HEALTH SYSTEMS RESEARCH UNIT

26 March 2018

A database search and categorized annotated bibliography:

MDR-TB drug treatment outcomes in pregnancy

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REQUESTOR

Marian Loveday, Specialist Scientist, Health Systems Research Unit, South African Medical Research Council.

TASK: A search of systematic reviews on MDR-TB treatment outcomes in pregnancy

The requestor is interested conducting a systematic review of the effectiveness evidence of drug intervention treatments outcomes for

- mothers who contract MDR-TB during pregnancy,
- women who have MDR-TB and fall pregnant and
- the foetus and babies born to treated mothers, i.e. the intrapartum and post-partum effects of MDR-TB treatment

Currently there are at least 6 different drugs and several regimens used to treat MDR-TB, but their effectiveness and safety during pregnancy is not known, nor is anything known about possible adverse side-effects and risks to the mother and foetus.

This systematic review will feed into her MDR-TB national policy committee work. Before she conducts this review, she wanted to know if there are any existing systematic reviews and/or meta-analyses. We therefore conducted a rapid and condensed search to find systematic review protocols and/or full systematic reviews on this topic.

METHODS

Search strategy
We used key words related to Multidrug-Resistant Tuberculosis (MDR-TB), Pregnancy and different TB drugs names to draft the strategy (see Table 1). The strategy was appropriately adapted for the respective databases. The search was not limited to any setting and period.

Databases searched
We searched the following databases, known for hosting systematic reviews and protocols.

- Epistemonikos
- Prospero
- Cochrane library
- PDQ
- Pubmed

Additionally, in Pubmed we searched for articles relevant to MDR-TB publications by Barbara Seaworth and Masud Parvez, as suggested by the requestor.

Results
No systematic review protocols or full systematic reviews were found. After screening the records from each database, we found 28 publications that could possibly be relevant to the topic: 3 literature reviews and 25 primary studies. These studies are presented as a categorized annotated bibliography, with abstracts for most of the studies. Please see Table 1 for the search strategy as well as the outcome of the strategy as applied to select databases.

FURTHER REFINING THE SEARCH

We suggest that the requestor review the bibliography for relevance. For those articles that the requestor finds particularly relevant to her question, we will do a further citation search. This means that we will use google scholar to find all articles citing that study. This will generate a list of related studies and may pick up any articles that were missed in the first search.

Table 1: Search strategy and database search results.

			Database search					*Grey Search*	
		SEARCH TERMS	***Epistemonikos***	***Prospero***	***PDQ***	***Cochrane library***	***Pubmed***	***Barbara Seaworth***	***Masud Parvez***
#1	**Condition**	Pregnancy OR Pregnancies OR Gestation	9286	2471	More than 110	37011	10340		
#2	**Disease**	"Multidrug-Resistant Tuberculosis" OR "Tuberculosis, Multidrug Resistant" OR "Tuberculosis, MDR" OR "MDR Tuberculosis" OR "Tuberculosis, Multi-Drug Resistant" OR "Multi-Drug Resistant Tuberculosis" OR "Tuberculosis, Multi Drug Resistant" OR "Tuberculosis, Drug-Resistant" OR "Drug-Resistant Tuberculosis" OR "Tuberculosis, Drug Resistant" OR "MDR TB" OR "MDR-TB"	334	313	More than 110	353	9883		
#3	**Intervention**	Isoniazid OR pyrazinamide OR ethambutol OR fluoroquinilones, ofloxacin OR "para-aminosalacylic acid" OR clofazimine OR ethionamide levofloxacin OR bedaquiline OR delaminid OR meropenem	12,334	66	More than 110	2188	2810716		
#4		#1 AND #2	4	Prospero does not have an advance search button. Thus, search #2 and #3 were screened individually.	0	2	73	23	8
#5		# 3 AND #4	Only 4 studies were found in search #4. All studies were screened. Hence, #5 was not run.			Only 2 studies were found in search #4. All studies were screened. Hence, #5 was not run.	30	2	0
Title and Abstract screening: Result *(in stage we also removed duplicates)*			**4**	**0**	**0**	**0**	**22**	**2**	**0**

Categorized Annotated Bibliography

Literature reviews

1. Lessnau, K. D. and S. Qarah (2003). **"Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature."** Chest **123**(3): 953-956.
   A woman at 23 weeks' gestation was treated with rifampin, isoniazid, and ethambutol for cavitary tuberculosis (TB). She did not respond within 3 weeks, and multidrug-resistant (MDR) TB was suspected. Direct plating on susceptibility media was performed immediately. Treatment was initiated with IV capreomycin, levofloxacin, para-aminosalicylic acid, pyrazinamide, cycloserine, and high-dose vitamin B(6) at 26 weeks' gestation. The patient delivered vaginally at week 35. The newborn was not infected. Following delivery, ethionamide was added as a sixth drug, and levofloxacin was replaced with moxifloxacin. The patient's sputum became smear-negative and culture-negative for TB. All reported cases of MDR-TB during pregnancy are reviewed.

