PRACTICAL DRUG SAFETY

Drug Safety 2001; 24 (7): 553-565
0114-5916/01/0007-0553/$22.00/0

Drug Treatment for Tuberculosis during Pregnancy

Safety Considerations

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Contents

Abstract

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 Guérin (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.

1. Tuberculosis in Pregnancy

Tuberculosis is a common disease in the world today, responsible for 2 million deaths and 8 million new cases each year and with a prevalence of 16 million cases and 1.86 billion infected individuals.[1] Tuberculosis is an infectious disease which is spread by coughing infectious particles into the air which are then breathed in by another individual. Approximately two-thirds of cases have tuberculosis affecting the lung of which half can transmit the disease (smear-positive pulmonary tuberculosis). The age distribution often means that tuberculosis is more common during pregnancy than in the general population, with rates as high as 0.1% even in areas of the US.[2]

Women have a higher proportion of nonpulmonary tuberculosis.[3,4] These forms of tuberculosis are more difficult to diagnose; indeed symptoms such as fatigue and loss of appetite are common in pregnancy itself, further delaying medical attention.[5] Untreated tuberculosis in pregnancy was thought not to have any worse outcome for the mother than pregnancy in women without tuberculosis.[6-8] A recent paper, however, did suggest some morbidity, which was entirely caused by the need to stay in hospital.[9] Mortality can be high in the presence of concurrent HIV infection.[10] Obstetric outcome, if the mother has tuberculosis, is poorer than for other pregnancies: the incidence of pre-eclampsia, vaginal bleeding, early fetal death, prematurity, small for dates and low birth weight, a low Apgar score and perinatal death are all more common than in pregnancies without tuberculosis.[11-13] Congenital tuberculosis, caused by the transfer of bacteria from the mother via the placenta, has a 50% mortality.[14] Early diagnosis and treatment of tuberculosis in pregnancy is, therefore, essential.

The purpose of this review is to discuss the safety of drug treatments for tuberculosis in pregnancy. In view of the importance of early diagnosis, especially in pregnancy, a section on the safety of tuberculin testing has been included. Preventive measures, especially bacille Calmette Guérin (BCG) vaccination, are valuable and a comment on the need to vaccinate before pregnancy is made.

2. Adherence to Treatment

Adherence depends on the agreement between the woman and doctor on the nature of the illness and the relative risks and benefits of treatment. There is a general perception that all medicines are dangerous during pregnancy. Pregnant women are especially concerned about the possible adverse effects of treatment, not only for themselves but also for their unborn child. Treatment of tuberculosis is particularly difficult, as the woman may attribute the nausea of pregnancy to the drugs used. At the other extreme, patients may not feel unwell from tuberculosis or may feel dramatically better within 2 weeks to 2 months into the 6 month course and so discontinue their treatment. As with antenatal care, a woman-centred approach and motivated staff can promote a trusting relationship within which treatment of tuberculosis can be successfully completed.

Interruption of treatment can be dangerous, especially where antituberculosis drugs are not available as combined preparations. Treatment with a single drug invariably leads to drug-resistance and relapse (as was noted shortly after the introduction of streptomycin).[15] The incidence of naturally occurring isoniazid resistance is approximately 5 to 10%,[16] so that treatment with rifampicin (rifampin) and isoniazid alone is not recommended.[17,18] Irregular treatment can prevent the expected cure of tuberculosis after 6 months treatment with 4 drugs in the initial phase. Relapse occurs and the implications are the same as for untreated tuberculosis, i.e. a poor obstetric outcome and significant risk of tuberculosis in close family members.

Adherence can be promoted by directly observed or supervised therapy.[19] Supervision can be carried out by family members, members of the community or health workers, or by attendance at

a local clinic. Studies in both Pakistan and the Punjab show that many believe pregnancy will increase the risks of recurrence of tuberculosis and that treatment will not work during pregnancy.[20] Failure to take treatment for tuberculosis is also more common among pregnant or lactating women in the Philippines because of fear that the drugs would cause a miscarriage, reduce the ability to breastfeed or harm the baby[21] and similar concerns are raised in the UK in all ethnic groups (unpublished observations). Local beliefs and fears about pregnancy and tuberculosis may, therefore, make supervision by members of the family or local community less effective than by trained health workers.

