Review Diagnosis and management of tuberculosis in pregnancy

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Key content:

- The UK has one of the highest incidence rates of tuberculosis (TB) in Western Europe.
- Tuberculosis in pregnancy appears to be limited exclusively to ethnic minority women.
- Timely investigation and diagnosis of TB are essential to initiate treatment and prevent maternal and neonatal morbidity and mortality.
- Diagnosis is difficult as symptoms can mimic physiological changes of pregnancy.

Learning objectives:

- To understand the various presentations and identify those at risk of infection or of developing the disease in pregnancy.
- To learn about various anti-TB treatment regimens and their adverse effects.
- To understand the issues of infection control and the multidisciplinary approach to care.

Ethical issues:

- Do newborn infants need to be separated from their mother if the mother has TB?
- Can breastfeeding still be recommended if the mother is being treated for TB?

Keywords bacille Calmette–Guérin / breastfeeding / ethnic minority / infection control / perinatal outcome

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Introduction

Tuberculosis (TB) is a disease of great antiquity and it remains an important cause of mortality and morbidity in both developed and developing countries.[1] The reported rate of TB in the UK in 2008 was 14.1 per 100 000 population, with the rate in London being 44.3 per 100 000 (**Figure 1**).[2] Rates of TB are at their highest since the late 1980s.[2] The UK national incidence of TB diagnosed in pregnancy was estimated as 4.2 per 100 000 maternities in 2005–2006.[1]

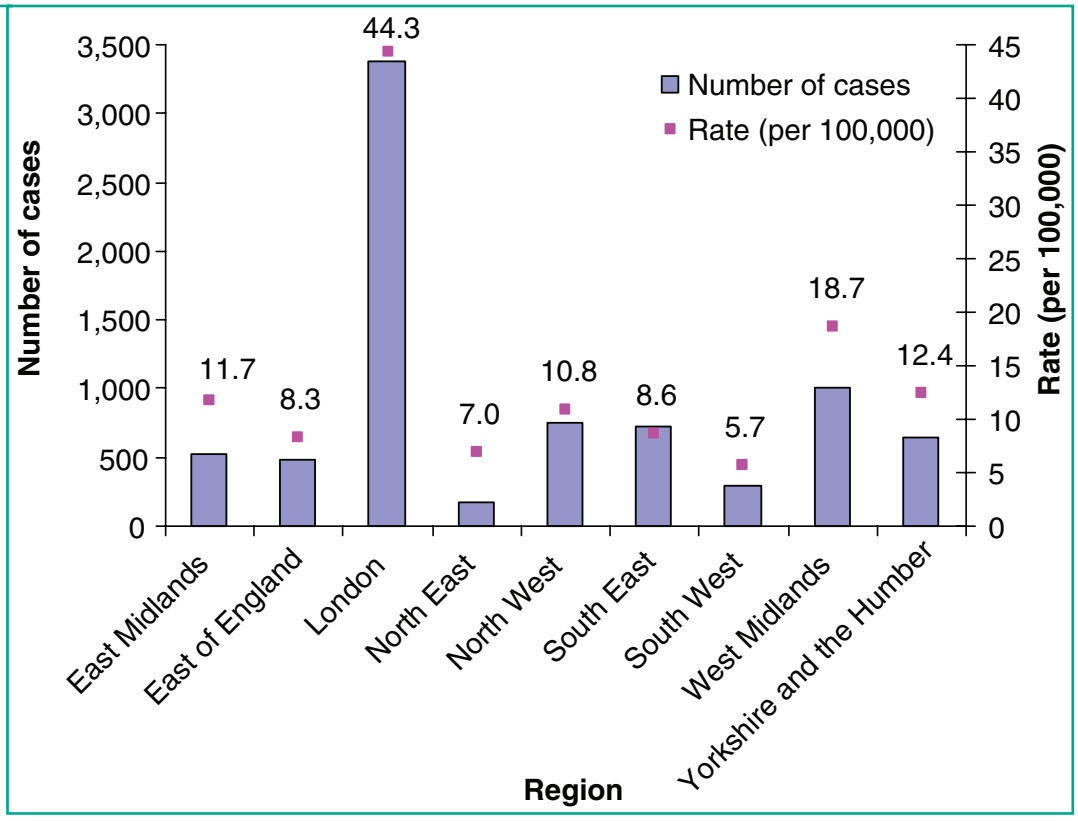
In the last report from the Confidential Enquiry into Maternal and Child Health (CEMACH)[3] there were three indirect maternal deaths due to tuberculous infection. These cases were diagnosed late, possibly because of a lack of awareness of TB in pregnancy among the obstetric and midwifery staff.[3] To control the disease it is important that we understand the bacterium causing TB; the associated risk factors; clinical, bacteriological and radiological measures to establish its diagnosis; and the role of chemoprophylaxis in contacts.

