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REVIEW

Less common bacterial, fungal and viral infections: review of management in the pregnant patient

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Abstract

This review is a comprehensive summary of treatment options for pregnant patients with less common bacterial, fungal, and viral infections. It offers guidance to clinicians based on the most recently published evidence-based research and expert recommendations. A search of MEDLINE (inception to March 2021) and the CDC website was performed. Liposomal amphotericin B is the preferred therapy for cryptococcosis, histoplasmosis, oesophageal candidiasis, and coccidioidomycosis, especially during the first trimester due to teratogenic concerns with azole antifungals. For oral candidiasis, clotrimazole troches or miconazole mucoadhesive buccal tablets are recommended. A β-lactam antimicrobial is preferred over doxycycline for various manifestations of Lyme disease and the drug of choice for *Pneumocystis* pneumonia is trimethoprim/sulfamethoxazole. Acyclovir is the preferred antiviral for varicella zoster virus. Fluoroquinolones, macrolides, and aminoglycosides should be avoided if possible and there are alternate agents available for an effective treatment regimen. There is a scarcity of clinical data in pregnant patients with less common bacterial, fungal and viral infections. This population lacks definitive recommendations in many clinical practice guidelines. The key to optimizing therapy is a comprehensive review of the available evidence and a careful balance of risks and benefits before final treatment decisions.

Keywords: antibiotics, antifungals, antivirals, bacterial infection, fungal infection, pregnancy, teratogenicity, viral infection.

Citation

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Introduction

Pregnancy encompasses several physiological changes that may complicate the treatment of less common bacterial, fungal and viral infections. Immunological changes may lead to altered severity and susceptibility of disease.[1] Additionally, fluctuating hormone levels modify the interplay with the immune system such as progesterone suppressing a normal immune response.[1] Furthermore, there may be unintended sequelae to the fetus from untreated infections or the anti-infective agents used to treat infections. Management of infections in the pregnant patient should include careful consideration of efficacy and safety data weighed against clinical outcomes data. Pregnant patients are often excluded from clinical trials, which has resulted in scant data to make evidence-based decisions. This review is a compilation of the current evidence available on the management of less common bacterial (e.g. tuberculosis, Lyme disease), fungal (e.g. histoplasmosis), opportunistic (e.g. toxoplasmosis) and viral infections (e.g. varicella) in the pregnant patient. Antimicrobial safety data in pregnancy are reviewed in detail elsewhere and are only included as appropriate in this review.[2] The management of common bacterial and viral infections during pregnancy has been previously published.[3]

Methods

Data sources

A literature search of MEDLINE from 1950 to March 2021 was performed using the search terms "pregnancy" and each of

Table 1. Medications included on the WHO Essential Medications List for the treatment of less common bacterial, fungal, and viral infections in the pregnant patient.[4]

Disease state	Medications on the Essential List
Opportunistic infections	Amphotericin B (deoxycholate and liposomal), azithromycin, clindamycin, dapsone, flucytosine, fluconazole, pentamidine, primaquine, pyrimethamine, sulfadiazine, trimethoprim-sulfamethoxazole
Mycobacterial infections	Azithromycin, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampicin
Selected fungal infections	Amphotericin B (deoxycholate and liposomal), fluconazole, itraconazole, nystatin
Tickborne infections	Azithromycin, amoxicillin, cefotaxime, ceftriaxone, chloramphenicol, clindamycin, doxycycline, rifampicin
Selected viral infections	Aciclovir

the following: "*Pneumocystis* pneumonia", "toxoplasmosis", "toxoplasmic encephalitis", "cryptococcosis", "tuberculosis", "*Mycobacterium avium* complex", "candidiasis", "histoplasmosis", "coccidioidomycosis", "Lyme disease", "ehrlichiosis", "human granulocytic anaplasmosis", "human monocytic ehrlichiosis", "babesiosis", "Rocky Mountain spotted fever", "varicella zoster virus", "herpes zoster", and "cytomegalovirus". National and international clinical practice guidelines (where appropriate) and the CDC website were reviewed for current evidence-based recommendations. A list of medications on the WHO Essential Medications List that are used to treat the above infections are listed in Table 1.[4] Additional references were collected from bibliographies of noteworthy articles.

