

Letrozole versus clomiphene for ovulation induction

👉 Will you start using letrozole for ovulation induction in your practice?



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The three most common causes of infertility are anovulation, tubal occlusion, and abnormal semen parameters. The most common cause of anovulatory infertility is polycystic ovary syndrome (PCOS). Options for initial treatment of anovulatory infertility caused by PCOS include optimizing body mass index (BMI), clomiphene, clomiphene plus dexamethasone, and metformin (TABLE 1). If these low-cost interventions are not successful, high-cost interventions are often very effective treatments, and include follicle-stimulating hormone (FSH) injections, laparoscopic ovarian drilling, and in vitro fertilization.

For many couples, the high-cost interventions are prohibitively expensive. Recently, results of a high-quality randomized clinical trial published by Legro and colleagues in the *New England Journal of Medicine* indicate that letrozole is more effective than clomiphene for the treatment of anovulatory infertility in women with PCOS.¹ Of great importance, letrozole was documented to be especially effective in women with a BMI greater than 30.3 kg/m².

Letrozole is another low-cost option for couples with anovulatory infertility (TABLE 2, page 10), and you

should consider it among your initial treatment choices. In this article, I outline when letrozole is your best first option for treatment.

Letrozole is more effective than clomiphene for ovulation induction in women with PCOS and BMI >30.3 kg/m²

Legro and colleagues¹ randomly assigned 750 women with anovulatory infertility and PCOS to receive ovulation induction with either clomiphene or letrozole. The medications were prescribed using an escalating dose if ovulation did not occur. For clomiphene, the doses prescribed were 50 mg, 100 mg, and 150 mg.

For letrozole, the doses were 2.5 mg, 5 mg, and 7.5 mg. The medications were given daily for 5 days on cycle days 3 to 7, following a spontaneous menses or a medroxyprogesterone acetate withdrawal bleed. Up to 5 cycles of ovulation induction were prescribed.

The ovulation rates for letrozole versus clomiphene were 61.7% and 48.3%, respectively ($P < .001$). The live birth rates for letrozole versus clomiphene were 27.5% and 19.1%, respectively ($P = .007$). Among women with a BMI of 30.3 kg/m² or less, both letrozole and clomiphene treatment resulted in a similar live birth rate of approximately 30% to 35%. Among

TABLE 1 Options for ovulation induction in women with anovulatory infertility caused by PCOS

Low-cost interventions	High-cost interventions
Optimize BMI (18.5–25 kg/m ²)	FSH injections
Clomiphene	Laparoscopic ovarian drilling
Letrozole	In vitro fertilization
Clomiphene plus dexamethasone	
Metformin	

BMI, body mass index; FSH, follicle-stimulating hormone; PCOS, polycystic ovary syndrome.

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TABLE 2 Estimated cost of various ovulation induction medications

Medication	Typical dose and duration for ovulation induction	Estimated cost per cycle, in US dollars*
Clomiphene	50 mg daily for 5 days	Discount pharmacy = \$9 List price = \$35
Letrozole	2.5 mg daily for 5 days	\$91
Metformin	1,500 mg extended release, daily for 90 days	Discount pharmacy = \$30 List price = \$201
Clomiphene plus dexamethasone	Clomiphene 100 mg daily for 5 days plus dexamethasone 2 mg daily for approximately 14 days	Discount pharmacy = \$18 clomiphene, \$8 dexamethasone List price = \$70 clomiphene, \$10 dexamethasone
Recombinant FSH injections	37.5 IU daily for 14 days	\$1,050
	75 IU daily for 14 days	\$2,100

*Discount prices may be available at Target, Walmart, or Walgreen's. Non-discount prices from Medispan (July 2014). FSH, follicle-stimulating hormone.

women with a BMI greater than 30.3 kg/m², however, the live birth rates with letrozole versus clomiphene were approximately 20% and 10%, respectively.

Consequently, in my practice, I prioritize the use of letrozole for women with a BMI of 30 kg/m² or greater.

Do not use anastrozole for ovulation induction

In a randomized trial of letrozole versus anastrozole for ovulation induction, 40 women with PCOS were randomly assigned to receive ovulation induction with letrozole (2.5 mg daily for 5 days) or anastrozole (1 mg daily for 5 days).² The resulting ovulation rate was 84% for letrozole, compared with 60% for anastrozole ($P < .05$). The pregnancy rate also was significantly higher for letrozole (19% vs 10% for anastrozole, $P < .05$).

Investigators of two large randomized trials of anastrozole versus clomiphene reported that

clomiphene was superior to anastrozole for induction of ovulation in the first cycle of treatment.^{3,4} Anastrozole, at doses of 1 mg, 5 mg, 10 mg, 20 mg, and 30 mg daily for 5 days, was less effective for ovulation induction in the first cycle of treatment than clomiphene at a dose of 50 mg.^{3,4}

If an aromatase inhibitor is going to be prescribed for ovulation induction, I recommend the use of letrozole and recommend against the use of anastrozole.

