Overview of Antifungals in Pregnancy

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Learning Objectives

At the end of this session, learners should be able to:

- Identify two fetal risks associated with systemic azoles in pregnant patients.
- Identify an appropriate indication where systemic fluconazole is appropriate in pregnant patients.
- Recognize a systemic antifungal drug of choice for invasive candidiasis in pregnant patients.
- Recall the preferred topical antifungal therapy class for vulvovaginal candidiasis in pregnant patients according to the 2021 CDC Sexually Transmitted Infections Treatment Guidelines.

Outline

- Pregnancy risk labeling
- Antifungal medications
  - Antifungal medication review
  - Appropriate indications of use in pregnancy
  - Fetal risks
- Invasive candidiasis
  - Background
  - Preferred therapy options in pregnancy
- Vulvovaginal candidiasis
  - Background
  - Preferred therapy options in pregnancy

Abbreviation Key

- AmB: amphotericin B
- ABX: antibiotics
- ADR: adverse drug reaction
- BSI: bloodstream infection
- CI: confidence interval
- CX: culture
- CDC: Centers for Disease Control and Prevention
- FDA: Food and Drug Administration
- HIV: human immunodeficiency virus
- HR: hazard ratio
- ICU: intensive care unit
- IDSA: Infectious Disease Society of America
- Infx: infection
- NVE: native valve endocarditis
- OR: odds ratio
- PD: pharmacodynamics
- PK: pharmacokinetics
- PLLR: The Prescription and Lactation Labeling Rule
- PVE: prosthetic valve endocarditis
- VVC: vulvovaginal candidiasis

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Pregnancy Risk Labeling[1]

- Pregnancy letter categories (A, B, C, D, and X) were eliminated in 2015
- The Prescription and Lactation Labeling Rule (PLLR) was issued to create clear recommendations for providers to make individualized pregnancy prescribing decisions that are safe and effective
- The PLLR uses narratives summaries of risk during pregnancy including supporting data to help guide individualized prescribing decisions

Antifungal Medications in Pregnancy

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Background[2]

- Antifungal medications are used to treat and prevent fungal infections during pregnancy
- Antifungal use in pregnancy is not commonly encountered in practice
- Limited data exists on optimal antifungal regimens and dosing in pregnancy
- Antifungals often have many side effects that require a risk versus benefit discussion

Systemic Antifungal Review[2]

Medication	Medication Class	Briggs Drugs in Pregnancy and Lactation: Pregnancy Recommendation	Crosses the Placenta?	Fetal Harm	Used in Pregnancy?	Common Indications
Amphotericin B (AmB) & liposomal AmB[3]	Polyene antifungal	Compatible	Yes	No teratogenicity reported	**Yes, considered safest systemic antifungal in pregnancy**	- Febrile neutropenia, if presumed fungal infection - Cryptococcal meningitis in HIV - Visceral leishmaniasis - Infection due to Aspergillus species, Candida species, or Cryptococcus species
Ketoconazole[4,5]	Azole antifungal	Limited human data—animal data suggest risk	Unknown	Embryotoxic & teratogenic: syndactyly & oligodactyly	**May be considered as an alternative agent**	- Cushing disease - Systemic fungal infection: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis

Systemic Antifungal Review[2]

Medication	Medication Class	Briggs Drugs in Pregnancy and Lactation: Pregnancy Recommendation	Crosses the Placenta?	Fetal Harm	Used in Pregnancy?	Common Indications
Voriconazole[6, 7]	Azole antifungal	Limited human data–animal data suggest risk	Unknown	Teratogenic in animals: cleft palate, hydronephrosis, reduced ossification, supernumerary ribs	**No – contraindicated (unless life-threatening infx with no alternatives)**	- Infection due to Aspergillus, Candida, Blastomyces, Coccidioides, Histoplasma - Cryptococcal meningitis - Neutropenic fever
Posaconazole[8, 9]	Azole antifungal	No human data–animal data suggest risk	Unknown	Embryotoxic & teratogenic in animals: skeletal malformations, rib abnormalities	**Should not be considered unless life-threatening infx**	- Infection due to Aspergillus, Candida, Histoplasma, Mucorales - Cryptococcal meningitis

Systemic Antifungal Review[2]