Opportunistic infections

Pneumocystis pneumonia

Cases of *Pneumocystis* pneumonia (PCP) during pregnancy are rare outside of people with HIV.[5,6] During pregnancy, the preferred therapy for PCP is trimethoprim/sulfamethoxazole (TMP-SXT; Table 2).[7] TMP-SXT is considered a first-line treatment due to its considerable benefit. However, there is a small risk of increased neural tube and other birth defects, particularly in the first trimester.[7–10] Folic acid supplementation can be given to restore the depleted stores caused by the folic acid inhibition of TMP-SXT. Studies have shown that folic acid supplementation of 6 mg/day may decrease the risk of congenital anomalies. Folic acid supplementation has also been associated with an increased risk of therapeutic failure and death.[8,11] Additionally, there are case reports of TMP-SXT prophylaxis failure with concomitant folic acid supplementation.[12] Based on these studies, high-dose folic acid supplementation should be limited to the first trimester during the teratogenic window.[7] Concerns related to neonatal death and kernicterus have previously been linked to TMP-SXT; however, currently, there are no data to support near-term exposure with these outcomes.[13,14] Adjunctive systemic steroids for the treatment of moderate-to-severe PCP should be used in pregnant patients as indicated for non-pregnant patients.[7] While alternatives typically recommended for nonpregnant patients may be used after carefully weighing the potential risks, the preferred alternative choice for mild-to-moderate disease is atovaquone based on lack of demonstrated toxicity.[7,15] Primaquine and dapsone-containing regimens should be avoided, if possible, due to the risk of severe haemolysis in glucose-6-phosphate dehydrogenase-deficient individuals. The preferred therapy for primary and secondary PCP prophylaxis is TMP-SXT. Due to the potential risks of TMP-SXT in the first trimester, inhaled pentamidine and oral atovaquone can be considered during this period for prophylaxis.[7]

Toxoplasmosis

The treatment of *Toxoplasma gondii* during pregnancy should be based on confirmed or suspected symptomatic disease and the risk of transmission to the fetus.[7] The estimated incidence of acute primary infection is 0.2 per 1000 pregnancies.[16] Patients suspected of having acquired *T. gondii* should be evaluated and managed with appropriate specialists to monitor and prevent transmission to the fetus. Pyrimethamine has been associated with birth defects in animals, but similar results have not been seen with human data. It should be considered safe to administer after the first trimester, especially if a fetal infection is documented or highly likely.[7,17] Sulfadiazine appears safe, although there is some concern with sulfa-containing agents, as discussed previously.[13,14] Spiramycin is typically used if a fetal infection is unlikely, especially in the first trimester.[7,17] Spiramycin should not be used to treat fetal toxoplasmosis because it does not cross the placenta well. It is primarily indicated for fetal prophylaxis and should be continued until delivery. Spiramycin is unavailable commercially in the United States but can be obtained through the Division of Anti-Infective Products of the US FDA (telephone 301-796-1400) after serologic confirmation of infection. In the case of fetal infection, pyrimethamine and sulfadiazine are recommended.[18]

For toxoplasmic encephalitis (TE), patients should be treated for at least 6 weeks and the preferred therapy is the same as in nonpregnant patients: pyrimethamine plus sulfadiazine plus leucovorin (Table 2).[7] This regimen should also prevent

Table 2. Preferred and alternative therapy for less common bacterial, fungal, and viral infections in the pregnant patient.

Disease state	Preferred therapy	Alternative therapy	Adverse effects/monitoring	Additional comments
Pneumocystis Pneumonia[7]	Severe: TMP-SXT 15–20 mg IV × 21 days (TMP/kg/day IV divided q6h or q8h); may transition to PO after clinical improvement	Severe: Pentamidine 4 mg/kg IV once daily infused over at least 60 minutes; may reduce the dose to 3 mg/kg IV once daily because of toxicities *or* Primaquine 30 mg (base) PO once daily + clindamycin (600 IV q6h or 900 mg q8h) or (450 mg PO q6h or 600 mg q8h) (last line)	TMP-SXT: Monitor CBC, potassium, renal function Dapsone: Monitor for jaundice, haemolysis, and blood dyscrasias, LFTs, CBC, reticulocyte counts; check for G6PD deficiency Primaquine: Monitor for haemolysis, CBC, check for G6PD deficiency Pentamidine: Monitor LFTs, renal function, blood glucose, potassium, calcium, platelets, ECG, blood pressure (hypotension)	If PaO_2 <70 mmHg at room air or alveolar–arterial O_2 gradient ≥35 mmHg, use adjunctive corticosteroids Prednisone doses: Day 1–4: 40 mg PO BID Day 6–10: 40 mg PO daily Day 11–21: 20 mg PO daily Consider 6 mg/day folic acid supplementation during the first trimester with TMP-SXT
	Mild–moderate: TMP-SXT 15–20 mg PO × 21 days (TMP/kg/day divided q6h or q8h)	Mild–moderate: Atovaquone 750 mg PO BID with food ("preferred" alternative) *or* Dapsone 100 mg PO daily + TMP 15 mg/kg/day PO (3 divided doses) *or* Primaquine 30 mg (base) PO daily + clindamycin PO (450 mg q6h or 600 mg q8h) (last line)		
Toxoplasmic encephalitis[7]	Pyrimethamine 200 mg PO once, followed by dose based on body weight: Body weight ≤60 kg: Pyrimethamine 50 mg PO daily plus sulfadiazine 1000 mg PO q6h plus leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID) Body weight >60 kg: Pyrimethamine 75 mg PO daily plus sulfadiazine 1500 mg PO q6h plus leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)	Pyrimethamine (leucovorin) plus clindamycin 600 mg IV or PO q6h (preferred alternative) *or* TMP-SXT (TMP 5 mg/kg) (IV or PO) BID *or* Atovaquone 1500 mg PO BID plus pyrimethamine plus leucovorin *or* Atovaquone 1500 mg PO BID plus sulfadiazine *or* Atovaquone 1500 mg PO BID *or* Pyrimethamine plus leucovorin plus azithromycin 900–1200 mg PO daily *or* Spiramycin (if fetal infection unlikely) 1 g (3 MU) PO TID	Pyrimethamine: Monitor CBC, LFTs, renal function Sulfadiazine: Monitor CBC and signs of severe blood disorders (e.g. dark urine, jaundice, purpura, etc.) TMP-SXT: Monitor CBC, potassium, renal function Spiramycin: Nausea, vomiting, diarrhoea, skin reactions	Treat for ≥ 6 weeks; longer duration if the clinical or radiologic disease is extensive or response is incomplete at 6 weeks After completion of acute therapy listed, all patients should be continued on chronic maintenance therapy All pregnant patients living with HIV with toxoplasmic encephalitis should be considered for immediate initiation of antiretroviral therapy

