The Journal of Obstetrics and Gynecology of India (November–December 2021) 71(6):577–582
https://doi.org/10.1007/s13224-021-01586-8

MINI REVIEW ARTICLE

Common Antifungal Drugs in Pregnancy: Risks and Precautions

Madhuri A. Patel[1,2,3] · **Veeral M. Aliporewala**[2,3] · **Disha A. Patel**[4]

Received: 11 July 2021 / Accepted: 21 October 2021 / Published online: 9 November 2021

Abstract
Fungal skin infections are on the rise in India, and pregnant women are not immune to them. They are one of the commonest causes of secondary pruritus in pregnancy and can worsen the quality of life. Cutaneous dermatophytic infections have seen a recent emergence as a public health problem in India with increasing incidence as well as failure to appropriately respond to treatment. Vaginal candidiasis may cause obstetric and perinatal complications such as chorioamnionitis, premature rupture of membranes, preterm labor and neonatal candidiasis. Antifungal drugs are commonly prescribed in pregnancy. The common oral antifungals used are fluconazole, ketoconazole, itraconazole, terbinafine and griseofulvin; whereas the common topical antifungals are azoles, ciclopirox oleamine, terbinafine, amongst others. There have been reports of congenital abnormalities in the fetus and spontaneous abortions attributed to oral antifungals. Prescribing antifungal drugs in pregnancy needs careful consideration. In this article, we discuss the safety profile and recommendations regarding the use of these drugs during gestation. We have performed a literature search of recent large-scale cohort, case-control, and meta-analysis studies and presented them in this review. Antifungals such as echinocandins, amphotericin B, flucytosine, etc. which are indicated for systemic mycoses are beyond the scope of this article. Finally, we have given authors' perspective regarding the justifiable use of these antifungals in pregnant women.

Keywords Pregnancy · Mycoses · Antifungals · Congenital abnormalities · Abortion

Introduction

Fungal skin infections are the most common infections in humans, affecting more than 20–25% of the world's population [1, 2]. They can be classified as superficial, cutaneous, or subcutaneous mycoses.

Superficial mycosis like tinea nigra and pityriasis versicolor are surface infections of the skin and hair and thus, do not elicit inflammation. Subcutaneous mycoses are soil saprophytes which are directly inoculated into the subcutis, usually due to an often-unnoticed minor trauma. They are commonly seen on the hands and feet in rural population who work in fields and walk barefoot. Since superficial mycoses are largely asymptomatic and the subcutaneous mycoses are relatively rare, we do not discuss these entities in detail here.

Dermatophytosis and candidiasis constitute the common cutaneous mycoses. Over the past few years, dermatophyte infections have increased manyfold in India and have even been labeled as fungal 'epidemic' [3], Dermatophytoses are caused by agents of the genera *epidermophyton, microsporum,* and *trichophyton;* and cause the commonly known 'tinea' group of infections. Patients typically present with itchy and scaly patches, usually in the flexural areas and waist. Although pruritus seems to be a minor symptom, if severe and chronic, it can drastically affect the quality of life in pregnancy. Changes in the disease presentation, severity, clinical failure, and relapse rate have consistently

Dr. Madhuri A. Patel is an Hon. Clinical Associate at N. Wadia Hospital, Parel, Mumbai, India; Hon. Consultant at Police Hospital Mumbai, India and Visiting Consultant at St. Elizabeth and Masina Hospitals, Mumbai, India. Dr. Veeral M. Aliporewala is an Hon. Consultant, Police Hospital, Mumbai and Practising dermatologist at Sion, Mumbai, India. Dr. Disha A. Patel is an Assistant Professor in Department of Community Medicine at TNMC and BYL Nair Charitable Hospital, Mumbai, India.

✉ Veeral M. Aliporewala
vral1204@gmail.com

1 N. Wadia Hospital, Parel, Mumbai, India

2 Police Hospital, Mumbai, India

3 Sion, Mumbai, India

4 Department of Community Medicine at TNMC, BYL Nair Charitable Hospital, Mumbai, India

been reported recently, with a general worsening of all these parameters [3–5].

It is estimated that up to 75% of women experience vaginal candidiasis at least once in their lifetime. Due to increased levels of estrogen and vaginal glycogen production, it occurs more frequently and with increased severity in pregnancy [6]. In affected pregnancies, there is associated risk of premature rupture of membranes, preterm labor, chorioamnionitis, and cutaneous candidiasis in the neonate.