Medication	Medication Class	Briggs Drugs in Pregnancy and Lactation: Pregnancy Recommendation	Crosses the Placenta?	Fetal Harm	Used in Pregnancy?	Common Indications
Fluconazole[10,11]	Azole antifungal	Human data suggests risk (≥400 mg/day)	Likely	Embryo-fetotoxic and teratogenic	**Avoid during first trimester, may be used in limited situations where alternative agents are not appropriate**	- Vaginal candidiasis - Invasive candidiasis - Secondary prophylaxis or chronic maintenance for esophageal, oropharyngeal, or vaginal candidiasis - Cryptococcal meningitis
Itraconazole[12, 13]	Azole antifungal	Human data suggest low risk	Likely	Embryotoxic and teratogenic in rodents	**Avoid during first trimester, contraindicated for treatment of onychomycosis during pregnancy**	- Invasive fungal infections including Aspergillosis

Systemic Antifungal Review[2]

Medication	Medication Class	Briggs Drugs in Pregnancy and Lactation: Pregnancy Recommendation	Crosses the Placenta?	Fetal Harm	Used in Pregnancy?	Common Indications
Caspofungin[14, 15]	Echinocandins	No human data–animal data suggest risk	Unknown	Embryotoxic & teratogenic in animals: reduced ossification, rib malformations	**Not considered safe**	- Infections due to Aspergillus, Candida - Neutropenic fever
Micafungin[16, 17]	Echinocandins	No human data–animal data suggest moderate risk	Unknown	Embryotoxic & teratogenic in animals: visceral abnormalities, abortions	**Not considered safe**	- Infections due to Aspergillus, Candida - Neutropenic fever

Systemic Antifungal Review[2]

Medication	Medication Class	Briggs Drugs in Pregnancy and Lactation: Pregnancy Recommendation	Crosses the Placenta?	Fetal Harm	Used in Pregnancy?	Common Indications
Anidulafungin [18, 19]	Echinocandins	No human data– animal data suggest low risk	Unknown	Possibly teratogenic in animals: skeletal abnormalities, reduced weight	**Not considered safe**	- Infection due to *Aspergillus, Candida* - Neutropenic fever
Flucytosine[20, 21]	Antimetabolite	Contraindicated – 1st trimester	Yes	Teratogenic: structural abnormalities, cleft lip and palate (in animals)	**Should not be used unless life-threatening infx**	- Candidiasis - Cryptococcal meningitis

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Systemic Antifungal Review[2]

Medication	Medication Class	Briggs Drugs in Pregnancy and Lactation: Pregnancy Recommendation	Crosses the Placenta?	Fetal Harm	Used in Pregnancy?	Common Indications
Terbinafine[22, 23]	Squalene epoxidase inhibitors	No human data—animal data suggest low risk	Unknown	No data to support teratogenicity	**Not recommended**	- Systemic therapy for onychomycosis or tinea capitis
Griseofulvin[24, 25]	Fungal cell mitosis inhibitor	Limited human data – potential toxicity	Yes	Embryotoxic & teratogenic, tumorigenic, possible conjoined twins	**No - Contraindicated, if must be given avoid during first trimester**	- Treatment of dermatophyte infections of skin, hair, and nails

Systemic Antifungal Review[2-25]

Safe in Pregnancy	Used if Benefit Outweighs Risk	Contraindicated
Amphotericin B	Ketoconazole	Voriconazole
	Posaconazole	Caspofungin
	Flucytosine	Micafungin
	Fluconazole	Anidulafungin
	Itraconazole	Terbinafine
		Griseofulvin

Fluconazole Fetal Risks[2,22]

