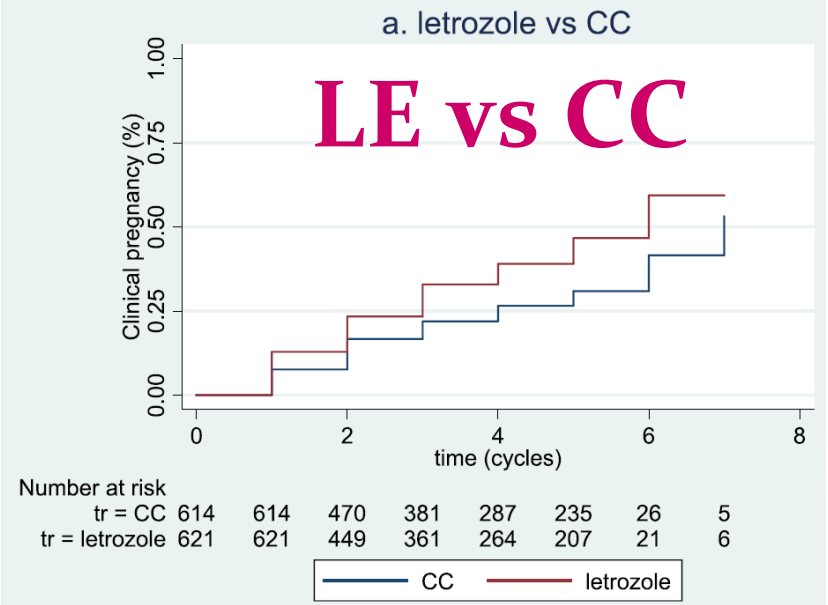
	CC ($n = 80$)		Letrozole ($n = 80$)	p value
Endometrial pattern[b,c]				.003
Multilayered	44 (55.0%)		62 (77.5%)	
Non-multilayered	36 (45.0%)		18 (22.5%)	
Day of hCG administration[d]				
Averaged uterine PI	2.1 ± 0.6		2.1 ± 0.6	.436
Averaged uterine RI	0.8 ± 0.1		0.9 ± 0.1	.690
Subendometrial region PI	1.2 ± 0.3		1.3 ± 0.2	.065
Subendometrial region RI	0.8 ± 0.1		0.6 ± 0.1	.057
Endometrial thickness (mm)	7.4 ± 1.3		10.7 ± 1.7	.037
Endometrial volume (cm^3)	2.8 ± 1.1		3.4 ± 1.0	.046
Endometrial VI (%)	1.7 ± 0.8	<	2.6 ± 0.9	.029
Endometrial FI (0–100)	20.1 ± 6.1		27.4 ± 7.0	.042
Endometrial VFI (0–100)	0.23 ± 0.1		0.5 ± 0.1	.023
7–9 days after ovulation[d]				
Averaged uterine PI	2.2 ± 0.9		2.4 ± 0.9	.658
Averaged uterine RI	0.82 ± 0.1		0.90 ± 0.1	.527
Subendometrial region PI	1.2 ± 0.5		1.3 ± 0.5	.319
Subendometrial region RI	0.7 ± 0.1		0.5 ± 0.1	.058
Endometrial thickness (mm)	7.8 ± 1.4		10.8 ± 1.9	.041
Endometrial volume (cm^3)	2.8 ± 0.9	<	3.7 ± 0.9	.044
Endometrial VI (%)	1.8 ± 0.8		2.7 ± 0.9	.036
Endometrial FI (0–100)	22.1 ± 6.8		29.4 ± 7.3	.039
Endometrial VFI (0–100)	0.3 ± 0.1		0.5 ± 0.1	.028
Biochemical pregnancy	17 (21.3%)		29 (36.3%)	.036
Clinical pregnancy	11 (13.8%)	<	24 (30.0%)	.013
Ongoing pregnancy	8 (10.0%)		18 (22.5%)	.032

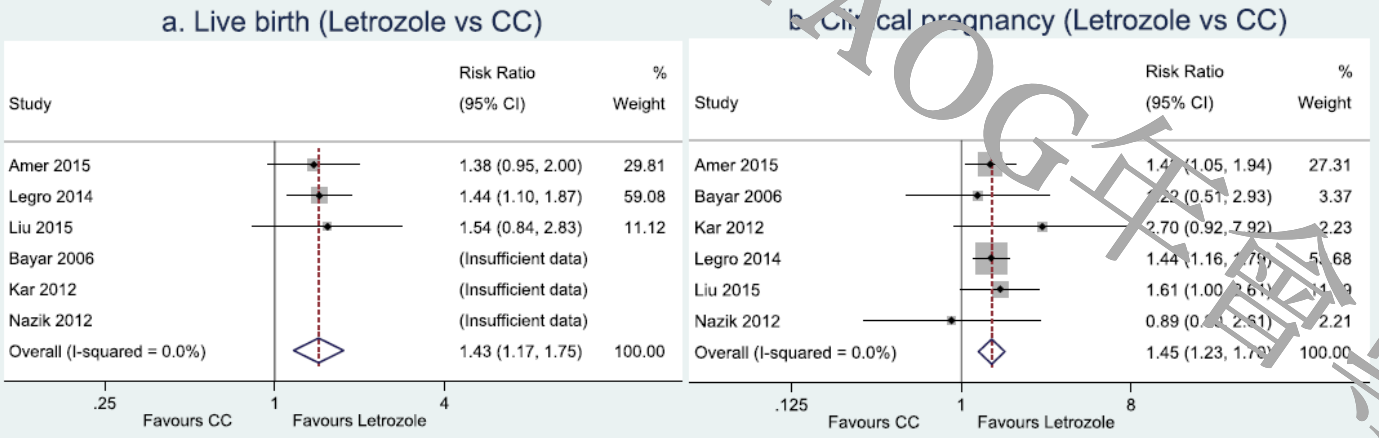
Human Reproduction Update, Vol.25, No.6, pp. 717–732, 2019
Advance Access Publication on October 23, 2019 doi:10.1093/humupd/dmz029

human reproduction update

First-line ovulation induction for polycystic ovary syndrome: an individual participant data meta-analysis

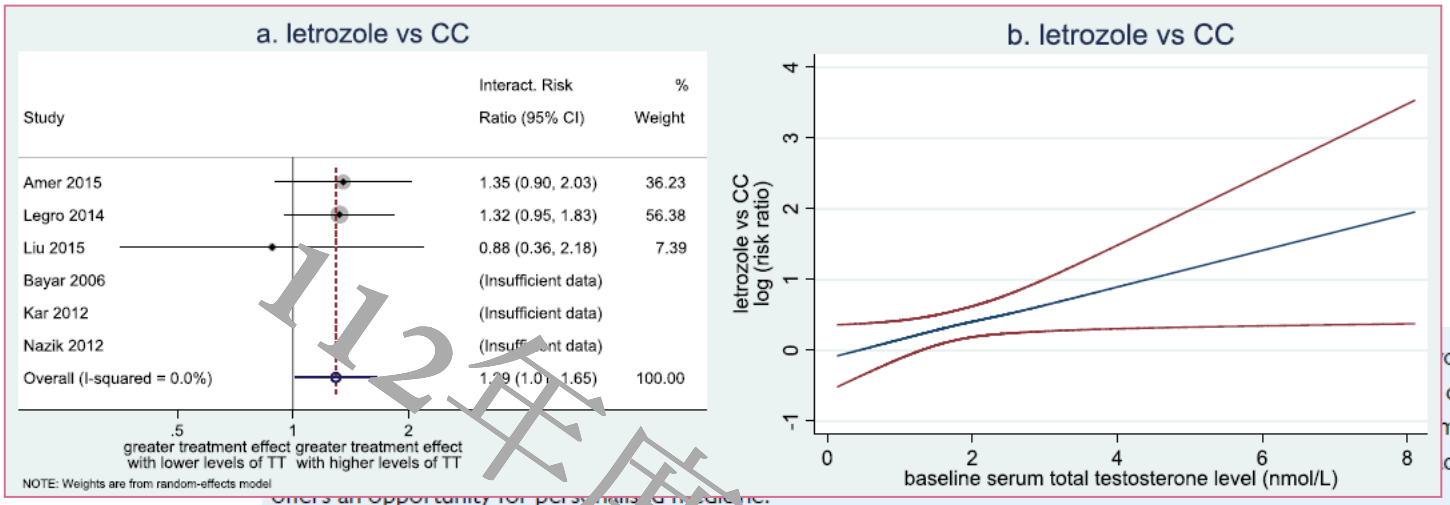
Rui Wang[1,2], Wentao Li[2], Esmée M. Bordewijk[3], Richard S. Legro[4], Heping Zhang[5], Xiaoke Wu[6], Jingshu Gao[6], Laure Morin-Papunen[7], Roy Homburg[8], Tamar E. Konig[9], Etelka Moll[10], Sujata Kar[11], Wei Huang[12], Neil P. Johnson[13], Saad A. Amer[14], Walter Vegetti[15], Stefano Palomba[16], Angela Falbo[17], Ülkü Ozmen[18], Hakan Nazik[19], Christopher D. Williams[20], Grasso Federica[21], Jonathan Lord[22], Yilmaz Sahin[23], Siladitya Bhattacharya[24], Robert J. Norman[1,25], Madelon van Wely[3], Ben Willem Mol[2,1], Reproductive Medicine Network+, the International Ovulation Induction IPDMA Collaboration





Comparison	Outcome	Number of RCTs	Number of participants	Risk ratio (RR)	95% confidence interval (CI)	I^2	Overall certainty of evidence (GRADE)
Letrozole vs CC	Live birth	3	1043	1.43	1.17–1.75	0	Moderate[a]
	Clinical pregnancy	6	1284	1.45	1.23–1.70	0	Moderate[a]
	Multiple pregnancy	2	909	1.45	0.17–12.45	50.9%	Very low[a,b,c]
	Miscarriage	3	1043	1.50	0.95–2.38	0	Low[a,c]
	Ovulation	5	1210	1.13	1.07–1.20	0	Moderate[a]

LE vs CC



Hum Reprod Update. 2019 Nov 5;25(6):717-732.

omen with PCOS, effective data (IPD) meta-analysis is mary randomised controlled ction analyses and therefore

Comparison	Baseline covariate	Number of RCTs	Number of participants	Interaction RR	Interaction 95% CI	Interaction I^2
Letrozole vs CC	Age	3	1043	0.98	0.93–1.05	24.9%
	BMI	3	1043	0.98	0.90–1.05	65.2%
	Ethnicity (non-Caucasian vs Caucasian)	2	909	1.42	0.80–2.45	0
	Treatment history (yes vs no)	1	750	1.07	0.63–1.82	/
	Type of infertility (secondary vs primary)	3	1043	0.83	0.43–1.60	52%
	Total testosterone (nmol/L)	3	1039	1.29	1.01–1.65	0
	SHBG (nmol/L)	2	907	1.00	0.99–1.02	69.7%
	Free androgen index	2	907	1.02	0.91–1.15	79.2%
	Fasting glucose (mmol/L)	3	1007	1.27	0.93–1.73	0
	Fasting insulin (μU/mL)	3	977	1.01	1.00–1.02	0
	HOMA-IR	3	975	1.02	0.98–1.09	0
	Ferriman–Gallwey score for hirsutism	2	884	1.03	0.99–1.06	0
	Ovarian volume (ml)	3	837	1.01	0.95–1.07	33.9%

Women with higher baseline serum levels of total testosterone may benefit more from letrozole compared to CC. Such an interaction was **consistent across studies.**

WIDER IMPLICATIONS: In women with PCOS, letrozole improves live birth and clinical pregnancy rates and reduces time-to-pregnancy compared to CC and therefore can be recommended as the preferred first-line treatment for women with PCOS and infertility. CC plus metformin may increase clinical pregnancy and may reduce time-to-pregnancy compared to CC alone, while there is insufficient evidence of a difference on live birth. Treatment effects of letrozole are influenced by baseline serum levels of total testosterone, while those of CC plus metformin are affected by baseline serum levels of insulin. These interactions between treatments and biomarkers on hyperandrogenaemia and insulin resistance provide further insights into a personalised approach for the management of anovulatory infertility related to PCOS.

Cochrane Library

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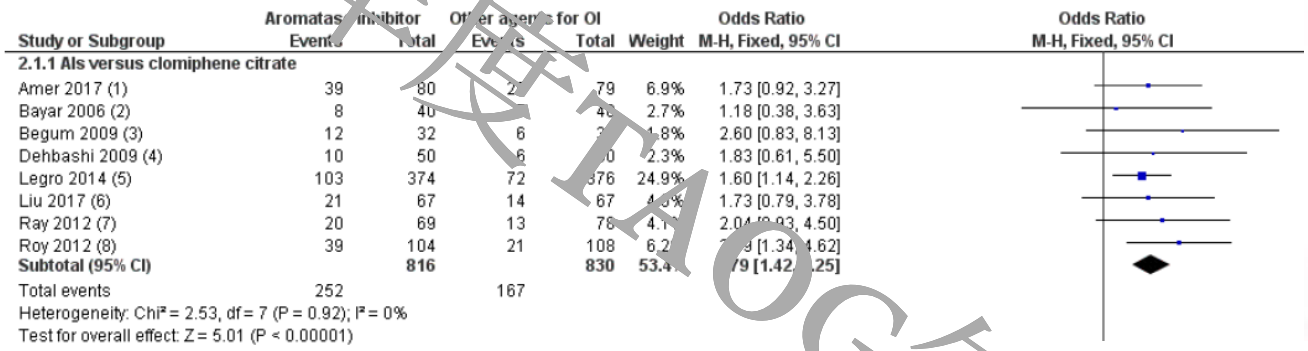
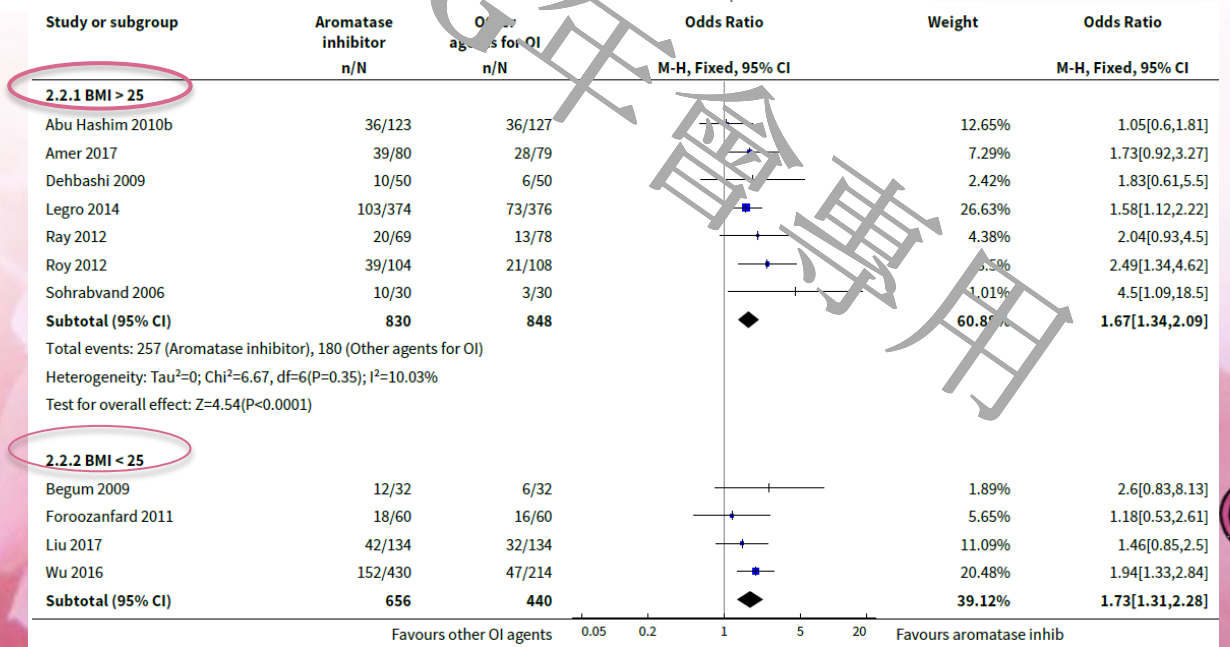
Aromatase inhibitors
polycystic ovary syn

