

# Fluconazole exposure during pregnancy

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## Abstract

**Question** One of my patients has just learned that she is 8 weeks pregnant. She took a 150-mg dose of fluconazole 2 weeks ago for the treatment of vaginal candidiasis and she is worried about the effect on her child and pregnancy. Can I reassure her?

**Answer** Short-term and low-dose fluconazole exposure, such as that indicated in the treatment of vaginal candidiasis, is not expected to increase the overall risk of major congenital malformations.

## Exposition au fluconazole durant la grossesse

### Résumé

**Question** L'une de mes patientes vient tout juste d'apprendre qu'elle est enceinte de 8 semaines. Elle a pris une dose de 150 mg de fluconazole il y a 2 semaines pour traiter une candidose vaginale et s'inquiète des répercussions sur son enfant et sa grossesse. Puis-je la rassurer?

**Réponse** L'exposition de courte durée et à faible dose au fluconazole, comme celle indiquée dans le traitement de la candidose vaginale, ne devrait pas augmenter le risque général de malformations congénitales majeures.

The vaginal colonization rates of *Candida* strains, and therefore the risk of vulvovaginal candidiasis, are increased in pregnancy owing to hormonal changes.<sup>1</sup> Fluconazole is a triazole antifungal agent with high oral bioavailability (>90%) and tissue penetration. It disrupts the cell membrane of fungi by inhibiting the cytochrome P450-dependent enzyme lanosterol 14  $\alpha$ -demethylase.<sup>2</sup> Fluconazole is given as a single 150-mg dose in the treatment of vaginal candidiasis; however, higher doses (200 to 400 mg/day) for longer durations (weeks to months) are considered for systemic infections.<sup>2</sup>

Fluconazole was shown to cause a dose-related increase in fetal adverse effects when given to pregnant rats during organogenesis. Doses of 5 to 10 mg/kg caused no adverse fetal effects, but increasing the dose to 25 and 50 mg/kg caused impairment of maternal weight gain, increased placental weight, and fetal toxicity (skeletal variations and renal pelvis dilation). Higher doses (80 to 320 mg/kg) led to embryoletality, abnormalities in rib formation, cleft palate, and abnormal craniofacial ossification. Inhibition of estrogen synthesis was a possible cause of the adverse effects.<sup>2</sup>

### Case reports of high-dose fluconazole

There have been 5 reported cases of infants born with multiple craniofacial and skeletal malformations after exposure in the first trimester to daily, oral, high-dose fluconazole (400 to 800 mg).<sup>3-6</sup> It has been suggested

that inhibition of cytochrome P450 or other enzymes by fluconazole might be an explanation for these defects.<sup>5</sup>

### Case series

Inman et al reported on a series of 43 infants whose mothers were treated with fluconazole during pregnancy; no congenital malformations were detected. Most of the mothers took fluconazole as a single 150-mg dose.<sup>7</sup> In another case series, no congenital malformations were detected among 17 infants whose mothers took fluconazole for the treatment of vaginal candidiasis during pregnancy, mainly in the first trimester.<sup>8</sup> Wilton et al reported no congenital malformations among 33 infants whose mothers took fluconazole in the first trimester.<sup>9</sup>

### Epidemiologic studies

In a prospective cohort study, malformation rates were not significantly different among the infants of 226 women who took fluconazole during their first trimester (4.0%) when compared with controls (4.2%) (odds ratio [OR] 1.07, 95% CI 0.41 to 2.77). Similarly, there was no increased risk of miscarriage or low birth weight in exposed pregnancies. Most of the mothers in this study took fluconazole as a single 150-mg dose for the treatment of vaginal candidiasis.<sup>10</sup>


Jick reported no increase in the rate of congenital malformations among the infants of 234 women who

took fluconazole as a single oral dose in the first trimester when compared with nonusers (1.7% vs 1.6%; OR 1.1, 95% CI 0.4 to 3.3).<sup>11</sup>

A registry-based study that evaluated 1079 women who filled a prescription for fluconazole during their first trimester found no increase in risk of major malformations among their infants when compared with unexposed infants (4.1% vs 3.6%; OR 1.0, 95% CI 0.8 to 1.4). As well, there was no increase in rates of craniofacial (OR 1.3, 95% CI 0.6 to 2.6) or cardiovascular (OR 1.3, 95% CI 0.7 to 2.1) malformations. In total, 797 women (74%) received 150 mg of fluconazole, 235 (22%) received 300 mg, and the remainder (n=47) received 450 or 600 mg. The study reported no increased risk of low birth weight, stillbirth, or prematurity in exposed pregnancies.<sup>12</sup>

A recent registry-based study that included 7352 women who filled prescriptions for fluconazole during their first trimester reported no increase in overall malformations or in 14 of 15 types of congenital malformations that had been previously associated with azole antifungal agents. However, a significant increase in risk of tetralogy of Fallot was observed in this study (prevalence 0.03%; adjusted OR 3.16, 95% CI 1.49 to 6.71). It is difficult to determine if this is a true risk or a chance finding.<sup>13</sup>

### Conclusion

To date, there have been 5 published cases showing skeletal malformations in children whose mothers had taken high doses of fluconazole (400 to 1200 mg/day) for prolonged durations (weeks to months) because of systemic mycosis. Epidemiologic studies that included nearly 9000 fluconazole-exposed pregnant patients did not show increased risk of congenital malformations in doses and durations typical in the treatment of vaginal candidiasis (150-mg single dose). In subgroup analysis of 15 types of malformations, the only significant increase detected was for tetralogy of Fallot. However, if this is a true risk, the absolute risk is very small (1 in 1000). Therefore, inadvertent exposure to fluconazole for vaginal candidiasis treatment is not expected to increase the baseline risk of congenital malformations. 

**Competing interests**  
None declared

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