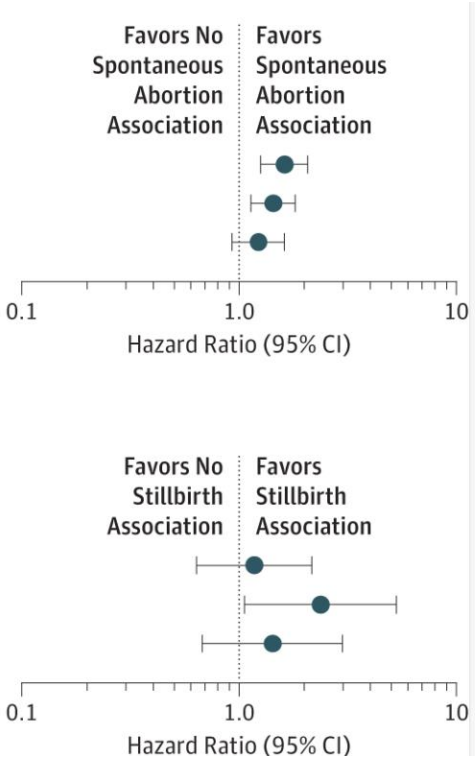
- Data suggests fetal risks associated with the **first trimester** exposure during pregnancy
- Previously, the risk of abnormalities was associated with doses of oral fluconazole of ≥400 mg/day
- New data has emerged that suggests low-dose fluconazole of ≤150 mg as a single dose or repeated doses during the first trimester may increase the risk of spontaneous abortions and malformations

Fluconazole Epidemiologic Studies[26]

Study Title	Published Year	Design	Objective	Results	Recommendations
Associations between low- and high-dose oral fluconazole and pregnancy outcomes[26]	2019	3 nested case–control studies	To assess the effect of exposure to low and high doses of fluconazole during pregnancy on the occurrence of spontaneous abortions, major congenital malformations, and stillbirths.	Increased risk of spontaneous abortion in those with oral fluconazole during early pregnancy compared with no exposure (adjusted OR to low-dose treatment 2.23, 95% CI: 1.96-2.54)	- Any exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion - Doses > 150 mg may increase the risk of cardiac septal closure anomalies

Fluconazole Epidemiologic Studies[27]

Study Title	Published Year	Design	Objective	Results	Recommendations
Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth[27]	2016	Cohort Study	To study the association between oral fluconazole exposure during pregnancy and the risk of spontaneous abortion and stillbirth.	Significant increased risk of spontaneous abortion associated with fluconazole exposure in pregnancy (HR 1.48, 95% CI: 1.23-1.77)	• Advise cautious prescribing of fluconazole in pregnancy



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Fluconazole Epidemiologic Studies[28]

Study Title	Published Year	Design	Objective	Results	Recommendations
Risk of congenital malformations and miscarriages following maternal use of oral fluconazole during the first trimester of pregnancy	2024	Systematic review and meta-analysis	To assess the association between oral fluconazole during the first trimester and major congenital malformations (MCM), minor malformations and miscarriages.	Significant association between any fluconazole use during the first trimester and overall MCM (OR 1.18, 95% CI: 1.08-1.29) but not for adjusted estimates (OR 1.02, 95% CI: 0.98-1.07) Significant association between fluconazole use and miscarriages (OR 1.60, 95% CI 1.06-2.42)	• Potential association between MCM and fluconazole use • Association between fluconazole use and miscarriages

Fluconazole Epidemiologic Studies[29]

Trial	The safety of oral fluconazole during the first trimester of pregnancy: a systematic review and meta-analysis				
Objective	Published Year	Design	Intervention	Results	Recommendations
Evaluate pregnancy outcomes associated with exposure to oral fluconazole during the 1st trimester of pregnancy	2019	Systemic review and meta-analysis	Six studies comparing fluconazole-exposed and fluconazole-unexposed neonates during 1st trimester of pregnancy	Combined OR of congenital malformation risk: 1.09 (P = 0.072)	• Use of oral fluconazole during the first trimester of pregnancy is associated with an increased risk of heart malformations and spontaneous abortion
			Four studies comparing fluconazole-exposed and fluconazole-unexposed pregnancies	Combined OR of heart malformations: 1.31 (P = 0.003)	
			Three studies comparing fluconazole-exposed and fluconazole-unexposed pregnancies	Combined OR of spontaneous abortion: 1.99 (P = < 0.001)	

Reported Systemic Azoles Fetal Risks[22, 23, 27, 30-32]

- Brachycephaly
- Abnormal looking face
- Abnormal calvarial development
- Cleft palate
- Femoral bowing
- Thin ribs and long bones
- Muscle weakness and joint deformities
- Arthrogryposis
- Congenital heart disease
- Spontaneous abortion

Assessment Question #1

Which two fetal risks have been associated with the use of systemic azoles in pregnancy?

a. Cleft palate & neonatal abstinence syndrome
b. Tetralogy of Fallot & cleft palate
c. Abnormal calvarial development & enamel hypoplasia
d. Patent foramen ovale & spina bifida