Antifungal agents are a group of structurally different molecules having in common the property to alter the cell wall/membrane of the fungus. Griseofulvin introduced in 1959 was the second antifungal invented after amphotericin B which is the first antifungal used for cutaneous mycoses. The next category to arrive was azoles starting with clotrimazole in 1973 followed by miconazole (1979), ketoconazole (1981), fluconazole (1990), itraconazole (1992), voriconazole (2002), posaconazole (2006), and most recently isavuconazole (2015); the latter three almost exclusively used in systemic mycosis. Terbinafine was approved for use in dermatophytic infections in 1996.

Many pregnant women affected with fungal skin infections require systemic antifungal therapy. Oral antifungals like fluconazole, itraconazole, and griseofulvin have been reported to cause birth defects as well as spontaneous abortions.

In this setting, we have reviewed some recent large-scale studies (case-control, cohort studies, and systematic reviews) regarding safety of these medications in pregnancy.

Discussion

Pregnancy poses ethical dilemma in conducting clinical trials, so the safety data is based on limited case reports, animal studies, review of population and hospital-based registries, and experts' opinions. The United States Food and Drug Administration (US FDA) is the federal agency responsible for regulating human drugs and its reference is commonly used by Indian physicians for safely prescribing drugs in pregnancy. Their definitions for pregnancy risk categories (A to D and X) provide a general framework for use; however, it makes the risk–benefit assessment difficult. To overcome this, the US FDA had called for gradual phasing out of this classification and issued a new Pregnancy and Lactation Labelling Rule (PLLR) and guidance document in 2014 [7, 8]. Classification of common antifungals and their conventional FDA categorization has been enlisted in Table 1.

Systemic azoles: Fluconazole and itraconazole are both fungistatic drugs belonging to this group. They are reported to be embryotoxic and teratogenic in rodents, inducing craniofacial and rib abnormalities [9]. Fluconazole use in pregnancy has been reported to be associated with spontaneous abortions, congenital heart disease (cardiac septal defects), and musculoskeletal malformations (short, broad head,

Table 1 US FDA categorization of common oral and topical antifungals

FDA categories	Oral agents	Topical agents
A Controlled studies of women failed to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote		Nystatin
B Either animal studies do not indicate a risk to the fetus and there have been no controlled studies in pregnant women, or animal studies have indicated fetal risk but controlled studies of pregnant women failed to demonstrate a risk	Terbinafine	Clotrimazole Terbinafine Ciclopirox Naftifine Oxiconazole
C Either animal studies indicate a fetal risk and there have been no controlled studies of women, or there are no available reports of studies of women or animals	Ketoconazole Fluconazole low-dose regimen (150 mg/day) Itraconazole Griseofulvin	Econazole Miconazole Ketoconazole Selenium sulfide
D There is positive evidence of fetal risk, but there may be certain situations where the benefit may outweigh the risk (e.g., life-threatening or serious diseases for which other drugs are ineffective or carry a greater risk)	Fluconazole high-dose regimen (400–600 mg/day) Voriconazole	
X There is definite fetal risk, according to studies of animals or humans or on the basis of human experience, and the risk clearly outweighs any benefit in pregnant women	–	–

abnormal development of the skullcap, oral cleft, bowing of the thigh bones, thin ribs, long bones, muscle weakness, and joint deformities).

A population-based cohort study [10] in 1,969,954 pregnancies was conducted to study association of oral fluconazole used in first trimester of pregnancy for the treatment of vulvovaginal candidiasis with fetal malformations [37,650 pregnancies exposed to oral fluconazole and 82,090 to topical azoles]. The risk of musculoskeletal malformations was 52.1 (95% confidence interval [CI] 44.8–59.3) per 10,000 pregnancies exposed to fluconazole versus 37.3 (33.1–41.4) per 10,000 pregnancies exposed to topical azoles. On adjusting the relative risk after fine stratification of the propensity score, it was found to be 1.30 (1.09–1.56) for musculoskeletal malformations. It was concluded that oral fluconazole use in first trimester was associated with musculoskeletal malformations, corresponding to adjusted risk difference of about 12 per 10,000 exposed pregnancies overall.

There are multiple other studies, which corroborate similar risk of defects [11–14]. A population-based cohort study in 976,300 live-born infants showed fluconazole to be significantly associated with tetralogy of Fallot [15].

A meta-analysis and systematic review by Zhang et al. [16] to study pregnancy outcome with exposure to fluconazole in the first trimester showed an increased risk of congenital malformations (odds ratio of 1.09, 95% CI 0.99–1.2, $P=0.088$; 6 studies), more for high-dose users (> 150 mg) (odds ratio of 1. 19, 95% CI 1.01–1.4, $P=0.039$; 2 studies). There was a greater risk of cardiac malformations, cardiac septal defects, and tetralogy of Fallot (odds ratio of 1.31, 1.3, and 3.39, respectively). There was also a higher risk of spontaneous abortion (odds ratio of 1.99, 95% CI 1.38–2.88, $P<0.001$; 3 studies).