Franik S, Eltrop SM, Kremer J
outcome: 2.1

Letrozole compared to clomiphene citrate (CC) with or without adjuncts followed by timed intercourse

Live birth rates were higher with letrozole (with or without adjuncts) compared to clomiphene citrate (with our without adjuncts) followed by timed intercourse (OR 1.68, 95% CI 1.42 to 1.99; 2954 participants; 13 studies; $I^2 = 0\%$; number needed to treat for an additional beneficial outcome (NNTB) = 10; moderate-quality evidence). There is high-quality evidence that OHSS rates are similar with letrozole or clomiphene citrate (0.5% in both arms: risk difference (RD) −0.00, 95% CI −0.01 to 0.00; 2536 participants; 12 studies; $I^2 = 0\%$; high-quality evidence). There is evidence for a higher pregnancy rate in favour of letrozole (OR 1.56, 95% CI 1.37 to 1.78; 4629 participants; 25 studies; $I^2 = 1\%$; NNTB = 10; moderate-quality evidence). There is little or no difference between treatment groups in the rate of miscarriage by pregnancy (20% with CC versus 19% with letrozole; OR 0.94, 95% CI 0.70 to 1.26; 1210 participants; 18 studies; $I^2 = 0\%$; high-quality evidence) and multiple pregnancy rate (1.7% with CC versus 1.3% with letrozole; OR 0.69, 95% CI 0.41 to 1.16; 3579 participants; 17 studies; $I^2 = 0\%$; high-quality evidence). However a funnel plot showed mild asymmetry, indicating that some studies in favour of clomiphene might be missing.





Letrozole has gradually replaced Clomiphene Citrate as the first-line ovulation induction agent administered to women with PCOS owing to the high rates of live birth.

IS THERE CONCERN OF FETAL HARM?

Human Reproduction Update, Vol.27, No.3, pp. 474–485, 2021
Advance Access Publication on December 29, 2020 doi:10.1093/humupd/dmaa055

human reproduction update

Risk of foetal harm with letrozole use in fertility treatment: a systematic review and meta-analysis

OUTCOMES: We included 46 studies (18 randomised trials; 21 comparative cohorts; 7 non-comparative cohorts). Overall 2.15% (101/4697; 95% CI 1.7 to 2.5) of babies conceived on letrozole for fertility treatment had congenital foetal malformations. We did not observe a significant increase in congenital malformations with letrozole versus clomiphene in the randomised trials (risk difference (RD) 0.01, 95% CI −0.02, 0.03; $I^2 = 0\%$; 14 studies) and found a significant reduction in the cohort studies (RD −0.02, 95% CI −0.04, −0.01; $I^2 = 0\%$, 11 studies). The fragility index was 4% (7/176) (either an increase in the intervention arm or a decrease in control arm was needed to alter the results). The risks of pregnancy loss were not increased with letrozole versus clomiphene in the 14 randomised trials (RD −0.01, 95% CI −0.06, 0.04; $I^2 = 0\%$), and the risks were reduced in the six cohort studies (RD −0.09, 95% CI −0.17, −0.00; $I^2 = 68\%$). The GRADE quality of evidence was low to moderate for congenital malformations and pregnancy loss. We did not find any increased congenital malformation risk with letrozole versus gonadotrophins, natural conception or natural cycle ART, but the number of studies was small.

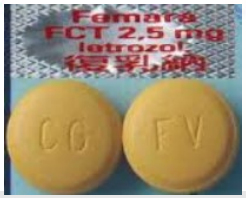
WIDER IMPLICATIONS: There is no evidence that letrozole increases the risk of congenital foetal malformation or pregnancy loss compared with clomiphene, natural conception or other fertility agents, to warrant warning against its use. Given its therapeutic benefits and lack of evidence of har

Comparator	Outcome	Studies Design	no.	Letrozole (n/N)	Comparator (n/N)	Risk difference (95% CI)	I^2
Clomiphene	Pregnancy loss	RCT	14	133/597	120/520	−0.01 (−0.06; 0.04)	0%
		Cohort	6	38/184	63/220	**−0.09 (−0.17; −0.00)**	68%
	Live birth	RCT	14	457/1740	400/1904	**0.04 (0.02; 0.07)**	63%
		Cohort	5	113/348	113/435	**0.07 (0.02; 0.12)**	68%
	Major malformation	RCT	5	7/241	4/241	0.01 (−0.02; 0.05)	0%
		Cohort	5	15/1047	24/900	−0.16 (−0.23; −0.10)	0%
Gonadotrophins	Pregnancy loss	RCT	2	32/103	59/158	−0.07 (−0.18; 0.05)	0%
		Cohort	6	416/2320	6618/22 581	−0.12 (−0.14; −0.10)	79%
	Major malformation	RCT	1	1/64	3/134	−0.01 (−0.05; 0.03)	
Natural conception	Pregnancy loss	RCT	1	7/36	4/21	0.00 (−0.21; 0.22)	
	Major malformation	RCT	1	2/30	0/23	0.07 (−0.05; 0.18)	
		Cohort	1	2/201	3/171	−0.01 (−0.03; 0.02)	
Natural cycle ART	Pregnancy loss	Cohort	4	498/2998	6351/23 350	**−0.10 (−0.12; −0.09)**	86%

Letrozole use in ovulation induction

DOES THE ESTRADIOL MATTERS?

The impact of estradiol on pregnancy outcomes in letrozole-stimulated frozen embryo transfer cycles



Objective: To assess the impact of low estradiol (E2) levels in letrozole-stimulated frozen embryo transfer (FET) cycles on pregnancy and neonatal outcomes.

Design: Retrospective cohort (not limited to PCOS pt)

Setting: University-affiliated fertility center.

Patient(s): All patients who underwent letrozole-stimulated FET cycles from January 2017 to April 2020 (n = 217). The "Low E2" group was defined as those with E2 serum levels on the day of trigger <10th percentile level (E2 <91.16 pg/mL, n = 22) and the "Normal E2" group was defined as those with E2 serum levels ≥10th percentile level (E2 ≥91.16 pg/mL, n = 195).

Intervention(s): None.

Main Outcome Measure(s): Pregnancy outcomes including rates of clinical pregnancy, clinical miscarriage, and live birth. Neonatal outcomes including gestational age at delivery, birth weight, and Apgar score.

Result(s): The mean ± SD estradiol level was 66.8 ± 14.8 pg/mL for the "Low E2" group compared with 366.3 ± 322.1 pg/mL for the "Normal E2" group. There were otherwise no substantial differences in cycle characteristics such as endometrial thickness on the day of ovulation trigger and progesterone levels in early pregnancy. The "Low E2" group had a significantly higher clinical miscarriage rate (36.4% vs. 8.8%, adjusted odds ratio 8.06) and lower live birth rate (31.8% vs. 57.9%, adjusted odds ratio 0.28). Neonatal outcomes such as gestational age at delivery, mean birth weight, Apgar scores, and incidence of newborn complications were not clinically different between the groups.

Conclusion: Low E2 levels were associated with a significantly higher miscarriage rate and lower live birth rate, suggesting that E2 levels in the follicular phase may have an effect on cycle outcomes. Given the rise in use of FET, further studies are needed to confirm our findings and understand the mechanisms. (Fertil Steril Rep® 2021;2:320–6. ©2021 by American Society for Reproductive M

Letrozole 5 mg/d from MC day 3~7
➔Ovidrel 1 amp if dominant follicle ≥18 mm or LH ≥20 IU/L

Adjusted odds ratios (aORs) for "Low E2" pregnancy outcomes.

	Adjusted odds ratio (aOR)[a]	95% CI	*P*-value
Pregnancy outcomes: "Low E2" defined as <10th percentile (n = 22)			
Clinical pregnancy	0.52	(0.18, 1.51)	.23
Clinical miscarriage	8.06	(1.36, 47.61)	.021
Live birth	0.28	(0.10, 0.81)	.019

Note: aOR = adjusted odds ratio; CI = confidence interval; E2 = estradiol.

[a] Primary pregnancy outcomes were adjusted for the following confounders: maternal age at frozen embryo transfer, maternal body mass index, number of previous miscarriages, embryo grade (categorized into AA, AB/BA, BB, and any C), endometrial thickness on the day of trigger, race/ethnicity, male factor infertility, and use of preimplantation genetic testing.

Zhang. Estradiol in letrozole frozen transfers. Fertil Steril Rep 2021.

Live birth associated with peak serum estradiol levels in letrozole intrauterine insemination cycles

Objective: To identify whether the serum estradiol (E2) level on the day of human chorionic gonadotropin (hCG) trigger or luteinizing hormone (LH) surge (hCG-LH) was associated with the live birth rate (LBR) during ovulation induction (OI) or controlled ovarian hyperstimulation with letrozole followed by intrauterine insemination (IUI).
Design: Retrospective cohort study.
Setting: Large, multicenter private practice.
Patient(s): A total of 2,368 OI-IUI cycles in patients treated with letrozole followed by IUI were evaluated from January 1, 2014, to July 31, 2019.
Intervention(s): Ovulation induction with letrozole, followed by autologous IUI.
Main Outcome Measure(s): The primary outcome measure was the LBR as a function of the serum E2 level at the time of hCG administration or LH surge, adjusting for age, body mass index, the largest follicle diameter, and the number of follicles ≥ 14 mm in diameter. The clinical pregnancy rate as a function of the E2 level, pregnancy rate as a function of the lead follicle diameter, and pregnancy loss rates were the secondary outcome variables.
Result(s): A total of 2,368 cycles met the inclusion criteria. Outcomes were evaluated at the 25th (E2 level, 110 pg/mL), 50th (157 pg/mL), 75th (225 pg/mL), and 90th (319 pg/mL) percentiles. The LBRs ranged from 9.4% to 11.1% in the lower E2 cohorts and from 12.5% to 13.5% in the higher E2 cohorts. The LBR was significantly greater in the cohort of women with higher E2 levels in all percentile comparisons except for the 90th percentile. The mean periovulatory follicle diameter of ≥20 or <20 mm was not independently associated with the LBR or clinical pregnancy rate, despite a significantly higher mean E2 level in the larger follicle group.
Conclusion(s): In letrozole OI cycles followed by IUI, lower LBRs and clinical pregnancy rates were found in women with lower E2 levels than in those with higher E2 levels at the 25th, 50th, and 75th percentile E2 level quartiles. Where possible, delaying hCG trigger until the E2 level increases after aromatase inhibition and approaches the physiologic periovulatory level may improve the pregnancy rates with letrozole followed by IUI. (Fertil Steril® 2023;119:785-91. ©2023 by American Society for Reproductive Medicine.)

18~46 y/o, BMI<44, not limited to PCOS pt

Letrozole 2.5-10 mg/d from MC day 3/4/5 for 5 days
➔Ovidrel 1 amp if dominant follicle ≥18 mm or LH ≥15 IU/L

MC d3-5 → +1–6d → Q1-3d →

5-day 2.5~10 mg/d

until at least 1 follicle attained a mean diameter of ≧18 mm or LH ≧15 IU/L: ovulation was triggered with human chorionic gonadotropin (hCG)➔IUI

Comparison of cycle characteristics between the different estradiol thresholds.

Outcome variable	Estradiol thresholds (pg/mL) 25th percentile ≤110 (n = 606)	25th percentile >110 (n = 1,762)	*P* value	50th percentile ≤157 (n = 1,188)	50th percentile >157 (n = 1,180)	*P* value	75th percentile ≤225 (n = 1,781)	75th percentile >225 (n = 587)	*P* value	90th percentile ≤319 (n = 2,131)	90th percentile >319 (n = 237)	*P* value
Age (y)	32.16 (4.11)	32.65 (3.81)	.007[a]	32.28 (4.07)	32.77 (3.69)	.002[a]	32.38 (3.91)	32.96 (3.80)	.002[a]	32.46 (3.91)	33.12 (3.70)	.013[a]
BMI (kg/m²)	28.89 (6.96)	26.56 (6.33)	<.001[a]	26.51 (6.84)	25.79 (5.99)	<.001[a]	27.91 (6.76)	24.86 (5.37)	<.001[a]	27.53 (6.68)	23.84 (4.31)	<.001[a]
Duration of time between the E2 level and insemination (d)	2.15 (3.03)	1.67 (8.82)	.189	2.07 (2.25)	1.52 (10.75)	.081	1.82 (8.93)	1.73 (0.93)	.803	2.07 (2.25)	1.60 (0.69)	.686
E2 level (pg/mL), mean (SD)	82.09 (19.80)	218.12 (104.43)	<.001[a]	107.38 (20.91)	259.75 (104.63)	<.001[a]	134.63 (47.48)	259.75 (104.63)	<.001[a]	155.70 (65.17)	259.75 (104.63)	<.001[a]
Largest mean (SD) follicle diameter (mm)	18.56 (5.76)	20.41 (4.44)	<.001[a]	19.1[illegible] (5.26)	[illegible].71 (4.32)	<.001[a]	19.48 (5.02)	21.31 (4.13)	<.001[a]	19.72 (4.93)	21.84 (3.94)	<.001[a]
Mean (SD) number of follicles ≥14 mm in diameter	1.59 (0.95)	1.71 (0.89)	.004[a]	1.59 (0.92)	1.77 (0.89)	<.001[a]	1.63 (0.91)	1.84 (0.87)	<.001[a]	1.65 (0.90)	2.02 (0.89)	<.001[a]

BMI = body mass index; E2 = estradiol; SD = standard deviation.
[a] Statistically significant difference.

Comparison of cycle outcomes between the different estradiol thresholds.

Outcome variable	Estradiol thresholds (pg/mL) 25th percentile ≤110[a] (n = 606)	25th percentile >110 (n = 1,762)	aOR (95% CI)[b] *P* value	50th percentile ≤157[a] (n = 1,188)	50th percentile >157 (n = 1,180)	aOR (95% CI)[b] *P* value
Clinical pregnancy rate	76 (12.5)	270 (15.3)	1.43 (1.08–1.90) .012	156 (13.1)	190 (16.1)	1.46 (1.14–1.85) .020
Live birth rate	57 (9.4)	219 (12.5)	1.53 (1.11–2.10) .010	119 (10.0)	157 (13.3)	1.56 (1.20–2.04) <.001
Clinical pregnancy loss	6 (1.0)	31 (1.8)	2.18 (0.88–5.42) .093	16 (1.3)	21 (1.8)	1.63 (0.81–3.29) .170

aOR = adjusted odds ratio; CI = confidence interval.
[a] Designates the reference group for the aOR.
[b] aOR (95% CI) with adjustments for patient age, body mass index, the largest mean follicle diameter, and the number of follicles ≥14 mm in diameter.