Systemic Azoles in Pregnancy[33]

The 2016 IDSA Guidelines for the Treatment of Coccidioidomycosis acknowledges pregnancy as an "at-risk" population

	Initial nonmeningeal coccidioidal infection during 1st trimester	Initial coccidioidal meningitis during 1st trimester	Coccidioidal meningitis after the 1st trimester	Remission of nonmeningeal coccidioidal infection on antifungal therapy who become pregnant	Active coccidioidal meningitis on antifungal therapy at time of pregnancy
Preferred Treatment	IV AmB	Intrathecal AmB	Azole antifungal – fluconazole or itraconazole	Discontinue azole antifungal with clinical & serological monitoring to assess for reactivation	Stop azole antifungal for the 1st trimester, initiate intrathecal AmB, then resume azole antifungal during the 2nd trimester
Alternative Treatment	-No therapy with monitoring -Azole antifungal – fluconazole or itraconazole*			Discontinue azole antifungal & start IV AmB during the 1st trimester then change back to azole antifungal after the 1st trimester, particularly if re-activated	-Stop azole antifungal for the 1st trimester, initiate intrathecal AmB for the remainder of pregnancy -Continue azole antifungal throughout gestation* -Stop azole antifungal during 1st trimester & monitor without treatment, restart during 2nd trimester

*must educate the mother on the fetal risks associated with use

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Systemic Azoles in Pregnancy[34, 35]

- The 2021 Center for Disease Control and Prevention (CDC) Guidelines for the Treatment of Sexually Transmitted Infections recommends:
  - Against the use of a single dose of 150 mg oral fluconazole for the treatment of vulvovaginal candidiasis (VVC)
- The 2016 Infectious Disease Society of America (IDSA) Guidelines for the Treatment of Candidiasis recommends:
  - Avoid azole antifungals, especially during the 1st trimester
  - Voriconazole is contraindicated in pregnancy

Systemic Azoles in Pregnancy[36]

- The 2025 Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommends:
  - IV AmB for invasive or refractory esophageal *Candida* infections in place of fluconazole during the 1st trimester
  - Secondary prophylaxis or chronic maintenance fluconazole therapy should not be initiated during pregnancy for candidiasis

Systemic Antifungal Key Points[2]

- Amphotericin is considered the safest systemic antifungal in pregnancy, therefore is generally the drug of choice[37]
- Systemic azole antifungals should generally be avoided, especially during the 1st trimester of pregnancy due to the risk of congenital malformations and spontaneous abortion[31]
  - Fluconazole or itraconazole may be used for the treatment of coccidioidomycosis

Topical Antifungal Key Points[2]

- When used topically, antifungals have limited systemic absorption
- Indications: superficial fungal skin infections, oral, and vulvovaginal candidiasis
- Topical antifungal agents include: terbinafine, ciclopirox, amorolfine, nystatin, topical azoles
- If benefits outweigh the risk, topical antifungals may be used in pregnancy

List of Pregnancy Exposure Registry[38]

- List of research studies that collect health information during pregnancy
  - Exposure to medications and vaccines
  - FDA does not endorse any registry
- Link: List of Pregnancy Exposure Registries | FDA

Medicine	Medical Condition	Registry	How to contact
Abilify (aripiprazole)	Mental Health Disorders	National Pregnancy Registry for Atypical Antipsychotics	Center for Women's Mental Health at Massachusetts General Hospital **Website:** https://womensmentalhealth.org/research/pregnancyregistry/ Phone: 1-866-961-2388

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Assessment Question #2

SM is a 28-year-old female who is currently 17 weeks pregnant (2nd trimester). She was recently diagnosed with active coccidioidal meningitis, what is the preferred treatment at this point in her pregnancy?

a. Voriconazole
b. Intrathecal amphotericin B
c. Fluconazole
d. No therapy is indicated, monitor symptoms

Invasive Candidiasis

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Background[34, 39]

- *Candida* infections major cause of morbidity and mortality
  - Increasing cause of invasive infections in ICU
- Candidemia one of the most common healthcare-associated BSIs
  - Non-albicans species represent 50% of relevant isolates
- Clinical manifestations
  - Candidemia
  - Intra-amniotic infections
  - Endocarditis
  - Intra-abdominal infections
  - Opportunistic infections

Risk Factors[34]

