Letrozole

IN OVULATION INDUCTION

SUN PHARMA

Image is for representation purpose only

“Our sincere thanks to Dr. Prof. (Col.) Pankaj Talwar, for reviewing this document and providing his valuable insights in developing this compilation of scientific information”

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SECTION 1

LETROZOLE ALONE

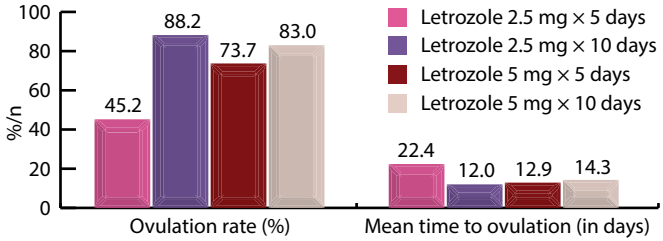
LETROZOLE DOSING REGIMENS IN WOMEN WITH PCOS/PMOS: BENEFITS OF A HIGHER STARTING DOSE OR A LONGER DURATION

Intervention

Letrozole treatment started on day 2–3 of the menstrual cycle*:

- ❑ Letrozole 2.5 mg × 5 days
- ❑ Letrozole 2.5 mg × 10 days
- ❑ Letrozole 5 mg × 5 days
- ❑ Letrozole 5 mg × 10 days.

*Anovulatory patients having low serum estradiol and progesterone levels were allowed to "random start" Letrozole.



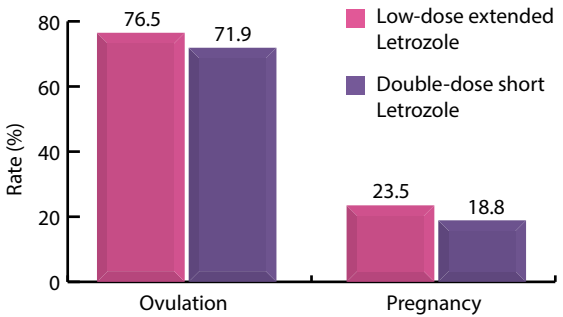
In obese women with PCOS/PMOS, a higher starting dose of Letrozole or a longer duration was associated with:

Source: Mandelbaum RS, Agarwal R, Melville S, *et al*. A comparison of letrozole regimens for ovulation induction in women with polycystic ovary syndrome. *F S Rep*. 2024;5(2):170-175.

LOW-DOSE EXTENDED LETROZOLE VS. DOUBLE-DOSE LETROZOLE PROTOCOL

Intervention

- **Low-dose extended Letrozole group: Letrozole 2.5 mg daily x 10 days (x 3 consecutive cycles)**
- **Double-dose short Letrozole group: Letrozole 5 mg daily x 5 days (x 3 consecutive cycles)**
- Treatment was started from the 2nd day of the menstrual cycle.



Compared with the double-dose short Letrozole (5 mg daily x 5 days) protocol, the low-dose extended Letrozole (2.5 mg daily x 10 days) protocol produces:

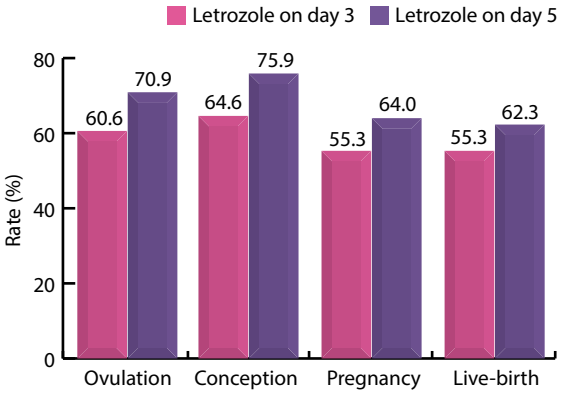
- More multifollicular growth
- Larger size dominant follicle
- A trend to raise the ovulation rate and pregnancy rate

Source: Jahan S, Deeba F, Ishrat S, *et al*. Low dose-extended letrozole versus double dose-short letrozole protocol for ovulation induction in polycystic ovary syndrome. *Int J Reprod Contracept Obstet Gynecol*. 2022;11(11):2974-2982.

