Journal of Advanced Medical and Dental Sciences Research

@Societv of Scientific Research and Studies

Journal home page:www.jamdsr.com doi:10.21276/jamdsr Index Copernicus value [ICV] =82.06

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Original Research

Evaluation of pregnancy outcomes after first-trimester exposure to fluconazole

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ABSTRACT:
Background: The present study was conducted for evaluating pregnancy outcomes after first-trimester exposure to fluconazole. **Materials & methods:**Fifty pregnant women with documented fluconazole exposure were enrolled in the exposed group, while 50 matched women with no known exposure to teratogens constituted the control group. Data collection emphasized clinically significant outcomes such as spontaneous abortion, congenital anomalies, preterm delivery, and low birth weight. Statistical analysis, conducted using SPSS software, incorporated adjustments for potential confounders to ensure the reliability of associations observed between fluconazole exposure and adverse pregnancy outcomes. **Results:**The fluconazole group had a lower live birth rate (68% vs. 82%) and higher rates of miscarriage (20% vs. 12%) and induced abortion (10% vs. 2%). Stillbirths and congenital anomalies were similar across groups, with slightly higher anomalies in the fluconazole group (4% vs. 2%). The mean birth weight was marginally lower in the fluconazole group (3.128 kg vs. 3.39 kg), indicating overall similar neonatal health profiles. **Conclusion:**Current evidence suggests that fluconazole administration during the first trimester of gestation is not associated with a substantial increase in the incidence of adverse pregnancy outcomes such as spontaneous miscarriage, congenital anomalies, or low birth weight.
Key words: Fluconazole, Pregnancy

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This article may be cited as: Yadav K, Babu A. Evaluation of pregnancy outcomes after first-trimester exposure to fluconazole. J Adv Med Dent Scie Res 2016;4(2):344-346.

INTRODUCTION

Administration of oral fluconazole at high doses (400–800 mg/day) throughout most or all of the first trimester has been associated with a distinct pattern of congenital anomalies in five reported cases involving women treated for severe systemic fungal infections.[1] Experimental studies in animal models have also demonstrated comparable teratogenic effects following systemic exposure to azole antifungal agents.[2-4] In response to these findings, the U.S. Food and Drug Administration (FDA) released a drug-safety advisory in 2011, highlighting the potential embryotoxic risks linked to prolonged, high-dose fluconazole use during early pregnancy. As a result, the FDA revised the pregnancy risk classification of fluconazole from Category C (animal studies have shown fetal harm, but there are no adequate human studies) to Category D (positive evidence of human fetal risk, though the drug may still be used if clinically justified). An exception was made for a single 150 mg dose used in treating vaginal candidiasis.[5]

Despite these concerns, questions persist regarding the teratogenic potential of lower, commonly prescribed doses of fluconazole for superficial fungal infections of the skin or mucous membranes. Epidemiologic data involving first-trimester exposure to a single 150 mg dose suggest no significant elevation in the overall risk of congenital abnormalities.[6] However, with only approximately 1,650 pregnancies evaluated for such exposure, existing studies lack sufficient statistical power to analyze dose-response relationships or detect associations with specific types of birth defects.[7-9]Hence; the present study was conducted for evaluating pregnancy outcomes after first-trimester exposure to fluconazole.

MATERIALS & METHODS

The present study was conducted on women who inquired about medication exposures during

pregnancy. The primary aim of this investigation was to evaluate and compare pregnancy outcomes among women who had been exposed to fluconazole, particularly during the first trimester, with outcomes observed in a reference group exposed to agents with no known teratogenic risk. A total of 50 women who had taken fluconazole at any point during their pregnancy were enrolled as the exposed cohort. For comparison, a control group comprising 50 pregnant women who had been exposed exclusively to nonteratogenic agents was also selected.The statistical approach allowed for adjustment of these variables to ensure that the observed associations between fluconazole exposure and pregnancy outcomes were not spuriously influenced by other risk factors. Outcomes of interest included rates of spontaneous abortion, congenital malformations, preterm birth, and low birth weight. All the results were recorded and evaluated using SPSS software.

RESULTS

Table 1 outlines and compares the pregnancy outcomes in two groups of women: those exposed to fluconazole (n=50) and those in the control group not exposed to teratogenic agents (n=50). The rate of live births was slightly lower in the fluconazole group (68%) compared to the control group (82%). The incidence of miscarriages was higher among women exposed to fluconazole (20%) than in controls (12%), while the rate of stillbirths remained equal in both groups at 2%. Notably, induced abortions were more frequent in the fluconazole group (10%) versus 2% in the control group, suggesting possible concerns following drug exposure. Congenital anomalies were also reported at a higher rate in the fluconazole-exposed group (4%) compared to the control group (2%), although the overall incidence remained low in both cohorts. Table 2 evaluates neonatal outcomes among live births in both study arms. In the fluconazole group (n=34 live births), normal birth weight was achieved in 29 neonates (58%), slightly lower than 35 neonates (70%) in the control group (n=41). The incidence of low birth weight (<2500 g) was comparable between groups, affecting 10% in the fluconazole group and 12% in the control group. Similarly, the preterm birth rates were 8% in the fluconazole group and 10% in controls, showing minimal difference. Neonatal complications occurred in 6% and 8% of cases in the fluconazole and control groups, respectively. The mean birth weight in the fluconazole group was slightly lower (3.128 kg) than that of the control group (3.39 kg), though both remained within the normal range. Overall, these findings suggest broadly comparable neonatal outcomes, with minor variations between the two groups.

