Respiratory diseases in pregnancy • 3

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Tuberculosis in pregnancy and the puerperium

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Incidence of tuberculosis and pregnancy

The occurrence of pregnancy in patients with tuberculosis is increasing in developed countries as a result of changes in the case mix and age distribution of cases of tuberculosis, with an increasing proportion coming from ethnic minority groups. In 1988 over 50% of cases in England and Wales were in the white ethnic group. Most of the white women were aged over 50 years, with only a minority of cases in the 15–40 age range in whom pregnancy is most likely.[1] Since 1988 the proportion of white ethnic cases has declined, reaching 43% in 1993[2] and down to 37% in 1998,[3] with still only a minority of cases of child bearing age. An increasing proportion—and now the majority—of cases of tuberculosis are from minority ethnic groups. In 1998 over 56% of cases were born abroad, with 39% coming from the Indian subcontinent and 13% of black African ethnic origin.[3] The cases of tuberculosis in all these ethnic minority groups have a very different age distribution from those of UK origin, with a median age usually under 30 years compared with over 50 years in the white population. The increase in the number of patients with tuberculosis who become pregnant is therefore due to the increasing proportion of women of child bearing age. Similar trends have been reported in the USA[4 5] and in most developed countries in Europe. In developing countries the rise in tuberculosis is also predominantly affecting the young, mainly the 15–44 age group, fuelled in sub-Saharan Africa by HIV co-infection.[6] This review considers aspects of tuberculosis in pregnancy and does not cover reduced fertility from genital tuberculosis, although this is an important cause of infertility, especially in developing countries.[7]

Pregnancy as a risk factor for tuberculosis

Views as to whether the incidence of tuberculosis is increased by pregnancy have varied over time. The Hippocratic view that pregnancy was beneficial to tuberculosis was generally held until the 19th century.[8] Grisolle reported in the mid 19th century that the course of disease in 24 pregnant women was less favourable than in non-pregnant women.[8] By the early 20th century opinion had swung to pregnancy having a deleterious effect on tuberculosis, so much so that abortion was recommended.[9 10] Immediately before the chemotherapy era, Hedvall[11] reported on 250 of his own pregnant patients and found that 9% improved, 7% deteriorated, and 84% were unchanged antepartum, with 9% improving, 15% deteriorating, and 76% remaining unchanged postpartum. Studies in London in the 1950s by Pridie and Stradling[12] showed rates of tuberculosis in the pregnant population to be the same as in the non-pregnant population. More recently, Schaefer reported a new case rate of 18–29/100 000 in pregnancy which was similar to that of 19–39/100 000 for the whole city of New York.[13] Data from San Domingo gave no evidence that pregnancy increased the chance of tuberculosis developing postpartum in either HIV positive or negative women.[14]

Presentation of tuberculosis in pregnancy

The presentation of tuberculosis in pregnant women is similar to that in non-pregnant women[15] but diagnosis may be delayed by the non-specific nature of early symptoms[16] and the frequency of malaise and fatigue in pregnancy.[17] The most common site in pregnancy is pulmonary and, of the 27 pregnancies reported by Good *et al*[15] with culture positive disease, 74% had cough, 41% had weight loss, 30% had fever, malaise or fatigue, and 19% had haemoptysis; 20% were asymptomatic but all had abnormal radiographs. The diagnosis of pulmonary tuberculosis is also complicated by the fact that women with tuberculosis associated with pregnancy are more likely to postpone having chest radiography[16] and that investigation of sputum smear negative tuberculosis is more difficult. Other studies have found less significant symptoms in pregnant women with tuberculosis.[18] Wilson *et al*[19] reported that 5–10% of pregnant women with tuberculosis in their series had extrapulmonary disease, a proportion comparable with non-pregnant women of the same age and ethnic group. A high index of suspicion needs to be maintained and in the USA tuberculin testing in high risk groups followed by chest radiography where appropriate (see below) is recommended.[20]

Skin testing in pregnancy

Tuberculin skin testing to detect latent infection in those thought to be at higher risk of tuberculosis—such as those with recent travel to or immigration from countries of high prevalence, intercurrent disease, or HIV co-infection—is widely recommended in the USA.[21] Pregnant women who meet the above