- *Candida* colonization
- Exposure to broad spectrum antibiotics
- Corticosteroid use
- Recent major surgery
  - Especially abdominal procedures
- Necrotizing pancreatitis
- Dialysis
- Parenteral nutrition

Diagnosis of Invasive Candidiasis[34, 40]

- Culture-based
  - Blood cultures
    - Overall sensitivity ~50%
    - Slow turnaround time
  - Tissue and fluid cultures
    - Poor sensitivity (< 50%)
    - Slow turnaround time
- Nonculture-based
  - Beta-D-glucan detection
    - FDA approved as adjunct to CX
  - Polymerase chain reaction
  - Antigen/antibody detection
    - Combined mannan/antimannan antibody assay

Guideline Recommendations by the IDSA[34]

The Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA states

- Amphotericin B is the treatment of choice for invasive candidiasis in pregnant women
- Fluconazole, itraconazole, posaconazole, and isavuconazole should be avoided in pregnancy, and voriconazole and flucytosine are contraindicated

Candidemia[34, 41, 42]

- No studies done in pregnant patients with candidemia
- Recommended therapy in pregnancy by the IDSA
  - AmB
- Duration
  - At least 2 weeks after clearance from blood CXs

Empiric Therapy in ICU Patients[34]

- 1/3 to 2/3 of all episodes of candidemia occur in ICU
- Estimated mortality 30-40%
  - Prompt and appropriate antifungal therapy often delayed
- Consider in patients with risk factors for invasive candidiasis
  - Start ASAP if risk factors + septic shock
- Recommended therapy in pregnancy: AmB

Candida Intra-amniotic Infections[39, 43]

- Uncommon but severe
  - Risk for neonatal infx & neurodevelopmental impairment
  - High neonatal mortality rate
- Case report
  - *Candida albicans* recovered from cervicovaginal sample
  - Initial treatment: ABX + fluconazole
    - Persistent yeast on gram stain
    - Start AmB 4mg/kg daily
  - Resulted in healthy newborn
- No consensus on first-line treatment

Candida Endocarditis and Intra-abdominal Infections[34]

- No literature available in pregnant patients
- Recommendations by the IDSA
  - Endocarditis
    - NVE: AmB
    - PVE: same treatment as for NVE
  - Intra-abdominal infections
    - Choice of therapy: same as for candidemia
  - Overall recommendation in pregnancy: AmB

Opportunistic Infections in Pregnancy[44]

- Special considerations for candidiasis based on the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV
  - Recommends substitution of fluconazole with AmB for invasive or refractory esophageal *Candida* infections in pregnancy (strong recommendation; expert opinion)
  - Human data on echinocandins unavailable
  - Monitor infant for ADRs

Overall Drug of Choice in Pregnancy[41]

- Amphotericin B
  - Liposomal formulation preferred
    - Liposomes prolong time in plasma
    - Significantly less nephrotoxic
  - Optimal dosing in pregnancy unknown
    - Case studies report using AmB 3-7 mg/kg
    - Using ideal body weight may result in less nephrotoxicity

Assessment Question #3

A 32-year-old woman in her first trimester of pregnancy presents with fevers, abdominal pain, and nausea/vomiting. Pertinent labs include WBC 22, procalcitonin of 10, and AST > 1,000. Imaging shows a small fluid collection in the abdomen with concern for an intra-abdominal abscess. What is the best treatment for this patient considering the Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA?

a. Micafungin
b. Flucytosine
c. Fluconazole
d. Amphotericin B

Vulvovaginal Candidiasis

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Background[45, 46]

- Common condition that affects more than 75% of all women
  - often occurring during reproductive ages
- Result of fungal overgrowth
  - primarily *Candida albicans* (~80-90%)
- Recurrence is common
  - can be a result of sexual activity, diet, antibiotic use, and genetic susceptibility

Background[45, 46]

- Symptoms include
  - vaginal and vulvar burning, itching, irritation
  - increased vaginal discharge
  - Some patients may be asymptomatic
- Diagnosis
  - based off clinical symptoms
  - diagnostic studies such as microscopy and pH testing

Background[47]

- Colonization of *Candida* species can increase to 30% during pregnancy
- Increased estrogen levels can lead to increased colonization
  - Facilitates adherence of yeast cells to epithelial cells and promotes virulence factors
  - Increased vaginal mucosal glycogen provides a nutrient source for *Candida albicans*
- Immune system alterations and hormone changes weakens the local genital tract response to *Candida* species