Congenital malformations and ovulation induction

The administration of clomiphene or letrozole to pregnant rats has adverse fetal effects.^{5,6} For example, in pregnant rats a low dose of letrozole (0.003 mg/kg) has been reported to increase intrauterine mortality, fetal resorption, and postimplantation loss; decrease live births; and result in fetal anomalies, including dilation of the ureter and shortening of renal papillae.⁶

However, in the setting of ovulation induction, letrozole is not administered while the patient is pregnant and is discontinued many days before ovulation and conception. Consequently, the results observed in animal studies (with the medications administered to pregnant animals) may not be particularly relevant to the clinical situation where the fertility medication is discontinued before ovulation and conception.

It is important to exclude pregnancy prior to initiating treatment with letrozole or clomiphene.

Birth defects affect approximately 5% of newborns in the United States.⁷ The relative impact of maternal age, obesity, ovulation induction medicines, and a history of infertility on the rate of birth defects is not fully characterized and is a subject of intense research. To date, there is no strong and consistent evidence that ovulation induction agents, per se, significantly increase the rate of birth defects.

Tulandi and colleagues reported on 911 newborns conceived following ovulation induction with clomiphene or letrozole.⁸ Overall, the congenital malformation plus chromosomal abnormality rates associated with letrozole and clomiphene ovulation induction were 2.4% and 4.8%, respectively. The major congenital malformation rate for letrozole was 1.2%, and 3.0% for clomiphene.

Many women with anovulatory infertility and PCOS have a BMI of 30 kg/m² or greater, and some are of advanced maternal age. It is known that women with such a BMI level have an increased risk of congenital malformations, including neural tube defects, spina bifida, septal anomalies, cleft palate, cleft lip, anorectal atresia, hydrocephaly, and limb reduction anomalies.⁹ The risk of gastroschisis is significantly reduced among obese pregnant women.⁹ Women aged 40 or older have an increased risk of having a fetus with cardiac defects, esophageal atresia, hypospadias, and craniosynostosis.¹⁰

Caution women of advanced maternal age with PCOS and a BMI of 30 kg/m² or greater about the increased rate of congenital malformations associated with their age and elevated BMI.

Prioritize letrozole when BMI ≥30 kg/m²


I recommend that clomiphene should remain the first-line ovulation induction agent for women with PCOS and a BMI less than 30 kg/m². This is because, among women with such a BMI level, both clomiphene and letrozole have similar efficacy, and clomiphene is approved by the US Food and Drug Administration for ovulation induction while letrozole is not.

Explore the use of clomiphene plus dexamethasone at obgmanagement.com:

Barbieri RL. Clomiphene failure? Try adding dexamethasone to your clomiphene infertility regimen. *OBG MANAGEMENT*. 2012;24(5):10, 12, 13.

However, for women with PCOS and a BMI of 30 kg/m² or greater—a clinical situation where letrozole is about twice as effective as clomiphene—letrozole may be the preferred agent.

When prescribing letrozole, start with a dose of 2.5 mg daily for cycle days 3 to 7, following a spontaneous menses or progestin-induced bleed. If ovulation occurs, continue with the dose. If ovulation does not occur, increase the dose to 5 mg daily for cycle days 3 to 7. The maximal dose is 7.5 mg daily for cycle days 3 to 7. When prescribing letrozole, counsel your patient about the increased rate of congenital anomalies among women with an elevated BMI and the possible teratogenic effects of fertility medications.

The aromatase inhibitor letrozole is an important addition to our options for ovulation induction in women with PCOS. Will you start using letrozole for ovulation induction in your practice? 



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References

1. Legro RS, Brzyski RG, Diamond MP, et al; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2014;371(2):119–129.

2. Al-Omari WR, Sulaiman WR, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2004;85(3):289–291.
3. Tredway D, Schertz JC, Bock D, Hemsey G, Diamond MP. Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: a phase II, randomized, dose-finding study. *Fertil Steril*. 2011;95(5):1720–1724.
4. Tredway D, Schertz JC, Bock D, Hemsey G, Diamond MP. Anastrozole single-dose protocol in women with oligo- or anovulatory infertility: results of a randomized phase II dose-response study. *Fertil Steril*. 2011;95(5):1725–1729.
5. Clomid (clomiphene citrate tablets USP) [package insert]. Bridgewater, NJ: sanofi-aventis. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016131s026lbl.pdf. Revised October 2012. Accessed October 20, 2014.
6. Femara (letrozole tablets) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. <https://www.pharma.us.novartis.com/product/pi/pdf/Femara.pdf>. Revised January 2014. Accessed October 20, 2014.
7. Christianson A, Howson CP, Modell B. March of Dimes Global Report on Birth Defects: Executive Summary. White Plains NY: March of Dimes Birth Defects Foundation; 2006:2–9. <http://www.marchofdimes.com/materials/global-report-on-birth-defects-the-hidden-toll-of-dying-and-disabled-children-executive-summary.pdf>. Accessed October 20, 2014.
8. Tulandi T, Martin J, Al-Fadhli R, et al. Congenital malformations among 911 newborns conceived after infertility with letrozole or clomiphene citrate. *Fertil Steril*. 2006;85(6):1761–1765.
9. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systemic review and meta-analysis. *JAMA*. 2009;301(6):636–650.
10. Gill SK, Broussard C, Devine O, Green RF, Rasmussen SA, Reefhuis J; National Birth Defects Prevention Study. Association between maternal age and birth defects of unknown etiology: United States, 1997–2007. *Birth Defects Res A Clin Mol Teratol*. 2012;94(12):1010–1018.