LETROZOLE IN PATIENTS WITH PCOS/ PMOS: WHEN TO START – DAY 5 OR DAY 3 OF THE MENSTRUAL CYCLE

Intervention

- Oral Letrozole 2.5 mg/d for 5 days starting on day 3 or 5 of the menstrual cycle
- HCG 5,000-10,000 IU administered to induce ovulation, when the largest diameter of the dominant follicle was ≥18mm.



In patients with PCOS/PMOS, Letrozole given on the 5th day of the menstrual cycle was associated with:

- Higher cumulative conception rates
- Significantly greater median endometrial thickness
- Higher cumulative ovulation per cycle rate

Source: Shi L, Ye S, Gao M, *et al*. Effect of different timing of letrozole initiation on pregnancy outcome in polycystic ovary syndrome. *Front Endocrinol (Lausanne)*. 2022;13:1059609.

LETROZOLE STEP-UP VS. FIXED DOSE PROTOCOL

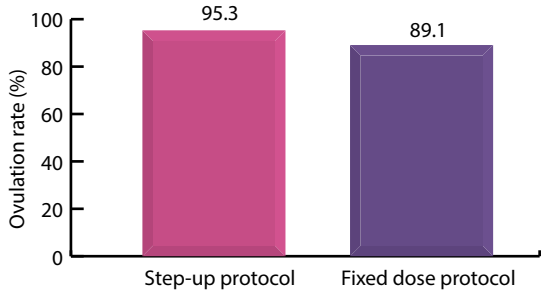
Intervention

- **Step-up dose protocol:** Letrozole given as step-up protocol starting by 2.5 mg on D2-D5 of menstruation, and then increasing doses 5 mg, 7.5 mg, 10 mg on the 3 successive days of menstruation respectively
- **Fixed dose protocol:** Letrozole given as fixed dose 5 mg starting from D2-D5 of menstruation, for 5 days.

Letrozole step-up dose protocol				
	2.5 mg	5 mg	7.5 mg	10 mg
DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
DAY 6	DAY 7	DAY 8	DAY 9	DAY 10

Letrozole step-up protocol was associated with:

- Better endometrial receptivity
- No significant increase in ovarian hyperstimulation syndrome (OHSS) or multifetal pregnancy



Source: Ali HAA, Farid EZE, Khaled WME, *et al*. Letrozole step up versus fixed dose protocols in ovulation induction in patients with unexplained infertility. *International Journal of Chemical and Biochemical Sciences (IJCBS)*, 2024;25(14):100-108.

SINGLE HIGH DOSE OF LETROZOLE ON DAY 3 OF THE MENSTRUAL CYCLE IN PATIENTS WITH INFERTILITY UNDERGOING OVARIAN STIMULATION AND IUI

Intervention

- **Letrozole as a single dose of 20 mg on day 3 of the menstrual cycle,** either alone or in conjunction with FSH 50–150 IU/day started on day 7 of the menstrual cycle
- **Letrozole 2.5 mg/day from day 3 to 7 of the menstrual cycle** (alone or together with FSH).

