Antifungal drugs during pregnancy: an updated review

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Antifungal prescription remains a challenge in pregnant women because of uncertainties regarding fetal toxicity and altered maternal pharmacokinetic parameters that may affect efficacy or increase maternal and fetal toxicity. We present updated data reviewing the available knowledge and current recommendations regarding antifungal prescription in pregnancy. Amphotericin B remains the first-choice parenteral drug in spite of its well-established toxicity. Topical drugs are used throughout pregnancy because of limited absorption. Recent data have clarified the teratogenic effect of high-dose fluconazole during the first trimester and provided reassuring cumulative data regarding its use at a single low dose in this key period. Recent data have also provided additional safety data on itraconazole and lipidic derivatives of amphotericin B. Regarding newer antifungal drugs, including posaconazole and echinocandins, clinical data are critically needed before considering prescription in pregnancy.

Keywords: fetus, placenta, antifungal therapy, fungal infections

Introduction

Pregnancy should be considered as a condition with increased vulnerability to infections, including some life-threatening fungal infections, but paradoxically little is known regarding optimal antifungal regimens and dosages in this setting.1 Drug prescription during pregnancy requires a delicate assessment of the balance between maternal benefit and fetal risks, including fetal loss, congenital malformations, organ toxicity and prematurity. In addition to the pharmacodynamics, pharmacokinetics and intrinsic antifungal activity of a given drug, specific parameters should be added to the challenging equation of antifungal prescription in pregnant women: term of pregnancy, level of fetal drug exposure and maternal physiological pharmacokinetic changes.2 Indeed vomiting-increased gastric pH, cardiac output, intestinal blood flow and time of intestinal process can modify oral absorption. Increased intra- and extravascular blood flow and reduced serum albumin concentration enhance the distribution of unbound drugs. Finally, increased renal filtration/elimination and increased (3A4, 2D6, 2C9, 2A6) or decreased (1A2, 2C19) cytochrome activities can modify drug clearance. Fetal exposure relies on the drug’s ability to cross the placenta, depending on the stage of pregnancy (placental maturation with enhanced fetal exposure in later term) and on intrinsic drug parameters (liposolubility, molecular weight, protein binding).3–5

Because pregnancy is a duly established contraindication for controlled studies involving antifungal drugs, data in this setting are extremely limited and based on in vitro or animal studies, pharmacological investigations, limited case reports and expert opinions. In this setting, the FDA definitions for pregnancy risk categories (A to X, in accordance with product’s estimated toxicity for fetus) provide a general framework that do not take into account the stage of pregnancy (Table 1). They globally reflect the paucity of available information (Table 2).

The last focus on antifungal drugs in pregnancy was published in 2003 by Moudgal and Sobel.6 Within the last 10 years the FDA has provided approval for three new antifungal drugs: posaconazole, micafungin and anidulafungin. Additional data regarding triazole use and antifungal recommendations have emerged, raising the need for an update on antifungal drug use in pregnancy.

Methods


Immunity during pregnancy and fungal infections

Pregnancy is a unique and complex situation during which the maternal immune system faces two issues: defending both the...
mother and fetus from pathogens, while at the same time tolerating the father’s fetal antigens. Immune functions are known to vary according to the phases of pregnancy, being more pro-inflammatory during implantation and delivery, and anti-inflammatory in-between. Post-implantation is characterized by both an up-regulation of monocytes displaying enhanced phagocytosis and IL1β and IL12 secretion ability, and a down-regulation of T cells displaying diminished proliferation and IL2/6 secretion ability. Humoral response is not altered. Recent work has emphasized the highly antigen-specific nature of regulatory T cell-driven maternal tolerance, which would not hamper adequate maternal immune responses against most pathogens. Yet pregnant women are considered at higher risk for some infections, like listeriosis, and for severe manifestations during dengue, measles or influenza.

