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Use of Antifungal Drugs in Pregnancy
A Focus on Safety

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Abstract

The use of antifungals in pregnancy requires special consideration for the safety of the developing fetus. Clinicians now have an increased repertoire of both topical and systemic antimycotics available to treat superficial or mucotaneous fungal infections including *Candida* vaginitis. The ability of many nontopical antifungals to penetrate the placenta and achieve measurable, often therapeutic, concentrations in cord blood, fetal tissue and amniotic fluid means that evidence exists of successful treatment of all varieties of systemic fungal disease in pregnant women, even with placental involvement. However, for the same reasons, safety considerations remain a concern.

Although the use of azoles as topical agents for superficial infections is both efficacious and well tolerated, especially when used for short periods, systemic azole therapy is not recommended in pregnancy. Accordingly, amphotericin B remains the drug of choice for systemic, invasive mycotic infections, whether life-threatening or less severe. Unfortunately little if any information is available regarding the safety of the newer lipid formulations of amphotericin B.

There is a general reluctance to perform randomised, comparative studies involving antifungal agents in pregnancy, hence cumulative anecdotal reports form much of the available data; animal studies, although useful, have several drawbacks. There is a need for additional safe and effective new antifungal agents for widespread use in pregnant women.

Several considerations are involved in managing fungal infections in pregnant women. Following diagnosis of fungal disease, the critical issue is selecting a systemic or topical antifungal agent which will do no harm to the developing fetus. This risk in no small way depends on the stage or duration of gestation, with special consideration applicable to the first trimester of pregnancy when the risk of teratogenicity is greatest.

Accordingly, antifungal drugs should be reviewed with regard to their capacity to cross the placenta and cause toxic sequelae in the fetus. Another consideration is the altered pharmacokinetics of antifungal agents in pregnant women. Finally, consideration should be given to the effect of pregnancy on fungal infection progression. Clinical experience has long recognised the altered behaviour and prognosis of several superficial and systemic fungal infections in pregnancy.

In spite of the above considerations, treatment of fungal disease during pregnancy closely follows guidelines used in treating these infections in nonpregnant women. This article will review the use and safety of antifungal drugs in pregnancy and address unique aspects of fungal disease in pregnancy, especially as they relate to safety.

In 1980 the US Food and Drug Administration published definitions for drug-associated pregnancy risk categories (table I).[1] Categories are assigned to drugs in accordance with the known or estimated potential harm to the fetus. The designated grade ranks the relative risk of using the drug in pregnancy. Ranking is derived from data obtained from pharmaceutical companies, retrospective human studies, animal studies and clinical experience.

Although by no means perfect, the category risk designation has proved invaluable to clinicians. Often however, the difference between grades designated for 2 comparable drugs is a function of whether safety studies have actually been performed on one or the other and not whether there is evidence that one is less safe or more toxic than the other. Classifications of antifungal agents are summarised in table II.

1. Influence of Pregnancy on Fungal Infection

Pregnant women are susceptible to the same fungal pathogens and disease as nonpregnant women. However, certain superficial and systemic fungal infections run a more aggressive course under the influence of the altered hormonal milieu of the gravid state.

1.1 *Candida* Vaginitis

It is frequently stated that *Candida* vaginitis is more common, more frequently refractory and more likely to relapse in pregnant women than in those who are not pregnant.[2] Vaginal carriage of *Candida* species has almost always been found to be more common in pregnant than nonpregnant women, with the highest prevalence observed in the third trimester.[3] Following delivery, the propor-

Table I. Classification of prescription drugs by the US Food and Drug Administration, according to risk in pregnancy (adapted from the Federal Register[1])

Pregnancy risk category	Description
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
B	Either animal studies do not indicate a risk to the fetus and there have been no controlled studies of pregnant women, or animal studies have indicated fetal risk but controlled studies of pregnant women failed to demonstrate a risk
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
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)
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

tion of women carrying detectable levels of vaginal yeast declines rapidly. The promotional role of estrogen in patients can be reproduced in the rodent models of *Candida* vaginitis, where experimental vaginal infection is enhanced by estrogenisation of castrated animals and resolution of infection rapidly follows cessation of exogenous estrogen replacement.[2]

Other factors that may contribute to the increased predisposition during pregnancy include decreased cellular immunity, reduced vaginal pH and increased vaginal glycogen concentration.[2,3] Vaginal colonisation with *Candida*, including moderate to heavy colonisation, has not been shown to have an adverse effect on pregnancy outcome.[4] Rarely, chorioamnionitis attributable to a variety of *Candida* species has been reported, especially in the presence of a retained intrauterine device.[5-7]

Although vaginal *Candid*a colonisation is more common in HIV seropositive women (including those who are pregnant) than in noninfected women, neither asymptomatic colonisation nor vulvovaginal colonisation are associated with increased risk of perinatal HIV transmission to infants.[8]

Treatment recommendations are discussed in section 2.2 and are based upon a perceived inferior response rate in pregnancy compared with therapy in nonpregnant women, with lower response and higher relapse rates in a vaginal environment which fosters yeast persistence.