Letrozole 20 mg

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
DAY 6	DAY 7	DAY 8	DAY 9	DAY 10

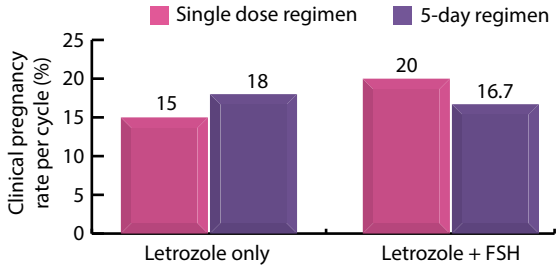
FSH injection 50-150 IU/day started from day 7 till the day of HCG administration

HCG given as a single injection of 10,000 IU - when the mean diameter of at least two ovarian follicles was >18mm

A single high dose of Letrozole on day 3 of the menstrual cycle showed:

Success rate comparable to a 5-day regimen for ovarian stimulation

Advantage of providing higher concentrations to achieve more potent aromatase inhibition when it is needed (early in the follicular phase)

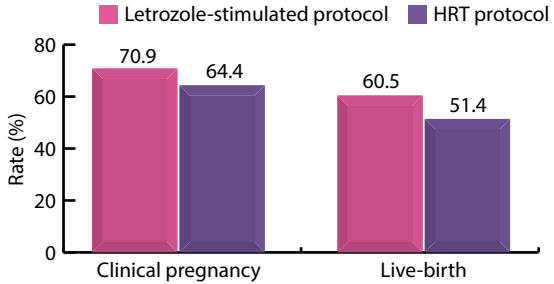


Source: Mitwally MFM, Casper RF. Single-dose administration of an aromatase inhibitor for ovarian stimulation. *Fertil Steril* 2005; 83:229–31.

LETROZOLE-STIMULATEDENDOMETRIAL PREPARATION PROTOCOL: A SUPERIOR ALTERNATIVE TO HRT FOR FROZEN EMBRYO TRANSFER IN WOMEN WITH PCOS/PMOS

Intervention

- **Letrozole-stimulated protocol:** Letrozole 2.5 mg was administered for 5 consecutive days, starting day 3 to day 5 of the menstrual cycle. Ultrasound monitoring and serum hormone measurement were performed from cycle days 12–13 onwards. If the leading follicle reached a diameter of ≥ 12 mm on days 12–13, transvaginal ultrasound was repeated until ovulation. When the diameter of the dominant follicle was ≥ 18-20 mm without ovulation and the endometrium thickness was ≥ 8 mm, HCG 5000-10,000 IU was injected for final oocyte triggering
- **HRT protocol:** Oral Estradiol (E2) valerate (3 mg, twice daily) administration was commenced on days 3–5 of the menstrual cycle. Ten days later, as the endometrial thickness reached ≥ 8 mm, Progesterone vaginal suppositories (200 mg, three times daily) were given and oral Dydrogesterone tablets (10 mg, twice daily) were initiated on the next day. If clinical pregnancy was confirmed, the E2 valerate dose was reduced to 4 mg/day, and the dose would be reduced again to 2 mg/day at 45 days after embryo transfer until the drug was discontinued at 55 days after embryo transfer. The combination of Progesterone and Dydrogesterone was used until 45 days after embryo transfer, and then Dydrogesterone was used alone until 70 days after embryo transfer.



As compared to the HRT protocol, Letrozole stimulation in Frozen Embryo Transfer cycles was associated with:

Source: Wang X, Li Y, Tan H, *et al*. Letrozole-stimulated endometrial preparation protocol is a superior alternative to hormone replacement treatment for frozen embryo transfer in women with polycystic ovary syndrome, a cohort study. *Reprod Biol Endocrinol*. 2023;21(1):101.

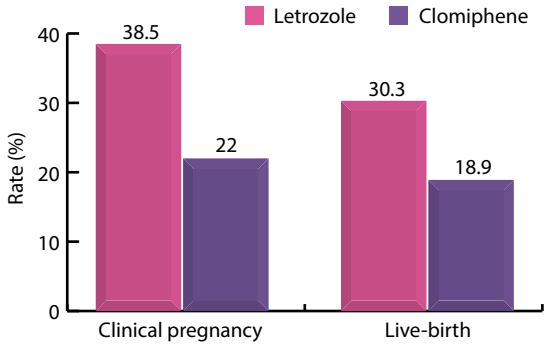
SECTION 2

LETROZOLE VS. CLOMIPHENE/ TAMOXIFEN

LETROZOLE VS. CLOMIPHENE IN TREATMENT-NAIVE INFERTILE WOMEN WITH PCOS/PMOS

Intervention

- Letrozole 2.5 mg daily for 5 days, or Clomiphene (100 mg) for up to five treatment cycles.