New. Estradiol level and pregnancy outcome. Fertil Steril 2023.

MC d3-5 → +1–6d → Q1-3d →

5-day 2.5~10 mg/d

until at least 1 follicle attained a mean diameter of ≧18 mm or LH ≧15 IU/L: ovulation was triggered with human chorionic gonadotropin (hCG)➔IUI

Comparison of cycle outcomes between the different estradiol thresholds-continued.

Outcome variable	Estradiol thresholds (pg/mL) 75th percentile ≤225[a] (n = 1,781)	>225 (n = 5[illegible])	aOR (95% CI)[b] *P* value	90th percentile ≤319[a] (n = 2,131)	>319 (n = 237)	aOR (95% CI)[b] *P* value
Clinical pregnancy rate	254 (14.3)	92 (15.7)	1.32 (1.00–1.73) .046	314 (14.7)	32 (13.5)	1.09 (0.73–1.64) .662
Live birth rate	197 (11.1)	79 (13.5)	1.46 (1.09–1.97) .012	247 (11.6)	29 (12.3)	1.27 (0.84–1.95) .263
Clinical pregnancy loss	26 (1.5)	11 (1.9)	1.63 (0.78–3.42) .191	34 (1.5)	3 (1.3)	1.00 (0.32–3.16) .994

aOR = adjusted odds ratio; CI = confidence interval.
[a] Designates the reference group for the aOR.
[b] aOR (95% CI) with adjustments for patient age, body mass index, the largest mean follicle diameter, and the number of follicles ≥14 mm in diameter.

Estradiol level and pregnancy outcome stratified on the basis of the periovulatory follicle diameter of <20 or ≥20 mm.

Outcome variable	Stratification on the basis of the dominant follicle mean diameter (mm) <20 (n = 981)	≥20 (n = 1,387)	*P* value/aOR (95% CI), *P* value
Dominant mean follicle diameter (mm)			
Age (y)	32.25 (4.02)	32.72 (3.80)	.003[b]
BMI (kg/m^2)	27.37 (6.64)	27.00 (6.52)	.180
Duration of time between the E2 level and insemination (d)	1.80 (11.92)	1.79 (1.53)	.969
Mean (SD) E2 level (pg/mL)	158.94 (96.48)	200.54 (1[illegible]91)	<.001[b]
Largest mean (SD) follicle diameter (mm)	16.71 (5.73)	22.22 (2.18)	<.001[b]
Number of follicles ≥14 mm in diameter (SD)	1.57 (0.99)	1.76 (0.84)	<.001[b]
Number (%) of LH surge only without trigger shot	39 (6.4)	57 (6.1)	.855
Clinical pregnancy rate	160 (16.3)	186 (13.4)[a]	1.22 (0.98–1.50), .056
Live birth rate	125 (12.7)	151 (10.9)[a]	1.17 (0.92–1.48), .187
Clinical pregnancy loss	13 (1.3)	24 (1.8)[a]	.76 (0.39–1.50), .539

aOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; E2 = estradiol; LH = luteinizing hormone; SD = standard deviation.
[a] Designates the reference group for the aOR.
[b] aOR (95% CI) with adjustments for patient age, the mean E2 level, the largest mean follicle diameter, and the number of follicles ≥14 mm in diameter.

New. Estradiol level and pregnancy outcome. Fertil Steril 2023.

Letrozole use in ovulation induction

DOES THE STARTING DAY MATTERS?

d3 vs d5 start

A Randomized Clinical Trial on Comparing The Cycle Characteristics of Two Different Initiation Days of Letrozole Treatment in Clomiphene Citrate Resistant PCOS Patients in IUI Cycles

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Int J Fertil Steril. 2015; 9(1): 17-26.

Abstract

Background: There are still many questions about the ideal protocol for letrozole (LTZ) as the commonest aromatase inhibitor (AI) used in ovulation induction. The aim of this study is to compare the ultrasonographic and hormonal characteristics of two different initiation times of LTZ in clomiphene citrate (CC) failure patients and to study androgen dynamics during the cycle.

Materials and Methods: This randomized clinical trial was done from March to November 2010 at the Mashhad IVF Center, a university based IVF center. Seventy infertile polycystic ovarian syndrome (PCOS) patients who were refractory to at least 3 CC treatment cycles were randomly divided into two groups. Group A (n=35) receiving 5 mg LTZ on cycle days 3-7 (CD3), and group B (n=35) receiving the same amount on cycle days 5-9 (CD5). Hormonal profile and ultrasonographic scanning were done on cycle day 3 and three days after completion of LTZ treatment (cycle day 10 or 12). Afterward, 5,000-10,000 IU human chorionic gonadotropin (hCG) was injected if at least one follicle ≥18 mm was seen in ultrasonographic scanning. Intrauterine insemination (IUI) has been done 36-40 hours later. The cycle characteristics, the ovulation and pregnancy rate were compared between two groups. The statistical analysis was done using Fisher's exact test, t test, logistic regression, and Mann-Whitney U test.

Results: There were no significant differences between two groups considering patient characteristics. The ovulation rate (48.6 vs. 32.4% in group A and B, respectively), the endometrial thickness, the number of mature follicles, and length of follicular phase were not significantly different between the two groups.

Conclusion: LTZ is an effective treatment in CC failure PCOS patients. There are no significant differences regarding ovulation and pregnancy rates between two different protocols of LTZ starting on days 3 and 5 of menstrual cycle (Registration Number: IRCT201307096467N3).

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d3 vs d5 start

OPEN ACCESS

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Effect of different timing of letrozole initiation on pregnancy outcome in polycystic ovary syndrome

Letrozole 2.5/d from MC d3 vs d5 for 5 days
➔hCG 5000-10000 IU if dominant follicle ≥18 mm or urine LH kit(+)➔IUI/timed intercourse

Objective: To investigate the efficacy of oral letrozole (LE) starting on day 3 or 5 of the menstrual cycle in patients with polycystic ovary syndrome.

Design: Retrosp

Setting: Reproc

Methods: In thi
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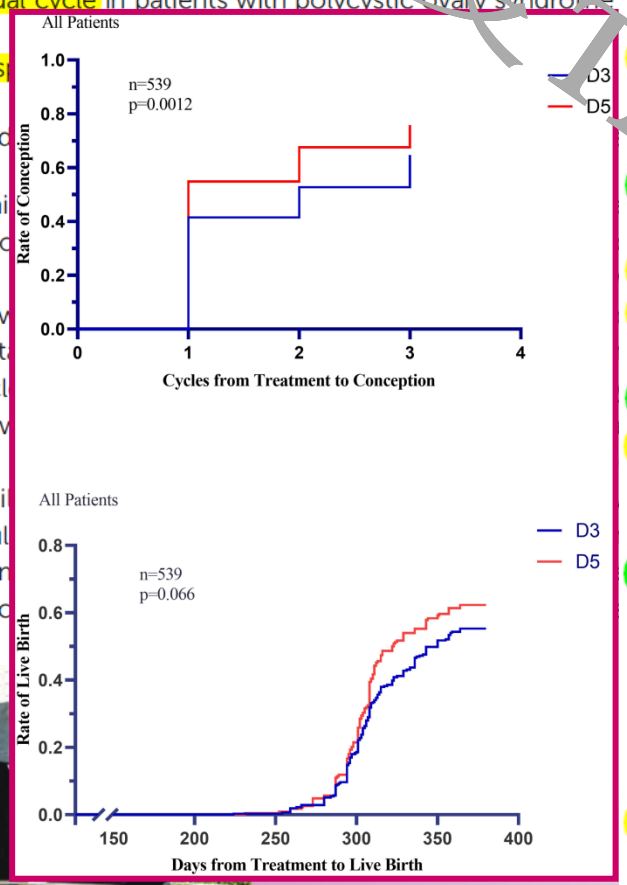

Results: Women who started LE on the 5th day of their menstrual cycle had more cumulative conception rates than those who started LE on the 3rd day (173 of 228[75.9%]*vs.* 201 of 311[64.6%], P= 0.005; rate ratio for conception, 1.174; 95% confidence interval,1.052 to 1.311) without significant differences in overall live birth rate, though there were 142 of 228[62.3%] in the D5 group versus 172 of 311[55.3%] in the D3 group (P= 0.105). The median (IQR) endometrial thickness was significantly (P = 0.013) greater during the D5 group treatment compared to the D3 group, which may be related to higher conception and clinical pregnancy rates. The median (IQR) maximum follicle diameter was not statistically (P = 0.056) different between the two groups. The cumulative ovulation per cycle rate was higher with D5 than with D3 (287 of 405 treatment cycles [70.9%] *vs.* 388 of 640 treatment cycles [60.6%], P=0.001). There were no significant between-group differences in pregnancy loss (31 of 173 conceptions in the D5 group [17.9%] and 29 of 201 conceptions in the D3 group [14.4%]) or multiples pregnancy (8.2% and 10.5%, respectively). Rates of other adverse events during pregnancy were similar in the two treatment groups.

Conclusion: As compared with D3 group, D5 group was associated with higher ovulation and conception rates, shorter time-to-pregnancy among infertile women with the PCOS.

d3 vs d5 start

D5胜

	D3(n=311)	D5(n=228)	Rate ratio(95% CI)	Absolute difference (95% CI)	P
OUTCOME	201/311(64.6%)	173/228(75.9%)	1.174(1.052 ,1.311)	11.3%(3.6% to 19.0%)	0.005
Age (years)					
<30	130/196(66.3%)	107/132(81.1%)	1.222(1.074,1.391)	14.7%(5.3% to 24.1%)	0.003
⩾30	71/115(61.7%)	66/96(68.8%)	1.114(0.914,1.356)	7.0%(−5.8% to 19.8%)	0.288
BMI(kg/m2)					
<18.5	22/29(75.9%)	19/26(73.1%)	0.963(0.706,1.314)	−2.8%(−26.6% to 20.3%)	0.813
18.5−25	136/215(63.3%)	117/154(76.0%)	1.201(1.049,1.375)	12.7%(3.4% to 22.0%)	0.009
>25	43/67(64.2%)	37/48(77.1%)	1.201(0.948,1.521)	12.9%(−3.6% to 29.4%)	0.138
LH/FSH					
<2	148/234(63.2%)	122/162(75.3%)	1.191(1.044,1.358)	12.1%(3.0% to 21.2%)	0.011
⩾2	53/77(68.8%)	51/66(77.3%)	1.123(0.92,1.37)	8.4%(−6.0% to 22.9%)	0.258
AMH(ng/ml)					
<4.15	54/76(71.1%)	37/56(66.1%)	0.93(0.734,1.178)	−5.0%(−21.0% to 11.0%)	0.541
4.15−9.995	96/157(61.6%)	88/115(76.5%)	1.251(1.066,1.469)	15.4%(4.5% to 26.3%)	0.007
>9.995	51/78(65.4%)	48/57(84.2%)	1.288(1.058,1.568)	18.8%(4.6% to 33.0%)	0.015
T(ng/ml) (Testosterone)					
<0.8	173/265(65.3%)	134/175(76.6%)	1.173(1.04,1.323)	11.3%(2.8% to 19.8%)	0.012
⩾0.8	28/46(60.9%)	39/53(73.6%)	1.209(0.912,1.603)	12.7%(−5.7% to 31.1%)	0.177
TSH					
<1.43	55/82(67.1%)	40/51(78.4%)	1.169(0.94,1.441)	11.3%(−3.9% to 26.5%)	0.159
1.43−2.61	93/146(63.7%)	98/123(79.7%)	1.25(1.05,1.52)	16.0%(5.4% to 26.6%)	0.004
>2.61	53/83...63.9%...	35/54(64.8%)	1.015(0.787,1.309)	0.9%(−15.6% to 17.2%)	0.9

0.5 0.8 1.1 1.4 1.7

The esti

Conception Rate

Live Birth Rate

	D3(n=311)	D5(n=228)	Rate ratio(95% CI)	Absolute difference (95% CI)	P
OUTCOME	172/311(55.3%)	142/228(62.3%)	1.126(0.977,1.298)	7.0%(−1.4% to 15.4%)	0.105
Age (years)					
<30	113/196(57.7%)	94/132(71.2%)	1.235(1.051,1.452)	13.5%(3.1% to 23.9%)	0.013
⩾30	59/115(51.3%)	48/96(50.0%)	0.975(0.746,1.274)	−1.3%(−14.8% to 12.2%)	0.85
BMI(kg/m2)					
<18.5	22/29(75.9%)	15/26(57.7%)	0.76(0.516,1.121)	−18.2%(−42.8% to 6.4%)	0.152
18.5−25	115/215(53.5%)	93/154(60.4%)	1.129(0.944,1.35)	6.9%(−3.3% to 17.1%)	0.187
>25	35/67(52.2%)	34/48(70.8%)	1.356(1.012,1.816)	18.6%(1.0% to 36.2%)	0.045
LH/FSH					
<2	122/234(52.1%)	98/162(60.5%)	1.16(0.974,1.382)	8.4%(−1.5% to 18.2%)	0.1
⩾2	50/77(64.9%)	44/66(66.7%)	1.027(0.8,1.301)	1.7%(−13.9% to 17.3%)	0.828
AMH(ng/ml)					
<4.15	48/76(63.2%)	29/56(51.8%)	0.82(0.6,1.113)	−11.4%(−28.4% to 5.6%)	0.19
4.15−9.995	80/157(51.0%)	74/115(64.3%)	1.263(1.029,1.55)	13.3%(1.6% to 25.0%)	0.028
>9.995	44/78(56.4%)	39/57(68.4%)	1.213(0.932,1.578)	12%(−4.3% to 28.3%)	0.157
T(ng/ml) (Testosterone)					
<0.8	149/265(56.2%)	111/175(63.4%)	1.128(0.966,1.317)	7.2%(−2.1% to 16.5%)	0.133
⩾0.8	23/46(50.0%)	31/53(58.5%)	1.17(0.81,1.689)	8.5%(−11.1% to 28.1%)	0.397
TSH					
<1.43	46/82(56.1%)	32/51(62.7%)	1.118(0.841,1.488)	6.7%(−10.4% to 23.8%)	0.449
1.43−2.61	80/146(54.8%)	80/123(65.0%)	1.182(0.973,1.436)	10.2%(−1.5% to 21.9%)	0.088
>2.61	46/83(55.4%)	30/54(55.6%)	1.002(0.738,1.362)	0.1%(−16.9% to 17.1%)	0.988

0.5 1 1.5 2

The estimates

Front Endocrinol (Lausanne). 2022 Nov 24;13:1059609.