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criteria should be tested. Tuberculin testing using 0.1 ml (5 tuberculin units) purified protein derivative (PPD) is regarded as safe in pregnancy.[17 22] According to the ATS-CDSC guidelines, an induration of 0–4 mm is negative, 5–10 mm is doubtfully positive, and more than 10 mm is reactive.[23] A doubtful reading without a history of recent exposure requires re-testing after 3 months. An increase from under to over 10 mm with an increase of at least 6 mm is consistent with new infection. A doubtful reaction with known recent exposure such as household or close occupational contact or an HIV positive patient may be significant and requires investigation.[23] Preventive chemotherapy with isoniazid is the US recommendation for those aged less than 35 years antepartum with a clear chest radiograph with (a) a tuberculin reaction of >15 mm not previously treated, (b) >10 mm induration and recent immigration from a high prevalence area, or (c) >5 mm induration if HIV positive or a known recent contact.[21] There has been some concern about isoniazid hepatitis in pregnant patients with a 2.5 fold increase in fulminant hepatitis and a fourfold higher death rate in pregnant and postpartum patients on preventive therapy over non-pregnant patients.[24] These differences, however, were not statistically significant and more recent analysis suggests over-reporting and a true isoniazid associated death rate of 0.001%.[25]

The detection of latent infection by tuberculin skin testing is not affected by pregnancy. While there is some evidence of a lower in vitro lymphocyte response to PPD, early clinical studies showed that pregnancy did not alter tuberculin reactivity.[26] More recent studies have shown no differences between HIV positive patients with pregnancy and non-pregnant HIV positive patients[27 28] or a mixed population.[29]

In the UK chemoprophylaxis or preventive treatment is used less widely in adults but tuberculin testing would still be appropriate for new immigrants, refugees, and asylum seekers, even if pregnant.[30] Tuberculin testing in the UK is usually by the multiple puncture (Heaf) method rather than the Mantoux test.[31] The only manufacturer of tuberculin in the UK, Celltech Medeva, has recently put in its data sheet that tuberculin testing should not be carried out in pregnancy, but does not provide any data to support this recommendation. This is not supported by the Joint Committee on Vaccination and Immunisation.[31] A negative tuberculin test in pregnancy should not lead to BCG vaccination which, as a live vaccine, is contraindicated in pregnancy.[31] In such circumstances the tuberculin test should be repeated after delivery and BCG vaccination given, if appropriate,[30] after a second negative test.

Treatment of tuberculosis in pregnancy

As with any other medication, particularly in the first trimester, the main concern about tuberculosis treatment in pregnancy is the risk of teratogenicity. Short course chemotherapy trials have shown that 6 month regimens of rifampicin and isoniazid, supplemented by 2 months initial treatment with pyrazinamide and either ethambutol or streptomycin, is the treatment of choice for tuberculosis.[32–36] The trials, however, were not performed in pregnant subjects. Details of the first line antituberculous drugs, relevant to pregnancy, are given below.

ISONIAZID

Isoniazid has a high lipid solubility, a low molecular weight, and crosses the placenta readily to reach fetal levels similar to those of the mother. A fetal cord to maternal ratio of 0.73 after a 100 mg dose given shortly before delivery has been reported.[37] Animal studies have shown no growth retardation in rats[38] and no increase in malformations in mice[39 40] or rabbits at up to 60 times the human dose.[41] Demyelination, depending on which day of gestation the drug was given, has been reported in chick embryos[42 43]; however, this can be blocked by the in vivo administration of pyridoxine (vitamin B_6).[42] No association has been found between carcinoma and maternal isoniazid administration.[44 45] However, most studies on potential fetal effects have been in patients on multiple drug therapy.[46]

RIFAMPICIN

Rifampicin is readily absorbed after oral administration with a peak serum concentration of 5–7 mg/l within 1.5–2 hours in non-pregnant subjects and good penetration into all tissues despite the fact that 75% is protein bound. At the end of the third trimester cord to maternal blood ratios of 0.12–0.33 have been reported.[47] Studies in mice or rats exposed to 2.5–10 times the usual human dose in utero[48] and in rabbits at similar doses[48–50] showed no increase in congenital abnormalities. Fetal abnormalities in 442 women exposed to rifampicin, including 109 exposed during the first trimester, were not significantly increased.[10] One study, however, did show a 4.4% malformation rate in 204 pregnancies[51] which was higher than the 1.8% rate noted in other studies.