With regard to fungal infections, two main types can occur:

(i) Vulvo-vaginal candidi-asis. This affects 75% of women at least once during their lifetime but occurs in up to 20% of pregnant women. Treatment failures and recurrences are frequently reported in this setting. Higher vaginal glycogen content is thought to play a major part in their development, favouring Candida sp. growth. In addition, oestrogen enhances the adherence of yeasts to vaginal epithelial cells, facilitating blastospore proliferation and germination.

(ii) Systemic fungal infections. Some systemic fungal infections appear more severe in pregnant women. Indeed the last trimester and immediate post-partum time are associated with higher risk of disseminated coccidioidomycosis. Histoplasmosis and blastomycosis might also be more frequently disseminated during pregnancy. Pulmonary cryptococcosis has seldom been described in young immunocompetent women. Other systemic mycoses do not appear to be significantly influenced by pregnancy.

### Antifungal agents and pregnancy

#### Systemic azoles

Azoles include imidazoles (see the ‘Topical drugs’ section) and more recent triazoles (ketoconazole, itraconazole, fluconazole, voriconazole and posaconazole). They act by targeting the C14-demethylase and thereby inhibiting the biosynthesis of ergosterol, an essential component of fungal cell membranes. Animal and human data provide evidence that azoles could be teratogenic.

#### Ketoconazole

Ketoconazole has been shown to be teratogenic and embryotoxic at high doses (80 mg/kg/day) in animals. Although ketoconazole has been shown to cross the placental barrier poorly in animal studies, it could theoretically affect sex organ differentiation in the fetus.

#### Fluconazole

Fluconazole is a systemic triazole with fungistatic effect only on yeasts like Candida sp. and Cryptococcus sp. It crosses the placenta and was shown to be embryotoxic in rabbits and embryo-fetotoxic and teratogenic in rats, inducing craniofacial and rib abnormalities. Five observations of congenital abnormalities in children exposed in utero have been reported. Their mothers had received fluconazole (400 mg/day or above)

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<td>Terbinafine B</td>
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<td>Miscellaneous</td>
<td>Griseofulvine C</td>
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Table 1. Classification of prescription drugs by the US FDA according to the risk in pregnancy

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Table 2. Antifungal drugs and risk category in pregnancy (adapted from the Federal Register)

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Topical antifungal. No human data.
during the first trimester (5/5) and beyond [4/5, until 4 months and 31 weeks of gestation (n=1, each) or throughout pregnancy (n=2)]. Lesions included trapezoiodephalopolys, mid-facial hypoplasia, cartilage abnormalities with multiple synostoses and skeletal fractures. Abnormalities were similar to those reported in the Antley–Bixler syndrome. In contrast, in mothers exposed during the first trimester to single doses of 50–150 mg of fluconazole, no adverse fetal outcome was observed.

**What is new?** The FDA reclassified fluconazole from category C to category D (except for single 150 mg doses for vaginal candidiasis). In addition, animal studies have further helped clarify the teratogenicity of high-dose fluconazole in rodents, with identification of the phase of maximal sensitivity (day 10 of gestation), and of the dose dependence of lesions that mostly involve branchial arches. Most importantly, large epidemiological studies have helped clarify the risk of fluconazole at low doses. Nørgaard et al., in a Danish population-based study performed from 1991–2005, identified 1079 pregnant women prescribed fluconazole during the first trimester, of whom 797 received 150 mg, 235 received 300 mg and only 47 (4%) 350 or 600 mg. No increase in malformation, fetal loss, preterm birth or low birth weight was found (OR=1.0, range 0.7–1.3). Carter et al. analysed patients from the US National Birth Defects Prevention prospective case–control study. Among 7047 women, 84 and 59 exposures to antifungals were reported in cases and controls, respectively. Exposures mostly involved miconazole, terconazole and clotrimazole, but included fluconazole in 12 cases. Dosages and duration were not specified. A slight increase in hypoplastic left heart syndrome was noted (OR 2.3, range 1.04–5.06), along with a nonsignificant increase in diaphragmatic hernia. Craniofacial malformations that were previously reported with fluconazole were not significantly increased. Recently, Mølgaard-Nielsen et al. provided the largest and strongest information on the safety of low doses of fluconazole in first-trimester pregnancies. They analysed fluconazole, itraconazole and ketoconazole first-trimester prescriptions for all Danish pregnant women from 1996 to 2011. A total of 976000 children with antenatal exposure were identified; 7352 were exposed to fluconazole. Cumulative doses were 150 mg (n=4082, 56%), 300 mg (n=2252, 31%) or 350–600 mg (n=1018, 14%). Risk of birth defect was not significantly increased in this cohort (OR 1.06, 95% CI 0.92–1.21) and no increase in the previously described malformation pattern was found.