3. Treatment of Tuberculosis in Pregnancy

Standard treatment for tuberculosis (rifampicin and isoniazid for 6 months, with pyrazinamide and ethambutol for the first 2 months) should be given in pregnancy (see table I).[22] In the US, the lack of published evidence on the possible teratogenicity of pyrazinamide has led the US Centers for Disease Control to recommend a 9 month regimen of rifampicin, isoniazid and ethambutol with pyridoxine (vitamin B6).[23,24] However, Davidson[25] recommends treating tuberculosis with the most effective regimen, including pyrazinamide, even in pregnant patients. Resistance to both rifampicin and isoniazid has become increasingly common, especially in those whose disease has relapsed after treatment for tuberculosis, such that a 4 drug regimen while awaiting the results of antibacterial sensitivities is now recommended.[22] Streptomycin should not be used in pregnancy because 1 in 6 babies develop problems with hearing or balance.[26,27] Combined preparations are especially important in preventing drug resistance and are available for 2 and 3 drugs of the recommended 4-drug regimen.

In experimental animal models, both ethambutol and rifampicin were more effective when given intermittently and isoniazid shared this feature for intervals of up to 4 days.[28] Intermittent regimens allow complete supervision of treatment and are also cheaper. Three times weekly regimens are recommended. Missing 1 day of a 3-weekly regimen can allow an effective twice-weekly regimen to be used for that week (the doses of rifampicin and isoniaizid remain the same but ethambutol is increased to 45 mg/kg and pyrazinamide to 75 mg/kg to a maximum of 3.5g). Twice weekly regimens are not recommended for continuous treatment as missing a dose leads to a long gap between treatment, such that the efficacy of isoniaizid is reduced and the serious adverse effects from rifampicin become more common (see section 3.2.4).[29]

3.1 Isoniazid

3.1.1 Mode of Action and Pharmacokinetics

Isoniazid is the 'penicillin' for *Mycobacterium tuberculosis*; it works by preventing cell wall formation, in particular the formation of mycolic acid,[30] and is especially active against rapidly dividing bacteria.[31] Isoniazid alone causes a 100-fold reduction in bacterial counts within 5 days of the start of treatment and is the agent with the greatest early bactericidal activity.[32] A concentration of 50 to 200 μg/L of isoniazid is bactericidal *in vitro*. In a study of 19 women, a single dose of isoniazid 100mg given 15 to 255 minutes before delivery gave a mean maternal and fetal blood concentrations of 320 and 220 μg/L, respectively (cord-to maternal ratio 0.73).[33] In 2 women receiving a conventional dose of isoniazid (300mg) an hour before delivery, blood concentrations reached 6500 and 4000 μg/L in the maternal and fetal circulations, respectively.[34]

3.1.2 Animal Studies

Pregnant mice or rabbits receiving isoniazid showed no increase in fetal malformations compared with controls, even when doses were increased to 300 mg/kg (60 times the normal dose);[35-37] rats did show an increase in skeletal malformations and growth retardation.[34,38] Chick embryos showed both demyelination and degeneration of the CNS with isoniazid, but supplementation with pyridoxine reversed these effects completely.[39] Mice given isoniazid 150 mg/kg during pregnancy and lacta-

tion showed a higher incidence of lung adenocarcinoma in their offspring.[40]

3.1.3 Observations from Human Pregnancies

No excess of fetal malformation had been observed in children born to mothers treated with isoniazid in pregnancy.[41] No malignancies were noted in 660 children aged 1 to 13 years who were born to women treated with isoniazid for various periods during their pregnancy.[42] A case control study of 11 169 pairs of children with cancer showed no apparent association with isoniazid treatment of their mother during their pregnancy, although only a few took isoniazid in each group.[43] A review of the literature prior to 1980 found reports of 1302 pregnant women who received isoniazid in 1480 pregnancies, 400 of whom were treated within the first 4 months of their pregnancy.[44] There were 5 miscarriages, 9 perinatal deaths and 16 abnormal fetuses – all at a lower frequency than found in the normal population at that time.