Variable	D3 (n = 311)	D5 (n = 228)	Rate ratio (95% CI)	Absolute difference (95% CI)	P
No. of ovulations/total treatment cycles	388/640 (60.6%)	287/405 (70.9%)		10.2% (4.3% to 15.9%)	0.001
ET (mm) [median (IQR)]	8.0 (7.0 to 10.0)	9.0 (8.0 to 10.0)			0.013
Maximum follicle diameter	1.88 (1.77 to 1.97)	1.84 (1.75 to 1.95)			0.073
Conception	201/311 (64.6%)	173/228 (75.9%)	1.174 (1.052 to 1.311)	11.3% (3.6% to 19.0%)	0.005
Pregnancy	172/311 (55.3%)	146/228 (64.0%)	1.158 (1.007 to 1.331)	8.7% (0.4% to 17.0%)	0.042
Singleton	154/172 (89.5%)	134/146 (91.8%)	1.025 (0.955 to 1.1)	2.3% (-4.1% to 8.7%)	0.495
Twins	16/172 (9.3%)	12/146 (8.2%)	0.884 (0.432 to 1.807)	-1.1% (-7.3% to 5.1%)	0.734
Multiples	18/172 (10.5%)	12/146 (8.2%)	0.785 (0.391 to 1.576)	-2.3% (-8.7% to 4.1%)	0.495
Pregnancy loss					
Total losses among subjects who conceived	29/201 (14.4%)	31/173 (17.9%)	1.242 (0.781 to 1.975)	3.5% (-4.0% to 11.0%)	0.359
Biochemical factor or no fetal heart motion	21/201 (10.4%)	20/173 (11.6%)	1.107 (0.621 to 1.972)	1.1% (-5.3% to 7.5%)	0.731
Ectopic pregnancy	8/201 (4.0%)	7/173 (4.0%)	1.017 (0.376 to 2.746)	0.1% (-4.0% to 4.0%)	0.974
Loss after observed heart motion	0/201 (0.0%)	4/173 (2.3%)		2.3%0.1% to 4.5%)	0.045
Events among ovulated cycles					
Conception	201/388 (51.8%)	173/287 (60.3%)	1.164 (1.017 to 1.331)	8.5% (0.9% to 15.9%)	0.029
Singleton pregnancy	154/388 (39.7%)	134/287 (46.7%)	1.176 (0.988 to 1.4)	7.0% (-0.5% to 14.5%)	0.069
Singleton live birth	154/388 (39.7%)	130/287 (45.3%)	1.141 (0.956 to 1.362)	5.6% (-2.0% to 13.1%)	0.145
Events among subjects who ovulated					
Conception	201/287 (70.0%)	173/210 (82.4%)	1.176 (1.066 to 1.298)	12.4% (4.7% to 19.5%)	0.002
Singleton pregnancy	154/287 (53.7%)	134/210 (63.8%)	1.189 (1.025 to 1.379)	10.2% (1.4% to 18.6%)	0.024
Singleton live birth	154/287 (53.7%)	130/210 (61.9%)	1.154 (0.992 to 1.342)	8.3% (-0.6% to 16.8%)	0.067

Categorical data: % (n/N); Ovulation was defined as serum progesterone level over 5ng/ml within one cycle; IQR, interquartile; ET, endometrial thickness on the day of intramural injection of HCG); Conception was defined as a serum level of human chorionic gonadotropin that was positive; Pregnancy was defined by the presence of fetal heart movements on ultrasound.

Front Endocrinol (Lausanne). 2022 Nov 24;13:1059609.

d3 vs d5 start

Outline

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Letrozole versus laparoscopic ovarian drilling in clomiphene citrate-resistant women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials

Qiong Yu[1†], Shifu Hu[2†], Yingying Wang[2], Qiping Cheng[2], Wei Xia[2,3*] and Changhong Zhu[2,3*]

Reprod Biol Endocrinol. 2019 Feb 6;17(1):17.

Abstract

The objective of this systematic review was to examine the literature and to compare the effectiveness of letrozole (LE) versus laparoscopic ovarian drilling (LOD) for the induction of ovulation in women with clomiphene citrate (CC)-resistant polycystic ovary syndrome (PCOS). The PUBMED, Web of Science, and EMBASE databases were searched systematically for eligible randomized controlled trials (RCTs) from English language articles published from database inception to September 2018. Data were independently extracted and analyzed using the fixed-effects model or random-effects model according to the heterogeneity of the data. Four RCTs including 621 patients (309 in the LE group and 312 in the LOD group) met the inclusion criteria. There were no differences with regard to ovulation rate (relative risk [RR] 1.12; 95% confidence interval [CI] 0.93 to 1.34; $P = 0.12$, $I^2 = 90\%$, 541 patients, three studies), pregnancy rate (RR 1.21; 95% CI 0.95 to 1.53; $P = 0.12$, $I^2 = 0\%$, 621 patients, four studies), live birth rate (RR 1.27; 95% CI 0.96 to 1.68; $P = 0.09$, $I^2 = 19\%$, 541 patients, three studies), and abortion rate (RR 0.7; 95% CI 0.3 to 1.61; $P = 0.40$, $I^2 = 0\%$, 621 patients, four studies) between the two groups. These results indicated that LE and LOD appear to be equally effective in achieving live birth rate in patients with CC-resistant PCOS.

Keywords: Letrozole, Laparoscopic ovarian drilling, Polycystic ovary syndrome, Ovulation induction

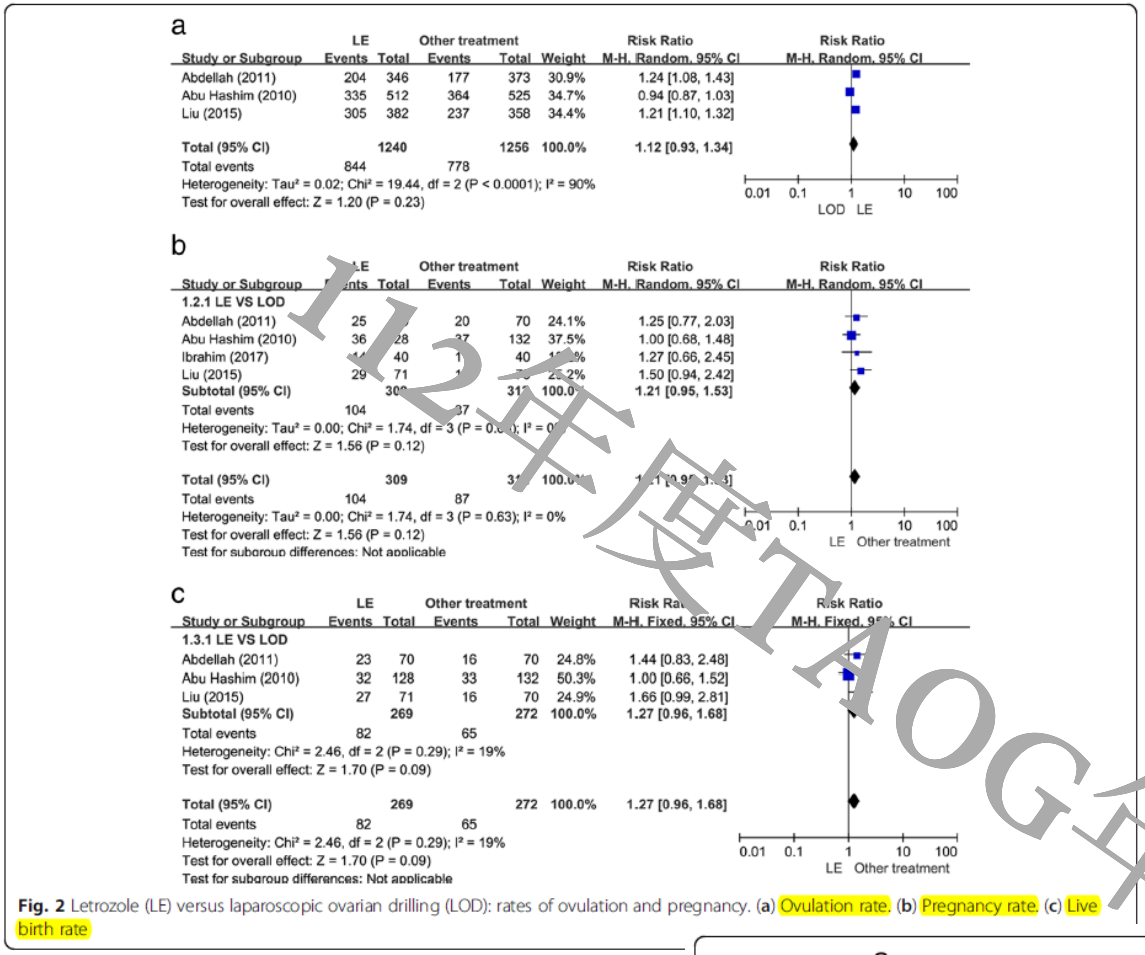

Fig. 2 Letrozole (LE) versus laparoscopic ovarian drilling (LOD): rates of ovulation and pregnancy. (**a**) Ovulation rate. (**b**) Pregnancy rate. (**c**) Live birth rate

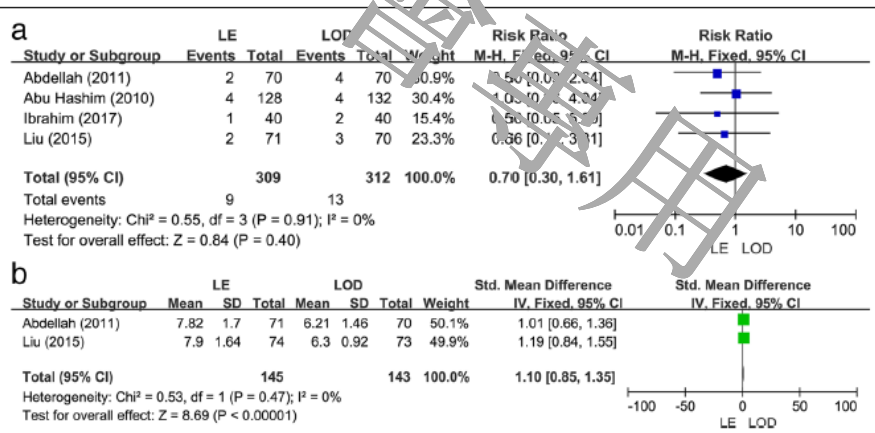

Fig. 3 Letrozole (LE) versus laparoscopic ovarian drilling (LOD): abortion rate and endometrial thickness at human chorionic gonadotrophin (HCG) injection. (**a**) Abortion rate. (**b**) Endometrial thickness at HCG injection

Reprod Biol Endocrinol. 2019 Feb 6;17(1):17.

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Aromatase inhibitors (le
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Franik S, Eltrop SM, Ki

Letrozole compared to laparoscopic ovarian drilling

There is low-quality evidence that live birth rates are similar with letrozole or laparoscopic ovarian drilling (OR 1.38, 95% CI 0.95 to 2.02; 548 participants; 3 studies; I^2 = 23%; low-quality evidence). There is insufficient evidence for a difference in OHSS rates (RD 0.00, 95% CI −0.01 to 0.01; 260 participants; 1 study; low-quality evidence). There is low-quality evidence that pregnancy rates are similar (OR 1.28, 95% CI 0.94 to 1.74; 774 participants; 5 studies; I^2 = 0%; moderate-quality evidence). There is insufficient evidence for a difference in miscarriage rate by pregnancy (OR 0.66, 95% CI 0.30 to 1.43; 240 participants; 5 studies; I^2 = 0%; moderate-quality evidence), or multiple pregnancies (OR 3.00, 95% CI 0.12 to 74.90; 548 participants; 3 studies; I^2 = 0%; low-quality evidence).

Analysis 4.1. Comparison 4 Letrozole compared to laparoscopic ovarian drilling, Outcome 1 Live birth rate.

Study or subgroup	Aromatase inhibitor n/N	LOD n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Abdellah 2011	23/74	16/73		24.42%	1.61[0.77,3.37]
Abu Hashim 2010a	37/128	33/132		53.61%	1[0.57,1.75]
Liu 2015	21/71	16/70		21.97%	2.07[0.99,4.32]
Total (95% CI)	**273**	**275**		**100%**	**1.38[0.95,2.02]**

Favours LOD 0.2 0.5 1 2 5 Favours Letrozole

Analysis 4.3. Comparison 4 Letrozole compared to laparoscopic ovarian drilling, Outcome 3 Clinical pregnancy rate.

Study or subgroup	Aromatase inhibitor n/N	LOD n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.3.1 AI versus LOD					
Abdellah 2011	25/74	20/73		18.32%	1.35[0.67,2.74]
Abu Hashim 2010a	36/128	37/132		35.97%	1[0.58,1.73]
Ibrahim 2017	14/40	11/40		9.82%	1.42[0.55,3.67]
Liu 2015	29/71	19/70		15.55%	1.85[0.91,3.76]
Subtotal (95% CI)	**313**	**315**		79.66%	**1.3[0.93,1.83]**
Total events: 104 (Aromatase inhibitor), 87 (LOD)					
Heterogeneity: Tau^2=0; Chi^2=1.88, df=3(P=0.6); I^2=0%					
Test for overall effect: Z=1.51(P=0.13)					
4.3.2 AI + metformin versus LOD					
Elgafor 2013	26/73	23/73		20.34%	1.2[0.6,2.39]
Subtotal (95% CI)	**73**	**73**		**20.34%**	**1.2[0.6,2.39]**
Total events: 26 (Aromatase inhibitor), 23 (LOD)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					

Outline

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Letrozole induction of ovulation in women with clomiphene citrate–resistant polycystic ovary syndrome may not depend on the period of infertility, the body mass index, or the luteinizing hormone/follicle-stimulating hormone ratio

Letrozole induction of ovulation in clomiphene citrate–resistant women with polycystic ovary syndrome is associated with an ovulation rate of 54.6% and pregnancy rate of 25%. There was no significant difference between letrozole responders and nonresponders in age, period of infertility, body mass index, waist circumference, LH, FSH, or LH/FSH ratio. (Fertil Steril® 2006;85:511–3. ©2006 by American Society for Reproductive Medicine.)

Clinical characteristics of letrozole responders and letrozole nonresponders.

Variable	Responders (n = 24)	Nonresponders (n = 20)	Significance
Age (years)	26.7 ± 4.21	28.35 ± 4.36	NS[a]
Period of infertility (y)	4.16 ± 3.29	5.05 ± 2.29	NS[a]
BMI (kg/m^2)	30.07 ± 3.23	29.06 ± 3.59	NS[a]
Waist (cm)	99 ± 9.5	101 ± 8.41	NS[a]
Waist/hip ratio	0.89 ± 0.04	0.90 ± 0.04	NS[a]
Menstrual pattern:			
Oligomenorrhea: no. (%)	16 (66.66%)	14 (70%)	NS[b]
Amenorrhea: no. (%)	8 (33.33%)	6 (30%)	NS[b]
Hirsutism: no. (%)	15 (62.5%)	13 (65%)	NS[b]
LH (IU/mL)	16.7 ± 3.21	17.9 ± 3.65	NS[a]
FSH (IU/mL)	6.5 ± 1.62	6.8 ± 1.81	NS[a]
LH/FSH ratio	2.68 ± 0.48	2.66 ± 0.45	NS[a]

Note: NS = not significant; BMI = body mass index.
Variables are given as mean ± SD.
$P = .05$.
[a] *t* test.
[b] χ^2 tests.

Elnashar. Letrozole induction of ovulation. Fertil Steril 2006.

Guo et al. BMC Endocrine Disorders (2023) 23:90
https://doi.org/10.1186/s12902-023-01336-z

BMC Endocrine Disorders

Letrozole 2.5 mg/d from MC day 3~7→no trigger

RESEARCH Open Access

Predictors of response to ovulation induction using letrozole in women with polycystic ovary syndrome

Zaixin Guo[1], Shuwen Chen[1], Zhiyan Chen[2], Pan Hu[1], Yanfang Hao[1] and Qi Yu[1*]

Abstract

Background This study aimed to evaluate the predictive value of the initial screening characteristics of women with anovulatory polycystic ovary syndrome (PCOS) who did or did not respond to 2.5 mg letrozole (LET).