ETHAMBUTOL

Ethambutol freely crosses the placenta with a cord to maternal serum ratio of 0.75.[52] There have been few reports of animal teratogenicity studies with ethambutol. Fetal malformation rates of 2.2% were reported in 638 infants whose mothers received ethambutol during pregnancy, including 320 in the first trimester.[10] Given the theoretical possibility of ocular toxicity, it is reassuring that six aborted fetuses assessed at 5–12 weeks gestation had no abnormality in the embryonic optical system.[53]

PYRAZINAMIDE

Pyrazinamide is readily absorbed from the gastrointestinal tract. No significant animal teratogenicity studies or reports of malformations in treated patients are available.[52]

STREPTOMYCIN

Peak blood concentrations of 40 μg/ml occur in non-pregnant patients within 1 hour of an

intramuscular injection of 15 mg/kg streptomycin. It rapidly crosses the placenta into the fetal circulation and amniotic fluid, usually at levels of less than 50% of the maternal levels.[54 55] The only adverse effects reported in studies in various animals have been ototoxicity.[54–56] Congenital deafness has been reported in infants with in utero exposure to streptomycin, although there is no consistent relationship between ototoxicity and the gestational age of exposure.[57–60] Variable effects on audiograms in children have been reported, ranging from no abnormalities in 50 children,[61] to two of 33 with minor hearing loss,[57] up to four of 13 with others having abnormal calorific tests.[62] Given the occurrence of ototoxicity from in utero exposure, which is predictable from adult toxicity data, recommendations from developed countries advise avoiding streptomycin in pregnancy.[21 32 63]

RESERVE DRUGS

Of the second line (reserve) drugs, kanamycin and amikacin are aminoglycoside variants and share the same potential problems as streptomycin. While capreomycin has a different chemical structure from the aminoglycosides, it has similar side effects in non-pregnant subjects and should therefore only be used if needed in pregnancy, usually for multidrug resistant tuberculosis (MDR-TB).

Ethionamide (and prothionamide) are thiomide derivatives which have good penetration into all tissues including the cerebrospinal fluid. Animal studies in mice[64 65] and rabbits[64] found no increase in induced birth defects but there was an increase in central nervous system defects in rats. Skeletal effects were also seen in rats at higher doses (5–10 times normal)[41] and an association has been reported with growth retardation in rabbits.[64] Conflicting data have come from human studies. No abnormalities were seen in a series of 38 cases[66] but seven of 23 patients had abnormalities in another study.[67] A review of ethionamide exposure in 1100 pregnancies noted that four out of five cases exposed to ethionamide during the first trimester had central nervous system defects.[68] Overall, ethionamide (and prothionamide) are regarded as potentially teratogenic and their use should be avoided in women of child bearing age unless they are needed as reserve drugs for MDR-TB.[32]

Perinatal outcome in tuberculosis

Various reports have given differing perinatal outcomes with increased abortion rates, high levels of pre-eclampsia, and increased levels of difficult labour requiring intervention in some studies,[69] but overall good fetal outcome in others.[13] More recent case control studies have shown that the outcome depends on whether the tuberculosis is pulmonary or extrapulmonary, and also whether it is diagnosed later in pregnancy. In a study of Indian women with pulmonary disease treated for 6–9 months in pregnancy,[70] perinatal mortality was six times higher than in controls and the incidence of prematurity, small for dates babies, and low birth weight (<2500 g) was doubled. These effects were even more pronounced in cases with late diagnosis, incomplete or irregular drug treatment, and in those with advanced pulmonary lesions. Figuera-Damien *et al*[71] reported substantially increased neonatal mortality of 18.7%, a relative risk of 14, with this effect being mainly the result of late diagnosis and treatment (during the second and third trimesters). The outcome for those diagnosed in early pregnancy was equivalent to that in non-pregnant patients.

The picture in extrapulmonary tuberculosis is mixed. With lymph node disease no effect was found in a study in India,[72] but for other sites such as the spine, abdomen, and meningitis there were adverse effects on the fetus with a lower Apgar score at birth and the proportion with low birth weight increased to 33% compared with 11% in controls.

Maternal outcome in pregnancy complicating tuberculosis

As with the fetal outcome, maternal outcome in pregnancy varies with the site of the tuberculosis and the timing of diagnosis in relation to delivery. There seems to be no adverse outcome with lymph node tuberculosis but increased admission rates have been reported during pregnancy because of the disability that can occur with tuberculosis at other extrapulmonary sites.[72] Pulmonary tuberculosis is the form which is associated with most problems. In those with a late diagnosis, obstetric morbidity is increased fourfold and preterm labour ninefold.[71] A higher frequency of abortion, toxaemia, and intrapartum complications were reported in another series.[69] In a small Indian study no maternal mortality was reported.[70] However, in sub-Saharan Africa tuberculosis is an increasingly important cause of non-obstetric mortality. In Zambia tuberculosis now accounts for 25% of all non-obstetric deaths, most in combination with HIV positivity,[73] the dual epidemic being a major factor in an eightfold increase in maternal mortality.