A meta-analysis and systematic review done in 2019 [17] concludes that the overall risk of fetal malformations is not significant; however, the limb defects and cardiac malformations need to be 'investigated cautiously'. This risk seems to be dose-related, with total dose up to 150 mg considered 'safer'. This is also reflected in the recent FDA recommendations, labeling the use of 150 mg of fluconazole as category C and more than 150 mg as category D [18].

Itraconazole use in 1st trimester has been evaluated in few large-scale studies. A prospective study to assess outcome after in-utero exposure to itraconazole involving 229 women did not identify any increased risk of fetal malformation [daily doses of 50–800 mg for a range of 1–90 days] [19]. Another smaller study in 206 females also concluded itraconazole to be associated with abortions (spontaneous or induced) but not with fetal malformation [20]. A recent metaanalysis [15] with pooled data from 971,450 pregnancies assessed the risk of fetal malformations due to itraconazole exposure. It found no significant association, but concluded that eye defects in the itraconazole-exposed population should be investigated cautiously (Frequency 0.56%, CI 95% 0.18–1.32, $P<0.05$).

Oral ketoconazole was once a popular choice for treating fungal infections, but due to its hepatotoxic and endocrinal adverse effects, is seldom preferred by physicians. Animal studies have shown ketoconazole to be teratogenic [3, 21], associated with various musculoskeletal malformations. Currently, oral formulations are not recommended for treating fungal infections.

Voriconazole is approved for some systemic fungal infections (candidiasis and aspergillus). However, of late, it is being marketed in India for 'resistant dermatophytosis' (author's opinion). Like other azoles, voriconazole has been shown to be teratogenic in rodents even at low doses (equivalent of 0.3 times the recommended human maintenance dose) with skeletal and visceral abnormalities [9]. Due to lack of human data, it is categorized as pregnancy category D and should be strictly avoided in pregnancy.

Topical agents: Due to paucity of high-quality studies, many topical agents are designated as category C whereas some better-evaluated agents are listed as category B. However, studies have shown that topical azoles are minimally or not absorbed systemically, and therefore can be prescribed at any stage of pregnancy [14]. A population-based retrospective cohort study of women exposed to vaginal azoles (clotrimazole and miconazole) from the first day of the last menstrual period until the 90th gestational day was undertaken [22] in a total of 101,615 pregnancies. No significant association was found between its use and fetal malformations or abortions.

Terbinafine is a squalene epoxidase inhibitor which is extensively used in practice, both in oral and topical preparations. Oral reproduction studies did not reveal any embryo– fetotoxicity in rabbits and rats even when it was administered up to 23 times the maximum recommended human dose. A nationwide, registry-based cohort study spanning 20 years was conducted in Denmark [23] from January 1, 1997, to December 31, 2016, in 1,650,649 pregnancies which did not find any significant associations. This is one of the largest studies up to date which shows the safety of terbinafine. It is recommended as FDA pregnancy category B and is considered the safest oral antifungal in 1st trimester of pregnancy.

Griseofulvin is an orally administered fungistatic drug commonly used in dermatophytosis. Griseofulvin crosses the placenta and is teratogenic in rodents. Griseofulvin use has been reported with conjoined twins [24]. However, one large population-based case-control study in 22,843 pregnancies in Hungary did not reveal any significant association [25]. It has been classified as pregnancy category C and its use is restricted in pregnancy. Studies