2. Loto, O. M. and I. Awowole (2012). **"Tuberculosis in pregnancy: a review."** J Pregnancy **2012**: 379271.
   Tuberculosis (TB) was declared a public health emergency by WHO in 2005. The disease is a significant contributor to maternal mortality and is among the three leading causes of death among women aged 15-45 years in high burden areas. The exact incidence of tuberculosis in pregnancy, though not readily available, is expected to be as high as in the general population. Diagnosis of tuberculosis in pregnancy may be challenging, as the symptoms may initially be ascribed to the pregnancy, and the normal weight gain in pregnancy may temporarily mask the associated weight loss. Obstetric complications of TB include spontaneous abortion, small for date uterus, preterm labour, low birth weight, and increased neonatal mortality. Congenital TB though rare, is associated with high perinatal mortality. Rifampicin, INH and Ethambutol are the first line drugs while Pyrazinamide use in pregnancy is gaining popularity. Isoniazid preventive therapy is a WHO innovation aimed at reducing the infection in HIV positive pregnant women. Babies born to this mother should be commenced on INH prophylaxis for six months, after which they are vaccinated with BCG if they test negative. Successful control of TB demands improved living conditions, public enlightenment, primary prevention of HIV/AIDS and BCG vaccination.

3. Rohilla, M., et al. (2016). **"Multidrug-Resistant Tuberculosis during Pregnancy: Two Case Reports and Review of the Literature."** Case Rep Obstet Gynecol **2016**: 1536281.
   Multidrug-resistant tuberculosis (MDR-TB) is identified from the time of introduction of antituberculosis treatment and is a known worldwide public health crisis affecting women of reproductive age group. Management issues raised by pregnant women with MDR tuberculosis are challenging due to the limited clinical experience available with the use of second line drugs. We hereby report two cases of MDR-TB during pregnancy: one patient was on second line drugs, while another one was evaluated and diagnosed to have MDR-TB in last trimester. At 6 months of follow-up both mothers and babies are doing well. The approach to such cases along with review of the literature is discussed.

Primary Studies

Treatment of Tuberculosis during pregnancy

1. Bothamley, G. (2001). **"Drug treatment for tuberculosis during pregnancy: safety considerations."** Drug Saf **24**(7): 553-565.
   Untreated tuberculosis in pregnancy poses a significant threat to the mother, fetus and family. Adherence to treatment is especially difficult in pregnancy because of the general fear of any medication and pregnancy-related nausea. Supervised treatment is especially helpful in

encouraging adherence. All 4 first line drugs [isoniazid, rifampicin (rifampin), ethambutol and pyrazinamide] have an excellent safety record in pregnancy and are not associated with human fetal malformations. Drug-induced hepatitis, especially with isoniazid, is a significant problem in treating tuberculosis, not peculiar to pregnancy; close monitoring of liver function is recommended. Liver enzyme induction by rifampicin alters the metabolism of other drugs, e.g. methadone doses will need to be increased. Streptomycin should not be used in pregnancy, as perhaps 1 in 6 babies will have problems with hearing and/or balance. Ciprofloxacin has the best safety profile of second line drugs in the treatment of drug-resistant tuberculosis. Preventive treatment with isoniazid can be undertaken safely during pregnancy. Pyridoxine (vitamin B6) should be added to the drug treatment of tuberculosis in all pregnant women taking isoniazid. Neither tuberculin nor the bacille Calmette Guerin (BCG) vaccine are treatments for tuberculosis, but they play an important role in the management of the disease. Tuberculin testing is safe, but BCG vaccination should be avoided in pregnancy and instead given earlier in life.