In treatment-naive infertile women with PCOS/PMOS, use of Letrozole vs. Clomiphene was associated with:

Significantly higher clinical pregnancy rate

Significantly higher live-birth rate

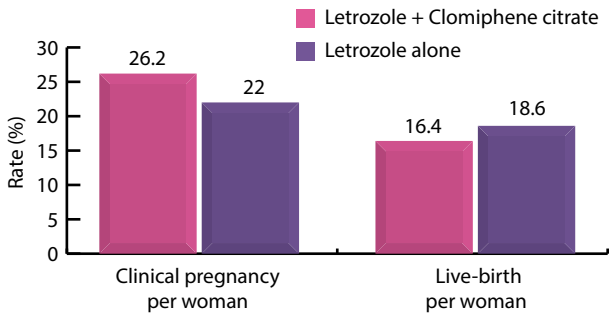
Source: Waanbah BD, Joseph T, Rebekah G, *et al*. Letrozole as first-line drug for ovulation induction in treatment-naïve infertile polycystic ovarian syndrome women. *J Obstet Gynaecol Res*. 2021;47(10):3583-3589.

LETROZOLE VS. CLOMIPHENE + LETROZOLE PROTOCOL

Intervention

- Letrozole 2.5 mg + Clomiphene citrate 50 mg daily
- Letrozole 2.5 mg alone
- Treatment was given from the 2nd to the 6th day of the menstrual cycle (x up to 3 treatment cycles).

"Combining Clomiphene citrate with Letrozole conferred no additional significant benefits than Letrozole alone in women with PCOS/PMOS"



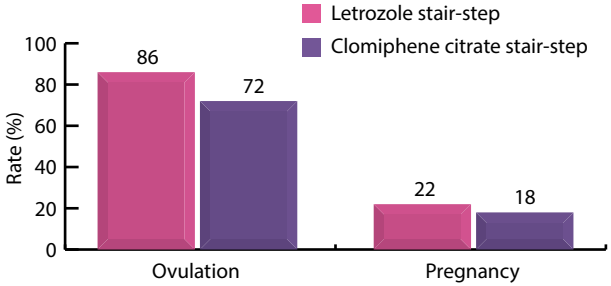
"OVULATION, CLINICAL PREGNANCY, AND LIVE-BIRTH RATES WERE COMPARABLE WITH A COMBINATION OF LETROZOLE AND CLOMIPHENE CITRATE VS. LETROZOLE ALONE"

Source: Sarkar S, Gupta N, Joseph T, *et al*. Comparison of Letrozole Versus Combination Letrozole and Clomiphene Citrate (CC) for Ovulation Induction in Sub Fertile Women with Polycystic Ovarian Syndrome (PCOS)-An Open Label Randomized Control Trial. *Reprod Sci*. 2024;31(12):3834-3842.

LETROZOLE STAIR-STEP VS. CLOMIPHENE CITRATE STAIR-STEP PROTOCOL

Intervention

- **Letrozole stair-step group:** Received Letrozole in a stair-step pattern (single daily dose of 2.5/5/7.5 mg for 5 days), for a maximum of three cycles
- **Clomiphene citrate stair-step group:** Received Clomiphene citrate in a stair-step pattern (single daily dose of 50/100/150 mg for 5 days), for a maximum of three cycles.



