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Tuberculosis in Pregnant and Postpartum Women: Epidemiology, Management, and Research Gaps

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Tuberculosis is most common during a woman's reproductive years and is a major cause of maternal–child mortality. National guidelines for screening and management vary widely owing to insufficient data. In this article, we review the available data on (1) the global burden of tuberculosis in women of reproductive age; (2) how pregnancy and the postpartum period affect the course of tuberculosis; (3) how to screen and diagnose pregnant and postpartum women for active and latent tuberculosis; (4) the management of active and latent tuberculosis in pregnancy and the postpartum period, including the safety of tuberculosis medications; and (5) infant outcomes. We also include data on HIV/tuberculosis coinfection and drug-resistant tuberculosis. Finally, we highlight research gaps in tuberculosis in pregnant and postpartum women.

Tuberculosis kills approximately 500 000 women annually, a disproportionate number of them during their reproductive years [1–4], yet there are critical research gaps regarding the epidemiological and clinical features of tuberculosis in pregnant and postpartum women. In this article, we review the current state of knowledge, highlighting those gaps.

WHAT IS THE GLOBAL BURDEN OF TUBERCULOSIS AND LATENT TUBERCULOSIS AMONG PREGNANT AND POSTPARTUM WOMEN?

The human immunodeficiency virus (HIV) epidemic, reduced healthcare access, and hormonal changes likely make tuberculosis a leading cause of morbidity and mortality in women of reproductive age [5–7].

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Burden of Active Tuberculosis

Table 1 summarizes the prevalence of active tuberculosis in pregnant and postpartum women from high-burden (>60 cases per 100 000 population per year) and low-burden tuberculosis countries (<20 cases per 100 000 population per year or <10 cases total). Rates of active tuberculosis ranges from 0.7% to 7.9% among HIV-positive women in high-burden countries, and is as high as 11% if they are positive for tuberculin skin test (TST) [8] (Table 1). High-burden countries may underestimate prevalence because many women do not have access to healthcare when pregnant [1]. Few national programs collect or report pregnancy-specific tuberculosis data to the World Health Organization (WHO).

Burden of Latent Tuberculosis

Latent tuberculosis prevalence in pregnancy likely mirrors that of the general population, which is 4.2% in the United States [22]. It is up to 10 times higher among foreign-born Americans [23], including pregnant women [11], regardless of HIV status. Inconsistent screening complicates estimates of latent tuberculosis prevalence in high-burden countries. Small studies report prevalence in pregnancy of 19%–34% among HIV-negative women in India [24] and

Table 1. Prevalence of Active Tuberculosis Among Pregnant and Postpartum Women

Study Site	Author	Sample Size, No.	HIV Positive, %	Locations of Tuberculosis Screening	Site of Infection	Tuberculosis Case Definition	Prevalence	
							Overall %	Drug Resistant, %
Low-burden countries								
United States	Good et al[4]	371	Unknown[a]	Inpatient	PTB	TST^+ or clinical features with sputum AFB^+/positive culture or gastric washing	7.20[b]	59.20
United States	Margono et al[9]	51 983	63 (7/11)[c]	Inpatient	PTB, EPTB	Positive culture of sputum, urine, or CSF	0.06	NA
United States	Schulte et al[10]	207	100	ANC	Unspecified	Positive sputum culture	1.00	NA
United States	Schwartz et al[11]	3847	0	ANC	PTB	Symptoms or TST^+/CXR^+ with sputum AFB^+	0.13	NA
United Kingdom	Llewelyn et al[12]	9069	0 (0/10)[d]	Inpatient	PTB, EPTB	Symptoms with CXR^+/response to treatment or positive culture/biopsy	0.14	0
United Kingdom	Kothari et al[13]	12 697	4 (1/24)[e]	ANC, inpatient, postpartum clinic	PTB, EPTB	Symptoms with TST^+ and sputum AFB^+/positive culture or CXR^+/US^+ with positive biopsy/bronch	0.25[f]	NA
High-burden countries								
India	Gupta et al[14]	715	100	ANC, inpatient	PTB, EPTB	Symptoms or TST^+ with sputum AFB^+/positive culture/biopsy	3.40	NA
Kenya	Jonnalagadda et al[15]	393	100	ANC	Unspecified	Symptoms with sputum AFB^+/positive culture or CXR	2.80	NA
Rwanda	Leroy et al[16]	431	49	Inpatient	PTB, EPTB	Symptoms with sputum AFB^+/positive culture or biopsy	HIV^+: 7.90, HIV^- : 0.46	NA
Tanzania	Sheriff et al[17]	396	5	ANC	PTB	Symptoms or TST^+ with sputum AFB^+ or CXR^+	HIV^+: 10.0[g], HIV^-: 0.53[g]	NA
South Africa	Nachega et al[8]	120[h]	100	Postpartum clinic	PTB, EPTB	TST^+, CXR^+, or symptoms with sputum AFB^+/positive culture	11.00	NA
South Africa	Pillay et al[18]	50 518	29	ANC, inpatient	PTB, EPTB	Symptoms with sputum AFB^+, CXR^+, or positive culture/biopsy	HIV^+: 0.77, HIV^-: 0.07	1.30
South Africa	Kali et al[19]	370	100	ANC, posttest counseling	Unspecified	Symptoms with sputum AFB^+/positive culture × 1 (MGIT)	2.16	NA
South Africa	Gounder et al[20]	3963	36	ANC pretest counseling	PTB	Symptoms with sputum AFB^+/positive culture × 1 (MGIT)	HIV^+: 0.69, HIV^-: 0.20	0.00

Table 1 continued.