Methods The clinical and laboratory characteristics of women with PCOS who underwent LET treatment were evaluated. Women with PCOS were stratified according to their responses to LET (2.5 mg). The potential predictors of their responses to LET were estimated using logistic regression analysis.

Results Our retrospective study included 214 eligible patients with a response to 2.5 mg LET (n = 131) and no response to 2.5 mg LET (n = 83). PCOS patients who responded to 2.5 mg LET showed better outcomes than those who did not (2.5 mg LET) for pregnancy rate, live birth rate, pregnancy rate per patient, and live birth rate per patient. Logistic regression analyses showed that late menarche (odds ratio [OR], 1.79 [95% confidence intervals (CI), 1.22–2.64], $P = 0.003$), and increased anti-müllerian hormone (AMH) (OR, 1.12 [95% CI, 1.02–1.23], $P = 0.02$), baseline luteinizing hormone (LH)/ follicle stimulating hormone (FSH) (OR, 3.73 [95% CI, 2.12–6.64], $P < 0.001$), and free androgen index (FAI) (OR, 1.37 [95% CI, 1.16–1.64], $P < 0.001$) were associated with a higher possibility of no response to 2.5 mg LET.

Conclusions PCOS patients with an increased LH/FSH ratio, AMH, FAI, and late menarche may need an increased dosage of LET for a treatment response, which could be helpful in designing a personalized treatment strategy.

Keywords Polycystic ovary syndrome, Letrozole, Ovulation

The cumulative ovulation rates of patients with **menarche < 13.5y, LH/FSH ratio < 1.83, AMH < 9.78ng/ml, and FAI < 5.99** were significantly higher.

The cumulative pregnancy rate of patients with **FAI < 5.99** was significantly higher than that of patients with FAI ≥ 5.99.

Table 3 Univariate and multivariate regression analyses that compare variable clinical markers with respective outcomes

	Univariate*		Multivariate*	
Variables	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Menarche	1.99 (1.45–2.75)	**< 0.001**	1.79 (1.22–2.64)	**0.003**
AMH	1.20 (1.10–1.30)	**< 0.001**	1.12 (1.02–1.23)	**0.02**
Baseline LH/FSH	3.02 (1.94–4.80)	**< 0.001**	3.73 (2.12–6.64)	**< 0.001**
FAI	1.41 (1.20–1.66)	**< 0.001**	1.37 (1.16–1.64)	**< 0.001**

AMH anti-müllerian hormone, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *FAI* free androgen index

*Adjusted for age

Ovarian Response can be Predicted in Women with PCOS who have Ovulation Induction with Letrozole

Ozlem Karabay Akgul and Hakan Guraslan

Department of Obstetrics and Gynaecology, University of Health Sciences Istanbul Bagcilar Research and Training Hospital, Istanbul, Turkey

Letrozole 5 mg/d from MC day 3~7
➔Ovidrel 1 amp if dominant follicle ≥18 mm➔IUI

ABSTRACT

Objective: To compare the clinical, metabolic, and hormonal characteristics of patients with and without selected dominant follicles in infertile women with PCOS who used letrozole for ovulation induction.

Study Design: A descriptive cohort study.

Place and Duration of Study: Department of Obstetrics and Gynaecology of Bagcilar Research and Training Hospital, Istanbul, Turkey, from October 2019 to November 2021.

Methodology: Eighty-eight female patients with PCOS, who underwent ovulation induction by giving 5 mg/day letrozole, were screened for demographic characteristics, laboratory values, and dominant follicle development. Those who were given letrozole as the first treatment agent, those who took clomiphene citrate (CC) and started letrozole the following month, and those who were treated with letrozole and given letrozole again were recorded separately. Seventy-five patients responded to letrozole and developed a dominant follicle; 13 patients did not develop a dominant follicle. Threshold values were determined for statistically significant parameters between patients with and without dominant follicles.

Results: Follicle development occurred in 85.2% of the women. A statistically significant variable in clinical and metabolic values, between ovulating and non-ovulating groups could not be found. There was a significant difference between the two groups for the serum AMH value, total testosterone value, and FSH level. The authors found that follicle response was higher in those with AMH values less than 11.89 ng/mL, FSH levels higher than 6.25 Iu/L, and total testosterone less than 0.96 ng/mL. In this study, the pregnancy rate was found to be lower than in the literature (11%).

Conclusion: Among the women with PCOS who had ovulation induction with letrozole, follicle development was higher in women with lower FSH, androgen and AMH values.

Table III: ROC curves of hormone values in follicle development and diagnostic performance.

	AUC 95% CI	p	Threshold	Sensitivity 95% CI Specificity 95% CI	PPV NPV
AMH	0.84 (0.69-0.99)	<0.001	<11.89	0.87 (0.77-0.92) 0.84 (0.57-0.96)	0.97 (0.90-0.99) 0.52 (0.41- 0.63)
FSH	0.68 (0.51-0.85)	0.041	>6.25	0.64 (0.52-0.74) 0.77 (0.49-0.92)	0.94 (0.86-0.97) 0.27 (0.18-0.37)
Total testosterone	0.83 (0.68-0.99)	<0.001	<0.96	0.95 (0.87-0.98) 0.69 (0.42-0.87)	0.95 (0.87-0.98) 0.69 (0.58-0.78)

J Coll Physicians Surg Pak. 2023 Feb;33(2):217-221.

Outline

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- Letrozole use in ovulation induction
- Letrozole versus laparoscopic ovarian drilling in clomiphene citrate (CC)-resistant PCOS women
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- Letrozole resistance: extended use?
- Ovulation induction using letrozole combined with other agents (dexamethasone/clomiphene/gonadotropin/metformin)

LE resistance

EXTENDED USE OF LETROZOLE

Extending letrozole treatment duration is effective in inducing ovulation in women with polycystic ovary syndrome and letrozole resistance

hypothesized that longer treatment with LE could extend the "FSH window", thereby inducing follicle growth in patients who initially do not respond to routine treatment

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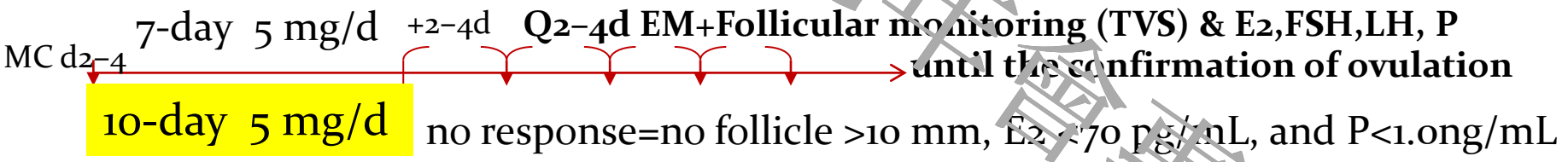
Fertil Steril 2023;119:107–13.

Objective: To evaluate whether extending letrozole (LE) treatment duration could induce ovulation in women with polycystic ovary syndrome (PCOS) who previously failed to ovulate after a 5-day regimen of 5 mg LE daily for at least 1 ovulation induction cycle, defined as "LE resistance".
Design: Retrospective cohort study.
Setting: Tertiary care academic medical center.
Patient(s): A total of 69 women with PCOS and LE resistance were included.
Intervention(s): The duration of LE treatment was increased in a stepwise manner (named as "2-step extended LE regimen"). A 7-day regimen of 5 mg LE daily was prescribed in the first ovulation induction cycle, and if ovulation did not occur, a 10-day regimen was prescribed in the subsequent cycle.
Main Outcome Measure(s): Ovulation rate was the primary outcome. Clinical pregnancy rate, live birth rate, spontaneous ovulation rate, and ovarian hyperstimulation syndrome rate were the secondary outcomes.
Result(s): Of the 69 patients, 48 ovulated after the 7-day and 16 after the 10-day regimen. Overall, the cumulative ovulation rate reached 92.75% (64/69) after the 2-step extended LE regimen, with a cumulative clinical pregnancy rate of 31.88% (22/69) and a cumulative live birth rate of 24.63% (17/69). All patients ovulated spontaneously without exogenous trigger agents and none experienced ovarian hyperstimulation syndrome.
Conclusion(s): Extending LE treatment duration is a feasible method for inducing ovulation in women with PCOS and LE resistance.

China
- timed intercourse, not ART
- No trigger
- Retrospective cohort

LE resistance Def.: failure of ovulation after a 5-day regimen of 5 mg of LE per day for at least 1 cycle

- 2-step extended LE regimen for women with PCOS and LE resistance: a 7-day regimen of 5 mg LE daily (starting on MC d2, 3, or 4) was prescribed in the first ovulation induction cycle, and if ovulation did not occur, a 10-day regimen was prescribed in the subsequent cycle



Fertil Steril 2023;119:107–13.

Ovulation

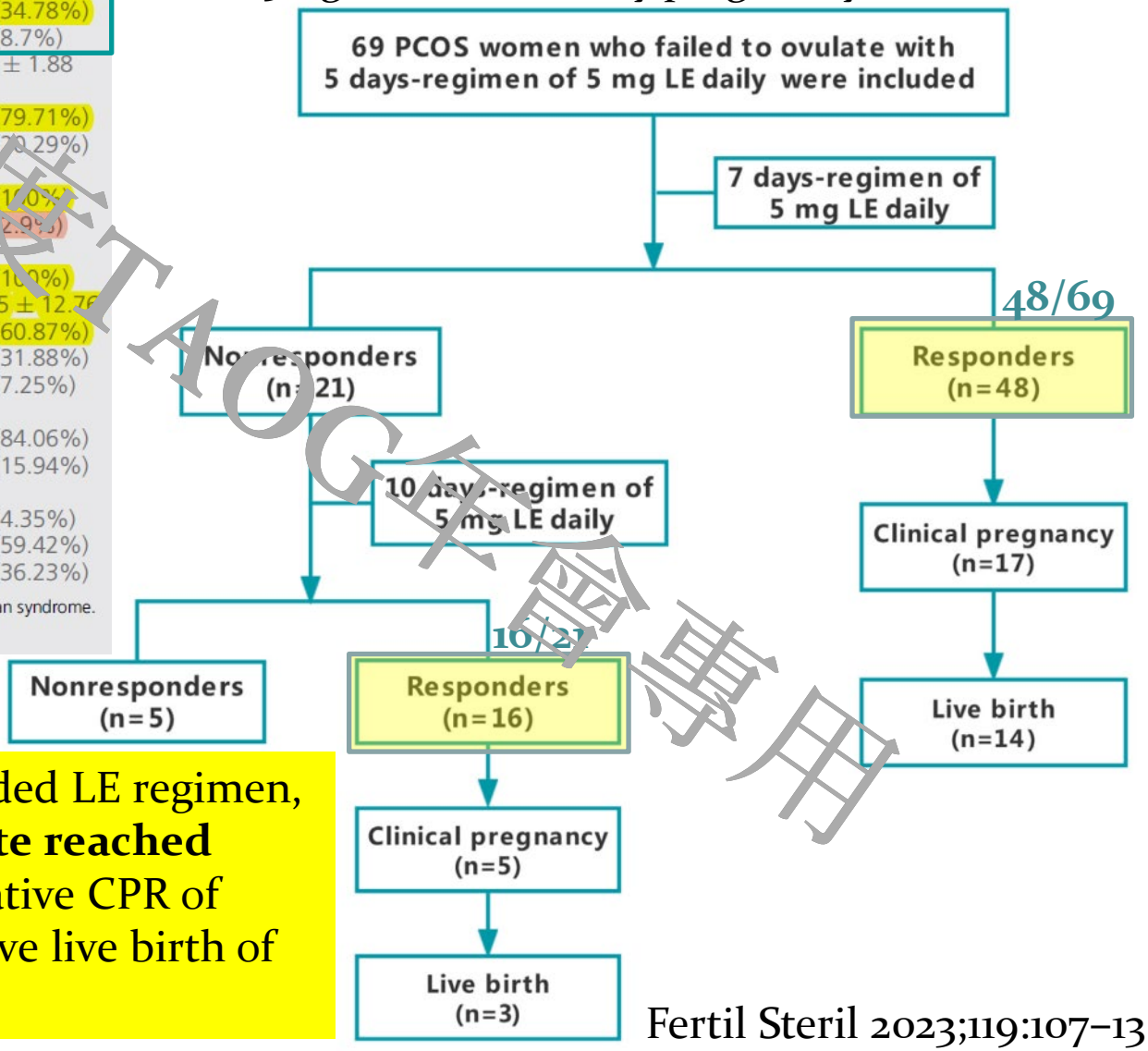
=disappearance of a follicle >14 mm
+E2 ↓ >50%+ ↑ P>1.0 ng/mL,
or
P>5 ng/mL followed by pregnancy or menses

Patient characteristics.

Characteristic	Value
No. of patients	69
Number of cycles (n)	90
Maternal age (y)	30.48 ± 3.7
BMI (kg/m^2), n (%)	24.8 ± 4.26
<18.5	2 (2.9%)
18.5–25	37 (53.62%)
25–30	24 (34.78%)
≥30	6 (8.7%)
Infertility duration (y)	3.51 ± 1.88
Type of infertility, n (%)	
Primary infertility	55 (79.71%)
Secondary infertility	14 (20.29%)
PCOS diagnosis, n (%)	
Polycystic ovaries	69 (100%)
Hyperandrogenism (clinical or laboratory)	2 (2.9%)
Menstrual dysfunction	69 (100%)
AFC in both ovaries, n (%)	38.25 ± 12.76
<40	42 (60.87%)
40–59	22 (31.88%)
≥60	5 (7.25%)
Menstrual dysfunction, n (%)	
Oligomenorrhea	58 (84.06%)
Amenorrhea	11 (15.94%)
Fallopian tube patency, n (%)	
One patent tube	3 (4.35%)
Bilateral patent tubes	41(59.42%)
No test records	25 (36.23%)

AFC = antral follicle count; BMI = body mass index; PCOS = polycystic ovarian syndrome.

Zhu. Extended letrozole regimen in PCOS. Fertil Steril 2022.



Overall, after the 2-step extended LE regimen, the **cumulative ovulation rate reached 92.75%** (64/69), with a cumulative CPR of 31.88% (22/69) and a cumulative live birth of 24.63% (17/69).

Fertil Steril 2023;119:107–13.

Measured parameters in patients who ovulated after the 2-step extended letrozole treatment.