2. Deshpande, D., et al. (2018). "**Antibacterial and Sterilizing Effect of Benzylpenicillin in Tuberculosis**." Antimicrob Agents Chemother **62**(2).
   The modern chemotherapy era started with Fleming's discovery of benzylpenicillin. He demonstrated that benzylpenicillin did not kill Mycobacterium tuberculosis In this study, we found that >64 mg/liter of static benzylpenicillin concentrations killed 1.16 to 1.43 log10 CFU/ml below starting inoculum of extracellular and intracellular M. tuberculosis over 7 days. When we added the beta-lactamase inhibitor avibactam, benzylpenicillin maximal kill (Emax) of extracellular log-phase-growth M. tuberculosis was 6.80 +/- 0.45 log10 CFU/ml at a 50% effective concentration (EC50) of 15.11 +/- 2.31 mg/liter, while for intracellular M. tuberculosis it was 2.42 +/- 0.14 log10 CFU/ml at an EC50 of 6.70 +/- 0.56 mg/liter. The median penicillin (plus avibactam) MIC against South African clinical M. tuberculosis strains (80% either multidrug or extensively drug resistant) was 2 mg/liter. We mimicked human-like benzylpenicillin and avibactam concentration-time profiles in the hollow-fiber model of tuberculosis (HFS-TB). The percent time above the MIC was linked to effect, with an optimal exposure of >/=65%. At optimal exposure in the HFS-TB, the bactericidal activity in log-phase-growth M. tuberculosis was 1.44 log10 CFU/ml/day, while 3.28 log10 CFU/ml of intracellular M. tuberculosis was killed over 3 weeks. In an 8-week HFS-TB study of nonreplicating persistent M. tuberculosis, penicillin-avibactam alone and the drug combination of isoniazid, rifampin, and pyrazinamide both killed >7.0 log10 CFU/ml. Monte Carlo simulations of 10,000 preterm infants with disseminated disease identified an optimal dose of 10,000 U/kg (of body weight)/h, while for pregnant women or nonpregnant adults with pulmonary tuberculosis the optimal dose was 25,000 U/kg/h, by continuous intravenous infusion. Penicillin-avibactam should be examined for effect in pregnant women and infants with drug-resistant tuberculosis, to replace injectable ototoxic and teratogenic second-line drugs.

3. Drobac, P. C., et al. (2005). **"Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents."** Clin Infect Dis **40**(11): 1689-1692.
   Treatment of gestational multidrug-resistant tuberculosis (MDR-TB) is controversial. We describe follow-up of 6 children exposed to second-line antituberculous agents in utero. Each child (average age, 3.7 years) underwent comprehensive clinical evaluation. One child had MDR-TB diagnosed. There was no evidence of significant late-presentation toxicity among the

children. The results suggest that aggressive management of gestational MDR-TB may benefit both mother and child

4. Jaspard, M., et al. (2017). **"Bedaquiline and Linezolid for Extensively Drug-Resistant Tuberculosis in Pregnant Woman."** Emerg Infect Dis **23**(10).
   A woman with extremely drug-resistant tuberculosis treated with a drug regimen including linezolid and bedaquiline during her last 3 weeks of pregnancy gave birth to a child without abnormalities. No fetal toxicities were noted by 2 years after delivery. This drug combination might be safe during the late third trimester of pregnancy.

5. Palacios, E., et al. (2009). **"Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru."** Clin Infect Dis **48**(10): 1413-1419.
   BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) disproportionately affects young adults, including women of childbearing age; however, treatment of MDR-TB during pregnancy is still controversial. This study looks at the treatment and pregnancy outcomes in a cohort of women who were treated for MDR-TB during pregnancy during a period of 10 years. METHODS: A retrospective case study was performed using a standardized data collection form and data from 3 ranked sources of patient records. All 38 participants were treated during pregnancy with individualized regimens that included second-line TB medications. We examined the frequency of favorable and adverse outcomes with regard to disease and pregnancy. RESULTS: After completion of MDR-TB treatment, 61% of the women were cured, 13% had died, 13% had defaulted, 5% remained in treatment, and 5% had experienced treatment failure. Four of the women experienced clinical deterioration of TB during pregnancy. Five of the pregnancies terminated in spontaneous abortions, and 1 child was stillborn. Among the living newborns, 3 were born with low birth weight, 1 was born prematurely, and 1 had fetal distress. CONCLUSIONS: The rates of success in treating MDR-TB in our cohort are comparable to those of other MDR-TB treatment programs in Peru. The birth outcomes of our cohort are similar to those among the general Peru population. Therefore, we advocate that a woman should be given the option to continue treatment of MDR-TB rather than terminating pregnancy or discontinuing MDR-TB treatment.