(Continued)

Table 2. (*Continued*)

Disease state	Preferred therapy	Alternative therapy	Adverse effects/monitoring	Additional comments
Toxoplasmic encephalitis[7] *(Cont)*				Spiramycin unavailable commercially in the United States (obtained through the US FDA – Division of Anti-Infective Products ; telephone 301-796-1400)
Cryptococcal meningitis[7,21]	Induction (≥2–4 weeks): Liposomal amphotericin B 3–4 mg/kg IV daily	Amphotericin B deoxycholate 0.7–1 IV mg/kg daily *or* Amphotericin B lipid complex 5 mg/kg IV daily *Flucytosine 25 mg/kg PO QID may be considered in addition to amphotericin in the second and third trimesters if the benefits outweigh the risks to the fetus	Amphotericin: Infusion reactions; monitor renal function, potassium, magnesium Fluconazole: Monitor LFTs, renal function, potassium Flucytosine: Bone marrow suppression, diarrhoea, rash, photosensitivity; monitor LFTs	Expert consultation is recommended for the timing of initiation of antiretroviral therapy for pregnant patients living with HIV with cryptococcal infections
	Consolidation (≥8 weeks): Liposomal amphotericin B 3–4 mg/kg IV daily throughout first trimester; after first trimester, may consider a transition to fluconazole 400 PO mg daily	Amphotericin B deoxycholate 0.7–1 mg/kg IV daily *or* Amphotericin B lipid complex 5 mg/kg IV daily throughout first trimester; after first trimester, may consider a transition to fluconazole 400 PO mg daily		
	Maintenance (to complete ≥1 year): Liposomal amphotericin B 3–4 mg/kg IV weekly throughout first trimester; after first trimester, may consider a transition to fluconazole 200 PO mg daily	Amphotericin B deoxycholate 0.7–1 mg/kg weekly *or* Amphotericin B lipid complex 5 mg/kg IV daily throughout first trimester; after first trimester, may consider a transition to fluconazole 200 PO mg daily		
Tuberculosis[24,29]	WHO: Rifampicin 10 mg/kg (typically 600 mg) PO daily		Rifampin: Monitor LFTs	In patients with peripheral neuropathy present, pyridoxine dose should be increased to 100 mg daily

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Table 2. (*Continued*)

Disease state	Preferred therapy	Alternative therapy	Adverse effects/monitoring	Additional comments
Tuberculosis[24,29] (*Cont*)	Isoniazid 5 mg/kg (typically 300 mg) PO daily Pyrazinamide 25 mg/kg PO daily Ethambutol 15 mg/kg PO daily IDSA: Rifampin 10 mg/kg (typically 600 mg) PO daily Isoniazid 5 mg/kg (typically 300 mg) PO daily Ethambutol – 40–55 kg: 800 mg PO daily 56–75 kg: 1200 mg PO daily 76–90 kg: 1600 mg PO daily (Based on estimated lean body weight. Optimal doses for obese patients are not established.)		Isoniazid: Peripheral neuropathy; monitor LFTs Ethambutol: Monitor visual acuity Pyrazinamide: Monitor LFTs	Avoid the use of fluoroquinolones and streptomycin if possible Rifampin associated with multiple drug–drug interactions; may cause an orange–red discoloration of secretions
Mycobacterium avium complex[7]	Azithromycin 500–600 mg PO daily plus ethambutol 15 mg/kg PO daily	Option to add rifabutin 300 PO mg daily	Azithromycin: Nausea, vomiting, abdominal pain, abnormal taste, and elevations in liver transaminase levels, QTc prolongation; monitor LFTs Rifabutin: Monitor LFTs	Avoid the use of fluoroquinolones if possible Rifabutin associated with multiple drug–drug interactions, may cause an orange–red discoloration of secretions
Oral and oesophageal candidiasis[50]	*Oral candidiasis* Clotrimazole troche 10 mg dissolved orally five times daily for 7–14 days *or* Miconazole buccal tablet 50 mg applied to upper gum once daily for 14 days	*Oral candidiasis* Nystatin oral suspension 400,000–600,000 units four times daily (swish and swallow)	Clotrimazole: Troche generally well tolerated Miconazole: Application site irritation Nystatin: Diarrhoea, nausea, vomiting, stomach pain	Minimal systemic absorption of all oral treatment options Miconazole buccal tablet should not be crushed Premedication with acetaminophen and diphenhydramine before amphotericin B