3.1.4 Hepatitis

Abnormal liver enzyme levels are common with isoniazid treatment, with estimates varying from 10 to 25%.[45] The incidence of symptomatic liver disease, caused or exacerbated by 12 months of isoniazid administration, was calculated to be 5.2 per 1000 patients (20 838 individuals with inactive pulmonary tuberculosis given isoniazid compared with 6991 individuals given placebo).[46] The risk increased from 2.8 per 1000 for patients under the age of 35 years to 7.7 per 1000 for those aged over 55 years. Mouldings et al.[47] described 20 deaths in California over 14 years from isoniazid-induced hepatitis, of which 4 were in women who started isoniazid treatment during pregnancy. Failure to stop isoniazid when the patient became symptomatic was frequent. Serious methodological criticisms were noted in an accompanying editorial, most notably the lack of rigorous diagnostic criteria for isoniazid-induced hepatitis, the lack of controls and the total population of pregnant women, with and without concurrent tuberculosis, during the period of study.[48] The reported increase in risk of isoniazid-induced hepatitis in pregnant and postpartum Hispanic women was also not statistically significant.[49] Those with pre-existing liver disease do seem to be more likely to develop isoniazid-induced hepatitis, whether caused by alcohol[50] or hepatitis B infection.[51] In the US, surveillance of 13 888 persons receiving isoniazid,

Table I. First-line drugs used in the treatment of tuberculosis

Drug	Dosage	Major adverse effects	Monitoring	Comments
Isoniazid	**Daily:** 5 mg/kg to a total dose of 300mg **Intermittent (3 x weekly):** 15 mg/kg	Hepatitis Peripheral neuropathy Skin hypersensitivity Hypomania CNS effects: giddiness, convulsions	Hepatic enzyme levels	Aluminium-containing antacids reduce absorption. Pyridoxine (vitamin B6) may decrease neuritis and CNS effects
Rifampicin (rifampin)	**Daily:** 10 mg/kg to a total dose of 600mg **Intermittent (3 x weekly):** 15 mg/kg	Hepatitis Skin reactions Gastrointestinal upset Effect on other drugs Low platelets Fever Flu-like symptoms	Hepatic enzyme levels	Orange colour of secretions Single dose on an empty stomach Increased doses of some drugs are required e.g. methadone, corticosteroids
Ethambutol	**Daily:** 15 mg/kg (25 mg/kg for tuberculous meningitis) **Intermittent (3 x weekly):** 30 mg/kg	Optic neuritis (decreased red-green discrimination)	Check colour vision and visual acuity	Check each eye separately as toxicity can be unilateral
Pyrazinamide	**Daily**: 25 (20 to 30) mg/kg to a total dose of 2g **Intermittent (3 x weekly):** 50 mg/kg	Hepatitis Vomiting Arthralgia Increased uric acid levels	Hepatic enzyme levels	

Table II. Comparison of risks from pregnancy and tuberculosis (TB)

Risk	Rate per 100 000 pregancies		
	normal pregnancy	pregnancy with TB	treatment-induced complications
Low birth weight (<2.5 kg)[13]	16 500	34 200	
Prematurity (<37 weeks)[13]	11 100	22 800	
Small for dates[13]	7900	20 200	
Pre-eclampsia[12]	4700	7400	
Vaginal bleeding[12]	2200	4400	
Perinatal death[13]	1600	10 100	
Fetal death (16 to 28 weeks) [12]	230	2010	
Maternal death	12.2	No data	
Isoniazid-induced hepatitis[45]			1600
Rifampicin-induced hepatitis[45]			1100
Hepatitis with standard TB treatment[45]			2700
Fatal hepatitis[48,49]			9.4 to 14