Table 2 List of studies evaluating safety of antifungals in pregnancy

No	Study	Design & Duration	Source	No. of participants		Fetal associated anomalies	Pregnancy associated complications
				Exposure	Cohort/control group		
1	Study 1 [10]	Population based cohort study; 2000–14	Nationwide Medicaid Analytic eXtract	37,650 (1.9%) pregnancies (oral fluconazole) 82,090 (4.2%) pregnancies (topical azoles)	19,69,954	Musculo-skeletal malformation	NA
2	Study 2 [11]	Population based cohort study 1997–2013 total 14,05,663 pregnancies	Nationwide register (Denmark)	*Spontaneous abortions*		NA	Spontaneous abortions with oral fluconazole
				3315 exposed to oral fluconazole (7–22 weeks)	13,246 Unexposed, matched		
				2823 exposed to oral fluconazole	2823 exposed to topical azoles		
				Stillbirths			Not significantly associated with stillbirths
				5382 exposed to fluconazole (week 7 to birth)	21,506 Unexposed, matched		
				4301 exposed to oral fluconazole	4301 exposed to topical azoles		
3	Study 3 [12]	3 nested case–control studies (1998–2015)	Quebec Pregnancy Cohort	*Spontaneous abortions*		NA	Increased risk of spontaneous abortions
				1701 (up to 150 mg fluconazole) 891 (> 150 mg fluconazole)	3,20,868 cohort		
				Congenital malformation		> 150 mg dose is associated with cardiac septal anomalies	NA
				913 (Up to 150 mg fluconazole) 400 (> 150 mg fluconazole)	2,26,599		
4	Study 4 [15]	Population based cohort (1996–2011) 976,300 live born infants	Nationwide Medical Birth Registry (Denmark)	7352 (Oral fluconazole)	968,236 unexposed pregnancies	Fluconazole associated with tetralogy of Fallot	NA
5	Study 5 [19]	Prospective cohort	Internanational Pharmacovigilance Department of the Manufacturer of Itraconazole (Belgium)	199 (Itraconazole)	198 (Matched control)	No significant association	Increased risk of abortions
6	Study 6 [20]	Prospective cohort (2002–2006)	Italian Teratology Information Services	206 (Itraconazole)	207 (matched control)	No significant association	Increased risk of abortions
7	Study 7 [22]	Population-based retrospective cohort study (1999 to 2009)	Computerised databases at Soroka Medical Center, Israel,	1993 (Clotrimazole topical) 313 (Miconazole topical)	1,01,615 cohort	No association	No association
8	Study 8 [23]	Cohort study 1997 to2016 1,650,649	Nationwide registry (Denmark)	891 (Terbinafine-oral) 3174 (Terbinafine-topical)	40,650 (matched, unexposed)	No association	No association

Table 2 (continued)

No	Study	Design & Duration	Source	No. of participants		Fetal associated anomalies	Pregnancy associated complications
				Exposure	Cohort/control group		
9	Study 9 [25]	Case–control study 1.1980–1996 2.1970–2002	1. Hungarian Case–Control Surveillance of Congenital Abnormalities 2. Hungarian Congenital Abnormality Registry	22,843 (Griseofulvin)	38,151 (control)	No association	No association

evaluating safety of antifungals in pregnancy have been listed in Table 2.

Conclusion

Superficial fungal infections such as vaginal candidiasis have potential for poor pregnancy and perinatal outcome [1]. Others, such as dermatophytosis have become more difficult to treat due to irrational use of antifungals, topical steroids, and poor patient compliance [3–5]. They need to be treated with judicious use of the available antifungal agents. Terbinafine is the safest oral antifungal. Low-dose fluconazole (up to 150 mg) may be used in vaginal candidiasis, however, higher doses are not recommended. Itraconazole, ketoconazole, and griseofulvin may be best avoided due to lack of reliable human data. The potential maternal complications with oral azoles are spontaneous abortions, and the reported fetal malformations include musculoskeletal, congenital heart anomalies, and eye defects. All topical agents can be safely used in pregnancy and are the preferred 1st line treatment in mild cases.

Authors' Perspective

Not every pregnancy results in the delivery of a perfectly healthy baby, and many physicians are anxious to avoid litigation for having given a medication that might possibly have contributed to the problem. Since antifungals are needed for prolonged periods ranging from 6–12 weeks, all oral agents are best avoided in 1st trimester especially in mild to moderate skin infections. Topical azoles and terbinafine are preferred during pregnancy. In recalcitrant/recurrent dermatophytosis, oral terbinafine is the safest choice. In authors' opinion, combination of an oral agent and a topical formulation with different mechanisms of action can be tried in such cases e.g., oral terbinafine with a topical azole or with ciclopirox oleamine. Other measures like laundering of clothes, avoiding occlusive clothing, and treatment of all affected co-habitants are also necessary. It is equally important to involve the patient in the decision-making process as her quality of life may be severely impaired due to fungal infection, and in desperation, she may end up taking medication prescribed to her by quacks without due consideration. Prescribing these drugs in lactating women also needs careful consideration, which we have not discussed in this article.

Declaration

Conflict of interest We, the authors of this study declare that no patient identity is revealed and we have no conflict of interest or financial interests for this article.