Epidemiology and natural history

(See **Figure 2** for natural history and **Figure 3** for rates in England by place of birth.) Rates of TB in the UK-born population have remained stable.[2] The UK has one of the highest incidence rates of TB in Western Europe.[2,7] There has been a significant change in the epidemiology of TB in the last two decades. It now largely affects population subgroups such as ethnic minorities, non-UK-born individuals such as black African and Indian/Pakistani/ Bangladeshi ethnic groups, the homeless and problem drug users.[2,8,9] The highest rates are in marginalised communities, along with higher rates of HIV co-infection and extrapulmonary disease. Tuberculosis in pregnancy is now seen exclusively in ethnic minority women and mostly in those who were born outside the UK.[1,9,10] Ethnic minority women born in the UK with links to endemic countries are also at increased risk.

Discovered in 1882 by Robert Koch, the name 'mycobacterium' is derived from the Greek words *mykēs*, meaning fungus, and *baktērion* meaning 'little rod', which it resembles when grown on liquid culture media.[11] The disease TB is caused by the *Mycobacterium tuberculosis* complex, which includes several species of mycobacteria such as *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. caprae*, *M. microti*, *M. canettii and M. pinnipedii.*[12,13] *Mycobacterium tuberculosis* was identified in 99% of the culture-confirmed cases, *M. africanum* in 0.5% and *M. bovis* in 0.4% of the culture-confirmed cases.[2] In the past, certain mycobacteria such as *M. kansaii, M. xenopi, M. avium intracellulare*, and *M. fortuitum*, which caused TB-like disease in birds and animals, were termed tubercle bacilli, but they are now recognised as environmental or atypical mycobacteria. They seldom cause disease in humans, but harmless infection in healthy humans can give rise to a weakly positive tuberculin skin test and they can cause resistant TB in people with HIV.[12,13] Information on species identification is collected

Figure 1
Tuberculosis case reports and rates by region, England, 2008.[2] (Reproduced with permission from the Health Protection Agency)



by the UK Mycobacterial Surveillance Network and will enable improved public health interventions and a better understanding of national epidemiology.[14]

Clinical features and diagnosis

Clinical features are the same in pregnant and non-pregnant women. Clinical diagnosis is only possible in the presence of active disease; however, one-half to two-thirds of pregnant women with TB are asymptomatic, possibly due to latent infection.[15,16] Early disease and non-specific constitutional symptoms such as malaise and fatigue in pregnancy can mimic the physiological changes in pregnancy.[9,17]

Both pulmonary (**Box 1**) and extrapulmonary (**Box 2**) TB can be associated with constitutional symptoms such as malaise, weight loss, loss of appetite, general and unusual tiredness, persistent fever and night sweats, all of which come on gradually over a period of weeks or months.

Investigations that help in establishing the diagnosis (**Box 3**) and the nature of the investigations depend on the clinical presentation. Recent UK data suggest that extrapulmonary TB in pregnancy is as common as pulmonary disease.[1,9,10]

A history of recent contact with a person with TB or the presence of any of the other risk factors (**Box 4**) should raise a suspicion of TB.