Finally, Bean et al. reported the safety and efficacy of intra-amniotic fluconazole 50–100 mg/week for 6–8 weeks in two patients with chorioamnionitis caused by *Candida albicans*.

**Key points** Fluconazole is embryo–fetotoxic and teratogenic in rodents and rabbits. Total fluconazole dose >300 mg should be considered teratogenic and remains contraindicated throughout pregnancy, with FDA designation D. A single low dose (≤300 mg total dose) of fluconazole does not increase the risk of congenital disorders and may be considered in the absence of a topical alternative after the first trimester.

*Itraconazole*

**What was known?** Itraconazole is a triazole with a broader spectrum of activity than fluconazole, including endemic fungi and most *Aspergillus* species. It was shown to be embryotoxic and teratogenic in rodents, inducing craniofacial and rib abnormalities. However, a prospective study involving 229 women exposed to itraconazole, including 198 during the first trimester [daily doses ranged from 50 to 800 mg (median=200 mg) for a median of 3 days (range 1–90)], failed to identify any increased risk of fetal malformation. A significantly higher rate of early fetal loss was reported (12% versus 4% in the control group), but questions were raised regarding a recall bias in the control group that had a very low rate of early fetal loss.

**What is new?** Animal studies have further analysed the teratogenicity of high-dose itraconazole in mice and have shown that the phase of maximal sensitivity and pattern of malformation are similar to those related to fluconazole. A large epidemiological study has helped clarify the risk of itraconazole during early pregnancy. De Santis et al. compared 206 Italian women exposed during the first trimester and 207 controls. First-trimester exposure to itraconazole was again not associated with increased risk of malformation (mean daily dose of 182±63 mg for a mean of 6.9±6.4 days). It was, however, associated with an increase in early fetal loss (11% versus 4.8%) that was not reported in former studies.

**Key points** Itraconazole is embryotoxic and teratogenic in rodents. Clinical studies have not detected any increased risk during pregnancy, especially during the first trimester, and the FDA labels itraconazole category C. Given the risk conveyed by the azole family in humans, the drug should still be avoided during pregnancy, especially during the first trimester. The manufacturer therefore recommends that effective contraception should be continued throughout treatment and for 2 months thereafter.

**Voriconazole**

**What was known?** Voriconazole is an azole displaying fungistatic activity against *Candida* spp. and *Candida neoformans* and fungicidal activity against *Aspergillus fumigatus*. Like other azoles, voriconazole has been shown to be teratogenic in rodents at high but also low doses (equivalent of 0.3 times the recommended human maintenance dose) with skeletal and visceral abnormalities. Plasma oestradiol concentration was reduced in pregnant rats at all studied doses. It was also shown to be embryo–fetotoxic in rabbits, and classified as category D by the FDA due to the lack of human data. The drug is therefore contraindicated during pregnancy.

**What is new?** Since its approval by the FDA and the EMA in 2002, only one report of voriconazole exposure during pregnancy has been reported. Indeed, our group recently reported the observation of a neutropenic pregnant woman with life-threatening refractory invasive aspergillosis who received voriconazole during the second and third trimesters of pregnancy. No adverse fetal/neonatal outcome was evidenced at birth or at a 6 month follow-up visit. Until further information is available, voriconazole remains contraindicated in pregnancy, and should be considered only in life-threatening cases in the absence of safer treatment alternatives after the completion of the first trimester.
Key points Voriconazole is labelled category D (FDA) because of its embryotoxic/teratogenic effects in rodents and rabbits. Data on pregnancy exposure are limited to a single observation with good materno-fetal outcome. It should not be considered in pregnancy, except in life-threatening maternal disease without a therapeutic alternative.