References

1. Aguin TJ, Sobel JD. Vulvovaginal candidiasis in pregnancy. Curr Infect Dis Rep. 2015;17(6):462.
2. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. Mycoses. 2008;52(1):95.
3. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: an appraisal. Indian J Dermatol. 2017;62(3):227–36.
4. Bishnoi A, Vinay K, Dogra S. Emergence of recalcitrant dermatophytosis in India. Lancet Infect Dis. 2018;18(3):250–1.
5. Verma SB, Zouboulis C. Indian irrational skin creams and steroid-modified dermatophytosis – an unholy nexus and alarming situation. J Eur Acad Dermatol Venereol. 2018;32(11):426–7.
6. Sobel JD. Vulvovaginal candidosis. Lancet. 2007;369(9577):1961–71.
7. Ramoz LL, Patel-Shori NM. Recent changes in pregnancy and lactation labeling: Retirement of risk categories. Pharmacotherapy. 2014;34(4):389–95.
8. Food and Drug Administration,HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labelling. Fed Regist 2014;79(233):72063–103.
9. King CT, Rogers PD, Cleary JD, et al. Antifungal Therapy during Pregnancy. Clin Infect Dis. 1998;27(5):1151–60.
10. Zhu Y, Bateman BT, Gray KJ, et al. Oral fluconazole use in the first trimester and risk of congenital malformations: population based cohort study. BMJ. 2020;369:1494–504.
11. Mølgaard-Nielsen D, Svanström H, Melbye M, et al. Association between use of oral Fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. JAMA. 2016;315(1):58–67.
12. Berard A, Sheehy O, Zhao JP, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. CMAJ. 2019;191(7):179–87.
13. Pilmis B, Jullien V, Sobel J, et al. Antifungal drugs during pregnancy: an updated review. J Antimicrob Chemother. 2015;70(1):14–22.
14. Budani MC, Fensore S, Di Marzio M, et al. Maternal use of fluconazole and congenital malformations in the progeny: A meta-analysis of the literature. Reprod Toxicol. 2021;100:42–51.
15. Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral Fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013;369:830–9.
16. Zhang Z, Zhang X, Zhou YY, Jiang CM, Jiang HY. The safety of oral fluconazole during the first trimester of pregnancy: a systematic review and meta-analysis. BJOG. 2019;126(13):1546–52.
17. Liu D, Zhang C, Wu L, Zhang L, et al. Fetal outcomes after maternal exposure to oral antifungal agents during pregnancy: A systematic review and meta-analysis. Int J Gynaecol Obstet. 2020;148(1):6–13.
18. U.S. FDA. FDA Drug Safety Communication: Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants [Internet]. USA: U.S. FDA; 2011 Aug 3 [updated 2017 Aug 4; cited 2021 May 20]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communicationuse-long-term-high-dose-diflucan-fluconazole-during-pregnancy-may-be
19. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. Am J Obstet Gynecol. 2000;183(3):617–20.
20. De Santis M, Di Gianantonio E, Cesari E, et al. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. Drug Saf. 2009;32(3):239–44.
21. Dodo T, Uchida K, Hirose T, et al. Increases in discontinuous rib cartilage and fused carpal bone in rat fetuses exposed to the teratogens, busulfan, acetazolamide, vitamin A, and ketoconazole. Hum Exp Toxicol 2010; 29(6):439–50
22. Rotem R, Fishman B, Daniel S, et al. Risk of major congenital malformations following first-trimester exposure to vaginal azoles used for treating vulvovaginal candidiasis: a population-based retrospective cohort study. BJOG. 2018;125(12):1550–6.
23. Andersson NW, Thomsen SF, Andersen JT. Evaluation of association between oral and topical terbinafine use in pregnancy and risk of major malformations and spontaneous abortion. JAMA Dermatol. 2020;156(4):375–83.
24. Rosa FW, Hernandez C, Carlo WA. Griseofulvin teratology, including two thoracopagus conjoined twins. Lancet. 1987;329(8525):171.
25. Czeizel AE, Métneki J, Kazy Z, et al. A population-based case-control study of oral griseofulvin treatment during pregnancy. Acta Obstet Gynecol Scand. 2004;83(9):827–31.

About the Author

Dr. Madhuri Patel is currently the Secretary General of FOGSI and Associate Editor, Journal of Obstetrics and Gynaecology of India (JOGI). She is Hon. Clinical Associate at N. Wadia Hospital and Hon. Consultant at Police Hospital, Mumbai. She is Ex. Professor & HOD OBGY, ESIC-PGIMSR, MGMH, Mumbai and Ex. Associate Professor, GMC, Mumbai, India. She served as Joint Secretary, FOGSI in 2009. She was former committee member, FIGO Preterm Birth. She was awarded the MOGS- Mrs. Shailaja and Mr. Narayan Pandit award for the year 2019–2020. She was Associate Editor of FOGSI Award Winning book "Gynaecolgical Cancer", 2007. She has delivered guest lectures and orations at National and International levels and has more than fifty publications in National and International Journals and has written several book chapters.