Is the use of letrozole to induce ovulation teratogenic?

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ABSTRACT

QUESTION A patient of mine has been prescribed letrozole to induce ovulation; however, a recent release from the Food and Drug Administration contraindicates the use of letrozole in premenopausal women owing to teratogenicity. Does the use of letrozole increase the risk of a child being born with a birth defect?

ANSWER The use of letrozole to induce ovulation has not been associated with an increased risk of a child being born with a birth defect; in contrast, the use of clomiphene citrate in pregnancy is associated with intrauterine growth restriction.

RÉSUMÉ

QUESTION L'une de mes patientes a reçu une ordonnance de létrozole pour induire l'ovulation; par ailleurs, selon un récent communiqué de la Food and Drug Administration, l'utilisation du létrozole est contre-indiquée chez les femmes avant la ménopause en raison de sa tératogénicité. L'usage du létrozole accroît-il le risque de malformations à la naissance?

RÉPONSE L'utilisation du létrozole pour induire l'ovulation n'a pas été associée à un risque plus élevé de malformations à la naissance, par opposition à l'usage du citrate de clomiphène qui est relié à une restriction de la croissance intra-utérine.

Ovulatory disorders are quite common, and often pharmacotherapy is the first-line treatment to induce ovulation. For the past 40 years, clomiphene citrate has been considered the gold standard treatment; however, its use is associated with several negative outcomes, including low pregnancy rates, multiple gestations, unfavourable cervical mucus, and thinning of the endometrium.[1]

In the late 1990s, aromatase inhibitors—specifically letrozole, which is indicated for the treatment and prevention of breast cancer—began to be used off-label to induce ovulation. The use of letrozole to induce ovulation was associated with higher pregnancy rates and avoided some of the negative effects often associated with clomiphene citrate.[1,2] In 2005, some concern was raised as a result of an abstract of a study that compared 150 babies born to women who had used letrozole with 36 005 babies born to low-risk pregnant women.[3] The results of this study, which had several methodological issues, suggested that letrozole might increase the risk of cardiac and bone anomalies; however, the overall rate of major malformations did not differ between the 2 groups.[3] Following the publication of this abstract, the manufacturer of letrozole issued a statement to physicians contraindicating the use of letrozole in premenopausal women.

Since that initial report, however, several full-length studies have not shown an increased risk for congenital malformations following the use of letrozole to induce ovulation. A study published in 2006 examined 514 babies born to mothers who had used letrozole to conceive, and compared them with 397 babies born to mothers who had conceived using clomiphene citrate.[4] There were no increased rates of major and minor malformations beyond what would be expected in the general population (1% to 3%).[4] Additionally, the number of cardiac anomalies in the letrozole group (0.2%) was slightly lower than that of the general population (0.4% to 1.2%).[4]

Recently, another study was conducted comparing pregnancy outcomes among women using letrozole to induce ovulation to age- and disease-matched controls.[5] Pregnancy outcomes of women who used letrozole (94) or clomiphene citrate (242) to become pregnant and women who conceived spontaneously (94) were examined.[5] There were no differences in the rates of major malformations among the 3 groups. Moreover, no major

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malformations were observed in the offspring born to mothers who had conceived using letrozole.[5] Other pregnancy outcomes, including gestational age at birth, birth weight, and maternal age at birth, were not substantially different among the groups.[5] When birth weight centiles were examined, babies born to mothers who had conceived using clomiphene citrate (and not letrozole) were found to be of lower birth weight than would be expected for their gestational age.[5] This finding suggests the potential for clomiphene citrate to cause intrauterine growth restriction, an outcome that has been observed in animal studies as well.[6]

Animal studies

Although the use of letrozole to induce ovulation has not been associated with teratogenicity in several recent, well-designed clinical studies, the use of letrozole during pregnancy has been shown to cause birth defects in animal studies, prompting the Food and Drug Administration warnings. Tests performed on pregnant rats treated with 1% of the human dose resulted in embryo and fetal death, edema, incomplete skeletal ossification, and congenital malformations of the kidney and ureter.[7,8] Similarly, embryo and fetal toxicity also occurred in rabbits treated with letrozole at concentrations much lower than 1% of the human dose.[7,8] Treatment of pregnant rats with letrozole at 1 mg/kg daily on days 21 and 22 of gestation resulted in evidence of altered sexual function in male offspring.[8] Clearly, there are concerns with the use of letrozole during pregnancy; however, when used to induce ovulation, letrozole is eliminated from the body before conception owing to its short elimination half-life (45 hours).

Conclusion

Based on the aforementioned findings, the use of letrozole to induce ovulation does not appear to be associated with an apparent increased risk of major congenital malformations in humans. Compared with clomiphene citrate, letrozole appears to be a more favourable first-line treatment to induce ovulation, as it is associated with higher pregnancy rates and has fewer unfavourable side effects than clomiphene citrate, such as the potential for intrauterine growth restriction. The use of letrozole to induce ovulation should be considered for women wishing to conceive, especially if clomiphene citrate has failed.

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