

Treatment of Tuberculosis during Pregnancy

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Introduction

- Untreated TB in pregnancy poses a significant threat to the mother, fetus and family
- The fear of fetal side-effects can sometimes impede proper treatment of the mother
- Early treatment of drug-sensitive TB in pregnancy with standard regimens is safe
- Little evidence to guide clinicians in the treatment of drug-resistant TB in pregnancy

TB is a major cause of mortality in pregnancy

- Johannesburg: 51% of deaths in HIV positive pregnant women were attributable to TB.
- TB was the third leading infectious cause of maternal deaths in Durban at 14.0% and Lusaka at 25% Botswana

Grange et al. **Tuberculosis in association with HIV/AIDS emerges as a major non- obstetric cause of maternal mortality in Sub-Saharan Africa.** *Int J Gynaecol Obstet.* 2010;108:181-183.

Black et al. Effect of HIV treatment on maternal mortality at a tertiary center in South Africa: a 5-year audit. *Obstet Gynecol.* 2009; 114:292-299,

Khan et al. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. *AIDS.* 2001;14:1857-1863

Treatment of drug-sensitive TB during pregnancy

- WHO and International Union against Tuberculosis and Lung Disease support the use of the standard regimen in pregnant women:
 - rifampicin, isoniazid for six months and ethambutol and pyrazinamide for the first two months (“rifair”)

Isoniazid

- Pyridoxine (vitamin B6) should be used during pregnancy
- **Safe in pregnancy:** no excess of birth defects have been noted in the babies of pregnant mothers taking rifampicin
- **Safe in breastfeeding**
- **Hepatitis:** some studies suggest higher incidence of drug-induced hepatitis during pregnancy
- Isoniazid is considered safe as preventative therapy in the form of **IPT**

Rifampicin

- Cytochrome P450 induction can result in clearance of contraceptive hormones and unplanned pregnancy
- **Safe in pregnancy:** no excess of birth defects have been noted in the babies of pregnant mothers taking rifampicin
- **Safe in breastfeeding**

Ethambutol

- **Safe in pregnancy:** no excess of birth defects have been noted in the babies of pregnant mothers taking rifampicin.
- **Safe in breastfeeding**

Pyrazinamide

- **No studies of safety in pregnancy:**
 - Extensive clinical experience supporting it's safety
 - WHO recommends the routine use of PZA in pregnancy

Options for treatment of DR-TB during pregnancy

- Need to consider risks and benefits for the mother and fetus.
 - Option 1: Stop or delay MDR-TB treatment
 - Option 2: Terminate the pregnancy
 - Option 3: Continue treatment while pregnant

Show of hands

- Option 1: Stop or delay MDR-TB treatment
- Option 2: Terminate the pregnancy
- Option 3: Continue treatment while pregnant

Guidelines – South Africa

- **SA DR-TB guidelines (2011):**
 - **Discuss condition and treatment plan with the patient**
 - Avoid injectable agents in the first trimester
 - Capreomycin is the drug of choice if an injectable agent cannot be avoided.
 - Ethionamide: Ethionamide should be given with caution

Evidence

- No conclusive evidence to aid clinicians
- Only case reports provide guidance for management of MDR-TB in pregnancy

Safety Classification of Medications During Pregnancy

- A = safety established in human studies
- B = safety presumed based on animal studies
- C = safety uncertain; no human or animal studies reveal an adverse effect
- D = safety uncertain; evidence of risk but use is justified in certain circumstances
- X = unsafe; evidence of fetal abnormalities and risk outweighs benefit of use

Streptomycin

- Safety class D
- Documented toxicity, worse in the first trimester
 - Study of 203 women who received streptomycin during pregnancy (72 during the first trimester)
 - 35 (17%) of infants developed hearing loss, vestibular dysfunction or 8th cranial nerve deficits
 - Use of streptomycin contraindicated in pregnancy

Robinson et al. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. NEJM 1964

MEDICAL INTELLIGENCE



HEARING LOSS IN INFANTS OF TUBERCULOUS MOTHERS TREATED WITH STREPTOMYCIN DURING PREGNANCY*

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IN a recent study¹ of the etiology of hearing loss in 200 preschool children the prenatal administration of streptomycin or dihydrostreptomycin for treatment of tuberculosis in pregnant women was not encountered. In the subsequent 100 cases, however, 2 children with congenital hearing loss were found whose mothers had received streptomycin for the treatment of tuberculosis during pregnancy.

The purpose of this report is to describe these 2 cases and to review the literature concerning congenital hearing loss from this cause.

Kanamycin, Amikacin

- Safety class D
 - Documented fetal ototoxicity with use of KM, 2.3%
 - No reports of amikacin associated fetal effects but the potential for ototoxicity must be assumed.

Briggs et al. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 6th ed. Philadelphia: Lippincott Williams & Wilkins, **2002**.