6. Seung, K. J., et al. (2015). **"Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis."** Cold Spring Harb Perspect Med **5**(9): a017863.
   The continuing spread of drug-resistant tuberculosis (TB) is one of the most urgent and difficult challenges facing global TB control. Patients who are infected with strains resistant to isoniazid and rifampicin, called multidrug-resistant (MDR) TB, are practically incurable by standard first-line treatment. In 2012, there were approximately 450,000 new cases and 170,000 deaths because of MDR-TB. Extensively drug-resistant (XDR) TB refers to MDR-TB strains that are resistant to fluoroquinolones and second-line injectable drugs. The main causes of the spread of resistant TB are weak medical systems, amplification of resistance patterns through incorrect treatment, and transmission in communities and facilities. Although patients harboring MDR and XDR strains present a formidable challenge for treatment, cure is often possible with early identification of resistance and use of a properly designed regimen. Community-based programs can improve treatment outcomes by allowing patients to be treated in their homes and addressing socioeconomic barriers to adherence

7. Shin, S., et al. (2003). **"Treatment of multidrug-resistant tuberculosis during pregnancy: a report of**

7 cases." Clin Infect Dis **36**(8): 996-1003.
Multidrug-resistant tuberculosis (MDR-TB) is a global public health problem affecting women of childbearing age. Little is known, however, about the safety of the drugs used to treat MDR-TB during pregnancy. We describe 7 patients who were treated for MDR-TB during pregnancy. These patients had chronic tuberculosis that had caused extensive parenchymal damage and had high-grade resistance to antituberculous drugs. All patients received individualized antituberculous therapy prior to delivery of healthy term infants. Neither obstetrical complications nor perinatal transmission of MDB-TB was observed. One patient experienced treatment failure, and another abandoned therapy. The other 5 patients are currently cured or in treatment and have culture-negative status. In each of these 7 cases, excellent treatment outcomes were obtained for the women and their children. Under certain circumstances, MDR-TB can be successfully treated during pregnancy.

8. Tabarsi, P., et al. (2007). **"Multi-drug resistant tuberculosis in pregnancy: need for more intensive treatment."** Infection **35**(6): 477-478.
No abstract found

9. Tabarsi, P., et al. (2011). **"Standardised second-line treatment of multidrug-resistant tuberculosis during pregnancy."** Int J Tuberc Lung Dis **15**(4): 547-550.
We describe the efficacy and outcome of standardised second-line anti-tuberculosis (TB) medications during pregnancy. Treatment outcomes of five pregnant women with documented multidrug-resistant TB (MDR-TB) referred to the National Research Institute of Tuberculosis and Lung Diseases from 2003 to 2009 were analysed in two categories, maternal and neonatal. Patients became pregnant during treatment for MDR-TB without any changes in their anti-tuberculosis regimen. None of them had any adverse effects during pregnancy and delivery. No adverse effects were observed in mothers or neonates. The treatment of MDR-TB during pregnancy with a standardised second-line regimen in this study population was safe, with an acceptable rate of treatment success.

10. Takashima, T., et al. (2006**). "[Treatment outcome of patients with multidrug-resistant pulmonary tuberculosis during pregnancy]."** Kekkaku **81**(6): 413-418.
PURPOSE: To know the treatment outcome of patients with multidrug-resistant tuberculosis (MDR-TB) during gestation. METHOD: Retrospective study of 3 cases of pregnant women, who were treated for MDR-TB with a regimen including pyrazinamide, ethambutol, para-aminosalicylic acid, cycloserine and amoxicillin-clavulanic acid. RESULT: All patients showed a good response to anti-tuberculosis chemotherapy without any serious adverse effect, and were culture-negative at the time of delivery. Two patients delivered vaginally at weeks 40, and one patient delivered surgically at weeks 38. All newborns were healthy, and their tuberculin skin tests and placental tissue examinations were negative for tuberculosis. CONCLUSION: MDR-TB can be successfully treated during pregnancy by using a regimen including effective second-line anti-tuberculosis drugs.

11. Van Kampenhout, E., et al. (2017). **"Pharmacokinetics of moxifloxacin and linezolid during and after pregnancy in a patient with multidrug-resistant tuberculosis."** Eur Respir J **49**(3).
No abstract found.

Management of pregnant women with TB

12. Mathad, J. S. and A. Gupta (2012**). "Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps."** Clin Infect Dis **55**(11): 1532-1549.
    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.