suggested that the risk of fatal liver damage was 9.4 per 100 000, except in Baltimore, Maryland, where there was a concurrent increase in fatal hepatitis unrelated to the use of isoniazid.[52] In the East European Prevention Trial, where isoniazid was used as chemoprophylaxis rather than as part of the treatment of tuberculosis, there were 3 deaths in 20 840 persons receiving the drug (i.e. 14 per 100 000).[53] These risks are 2 orders of magnitude less than the effect of tuberculosis on pregnancy (table II). Significant isoniazid-induced hepatotoxicity can be avoided by attention to the symptoms of a flu-like illness or nonspecific gastrointestinal upset, regular monitoring of hepatic enzymes levels and stopping isoniazid promptly if an adverse reaction occurs. Liver function should be assessed before starting treatment with isoniazid and repeated if the patient has fever, malaise, loss of appetite, nausea, vomiting, jaundice unexplained symptoms or abnormal baseline test.[54] Since nausea and vomiting are common during pregnancy, fortnightly measurement of liver enzymes for the first 8 weeks of treatment (weekly for the first 2 weeks if there is chronic liver disease) and monthly measurements thereafter has been recommended.[45,55] Isoniazid (and the other potentially hepatotoxic drugs, rifampicin and pyrazinamide) should be stopped if the transaminases or bilirubin levels are 3 to 5 greater than the upper limit of normal.[22,24] Close monitoring during pregnancy might, therefore, reduce the low risk of treatment with isoniazid still further.

3.1.5 Chemoprophylaxis

The safety of isoniazid is considered sufficient to recommend its use as preventive therapy in pregnancy, i.e. in those who have a positive tuberculin skin test and who have reasonable grounds for suspecting exposure to tuberculosis, but who have not developed the disease. In this group, the life time risk of developing tuberculosis is considered to be 10% and the likelihood of developing tuberculosis within 2 years of a positive skin test is approximately 2%.[56,57]

Preventive treatment can be delayed until after delivery, in view of the general fear of taking any medication during pregnancy. However, those with recent contact or with concurrent HIV infection should take chemoprophylaxis after the first trimester.[58] If preventive treatment was started before pregnancy, it should be continued. Such a person can be reassured that the likelihood of fetal abnormality has not increased.

3.1.6 Pyridoxine (Vitamin B) Should Be Used with Isoniazid in Pregnancy

Isoniazid exhibits competitive inhibition of the co-enzymes pyridoxal phosphate and pyridoxamine, formed from vitamin B6. Pyridoxine is an important co-factor in the production of amines

which act as neurotransmitters. This competitive inhibition explains the neurological toxicity of isoniazid which includes a sensory peripheral neuropathy, optic neuritis, mania, giddiness and convulsions. Although pyridoxine deficiency is rare in well nourished individuals, it may occur during pregnancy.[59] All those taking isoniazid in pregnancy should therefore take pyridoxine 10 mg/day. Higher doses of pyridoxine may reduce the bactericidal effect of isoniazid, but can be used to treat the neuropathy should it develop.

3.1.7 Other Adverse Effects

Other rare adverse effects of isoniaizd include pellagra (possibly caused by inhibition of kynureninase which requires pyridoxal phosphate as a cofactor), haemolytic anaemia in those with glucose-6-phosphate dehydrogenase deficiency, lupoid reactions and arthralgia, none of which are peculiar to pregnancy.

3.2 Rifampicin (Rifampin)

3.2.1 Mode of Action and Pharmacokinetics

Rifampicin is the next most important drug in the treatment of tuberculosis. Rifampicin acts by binding to the β-subunit of bacterial DNA-dependent RNA polymerase to prevent initiation of transcription.[60] By stopping or slowing protein synthesis, rifampicin (and other rifamycins such as rifabutin and rifapentane) can kill tubercle bacilli, which are not actively dividing. Although the early bactericidal activity of rifampicin is low, the effectiveness of the drug becomes more apparent with time.[61] Rifampicin is readily absorbed and peak concentration of 6 to 7 μg/ml occur after 1.5 to 2h.

3.2.2 Animal Studies

Early studies suggested that there was no increase in congenital anomalies in mice or rats exposed to 2.5 to 10 times the usual human dose of rifampicin.[62] However, 15 times the normal dose in rats, given from day 1 to 12 from conception, was occasionally associated with spina bifida, anencephahly and cleft palate, even though 20 times the dose in rabbits from day 6 to 15 was without adverse effect.[63]

3.2.3 Observations from Human Pregnancies

Rifampicin induces cytochrome P450 microsomal hepatic enzymes, which are responsible for the metabolism of a large number of drugs including the oral contraceptive pill. The rapid clearance of contraceptive hormones from the blood can lead to unplanned pregnancy during treatment of tuberculosis, where advice to change to an alternative method of contraception has either been not given or ignored. This would inevitably result in early exposure of the developing fetus to rifampicin.[64]