Study Site	Author	Sample Size, No.	HIV Positive, %	Locations of Tuberculosis Screening	Site of Infection	Tuberculosis Case Definition	Prevalence	
							Overall %	Drug Resistant, %
Sub-Saharan African countries	Toro et al[21]	1536	100	ANC	Unspecified	Symptoms with response to treatment	2.10	3.00

Abbreviations: AFB, acid-fast bacilli; ANC, antenatal clinic; CSF, cerebrospinal fluid; CXR, chest radiograph; EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; MGIT, Mycobacteria growth indicator tube (liquid medium); NA, not applicable; PTB, pulmonary tuberculosis; TST, tuberculin skin test; US, ultrasound.

[a] No HIV testing performed.

[b] A total of 78% of those diagnosed were postpartum.

[c] Only 11 women tested for HIV.

[d] Only 10 women tested for HIV.

[e] Only 24 women tested for HIV.

[f] A total of 38% were pulmonary, 53% extrapulmonary.

[g] All diagnosed with AFB-negative tuberculosis.

[h] All TST-positive women.

up to 49% in HIV-positive women in South Africa [8] (Table 2).

DOES PREGNANCY OR THE POSTPARTUM PERIOD AFFECT THE COURSE OF TUBERCULOSIS?

Pregnancy suppresses the T-helper 1 (Th1) proinflammatory response, which may mask symptoms while increasing susceptibility to new infection and reactivation of tuberculosis [30–32]. (These effects are seen in other infectious diseases, such as influenza and *Mycobacterium leprae*, which are more common and severe during pregnancy [33].) After delivery, Th1 suppression reverses—similar to immune reconstitution syndrome in HIV patients starting antiretroviral therapy (ART)—and symptoms are exacerbated [31]. A large study recently found that early postpartum women are twice as likely to develop tuberculosis as nonpregnant women [34]. This and other studies suggest that biologic changes in pregnancy and postpartum influence tuberculosis epidemiology [4, 14, 35, 36], challenging the findings of earlier, smaller studies that found no effect [37, 38]. Practitioners should be cognizant of the unpredictable symptomatology of tuberculosis during pregnancy.

SCREENING PREGNANT WOMEN FOR ACTIVE AND LATENT TUBERCULOSIS

Active Tuberculosis Screening

Tuberculosis increases mortality during pregnancy or postpartum, especially in HIV-positive women [14, 39–41]. Pregnant women with pulmonary or extrapulmonary tuberculosis, other than lymphadenitis, also have increased risk of complications including antenatal hospitalization and miscarriages (Table 3) [3, 4, 42–48].

Lack of awareness is a barrier to diagnosis in low-burden countries. In high-burden countries, healthcare workers often lack diagnostic tests, relying on clinical presentation. Women are less likely than men to present with symptoms like hemoptysis, fever, and night sweats [49], and pregnancy further masks these symptoms. In South Africa, 60% of antenatal women diagnosed with tuberculosis reported cough of ≥2 weeks, but <30% had fevers or night sweats [20]. In Tanzania, the most common tuberculosis symptoms were malaise and anorexia [17].

Many tuberculosis-endemic countries also have a high prevalence of HIV, which further masks symptoms and causes atypical symptoms. Acid-fast bacilli stains and chest radiographs are less sensitive in HIV-infected patients [50], and cultures can take 4–10 weeks to become positive.

The complex symptomatology notwithstanding, WHO recommends screening for symptoms of cough of any duration,

Table 2. Prevalence of Latent Tuberculosis Infection Among Pregnant and Postpartum Women

Study Site	Author	Sample Size, No.	HIV Positive, %	Location of Tuberculosis Screening	Prevalence	
					TST+, %	IGRA, %
Low-burden countries						
United States	Mofenson et al[25]	46	100	ANC, inpatient, postpartum clinic	11	…
United States	Medchill et al[26]	1497	0	ANC	15	…
United States	Schulte et al[10]	176	100	ANC	26	…
United States	Schwartz et al[11]	3847	0	ANC	50[a]	…
United States	Chehab et al[27]	102	0	ANC	10	7
United States	Worjoloh et al[28]	199	0	ANC	23[b]	14[c]
High-burden countries						
India	Gupta et al[14]	688	100	ANC, inpatient	21	…
India	Mathad et al[24]	152	0	ANC	18	34
Kenya	Jonnalagadda et al[15]	333	100	ANC	…	36[d]
South Africa	Nachega et al[8]	318	100	Postpartum clinic	49	…
Tanzania	Sheriff et al[29]	286	14.5	ANC	HIV+: 23, HIV− : 31	…

Abbreviations: ANC, antenatal clinic; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; TST, tuberculin skin test.

[a] A total of 89% were foreign-born.

[b] A total of 65% were born in tuberculosis-endemic countries.

[c] QuantiFERON-TB In-Tube.

[d] TSPOT.TB (on cryopreserved peripheral blood mononuclear cells).

fever, night sweats, and weight loss [51]. The absence of these symptoms has a negative predictive value of 90%–97.7% [52], even in peripartum women [53], but poor sensitivity and positive predictive value [52, 53].

In symptomatic women and asymptomatic women with a recent tuberculosis contact, the Centers for Disease Control and Prevention (CDC) and others recommend a shielded chest radiograph, which poses minimal risk to the fetus [54–56]. If findings are abnormal, sputum samples should be submitted for microscopy and culture [56]. The British Health Protection Agency has similar guidelines, but adds sputum studies in all women with HIV [57]. Note that chest radiography and sputum examination may miss miliary and extrapulmonary tuberculosis disease. Common extrapulmonary sites of tuberculosis in pregnancy include lymph nodes, intestines, and bones [44, 58]. Additional diagnostic testing (eg, biopsy) should be pursued if clinical suspicion is high.

Some experts advocate integrating active tuberculosis case-finding into peripartum care, but best approaches are unknown. Universal antenatal tuberculosis screening in South Africa found that symptoms of tuberculosis were common whether or not the patient had tuberculosis, wasting resources on unnecessary evaluations [19, 20]. Cost-effective tuberculosis screening approaches are urgently needed.