13. Nitta, A. T. and D. Milligan (1999). **"Management of four pregnant women with multidrug-resistant tuberculosis."** Clin Infect Dis **28**(6): 1298-1304.
    This case series describes the medical management of four pregnant women with active multidrug-resistant tuberculosis. None of the four patients were infected with human immunodeficiency virus. Three patients had disease due to multidrug-resistant Mycobacterium tuberculosis, and one had disease due to multidrug-resistant Mycobacterium bovis. Only one patient (patient 3) began retreatment during pregnancy, because her organism was susceptible to three antituberculosis drugs that were considered nontoxic to the fetus. Despite concern over teratogenicity of the second-line antituberculosis medications, careful timing of treatment initiation resulted in clinical cure for the mothers, despite some complications due to chronic tuberculosis and/or therapy. All infants were born healthy and remain free of tuberculosis. Pregnancy and multidrug-resistant tuberculosis need not be a public health disaster, as both conditions can be managed concurrently and successfully.

14. Signorini, L., et al. (1998). **"Tuberculosis due to drug-resistant Mycobacterium bovis in pregnancy."** Int J Tuberc Lung Dis **2**(4): 342-343.
    We describe the management practices adopted in a case of pulmonary and extra-pulmonary tuberculosis caused by an isoniazid/pyrazinamide resistant strain of Mycobacterium bovis in a 26-week pregnant woman. She was initially treated with rifampin, isoniazid and ethambutol, pre-term delivery was induced and streptomycin was then added to the regimen. Screening of the new-born revealed no signs of either disease or infection. Isoniazid prophylaxis was not administered and the new-born was vaccinated and isolated from the mother for two months; however she continued to be fed with her mother's milk for the whole period.

Tuberculosis in children

15. Skevaki, C. L. and D. A. Kafetzis (2005). **"Tuberculosis in neonates and infants: epidemiology, pathogenesis, clinical manifestations, diagnosis, and management issues."** Paediatr Drugs **7**(4): 219-234.
    Tuberculosis is one of the leading infectious causes of death and as such represents a major

global health problem. Infants may develop congenital tuberculosis from an infectious mother or, most commonly, they may acquire postnatal disease by contact with an infectious adult source. Important epidemiologic, pathogenetic, and clinical data regarding the management of infantile disease are reviewed. Diagnostic evaluation includes tuberculin skin tests, chest radiography and other imaging studies, smears and cultures, examination of the cerebrospinal fluid, and polymerase chain reaction, as well as the more recent interferon-gamma assay. Pregnant women with a positive Mantoux skin test but normal chest x-ray should either start chemoprophylaxis during gestation or after delivery depending on the likelihood of being recently infected, their risk of progression to disease, as well as their clinical evidence of disease. Pregnant women with a positive Mantoux skin test and chest x-ray or symptoms indicative of active disease should be treated with non-teratogenic agents during gestation; all household contacts should also be screened. When tuberculosis is suspected around delivery, the mother should be assessed by chest x-ray and sputum smear; separation of mother and offspring is indicated only if the mother is non-adherent to medical treatment, needs to be hospitalized, or when drug-resistant tuberculosis is involved. According to the American Academy of Pediatrics, treatment of latent infection is highly effective with isoniazid administration for 9 months. This regimen may be extended to 12 months for immunocompromised patients. When drug resistance is suspected, combination therapies, which usually consist of isoniazid with rifampin (rifampicin), are administered until the results of susceptibility tests become available. Organisms resistant to isoniazid only may be treated with rifampin alone for a total of 6-9 months. All infants with tuberculosis disease should be started on four agents (isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin) until drug susceptibility is assessed. For susceptible intrathoracic tuberculosis, isoniazid, rifampin, and pyrazinamide are administered for a total of 2 months, at which point pyrazinamide is withdrawn and the other two agents are continued for another 4-10 months depending on the severity of the disease. The same regimen may be applied in extrapulmonary tuberculosis with the exception of skeletal, miliary, and CNS disease, which require daily administration of isoniazid, rifampin, pyrazinamide, and streptomycin for 1-2 months, followed by isoniazid and rifampin daily or twice weekly for another 10 months. When drug-resistant tuberculosis is suspected, a regimen of isoniazid, rifampin, and pyrazinamide plus either streptomycin or ethambutol should be initially prescribed, until the results of susceptibility tests become available. HIV-seropositive infants with pulmonary tuberculosis should receive isoniazid, rifampin, pyrazinamide, and ethambutol or an aminoglycoside for 2 months, followed by isoniazid and rifampin for a total of at least 12 months. Apart from conventional antimycobacterial agents, novel therapeutic modalities, which stimulate the host immune system such as interleukin-2 (IL-2), IL-12, interferon-gamma, and tumor necrosis factor antagonists have been tested with promising results.