A review of 442 women taking rifampicin during 446 pregnancies, including 109 exposed during the first trimester, did not show an excess of birth defects.[44] One of these studies[62] reported a malformation rate of 4.4% in 204 pregnancies, including hydrocephalus (1 case), anencephaly (1) and limb defects (4), at rates significantly higher than the general rate of 1.8%, but was counterbalanced by the other studies in which malformations were rarer than expected.[44] No excess of birth defects has been noted in the babies of more than 2000 pregnant mothers taking rifampicin.[44]

An association between rifampicin and haemorrhagic disease of the newborn has been suggested and prophylactic vitamin K is especially recommended in the infants of mothers treated for tuberculosis.

3.2.4 Adverse Effects

Rifampicin will cause an orange to red discolouration of the urine and body secretions, affecting soft contact lenses permanently. It may cause itching or flushing (which is usually mild, self limiting and apparently not caused by a hypersensitivity reaction), fever, nausea and vomiting, hepatitis and more rarely bruising. Serious liver injury caused by rifampicin alone is rare, but in combination with isoniazid is more common than with isoniazid alone. The incidence of a rise in liver enzyme levels has been estimated as 1.1% for rifampicin, without isoniazid, 1.6% with isoniazid alone and 2.73% for the combined drugs, suggesting that the risk is merely additive rather than synergistic.[65] Again, regular monitoring is helpful in preventing significant liver damage in this small number of patients.

Bruising or bleeding can rarely occur with rifampicin (e.g. 3 in 1710 patients)[66] and is an indication for discontinuing the drug immediately and prohibiting its use in that patient. A 'flu' like syndrome with shock, breathlessness, haemolytic anaemia and renal failure has been associated with regimens where rifampicin is given intermittently, at intervals greater than 3 times per week.[29] In view of difficulties in adhering to drug treatment in tuberculosis, intermittent treatment should be closely supervised in pregnancy and, if days are missed, then a daily supervised regimen would be most appropriate.

3.2.5 Breastfeeding

Rifampicin is excreted into human breast milk, with a milk-to-plasma ratio of 0.20.[34] The small amount of drug given to the feeding infant has not been associated with adverse effects and rifampicin has been accepted as compatible with breastfeeding.[67]

3.3 Pyrazinamide

3.3.1 Mode of Action and Pharmacokinetics

Pyrazinamide has a special place in the modern treatment of tuberculosis as its use has permitted the introduction of an effective, short course (6-month) regimen. Pyrazinamide has little bactericidal activity, except in acidic environments where rifampicin and isoniazid lose their potency.[28] Pyrazinamide inhibits fatty acid synthetase I and thereby the metabolic change from using carbohydrates to lipids as a source of energy, a process essential in adapting to the granuloma and entering the 'dormant' phase of survival in human tissues.[68]

3.3.2 Adverse Effects

No animal or epidemiological studies of congenital abnormalities with pyrazinamide during pregnancy have been reported. Some authorities have therefore recommended that pyrazinamide not be used during pregnancy. The 2 most important adverse reactions are hepatitis and joint pains. Liver damage was not greater in pyrazinamide-containing regimens compared with those without the drug at doses of 35 mg/kg in combination with other antituberculosis drugs.[69] The main metabolite of pyrazinamide, pyrazinoic acid, inhibits the renal secretion of uric acid, which may be responsible for arthralgia. The joint pains readily respond to aspirin and are not usually an indication for stopping the drug. Other adverse effects include flushing, itching, photosensitivity, anorexia and nausea.

3.3.3 Safety in Pregnancy

Davidson[25] has endorsed the use of pyrazinamide in pregnancy despite the absence of animal studies to support its lack of teratogenicity. Sputum conversion was significantly improved at 2 months with the 6-month regimen of rifampicin, isoniazid and pyrazinamide, compared with the 9-month regimen of rifampicin, isoniazid and ethambutol.[70] Adherence falls with duration of treatment and 6 months treatment with rifampicin, isoniazid and ethambutol was associated with a significant relapse rate.[71] The increase in multidrug resistant tuberculosis means that treatment with 4 drugs (e.g. rifampicin, isoniazid, pyrazinamide and ethambutol) in the initial phase has become more and more common. Inclusion of pyrazinamide in the treatment of tuberculosis in pregnancy therefore reduces the risk of ineffective treatment and must be balanced against the lack of animal studies. To date, there are no reports linking pyrazinamide to fetal malformation.