Latent Tuberculosis Screening

Screening for latent tuberculosis should identify patients at high risk of developing active disease who would benefit from prophylactic therapy. Current latent tuberculosis screening tools—the TST and the newer interferon (IFN)–γ release assays (IGRAs)—do not sufficiently differentiate between latent tuberculosis and active tuberculosis. Both tests have other limitations. TST, because of potential cross-reactivity with BCG and environmental mycobacteria, as well as challenges with proper test placement, has low specificity and sensitivity, particularly among HIV-positive patients [59, 60] and possibly among pregnant women [24, 60]. TST requires reagents, trained operators, and a return visit within 72 hours, which does not happen in 20%–30% of pregnant women [8, 10].

IGRAs, such as QuantiFERON Gold Test In-Tube (QGIT; Cellestis) and Tspot.TB (Oxford Immunotech), measure IFN-γ released from white blood cells when exposed to tuberculosis-specific antigens. IGRAs do not cross-react with BCG or environmental bacteria and do not require a return visit; but are costly, require blood collection, proper processing, and lab infrastructure, and have not been widely validated in high-burden settings or among pregnant women [61, 62], although a study group of pregnant HIV-positive Kenyan women with

Table 3. Outcomes for Pregnant Women With and Without Active Tuberculosis Disease and Their Infants

Site	Author	Cases	Controls/ Comparison Group	Maternal Sample Size	HIV Positive, %	Maternal Mortality, Case % vs Control %	RR (95% CI)	Infant Mortality[a], Case % vs Control % (RR [95% CI])	RR (95% CI)	Other Outcomes, Case % vs Control %
Case-control										
Norway	Bjerkedal et al[42]	PTB	No TB	542	NR	NR	…	1.5 vs 1.1	1.3 (0.6–2.6)[b]	Vaginal hemorrhage: 4.1 vs 2.2[c]
										Maternal toxemia: 7.4 vs 4.7[c]
										Miscarriage: 2.0 vs 0.2[c]
										Premature: 5.2 vs 5.0
										LBW: 3.9 vs 3.7
										Congenital defect: 2.9 vs 2.2
Mexico	Figueroa-Damián & Arredondo-García[3]	TB	No TB	35	2.8	NR	…	8.6 vs 0.9[c]	3.1 (1.1–4.9)	Maternal medical complications: 23 vs 3.8[c]
										Premature: 14.3 vs 4.8[c]
										Birthweight (mean): 2.9 kg vs 3.1 kg[c]
India	Jana et al[43]	PTB	No TB	79	NR	0.0 vs 0.0	…	10.1 vs 1.6[c]	6.4 (2.1–19)[b,d]	Antenatal hospitalization: 3.8 vs 0.0
										Perinatal TB: 0.0 vs NA
										Premature: 22.8 vs 11.1[c]
										LBW: 34.2 vs 16.5[c], SGA: 20.2 vs 7.9[c]
India	Jana et al[44]	EPTB	No TB	33	NR	0.0 vs 0.0	…	10.0 vs 2.0	4.0 (0.5–27)[b]	Antenatal hospitalization 24.0 vs 2.0[c]
										Perinatal TB: 0.0 vs NA
										Premature: 10.0 vs 8.0
										LBW: 33.0 vs 11.0[c]

Table 3 continued.

Site	Author	Cases	Controls/ Comparison Group	Maternal Sample Size	HIV Positive, %	Maternal Mortality, Case % vs Control %	RR (95% CI)	Infant Mortality[a], Case % vs Control % (RR [95% CI])	RR (95% CI)	Other Outcomes, Case % vs Control %
Taiwan	Lin et al[45]	TB	No TB	761	0.0	NR	…	NR	…	Premature: 8.0 vs 7.9
										LBW: 8.5 vs 6.4[c]
										SGA: 19.7 vs 16.7[c]
Cohort										
United States	Ratner et al[39]	TB and preterm infant	TB and full term infant	55	NR	16.3 vs 3.6[c]	5.8 (1.3–24)[b]	7 vs 0[e]	11.5 (0.65–204)[b]	Premature: 44.0 vs NA
										Birthweight (mean): 4.2 lbs vs 7.0 lbs
United States	Schaefer et al[46]	TB from 1952–1972	TB from 1933–1951	1565	NR	0.4 vs 0.5	1.4 (0.2–7.0)[b]	NR	…	Perinatal TB: 0.0 vs NA
										Premature: 3.7 vs 9.1
United Kingdom	Kothari et al[13]	Delay in TB diagnosis	No delay in TB diagnosis	32	3.1	0 vs 0	…	0 vs 0	…	Miscarriage: 6.3 (overall)
										Premature: 6.7 (overall)
										IUGR: 16.0 (overall)
India	Gupta et al[14]	HIV^+ with TB	HIV^+ without TB	24	100.0	12 vs 1	12.2 (2.0–53.3)[g]	17 vs 4[f]	4.7 (1.1–13.5)[g]	Perinatal TB: 0.8 vs NA
										Perinatal HIV: 37.5 vs 9.1[c]
Sub- Saharan Africa	Toro et al[21]	HIV^+ on ART and TB treatment	HIV^+ on ART treatment	33	100.0	3 vs NR	…	15.2 vs 5.9[c,e]	2.6 (1.1–6.1)[b]	Perinatal HIV: 4.0 vs NR
Prospective case series										
South Africa	Pillay et al[47]	HIV^+ with TB	HIV negative with TB	107	77.0	1.2 vs 0.0	0.93 (0.03–22)[b]	7.3 vs 0	4.0 (0.23–69)[b]	Maternal Hb: 9.4 g/dL vs 10.6 g/dL[c]
										Vaginal hemorrhage: 4.0 vs 0.0
										Postpartum complications: 5.0 vs 0.0
										Perinatal TB: 14.0 vs 11.0
										Premature: 46.0 (overall)

Table 3 continued.