Other Primary Studies that might be of interest

Tuberculosis and pregnancy

16. Bates, M., et al. (2015). **"Perspectives on tuberculosis in pregnancy."** Int J Infect Dis **32**: 124-127. Tuberculosis (TB) has been recognized as an important cause of morbidity and mortality in pregnancy for nearly a century, but research and efforts to roll out comprehensive TB screening and treatment in high-risk populations such as those with a high prevalence of HIV or other

diseases of poverty, have lagged behind similar efforts to address HIV infection in pregnancy and the prevention of mother-to-child-transmission. Immunological changes during pregnancy make the activation of latent TB infection or de novo infection more likely than among non-pregnant women. TB treatment in pregnancy poses several problems that have been under-researched, such as contraindications to anti-TB and anti-HIV drugs and potential risks to the neonate, which are particularly important with respect to second-line TB treatment. Whilst congenital TB is thought to be rare, data from high HIV burden settings suggest this is not the case. There is a need for more studies screening for TB in neonates and observing outcomes, and testing preventative or curative actions. National tuberculosis control programmes (NTPs) should work with antenatal and national HIV programmes in high-burden populations to provide screening at antenatal clinics, or to establish functioning systems whereby pregnant women at high risk can drop in to routine NTP screening stations.

17. Efferen, L. S. (2007). **"Tuberculosis and pregnancy."** Curr Opin Pulm Med **13**(3): 205-211.
    PURPOSE OF REVIEW: To provide a summary of the diagnostic and therapeutic challenges, including risks and benefits of treatment, of tuberculosis and latent Mycobacterium tuberculosis infection during pregnancy. RECENT FINDINGS: Recent developments in diagnostic options have added to the armamentarium of tests available to diagnose latent Mycobacterium tuberculosis infection. Increasing evidence supports the potential for successful treatment of multidrug-resistant tuberculosis during pregnancy with good maternal and neonatal outcomes. The impact of genital tuberculosis on the outcome of assisted in-vitro fertilization techniques is noted. SUMMARY: The diagnostic approach for the evaluation of tuberculosis or latent Mycobacterium tuberculosis infection is unchanged by pregnancy, and includes clinical suspicion of disease, tuberculin skin testing or interferon-gamma-based assay, chest radiography with appropriate shielding when indicated, and acid-fast bacillus stain and culture of clinical material. For patients with active tuberculosis, therapy should be initiated as soon as the diagnosis is established. Initiation of treatment for latent infection during pregnancy should be considered based on the risk for progression to active disease.

18. Gach, O., et al. (1999). **"[Breast abscess and pregnancy toxemia revealing multidrug resistant tuberculosis]."** Rev Mal Respir **16**(5): 842-845.
    We report here the case of a 33-year-old woman admitted in hospital for eclampsia. An infectious course led to the diagnosis of tuberculosis breast abscess with laryngitis and tuberculous bilateral excavated bronchopneumonia. The isolated strain demonstrated resistance to the principals antituberculous agents. However, outcome was favorable after cesarean and treatment adapted to sensitivity studies.

19. Padmapriyadarsini, C., et al. (2007). **"Multidrug-resistant tuberculosis in pregnancy."** J Coll Physicians Surg Pak **17**(10): 637-639.
    This is a case report of 26 years old pregnant woman with multidrug-resistant tuberculosis (MDR TB), treated at outpatient department of New Delhi Tuberculosis (NDTB) Centre, India with second line agents. Before presentation at NDTB Centre, she had been treated with first line drugs for approximately one and-a-half-year, including category II re-treatment DOTS regimen under RNTCP. Patient conceived twice during her anti-TB treatment. The first one was during her category II treatment, when put on second line drugs. We describe congenital abnormalities documented in her second child exposed in-utero to second line anti-tubercular drugs with a brief review of treatment of MDR TB in pregnancy.