Treatment Options[48, 49]

Per the 2021 CDC Sexually Transmitted Infections Treatment Guidelines

- Topical (intravaginal) azole therapies are recommended as first line agents for pregnant patients
- Duration of therapy is 7 days
- Standard treatment option in non-pregnant patients is a single dose of oral fluconazole 150mg
  - Not recommended in pregnancy due to the potential fetal risks

Treatment Options – OTC[48, 49]

Drug	Dose	Duration
Clotrimazole 1% cream	5g intravaginally daily	7 days
Miconazole 2% cream	5g intravaginally daily	7 days
Miconazole 100mg vaginal suppository	One suppository daily	7 days

Treatment Options – RX[48, 49]

Drug	Dose	Duration
Terconazole 0.4% cream	5g intravaginally daily	7 days

Alternative Agents[50]

Study Title	Published Year	Design	Objective	Results
Oral Probiotics to Prevent Recurrent Vulvovaginal Infections During Pregnancy[49]	2025	Multicenter Double-Blind, Randomized, Placebo-Controlled Trial	To investigate effectiveness of oral probiotics in secondary prevention of vulvovaginal infections in pregnant women	Use of oral probiotics as secondary prevention did not reduce vulvovaginal infections after initial eradication compared to placebo. Vulvovaginal infection rates were 67% probiotic vs 48% placebo (P = 0.19)

Alternative Agents[51]

Study Title	Published Year	Design	Objective	Results
Efficacy of Oral Probiotic Supplementation in Preventing Vulvovaginal Infections During Pregnancy[50]	2024	Randomized and Placebo-Controlled Clinical Trial	To investigate efficacy of oral probiotic supplementation in preventing vulvovaginal infections in pregnant women	Vulvovaginal infection rate was not reduced with administration of oral probiotic rate. Vulvovaginal infection rate was ~30% in both groups [29% probiotic vs 27% placebo; (P = 0.80)]

Alternative Agent Recommendations

- Probiotics[50-52]
  - Limited efficacy data
  - No differences in neonatal effects
  - No evidence of fetal harm
- Boric acid[53]
  - Limited safety data available for humans
  - In animal studies, large amounts of boric acid led to fetal toxicities
  - Some reports of decreased birth weights in babies born to women exposed to boron in the water supply
  - Overall, not recommended for use in pregnant individuals

Novel Agents

Medication	Medication Class	Fetal Harm	Used in Pregnancy?	Common Indications	Unique Features
Oteseconazole (Vivjoa)[54,55]	Tetrazole antifungal	Yes, reported ocular abnormalities in animals	**No, contraindicated**	- Recurrent vulvovaginal candidiasis (FDA approved) - Fluconazole resistant Candida, patients with complicated drug regimens - Possible future uses in onychomycosis, oropharyngeal candidiasis	- More specific binding to fungal CYP51 (limiting interactions) - Long half-life - Minimal to no effect on QT prolongation
Ibrexafungerp (Brexafemme) [56, 57]	Triterpenoid Antifungal	Yes, reported in animal reproduction studies (ongoing data collection)	**No, contraindicated (BBW)**	- Vulvovaginal candidiasis, (alternative agent for acute infection) - Recurrent Vulvovaginal candidiasis	- Inhibits β-1,3-D-glucan synthase (alternative for azole-resistant infections) - Maintains activity in acidic vaginal environment

Assessment Question #4

MC is a 27 year old pregnant patient presenting to a follow up appointment. She has had increased vaginal irritation, discharge and burning. Which of the following would be the most appropriate treatment option for MC at this time according to the 2021 CDC Sexually Transmitted Infections Treatment Guidelines?

a. Oral fluconazole 150mg once
b. Terconazole 0.4% cream intravaginally for 4 days
c. Miconazole 100mg vaginal suppository intravaginally for 14 days
d. Clotrimazole 1% cream intravaginally for 7 days

Conclusion

- Pregnant patients often are not represented in many clinical trials therefore data is limited in this patient population
- Antifungal medications are treatment options for pregnant patients although not all agents within the class have the same safety profile
- Medication regimens should be tailored to patient specific factors, taking into consideration all risks and benefits

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