Site	Author	Cases	Controls/ Comparison Group	Maternal Sample Size	HIV Positive, %	Maternal Mortality, Case % vs Control %	RR (95% CI)	Infant Mortality[a], Case % vs Control % (RR [95% CI])	RR (95% CI)	Other Outcomes, Case % vs Control %
										LBW: 49.0 (overall)
										IUGR: 66.0 (overall)
Retrospective case series										
United Kingdom	Lowe[48]	Treated TB	Untreated TB	253	NR	NR	…	3.6 (overall)[f]	…	Congenital defect: 2.7 vs. 4.1
United States	Good et al[4]	DR TB	DS TB	27	NR	17 vs 0	3.5 (0.18–67)[b]	19 vs 9[f]	2.0 (0.24–17)[b]	Perinatal TB: 19.0 vs 9.0
United States	Margono et al[9]	TB	None	16	64.0[h]	6.3	…	NR	…	Preterm labor: 31.0
										Perinatal TB: 0.0
										IUGR: 31.3

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; DR, drug resistant; DS, drug sensitive; EPTB, extrapulmonary tuberculosis; Hb, hemoglobin; HIV, human immunodeficiency virus; IUGR, intrauterine growth retardation; LBW, low birth weight; NA, not applicable; NR, not reported; PTB, pulmonary tuberculosis; RR, relative risk; SGA, small for gestational age; TB, tuberculosis.

[a] Infant mortality defined as stillbirth greater than 28 weeks or death within 7 days of birth.

[b] RRs and CIs calculated from data reported.

[c] Statistically significant, $P < .05$.

[d] RR 6.3 (95% CI, .9–42.5) if tuberculosis lymphadenitis excluded.

[e] Infant mortality defined as stillbirth or death within 24 hours of birth.

[f] Infant mortality defined as stillbirth or death within 1 year of birth.

[g] Incident relative risk.

[h] Only 11 women tested.

a positive IGRA showed a 4.5-fold increased risk of developing active tuberculosis [15].

IGRAs demonstrate only fair concordance with the TST in pregnancy. Two US studies screening pregnant women for latent tuberculosis found that most discordance was IGRA negative/TST positive [27, 28], attributed to previous BCG vaccination among the foreign-born [28]. In contrast, in India, discordance was largely IGRA positive/TST negative [24]. Epidemiological (eg, recent tuberculosis exposure) and biological factors (eg, malnutrition, immune changes of pregnancy) may explain this, although the significance of this discordance needs further study [61, 63, 64].

In low-burden countries, the CDC recommends latent tuberculosis screening only for high-risk women—those with known or suspected tuberculosis contacts, injection drug use, HIV or other immunosuppression, foreign birth, and/or residence in congregate settings [65]. Pregnancy by itself is not considered high-risk. In high-burden countries, latent tuberculosis screening is not routinely recommended, though TST screening is useful for identifying the HIV-infected patients most likely to benefit from isoniazid (INH) preventive therapy (IPT) [51, 66]. Thresholds for TST or IGRA interpretation do not change during pregnancy; a positive TST is induration ≥10 mm for HIV-negative and ≥5 mm for HIV-positive pregnant women whereas a positive IGRA is a difference in IFN-γ concentration of >0.35 IU/mL (QGIT) or >6 spots (Tspot.TB) between the tuberculosis antigen and negative control sample, regardless of HIV status [67].

The CDC states that IGRAs can be used in place of TST, and are preferred in BCG-vaccinated individuals and those unlikely to return for interpretation. WHO does not recommend routine use of IGRAs for latent tuberculosis screening [62]. Neither organization comments on IGRAs in pregnancy [62, 68].

ACTIVE TUBERCULOSIS MANAGEMENT DURING PREGNANCY

Adequate data assessing the safety, tolerability, and long-term treatment outcomes of pregnant and postpartum women with tuberculosis are lacking, particularly for HIV-positive women on ART. The benefits of treatment during pregnancy, however, outweigh the risks [69].

Pregnancy changes tuberculosis treatment very little. CDC and WHO guidelines are shown in Table 4 [70, 71]. INH, rifampin (RIF), and ethambutol (EMB) are all Food and Drug Administration (FDA) pregnancy category C (Table 6), but available data do not suggest any significant adverse maternal–fetal effects or need for dose adjustment in pregnancy. INH rarely causes peripheral neuropathy in well-nourished adults. Pregnancy may increase risk, but this is not well studied. Pregnant women on INH should take pyridoxine to prevent this complication. Some experts recommend vitamin K for infants born to mothers taking RIF because of its potential association with hemorrhagic disease in newborns [72, 73]. RIF also has drug interactions, including decreased efficacy of oral contraceptives. Adjunctive nonhormonal contraceptive methods in postpartum women are advisable [74]. High doses of EMB are associated with retrobulbar neuritis in adults, but no findings have been reported in infants of mothers taking EMB [72, 73].

Most individuals with active tuberculosis become sputum smear-negative within a few weeks of antituberculosis therapy (ATT). Pregnant and postpartum women should submit sputum samples at least every 2 months until 2 consecutive samples are negative. Failure to become sputum-negative may indicate poor adherence or drug resistance. More frequent sputum checks may help determine when the mother is no longer infectious to her infant, but no evidence-based guidance exists. Follow-ups are essential to monitor maternal treatment response and assess for tuberculosis infection or disease in the infant [70, 71].

HIV-Positive Women

Management of tuberculosis/HIV coinfection in pregnancy is complicated. It remains unknown whether pregnancy affects the metabolism of ATT or whether ART interacts with ATT differently during pregnancy. From a study in Soweto, South Africa, HIV-positive pregnant women on efavirenz-based ART and rifampin-based ATT had no significant differences in efavirenz levels, HIV virologic suppression, or 6-week HIV transmission rates as compared with HIV-positive women without tuberculosis [77]. Efavirenz is usually delayed until the second trimester because of neural tube defect concerns. Recent data, however, suggest that efavirenz may be safe in all trimesters [78] and, as of 2012, the British HIV Association's guidelines no longer prohibit its use in pregnancy [79].