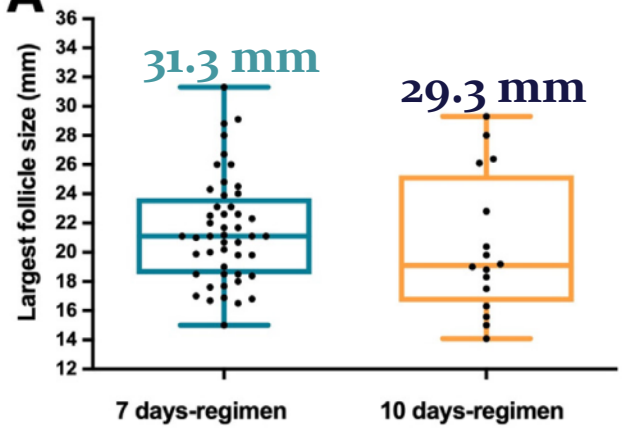
Measured parameters	7-Day regimen	10-Day regimen	*P* value
No. of patients	48	16	—
Number of cycles	48	16	—
No. of follicles >14 mm (n)	1.35 ± 0.53	1.31 ± 0.48	.842[a]
No. of follicles >18 mm (n)	1.02 ± 0.56	1 ± 0.52	.984[a]
Largest follicle size (mm)	21.5 ± 3.63	20.41 ± 4.75	.212[a]
Time to ovulation (d) (days from the first dose of LE to ovulation)	16.19 ± 3.04	17.44 ± 3.01	.158
Endometrial thickness (mm) (before ovulation)	10.58 ± 2.63	10.8 ± 2.74	.609[a]
No. of spontaneous ovulation	48	16	—
OHSS (n)	0	0	—
Biochemical pregnancy rate, % (n)	37.5% (18/48)	37.5% (6/16)	1.000
Clinical pregnancy rate, % (n)	35.42% (17/48)	31.25% (5/16)	.761
Multiple pregnancy rate, % (n)	5.88% (1/17)	20% (1/5)	.411[b]
Ectopic pregnancy rate, % (n)	5.88% (1/17)	0% (0/5)	1.000[b]
Early miscarriage rate, % (n)	5.88% (1/17)	20% (1/5)	.411[b]
Late miscarriage rate, % (n)	0% (0/17)	20% (1/5)	.227[b]
Live birth rate, % (n)	29.17% (14/48)	18.75% (3/16)	.525[b]

Data are means ± standard deviations. There were no significant differences between groups.
[a] Mann-Whitney *U* test (for continuous variables).
[b] Fisher's exact test (for categorical variables). OHSS = ovarian hyperstimulation syndrome.

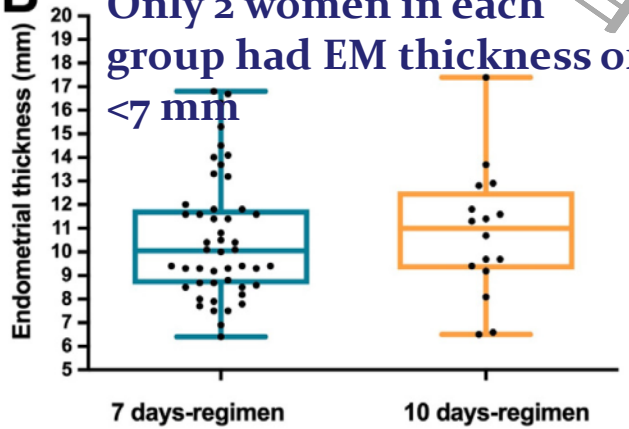
Zhu. Extended letrozole regimen in PCOS. Fertil Steril 2022.

EM thickness: No duration-dependent reduction. Only 2 women in each group had EM thickness of <7 mm

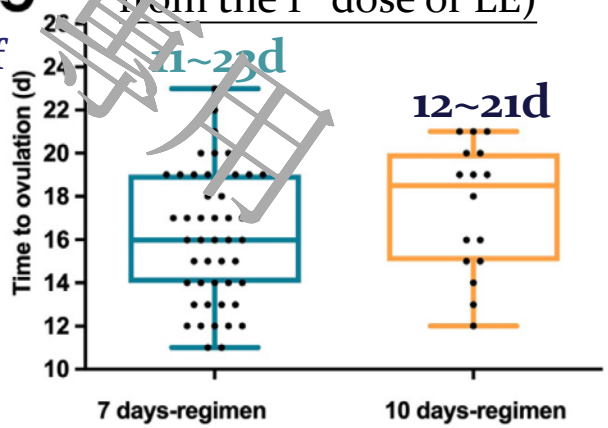
A The largest follicle diameter



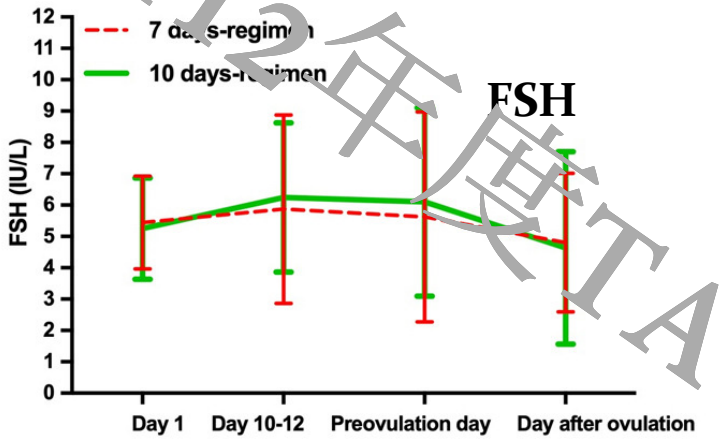
B

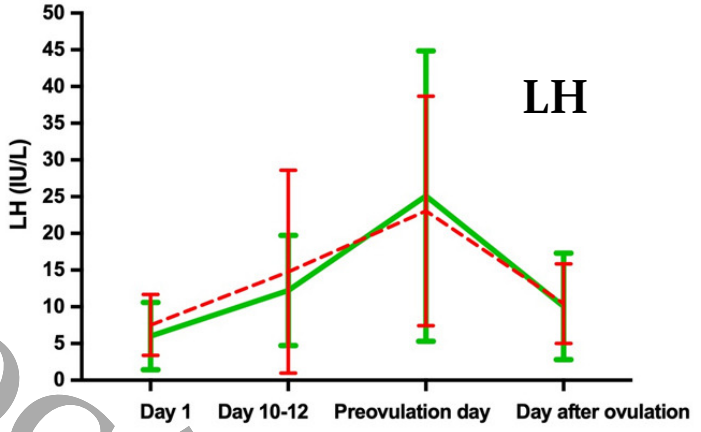


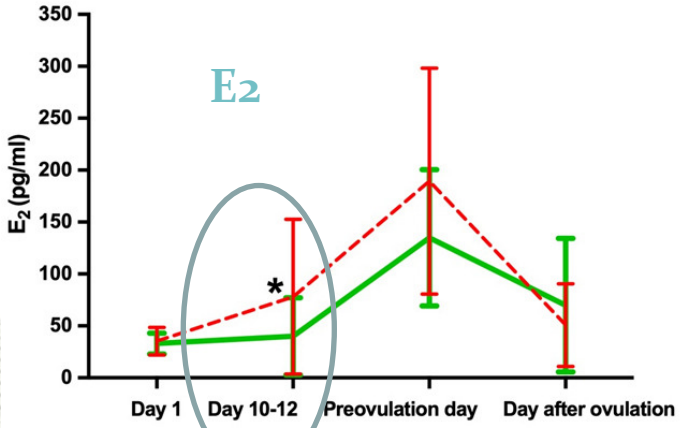
C The time to ovulation (days from the 1st dose of LE)

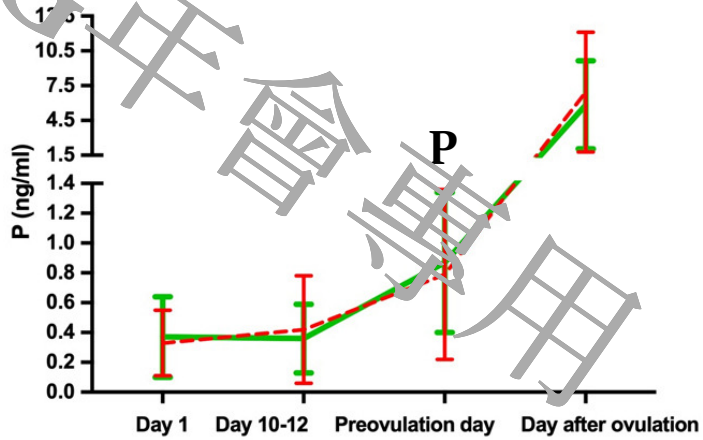


Serum hormone levels during ovarian stimulation in ovulatory cycles









day 1=LE start

Fertil Steril 2023;119:107–13.

Who tends to ovulate via extended use?

Supplemental Table 1 Unadjusted and adjusted ORs for ovulation in patients undergoing two-step extended letrozole treatment

Fertil Steril 2023;119:107–13.

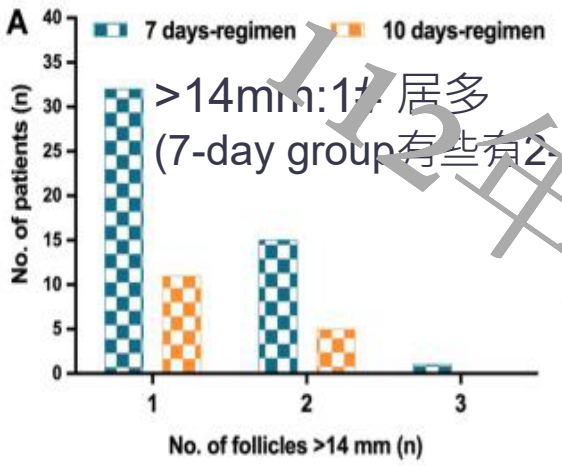
Variables	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Maternal age (years)	0.788 (0.594–1.046)	0.099	0.688 (0.459–1.032)	0.07
BMI (kg/m²)	0.841 (0.705–1.027)	0.092	0.787 (0.567–1.093)	0.153
Infertility duration (years)	1.034 (0.631–1.694)	0.894	0.97 (0.491–1.913)	0.929
AFC (n)				
<40	8 (0.43–148.86)	0.163	2.778 (0.056–138.846)	0.609
40–59	1.267 (0.107–14.949)	0.851	0.13 (0.002–6.985)	0.316
≥60	Reference	—	Reference	—
Menstrual cyclicity (n)				
Oligomenorrhea	10.5 (1.514–72.811)	0.017	21.077 (1.057–420.386)	0.046
Amenorrhea	Reference	—	Reference	—

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; AFC, antral follicle count

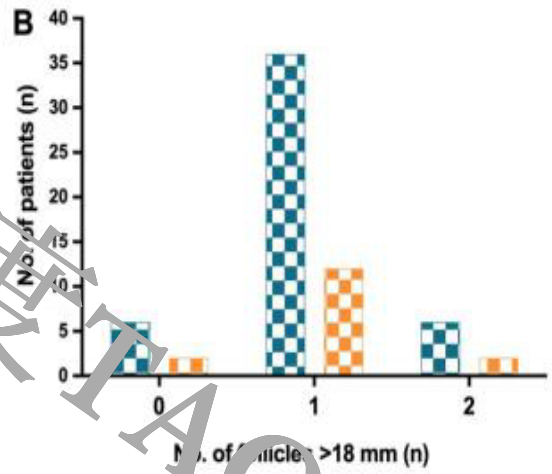
Menstrual cyclicity was an independent risk factor for anovulation—Oligomenorrhea (35d~<3M interval) vs amenorrhea (>3M interval): 21.077 times more likely to ovulate

The severity of menstrual dysfunction may potentially reflect the sensitivity of the ovaries to LE

--menstrual history may help determine the initiation and duration of LE treatment and reduce the rates of nonresponse among women

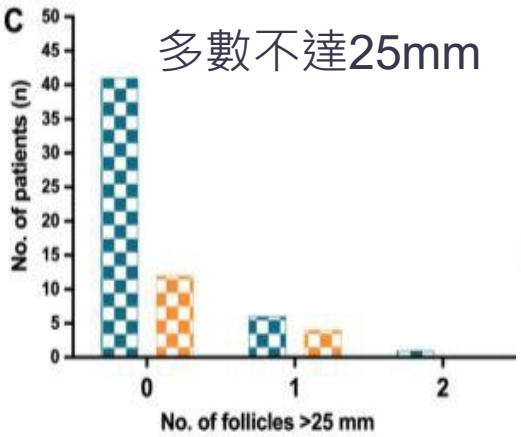


>14mm:1# 居多
(7-day group有些有2-3#)



>18mm:1# 居多，有些有2#

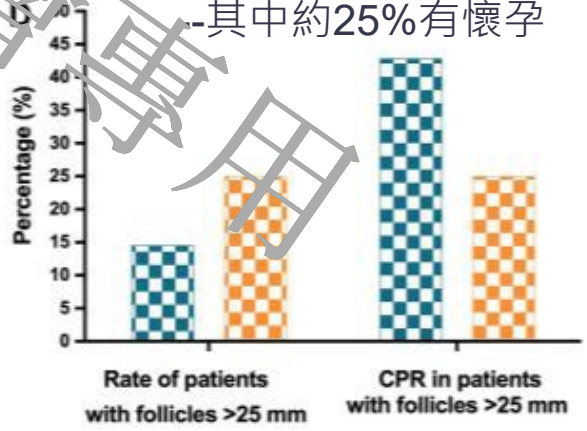
➢有8位不達18mm就排卵了
—這8位皆無懷孕



多數不達25mm

All >25 mm spontaneously ovulated without trigger

7-day group中約15%有1-2#
--其中約43%有懷孕
10-day group中25%有1#
--其中約25%有懷孕



Fertil Steril 2023;119:107–13.

Fertil Steril. 2009 Jul;92(1):236-9

POLYCYSTIC OVARY SYNDROME

Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol

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Objective: To evaluate the outcome of long letrozole therapy for induction of ovulation in patients with clomiphene-resistant polycystic ovary syndrome (PCOS).
Design: Prospective randomized controlled study.
Setting: University teaching hospital and a private practice.
Patient(s): The study comprised 218 patients with clomiphene-resistant PCOS.
Intervention(s): Patients were randomly allocated to treatment with either long letrozole therapy (n = 108; 219 cycles) or short letrozole therapy (n = 110; 225 cycles).
Main Outcome Measure(s): Number of growing and mature follicles, serum E2 (pg/mL), serum P (ng/mL), endometrial thickness, occurrence of pregnancy and miscarriage.
Result(s): The number of ovulating patients was greater in the letrozole group (... vs. 61.8%), but without statistical differences. The total number of follicles during stimulation was significantly greater in the long letrozole group (6.7 ± 0.3 vs. 3.9 ± 0.4). The number of follicles ≥14 mm and ≥18 mm were significantly greater in the long letrozole group. There was no significant difference in the pretreatment endometrial thickness or endometrial thickness at the time of hCG administration between the groups. Pregnancy occurred in 28 of 225 cycles in the short group (12.4%) and 38 of 219 cycles (17...%) in the long group, and the difference was statistically significant.
Conclusion(s): The long letrozole protocol (10 days) can induce more mature follicles and subsequently more pregnancies than the short letrozole therapy (5 days). Fertil Steril 2009;92:236–... ©2009 American Society for Reproductive Medicine.)

Key Words: Letrozole, clomiphene-resistant, PCOS

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in young women which manifests itself in a variety of clinical ways. Although clomiphene citrate (CC) is still the traditional therapy used for inducing ovulation in this condition, clomiphene resistance, which refers to persistence of anovulation after six cycles of CC therapy, occurs in 15%–20% of patients (1). Aromatase inhibitors (AIs), such as letrozole or anastrozole, have been advocated for treatment of PCOS women with CC resistant anovulation. It has been postulated that by inducing ovulation by inhibiting aromatization in the ovary would release the hypothalamic-pituitary axis from estrogen negative feedback. As a result, FSH secretion increases, stimulating the development of ovarian follicles. Preliminary studies have reported that aromatase inhibitors were useful for inducing ovulation and in superovulation (2, (2.5 mg, 5 mg, and 7.5 mg) on ovulation (4). ... have been no studies looking for the optimum duration of letrozole therapy. The intention of the present study was to evaluate the effect of extended letrozole protocol compared with short letrozole protocol in the management of clomiphene-resistant women with polycystic ovary syndrome.