The effects of pregnancy on TB

Pregnancy has neither a beneficial nor a detrimental effect on the course of TB, including sputum conversion rate, stabilisation of the disease and relapse rate,[24] as long as it is diagnosed and treated appropriately without delay.[15,25] It is the anatomical extent of the disease, the radiographic pattern and the susceptibility of the individual woman to TB, rather than pregnancy itself, which determines the course and prognosis of the disease in pregnancy.[5]

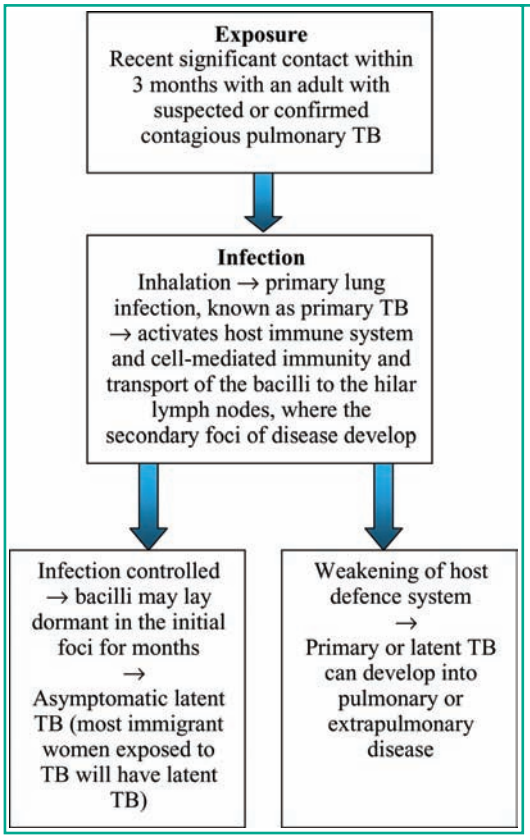


Figure 2
Natural history of TB[4–6]

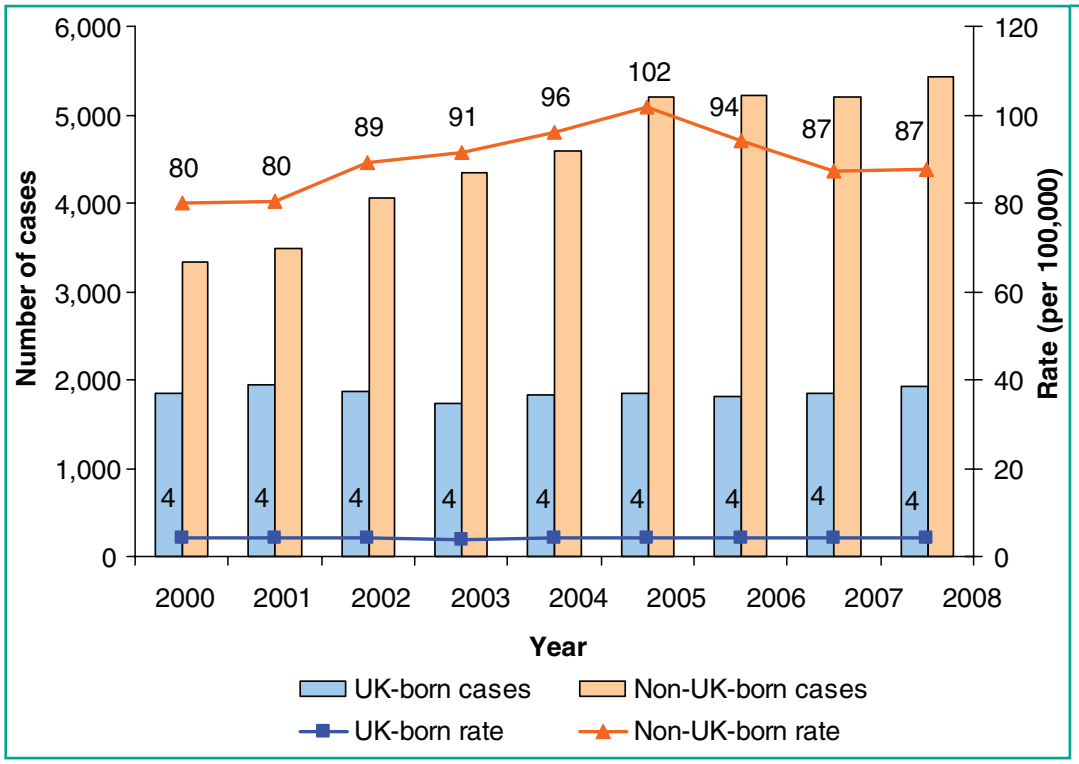


Figure 3
Tuberculosis case reports and rates by place of birth, England, 2000–2008.[2] (Reproduced with permission from the Health Protection Agency)