As compared to Clomiphene citrate stair-step protocol, Letrozole stair-step protocol was associated with:

- Higher ovulation rate
- Slightly higher pregnancy rate
- Significantly shorter mean time from menstruation to ovulation

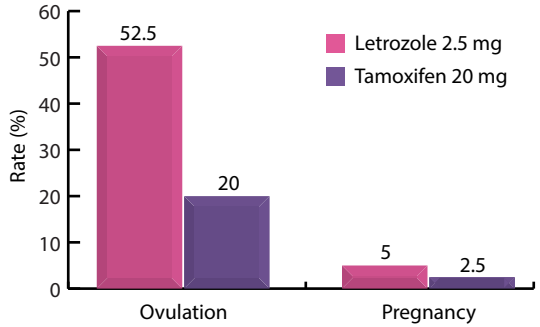
"LETROZOLE STAIR-STEP PROTOCOL WAS WELL-TOLERATED, AND DEMONSTRATED A SHORTER TIME TO OVULATION THAN CLOMIPHENE CITRATE STAIR-STEP PROTOCOL"

Source: Al-Thuwaynee S, Swadi AAJ. Comparing efficacy and safety of stair step protocols for clomiphene citrate and letrozole in ovulation induction for women with polycystic ovary syndrome (PCOS): a randomized controlled clinical trial. *J Med Life*. 2023;16(5):725-730.

LETROZOLE IN CLOMIPHENE CITRATE-RESISTANT PCOS/PMOS: HOW IT SCORES OVER TAMOXIFEN?

Intervention

- **Letrozole 2.5 mg:** Letrozole 2.5 mg orally twice per day from day 3 to day 7 of the menstrual cycle for 3 successive cycles
- **Tamoxifen 20 mg:** Tamoxifen 20 mg once per day from day 3 to day 7 of the menstrual cycle for 3 successive cycles
- HCG 10,000 IU was administered when at least one mature follicle >18mm was observed.



In Clomiphene citrate-resistant women with PCOS/PMOS, Letrozole is distinguished from Tamoxifen in achieving:

- Significantly higher ovulation rate
- Higher mean number of follicles (≥18 mm)

"LETROZOLE SHOULD BE CONSIDERED FOR CLOMIPHENE CITRATE-RESISTANT WOMEN WITH PCOS/PMOS"

Source: Saad AEHS, Saleh SAEA, El-Melih AHM, *et al*. Letrozole Versus Tamoxifen in Infertile Woman with Clomiphene Citrate Resistant Polycystic Ovarian Syndrome. *EBWHJ* 2023;13(4):311-316.

SECTION 3

LETROZOLE + GONADOTROPIN

LETROZOLE AND GONADOTROPIN VS. ONLY GONADOTROPIN PROTOCOL IN IUI CYCLES

Intervention

- A total of 764 IUI cycles were included:
  - **In Group 1 (Standard rFSH group):** Ovarian stimulation commenced on cycle day 2 or 3 using rFSH alone
  - **In Group 2 (Letrozole + late rFSH group):** Letrozole (2.5–5 mg/day) was administered orally from cycle day 3 to day 7. Gonadotropin stimulation was initiated on cycle day ≥6 using rFSH. Initial Gonadotropin doses ranged from 37.5 to 250 IU/day
- Follicular development and endometrial growth were monitored by transvaginal USG and serial serum Estradiol (E2) measurements performed every 2–3 days
- Ovulation was triggered with a subcutaneous injection of recombinant hCG when at least one follicle reached a mean diameter of ≥17 mm. IUI was performed 36–38 h after hCG administration
- All patients received luteal phase support with vaginal Progesterone (200 mg/day) for 14 days following insemination. Serum β-hCG levels were measured 14 days after IUI. In cycles with positive β-hCG results, transvaginal USG was performed 20–25 days later to confirm clinical pregnancy.