1.2 Endemic Mycoses

Coccidioidomycosis is reported to disseminate more frequently in pregnant females.[9,10] The aggressive nature of primary infection with *Coccidioides immitis* in pregnant women is thought to result from reduced protective cell-mediated immunity. Although not on a similar scale, primary disseminated infection is also described in pregnant women infected with Paracoccidioides braziliensis, Blastomyces dermatidis and Histoplasma capsulatum organisms.[11-18] The implications of severe dissemination apply primarily to the infected woman, who may be faced with a fulminant process and high mortality, but in addition fungal microorganisms can also infect the placenta and constitute a major threat to the fetus.

Table II. Antifungal drugs and risk cateogry in pregnancy (adapted from the Federal Register[1])

	Designation
Polyenes	
amphotericin B	B
nystatin[a]	A
Antimetabolites	
flucytosine	C[b]
Imidazoles	
clotrimazole[a]	B
butoconazole[a]	C
econazole[a]	C
tioconazole[a]	C
miconazole[a]	C
Triazoles	
terconazole[a]	C
ketoconazole	C
itraconazole	C
fluconazole	C
Squalene eposidase inhibitors	
terbinafine[a]	B
Miscellaneous	
potassium iodide	D[b]
griseofulvin	D[b]

a Topical.
b Contraindicated in pregnancy.

2. Treatment of Fungal Infections in Pregnancy

2.1 Superficial Fungal Infections

Most fungal infections involving the skin, nails and hair are caused by dermatophytes, although increaing numbers are caused by *Candida* species and *Malassezia furfur*.[19] The majority of localised nonextensive cutaneous fungal infections can be controlled or eradicated using topical antifungal agents, including imidazoles, triazoles and a variety of antifungal chemical agents such as dyes and phenols, most of which are nonprescription medications. Little is known about the safety of these chemicals in pregnancy.

The polyenes (nystatin and amphotericin B) are minimally absorbed from the skin, but have an extremely limited role because of their narrow spectrum of activity against dermatophytes. They are used rarely in superficial fungal infections, and mainly as backup in the treatment of ringworm.

In contrast, topical azoles especially clotrimazole and miconazole, are widely used. Systemic absorption of these agents is minimal and hence safety in pregnancy is not an issue. Dermatomycoses are usually responsive to these azole agents, although relapse is common. Unfortunately, nail or extensive cutaneous fungal involvement is usually not responsive to topical medications and requires the use of oral agents such as griseofulvin, ketoconazole, itraconazole, fluconazole or terbinafine for resolution. In spite of increased efficacy, convenience and a variety of innovative dosage regimens, onychomycosis and dermatophyte infections have a high relapse rate in excess of 30% for both topical and oral routes of administration.

Griseofulvin is highly effective as oral therapy in the treatment of ringworm and other dermatophyte infections; however, it is best avoided during pregnancy.[20,21] This is because of frequent adverse effects, especially gastrointestinal symptoms, hepatotoxicity, headache and other CNS manifestations. Moreover, griseofulvin is embryotoxic and teratogenic in animals exposed to high doses,[21] and the drug readily crosses the placental barrier.[21] Given the variety of safer and equally effective alternatives it is best not to prescribe griseofulvin during pregnancy.

Terbinafine is an oral squalene epoxidase inhibitor that is highly effective in the treatment of dermatophyte infections, especially onychomycoses.[22] Although well tolerated by nonpregnant women, little information is available regarding its safety in pregnant women. Based upon its extensive use in millions of women, the manufacturers of this drug have classified terbinafine as class B; nevertheless caution should be exercised until more data are published, including results from animal studies.

2.2 *Candida* Vaginitis in Pregnancy

Asymptomatic colonisation of the vagina is more common in pregnancy than in the nonpregnant state.[3] However, there is little justification in treating colonisation in the absence of symptoms, since the majority of affected individuals never become symptomatic and no adverse effects of yeast colonisation on the pregnancy, such as prematurity or preterm labour, have been reported. Although asymptomatic vaginal colonisation at term is a risk factor for neonatal oral thrush, it is not considered the standard of care to screen or treat colonisation at term.