Infection control in late pregnancy and puerperium

The same infection control measures apply to tuberculosis in pregnancy as to tuberculosis in other settings.[30] Only those cases with pulmonary disease are potentially infectious, but in those with fully susceptible organisms they are rendered non-infectious by 2 weeks of treatment including rifampicin and isoniazid.[30] There is therefore no significant infection control risk in such cases after this time[74 75] and the mother can be allowed to deliver normally. There is a small potential risk with cases diagnosed within 2 weeks of birth if the mother is sputum positive for acid fast bacilli. If the mother has significant risk factors for MDR-TB,[30] molecular tests for rifampicin resistance should be carried out. Should these be positive, infection control measures should be as for MDR-TB with staff using dust mist fume masks meeting the 1992 Personal Equipment (EC Directive) Regulations,[76] and the mother should be isolated in a negative pressure room.

For mothers who are sputum microscopy positive who are not known or suspected to have MDR-TB, staff should already be protected by the pre-employment or on-employment measures.[30] It used to be recommended that newborn infants should be separated from their mother[15 22] but this is no longer appropriate in most cases if the mother is on effective treatment. Infants staying with their mother who has had less than 2 weeks of treatment and is sputum microscopy positive should be treated prophylactically with isoniazid (5 mg/kg) and have a tuberculin test performed at 6 weeks.[30] If this is negative, BCG vaccination should be given and chemoprophylaxis stopped. If the tuberculin test is positive, the child should be assessed for congenital and perinatal infection and chemoprophylaxis continued if these are excluded. In the USA, BCG vaccination is only advocated for those infants with a negative tuberculin test who remain at high risk from untreated (or undertreated) persons with infectious pulmonary tuberculosis and those remaining exposed to drug resistant tuberculosis.[77] Separation of the infant from the mother is likely to be required if the mother has MDR-TB because of the prolonged infectivity and the lack of an effective chemoprophylaxis regimen,[32] and should be considered if there is maternal non-compliance with treatment.

Congenital tuberculosis

The fetus can only be infected in utero via the umbilical cord. This is rare, with fewer than 300 cases having been reported.[78] Haematogenous congenital tuberculosis occurs when placentitis results from dissemination in the mother. In these circumstances *Mycobacterium tuberculosis* has been identified in the amnion, decidua, and the chorionic villi.[79] Placental involvement does not, however, automatically lead to congenital tuberculosis.[80] Although fetal infection directly from the mother's bloodstream without formation of a caseous lesion in the placenta has been described in experimental animal models,[81] it is unclear whether this happens in humans. Congenital tuberculosis is rare if the mother has been on effective treatment in pregnancy.[13]

The first diagnostic criteria used to distinguish congenital tuberculosis from postnatally acquired tuberculosis were largely based on necroscopic data.[79] These required that the infant had proven tuberculosis lesions and one of the following: (a) lesions in the first few days of life; (b) a primary hepatic complex; (c) exclusion of postnatal transmission to the infant at birth from the mother and other sources of infection. In current practice these conditions can now rarely be met. Cantwell *et al*[82] have therefore suggested revised criteria for the diagnosis, including documentation of tuberculous infection of the genital tract. The modified criteria include tuberculosis lesions in the infant and one of the following: (a) lesions in the first week of life; (b) a primary hepatic complex or caseating granuloma; (c) documented tuberculous infection of the placenta or endometrium; (d) exclusion of tuberculosis infection by a carer in the postnatal period.