Total Gonadotropin dose (IU)

- Standard rFSH group: **750**
- Letrozole + late rFSH group: **375 (50% reduction)**

Crude pregnancy rate

- Standard rFSH group: **9.9%**
- Letrozole + late rFSH group: **14.8%**

Sequential stimulation with Letrozole + late-onset recombinant FSH showed associations with:

- Significantly reduced Gonadotropin requirements
- Higher rates of clinical pregnancy
- Better cost-effectiveness
- Low cycle cancellation rate
- Reduced risk of ovarian hyperstimulation.

Source: Yesildager E, Yesildager U, Arlıer S. Minimal Dose Paradigm in IUI Stimulation for Unexplained Infertility: Letrozole-Initiated Late Gonadotropin Protocol. *J. Clin. Med.* 2026;15:1050.

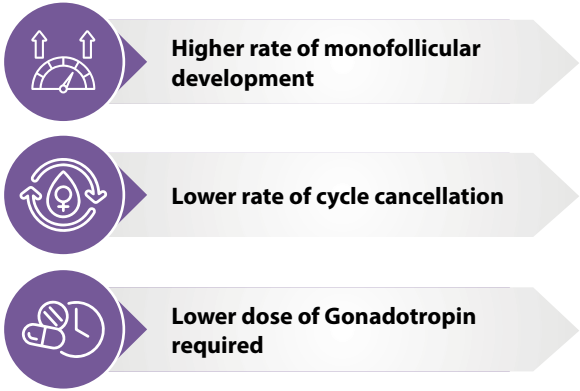
GONADOTROPIN ALONE VS. COMBINATION WITH LETROZOLE OR CLOMIPHENE IN PCOS/PMOS

Intervention

- **Letrozole + Gonadotropin group:** Letrozole 2.5 mg from day 3 to 7 + HMG 75 IU on alternate days starting from day 7 and maintained for up to 10 days
- **Clomiphene citrate + Gonadotropin group:** Clomiphene citrate 50 mg/day from day 3 to day 7 + HMG 75 IU on alternate days starting from day 7 and maintained for up to 10 days
- **Gonadotropin alone group:** HMG administered in a step-up protocol starting with 75 IU on alternate days daily from cycle day 3 and maintained for up to 14 days.

Variables	Letrozole + Gonadotropin	Clomiphene citrate + Gonadotropin	Gonadotropin alone
Total amount of HMG (IU)	714.8± 265.5	731.3± 290.3	991.5± 242.1
Monofollicular cycles/ complete cycle (%)	**65/81 (80.2)**	**47/72 (65.3)**	**29/53 (54.7)**
Ovulation/ started cycle (%)	**81/94 (86.2)**	**72/90 (80)**	**53/71 (74.6)**
Pregnancies/ complete cycle (%)	20/81 (24.7)	17/72 (23.6)	12/53 (22.6)

In Clomiphene citrate-resistant infertile women with PCOS/PMOS, Letrozole was associated with:

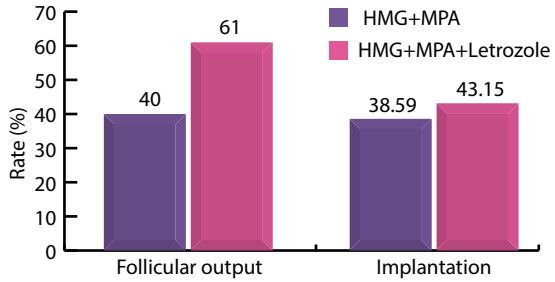


Source: Xi W, Liu S, Mao H, *et al*. Use of letrozole and clomiphene citrate combined with gonadotropins in clomiphene-resistant infertile women with polycystic ovary syndrome: a prospective study. *Drug Des Devel Ther*. 2015;9:6001-8.