(*Continued*)

Table 2. (*Continued*)

Disease state	Preferred therapy	Alternative therapy	Adverse effects/monitoring	Additional comments
Oral and oesophageal candidiasis[50] *(Cont)*	*Oesophageal candidiasis* Amphotericin B deoxycholate 0.3–0.7 mg/kg IV daily for 14–21 days		Amphotericin B: Infusion reactions; monitor renal function, potassium, magnesium	Bolus IV fluids predose and postdose may reduce the risk of nephrotoxicity with amphotericin B
Histoplasmosis[51]	Liposomal amphotericin B IV 3–5 mg/kg IV daily for 4–6 weeks	Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily for 4–6 weeks	Amphotericin B: Infusion reactions; monitor renal function, potassium, magnesium	Premedication with acetaminophen and diphenhydramine before amphotericin B Bolus IV fluids predose and postdose may reduce the risk of nephrotoxicity with amphotericin B
Coccidioidomycosis[54,57,58]	Nonmeningeal disease -First trimester: Liposomal amphotericin B IV 3–5 mg/kg daily -Second or third trimester: Fluconazole 400–800 mg PO daily *or* Itraconazole 200 mg PO BID	Nonmeningeal disease -First trimester: No therapy with close monitoring -Second or third trimester: Liposomal amphotericin B 3–5 mg/kg IV daily	Amphotericin B IV: Infusion reactions; monitor renal function, potassium, magnesium Intrathecal amphotericin B: Headache, nausea, vomiting, neurotoxicity including ophthalmoplegia, hearing loss, ataxia, paraplegia, neurogenic bladder (neurotoxicity generally temporary)	Treatment duration varies based on clinical response and type of coccidioidal infection, though it is continued for a minimum of 3–6 months Therapeutic drug monitoring of itraconazole is recommended to ensure adequate absorption
	Coccidioidal meningitis -First trimester: Intrathecal amphotericin B 0.1 mg IV three times weekly (initial dose) -Second or third trimester: Fluconazole 800–1200 mg PO daily *or* Itraconazole 200 mg PO 2–4 times daily	Coccidioidal meningitis -First trimester: Fluconazole or itraconazole -Second or third trimester: Intrathecal amphotericin B	Fluconazole: Monitor LFTs, renal function, potassium Itraconazole: Monitor LFTs, renal function, serum trough concentrations, potassium	Intrathecal amphotericin B dose should be gradually titrated as tolerated, with dose tapering recommended over three phases

(Continued)

Table 2. (*Continued*)

Disease state	Preferred therapy	Alternative therapy	Adverse effects/monitoring	Additional comments
Lyme disease[99,100]	Early Lyme disease Erythema migrans Amoxicillin 500 mg PO TID *or* Cefuroxime axetil 500 mg PO BID for 14 days (range 14–21 days)	Azithromycin 500 mg PO daily for 7–10 days	Amoxicillin/cefuroxime: Rash, itching, GI effects Azithromycin: GI effects, additive QTc prolongation Ceftriaxone: Rash, itching, uncommonly associated with biliary sludging and increased bilirubin	Patients should be monitored closely for resolution of symptoms In patients with severe allergies to both penicillin and cephalosporins, proper allergy reconciliation, and/or consideration of PAST is preferred as macrolide alternatives are associated with inferior outcomes Lyme arthritis: if refractory or persistent symptoms repeat an oral course or parenteral antibiotic therapy recommended
	Early Lyme disease Lyme meningitis Ceftriaxone 2 g IV daily for 14 days (range 10–28 days)	Penicillin G 18-24 MU IV per day (CI or divided q4 hours) *or* Cefotaxime 2 g IV q8 hours		
	Late Lyme Disease Lyme arthritis Amoxicillin 500 mg PO TID *or* Cefuroxime axetil 500 mg PO BID for 28 days			
	Late Lyme disease with neurologic involvement Ceftriaxone 2 g IV daily for 2–4 weeks	Penicillin G 18-24 MU IV per day (CI or divided q4 hours) Cefotaxime 2 g IV q8 hours		
Human granulocytic anaplasmosis[65,67]	Rifampin 300 mg PO BID for 7–10 days		Rifampin: Monitor LFTs	Rifampin associated with multiple drug–drug interactions; may cause an orange–red discoloration of secretions

(Continued)

Table 2. (*Continued*)