Nevirapine-based ART is generally not recommended in women with tuberculosis, as rifampin significantly reduces nevirapine concentrations [80]. Rifampin also decreases protease inhibitor (PI) levels by 80%. Rifabutin can be substituted for rifampin if a PI is used, but optimal dosing of rifabutin is unknown and, in many settings, rifabutin is not readily available [81]. Some physicians double the PI dose when using rifampin-based ATT, but tolerability is a concern, particularly in the third trimester when the recommended PI dosing is 50% higher than normal [81]. The dose of raltegravir, an integrase inhibitor, should be doubled with rifampin-based ATT, but the pharmacokinetics (PK), drug interactions, and outcomes remain inadequately studied in pregnant and postpartum women [82].

If neither nonnucleoside reverse transcriptase inhibitors nor PIs are appropriate, triple or quadruple nucleoside reverse

Table 4. Treatment of Active Pulmonary[a] Tuberculosis in Pregnant and Postpartum Women

	Low-Burden Countries[b]	High-Burden Countries[c]
HIV-negative	Isoniazid 5 mg/kg/d × 9 mo	Isoniazid 5 mg/kg/d × 6 mo
	Rifampin 10 mg/kg/d × 9 mo	Rifampicin 10 mg/kg/d × 6 mo
	Ethambutol[d] × 2 mo	Ethambutol 15 mg/kg/d × 2 mo
	Pyridoxine 25 mg/d × 9 mo	Pyrazinamide 25 mg/kg/d × 2 mo
		Pyridoxine 10–25 mg/d × 6 mo
HIV-positive	Isoniazid 300 mg/d × 6 mo	Isoniazid 5 mg/kg/d × 6 mo
	Rifampin 600 mg/d × 6 mo	Rifampicin 10 mg/kg/d × 6 mo
	Ethambutol[d] × 2 mo	Ethambutol 15 mg/kg/d × 2 mo
	Pyrazinamide[e,f] × 2 mo	Pyrazinamide 25 mg/kg/d × 2 mo
	Pyridoxine 25 mg/d × 6 mo	Pyridoxine 10–25 mg/d × 6 mo

Abbreviation: HIV, human immunodeficiency virus.

[a] Treatment of extrapulmonary tuberculosis involves the same medications as pulmonary tuberculosis, but many experts recommend 9–12 mo of treatment for tuberculosis meningitis (plus steroids) or tuberculosis bone/joint infections [70, 71].

[b] Based on recommendations of the Centers for Disease Control and Prevention, American Thoracic Society, and Infectious Diseases Society of America [70].

[c] Based on recommendations of the World Health Organization and International Union Against Tuberculosis and Lung Disease [71].

[d] Ethambutol weight-based dosing: 800 mg/d for 40–55 kg, 1200 mg/d for 56–75 kg, 1600 mg/d for ≥76 kg.

[e] Pyrazinamide weight-based dosing: 1000 mg/d for 50–55 kg, 1500 mg/d for 56–75 kg, 2000 mg/d for ≥76 kg.

[f] Pyrazinamide is only recommended in HIV-positive women because the benefit of potent 4-drug therapy in HIV-positive women outweighs the potential risk of pyrazinamide use during pregnancy [70].

transcriptase inhibitor therapy may be considered, but higher virological failure rates are a concern [70, 71]. Despite the challenge of finding an optimal treatment regimen for pregnant women with HIV/tuberculosis, coinfected women should be treated for both diseases [83].

Multidrug-Resistant Tuberculosis

Only case reports provide guidance for management of multidrug-resistant (MDR) tuberculosis in pregnancy [84–91] (Table 7). Most second-line agents are FDA pregnancy class C, except for aminoglycosides, which are mainly class D (Table 6).

Some women terminate their pregnancy to avoid teratogenicity of ATT. While there are obstetric, fetal, and infant complications associated with MDR tuberculosis regimens, small case series suggest that good outcomes are achievable [88, 91], but close monitoring is essential. Among 38 Peruvian pregnant women treated for MDR tuberculosis, 23 (60%) were cured, 5 (13%) died (4 from tuberculosis), and 2 experienced treatment failure. Eight (21%) experienced pregnancy complications, such as spontaneous abortion and vaginal bleeding. No infants displayed teratogenic effects [91] (Table 7).

Among 5 South African pregnant women with MDR tuberculosis, 3 of whom had HIV, 2 experienced adverse drug events (deafness and drug-induced hepatitis). The infants showed no evidence of teratogenicity [89].

Should a Woman With Active Tuberculosis Breastfeed?

The CDC encourages breastfeeding if a woman has been on first-line ATT and is no longer infectious [70]. WHO recommends breastfeeding once the mother is smear-negative [71, 92], because breastfeeding prevents other infections and malnutrition in resource-limited countries. There have been no documented cases of tuberculosis transmission via breast milk since the development of ATT [93]. Women with tuberculosis mastitis should breastfeed from the unaffected breast. Small concentrations of ATT are secreted into the breast milk (Table 6), posing minimal risk to the infant.

More caution is required with second-line ATT as there are minimal data regarding breast milk concentrations or potential adverse effects on infants (Table 6). Breastfeeding women should be advised of potential risks, but there are no absolute contraindications [75].

LATENT TUBERCULOSIS MANAGEMENT IN PREGNANCY

Women with latent tuberculosis have a 10% lifetime risk of reactivation. With HIV, the risk is 5%–10% per year without ART and approximately 2% on ART [92, 93]. These statistics demonstrate the need to treat latent tuberculosis, but there is disagreement over whether to do so during pregnancy (Table 5). WHO does not comment on whether to offer HIV-negative women INH during pregnancy, whereas the CDC

recommends delaying treatment of latent tuberculosis until 2–3 months postpartum, unless the patient has had a recent known tuberculosis contact [96].