Unfortunately, there are scant data on the optimal treatment of symptomatic *Candida* vaginitis in pregnant women,[23] as pharmaceutical companies have been reluctant to perform prospective studies evaluating new topical or systemic agents in this population. Given the plethora and efficacy of topical azole and polyene agents, it seems reasonable to avoid the systemic azoles that are so popular in nonpregnant women.

Data have been forthcoming only on oral fluconazole, and there is a dearth of information on oral intraconazole and ketoconazole. Although prolonged, high dosage (200 to 400 mg/day) oral fluconazole administered to severely ill pregnant women was associated with congenital limb deformities,[24,25] considerable data have accumulated attesting to the safety of conventional doses of fluconazole prescribed for vulvovaginal candidiasis.[26,27] Jick[26] found no evidence that the overall risk for congenital disorders in infants of 234 women exposed to both topical and oral fluconazole was increased in the first trimester of pregnancy compared with infants of nonexposed women. Specifically, no evidence of increased risk of heart defects, limb disorders or cleft lip or palate was found in infants exposed to fluconazole.

In the same study, 492 pregnant women exposed to topically administered azole preparations in the first trimester were evaluated and no increased risk of congenital disorders in infants was found. The various available topical imidazoles and triazoles are classified as risk category or class C agents, with the exception of clotrimazole which is graded as

class B (table II). This distinction is not based on evidence of lack of safety of the topical azoles but on the lack of studies in animals or humans proving safety. Data are, however, available on the safety of topical nystatin; hence this agent has been the drug of choice in pregnant women for many years in spite of lower efficacy rates and need for longer duration of treatment (14 days).[28,29]

In part the use of nystatin was also based upon its negligible systemic absorption.[21] The topical azole miconazole is classified as class C and has similar minimal systemic absorption (1.4%) as does tioconazole, whereas slightly increased but still low rates of absorption are reported with butoconazole (5%) and clotrimazole (3 to 10%).[21] Higher absorption is seen with prescription terconazole (5 to 16%).[21]

In the last few years, consultants advising the US Centers for Disease Control and Prevention responsible for developing treatment guidelines have progressively diminished the restrictions on the use of topical azoles in pregnancy.[30] This started a decade ago with recommendation of the use of all topical azoles (regardless of class) in late pregnancy to clearing the way to recommending their use in the first trimester. The evidence indicating any adverse effect of topical azoles in any stage of pregnancy is almost nonexistent and the sacred role of topical nystatin has come to an end. In practice, practitioners have been prescribing all topical azoles for many years.

There appears to be no difference in overall potency and effectiveness of the various azoles but once more few controlled, comparative studies have been performed.[28,31-34] As in nonpregnant patients, these topical agents all appear to be highly effective in pregnant women as long as treatment duration is sufficient. The only study showing some level of disagreement was that of Rosa et al.,[35] who found an increased risk of spontaneous abortions in patients treated with miconazole [relative risk of 1.4 (95% confidence interval 1.2 to 1.5)] and clotrimazole [relative risk of 1.4 (95% confidence interval 1.1 to 1.6)]. However, overall the study found no statistically significant association for any of the agents studied (miconazole, clotrimazole, nystatin, candicidin, aminacrine compounds and metronidazole) for the overall frequency of birth defects or for specific birth defects analysed (cardiovascular defects, oral clefts, and spina bifida). This controversial study, however, has been heavily criticised on a methodological basis and is not thought to justify withholding topical imidazoles in early pregnancy.

The optimal duration of topical therapy is unknown. Anecdotal data from the 1970s suggest that vaginitis is more difficult to control in pregnancy, perhaps resulting from experience with nystatin.[32] A recent consensus committee classified vulvovaginal candidiasis in pregnancy as a form of complicated vaginitis requiring more prolonged therapy of at least 1 week, rather than single dose or 3-day regimens.[36] However, this conclusion was largely based upon opinion and clinical experience rather than evidence. It seems reasonable to treat a mild to moderate first episode of symptomatic vaginitis in pregnancy with a short course of topical azoles; however, if the symptoms appear refractory or relapse occurs, then a more prolonged course lasting at least 7 days appears justified.