3.4 Ethambutol

3.4.1 Mode of Action and Pharmacokinetics

Ethambutol was the third drug in the treatment of tuberculosis until the effectiveness of pyrazinamide was demonstrated. Like isoniazid it affects the synthesis of material for the cell wall, but the formation of specific sugar components (arabinogalactan) rather than mycolic acid.[72] Ethambutol is bacteriostatic at concentrations of 1 to 5 μg/ml. The peak serum concentrations occur 2 to 4 h after ingestion, giving levels of 4 μg/ml after a dose of 15 mg/kg. The drug crosses the placenta freely and maternal and serum levels of 5.5 and 4.1 μg/ml, respectively, 30h after a 15 mg/kg dose have been recorded.[34]

3.4.2 Animal Studies

No animal studies of the teratogenicity of ethambutol have been reported in the literature, although a commercial publication suggests that there is decreased fertility in rats, cleft palate and exencephaly in mice and monophthalmia in rabbits given doses significantly greater than recommended for human use.[73]

3.4.3 Observations from Human Pregnancies

A review of 650 women taking ethambutol with 655 pregnancies, of whom 320 received the drug in the first trimester, showed no increase in miscarriages (1 case), premature births (26), stillbirths (5) or congenital malformations (14).[44] The malformations included a supernumerary nipple, an umbilical hernia in a Black African patient, a left hydrocoele and a skin tag on the left fifth finger with 2 birthmarks on the chest. Ethambutol is associated with the development of retrobulbar neuritis in high dose or after prolonged use. In 2184 patients, there were 10 cases of ocular toxicity and all occurred in those (1256 patients) who took ethambutol for more than 2 months.[74] Even so, there have been no reports of visual problems in children born to mothers taking ethambutol during pregnancy.

3.5 Streptomycin

Streptomycin should not be given for the treatment of tuberculosis during pregnancy. 35 fetuses were found to have abnormalities after streptomycin was given to 203 women with 206 pregnancies, 72 whom received the drug during the first trimester.[44] All except 1 fetus had damage to the eighth nerve. Hearing loss was more common than vestibular damage and ranged from minor high frequency loss to severe bilateral deafness.[26,27]

3.6 Treating Relapsed Tuberculosis

Successful re-treatment requires careful consideration of the individual patient's previous treatment.[75] If combined drug preparations have been used, then drug resistance should not have developed and treatment should be restarted with the 4 first-line drugs but given for the full 6 months. The sensitivity of the tubercle bacillus should be re-examined, preferably using rapid tests which can indicate rifampicin resistance, such as the polymerase chain reaction tests based on the DNA sequence of the RNA polymerase.[76] If the patient admits to taking only 1 drug, then resistance to that drug should be assumed and a regimen, which includes at least 3 other drugs should be instituted. Similarly, if only 2 drugs were used at any stage, resistance to these 2 drugs should be assumed and a regimen, which includes at least 3 other drugs, should be given. Where the patient has been treated for tuberculosis before, resistance to both rifampicin and isoniazid is especially common. Treatment of these patients should be supervised by a physician highly experienced in the management of drug-resistant tuberculosis and recommendations suggest 1 injectable drug, which has not been used before, and a regimen including 5 drugs in all. Streptomycin, capreomycin, kanamycin and amikacin all have significant risks for the fetus. Experience using regimens such as ciprofloxacin or ofloxacin, amoxicillin-clavulanic acid, rifabutin, ethambutol and pyrazinamide have not been evaluated, but have a theoretical advantage in pregnancy. Treatment should be supervised throughout and continued with all 5 drugs until samples from the site of disease are culture-negative and then continued with at least 3 drugs to which the strain of tuberculosis was sensitive for a further 9 months. Overall the treatment of multidrug resistant tuberculosis has a poor prognosis with a mortality of 37% and a projected cure rate of 56%.[77] Prevention by good quality treatment of tuberculosis from the time of diagnosis is the best course of action and unfounded fears about the use of antituberculosis drugs in pregnancy must not permit deviation from this course of action.