One study from the pre-HIV era suggested that pregnant women treated with IPT had a 2.5–4 times increased risk of hepatitis and death compared with nonpregnant women [97]. The results, however, were not statistically significant.

Treatment regimens are described in Table 5, but there is a lack of clinical trial data in this area. Pregnant women were excluded from the recent trial demonstrating the efficacy of a 3-month INH/rifapentine regimen for latent tuberculosis [98]. Rifapentine is FDA category C and carries a risk of bleeding similar to its close relative, rifampin (Table 6) [99].

Safety Monitoring During Treatment

INH-associated hepatotoxicity ranges from 0.1% to 4%, but data from pregnant women are inadequate [72, 100]. Pregnancy induces cytochrome P450 [101], which may increase the risk of developing drug-induced liver injury. Although not formally validated, the American Thoracic Society/CDC/Infectious Diseases Society of America recommend assessment of baseline liver function tests (LFTs) prior to treatment initiation and every 4 weeks thereafter in pregnancy and early postpartum. If symptoms of hepatitis (eg, nausea, vomiting) develop, INH should be suspended and LFTs checked [102]. If the alanine aminotransferase level surpasses 5 times the upper limit of normal (ULN), or 3 times the ULN with symptoms, INH should be discontinued.

Because symptoms of pregnancy overlap with those of hepatitis, some experts recommend monitoring labs every 1–2 weeks in pregnancy for at least the first 8 weeks of therapy regardless of symptoms [72, 103]. A decision analysis found that antepartum IPT had a higher mortality rate from hepatitis than postpartum, but proper monitoring negates this effect [104]. Moreover, antepartum IPT resulted in the lowest number of tuberculosis cases, the lowest cost, and the highest life expectancy if the case fatality rate was >0.45%.

HIV-Positive Women

Although the CDC and WHO recommend early treatment of latent tuberculosis in HIV-positive pregnant women [51, 96], they may be at particular risk for drug-induced liver injury. HIV-positive pregnant women had 3.8 times increased risk of severe elevated LFTs compared to nonpregnant women, and hepatotoxicity from ART during pregnancy ranged from 0.5% to 25.9% [105, 106]. A recent study showed that concurrent ART with INH in nonpregnant adults is associated with increased rates of LFT abnormalities [107]. No preventive trials involving INH have included HIV-positive pregnant women. A trial funded by the National Institutes of Health (NIH), IMPAACT P1078, is assessing the safety of antepartum vs postpartum initiation of IPT in HIV-infected women residing in tuberculosis-endemic settings.

WHAT ARE THE INFANT OUTCOMES WITH TUBERCULOSIS DURING PREGNANCY?

Congenital Tuberculosis

Tuberculosis can be transmitted through hematogenous spread during pregnancy, aspiration of amniotic fluid during delivery, or respiratory droplets postpartum. Although congenital tuberculosis appears rare, in one small study in South Africa, vertical tuberculosis transmission occurred at a 16% rate, independent of maternal HIV status [47].

Infant Mortality and Other Complications

Infant mortality rates from tuberculosis vary dramatically between studies. In one study of 29 cases of perinatal tuberculosis, infant mortality was 38% [108]. In a separate study, of

Table 5. Preventive Tuberculosis Therapy in Pregnant Women

	Low-Burden Countries[a]	High-Burden Countries[b]
Regimen	Isoniazid 300 mg/d × 6–9 mo	Isoniazid 300 mg/d × 6 mo or 36 mo[c]
	Pyridoxine 25 mg/d × 6–9 mo	Pyridoxine 10–25 mg/d × 6 mo or 36 mo
	OR	
	Isoniazid 900 mg twice weekly × 9 mo	
	Pyridoxine 25 mg/d × 9 mo	
HIV-negative	Defer treatment for TST^+ or $IGRA^+$ until 2–3 mo postpartum unless recent known tuberculosis contact	No recommendations
HIV-positive	Immediate treatment for TST^+ or $IGRA^+$	Immediate treatment for all HIV- positive without active tuberculosis

Abbreviations: HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; TST, tuberculin skin test.

[a] Based on recommendations of the Centers for Disease Control and Prevention [96].

[b] Based on recommendations of the World Health Organization [51].

[c] Consider 36 months if in a setting with high tuberculosis prevalence and transmission.

Table 6. Pregnancy Safety and Breast Milk Information for Tuberculosis Medications

Drug	FDA Category[a]	Crosses Placenta (Cord:Maternal Ratio)	Fetal Toxicity	AAP Compatible With Breastfeeding	Present in Breast Milk (% of Infant Dose)	Other Information
First-line medications[b]						
INH	C	Yes (0.73)	CNS defects[c]	Yes	Yes (6.4–25)	Monitor maternal LFTs
RIF[d]	C	Yes (0.12–0.33)	Hemorrhage	Yes	Yes (0.57–7.3)	May require vitamin K; monitor HIV viral load if on NNRTIs and PIs; causes decreased efficacy of hormone-based contraceptives
EMB	C	Yes (0.75)		Yes	Yes (2.8–6.9)	
PZA	C	Unknown	Jaundice	Unknown	Yes (0.75–1.5)	Monitor PZA levels if on AZT[e]
Second-line medications						
Aminoglycosides[f]						
Streptomycin	D	Yes (<0.5)[72]	Ototoxicity, thrush, diarrhea	Yes	Yes (0.95–22.5)	
Capreomycin	C	Yes (Unknown)		Unknown	Unknown	
Kanamycin	D	Yes (Unknown)	Ototoxicity	Yes	Yes (0.95–18)	
Amikacin	D	Yes (<0.5)[73]	Ototoxicity likely	Unknown	Unknown	
Ethionamide/ prothionamide[f]	C	Unknown	Developmental anomalies	Unknown	Unknown	Monitor LFTs if on PZA, INH, RIF, EMB, or PAS; avoid use with cycloserine if seizure disorder
PAS	C	Unknown	Diarrhea	Unknown	Yes (0.05–0.95)	Monitor LFTs if on ethionamide and INH toxicity
Cycloserine	C	Unknown		Yes	Yes (11–28)	Avoid use with ethionamide if seizure disorder. Monitor for CNS toxicity with INH
Fluoroquinolones						
Levofloxacin	C	Yes (0.66)		Unknown	Yes	Absorption inhibited by ddI
Moxifloxacin	C	Yes (0.74)		Unknown	Unknown	Absorption inhibited by ddI
Gatifloxacin	C	Unknown		Unknown	Unknown	Absorption inhibited by ddI
Other						
Thioacetazone	N/A	Unknown		Unknown	Unknown	
Clofazimine	C	Unknown	Reversible skin pigmentation	No	Yes	
Clarithromycin	C	Yes (0.15)		Unknown	Unknown	Reduced if given with PIs or RIF, decreases maraviroc