Capreomycin

- Safety class C
 - Less ototoxicity in adults compared with the aminoglycosides
 - No human or animal studies in pregnancy
 - Often recommended in the place of an aminoglycoside for use during pregnancy – evidence?

Fluoroquinolones

- Safety class C
 - Study of 200 women exposed to ciprofloxacin during the first trimester:
 - No documented teratogenic effects
 - Mean duration of exposure very short (only 5 to 10 days)
- Data regarding the prolonged use in pregnant patients is limited, but benefits likely outweigh risks.
- Data about newer fluoroquinolones such as moxifloxacin are still scarce

Schaefer et al.. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). Eur J Obstet Gynecol Reprod Biol **1996**; 69:83–9.

Ethionamide

- Safety class C
 - Animal studies (high doses) associated with congenital malformations
 - 2 studies of 47 cases and 1 of 70 cases without adverse effects;
 - In another study, 7 of 23 children had congenital malformations. (2 had down syndrome, spina bifida, gastrointestinal atresia, congenital heart defects)
- The use is controversial given the mixed data

Jentgens M. Ethionamide and teratogenic effect. *Prax Pneumol* **1968**; 22:699–704.

Zierski M. Influence of ethionamide on development of human fetus. *Grazlica I Choroby Plac* **1966**; 34:349–52.

Schardein JL. Chemically induced birth defects. New York: Marcel Dekker, **1993**:370.

Potworowski M, Sianozecka E, Szufiadowicz R. Ethionamide treatment and pregnancy. *Pol Med J* **1966**; 5:1152–8.

Cycloserine / Terizidone

- Safety class C
 - Few studies in pregnant patients
 - Animal studies do not document toxicity

PAS: para-aminosalicylic A=acid

- Safety class C
- Small epidemiological studies:
 - Case series of 43 women: 5 infants had congenital abnormalities
 - Case series of 123 women: 9.8% of infants

Clofazimine

- Known to cross the placenta
- Not associated with teratogenic effects in animal studies.
- Case reports of successful treatment of pregnant patients with leprosy without harm to the fetus.
- Infants may acquire bronze skin color from exposure in utero or through breast milk

Bedaquiline

- Category B drug
- No evidence of fetal harm in animal studies
- No data yet from human use

Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate for the Treatment of Multidrug-Resistant Tuberculosis. MMWR CDC. 2013;62:1-12

Linezolid

- Category C
- Not teratogenic in mice at high doses
- Some non-teratogenic fetal effects in animal studies were seen: i.e. low birth weight.
- No studies in women.
- It is not known if linezolid is excreted into breast-milk

Peru: Pregnancy and MDR-TB

10 year retrospective case study (1996-2005)

- 38 women treated during pregnancy
- 3.6% of the women in the larger cohort of 3089 patients
- 8% HIV infection rate

Palacios E, Dallman R, Muñoz M, et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. *Clin Infect Dis* 2009;48(10):1413-9.

Failure to provide contraception

- Of the 38 Peruvian women who received MDR-TB therapy while pregnant:
 - 3 patients were pregnant at the initiation of MDR-TB therapy
 - 35 patients (92.1%) became pregnant while receiving treatment
 - Integrated family planning with MDR-TB treatment was not available in Peru during this period

Peru cohort – TB outcomes

- TB outcomes:
 - 61% cured, 13% died, 13% defaulted, 5% remained in treatment and 5% treatment failure.

Pregnancy and infant outcomes

- 5 pregnancies terminated by spontaneous abortions, 1 stillborn
- 32 living newborns:
 - 25 healthy infants
 - No birth defects attributable to second line drugs
 - There was no monitoring of hearing function in these children
 - 7 infants with complications: MDR-TB, pneumonia, low-birth-weight