In spite of the recent reassurance of lack of teratogenicity of low dosage oral fluconazole,[26,27] use of systemic agents cannot be endorsed.[36] On the other hand, inadvertent use of low dosage fluconazole in early pregnancy should not elicit concern or precipitate actions such as pregnancy termination. Moreover, fluconazole has been used safely and effectively for life-threatening fungal sepsis in pregnancy.[37]

2.3 Systemic and Invasive Fungal Infections

Fortunately, deep-seated infections in pregnancy are relatively uncommon; in addition, the course of these infections is similar to that in the nonpregnant state and patient response to antifungal therapy is similar.[21] The exceptions to this principle include primary coccidioidomycosis and, on occasion, primary infections with other endemic mycoses.[9]

Until the 1990s, the only antifungal agents available were amphotericin B and flucytosine as well as

a limited role for potassium iodide for lymphocutaneous sporotrichosis. Not surprisingly, given the well recognised toxicity of these drugs (see sections 2.4 and 3.2), their use in pregnancy was limited to life-threatening fungal infections and experience with these agents in pregnancy is limited. The availability in the 1990s of oral and intravenous azole drugs dramatically increased the therapeutic armamentarium; however, data remain scant and no randomised studies have been undertaken regarding the use of these drugs in pregnancy.

2.4 Sporotrichosis

Management of sporotrichosis in pregnancy is extremely problematic, given that the 2 drugs of choice are relatively contraindicated [itraconazole (class C) and potassium iodide (class D)] and both require fairly prolonged therapy. Iodides are usually contraindicated in pregnancy because of the risk of congenital goitre, often with fatal consequences to the fetus or neonate.[1] Short courses of therapy with either agent may be reasonable, avoiding the use of iodides close to term. Occasional cases of lymphocutaneous sporotrichosis have responded successfully to local heat application.[38]

3. Antifungal Agents

3.1 Flucytosine

Flucytosine or 5-fluorocytosine has a relatively narrow spectrum and its clinical utility is confined to *Candida* and cryptococcal infections.[39] Moreover, both its toxicity and the tendency for rapid acquisition of resistance have hampered its use in general, and in pregnant women in particular.

Common adverse effects include gastrointestinal symptoms and hepatotoxicity as well as bone marrow suppression.[39] In addition, its mode of action of interfering with DNA synthesis is incompatible with use in early pregnancy. Flucytosine is teratogenic in rats at doses lower than those used in humans on a bodyweight basis[21] and the drug crosses the human placenta, achieving high concentrations in the amniotic fluid and cord blood.[21]

Although rare cases reporting the safe and effective use of flucytosine in late pregnancy for cryptococcal meningitis have appeared,[40] the value of this drug in pregnancy is small and, despite its designation as a class C drug, most investigators consider flucytosine to be contraindicated in pregnancy. In general, given the widespread availability and efficacy of amphotericin B (section 3.2) and the marginal advantages gained by combining it with flucytosine in the treatment of cryptococcal meningitis,[41] flucytosine offers a minimal contribution in pregnancy. Similarly, the advantages of combination therapy with flucytosine over high dosage amphotericin B alone in candidiasis are questionable even in nonpregnant women.[42]

3.2 Amphotericin B

The polyene antifungal amphotericin B, which has the broadest spectrum of action of all the antifungals, remains the most potent agent available with fungicidal activity. In addition, it has been used in pregnancy more than any other antifungal. Dose-limiting adverse effects are all too common even in the nonpregnant state; nevertheless, parenteral amphotericin B remains the antifungal drug of first choice in pregnancy for serious fungal infections.[21]

There is little information on the pharmacokinetics of amphotericin B in pregnant women. The few studies available indicate that amphotericin B crosses the placenta, achieving therapeutic concentrations in the fetal circulation; it is also detectable in amniotic fluid.[11,12,43] In spite of limited reports in the literature, fetal toxicity attributable to amphotericin B appears extremely rare,[21] whereas maternal toxicity appears similar to that experienced by nonpregnant women and is dosage-dependent and usually reversible. Animal teratogenicity has not been reported and the drug is classified as class B.

On the other hand, the literature is replete with case reports of successful treatment with amphotericin B, including patients with disseminated infection and likely fetal involvement. Certainly, patients with placental involvement have been successfully treated.[12,40] This includes patients with amnionitis due to *Candida* species.[5,7] Currently 3 lipid formu-

lations of amphotericin B are now available; after relatively little preapproval study, these 3 commercial preparations are now approved for a variety of indications, specifically refractory aspergillosis, candidiasis and cryptococcal meningitis in nonpregnant women.