Posaconazole

Posaconazole is the most recently available triazole. It received EMA and FDA approval in October 2005 and September 2006, respectively. It has expanded antifungal spectrum including Mucorales and has otherwise broad spectrum against most of the common yeasts and moulds.41

What is new? The manufacturer has reported teratogenic effects in rats at 1.4 times the recommended human dose (skeletal malformations and rib abnormalities). It was also shown to be embryotoxic and teratogenic in rabbits, at 2.9–5.2 times the recommended human dose (reduction in body weight gain of females, reduction in litter size).42 No published human data are available but the FDA labels posaconazole category C.

Key points The FDA labels posaconazole category C. It is embryotoxic and teratogenic in rodents and rabbits. No human data are available so far and it should not be considered in pregnancy, except in life-threatening maternal disease without a therapeutic alternative.

Isavuconazole

Isavuconazole is a new investigational azole with broad-spectrum and large coverage of both yeasts and moulds, including Mucorales. It is currently in Phase III of clinical development. To our knowledge, no data regarding isavuconazole and pregnancy have been reported.

Echinocandins

Echinocandins inhibit the 1,3-β-D-glucan synthase involved in fungal wall synthesis. They display an excellent tolerance profile, and a broad fungal spectrum, including yeasts such as Candida spp. and Aspergillus spp., but not Cryptococcus spp. or moulds like Mucorales and Fusarium spp.

What was known?

Caspofungin was approved in January 2001 by the FDA and in October 2001 by the EMA. It crosses the placenta of rats and rabbits and was shown to be embryotoxic and teratogenic in both at the recommended human dose (reduction of litter size, ossification and rib malformations).43 It is not known if it crosses the human placenta. Its molecular weight and extensive plasma binding could limit the amount of crossing, but this could be counterbalanced by the long half-life of the molecule (9–11 h).44 No case of caspofungin exposure during pregnancy has been reported.

What is new?

Two new echinocandins have been commercialized within the last 10 years.

The FDA and the EMA approved micafungin in March 2005 and April 2008, respectively, and anidulafungin in February 2006 and September 2010, respectively. Micafungin crosses the placenta and was shown to be embryotoxic and teratogenic in rabbits (visceral abnormalities and abortions at the equivalent of 4 times the recommended human dose).44 Anidulafungin crosses the placenta of pregnant rats and was shown to be possibly teratogenic in rodents (skeletal abnormalities reported at the equivalent of 2 times the recommended human dose, but in the range of a historical control database). It was associated with reduced fetal weight in pregnant rabbits at the equivalent of 4 times the recommended human dose.45

Whether either drug transfers across the human placenta remains unknown. High molecular weight (around 1100) and extensive plasma binding could limit the amount of crossing, but this could be counterbalanced by the long half-life (16–50 h).21 There are no available data on the use of these drugs in pregnancy.

Key points

All echinocandins are classified as pregnancy category C agents; embryotoxic and teratogenic effects have been reported in rodents and rabbits. Human data are still non-existent in 2014, and these drugs are not considered safe during pregnancy.

Flucytosine

Flucytosine was originally developed as an antimetabolite. It is also converted in fungal cells into fluorouracil, which interferes with both DNA and protein synthesis. Its antifungal spectrum is limited to yeasts (Candida spp., Cryptococcus spp.). Side effects include bone marrow, liver and gastrointestinal tract toxicities; they are mostly related to the small amount (<5%) of flucytosine converted into fluorouracil during intravenous infusion or in the gastrointestinal tract upon ingestion.46

What was known?