20. Khan, M., et al. (2007). **"Pregnancies complicated by multidrug-resistant tuberculosis and HIV co-infection in Durban, South Africa."** Int J Tuberc Lung Dis **11**(6): 706-708.
SETTING: Tertiary hospitals in KwaZulu Natal, South Africa. OBJECTIVE: To study the impact of multidrug-resistant tuberculosis (MDR-TB) and human immunodeficiency virus-1 (HIV-1) co-infection during pregnancy on maternal and perinatal outcome. DESIGN: Prospective study performed between 1996 and 2001. Symptomatic pregnant women were investigated for TB. Those with confirmed MDR-TB were reported on. RESULTS: Three of five pregnant women with MDR-TB were HIV-1 co-infected. One woman decided to terminate the pregnancy and one experienced pre-term labour. Two neonates had features of growth restriction. CONCLUSION: Management of pregnant women with MDR-TB in an HIV-endemic area is possible in developing countries.

21. Oliveira, H. B. and S. H. Mateus (2011). **"[Characterization of multidrug-resistant tuberculosis during pregnancy in Campinas, State of Sao Paulo, Brazil, from 1995 to 2007]."** Rev Soc Bras Med Trop **44**(5): 627-630.
INTRODUCTION: There was a follow-up of pregnant women treated for multidrug-resistance tuberculosis (MDR-TB) during pregnancy in Campinas, State of Sao Paulo, Brazil, from 1995 to 2007. METHODS: In a retrospective study, patients with tuberculosis who were resistant to at least isoniazid and rifampicin and had pregnancy at any time during the treatment were included. The cases were individually treated, considering drug susceptibility test results and patients' prior treatments. RESULTS: Seven cases presented resistance to two or more drugs. Three were already pregnant before the beginning of the treatment, and four conceived after. Two were with AIDS; one died, and the therapeutic program in the other one failed. All showed advanced tuberculosis with acute radiological findings, and the median sputum conversion time for five patients was four months. Two patients were cured. Two newborn babies were infected with HIV by their mothers. CONCLUSIONS: The outcome was unsatisfactory, and direct supervision is imperative in MDR-TB during pregnancy. The family planning program should be strongly recommended.

22. Signorini, L., et al. (1998). **"Tuberculosis due to drug-resistant Mycobacterium bovis in pregnancy."** Int J Tuberc Lung Dis **2**(4): 342-343.
We describe the management practices adopted in a case of pulmonary and extra-pulmonary tuberculosis caused by an isoniazid/pyrazinamide resistant strain of Mycobacterium bovis in a 26-week pregnant woman. She was initially treated with rifampin, isoniazid and ethambutol, pre-term delivery was induced and streptomycin was then added to the regimen. Screening of the new-born revealed no signs of either disease or infection. Isoniazid prophylaxis was not administered and the new-born was vaccinated and isolated from the mother for two months; however she continued to be fed with her mother's milk for the whole period.

Sharma, J. B., et al. (2017). "**Multi drug resistant female genital tuberculosis: A preliminary report**." Eur J Obstet Gynecol Reprod Biol **210**: 108-115.
OBJECTIVE: Evaluation of 6 patients presenting with tubo-ovarian mass or infertility with multi drug resistant (MDR) female genital tuberculosis (FGTB). STUDY DESIGN: It was an observational study in a tertiary referral centre, India on subjects with MDR FGTB on clinical examination and investigations. All patients were given category IV drugs using kanamycin (intramuscular), levofloxacin, pyrazinamide, cycloserine, ethionamide and ethambutol (or para aminosalicylic

acid [PAS] for ethambutol resistant cases) for 6 months intensive phase followed by oral levofloxacin, cycloserine, ethionamide and ethambutol (or PAS for ethambutol resistant cases) for 18 months continuation phase. Patients were evaluated for primary end points (complete cure, partial response, no response, treatment completed) and secondary end points (recurrence rate, pregnancy rate) during treatment. RESULTS: There were 2 (33.3%) primary MDR FGTB patients and 4 (66.6%) secondary MDR FGTB (three pulmonary MDR and one MDR lymphadenitis) patients. Mean age was 23.6 years. Presenting features were menstrual dysfunction in all patients (100%) especially oligomenorrhea in 3 (50%) patients, weight loss in all the patients (100%), cough with expectoration in three patients (50%), tubo-ovarian masses in five (83.3%) patients. Endometrial biopsy showed positive culture for AFB with rifampicin and isoniazid (INH) resistance in both primary MDR FGTB patients and in two secondary MDR FGTB patients who were sexually active. In secondary MDR FGTB, three pulmonary MDR patients had positive sputum AFB smear and culture, while the patient with MDR lymphadenitis had lymph node aspirate for AFB smear and culture positive with all showing resistance to rifampicin and isoniazid. Gene Xpert on endometrial biopsy or sputum was positive in 5 (83.3%) patients. Three (50%) patients (one primary and two secondary) have completed therapy while other 3 (50%) are in continuation phase. All patients are asymptomatic with one having 12 weeks ongoing successful pregnancy. CONCLUSION: MDR FGTB should be thought of in women of FGTB with tubo- ovarian masses who are not responding to first line drugs. Gene Xpert can be used in early diagnosis of MDR FGTB.