Clinically, tuberculosis in the newborn infant simulates other congenital infections such as syphilis or cytomegalovirus or bacterial sepsis. Congenital tuberculosis should be suspected if aggressive broad spectrum antibiotics are ineffective and tests for other congenital infections are negative, particularly if the mother is known to have tuberculosis and especially if recently diagnosed.[83] Symptoms may be present at birth but are usually seen in the second and third weeks. Hepatosplenomegaly is found in 76%, respiratory distress in 72%, fever in 48%, and lymphadenopathy in 38%.[82 84] Virtually all infants have an abnormal chest radiograph, with nearly half having a miliary pattern. The chest radiograph may be normal immediately after birth, but rapidly progresses with even cavitation being described.[85] If possible, the placenta should be examined and cultured for tubercle bacilli.[83] The tuberculin skin test result is unhelpful since it is always negative initially and can take 1–3 months to become positive. Diagnosis rests on clinical suspicion and demonstration of acid fast bacilli in tissue or fluids, particularly on the culture of *M tuberculosis.* Early morning gastric washings that are positive for acid fast bacilli on microscopy should be regarded as indicative of tuberculosis,[83] although false positives can occur.[86] Hageman *et al* found positive cultures for *M tuberculosis* in 10 of 12 gastric aspirates, all three liver biopsy specimens, all three lymph node biopsy specimens, and two of four bone marrow aspirates.[84] Culture of cerebrospinal fluid is also recommended but has a lower yield.[84 87] Open lung biopsy has also been used to establish the diagnosis.[88]

Other routes of infection of the fetus before or during birth—from aspiration of infected amniotic fluid to direct contact with tuberculous cervicitis or endometritis—were excluded from the original Bietzke[79] criteria but are included in the modified Cantwell criteria.[82] In some series of congenital tuberculosis, fewer than half of the mothers were known to be suffering from tuberculosis at the time of delivery, the diagnosis in the infant then leading to the maternal diagnosis.[82 87] Perinatal tuberculosis occurs from airborne infection from either the mother, an adult family carer, or another infectious adult with whom the neonate has had contact. This can include nursing and medical health care workers.[89 90] These cases may become more frequent with increasing numbers of both mothers and neonates being infected with HIV, something which is already being observed in sub-Saharan Africa.[91]

Breast feeding

The first line antituberculous drugs cross into breast milk in variable amounts. Rifampicin is excreted into breast milk with a milk to plasma ratio of 0.2. The amount transferred to the infant (0.05% of maternal dose) does not cause adverse effects. Pyrazinamide excretion into breast milk is minimal[92] with a maximum of 0.3% of the ingested dose reaching the infant.[93]

Streptomycin is excreted into breast milk with a milk to plasma ratio of 0.5–1.0.[94] Since the drug is very poorly absorbed orally, no significant absorption by the infant is to be expected from this. Ethambutol is secreted into breast milk with an approximate milk to serum ratio of 1. All these antituberculous drugs are thought to be compatible with breast feeding by paediatric groups such as the American Academy of Pediatrics[95] and also by respiratory organisations.[21 32 63]

Conclusion

Because of demographic changes, pregnancy and tuberculosis will be seen more frequently in both developing and developed countries and will need heightened awareness to consider the diagnosis. "Standard" short course chemotherapy is recommended but the outcome for both the mother and the fetus is improved by early diagnosis. Congenital tuberculosis will remain uncommon, but perinatal tuberculosis will almost certainly increase, particularly in HIV endemic areas.