Flucytosine has been shown to be teratogenic in rats at the equivalent of 0.27–4.7 times the recommended human dose (bone and craniofacial malformations).47 Fluorouracil crosses the human placenta and achieves high concentrations in amniotic fluid and cord blood. It has been shown to be teratogenic and embryotoxic in rodents given the equivalent of human doses, but not in monkeys.47 Structural abnormalities have been reported in aborted fetuses exposed in the first trimester, indicating its use during this period.21 No increased adverse effect was noted thereafter. Flucytosine is classified as category C by the FDA. Seven case reports have been published describing good materno-fetal outcome following administration during the first (n = 1), second (n = 2) and third (n = 4) trimesters.64,48,49

What is new?

To our knowledge, no new report of pregnancy exposure has been published over the last 10 years. International recommendations, however, have been published suggesting the use of flucytosine in selected situations, detailed below.50

Key points

Flucytosine is classified as category C by the FDA. Limited case reports did not evidence adverse outcome after flucytosine exposure during the second and third trimesters. Data are lacking.
to study further its fetal toxicity and it should not be considered in pregnancy, except after the first trimester in life-threatening maternal infections where the benefits of adding flucytosine may justify the risk.

**Systemic polyenes**

Polyenes are among the oldest antifungal drugs. They bind to ergosterol, forming transmembrane pores leading to ionic leakage and fungal death.

Amphotericin B displays the broadest antifungal spectrum, including most yeasts, molds including Mucorales and dimorphic fungi. Lipid formulations were later developed to limit amphotericin B nephrotoxicity: liposomal, colloidal dispersion and lipid complex forms. A lipid complex form of amphotericin B was approved by the FDA in 1997 and by the EMA 1 year later. A liposomal colloidal dispersion form was approved by the FDA in 1996.

**What was known?**

Amphotericin B is the safest systemic antifungal drug in pregnancy. Maternal nephrotoxicity is reported to be similar to that of non-pregnant patients. 1 Amphotericin B crosses the placenta and achieves therapeutic concentrations in the fetal circulation, with cord blood:maternal serum ratios ranging from 0.38 to 1.51,52 No teratogenicity has been shown in rodents or rabbits at 10 times the recommended human dose, even during the first trimester.21,53–55 The safety of lipid formulations was, however, poorly evaluated.6

**What is new?**

Case reports and series have provided further insight into the safety and efficacy of liposomal amphotericin B in pregnancy. Mueller et al.56 retrospectively compared liposomal amphotericin B and sodium stibogluconate in 39 Sudanese pregnant women with visceral leishmaniasis. First- or second-trimester abortion was reported in 13/23 (57%) women receiving sodium stibogluconate versus 0/16 in the liposomal amphotericin B group. No fetal malformations were reported. Pagliano et al.57 and Figueirô-Filho et al.58 additionally reported five and four cases of visceral leishmaniasis treated with liposomal amphotericin B during pregnancy (median term of 11 ± 2 and 28 ± 7 weeks of gestation, respectively). All had good maternal and fetal/neonatal outcome.

**Key points**

Amphotericin B is classified as category B by the FDA. It is considered as the safest antifungal drug in pregnancy and is a major tool in the fungal armamentarium in this setting. Liposomal amphotericin B should also be considered safe in pregnancy. Data regarding other lipidic derivatives remain scarce and they should be used only in case of unavailability of other polyenes.

**Terbinafine**

Terbinafine is an allyamine available as topical and oral preparations. It acts by selectively inhibiting the fungal squalene epoxidase, which increases squalene to toxic levels, thus killing fungal cells. It is indicated for the treatment of dermatophytic skin infections, onychomycosis and other cutaneous dermatophytoses, including chromomycosis and mycetoma, which are usually not therapeutic emergencies during pregnancy.

**What was known?**

Oral reproduction studies did not evidence any embryo-fetotoxicity in rabbits and rats administered up to 23 times the maximum recommended human dose.21 Whether or not terbinafine crosses the human placenta is unknown and human oral exposure during pregnancy has never been reported. Although it is classified as pregnancy category B, oral prescription should be postponed until after delivery. Breastfeeding should also be avoided, given terbinafine’s active excretion in milk.59 In contrast, topical terbinafine displays minimal absorption and can be prescribed in pregnancy.