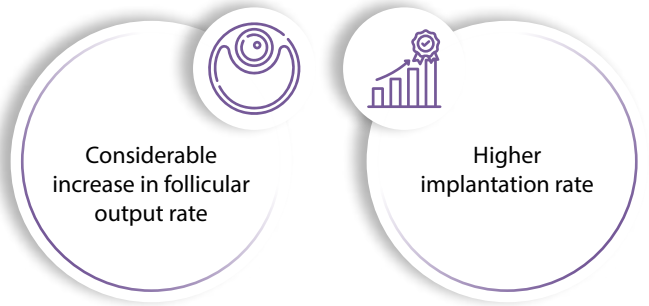
LETROZOLE + PROGESTIN-PRIMED OVARIAN STIMULATION IN PCOS/ PMOS WOMEN WITH HIGH BMI UNDERGOING IVF TREATMENT

Intervention

- **HMG+MPA group:** Controlled ovarian stimulation – Human Menopausal Gonadotropin (HMG) 150-225 IU/d and Medroxyprogesterone Acetate (MPA) 4 mg/d from the 3rd day of the menstrual cycle until the trigger day
- **HMG+MPA+Letrozole group:** Controlled ovarian stimulation plus Letrozole 2.5 mg/day starting on day 3 of the menstrual cycle and continuing for 5 days.



In PCOS/PMOS women with high body mass index (BMI), Letrozole in combination with progestin-primed ovarian stimulation was associated with:

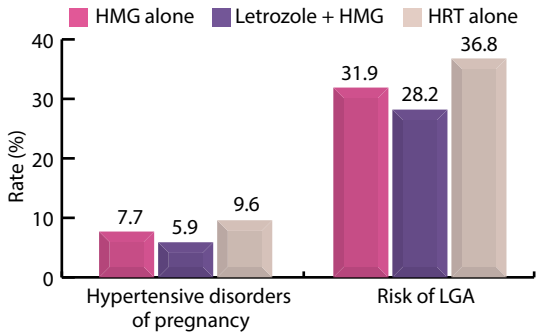


Source: Liu Y, Lin J, Shen X, *et al*. Letrozole cotreatment improves the follicular output rate in high-body-mass-index women with polycystic ovary syndrome undergoing IVF treatment. *Front Endocrinol (Lausanne)*. 2023;14:1072170.

LETROZOLE + HMG VS. HMG ALONE OR HRT ALONE FOR ENDOMETRIAL PREPARATION IN WOMEN WITH PCOS/ PMOS UNDERGOING IVF

Intervention

- **Human Menopausal Gonadotropin (HMG) alone group** (75 IU/day HMG administered intramuscularly starting on day 3–5 of the menstrual cycle)
- **Letrozole + HMG group** (2.5–5.0 mg/day Letrozole for 5 consecutive days beginning from day 2–5; then 75 IU/day HMG given, with dosage increases of 37.5–75 IU every 5–7 days as required)
- **Hormone replacement therapy (HRT) alone group** [oral Estrogen 4–8 mg per day for at least 10 days, beginning from day 2 to day 5 of the menstrual cycle. When endometrial thickness reached 8 mm, Progesterone administered both orally (40 mg/day) and vaginally (200 mg/day) along with oral Estradiol].



In women with PCOS/PMOS, ovarian stimulation protocol with Letrozole + HMG was associated with:

- **Lower risk of hypertensive disorders of pregnancy**
- **Lower risk of large for gestational age (LGA) infants**

Source: Zhang Y, Fu X, Gao S, *et al*. Letrozole use in vitrified single-blastocyst transfer cycles is associated with lower risk of large for gestational age infants in patients with polycystic ovary syndrome. *J Assist Reprod Genet*. 2023;40(12):2885-2894.