Disease state	Preferred therapy	Alternative therapy	Adverse effects/monitoring	Additional comments
Human granulocytic anaplasmosis[65,67] (*Cont*)				If coinfection with *B. burgdorferi* is suspected, amoxicillin or cefuroxime should also be initiated
Babesiosis[72]	Clindamycin 300–600mg IV q6 hours plus quinine 650 mg PO q6–8 hours If clindamycin PO: Clindamycin 600 mg PO q8 hours is recommended		Azithromycin: GI effects, additive QTc prolongation	Azithromycin doses of 600–1000 mg daily have been used in immunocompromised hosts
Rocky Mountain spotted fever[63,77]	Doxycycline 100 mg PO BID for 5–7 days or 3 days after fever resolution	Chloramphenicol IV/PO 500 mg QID	Chloramphenicol: Aplastic anaemia Doxycycline: Rash, diarrhoea	Oral formulations of chloramphenicol are not available in the United States
Varicella zoster virus[82]	If exposed to varicella zoster virus: acyclovir 800 mg PO five times per day PLUS Varicella zoster immunoglobulin 125 units/10 kg intramuscularly x 1 dose (maximum dose: 625 units)		Acyclovir: Malaise, headache, nausea, vomiting, diarrhoea	Begin therapy within 96 hours of exposure

BID, twice daily; CBC, complete blood count; CI, continuous infusion; ECG, electrocardiogram; G6PD, glucose-6-phosphate-dehydrogenase; GI, gastrointestinal; IDSA, Infectious Diseases Society of America; IV, intravenous; LFTs, liver function tests; MU, million units; PAST, penicillin allergy skin testing; PO, by mouth; QID, four times daily; TID, three times daily; TMP-SXT; trimethoprim/sulfamethoxazole.

transmission to the fetus and treat the fetus if infected.[19] If failure or intolerability of the preferred therapy occurs, pyrimethamine plus clindamycin plus leucovorin can be used.[7] Although there are limited safety data with its use in pregnancy, atovaquone-containing regimens may also be used if needed. Chronic maintenance therapy with pyrimethamine plus sulfadiazine plus leucovorin should be started after completing treatment for TE (Table 2). The risks of TMP-SXT in the first trimester and near term, as discussed previously, need to be balanced against the risks of TE.[8–10,13] TMP-SXT is preferred for *T. gondii* primary prophylaxis.[7]

Cryptococcosis

Cryptococcal disease is rare in pregnancy outside of people living with HIV, although there are case reports of pneumonia.[20,21] Treatment should be initiated as soon as the diagnosis of cryptococcal infection is confirmed, beginning with induction followed by consolidation and/or maintenance therapy.[7] Preferred treatment in pregnancy for cryptococcal meningitis, meningoencephalitis, disseminated disease and severe pulmonary cryptococcosis is liposomal amphotericin B (Table 2).[7] Flucytosine is teratogenic in animal studies and is not recommended during the first trimester of pregnancy. Flucytosine should only be used as a part of combination therapy for cryptococcal meningitis in the second and third trimesters if the benefits outweigh the risks.[22] Liposomal amphotericin B should be used throughout the first trimester. Azole antifungal drugs should be avoided, especially in the first trimester, due to the risk of congenital malformations.[7,21,23] Consolidation therapy and/or maintenance therapy with oral fluconazole, after at least 2 weeks of liposomal amphotericin B, can be considered if clinically appropriate after the first trimester.[7,21]

Mycobacterial infections

Tuberculosis

Treatment for *Mycobacterium tuberculosis* is indicated when the probability of disease is moderate to high due to the risk of untreated tuberculosis to the patient and fetus.[24] The incidence of tuberculosis in pregnant patients in 2011 was reported as 26.6/100,000 births in the United States and there were more than 200,000 cases of active tuberculosis globally.[25,26] Disease presentation may be atypical in this patient population with patient complaints of nonspecific symptoms and, thus, diagnosis may be delayed.[27,28] A descriptive study of the United Kingdom Obstetric Surveillance System reported that half of the cases diagnosed were extrapulmonary.[27]

Active treatment is completed in two phases, the intensive phase and the continuation phase. According to the American Thoracic Society/CDC/Infectious Diseases Society of America, the preferred treatment regimen includes rifampin, isoniazid and ethambutol.[24] Pyridoxine supplementation (25–50 mg/day) should also be provided in any pregnant or nursing patient to prevent peripheral neuropathy development. The inclusion of pyrazinamide in the regimen is controversial in the United States due to a lack of well-controlled human studies and safety data. In contrast, the WHO recommends pyrazinamide as part of standard treatment with isoniazid, ethambutol and rifampin.[29] Expert consultation is suggested to determine the duration of therapy based upon patient-specific factors and chosen regimen; the usual duration is 2 months of intensive treatment followed by 7 months of continuation treatment.[29]