**What is new?**

No new data have arisen regarding the use of terbinafine during pregnancy.

**Key points**

Terbinafine is classified as category B by the FDA. It was not shown to be toxic in animal pregnancies, but human data are not available, hence hampering its systemic use in pregnancy. In contrast, topical terbinafine, which has limited absorption ability, can be prescribed.

**Griseofulvin**

Griseofulvin is an orally administered fungistatic drug that acts by altering DNA replication thereby blocking fungal mitosis. It is indicated in dermatophytoses and classified as category C by the FDA.39,60

**What was known?**

Griseofulvin crosses the placenta61 and was shown to be tumorigenic, embryotoxic and teratogenic in rodents at 3–45 times the recommended human dose.21 Data on human exposure during pregnancy are scarce. An FDA report suggested a possible association between griseofulvin prescription and conjoined twins that was not confirmed later.62

**What is new?**

A Hungarian retrospective study based on the Hungarian case–control cohort compared 38151 normal pregnancies and 22843 pregnancies with birth defects in relation to their exposure to griseofulvin (reported in 7 and 21 cases, respectively).63 It did not appear to be associated with any birth defect or with any excess of conjoined twins.62

**Key points**

Griseofulvin is classified as category C by the FDA. It is carcinogenic, embryotoxic and teratogenic in rodents. Human data are too limited to allow its use in pregnancy, especially in the first trimester.

**Topical drugs**

**Topical azoles**

Topical azoles include bifonazole, clotrimazole, fenticonazole, isoconazole, ketoconazole, omoconazole, oxiconazole, sertaconazole, tioconazole, miconazole and econazole. They are indicated for superficial fungal infections involving the skin (Candida sp.
Malassezia furfur, dermatophytes), and oral and vulvo-vaginal candidiasis.

**What was known?** Topical azoles are not or are minimally absorbed and hence are allowed at any stage of pregnancy.

**What is new?** A miconazole muco-adhesive tablet received EMA and FDA approval in June 2008 and April 2010, respectively. The FDA has assigned miconazole, irrespective of its galenic formulation, to pregnancy category C. Like other topical azoles, animal studies did not evidence embryo–fetotoxicity or teratogenicity with topical miconazole. No specific study has been performed in pregnancy, and miconazole should only be used in this setting in the absence of an alternative and if benefits outweigh risk.6,21

Miconazole cream was also evaluated in two studies from the Hungarian Case–Control Surveillance of Congenital Abnormalities, which compiled 22,843 newborns/fetuses with congenital abnormalities and 38,151 control newborns from 1980 to 1996. Treatment with topical miconazole during the first trimester did not increase the risk of congenital abnormalities (OR 0.9, range 0.6–1.6),66 but combined vaginal metronidazole and miconazole therapy may be associated with a slight increase in polydactily or syndactyly (OR 1.2, range 1.0–1.3).5

**Nystatin**

**What was known?** Nystatin is poorly absorbed orally, if at all. No animal data are available for this drug. Nystatin is classified as category A by the FDA in pregnancy.39

**What is new?** Czeizel et al.65 investigated the teratogenicity of oral nystatin during pregnancy. In this population-based case–control study, treatment with oral nystatin during pregnancy was identified in 249 of >50,000 pregnant women. It was associated with a slightly increased risk of congenital abnormalities compared with unexposed women (OR 1.2, range 1.0–1.6). The authors identified a possible association between exposure to oral nystatin and hypospadias (OR 1.94, range 1.22–3.09) that requires further confirmation.66

**Key points** Nystatin is classified as category A by the FDA. It is poorly absorbed and for many years was considered safe during pregnancy. However, recent Hungarian data raise the possibility of a slightly increased risk of hypospadias in exposed fetuses. Accordingly it may be prudent to avoid use during the critical period for this malformation (8–14 weeks of gestation).

**Terbinafine**

Terbinafine is detailed above.