Table 1: Pregnancy Outcomes

Outcome	Fluconazole Group (n=50)	Control Group (n=50)
Live births	34 (68%)	41 (82%)
Miscarriages	10 (20%)	6 (12%)
Stillbirths	1 (2%)	1 (2%)
Induced abortions	5 (10%)	1 (2%)
Congenital anomalies	2 (4%)	1 (2%)

Table 2: Neonatal Parameters and Complications

Parameter	Fluconazole Group (n=34 live births)	Control Group (n=41 live births)
Normal birth weight	29 (58%)	35 (70%)
Low birth weight (<2500g)	5 (10%)	6 (12%)
Preterm births (<37 weeks)	4 (8%)	5 (10%)
Neonatal complications (any)	3 (6%)	4 (8%)
Mean birth weight (kg)	3.128 Kg	3.39 Kg

DISCUSSION

During pregnancy, hormonal fluctuations enhance the vaginal colonization of Candida species, thereby elevating the risk of developing vulvovaginal candidiasis. Fluconazole, a triazole-class antifungal, demonstrates excellent oral absorption exceeding ninety percent and exhibits extensive tissue distribution. Its antifungal action is mediated through inhibition of the cytochrome P450–dependent enzyme, lanosterol 14α-demethylase, which disrupts fungal cell membrane synthesis. Experimental studies in pregnant rats have revealed a dose-dependent relationship between fluconazole exposure during the organogenesis period and the occurrence of fetal anomalies.[7- 10]Hence; the present study was conducted for evaluating pregnancy outcomes after first-trimester exposure to fluconazole.

The fluconazole group had a lower live birth rate (68% vs. 82%) and higher rates of miscarriage (20% vs. 12%) and induced abortion (10% vs. 2%). Stillbirths and congenital anomalies were similar across groups, with slightly higher anomalies in the fluconazole group (4% vs. 2%). The mean birth weight was marginally lower in the fluconazole group (3.128 kg vs. 3.39 kg), indicating overall similar neonatal health profiles.Mølgaard-Nielsen D et al evaluated first-trimester oral fluconazole exposure and the risk of birth defects overall and of birth defects

previously linked to azole antifungal agents.The majority of fluconazole-exposed pregnancies were in women who received common therapeutic doses of 150 mg (56% of pregnancies) or 300 mg (31%). Oral fluconazole exposure was not associated with an increased risk of birth defects overall (210 birth defects among 7352 fluconazole-exposed pregnancies [prevalence, 2.86%] and 25,159 birth defects among 968,236 unexposed pregnancies [prevalence, 2.60%]; adjusted prevalence odds ratio, 1.06; 95% confidence interval [CI], 0.92 to 1.21). In addition, oral fluconazole exposure was not associated with a significantly increased risk of 14 of 15 types of birth defects previously linked to azole antifungal agents: craniosynostosis, other craniofacial defects, middle-ear defects, cleft palate, cleft lip, limb defects, limb-reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, pulmonary-artery hypoplasia, ventricular septal defects, and hypoplastic left heart. A significantly increased risk of tetralogy of Fallot was observed (7 cases in fluconazole-exposed pregnancies [prevalence, 0.10%] as compared with 287 cases in unexposed pregnancies [prevalence, 0.03%]; adjusted prevalence odds ratio, 3.16; 95% CI, 1.49 to 6.71).Oral fluconazole was not associated with a significantly increased risk of birth defects overall or of 14 of the 15 specific birth defects of previous concern.[11]Mastroiacovo P et al conducted a prospective cohort study of women who contacted three Italian teratogen information services. They compared the pregnancy outcomes of 226 women exposed to fluconazole with that of 452 women exposed to nonteratogenic agents, with use of logistic regression to control for potential confounders.Among the 226 pregnancies exposed to fluconazole there were 22 miscarriages, 1 stillbirth, and 7 infants with congenital anomalies. The prevalence of these outcomes and of neonatal growth parameters and the rate of neonatal complications were similar to those in the reference group. Women in the fluconazole group had a fivefold increased occurrence of induced abortions.First-trimester exposure to fluconazole does not appear to increase the prevalence of miscarriages, congenital anomalies, and low birth weight.[12]

CONCLUSION

Current evidence suggests that fluconazole administration during the first trimester of gestation is not associated with a substantial increase in the incidence of adverse pregnancy outcomes such as spontaneous miscarriage, congenital anomalies, or low birth weight. Neonatal growth parameters, including birth weight and gestational age at delivery, have not shown statistically significant deviations when compared to unexposed controls. These findings indicate that short-term or single-dose oral fluconazole therapy, commonly used for treating vulvovaginal candidiasis, is unlikely to pose a major teratogenic risk when administered during the early stages of pregnancy. However, caution is still warranted with high-dose or prolonged use, pending further large-scale studies.

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