3.7 Second-Line Drugs

The increasing incidence of drug-resistant tuberculosis[23] poses a significant problem in pregnancy. Most second-line drugs have a greater incidence of adverse effects and/or an increased risk to the fetus in pregnancy. However, fluoroquino-

lones, which are increasingly used in the treatment of multidrug resistant tuberculosis, have a better safety profile in pregnancy than the older second-line drugs.

3.7.1 Fluoroquinolones

The bactericidal effect of fluoroquinolones involves the interaction between DNA-gyrase and DNA topisomerase IV and thereby affects both replication of DNA and the transcription of DNA to mRNA. The mechanism of action in *M. tuberculosis* has yet to be confirmed, but resistance to ofloxacin is conferred by mutations in the DNA-gyrase gene, *gyr*.[78] Ciprofloxacin is well absorbed and serum concentrations reflect those in amniotic fluid and breast milk closely.[79] Early studies confirmed bactericidal activity of ciprofloxacin in patients with tuberculosis,[80] but subsequently, high doses (as much as 1500mg) were found to be most successful.[81] The optimal dosage in treating tuberculosis is not known, but personal experience to date has shown that ciprofloxacin 500mg twice daily or ofloxacin 400 mg/day can be effective as part of a multiple drug regimen.

Animal studies raised the possibility that ciprofloxacin might damage articular cartilage and lead to juvenile arthritis.[82] A review of 200 women exposed to ciprofloxacin during the first trimester failed to note any musculoskeletal abnormalities, although those treated had a higher rate of medical abortion.[83] This information relates to short exposures of 5 to 7 days at low dosages (e.g. 250mg twice daily). Extrapolation to the more prolonged use of quinolones in the higher doses required for the treatment of tuberculosis suggests that close attention should be paid to musculoskeletal abnormalities in the fetus.

3.7.2 Macrolides

These antibacterials affect bacterial protein synthesis by binding to a single high affinity site in the peptidyl tRNA binding region of the 50S ribosome subunit. Although erythromycin and azithromycin are ineffective in the treatment of tuberculosis, the activity of clarithromycin has been disputed.[84,85] Synergism with pyrazinamide[86] and a proton pump inhibitor[87] against *M. tuberculosis* has been noted. In terms of safety, in 157 pregnant women exposed to clarithromycin in pregnancy, 122 in the first trimester, the incidence of malformation was 2.3% compared with 1.4% in the control group receiving other nonteratogenic antibacterials, and spontaneous abortions were 14% compared with 7%.[88] The lack of proven benefit and the higher risk in pregnancy compared with other macrolides would not recommend the use of clarithromycin in the treatment of drug-resistant tuberculosis in pregnancy at present.

3.7.3 Amoxicillin-Clavulanic Acid

The combination of a penicillin in combination with a β-lactamase inhibitor has been reported to treat multidrug resistant tuberculosis successfully[89] and to have an early bactericidal activity comparable with other antituberculosis drugs, with the exception of isoniazid.[90] This combination has been used as antibacterial prophylaxis in preventing infection following the premature rupture of membranes in 72 women from 26 to 36 weeks of pregnancy with proven benefit for the prolongation of pregnancy.[91] There are no data on the use of clavulanic acid in early pregnancy, but the increasing use of this combination suggests that it may have a role in the treatment of multidrug resistant tuberculosis.

3.7.4 Para–Aminosalicylic Acid

Para-aminosalicylic (PAS) is a bacteriostatic compound whose mechanism of action is uncertain. Some have suggested that it competes with p-aminobenzoic acid, in a manner similar to the action of sulphonamides. Alternatively, PAS may interfere with the salicylate-dependent biosynthesis of iron-chelating mycobactins. Gastrointestinal adverse effects are common and occur in 10 to 30% and a hypersensitivity rash can occur in 5 to 10% of patients.[92] These adverse effects are responsible for its relegation to a second-line drug.