Peru cohort outcomes

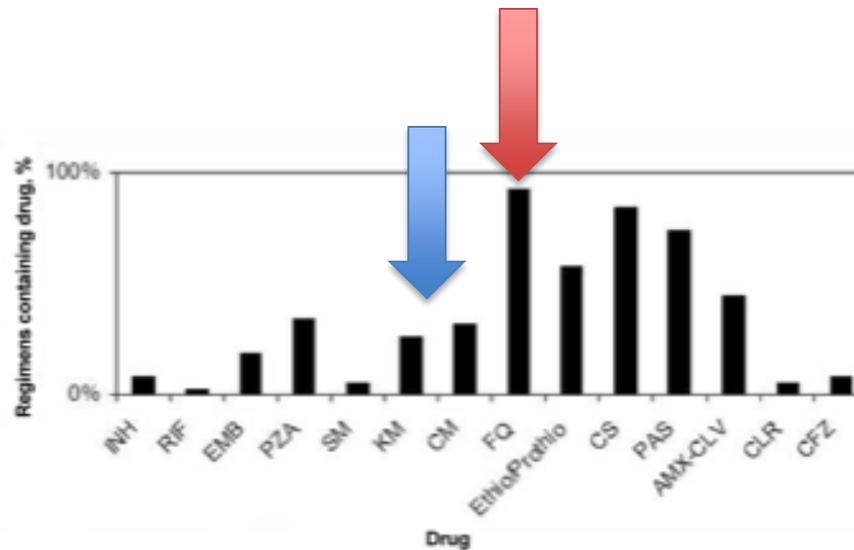


Figure 2. Frequency of use of each drug in initial multidrug-resistant tuberculosis treatment regimens ($n = 38$). AMX-CLV, amoxicillin–clavulanic acid; CFZ, clofazimine; CLR, clarithromycin; CM, capreomycin; CS, cycloserine; EMB, ethambutol; Ethio/Prothio, ethionamide/prothionamide; FQ, fluoroquinolone; INH, isoniazid; KM, kanamycin; PAS, para-aminosalicylic acid; PZA, pyrazinamide; RIF, rifabutin; SM, streptomycin.

Modifications to therapy

- Modifications were highly variable and patient specific
- No changes in regimen for 14/38 patients
- 30 women who were on an injectable at pregnancy diagnosis
 - 20 of them had their aminoglycosides temporarily or permanently stopped (median time on an aminoglycoside 4 to 8 months)
- Ethionamide stopped in 14 of 28 patients
- Fluoroquinolones, cycloserine, PAS were continued throughout the duration of pregnancy in the majority of patients

Peru: long term follow-up of children exposed to MDR drugs in utero

- 6 children were evaluated (ages 1 through 6)
- Early outcomes:
 - No perinatal complications or malformations
 - Babies exposed to clofazimine had bronzing of the skin which faded with time
- Late outcomes:
 - 1 child failure to thrive (below 3rd percentile)
 - 1 mild language delay
 - 4/6 children were exposed to AG – none had clinical hearing loss (3 of these were in the first trimester)
 - 1 child with MDR-TB at age 2, mother cured by birth, source presumed to be uncle

Iran: no complications with standard regimens

- Case series of 5 women treated in Tehran 2003-2009
- All HIV negative
- No changes were made to the treatment regimen:
AMK,CFZ,OFX,PTH,PZA +/- CS
- No obstetrical, congenital or neonatal complications or perinatal transmission of TB was observed

South African experience: poor outcomes in the pre-ART era

- Prospective study
- Case series of 5 HIV infected women treated between 1996-2001 at King Edward VIII, Durban
- Complications:
 - Prematurity, intrauterine growth restriction, maternal complications (hepatitis, hearing loss) were observed.
- Clinical signs of unconfirmed MDR-TB transmission to 2 infants

Start early or wait until the second trimester?

- Deferring treatment until second trimester:
 - Mexico City experience (drug sensitive TB): higher rates of obstetrical complications, preterm labor, and neonatal complications when TB treatment is delayed
 - US experience: 16 pregnancies with DR-TB: TB transmission amongst neonates 3 cases of active disease and 2 positive TSTs
 - Delaying DR-TB treatment to the second trimester is not benign

Figueroa-Damian et al. Pregnancy and tuberculosis: influence of treatment on perinatal outcome. 1998;15(5)303-306

Good et al. Tuberculosis in association with pregnancy. Am J Obstet Gynecol 1981; 140:492–8.

Delaying DR-TB treatment

- If DR-TB treatment is delayed should ART initiation also be delayed to reduce the risk of IRIS?
- Maternal HIV and TB co-infection increases rates of vertical transmission of HIV.
 - India: 30% of HIV and TB infected mothers transmitted HIV to their newborns, compared with only 12% of mothers uninfected with TB
- Delaying ART initiation is not benign

In Summary

- Insufficient data rather than compelling evidence of toxicity causes clinicians to err on the side of caution and undertreat pregnant patients DR-TB
- Compelling arguments to start treatment early (in the first trimester) especially in patients who are HIV co-infected
- Treatment delay can be considered if patient is stable and HIV negative

Recommendations

- Provide individualized care based on risks and benefits to the patient and foetus
- The patient should be involved in therapeutic decisions
- Pregnancy should not be terminated because of DR-TB infection

Recommendations

- There is limited evidence, but clinical experience has shown that **terizidone, moxifloxacin, and PAS** may be used safely in pregnant patients
- **During the first 20 weeks of pregnancy, avoid the injectable if possible.**
 - Exception: if the risk of mortality is high, an injectable agent should be used.
 - **Which injectable: Capreomycin or Kanamycin?**
- **Ethionamide:** Not enough data to confirm the safety or risk

Conclusion

- The best way to deal with DR-TB and pregnancy is to prevent it.
- DR-TB treatment programs must provide integrated contraceptive services
 - Depo-Provera can be provided at 3 month intervals during clinic visits
- Pregnancies should not be terminated because of DR-TB
- We need more data! Especially in the management of HIV and DR-TB co-infection!