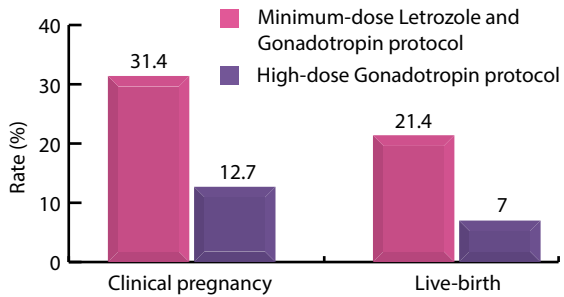
SECTION 4

LETROZOLE + GnRH ANTAGONIST

ANTAGONIST REGIMEN COMPARING MINIMUM-DOSE LETROZOLE AND GONADOTROPIN VS. HIGH-DOSE GONADOTROPIN PROTOCOL IN IVF

Intervention

- **Minimum-dose Letrozole and Gonadotropin protocol:** Letrozole 2.5 mg over 5 days, starting from cycle day 2, with overlapping Gonadotropins 150 units daily, starting from the 3rd day of Letrozole
- **High-dose Gonadotropin protocol:** High levels of Gonadotropins (≥300 IU/day), starting from day 2 of their cycle, and throughout their short antagonist cycle
- GnRH antagonist initiation (once one or more follicles reached 14mm or larger), HCG administration timing, and oocyte retrieval timing were the same in both protocols.



Compared with high-dose Gonadotropin stimulation, the minimum-dose Letrozole and Gonadotropin protocol was associated with:

- Lower Gonadotropin dosage
- Improved clinical pregnancy rates
- Improved live-birth rates

Source: Lazer T, Dar S, Shlush E, *et al*. Comparison of IVF Outcomes between Minimal Stimulation and High-Dose Stimulation for Patients with Poor Ovarian Reserve. *Int J Reprod Med*. 2014;2014:581451.

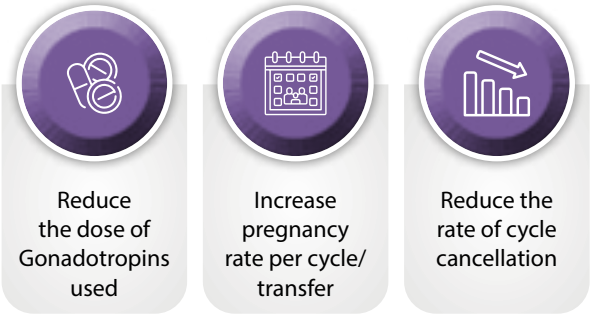
ANTAGONIST REGIMEN COMPARING HIGH DOSE LETROZOLE (20 MG) + GONADOTROPIN VS. HIGH-DOSE GONADOTROPIN PROTOCOL FOR IVF IN POOR RESPONDERS

Intervention

- Patients were treated with the GnRH antagonist cycle
- **High-dose Letrozole + Gonadotropin group:** Letrozole 20 mg daily from cycle day 3, with GnRH antagonist commencing when lead follicle was 14mm in diameter; at this point, 150 IU of Menopausal Gonadotropins was also instituted. Letrozole was continued until the day of trigger
- **High-dose Gonadotropin group:** GnRH antagonist cycle and 300–450 IU daily of Menopausal Gonadotropins
- HCG 10,000 IU, when follicles at least 18 mm in diameter
- Oocyte collection and IVF/ICSI after 36 h.

Variables	High-dose Gonadotropin	High-dose Letrozole + Gonadotropin
Total dose of Gonadotropins, IU	5360 ±1028	645 ± 175
Cycles cancelled for no stimulation (%)	95/247 (38%)	7/62 (11%)
Ongoing pregnancy rate per transfer	11/152 (7%)	9/55 (16%)

Incorporation of high-dose Letrozole in stimulation protocols in poor responders may:



Source: Khojah M, Khayat S, Dahan MH. Comparison of in vitro fertilization cycles stimulated with 20 mg letrozole daily versus high-dose gonadotropins in Rotterdam Consensus ultra-poor responders: A proof of concept. *Int J Gynaecol Obstet*. 2022 Jan;156(1):102-106.

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The approved dosage for letrozole in the induction of ovulation in women with anovulatory infertility is 2.5 mg daily for 5 days. These protocols have been derived from published literature. This information is provided for scientific reference only and does not constitute an endorsement of any specific protocol or regimen.

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