Table 6 continued.

Drug	FDA Category[a]	Crosses Placenta (Cord:Maternal Ratio)	Fetal Toxicity	AAP Compatible With Breastfeeding	Present in Breast Milk (% of Infant Dose)	Other Information
Amoxicillin-clavulanic acid	B	Yes (0.56)	Necrotizing enterocolitis, transaminitis	Yes	Yes	
Rifabutin[f]	B	Unknown		Unknown	Unknown	Monitor for neutropenia with PIs, monitor HIV viral load on AZT and maraviroc
Rifapentine	C	Unknown		Unknown	Unknown	Monitor clotting factors; not recommended w/NNRTIs, PIs, monitor HIV viral load w/AZT
Linezolid[g]	C	Unknown		Unknown	Unknown	Reduced efficacy with RIF

Abbreviations: AAP, American Academy of Pediatrics; AZT, zidovudine, antiretroviral; CNS, central nervous system; ddI, didanosine, antiretroviral; EMB, ethambutol; FDA, Food and Drug Administration; LFT, liver function test; HIV, human immunodeficiency virus; INH, isoniazid; NNRTI, nonnucleoside reverse transcriptase inhibitor, antiretroviral; PI, protease inhibitor, antiretroviral; PAS, para-aminosalicylic acid; PZA, pyrazinamide; RIF, rifampin.

Sources: AAP Statement (2001); Micromedex 2.0; www.fda.gov.

[a] FDA category definitions:

A. Adequate and well controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy;

B. Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in humans AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

C. Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

D. There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

[b] Doses for first-line therapy for pregnant women are: INH 5 mg/kg (max: 300 mg orally daily), RIF 10 mg/kg (max: 600 mg orally daily), EMB 15 mg/kg, and PZA 25 mg/kg (max: 2 g orally daily). Treatment of MDR tuberculosis in pregnancy should be individualized but there are no established dosage adjustments for pregnancy.

[c] Earlier studies found increased frequency of mental retardation and seizures but more recent studies have not.

[d] Potent inducer of cytochrome P450. It is critical to check drug interactions with all medications patient is taking.

[e] No standard way to reliably measure PZA levels.

[f] Decreases efficacy of BCG vaccine.

[g] Not yet approved for tuberculosis treatment.

Table 7. Outcomes for Pregnant Women With Drug-Resistant Tuberculosis and Their Infants

Site	Study	Sample Size, No.	History of Tuberculosis, No.	Resistance Profile, No.	Treatment Regimen	Pregnancy Outcome	Average Time to Sputum Conversion, mo (Range)	Maternal Outcome	Infant Outcome
United States	Good et al[4]	16	16	INH: 16, PZA: 3, EMB: 1	Variable	1 spontaneous abortion	4.3 (1–12)	7 healthy	11 healthy
								2 dead	2 dead (miliary TB and TB meningitis)
								3 pulmonary insufficiency	2 TST positive
								1 deaf from streptomycin	1 pulmonary TB
								3 LTF	
Italy	Signorini et al[82]	1	Unknown[a]	INH, PZA[b]	RIF/EMB in pregnancy, Stm postpartum	C-section at 35 wk	2.75	healthy	Healthy
United States	Nitta and Milligan[83]	4	4	INH, RIF: 4, EMB: 2, Cyse, PAS, Stm, Eth-1	Variable (incl. Clof, Cpm, Cyse, Ofx, PAS, Ami, Eth, high-dose INH)	1 abortion (elective)	4 (3–5)	Healthy, completed 17–24 mo treatment	3 healthy
									2 TST positive
United States	Lessnau and Qarah[84]	1	0	INH, RIF, EMB, Stm	Cpm, Cyse, Levo, PAS, PZA	Spontaneous @ 35 wk	NR	healthy, completed 18 mo treatment	LBW
Peru	Shin et al[85]	7	7	INH, RIF, EMB: 7, Stm: 6, PZA: 5, Eth: 3, Cpm: 1	Variable (incl Stm, PAS, Cyse, Cpm, Ofx, Cipro, Eth, Amox-CA)	Normal term deliveries	1.8 (1–3)	3 healthy	7 healthy
	Drobac et al[86]							1 death	2 reversible skin bronzing from Clof
									1 MDR TB
									1 speech delay
South Africa	Khan et al[87]	5 (3 HIV$^+$)	5	INH, RIF, Stm: 5, EMB: 3, Eth, Thia: 1	NR	3 drug-related complications	13 (10–14)	HIV$^+$: 1 healthy, 1 discharged to other clinic, 1 LTF	HIV-exposed: 2 growth restricted; tx for TB
						1 elective abortion (HIV pos)		HIV$^-$: 2 healthy	HIV-unexposed: 2 healthy
						1 preterm delivery @34 wk (HIV neg)			
Iran	Tabarsi et al[88]	1	1	INH, RIF, EMB, Stm	Ofx, Ami, PZA, Pth, Amox-CA, high-dose INH	Normal term delivery	5	Healthy, completed 18 mo treatment	Healthy, empirically given EMB/PZA × 2 mo

Table 7 continued.