Treatment with second-line agents due to resistance should be offered and thoughtfully planned.[30] A specific second-line regimen is not recommended over another at this time and treatment duration should be extended.[24] Streptomycin should be avoided due to the risk of hearing loss in the fetus.[28,29] Fluoroquinolones and aminoglycosides should be avoided when alternate agents are available for an effective regimen.[31,32] Ethionamide, para-aminosalicylic acid and cycloserine have unfavourable side effects (e.g. hypothyroidism, psychosis) and mixed safety data in pregnant patients.[33] A case report of two pregnant patients treated with second-line agents, including kanamycin, ethionamide, cycloserine and levofloxacin, resulted in one preterm labour and one full-term caesarean section; in both cases, the babies were healthy.[34] Bedaquiline was independently associated with low birth weight (n=49 babies exposed *in utero*) and, in one case report, there were no fetal toxicities noted.[35,36] Linezolid use has been reported; however, adverse events associated with long-term treatment (e.g. haematological effects) may limit usefulness.[37] Pretomanid is approved in combination with linezolid and bedaquiline and warnings for these two agents apply to therapy.[38] No clinical data or case reports in pregnant patients are available; however, animal reproduction studies revealed increased postimplantation loss during organogenesis at doses approximately four times the exposure at the recommended human dose. There were no adverse effects at doses up to approximately two times the exposure in humans. Safety data are limited for delamanid and, at this time, its use should be avoided.[34]

Treatment of latent disease may be deferred until 3 months after pregnancy unless the patient is immunocompromised, living with HIV or has had a recent exposure.[39] Isoniazid supplemented with pyridoxine is the therapy of choice. There are limited data regarding the safety of once-weekly isoniazid plus rifapentine (12-dose regimen)[40]; therefore, it is not currently recommended for pregnant patients.[7]

Mycobacterium avium complex

Most of the available literature for the treatment of *Mycobacterium avium* complex (MAC) is for people with HIV and MAC cases in immunocompetent pregnant patients are rare. Azithromycin plus ethambutol is the preferred treatment regimen.[7] Clarithromycin should be avoided due to the risk of birth defects. A meta-analysis of 19 studies found that the following were associated with macrolide prescribing

(including erythromycin, clarithromycin and azithromycin) during pregnancy compared to alternative antibiotics: an increased risk of miscarriage, cerebral palsy and/or epilepsy, epilepsy alone, and gastrointestinal malformations.[41] A recent cohort study noted that macrolide antibiotics prescribed during the first trimester were associated with an increased risk of cardiovascular malformation compared to penicillin antibiotics.[42]

If alternative MAC therapy is required with an aminoglycoside or fluoroquinolone due to resistance or other patient characteristics, the risks and benefits of treatment should be carefully considered due to the potential adverse effects on the fetus. For pregnant patients with HIV who are not treated with effective antiretroviral therapy, azithromycin should be used as primary prophylaxis and azithromycin plus ethambutol are preferred for secondary prophylaxis.[7]

Selected fungal infections

Oral and oesophageal candidiasis

While pregnancy increases the risk of vaginal colonization with *Candida* species, it has not been associated explicitly with oropharyngeal or oesophageal candidiasis.[43] However, *Candida* colonization of the vagina increases to 30% of women in pregnancy. In one meta-analysis, the incidence of oral candidiasis was reported to be 4.4%.[44] For the treatment of oral candidiasis, topical therapy is preferred over oral azole therapy due to a concern for poor pregnancy outcomes such as spontaneous abortion and stillbirth.[45–48] Clotrimazole troches or miconazole mucoadhesive buccal tablets for 7–14 days are preferred options with nystatin oral suspension as an alternative option (Table 2). Topical use of these agents has not been associated with an increase in congenital malformations and is considered safe due to limited systemic absorption.[49] For systemic therapy of oesophageal candidiasis, intravenous amphotericin B deoxycholate is preferred in place of fluconazole in pregnancy, especially in the first trimester due to the possibility of birth defects.[50]

Histoplasmosis

Histoplasmosis (*Histoplasma capsulatum*) is the most common endemic fungal infection in the United States, with the Ohio and Mississippi River Valleys being the most highly endemic regions.[51] Symptomatic histoplasmosis during pregnancy is relatively rare; however, histoplasmosis cases have been described in otherwise healthy pregnant patients.[52] Another unique consideration in pregnancy is the potential transplacental transmission to the fetus in disseminated disease.[52] Treatment is indicated in moderately severe or severe acute pulmonary disease, chronic pulmonary disease, or disseminated disease and any disease involving the central nervous system.[51] In other less severe manifestations, therapy is not always indicated. Because itraconazole may cause fetal malformations, liposomal amphotericin B is preferred in pregnant patients when treatment is necessary for a total of 4–6 weeks.[51] A case of a pregnant outpatient treated with thrice-weekly liposomal amphotericin B step-down therapy for 6 weeks has been reported.[53] Except for avoiding azoles, all recommendations for the treatment of histoplasmosis in pregnancy remain the same as for a nonpregnant patient.[51]