1 Medical Research Council Cardiothoracic Epidemiology Group. National survey of notifications of tuberculosis in England and Wales in 1988. *Thorax* 1992;**47**:770–5.
2 Kumar D, Watson JM, Charlett A, *et al*. Tuberculosis in England and Wales in 1993: results of a national survey. *Thorax* 1997;**52**:1060–7.
3 Rose AMC, Watson JM, Graham C, *et al*. Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* 2001;**56**:173–9.
4 Jereb JA, Kelly GD, Dooley SW, *et al*. Tuberculosis morbidity in the United States: final data 1990. *MMWR* 1991;**40**: 23–7.
5 Neville K, Bromberg A, Bromberg R, *et al*. The third epidemic: multi drug resistant tuberculosis. *Chest* 1994; **105**:45–8.
6 Harries AD, Parry C, Mbewe LN, *et al*. The pattern of tuberculosis in Queen Elizabeth Central Hospital, Blantyre, Malawi: 1986–1995. *Int J Tuberc Lung Dis* 1997;**1**: 346–51.
7 Parikh FR, Naik K, Nadkarni SG, *et al*. Genital tuberculosis: a major pelvic factor causing infertility. *Fertil Steril* 1997;**67**:497–500.
8 Snider DE Jr. Pregnancy and tuberculosis. *Chest* 1984;**86**: 115–18.
9 Vallejo JG, Starke JR. Tuberculosis and pregnancy. *Clin Chest Med* 1992;**13**:693–707.
10 Snider DE Jr, Layde PM, Johnson MW, *et al*. Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122**:65–79.
11 Hedvall E. Tuberculosis and pregnancy. *Acta Med Scand* 1953;**148**(Suppl 286):1–18.
12 Pridie RB, Stradling P. Management of pulmonary tuberculosis during pregnancy. *BMJ* 1961;3:78–81.
13 Schaefer G, Zervoudakin IA, Fuchs FF, *et al*. Pregnancy and pulmonary tuberculosis. *Obstet Gynaecol* 1975;**46**:706–15.
14 Espinal MA, Reingold AL, Lavendra M. The effect of pregnancy on the risk of developing active tuberculosis. *J Infect Dis* 1996;**173**:488–91.
15 Good JT, Iseman MD, Davidson PT, *et al*. Tuberculosis in association with pregnancy. *Am J Obstet Gynecol* 1981;**140**: 492–8.
16 Doveren RFC, Block R. Tuberculosis and pregnancy: a provincial study (1990–96). *Neth J Med* 1998;**52**:100–6.
17 Hamadeh MA, Glassroth J. Tuberculosis and pregnancy. *Chest* 1992;**101**:1114–20.
18 Carter EJ, Mates S. Tuberculosis during pregnancy. The Rhode Island experience, 1987–1991. *Chest* 1994;**106**: 1466–70.
19 Wilson EA, Thelin TJ, Dilts PV. Tuberculosis complicated by pregnancy. *Am J Obstet Gynecol* 1972;**115**:526–9.
20 Centres for Disease Control. Initial therapy for tuberculosis in the era of multiple drug resistance: recommendations of the Advisory Committee on the Elimination of Tuberculosis. *MMWR* 1993;**42**:1–8.
21 American Thoracic Society and Centers for Disease Control. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994;**149**:1359–74.
22 Medchill MT, Gillum M. Diagnosis and management of tuberculosis during pregnancy. *Obstet Gynecol Surv* 1989; **44**:81–4.
23 Centers for Disease Control and Prevention. Anergy skin testing and tuberculosis preventive therapy for HIV infected persons: revised recommendations. *MMWR* 1997; **46**:1–10.
24 Franks AL, Binkin NJ, Snider DE Jr, *et al*. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Publ Health Rep* 1989;**104**:151–5.
25 Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis* 1992; **145**:494–7.
26 Present PA, Comstock GW. Tuberculin sensitivity in pregnancy. *Am Rev Respir Dis* 1975;**112**:413–6.
27 Eriksen NL, Helfgott AW. Cutaneous anergy in pregnant and nonpregnant women with human immunodeficiency virus. *Infect Dis Obstet Gynecol* 1998;**6**:13–17.
28 Mofenson LM, Rodriguez EM, Hershaw R, *et al*. *Mycobacterium tuberculosis* infection in pregnant and non-pregnant women infected with HIV in the Women and Infants Transmission Study. *Arch Intern Med* 1995;**155**:1066–71.
29 Nolan TE, Espinosa TL, Pastorek JG. Tuberculin skin testing in pregnancy: trends in a population. *J Perinatol* 1997; **17**:199–201.