Box 1
Pulmonary TB[18]

Symptoms	Pathogenesis
Asymptomatic	Latent infection
Persistent cough—the most common symptom. Initially dry and non-productive but may later become productive. Associated with haemoptysis in some cases when a granuloma erodes into blood vessels	Enlargement of mediastinal nodes which press on the bronchus or inflammation of the airways. It becomes productive, with inflammatory exudates and/or discharging granulomatous lesions
Breathlessness—a late feature	Destruction of substantial lung tissue or significant pleural effusion
Chest pain—relatively uncommon. Dull, ill-localised or pleuritic in nature	Pleuritic if peripheral granulomatous lesions are present
Localised wheeze	Collapse of distal lung caused by hilar lymph node or bronchial narrowing secondary to compression by lymph node
Signs suggestive of pleural disease, pleural effusion or lung collapse	

Box 2
Extrapulmonary TB.[18] (Usually, constitutional symptoms of gradual onset with or without site-specific symptoms are present)

Sites	Clinical features
Central nervous system • Responsible for 5% of non-respiratory TB • Associated with significant morbidity and mortality • TB meningitis responsible for two-thirds of maternal deaths in the last CEMACH report[3]	• Early constitutional symptoms of anorexia and malaise may be associated with headache, vomiting and altered behaviour • Focal neurological signs, depending on the site of involvement, i.e. cerebellar signs, extrapyramidal movements, hemiparesis or monoparesis • Decreasing level of consciousness can occur after a few weeks or months
Lymph nodes • The most common site of extrapulmonary disease	• Persistent lymphadenopathy of >4 weeks' duration in people other than white UK-born should be regarded as TB until demonstrated otherwise and investigated appropriately • Gradual painless enlargement of lymph nodes, fluctuant swelling, superficial ulceration and sinus formation with discharge
Bones and joints • Pregnancy can unmask subtle manifestations and hasten progress of the disease	• Lower back pain is often mistaken for a physiological change associated with pregnancy[20] • An isolated lesion of the joint or a mono-arthritis in a woman from an ethnic minority group should raise suspicion of joint TB • Spinal disease is associated with local tenderness, kyphosis, paraspinal abscesses presenting as a loin mass or psoas abscess or signs of spinal cord compression
Gastrointestinal system • The ileocaecal area is the most common site • Varied presentations make it difficult to diagnose	• Unexplained lower abdominal, right iliac fossa pain with the systemic features should raise a suspicion of TB • Ileocaecal TB can present with acute onset of right iliac fossa pain, simulating acute appendicitis and/or features of acute intestinal obstruction with vomiting, pain and abdominal distension • Some present with constitutional symptoms of fever, malaise, failure to gain weight in pregnancy or weight loss, abdominal pain and abdominal distension or altered bowel habit
Other sites	• Genitourinary, miliary, skin and pericardial TB are very rare in pregnancy. Tuberculosis can also present with cold abscesses in the liver, adrenals and pancreas