Coccidioidomycosis

Pregnancy is one of the most common risk factors for developing severe and disseminated coccidioidomycosis caused by *Coccidioides immitis* or *Coccidioides posadasii*.[54] Endemic areas of coccidioidomycosis include the southwestern United States, Mexico, Central America and South America. One in 1000 pregnancies in these endemic regions are reported to be impacted by coccidioimycosis.[55,56] The likelihood of severe disease increases as the pregnancy progresses. The greatest severity occurs during the early postpartum period. The risk for fetal transmission is also present.[57] For non-meningeal disease, liposomal amphotericin B is the preferred therapy in the first trimester (Table 2); fluconazole or itraconazole may be considered after the first trimester.[54] In general, although there are little data on the safety of fluconazole after the first trimester, published reports suggest that exposure later in pregnancy may be safe.[57] Intrathecal amphotericin B should be considered in consultation with a specialist and administered by an experienced clinician to treat coccidioidal meningitis during the first trimester.[58] After the first trimester, an azole may be considered. For patients with a history of coccidioidomycosis, close follow-up with serologic testing at the initial visit and every 6–12 weeks until delivery is recommended though the risk of reactivation is low.[54]

Tickborne infections

Lyme disease

Transmitted by the *Ixodes* tick species, Lyme disease is caused by the spirochete *Borrelia burgdorferi*. The incidence of Lyme disease is higher in endemic areas in North America and Europe, although there are rare reports of cases during pregnancy.[59–61] Treatment of gestational Lyme disease is essential as data show reduced adverse outcomes in treated (11–16%) compared to untreated disease (50–60%).[61,62] Doxycycline should not routinely be used in pregnancy for Lyme disease, especially with proven alternatives, due to transient suppression of bone growth and staining of developing teeth.[63] Amoxicillin is preferred in the absence of neurological manifestations (e.g. Lyme meningitis) or atrioventricular heart block.[63] Ceftriaxone is typically reserved for patients with severe neurological or cardiac manifestations.[62–64] One study noted a non-significant increase in adverse pregnancy outcomes, such as pregnancy loss, among orally treated (31.6%) compared to parenterally treated (12.1%) pregnant patients.[62] Alternative oral therapy is cefuroxime axetil and parenteral therapies include penicillin G or cefotaxime. Late Lyme disease, often manifesting as Lyme

arthritis, may be managed with oral or parenteral β-lactams as described above, typically for up to 4 weeks of therapy.[63]

Ehrlichiosis

Ehrlichiosis is characterized by two similar diseases transmitted by the *Ixodes* ticks: human granulocytic anaplasmosis (HGA) caused by *Anaplasma phagocytophilum* and human monocytic ehrlichiosis caused by *Ehrlichia chaffeensis*. Although severe cases in pregnancy have not been reported, case reports are available.[65] If HGA or human monocytic ehrlichiosis infection is suspected, treatment should occur due to the likelihood of complications and potential for vertical transmission.[65,66] Rifampin has exhibited *in vitro* activity against *Ehrlichia* species and has been used successfully in limited case reports of pregnant women with HGA.[65,67] Successful use of doxycycline for ehrlichiosis treatment has also been documented.[68,69] Due to a lack of data, these patients should be closely monitored for resolution.[67,69] If coinfection with Lyme disease is suspected, the addition of amoxicillin or cefuroxime is suggested as rifampin does not have activity against *B. burgdorferi*.[63]

Babesiosis

Babesiosis is caused by the parasite *Babesia microti* and transmitted by the hard-shelled *Ixodes* tick. There are few documented babesiosis cases during pregnancy, although congenital infection is possible.[70,71] All patients with suspected babesiosis should be treated due to potential complications, including possible vertical transmission.[71] Combination therapy is preferred with clindamycin plus quinine.[72] This combination may be associated with improved placental penetration as compared with atovaquone plus azithromycin.[59,63] Resolution of parasitaemia should be used to determine if longer treatment courses are needed or if retreatment may be needed in cases with symptoms and/or parasitaemia persisting >3 months.[73]

Rocky Mountain spotted fever

Rocky Mountain spotted fever (RMSF) is caused by the gram-negative bacteria *Rickettsia ricketsii* and is commonly transmitted in the United States by the dog tick. Very few cases of gestational RMSF have been reported in the literature. Cases are associated with poor outcomes for the fetus, regardless of the treatment administered.[74,75] Therefore, preventive methods are crucial for pregnant patients, and treatment should be provided within 3–5 days of exposure. Doxycycline is the preferred therapy for typically 5–7 days in duration or 3 days after fever resolution.[63]

Chloramphenicol is proposed as an alternative treatment; however, there is a concern with significant adverse effects, including myelosuppression, aplastic anaemia, and grey baby syndrome, specifically at or near birth.[76,77] Additionally, chloramphenicol is associated with higher mortality in RMSF.[78] Of note, chloramphenicol is not available as an oral formulation in the United States.