30 Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000;**55**:887–901.
31 Departments of Health. *Immunisation against infectious disease*. London: HMSO 1996:219–41.
32 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis: recommendations 1998. *Thorax* 1998;**53**:536–48.
33 Singapore Tuberculosis Service and British Medical Research Council. Clinical trial of six-month and four-month chemotherapy in the treatment of pulmonary tuberculosis. The results up to 30 months. *Tubercle* 1981;**62**:95–102.
34 East and Central African and British Medical Research Council. Clinical controlled trial of four short course regimens of chemotherapy (three six-month and one eight-month) for pulmonary tuberculosis. *Tubercle* 1983;**64**:153–66.
35 British Thoracic Society. A controlled trial of six months chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. *Br J Dis Chest* 1984;**78**:330–6.
36 Ormerod LP. Chemotherapy of tuberculosis. *Eur Respir J* 1997;**12**(Suppl 4):273–97.
37 Bromberg YM, Salzberger M, Bruderman I. Placental transfer of isonicotinic acid hydrazide. *Gynecologia* 1955; **140**:141–4.
38 Marlow R, Freeman SJ. A comparison of the in vitro embryotoxicity of three lathyrogens, beta-apn, semicarbazide and isoniazid. *Tetralogy* 1988;**38**:24A.
39 Kalter H. Nonteratogenicity of isoniazid in mice. *Tetralogy* 1972;**5**:259.
40 Menon MM, Bhide SV. Transplacental, biological and metabolic effects of isoniazid (INH) in Swiss mice. *Ind J Exp Biol* 1980;**18**:1104–6.
41 Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberculostatic drugs. *Diss Pharm Pharmacol* 1971;**23**:383–92.
42 Levene CI, Carrington MJ. The inhibition of protein-lysine 6-oxidase by various lathyrogens: evidence for two different mechanisms. *Biochem J* 1985;**232**:293–6.
43 Pandet SK, Sensharma S. Neuroembryopathic effect of INH on the cerebellum of chick embryo. *Ind J Med Sci* 1988;**42**:291–3.
44 Sanders BM, Draper GJ. Childhood cancer and drugs in pregnancy. *BMJ* 1979;1:717–8.
45 Hammond EC, Selioff IJ, Robitzek EH. Isoniazid therapy in relation to later occurrence of cancer in adults and in infants. *BMJ* 1967;2:792–5.
46 Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. Baltimore: Williams and Wilkins, 1994: 342.
47 Kenny MT, Strates B. Metabolism and kinetics: pharmacokinetics of the antibiotic rifampin. *Drug Metab Rev* 1981; **12**:159–218.
48 Statford BF. Observations on laboratory rodents treated with 'Rifamide' during pregnancy. *Med J Aust* 1966;**1**:10–12.
49 Anonymous. Rifampicin: a review. *Drugs* 1971;**1**:354–98.
50 Tuchmann-Duplessis H, Mercier-Parot L. Influence d'un antibiotique, las rifampicine, sur le development prenatal de ronguers. *C R Acad Sci* 1969;**269**:2147–9.
51 Steen JSM, Stainton-Ellis DM. Rifampicin in pregnancy. *Lancet* 1977;ii:604–5.
52 Brost BS, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol Clin North Am* 1997;**24**:659–73.
53 Lewit T, Nebel L, Terracina S, *et al*. Ethambutol in pregnancy: observations on embryogenesis. *Chest* 1974;**66**: 25–6.
54 Heilman D, Heilman F, Hinshaw H, *et al*. Streptomycin: absorption, diffusion, excretion and toxicity. *Am J Med Sci* 1945;**210**:576–84.
55 Woltz J, Wiley M. Transmission of streptomycin from maternal blood to the fetal circulation and amniotic fluid. *Proc Soc Exp Biol Med* 1945;**60**:106–7.
56 Risker N, Christensen E, Hertz H. The toxic effects of streptomycin and dihydrostreptomycin in pregnancy, illustrated experimentally. *Acta Tuberc Pneumonol Scand* 1952; **27**:211–16.
57 Donald PR, Sellers SL. Streptomycin ototoxicity in the unborn child. *S Afr Med J* 1981;**60**:316–18.
58 Kern G. Zur frage der interuteruinen streptomycin schadigung. *Med Wochenshcr* 1962;**92**:77–9.
59 Leroux MI. Existe-t-il une srdete congenitale axquise due a la strepomycine? *Ann Otolaryngol* 1950;**67**:194–6.