The effects of TB on pregnancy

Although much literature[26] is available on this subject, information on perinatal outcome is limited and sometimes contradictory. A Norwegian study[15] revealed a higher incidence of pre-eclampsia, postpartum haemorrhage and difficult labour in mothers with TB compared with control subjects. Subsequent studies have revealed that pulmonary TB, if associated with late diagnosis, increases the obstetric morbidity in the form of pre-eclampsia or acute respiratory failure and preterm labour.[26,27] Extrapulmonary TB has no direct effect on the course of pregnancy, pre-eclampsia or mode of delivery but is associated with maternal morbidity in the form of recurrent admission rates and disability[28] as well as increased mortality in cases of TB of the central nervous system and other complications.[1,3,28] Perinatal outcome depends on whether TB is pulmonary or extrapulmonary and also whether it is diagnosed late in pregnancy. In a study of Indian women[26] with pulmonary disease treated for 7–9 months in pregnancy, perinatal mortality was six times higher than in controls. The incidence of prematurity, small for dates and low birthweight was doubled.[26] The rate of adverse effects was

Box 3
Investigations for diagnosing TB in pregnancy

Investigation	Role	Interpretation
Tuberculin skin testing (Mantoux test) • 0.1 ml (5 tuberculin units) purified protein derivative is regarded as safe in pregnancy[19,20] • Results are not affected by pregnancy[19,20]	• Representative of latent infection • False positive: infection with non-TB mycobacteria, previous BCG vaccination, technical errors • False negative: recent or very old TB infection, recent live-virus vaccination, overwhelming TB disease, some viral illnesses	• Reaction is classified by the diameter of induration perpendicular to the long axis of the forearm 0–4 mm: no further action; 5–10 mm: doubtfully positive; 10–15 mm: reactive in high risk cases; >15 mm: positive in all cases
Chest X-ray • Radiation exposure of <0.01 mGy (no evidence of any fetal damage at 100 mGy, so can be done safely in pregnancy[20,21]	• Defines the extent of pulmonary involvement and diagnosis of active disease • Can be used to identify improvement by comparison	• Patch or nodular shadows in the upper zones • Loss of volume and fibrosis with or without cavitation • Primary focus may be present in latent TB
Other imaging • CT/MRI of spine/abdomen/brain, etc, to be used with caution after appropriate counselling[21]	• Helps in establishing diagnosis and extent of extrapulmonary TB	• Depends on the site of the lesion
Smear and/or culture sensitivity • Any tissue specimen or tissue fluid, i.e. sputum; gastric, tracheal or bronchial lavage; CSF, etc.	• Gold standard for diagnosis • May be negative in paucibacillary cases, sampling error	• Gram-positive, acid-fast bacilli in the culture
Interferon-gamma release assays; immunological test such as QuantiFERON Gold or T-SPOT.TB[18,22,23]	• Currently, there is a lack of evidence for use in pregnancy or long-term safety[18] • Improved specificity over the Mantoux test • Reduced cross-reactivity with the BCG and most non-tuberculous mycobacteria	• QuantiFERON TB Gold In-Tube assay reports a value of ⩾35 iu as a positive test • T-SPOT.TB reports a value of ⩾6 spots as a positive value • An indeterminate result may be reported in both tests; the laboratory should be contacted for further details

BCG = bacille Calmette–Guérin; CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging

Box 4
Risk factors for TB[5,18]

- Close contact with infectious cases
- Living in, travel to or receiving visitors from places where TB is still very common i.e. developing Asian and African countries
- Living in ethnic minority communities originating from places where TB is still very common
- Having an immune system weakened by HIV infection or other medical problems
- Being very young or elderly, as their immune systems are less robust
- Chronic poor health and nutrition because of lifestyle problems such as homelessness, drug abuse or alcoholism, being a migrant worker or their family
- Living in poor or crowded housing conditions, including living in hostels

higher if maternal TB was diagnosed in the third trimester, disease was in advanced stage or the woman was non-compliant with the treatment. Figuera-Damien *et al.*[27] in Mexico reported a substantial increase in neonatal mortality, with this effect being mainly the result of late diagnosis and treatment. Another prospective study[24] has shown that if adequate chemotherapy is given to pregnant women with TB they are not at any higher risk than non-pregnant women with TB. These studies were conducted in developing countries and had limited numbers. Second, interpreting these results and comparing them with the UK population data requires detailed insight into the socioeconomic, psychological and sociomedical conditions in developing and developed countries.