Azithromycin has been considered but was less effective when compared to doxycycline in an animal model.[79] Given the lack of safe and effective alternative treatments, doxycycline remains preferred for RMSF in pregnancy. Concerns of doxycycline-associated adverse outcomes in pregnancy continue to wain among some experts, especially with relatively short duration of therapy.[80]

Selected viral infections

Varicella zoster virus

Varicella zoster virus (VZV) is a DNA virus and a member of the herpes virus family.[81] More than 90% of women are estimated to be seropositive for VZV and the incidence of chickenpox is reported to be 0.7–3 per 1000 pregnancies.[82–84] The risk of vertical transmission is highest when the primary maternal infection occurs between 5 days predelivery and 2 days post-delivery. However, VZV can also rarely be transferred *in utero*. *In utero* acquisition, especially within the first 20 weeks, can lead to fetal death, neurological defects and other birth defects.[81,84] Infection acquired at birth results in neonatal VZV.

Because VZV infections worsen with age and can become more complicated during pregnancy, routine screening and/or documentation of immunity are recommended as part of prenatal care.[84] The VZV vaccine is a live, attenuated virus and vaccination is not recommended during pregnancy but may be given after delivery.[81] Pregnant patients who are not immune should avoid close contact or exposure to VZV. If there is an exposure to an active case of VZV, nonimmune, pregnant patients should receive varicella zoster immunoglobulin (VZIG) within 96 hours of the exposure.[84] In one study, the risk of developing VZV was significantly lower in those who received VZIG (42% *versus* 72% in those who did not receive VZIG; p=0.0263).[85] Additionally, because patients who develop VZV during pregnancy are at increased risk of developing pneumonia and death, it is recommended that acyclovir be used in addition to VZIG.[84,86] This recommendation is based on data from two studies demonstrating acyclovir treatment reduced fever duration and symptoms of infection in immunocompetent adults (acyclovir significantly reduced time to crusting by 1.8 days (p=0.001) and number of lesions by 46% (p=0.04)) and immunocompromised children (acyclovir significantly reduced time to full crusting by 1.4 days (p=0.01)) when given within 24 hours of rash onset.[87,88]

Herpes zoster virus

Herpes zoster during pregnancy is rare, and it is considered a benign disease with limited consequences.[89] If treatment is required for severe disease, acyclovir is the preferred therapy; treatment should be initiated early to accelerate cutaneous lesion healing.[82] One study reported a higher incidence in women with caesarean deliveries receiving general anaesthesia (0.46%) compared to those who received regional anaesthesia (0.35%).[90]

Cytomegalovirus

Cytomegalovirus (CMV) seropositivity rates are up to 60% among women of childbearing age.[91] During primary infection, the risk of transmission is highest during the third trimester of pregnancy (40–70%), but complications can be worse if CMV is acquired in the first or second trimesters.[92] Although 85–90% of infants will be asymptomatic initially, neonatal CMV acquisition can lead to symptoms or complications in up to 20% of neonates.[91] CMV is the leading cause of congenital hearing loss and can lead to premature birth, the development of liver, lung and spleen problems, and neurological complications such as microcephaly, vision loss, weakness, lack of coordination and seizures.[91,92]

Routine serological testing for CMV is only recommended for patients who develop symptoms during pregnancy or who have findings on sonography suggestive of CMV infection.[84,93] Because these findings on sonography (often including growth restriction, microcephaly and other complications) are not specific to CMV, prenatal diagnosis of congenital CMV is confirmed by amniocentesis performed at least 6–7 weeks after the presumed acquisition of material infection and after 21 weeks of gestation.[84,91]

No antiviral treatment is universally recommended in healthy adults with CMV, even during pregnancy, due to the lack of evidence that antiviral therapy prevents congenital CMV infection.[93,94] There was no difference in infant CMV acquisition (66% *versus* 66%, respectively; p=1.0) or time to CMV detection in a study of pregnant women at 34 weeks' gestation living with HIV and CD4 T lymphocyte count of <250 cells/μL who received either valacyclovir or placebo for 12 months.[95]

Ganciclovir and valganciclovir both have black-boxed warnings for birth defects and should not be used in pregnancy.[49] However, there has been some evidence, albeit controversial, that intravenous administration of CMV-hyperimmune globulin (HIG) 200 U/kg may help reduce neonatal disease.[84,94] In one study, women who received HIG were significantly less likely to have symptomatic infants compared to those who did not receive HIG (3% *versus* 50%, respectively; p<0.001).[96] In a subsequent randomized, placebo-controlled trial, congenital infection rates were not statistically different between women who received HIG *versus* those who received placebo (30% *versus* 44%, respectively; p=0.13).[97] The most important strategy to prevent congenital CMV is the avoidance of maternal CMV exposure, including proper hand hygiene (especially in childcare workers) and avoidance of sexual exposure to partners with known CMV.[98]

Conclusion

Limited data of medication use in treating less common bacterial, fungal, opportunistic and viral infections during pregnancy pose a challenge to clinicians to provide evidence-based guidance and accurate assessment of risks and benefits. The risks of inadequately treating the infection should be weighed against the risk of the treatment. Original research and case reports are limited in scope and generalizability due to the nature of this patient population. Ultimately, treatment recommendations should consider a comprehensive review of the most recently published evidence-based research and expert guidance.

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