23. Zumla, A., et al. (2014). **"The neglected global burden of tuberculosis in pregnancy**." Lancet Glob Health **2**(12): e675-676.
    No Abstract found.

24. Ghosh, K., et al. (2011). **"Tuberculosis and female reproductive health."** J Postgrad Med **57**(4): 307-313.
    Tuberculosis (TB) is an important cause of mortality and morbidity all over the world and is particularly relevant in developing countries like India where the disease is endemic. Female reproductive system is very vulnerable to this infection and clinical presentation of this disease in female reproductive tract is protean in nature and in a large majority of patients could be completely silent. This disease is an important cause of infertility, menstrual irregularity, pregnancy loss, and in association with pregnancy, morbidity to both the mother and child increases. Some of the effects of TB infection on female genital tract could be remote in nature due to infection elsewhere. Medicines used to treat TB infection can also have adverse effects on contraception and other areas of female reproductive health. HIV coinfection and multidrug-resistant tuberculosis (MDR-TB) and increased population migration from developed to developing countries have now added a whole new dimension to this infection. Though new, finer diagnostic tools of detection of TB are increasingly available in the form of bacterial cultures and polymerase chain reaction (PCR) based diagnostics, suspicion by clinicians remains the main tool for diagnosis of the condition. Hence, doctors need to be properly trained to become "Tuberculosis Minded".

Tuberculosis diagnosis during pregnancy

25. Bates, M., et al. (2013). **"Use of the Xpert((R)) MTB/RIF assay for diagnosing pulmonary tuberculosis comorbidity and multidrug-resistant TB in obstetrics and gynaecology inpatient**

wards at the University Teaching Hospital, Lusaka, Zambia." Trop Med Int Health **18**(9): 1134-1140.
OBJECTIVES: In high-tuberculosis (TB)-endemic countries, comorbidity of pulmonary TB in hospitalised patients with non-communicable diseases is well documented. In this study, we evaluated the use of the Xpert((R)) MTB/RIF assay for the detection of concomitant pulmonary TB in patients admitted to the University Teaching Hospital, Lusaka, Zambia, with a primary obstetric or gynaecological condition. METHODS: The Study population were inpatients admitted with a primary obstetric or gynaecological problem who had a concomitant cough and were able to expectorate a sputum sample. Sputum samples from 94 patients were analysed for the presence of Mycobacterium tuberculosis (M.tb) by standard smear microscopy, MGIT culture, MGIT drug-susceptibility testing (DST) and the Xpert((R)) MTB/RIF assay. The sensitivity and specificity of the Xpert((R)) MTB/RIF assay were evaluated against the culture gold standard. RESULTS: Twenty-six of 94 (27.7%) patients had culture-confirmed pulmonary TB. The Xpert((R)) MTB/RIF assay had a sensitivity of 80.8% [95% CI: 60.0-92.7%]) compared against MGIT culture. The Xpert((R)) MTB/RIF assay was more sensitive than sputum smear microscopy (21/26 (80.8%) vs. 13/26 (50.0%), P = 0.02) and detected an additional eight culture-confirmed cases. Culture DST analysis identified two monoresistant M.tb strains: one resistant to rifampicin (rifampicin sensitive by the Xpert((R)) MTB/RIF assay) and one to ethambutol. HIV infection was linked with a 3-fold increase in risk of TB, accounting for 87.5% (21/24) of TB cases. 50% of cases presented as comorbidities with other communicable diseases (CDs) and non-communicable diseases (NCDs). CONCLUSIONS: As an alternative to sputum microscopy, the Xpert((R)) MTB/RIF assay provides a sensitive, specific and rapid method for the diagnosis of pulmonary TB in obstetric or gynaecological inpatients. Pulmonary TB is an important cause of concomitant comorbidity to the obstetric or gynaecological condition necessitating admission. TB and HIV comorbidities with other communicable and non-communicable diseases were also common. More proactive screening for TB comorbidity is required in obstetric and gynaecological wards.

SYNTHESIS TEAM

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