Most of the advantages offered by these products relate to confirmed significant reductions in nephrotoxicity as well as decreased possible infusion-related toxicity.[42] At conventional dosages of 4 to 6 mg/kg/day, the lipid formulation products are now considered as being of at least comparable efficacy and effectiveness to standard formulations, regardless of the site of fungal infection. In addition, there may be some therapeutic advantage with regard to the maximum tolerated dosage of amphotericin B when used at high dosages, often exceeding 6 mg/kg/day.[42]

Whether the lipid formulations of amphotericin B offer any additional advantage in pregnant women is unclear, but in my opinion their use should be predicated on the same considerations used in nonpregnant women. Although classified as class B by their manufacturers, there is virtually no information on the safety of these products in pregnancy. Animal studies have been extremely limited, although so far no detrimental effects, such as teratogenicity or fetal abnormalities, have been seen.[21]

3.3 Azoles

The azole agents available to clinicians have grown in number over the last 2 decades, and newer and more advanced generation azoles are in early phase studies. Oral azoles currently available for the treatment of mycoses include ketoconazole, itraconazole and fluconazole. The latter 2 (both triazoles) are also available as intravenous preparations.

In general, the azoles represent a major advance in treating fungal infections, particularly as safer and more convenient alternatives to parenteral amphotericin B. Azoles have proven particularly valuable in treatment of locally invasive and systemic mycoses that are not life-threatening, including candidemia and systemic candidiasis syndromes, cryptococcal disease, histoplasmosis, blastomycosis, coccidioidomycosis and sporotrichosis.[44] Although itraconazole has moderate activity against *Aspergillus* species,[44] clinical utility has been limited. A major use of oral systemic azoles is in conjunction with amphotericin B: not concomitantly, but following an initial induction course of amphotericin B prescribed in the acute phase of the disease.[44]

Clinical use of azoles during pregnancy has been extremely limited. Considerations for their use have been dominated by fetal toxicity concerns rather than efficacy limitations. There is no reason to believe that systemic azoles would not be as efficacious as in the nonpregnant state. On the other hand, safety concerns predominate.

Ketoconazole, an imidazole, has proven both teratogenic and embryogenic at high doses in animals (80 mg/kg bodyweight), and crosses the placental barrier.[44] Another concern is its capacity to inhibit adrenal and gonadal steroid synthesis, which could theoretically affect sex organ differentiation in the fetus.[44] This drug should not be used in pregnancy, especially as indications for its use in preference to other azoles are rare.

In contrast, oral and intravenous triazoles have had a major impact on the treatment of systemic mycoses. Fluconazole is teratogenic and embryotoxic at high doses in animals and is classified as class C. Congenital anomalies have been reported in 4 infants whose seriously ill mothers received high dosage (200 to 400 mg/day) fluconazole for prolonged periods in pregnancy.[25] Although the underlying disease may have contributed to skeletal anomalies, careful study of the few cases reported is compelling in linking the skeletal anomalies with exposure to high dosage fluconazole. This conclusion is endorsed by the animal studies of Tiboni.[45] Accordingly, use of high dose prolonged therapy of fluconazole in pregnancy is not only not recommended, but should only be used in a life-threatening situation when there are no alternative measures.[37]

On the other hand, as discussed in the section on vaginal candidiasis, several studies have not found teratogenic effects with low doses of fluconazole (50mg), especially when used for short durations.[26,27] Resolution of these conflicting findings

is unlikely to occur in the near future and this appears to be a pure dose-toxicity relationship. Given available options, it is recommended to avoid even low dose, short term fluconazole therapy in the first trimester of pregnancy.[42]

Less information is available regarding the fetal toxicity of itraconazole, with no published human studies. As with other triazoles, experimental animal studies indicate embryotoxicity and teratogenicity.[21] Accordingly it is prudent to apply the same limitations regarding the use of fluconazole to itraconazole.

4. Conclusion

After years of practitioners having too few drugs to treat fungal infections, the last decade has seen a dramatic increase in available effective and safe antifungal agents. In spite of this, for life-threatening fungal infection in pregnancy, amphotericin B remains the drug of first choice, whereas the role of the new amphotericin B lipid formulations is not yet clear.

In spite of the utility of systemic azoles in nonpregnant patients, their use in pregnancy is extremely limited with minimal safety data to support prolonged high dosage administration and some convincing evidence of teratogenicity in high doses. Their use cannot be recommended. In contrast, short courses of treatment with topical cutaneous and vaginal use of azoles appear safe and have widespread utility throughout pregnancy for the treatment of superficial fungal infections and *Candida* vaginitis although comparative studies are rare.

There is a reluctance to perform prospective randomised studies in pregnant patients, even those with only superficial fungal infections, and extrapolating animal studies to humans has limitations. In general, as long as safety is taken into account, effective treatment of antifungal infections is equally possible in pregnant and nonpregnant patients.

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