**Ciclopiroxolamine**

Ciclopiroxolamine is only used topically and displays poor systemic absorption. It is classified as category B by the FDA and may be used in pregnancy if the benefit justifies the potential risk to the fetus.67,68

**Amorolfine**

Amorolfine is a morpholine derivative that acts by inhibition of the fungal ergosterol biosynthesis, leading to membrane permeability and disruption of key fungal metabolic processes. Amorolfine is used as a nail lacquer in onychomycosis. This drug presents with poor systemic absorption and it was not shown to be deleterious in animal pregnancies.21 Systemic absorption is considered very low, if it occurs at all. Amorolfine may hence be used in pregnancy.

**Potassium iodide**

Potassium iodide is still used in some geographical areas for the treatment of cutaneous sporotrichosis or basidibolosis because of its efficacy, safety and low cost. Iodides readily cross the placenta and their use has been associated with fetal goitre development with some cases of tracheal compression and death; alternatively, other authors have reported fetal exposure during the third trimester without deleterious materno-fetal consequence.69–71

**Key points for topical antifungal drugs** Topical antifungals all display limited if any systemic absorption, and they may be used in pregnancy, except for potassium iodide, which was shown to be associated with fetal goitre.

**Updated therapeutic recommendations in pregnant women**

Updated available recommendations regarding the main systemic fungal infections are summarized in Table 3. Amphotericin B and its lipid derivatives are considered the cornerstone of treatment in any invasive fungal infection during pregnancy. Some experts like Bercovitch et al.16 additionally suggest that fluconazole could be considered after the first trimester in the absence of an alternative agent.

Superficial infections during pregnancy require topical treatment, which can be prescribed throughout pregnancy, including topical azoles. Superficial fungal infections requiring systemic treatment, like dermatophytic onychomycosis, chromomycosis and mycetoma, should be treated after delivery.

**Gaps of knowledge and future prospects**

The need for precise knowledge regarding antifungals in pregnant women is greater than ever before. A rising number of immunocompromised patients experience pregnancy. Their vulnerability towards fungal infections is higher than that of the general population or other pregnant women, and exacerbates the need for precise and accurate data regarding the use of antifungal drugs in pregnancy. More than 4000 pregnancies have already been reported worldwide in solid-organ-transplanted women.72 Tailored immunosuppressive protocols have also helped young women with auto-immune disorders both protect their fertility and better control their underlying disease, and hence undergo a pregnancy. In addition, emerging fungal infections, as exemplified by the Cryptococcus gattii North American outbreak, have recently been reported outside their classical geographical areas; they have the potential to affect immunocompetent pregnant women from previously unaffected areas.13

Yet this update illustrates the slow progress made in the field of antifungal use in pregnancy. Where do we stand 10 years after the latest review? Studies have further established the teratogenic effect of high-dose fluconazole during the first trimester, and yet
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Practice guidelines</th>
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<th>Alternative proposition</th>
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have provided considerable reassuring data regarding its use at single and low dose in this key period. Studies have also provided additional safety data on lipid derivatives of amphotericin B.

However, major continuing gaps remain to be filled. We have experienced in the last 10 years a large expansion of the antifungal armamentarium, with the rise of new drugs exhibiting an excellent tolerance profile and efficacy and a new activity spectrum. Despite these advances, amphotericin B deoxycholate, one of the oldest antifungals and for sure the one displaying the worst tolerance profile, remains in 2014 the pivotal antifungal drug in pregnant women. Fetal toxicity indeed remains the major therapeutic concern, above potential maternal toxicity. Alternatives are almost non-existent. Whereas some experts consider the use of fluconazole in very selected situations after the first trimester, the safety of long-term exposure to fluconazole beyond this period has still not been assessed. Posaconazole and echinocandins have never been evaluated in pregnant women, and should therefore not be used. Because only scant pharmacokinetics and tolerance data are available, careful pharmacovigilance and reporting of any antifungal prescription during pregnancy is mandatory to improve our knowledge on drug safety and efficacy during pregnancy. Meanwhile, cautious multidisciplinary evaluation of the maternal–fetal risks and benefits should guide a personalized and expert antifungal prescription.

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