In the case of extrapulmonary disease, tuberculous lymphadenitis does not appear to have any significant effect on perinatal outcome, whereas disease at other extrapulmonary sites such as the spine, abdomen and central nervous system was associated with increased rates of fetal growth restriction and low Apgar scores.[28]

Data on perinatal outcome in the UK are limited, with a small number of reported cases in the recent literature. The statistical power in these studies is not sufficient to detect any significant difference.[1,10] In a London-based case series[10] of 32 women with TB in pregnancy, five babies (16%) were classified as growth-restricted. Similarly, in the UK Obstetric Surveillance (UKOSS study),[1] one infant died from extreme prematurity among 32 infants with

reported outcomes. Severe morbidity was reported in two infants: one had chronic lung disease following early delivery due to pre-eclampsia and one was born with a congenital anomaly.

Congenital TB

Congenital TB is very rare. Typically, infected infants present in the second or third week of life with hepatosplenomegaly, respiratory distress, fever, low weight gain, irritability and poor feeding. Cantwell's diagnostic criteria for congenital TB are:[29] presence of TB lesions in the infant and one of the following: lesions in the first week of life, a primary hepatic complex or caseating granuloma, documented tuberculous infection of the placenta or endometrium and/or exclusion of the possibility of postnatal transmission by a thorough investigation of contacts.

Treatment of TB in pregnancy

(See **Box 5**, **Table 1** and **Figure 4**.) The aims of treatment are to:

- achieve cure without relapse
- prevent progression of the disease or occurrence of complications
- stop transmission to other individuals, healthcare professionals or newborns and prevent emergence of drug resistance.

Pregnant women with TB are managed by a multidisciplinary team consisting of a bacteriologist, chest physician, specialist TB nurse and obstetrician. Treatment is initiated and monitored by the chest physician and the specialist TB nurse. The role of the obstetrician is to ensure that antituberculous medication is administered safely and to monitor the well-being of the mother and the baby. Hospitalisation for a brief period may be needed in extremely ill women and smear-positive, highly infectious and multidrug-resistant (MDR)-TB cases. It may also be necessary for those in whom diagnosis is uncertain or to gain co-operation. Any hospital admission with suspected or diagnosed TB should prompt advice from the hospital's infection control department to prevent infectious patients coming into contact with others.

Chemotherapy

Treatment depends on the disease status, i.e. whether it is latent or active TB or whether there is drug resistance. It is divided into an initial intensive phase, which aims to kill actively growing and semi-dormant bacilli, followed by a continuation phase, which eliminates most of the residual bacilli and reduces failures and relapses.[33] In the case of active TB, isoniazid, rifampicin and ethambutol are considered to be the first-line antituberculous drugs. During pregnancy, a regimen that includes pyrazinamide for the first 2 months can be considered. It is considered that the use of at least two, but usually three or more drugs will prevent the increasing incidence of single-drug-resistant TB and multi-drug-resistant TB.

In the follow-up, women should be seen regularly to identify improvement and ensure their conversion from being infectious to non-infectious. A worsening chest radiograph on treatment or no improvement of symptoms should prompt exclusion of other differential diagnosis and MDR-TB. Follow-up after 3 months is necessary, as relapse can occur within this time. Multidrug-resistant cases should be followed for at least 1 year after treatment has been completed.

Latent TB and the role of chemoprophylaxis

The role of treatment in latent TB infection, especially in pregnant women, is controversial. Some experts prefer to delay treatment until after delivery because pregnancy itself does not increase the risk of progression of the disease, and two studies suggest that women in pregnancy and the early postpartum period may be vulnerable to isoniazid hepatotoxicity.[34,35]

Infection control in late pregnancy and the puerperium

Pulmonary TB is potentially infectious, particularly when the index case has sputum that is smear positive for the bacilli on microscopy. These women

Box 5
Tuberculosis treatment regimens[18,30,31]

