Young women of child-bearing age presenting with DR TB

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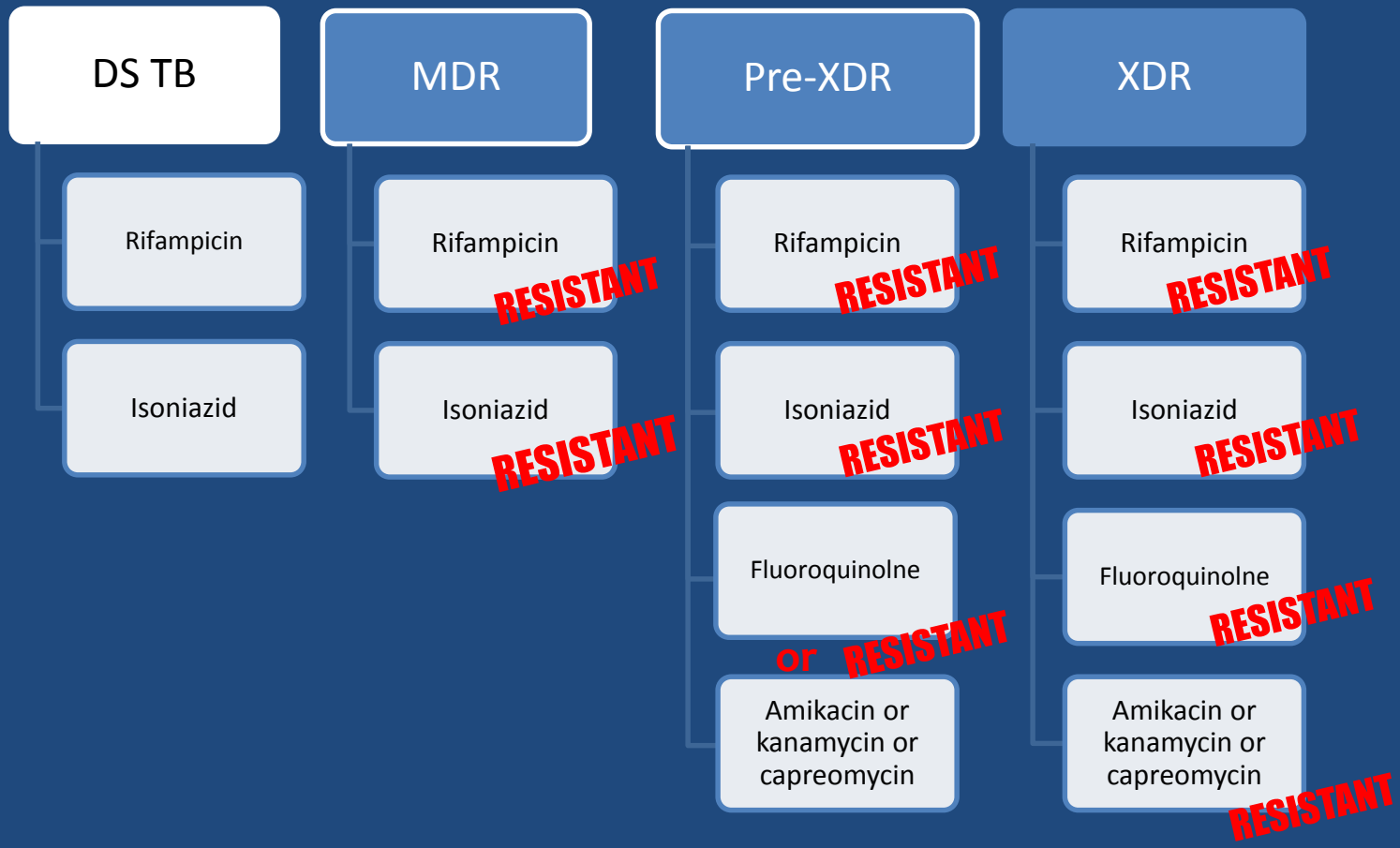
Definitions



Overview of the treatment of DR TB

- For Rifampicin resistant TB treatment duration is 18-24 months
- Standardised regimen:
  - Intensive phase Injectable aminoglycoside, quinolone, PZA, ethionamide and terizidone/ cycloserine for 6 months
  - Continuation phase quinolone, PZA, ethionamide and terizidone/ cycloserine for up to 18 months