MATERIALS AND METHODS

The study comprised 218 women (444 cycles) with clomiphene-resistant PCOS among those attending the gynecology outpatient clinic in Mansoura University Hospitals, Egypt, and a private practice setting in the period from December 2005 to December 2007. The diagnosis of PCOS based on the revised 2003 consensus on diagnostic criteria and long-

MCd1-5: 5 mg of letrozole < MCd1-10: 2.5 mg of letrozole

LE resistance

LETROZOLE+ DEXAMETHASONE

Ovulation induction with letrozole and dexamethasone in infertile patients with letrozole-resistant polycystic ovary syndrome

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◆timed intercourse/IUI
◆LH kit if dominant follicle >14 mm or hCG trigger at follicle 20 mm assumed

Abstract

Purpose To assess efficacy of adjuvant dexamethasone during letrozole cycles for ovulation induction (OI) in women with letrozole-resistant polycystic ovary syndrome (PCOS).

Methods We retrospectively evaluated 42 cycles of OI from 28 infertile women with letrozole-resistant PCOS between September 2019 and November 2022. Letrozole was initiated on cycle day 3 for 5 days and increased via a stair-step approach to 7.5 mg as indicated. Patients were deemed letrozole-resistant if no dominant follicle was identified on transvaginal ultrasound following this dose. Resistant patients then received 5 additional days of letrozole 7.5 mg with low-dose dexamethasone 0.5 mg for 7 days and had a repeat ultrasound. The primary outcome was ovulation rate determined by the presence of a d

MC d3 → +3–5d or MCd10-12 → +7 days

5-day 2.5~7.5 mg/d
(stair-step if no response on TVS)

no response=no follicle >14 mm following 7.5 mg/d of LE

5 more days of LE 7.5 mg/d
+7-day dexamethasone 0.5 mg/d

Check ovulation: urine LH kit if follicle >14 mm or post trigger appropriately timed **menses/implantation**

Glucocorticoids:
1. suppress adrenal androgen production, which may decrease hyperandrogenic anovulation.
2. appear to modify GnRH pulsatility to increase FSH release

Table 1 Patient characteristics[a]

	Overall n=28	Missing (%)	(79%) Responders n=22	(21%) Non-Responders n=6	P-value
Age, years	30 (27–31)		30 (27–31)	27 (24–30)	0.2
Body mass index, kg/m²	30 (26–37)	(obesity)	32 (26–38)	27 (24–33)	0.3
Race, n (%)					
White/Non-Hispanic	24 (86)		20 (91)	4 (67)	
White/Hispanic	2 (7)		0	2 (33)	
Asian	2 (7)		2 (9)	0	
Black	0		0	0	
Infertility duration, years	2 (1–3)		1 (1–2)	3 (2–4)	0.02*
Cycle regularity, n (%)					0.1
Oligo-ovulatory	16 (57)		15 (68)	1 (17)	
Anovulatory	12 (43)		7 (32)	5 (83)	
Number of treatment cycles	1 (1–2)		1 (1–1.75)	1.5 (1–2)	0.3
Total testosterone, ng/dL	51 ([illegible]–70)	5 (18)	51 (40–66)	53 (46–69)	0.5
Free testosterone, ng/dL	1.[illegible]9 (0.82–1.4[illegible])	9 (32)	1.08 (0.75–1.38)	1.28 (0.96–2.61)	0.5
Dehydroepiandrosterone Sulfate, mcg/dL	218 (14[illegible]–[illegible])	10 (36)	224 (146–328) >	186 (141–252)	0.8
Follicle-stimulating hormone, IU/L	5.3 (4.3–6.[illegible])	7 (25)	5.7 (4.7–6.5)	5.2 (4.1–5.3)	0.6
Luteinizing hormone, IU/L	10.5 (8.9–15.8)	[illegible] (57)	10.5 (9.1–18.6)	10.7 (9.6–11.9)	0.8
Anti-Mullerian hormone, ng/mL	12 (8.1–19)	4 ([illegible])	1[illegible] (9.6–19)	9.3 (8.5–11)	0.3
Glycemic status, n (%) (Pre-treatment OGTT/ fasting glucose/ HbA1c)					0.8
Normal	20 (71)	(no DM)	1[illegible] (73)	4 (67)	
Impaired	8 (29)		6 (27)	2 (33)	
Partner total motile sperm count (× 10⁶)	123 (64–191)	6 (21)[b]	118 (60–1[illegible]1)	154 (125–191)	0.3

The asterisk indicates statistically significance, p<0.05

[a]Values are in medians (1st and 3rd interquartile ranges) unless stated otherwise

Journal of Assisted Reproduction and Genetics (2023) 40:1461–1466

(with the addition of dexamethasone)

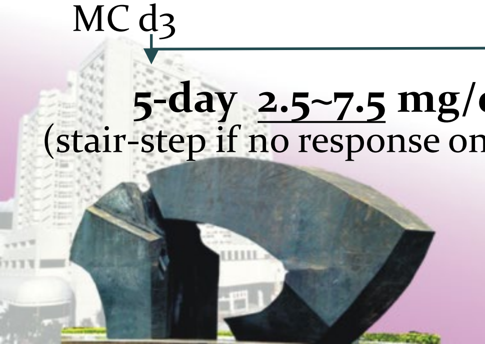
MC d3 — +3–5d or MCd10-12 — +7 days

5-day 2.5~7.5 mg/d
(stair-step if no response on TVS)

Ovulation= urine LH kit (+)/ post-hCG trigger
appropriately timed **menses/implantation**

no response=no follicle >14 mm following 7.5 mg/d of LE

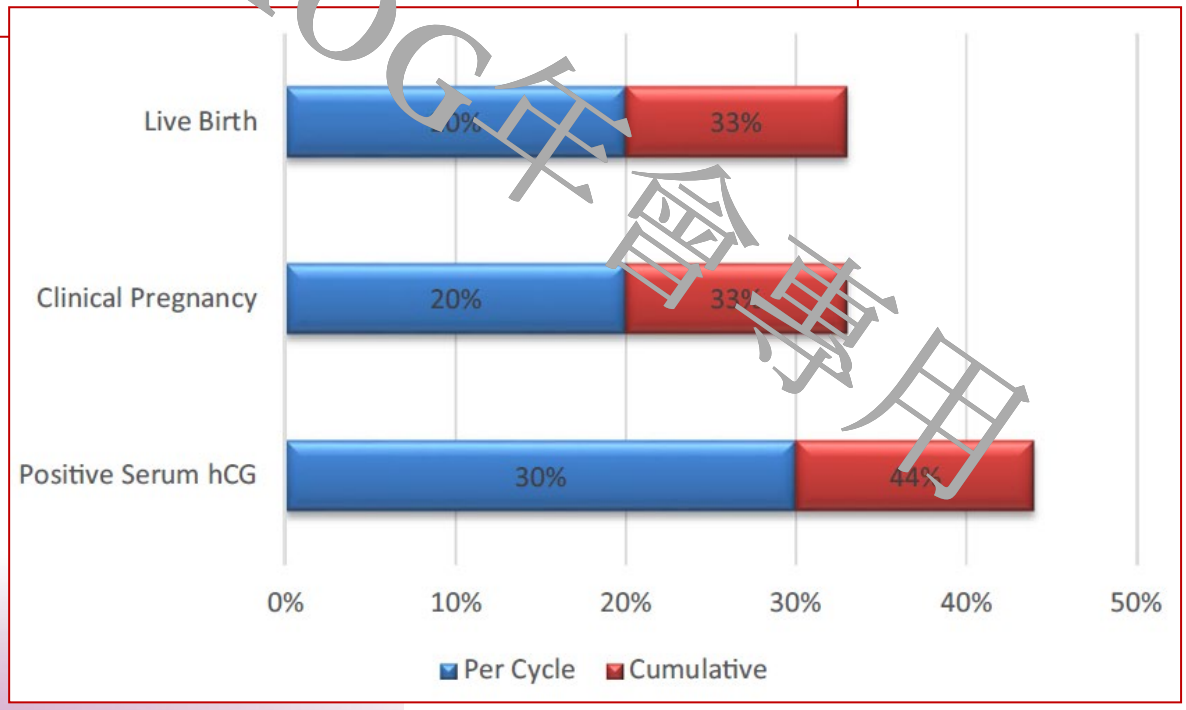
5 more days of LE 7.5 mg/d
+7-day dexamethasone 0.5 mg/d



	Response cycles $n=35$	Live birth[b] $n=7$	No live birth[b] $n=28$	*P*-value
Endometrial stripe thickness, mm	7 (2)	6 (3)	7 (2)	0.5
Number of measurable follicles > 10 mm	2 (1.4)	2 (0.6)	2 (1.5)	0.6
Leading follicle size, mm	19 (4)	19 (4)	19 (4)	0.8
Ovulation detection, *n* (%)				0.8
hCG trigger	29 (83)	6 (86)	23 (82)	
Ovulation predictor kits	6 (17)	1 (14)	5 (18)	
Treatment modality, *n* (%)				0.7
Timed intercourse	27 (77)	5 (71)	22 (79)	
Intrauterine insemination	8 (23)	2 (29)	6 (21)	

[a]Values are in means (standard deviation) unless stated otherwise

[b]35 of 42 cycles responded after the addition of dexamethasone are included in live birth verses no live birth analysis



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Production and Hosting by Knowledge E

Int J Reprod Biomed. 2020;18:307–10

Knowledge E
enriching | engaging | empowering

Check for updates

- PCOS, 18-39 y/o (**not identify patients resistant to letrozole**)

Short Communication

Comparison of ovulation induction with letrozole plus dexamethasone and letrozole alone in infertile women with polycystic ovarian disease: An RCT

Farahnaz Farzaneh[1] M.D., Fatemeh Afshar[2] M.D.

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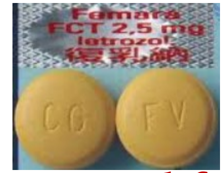

Letrozole 5 mg/d from MCd3-7 for 5 days

± Dexamethasone 0.5 mg/d from MCd 4-15

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Production and Hosting by Knowledge E

Abstract

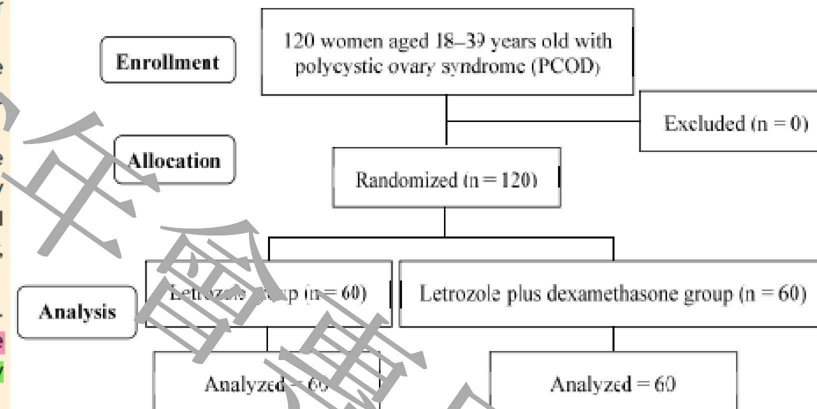
Background: Infertility is characterized by the inability to obtain a successful pregnancy after 6 months or more with unprotected and regular intercourse. In developing countries, the incidence of infertility is 2%. The causes of infertility could be male factor or female factor, or mixed factor.

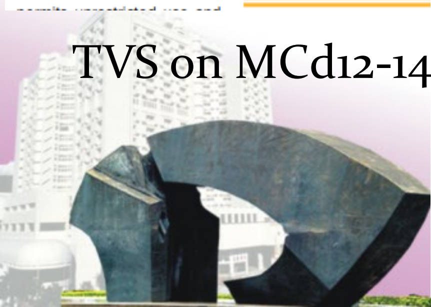
Objective: This study was conducted with the aim of comparison the ovarian response to letrozole alone and letrozole plus dexamethasone in infertile women with polycystic ovarian disease (PCOS).

Materials and Methods: This randomized clinical trial was conducted on 120 infertile women with PCOS referred to Ali-Ebne-Abitaleb hospital, Zahedan, Iran from February to August 2017 into two groups: group I received letrozole alone and group II recived letrozole plus dexamethasone. The endometrial thickness, follicle diameter, and ovulation were evaluated and compared by ultrasound on days 12 to 14.

Results: The mean thickness of endometrium was not different between two groups. Pregnancy rate was 8% in letrozole group and 23% in Letrozole plus Dexamethasone (p = 0.024). Also, the mean diameter of follicles in two groups were not statistically significant.

Conclusion: Overall, this study showed that dexamethasone may increase pregnancy rate.





TVS on MCd12-14

Variables	Group I (Letrozole)	Group II (Letrozole + Dexametasone)	P-value
Endometrial thickness (mm)**	7.4 ± 2.2	8 ± 2.3	0.11[a]
Pregnancy rate (%)**	5 (%8)	14 (%23)	0.024[b]
Diameter of follicles (Right ovary) (mm)*	16.4 ± 3.3	16.9 ± 3.3	0.465[a]
Diameter of follicles (Left ovary) (mm)*	16.2 ± 3	16.2 ± 3	0.821[a]

* Data presented as Mean ± SD, ** Data presented as n(%), a: Independent *t* test, b: Chi-square

LE resistance

LETROZOLE+ CLOMIPHENE

Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome

CC failed X6 cycles → Letrozole failed x4 cycles → Letrozole +CC

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
2 December 2013
Number of times this article has been viewed

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Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age (6.8%–18%), is among the most common causes of infertility due to ovulation factors, and accounts for 55%–70% of infertility cases caused by chronic anovulation. In this study, we used a combination of letrozole and clomiphene in patients resistant to both drugs individually, and studied the effects of this combination in ovulation and pregnancy in resistant PCOS patients.

Methods: The study population included infertile couples diagnosed as PCOS in the wife. The women used clomiphene for at least six cycles in order to ovulate after failure to form the dominant follicle, and were then put on letrozole for four cycles. Patients who were unable to form the dominant follicle were enrolled on letrozole and clomiphene combination therapy.

Results: One hundred enrolled patients underwent 257 cycles of combination of letrozole and clomiphene, in which 213 were able to form the dominant follicle (82.9%) and 44 were unable to do so (17.1%). The number of mature follicles was 2.3±1.1. The mean endometrial thickness in patients on the day of human chorionic gonadotropin administration was 8.17±1.3 mm. The pregnancy rate was 42%.

Conclusion: According to the results of this study, it can be proposed that in PCOS patients resistant to clomiphene and letrozole used as single agents, a combination of the two drugs can be administered before using more aggressive treatment that may have severe complications or surgery. This combination may also be used as a first-line therapy to induce ovulation in severe cases of PCOS in order to save time and expense.

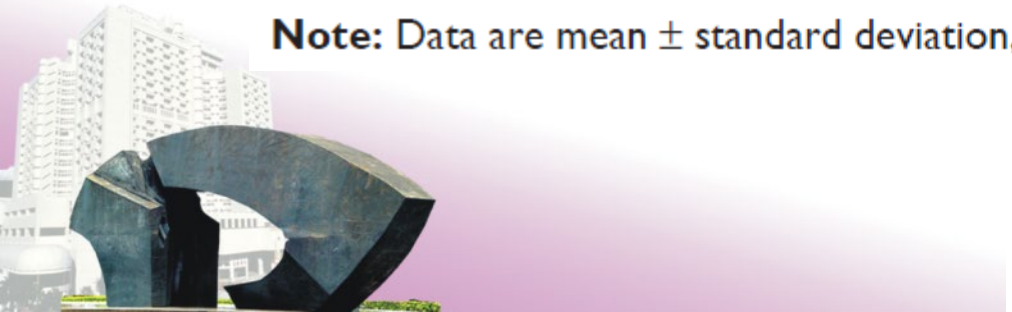
Over a period of 3 years, 100 PCOS patients who were resistant to clomiphene and letrozole were enrolled into the study. A dose of **5 mg Letrozole** every night and **100 mg clomiphene** every day after lunch was prescribed for 5 days from MC day 2 or 3

Drug Des Devel Ther 2013;7:1427–31.

