

HOW EFFECTIVE & SAFE IS LETROZOLE FOR OVULATION INDUCTION?

EFFECTIVENESS

Letrozole (Femara), when taken during the first few days of the menstrual cycle, makes the body think that there is insufficient estrogen being produced. The brain responds to this by releasing more of the major hormone responsible for egg development, FSH (Follicle Stimulating Hormone). The goal is to bring about the stimulation or regulation of ovulation.

Letrozole has several features that are desirable in a medication used to stimulate ovulation. Most of these features owe to its short lifespan in the body compared to other medications, like clomiphene citrate (Clomid). Letrozole is more likely to result in a single follicle/egg developing, as usually occurs in a natural unmedicated cycle, rather than multiple follicles. Multiple follicles can increase the risk of ovarian overstimulation and of multiple pregnancies. Due to its short 'half life' in the body, letrozole also has fewer anti-estrogen side effects like hot flashes and less negative impact on the estrogen responsive uterine lining (1, 2).

In 2001, a study from several fertility clinics evaluated letrozole vs. Clomid for ovulation induction (3). In this study, 75% of the patients ovulated with letrozole compared to 44% with previous Clomid therapy. Furthermore, the uterine lining, important for implantation, was significantly thicker for patients taking letrozole than those on Clomid.

In 2014, the New England Journal of Medicine (NEJM) published a multi-center study performed through the Reproductive Medicine Network (4). This study included 750 women with polycystic ovarian syndrome (PCOS) who were randomized to treatment with either letrozole or Clomid. A significantly larger percentage of women who received letrozole ovulated (88.5% in letrozole group vs. 76.6% in Clomid group). There was also a significantly higher live birth rate in women who received letrozole versus Clomid (27.5% vs. 19.1%). There was no difference in rates of pregnancy loss or complications between these groups.

An important review of the use of letrozole, and medications like it, included 26 randomized controlled trials including 5,560 women (5). The odds for both clinical pregnancy and live birth were higher for patients who received letrozole than those that received Clomid.

Finally, a recent NEJM publication evaluated the use of letrozole, injectable fertility medications, or Clomid for unexplained infertility (6). This multicenter trial randomized 900 couples with unexplained infertility to ovulation induction and intrauterine insemination (IUI) with letrozole, injectable gonadotropins, or Clomid. There was no difference in the live birth rate (19 vs. 23%) or multiple pregnancy rate (13 vs. 19%) between the letrozole and Clomid groups, respectively. Further, there was no increased risk of maternal, fetal, or neonatal complications with the use of letrozole.

Thus, due to its mechanism of action and short active life span in the body, letrozole, in a number of trials and reviews, appears more effective than Clomid.

SAFETY

In 2005, an abstract presented at the annual meeting of the American Society for Reproductive Medicine (ASRM) suggested that letrozole use for infertility was associated with congenital heart defects in some of the infants born after treatment (7). Following this one abstract, the manufacturer of the medication stated that letrozole should not be used to help women achieve pregnancy, leading to the detailed Informed Consent that we have patients sign before utilizing this medication. However, this abstract was never then published or peer-reviewed and no other researchers have found similar findings. There are many flaws that we feel need to be further considered in this single report: 1) As described above, letrozole has a short half-life (30-60 hours). Therefore, if letrozole is taken on cycle days 3-7, it should be cleared from the body before implantation occurs. This means that letrozole should not be present during fetal development, making any effect on the infant seem unlikely. 2) The control group in the abstract was a very different group than the patients who took letrozole, making comparisons problematic. Most of the women in the control group were younger, were not having difficulty getting pregnant, and conceived spontaneously without infertility treatment and without

medication. In fact, the number of heart defects in the children conceived with letrozole was similar to that in the general population (7, 8).

Importantly, many follow-up studies since the 2005 abstract have demonstrated safety for letrozole's use. In 2006, Tulandi et al. performed a study of 911 newborns conceived at five fertility centers (9). There was no difference in any birth defects or genetic abnormalities in infants conceived after letrozole or Clomid therapy. In fact, there were significantly fewer heart problems in the letrozole group compared to the Clomid group! Additionally, as described above, two large multi-center studies (4, 6) confirmed the safety of letrozole use - there were no differences in the rates of fetal complications in women who received letrozole compared to those who received Clomid or injectable fertility medications.

SUMMARY

The effectiveness and safety of letrozole is demonstrated by the studies from the medical literature reviewed here. In total these studies seem more convincing than a single abstract. We hope these data provide some degree of reassurance to you. All medications have some risk, and require our providing you information and informed consent. While these Informed Consent documents detail potential risks and detail the manufacturers' warnings, most of the evidence indicates that letrozole is safe for use in most patients and may be more effective in women with irregular or absent ovulation and infertility. Furthermore, letrozole may have fewer side effects than Clomid (6).

We, your medical team, remain open to your questions at any time about your evaluation and decision making on your road to building your family.

The Medical Team at Shady Grove Fertility Center

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