Epidemiology of MDR TB in South Africa

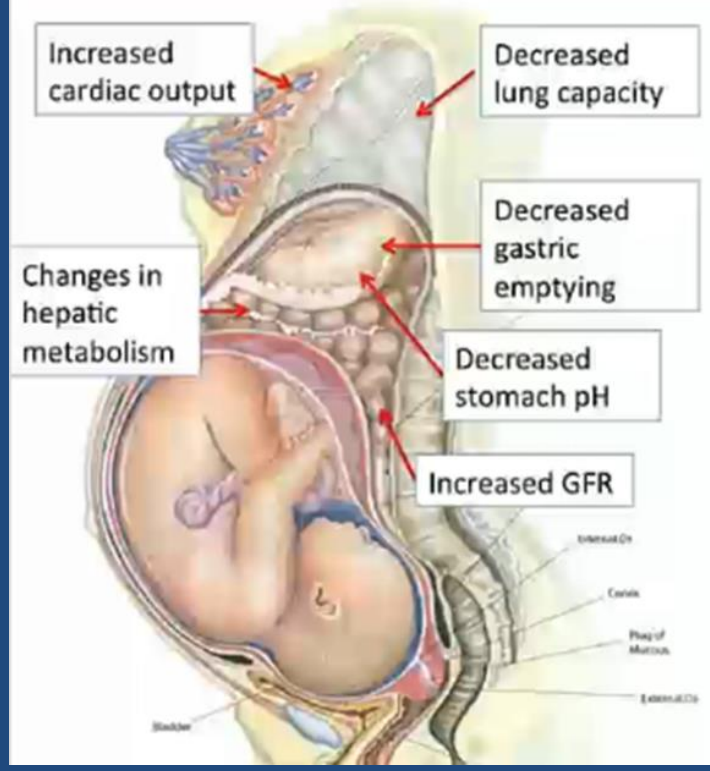
- **From 2009 to 2014**, 50 000 cases of RR-TB were registered
- Half were female
- Women were younger age (37 (IQR: 30–45) males and 32 (IQR: 26-40) for females)).
- Women were more likely to be HIV-infected (68.0% vs. 57.2%)

What is needed?

- Collect more evidence of the safety of second-line TB treatment during pregnancy
- Ensure access to effective contraception during second-line TB treatment
- Ensure women's health is included in research on prevention and treatment of TB

Safety of second-line TB treatment during pregnancy

Physiology Changes of Pregnancy Can Significantly Impact Drug Metabolism, Safety and Efficacy



- Increased body fat
- Increased total body weight
- Decreased albumin
- Hepatic metabolism
  - Increased CYP3A4
  - Decreased CYP1A2 and CYP2C19

Frederiksen, Sem Perinatol 2001; Anderson, Clin Pharmacokinetics 2005

- Untreated TB in pregnancy poses a significant threat to the mother, foetus and family
- The fear of foetal side-effects can sometimes impede proper treatment of the mother
- Little evidence to guide clinicians in the treatment of Drug-Resistant TB in pregnancy

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 8thcranial 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 study[1] 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 foetal ototoxicity with use of kanamycin- 2.3%
- No reports of amikacin associated foetal 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**.

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 EuoropeanNetwork of Teratology Information Services (ENTIS). EurJ ObstetGynecolReprodBiol**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

- JentgensM. Ethionamide and teratogenic effect. PraxPneumol**1968**; 22:699–704.
- ZierskiM. Influence of ethionamide on development of human fetus. GrazlicaI ChorobyPlac**1966**; 34:349–52.
- SchardeinJL. Chemically induced birth defects. New York: Marcel Dekker, **1993**:370.
- PotworowskiM,SianozeckaE,SzufladowiczR.Ethionamidetreatmentand pregnancy. Pol Med J **1966**; 5:1152–8.

Cycloserine / Terizidone

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

Options for treatment of DR-TB during pregnancy

- Options for treatment of DR-TB during pregnancy
  - Option 1: Stop or delay MDR-TB treatment
  - Option 2: Terminate the pregnancy
  - Option 3: Continue treatment while pregnant

Case study from Sizwe (1)

- 32 year old HIV non infected woman presented with rif resistance on GeneXpert
  - 32 weeks pregnant
  - First episode of TB
  - Non known MDR TB contact
  - Diagnosis confirmed on LPA and later on culture
  - INH and rif resistant, ethambutol resistant. Aminoglycoside and quinolone sensitive
  - CXR consistent with TB

Case study from Sizwe (2)

- Regimen chosen by clinician: Moxi, terizidone, PZA, clofazamine and PAS
- Culture positive at 4 weeks, same resistance pattern
- Deliver a full term infant 6 weeks after starting TB treatment
- Culture positive at 8 weeks, resistant to quinolones on LPA, confirmed later by culture.

Case study from Sizwe (3)

- Granted access to bedaquiline on clinical access program.
- Started on kanamycin, high dose levo, bedaquiline, terizidone, linezolid, clofazimine, PZA and ethionamide.
- Culture converted 8 weeks after starting modified regimen
- Cured at 24 months

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 should be given with caution

Ensure access to effective contraception during second-line TB treatment

- Treatment duration is long
- Clinical response occurs within three to six months
- TB services and Contraceptive services (and HIV services) are not always in the same clinic.

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, DallmanR, Muñoz M, et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. ClinInfect Dis2009;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: 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 3rdpercentile)
  - 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

Ensure women's health is included in research on prevention and treatment of TB

- Third pillar of the WHO strategy to end TB.
  - Reproductive health
  - Effective TB prophylaxis for women and infant
  - Pharmacokinetics of TB drugs in pregnancy
  - Pharmacokinetics of contraceptives and antiretrovirals during TB treatment

Conclusion

- Women of child bearing potential form a significant portion MDR TB patients
- Little guidance on treatment of pregnant women
- Need for on-going research