Table 2 Treatment outcome in patients

Formation of dominant follicle	213 (82.9%)
Number of dominant follicles	2.3±1.1
Mean endometrial diameter (mm)	8.17±1.3
Number of recombinant human follicle-stimulating hormone treatments used	3.7±0.9
Occurrence of pregnancy	42 (42%)
Miscarraige	10 (23.8)
Single fetus	37 (88%)
Twin fetus	5 (12%)

Note: Data are mean ± standard deviation, or mean (percentage).



A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome

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and Bradley J. Van Voorhis, M.D.

Department of Obstetrics and Gynecology

(not identify patients resistant to letrozole)
on cycle days 3–7 for one treatment cycle:
2.5 mg letrozole daily vs.
a combination of 2.5 mg letrozole daily and 50 mg CC daily

Fertil Steril. 2019;111:571-8

Objective: To evaluate whether a combination of letrozole and clomiphene citrate (CC) results in higher ovulation rates than letrozole alone in infertile women with polycystic ovary syndrome (PCOS).
Design: Open-label randomized controlled trial.
Setting: Academic medical center using two clinic sites.
Patient(s): Women 18–40 years of age with a diagnosis of infertility and PCOS as defined by the Rotterdam criteria and no other known cause of infertility.
Interventions(s): Participants were randomized in a 1:1 ratio, stratified by age and body mass index, to either 2.5 mg letrozole alone or the combination of 2.5 mg letrozole and 50 mg CC daily on cycle days 3–7 for one treatment cycle.
Main Outcome Measure(s): Ovulation defined as mid-luteal serum progesterone concentration ≥3 ng/mL.
Result(s): Seventy patients were randomized: 35 to letrozole alone and 35 to letrozole and CC. Results were analyzed according to the intention-to-treat principle. Women who received the combination of letrozole and CC had a statistically higher ovulation rate compared with those who received letrozole alone (27 of 35 women [77%] vs. 15 of 35 women [43%]). There were no serious adverse events or multiple-gestation pregnancies in either group. The side-effects profile was similar in the two treatment groups.
Conclusion(s): The combination of letrozole and CC was associated with a higher ovulation rate compared with letrozole alone in women with infertility and PCOS. Further studies are needed to evaluate the effect on live birth rate.
Clinical Trial Registration Number: NCT02802865. (Fertil Steril® 2019;111:571–8. ©2018 by American Society for Reproductive Medicine.)

Outcome	Letrozole	Letrozole + CC	Absolute difference between groups (95% CI)[c]	Rate ratio in combination group (95% CI)	*P* value[d]
Intention-to-treat analysis/ primary outcome[a]					
Ovulation	15 (42.9)	27 (77.1)	33.8 (9.31 to 54.25)	1.80 (1.18 to 2.75)	.007
Per-protocol analysis/ primary outcome[b]					
Ovulation	14 (41.2)	25 (75.8)	34.6 (8.9–54.9)	1.84 (1.18–2.87)	.009
Secondary outcomes					
Pregnancy					
Conception	3 (8.8)	4 (12.1)	3.3 (−14.7 to 21.5)	1.37 (0.33–5.67)	.709
Clinical pregnancy	1 (2.9)	3 (9.1)	6.2 (−9.5 to 22.8)	3.09 (0.34–28.23)	.356
Singleton pregnancy	1 (2.9)	3 (9.1)	6.2 (−9.5 to 22.8)	3.09 (0.34–28.23)	.356
Twin pregnancy	0	0	0.000	–	–
Singleton live birth	1 (3)	3 (9.1)	6.2 (−9.5 to 22.8)	3.09 (0.34–28.23)	.356
Pregnancy loss among those who conceived	2/3 (67)	1/4 (25)	−41.7	0.38 (0.06–2.45)	.486
Fecundity among those who ovulated					
Conception	3/14 (21)	4/25 (16)	−5.4 (−34.6 to 21.6)	0.75 (0.19–2.87)	.686
Live birth	1/14 (7)	3/25 (12)	4.7 (−27.2 to 26.3)	1.68 (0.19–14.66)	1.00

[a] Letrozole, n = 35; letrozole + CC, n = 35.
[b] Letrozole, n = 34; letrozole + CC, n = 33.
[c] Differences are expressed as percentage points for all outcomes.
[d] *P* values were calculated with the use of chi-square or Fisher exact te

Mejia. Clomiphene citrate and letrozole combination. Fertil Steril 2018.

- ◆timed intercourse, not ART
- ◆Urine LH kit. No trigger
- ◆RCT

Characteristic	Letrozole group (n = 34)	Letrozole + CC group (n = 33)	*P* value
Progestin withdrawal	18 (53)	17 (52)	1.00
Ultrasound cycle day	13 ± 0.9	13 ± 1.0	.975
Reported LH surge	18 (53)	25 (76)	.143
Cycle day of LH surge	16 ± 3.7	16 ± 1.9	.960
No. of follicles >10 mm	0 (0–1)	1 (0–3)	<.001[b]
No. of women with follicles >15 mm	9 (27)	19 (58)	.020
No. of follicles >15 mm	0 (0–1)	1 (0–1)	.004[b]
Largest follicle size, mm	10.00 (8.75–11.25)	16.00 (10.00–19.00)	.004[b]
Endometrial lining thickness, mm	6.2 ± 2.2	8.3 ± 3.6	.006
Cycle day progesterone level obtained	23.4 ± 2.7	23.6 ± 2.8	.742
Progesterone level, ng/mL	0.5 (0.3–8.9)	9.7 (2.5–19.4)	.002[b]
Cycle characteristics among those who ovulated	(n = 14)	(n = 25)	
Progestin withdrawal	6 (43)	11 (44)	1.00
Ultrasound cycle day	13 ± 1.1	13 ± 1.0	.873
Reported LH surge	11 (79)	22 (88)	.647[a]
Cycle day of LH surge	16 ± 3.9	16 ± 1.9	.886
No. of follicles >10 mm	1 (0–1)	2 (1–4)	.002[b]
No. of women with follicles >15 mm	7 (50)	18 (72)	.305
No. of follicles >15 mm	0.5 (0–1)	1 (0–1.5)	.081[b]
Largest follicle size, mm	15.5 (10.0–18.3)	17.0 (13.5–19.5)	.228[b]
Endometrial lining thickness, mm	7.4 ± 2.3	8.6 ± 3.9	.286
Cycle day progesterone level obtained	24 ± 2.6	24 ± 2.7	.355
Progesterone level, ng/mL	10.95 (5.07–14.30)	13.30 (9.45–25.70)	.093[b]

Note: Values are presented as n (%), mean ± SD, or median (interquartile range).
[a] Fisher exact test.
[b] Mann-Whitney *U* test.

Mejia. Clomiphene citrate and letrozole combination. Fertil Steril 2018.

Fertil Steril. 2019;111:571-8

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Ovulation induction using sequential letrozole/gonadotrophin in infertile women with PCOS: a randomized controlled trial

KEY MESSAGE

Sequential letrozole/HMG is more effective than letrozole alone in inducing ovulation and promoting pregnancy, with no increase in side effects, and so provides a promising option for the treatment of patients with PCOS infertility.

ABSTRACT

Research question: Is sequential letrozole/human menopausal gonadotrophin (HMG) superior to letrozole alone in ovulation induction and pregnancy promotion among infertile women with polycystic ovary syndrome (PCOS)?

Design: This open-label randomized controlled trial comparing sequential letrozole/HMG and letrozole alone included 174 participants enrolled from August 2019 to January 2020 at the Union Hospital of Tongji Medical College, Huazhong University of Science and Technology. Infertile women aged between 18 and 40 years who met Rotterdam criteria for PCOS and without other known causes of infertility were selected for this study. Patients were randomly assigned at a 1:1 ratio to receive 2.5 mg letrozole on cycle days 3–7 (n = 87) or 2.5 mg letrozole on cycle days 3–7 with a sequential injection of 75 IU HMG on cycle days 8–10 for one treatment cycle (n = 87). The pregnancy outcome was recorded after one treatment cycle.

Results: Women receiving sequential treatment achieved a significantly higher ovulation rate than those in the letrozole group (90.8% versus 70.1%, P = 0.001) and the live birth rate of the sequential group was significantly higher than that of the letrozole protocol (23.0% versus 10.3%, P = 0.025); there was no statistical variation with respect to adverse events.

Conclusions: The data suggest that the sequential letrozole/HMG protocol may be superior to the letrozole alone protocol in terms of ovulation induction and pregnancy promotion among infertile women with PCOS.

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Efficacy of combined metformin–letrozole in comparison with metformin–clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease

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BACKGROUND: Adding metformin to clomiphene citrate in clomiphene-resistant polycystic ovary syndrome (PCOS) patients increases ovulatory response. However, because of anti-estrogenic effects of clomiphene it may be associated with lower pregnancy rate, offsetting the ovulation rate benefit. Letrozole is an aromatase inhibitor which induces ovulation without anti-estrogenic effects. METHODS: Infertile women with PCOS were randomly divided into metformin–letrozole (29 patients) and metformin–clomiphene groups (30 patients). After an initial 6–8 weeks of metformin, they received either letrozole (2.5 mg) or clomiphene (100 mg) from day 3–7 of their menstrual cycle. Estradiol (E_2) levels, number of follicles, pregnancy rates and endometrial thickness were measured on the day of HCG administration. RESULTS: Mean total E_2 and E_2 per mature follicle were significantly higher in clomiphene group without a difference in mean number of mature follicles >18 mm and ovulation rate. Endometrial thickness was significantly higher in letrozole group. The pregnancy rate in letrozole group (10 patients, 34.50%) as compared with clomiphene group (5 patients, 16.67%) did not show significant difference, whereas full-term pregnancies were higher in letrozole group [10 patients (34.50%) versus 3 patients (10%)]. CONCLUSION: In clomiphene-resistant PCOS patients, the combination of letrozole and metformin leads to higher full-term pregnancies.

Variable	Group A (metformin–letrozole group)	Group B (metformin–clomiphene citrate group)	*P*-value
Comparison of baseline parameters			
Number	29	30	
Age	28.24 ± 3.11	29.55 ± 3.47	NS (0.14)
BMI	29.98 ± 4.83	30.21 ± 3.92	NS (0.84)
Comparison of different variables			
Duration of infertility (years)	3.78	3.81	NS (0.94)
Endometrial thickness on day of HCG administration (cm)*	0.82 ± 0.13	0.55 ± 0.28	0.0009
Number of follicles >18 mm in diameter	1.90 ± 0.29	1.80 ± 0.39	NS (0.13)
Mean total estradiol level on day of HCG administration (pM/l)*	981.35 ± 648.44	1664.63 ± 1349.88	0.001
Mean estradiol level per mature follicle (pM/l)*	447.60 ± 133.36	783.38 ± 251.50	0.0009

◆Metformin: 500 mg TID for 6–8 weeks➔OI➔HCG 10000 IU trigger at follicle was ≥18 mm in size ➔timed intercourse➔FHB

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Comparison of the efficiency of clomiphene citrate and letrozole in combination with metformin in moderately obese clomiphene citrate – resistant polycystic ovarian syndrome patients

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retrospective

SUMMARY

Introduction Polycystic ovary syndrome is the most common endocrinopathy in women of reproductive-age. Therapy for those who want to get pregnant involves ovulation induction using clomiphene citrate, metformin, letrozole and gonadotropins.

Objective The aim of the study was to compare the efficacy of combinations of clomiphene citrate–metformin and letrozole–metformin in obese patients who are resistant to clomiphene citrate alone.

Methods The investigation was conducted as a retrospective study involving 60 moderately obese patients with polycystic ovary syndrome. Thirty-one of them received the clomiphene citrate–metformin, and 29 letrozole–metformin therapy. Stimulation was carried out for the procedures of intrauterine insemination (IUI).

Results The age of patients, duration of infertility, and body mass index in both groups were similar. There was statistically significant difference in the thickness of the endometrium in favor of the group having the letrozole–metformin therapy (8.9 ± 1.7 mm) compared with the group receiving the clomiphene citrate–metformin treatment (6.3 ± 1.3 mm). The number of follicles was not statistically significantly different. Pregnancy rate in the first cycle of IUI in the clomiphene citrate group was 6.4%, and 17.2% in the letrozole group, which also was not statistically different. After the third IUI cycle, the pregnancy rate was significantly higher in the letrozole group (20.6%), while in the clomiphene citrate group it was (9.6%).

Conclusion This retrospective study demonstrated the advantages of the use of letrozole over clomiphene citrate in combination with metformin in moderately obese patients with polycystic ovary syndrome who are resistant to stimulation with clomiphene citrate alone.

BMI > 30+ CC-resistance

↓

Metformin 1,500 mg/day for >3 months after establishing CC resistance.

↓

LE 5 mg/d vs CC 100 mg/d from MCd3~7

	clomiphene citrate + metformin	letrozole + metformin	p
Number of patients	31	29	0.267
Age	27.3	28.4	0.258
Sterility duration, years	3.9	4.2	0.129
BMI	33.1	31.9	0.317

	clomiphene citrate–metformin	letrozole–metformin	p
Endometrium thickness (mm)	6.3 ± 1.3	8.9 ± 1.7	0.001
Number of follicles larger than 18 mm	1.9 ± 0.9	1.7 ± 0.3	0.241
Clinical pregnancies after the first IUI cycle	2 (6.4%)	5 (17.2%)	0.257
Cumulative pregnancy rate after three IUI cycles	9 (9.6%)	20 (20.6%)	0.024

Take Home Message (1)

- Letrozole is orally administered, rapidly absorbed (within an hour) from the GI tract without first-pass elimination and is not influenced by either the food consumed or fasting status. Bioavailability: 99.9 %. Half-life:48 h
- 1st line oral agent for ovulation induction, esp. for obese PCOS patients, without risk of fetal harm
- **Women with higher baseline serum levels of total testosterone may benefit more from letrozole compared to CC**
- Low E2 levels (<91.16 pg/mL) a/w significantly higher miscarriage rate and lower live birth rate in Letrozole-stimulated FET.
- Higher E2 Levels (>225 pg/ml) a/w significantly higher liver birth rate in Letrozole-hCG triggered IUI cycles (not related to follicle size).

Take Home Message (2)

- D5 start might be better than D3, esp. in pt: <30 y/o/ BMI>18.5/ AMH>4.15 ng/ml
- Letrozole versus laparoscopic ovarian drilling in clomiphene citrate (CC)-resistant PCOS women: similar outcome but safer.
- pre-treatment predictors for the ovarian response to letrozole: **menarche < 13.5y, LH/FSH ratio < 1.83, AMH < 9.78ng/ml, and FAI < 5.99/ FSH <6.25, total testosterone <0.96**
- Letrozole resistance: consider extended use to 7~ 10 days or combined with other agents (dexamethasone/clomiphene/gonadotropin/metformin)

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Thank you &