Site	Study	Sample Size, No.	History of Tuberculosis, No.	Resistance Profile, No.	Treatment Regimen	Pregnancy Outcome	Average Time to Sputum Conversion, mo (Range)	Maternal Outcome	Infant Outcome
Peru	Palacios et al[89]	38 (3 HIV^+)	34	MDR TB: 31, XDR TB: 1, DR TB: 4, clinical history: 3	Variable, incl INH, RIF, EMB, PZA, Stm, Cpm, Ofx, Levo, Eth, Pth, Cyse, PAS, Amox-CA, Clarithro	10 postpartum surgeries for TB	NR	23 cured[c]	25 healthy
						5 spontaneous abortions		5 dead	3 LBW
						4 worsened TB		5 LTF	2 latent TB
						2 vaginal bleeding		2 treatment failure	2 meconium aspiration
						2 premature rupture of membranes		2 still on treatment	1 active TB
									1 stillborn
									1 fetal distress
									1 dead

Abbreviations: DR, drug resistant; HIV, human immunodeficiency virus; LBW, low birth weight; LTF, lost to follow-up; MDR, multidrug resistant; NR, not reported; TB, tuberculosis; TST, tuberculin skin test; XDR, extremely drug resistant.

Drugs: Ami, amikacin; Amox-CA, amoxicillin-clavulanic acid; Cipro, ciprofloxacin; Clarithro, clarithromycin; Clof, clofazimine; Cpm, capreomycin; Cyse, cycloserine; EMB, ethambutol; Eth, ethionamide; INH, isoniazid; Levo, levofloxacin; Ofx, ofloxacin; PAS, para-amino salicylic acid; Pth, prothionamide; PZA, pyrazinamide; Stm, streptomycin; Thia, thiacetazone.

[a] Patient had received ceftriaxone, Ami, and Clarithro for bacterial pneumonia.

[b] Diagnosed with *Mycobacterium bovis*.

[c] Two died after treatment completion: 1 from tuberculosis, 1 from HIV.

32 infants born to 38 mothers with MDR tuberculosis, only 1 infant died of pneumonia [91].

Studies are similarly inconsistent on other adverse effects of maternal tuberculosis on the infant. There was no difference in outcomes among infants born to mothers treated for tuberculosis during pregnancy vs without tuberculosis in the United States [46], nor were there differences in perinatal complications in Indian women with tuberculosis lymphadenitis vs without tuberculosis [44]. However, babies born to Indian mothers with pulmonary or extrapulmonary tuberculosis other than lymphadenitis had increased risk of fetal distress, low birth weight, prematurity, and infant mortality [43, 44] (Table 3). Of infants born to mothers with MDR tuberculosis in Peru, similar complications occurred, although the rate was comparable to that of the general population [91].

HIV-Positive Women

Perinatal mortality, intrauterine growth restriction, and low birth weight are higher among women with tuberculosis/HIV coinfection as compared with HIV or tuberculosis monoinfection [47]. Infants of HIV-positive women who developed tuberculosis in the first year were more likely to die and to be HIV-infected than infants born to mothers with HIV alone [14, 109]. Larger prospective studies are ongoing.

IPT AND BCG VACCINATION

IPT reduces the negative consequences of infant exposure to maternal tuberculosis, but it has been poorly implemented in high-burden countries [110]. If the mother has received tuberculosis treatment for <2 months before delivery or remains potentially infectious, the child should be given IPT first. Several tuberculosis endemic countries only recommend IPT for children <5 years as they are at highest risk of developing tuberculosis [111].

In endemic countries, WHO recommends BCG vaccination in infants born to mothers with active tuberculosis after completion of infant IPT, as INH inhibits vaccine efficacy [92]. BCG vaccination is not recommended in HIV-infected infants because of the risk of disseminated BCG disease [112, 113].

FUTURE RESEARCH NEEDS

Women—especially pregnant and postpartum women—have been underrepresented in clinical trials, although progress has been made. In 1993, the FDA recommended including pregnant women in clinical trials of any medication likely to be used in pregnancy [114]. In 2009, the Medication Exposure in Pregnancy Risk Evaluation Program was launched to study prescription medications during pregnancy [115], but little information on tuberculosis medications has been collected.

Interventions affecting pregnant women also affect neonates. There is an urgent need for research in pregnant and postpartum women, including those who are HIV-positive, in these areas:

- Epidemiology of active tuberculosis and latent tuberculosis
- Immunology and pathogenesis of tuberculosis
- Cost-efficacy of screening methods for active tuberculosis and latent tuberculosis
- Performance of IGRAs with follow-up of persons with discordant IGRA/TST results
- Development of low-cost assays that distinguish active tuberculosis from latent tuberculosis
- PK, safety, and optimal timing of latent tuberculosis regimens, including INH and INH/rifapentine
- PK, safety, and outcome studies of first-line ATT and MDR tuberculosis medications
- Epidemiology and management of active tuberculosis and latent tuberculosis in infants born to mothers with tuberculosis

NIH-funded studies are under way to assess optimal timing of INH for HIV-infected women (IMPAACT P1078), pharmacology of ATT in HIV-infected and HIV-uninfected pregnant and postpartum women (IMPAACT P1026s), and outcomes of pregnant women with tuberculosis (RO1HD06435). Studies of PK and outcomes of novel combinations for latent tuberculosis and MDR tuberculosis are lacking. A tuberculosis pregnancy register, similar to the FDA ART pregnancy register, should be created to collect safety and outcome data from pregnant women taking ATT. Tuberculosis is the third leading cause of maternal mortality in the world. To stay on track with the Millennium Development Goal to decrease maternal mortality by 75% by 2015 and reduce tuberculosis-related infant morbidity and mortality, more focused attention on tuberculosis in pregnant and postpartum women is critical.

Notes

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