A single report of its use in rats and rabbits found no evidence of teratogenicity.[37] Data from the Collaborative Perinatal Project identified 43 women who had been exposed to the drug in the first trimester with 5 babies showing various malformations. A further 123 women treated with PAS

during pregnancy gave birth to children who appeared to have a higher incidence of limb and ear abnormalities, but no consistent pattern of defect emerged.[93]

3.7.5 Ethionamide

Ethionamide has a similar action to isoniazid but has been relegated to a second-line drug because *in vitro* studies show resistance develops readily. Animal studies have shown a small increase in birth defects in rats (omphalocele, anencephaly and cleft palate),[94] but not in mice[95] or rabbits.[96] No fetal abnormalities were found in 38 infants exposed *in utero* to ethionamide in 1 study,[97] although another noted 7 malformations in 23 exposed infants.[98]

3.7.6 Cycloserine

Cycloserine is a structural analogue of D-alanine and blocks the synthesis of the cell wall core (mycolylarabinogalactan-peptidoglycan).[99] Adverse effects on the CNS are responsible for its limited use. These include dizziness, headache, slurred speech, tremor and insomnia and potentially serious episodes of depression, anxiety and psychosis. Seizures may occur and are more common with higher doses and with alcohol consumption. No animal studies have been reported.

4. Use of Tuberculin-Purified Protein Derivative for the Diagnosis of Infection

Adverse reactions to tuberculin-purified protein derivative (PPD) are very uncommon. No allergic reactions to the phosphate buffered saline diluent, the phenol used as a preservative or the Tween® 80 have been documented, despite the millions of tests carried out.[100] The dose of PPD is too small to induce delayed hypersensitivity. A few exquisitely sensitive individuals may respond to tuberculin with vesiculation or ulceration at the site of injection. Even fewer individuals may react with lymphangitis, swelling of the local lymph nodes and fever.[101] No adverse effect of tuberculin peculiar to pregnancy or affecting the fetus has been noted.[44]

The main concern of the literature has been whether the tuberculin skin test can be reliably interpreted during pregnancy. Immunological considerations suggest that the response to tuberculin might be reduced.[102] However, 2 studies found no observable difference in tuberculin sensitivity.[103,104] Even in pregnant women infected with HIV, there was no additional effect of pregnancy on tuberculin sensitivity.[105]

5. Bacille Calmette Guérin Vaccination for Prevention of Tuberculosis in Pregnant Women

Prior vaccination with *Mycobacterium bovis*-BCG is the most effective means of preventing tuberculosis in pregnancy available at the present time. BCG vaccination appears to be especially effective against forms of tuberculosis that are found more commonly in pregnancy than against smear-positive pulmonary tuberculosis, which is more common in men.[106] Vaccination should occur at birth in areas of the world where tuberculosis is common. There are no data to assess the danger of BCG vaccination in pregnancy, except to note that the review of Lotte et al.[107] of 10 371 complications after vaccination of an estimated 500 million vaccinations included no mention of pregnancy or congenital tuberculosis caused by *M. bovis*-BCG. However, the use of live vaccines during pregnancy is not recommended.

6. Conclusions

First line treatment of tuberculosis with isoniazid, rifampicin and ethambutol is widely recognised to be safe in pregnancy; vitamin supplementation with pyridoxine should be used routinely. A 4-drug regimen, adding pyrazinamide to the above 3 drugs, affords protection against multidrug resistant tuberculosis and lasts for 6 as opposed to 9 months, thereby encouraging successful completion of treatment and should now be the treatment of choice.[25] Combined preparations of drugs are especially helpful in preventing drug resistance and should be used whenever possible. Adherence is more difficult in pregnancy and every effort should be made to help patients complete their treatment course; directly observed or supervised

therapy for tuberculosis is helpful in ensuring a successful outcome to treatment. Attention to an effective regimen, good adherence to the treatment programme and a documented cure must be stressed in view of the risks presented by second line drugs. The treatment of multidrug resistant tuberculosis is more difficult: ciprofloxacin and amoxicillin-clavulanic acid have a reasonable safety record and efficacy; other second-line drugs have significantly greater adverse effects but are of proven effectiveness. The risk-benefit ratio for isoniazid is such that preventive treatment can be safely continued in pregnancy.

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