60 Robinson GC, Cambon KG. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. *N Engl J Med* 1964;**271**:949–51.
61 Varpela E, Hietalahti J, Aro MJT. Streptomycin and dihydrostreptomycin medication during pregnancy and their effects on the child's inner ear. *Scand J Respir Dis* 1969;**50**:101–9.
62 Conway N, Birt BD. Streptomycin in pregnancy: effect on the fetal ear. *BMJ* 1965;2:260–3.
63 Migliori GB, Raviglione MC, Schaberg MC, *et al*. Tuberculosis management in Europe. *Eur Respir J* 1998;**14**:978–92.
64 Khan I, Azam A. Study of teratogenic activity of trifluoperazine, amitriptyline, ethionamide and thalidomide in pregnant rabbits and mice. *Proc Eur Soc Study Drug Toxic* 1969; **10**:235–42.
65 Takekoschi S. Effects of hydroxymethylpyrimidine on isoniazid and ethionamide induced teratosis. *Gunma J Med Sci* 1965;**14**:233–44.
66 Zierski M. Influence of ethionamide on development of human fetus. *Grazlica Choroby Plac (Warsaw)* 1966;**34**: 349–52.
67 Potworowski M, Sianozecka E, Szufladowicz R. Ethionamide treatment and pregnancy. *Pol Med J* 1966;**5**:1152–8.
68 Schardein JL. *Chemically induced birth defects*. New York: Marcel Dekker, 1993: 378.
69 Bjerkedal T, Bahna SL, Lehmann EH. Course and outcome of pregnancy in women with pulmonary tuberculosis. *Scand J Respir Dis* 1975;**56**:245–50.
70 Jana N, Vasishta K, Jindal SK, *et al*. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. *Int J Gynecol Obstet* 1994;**44**:119–24.
71 Figueroa-Damien R, Arredondo-Garcia JL. Pregnancy and tuberculosis: influence of treatment on perinatal outcome. *Am J Perinatol* 1998;**15**:303–6.
72 Jana N, Vasishta K, Saha SC, *et al*. Obstetrical outcomes among women with extra-pulmonary tuberculosis. *N Engl J Med* 1999;**341**:645–9.
73 Ahmed Y, Mwamba P, Chintu C, *et al*. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. *Int J Tuberc Lung Dis* 1999;**3**:675–80.
74 Jindani A, Aber VR, Edwards EA, *et al*. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1980;**121**:139–48.
75 Rouillon A, Predizet S, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. *Tubercle* 1976;**57**:275–99.
76 The Interdepartmental Working Group on Tuberculosis. *The prevention and control of tuberculosis in the United Kingdom: UK guidance on the prevention and control of transmission of (1) HIV related tuberculosis and (2) drug-resistant, including multiple drug-resistant, tuberculosis*. Department of Health, The Scottish Office, The Welsh Office, September 1998.
77 Centers for Disease Control. The role of BCG vaccine in the prevention and control of tuberculosis in the United States: a joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunisation Practices. *MMWR* 1996;**45**:1–18.
78 Cantwell M, Snider DE Jr, Cauthen G, *et al*. Epidemiology of tuberculosis in the United States, 1985 through 1992. *JAMA* 1994;**272**:535–9.
79 Beitzke H. Ueber die angeborene tuberkuloese infektion. *Ergeb Ges Tuberk Forsch* 1935;**7**:1–30.
80 Rich AR. The mechanism of acquired sensitivity. In: *The pathology of tuberculosis.* Springfield, IL: C C Thomas, 1994: 513.
81 Smith JK, Caspary EA, Field EJ. Lymphocyte reactivity to antigen in pregnancy. *Am J Obstet Gynecol* 1972;**113**:602–6.
82 Cantwell MF, Shehab ZM, Costello AM, *et al*. Brief report: congenital tuberculosis. *N Engl J Med* 1994;**330**:1051–4.
83 Starke JR. Tuberculosis: an old disease but a new threat to the mother, fetus and neonate. *Clin Perinatalol* 1997;**24**: 107–27.
84 Hageman J, Shulman S, Schreiber M, *et al*. Congenital tuberculosis: critical reappraisal of clinical findings and diagnostic procedures. *Pediatrics* 1980;**66**:980–4.
85 Cunningham DG, McGraw TT, Griffin AJ, *et al*. Neonatal tuberculosis with pulmonary cavitation. *Tubercle* 1987;**63**: 217–9.
86 Klotz SA, Penn RL. Acid fast staining of urine and gastric contents is an excellent indication of mycobacterial disease. *Am Rev Respir Dis* 1987;**136**:1197–8.
87 Nemir RL, O'Hare D. Congenital tuberculosis. *Am J Dis Child* 1985;**139**:284–7.
88 Stallworth JR, Brasfield DM, Tiller RE. Congenital miliary tuberculosis proven by open lung biopsy specimen and successfully treated. *Am J Dis Child* 1980;**134**:320–1.
89 Burk JR, Bahar D, Wolf FS, *et al*. Nursery exposure of 528 newborns to a nurse with pulmonary tuberculosis. *South Med J* 1978;**71**:7–10.
90 Steiner P, Rao M, Victoria MS, *et al*. Miliary tuberculosis in two infants after nursery exposure. Epidemiologic, clinical and laboratory findings. *Am Rev Respir Dis* 1976;**113**:267–71.
91 Adikhari M, Pillay T, Pillay DG. Tuberculosis in the newborn, an emerging disease. *Paediatr Infect Dis J* 1997;**16**:1108–12.
92 Holdiness MR. Antituberculosis drugs and breastfeeding. *Arch Intern Med* 1984;**144**:1888.
93 WHO Working Group. In: Bennett PN, ed. *Drugs and human lactation*. New York: Elsevier, 1988: 281–2.
94 Wilson JT. Milk/plasma ratios and contraindicated drugs. In: Wilson TJ, ed. *Drugs in breast milk*. Balgowlah, Australia: ADIS Press, 1981: 79.
95 Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 1994;**93**:137–50.