Standard regimen for active disease (supervised treatment may be necessary if non-compliance is suspected)	Isoniazid 300 mg once daily + rifampicin 600 mg once daily for 6 months + pyridoxine 10 mg daily to reduce the risk of isoniazid-induced neuropathy. Liver function tests should be performed at least monthly. Ethambutol is the first-line drug for the treatment of TB during pregnancy in combination with isoniazid and rifampicin. (Pyrazinamide 1.5–2 g daily can be added for the first 2 months in those cases where resistance of the other first-line drugs is suspected or documented)
Longer regimens	Same drugs but for 9 months in cases of bone TB and 12 months in cases of central nervous system TB
Multidrug-resistant organisms	Primary seen in immigrants to UK and secondary develops due to non-compliance with initial treatment. It is also a problem in HIV-infected women with TB. Treatment with second-line drugs to which the sputum culture is sensitive should be used
	Ethionamide,[a] capreomycin, cycloserine, clarithromycin, azithromycin, ciprofloxacin, ofloxacin, kanamycin[a] and amikacin
	The duration of therapy should be 2 years; in HIV-positive women, ⩾12 months after negative cultures

[a]Ethionamide and kanamycin are not available in the UK

Table 1
Antituberculous drugs[30–32]

Drugs	Use	Dosage	Adverse effects	Effects on fetus
Isoniazid	First-line therapy	3–5 mg/kg up to 300 mg/day	Skin rash and fever, rarely hepatitis, peripheral neuropathy in high doses	No increase in malformations or growth restriction Safest in pregnancy Can cross placenta and cause demyelination, so pyridoxine supplementation advised
Rifampicin	Used in intensive phase	10–20 mg/kg up to 600 mg orally four times daily	Enzyme inducer Hepatitis Cutaneous hypersensitivity Gastrointestinal reactions Thrombocytopenic purpura	Theoretical risk of teratogenesis One study: increased risk of central nervous system abnormalities, limb reduction defects and hypoprothrombinaemia and haemorrhagic disease of newborn Overall risk of congenital malformations not increased
Ethambutol	Overall relatively safe in pregnancy second to isoniazid	15 mg/kg	Dose-related optic retrobulbar neuritis Arthralgia	It readily crosses the placenta and there have been few reports of animal teratogenicity with its use Theoretical possibility of ocular toxicity
Pyrazinamide	Used with caution in pregnancy	20–30 mg/kg	Anorexia Nausea Photosensitivity Flushing Hepatotoxicity	No significant animal teratogenicity studies or reports of malformations in treated patients are available
Streptomycin	No consistent relationship between gestational age at exposure and ototoxicity—should be avoided throughout the entire gestation period	12–15 mg/kg	Cutaneous hypersensitivity Giddiness Numbness and tinnitus Vertigo Ataxia Deafness	Variable transplacental passage Ototoxicity varying from minor vestibular and/or auditory impairment, to cases of severe, irreversible bilateral loss of hearing and marked vestibular abnormalities
Kanamycin,[a] amikacin, capreomycin, ofloxacin, ciprofloxacin, ethionamide,[a] prothionamide, cycloserine, *para*-aminosalicyclic acid	Safety profile in pregnancy has not been ascertained and should generally be avoided unless necessary for maternal well-being	Second-line drugs useful in multidrug-resistant cases	Otoxicity, nephrotoxicity, gastrointestinal reaction	Same potential problems as streptomycin. Inadvertent use does not require termination of pregnancy or invasive diagnostic procedures, but hearing tests should be performed after birth

[a]Ethionamide and kanamycin are not available in the UK

can be rendered non-infectious by 2 weeks of treatment which include rifampicin and isoniazid.[36,37] If admitted to hospital, the decision about isolation depends on the initial assessment of infectivity, the possibility of multiple-drug resistance and the immune status of the individual.[36] Women with suspected or confirmed MDR-TB should be admitted to a negative-pressure ventilation room.[36,37] Control of infection in healthcare settings among patients and healthcare workers is the responsibility of infection control teams.[38] When admitted to the hospital, responsibility of care should be shared by the multidisciplinary team and in no case should treatment be delayed because of infection control issues.[3] Tuberculosis is a notifiable disease and the clinician in charge of the patient is responsible for notification to the consultant in communicable disease control. If the woman is later found to be negative they can be denotified.[39]

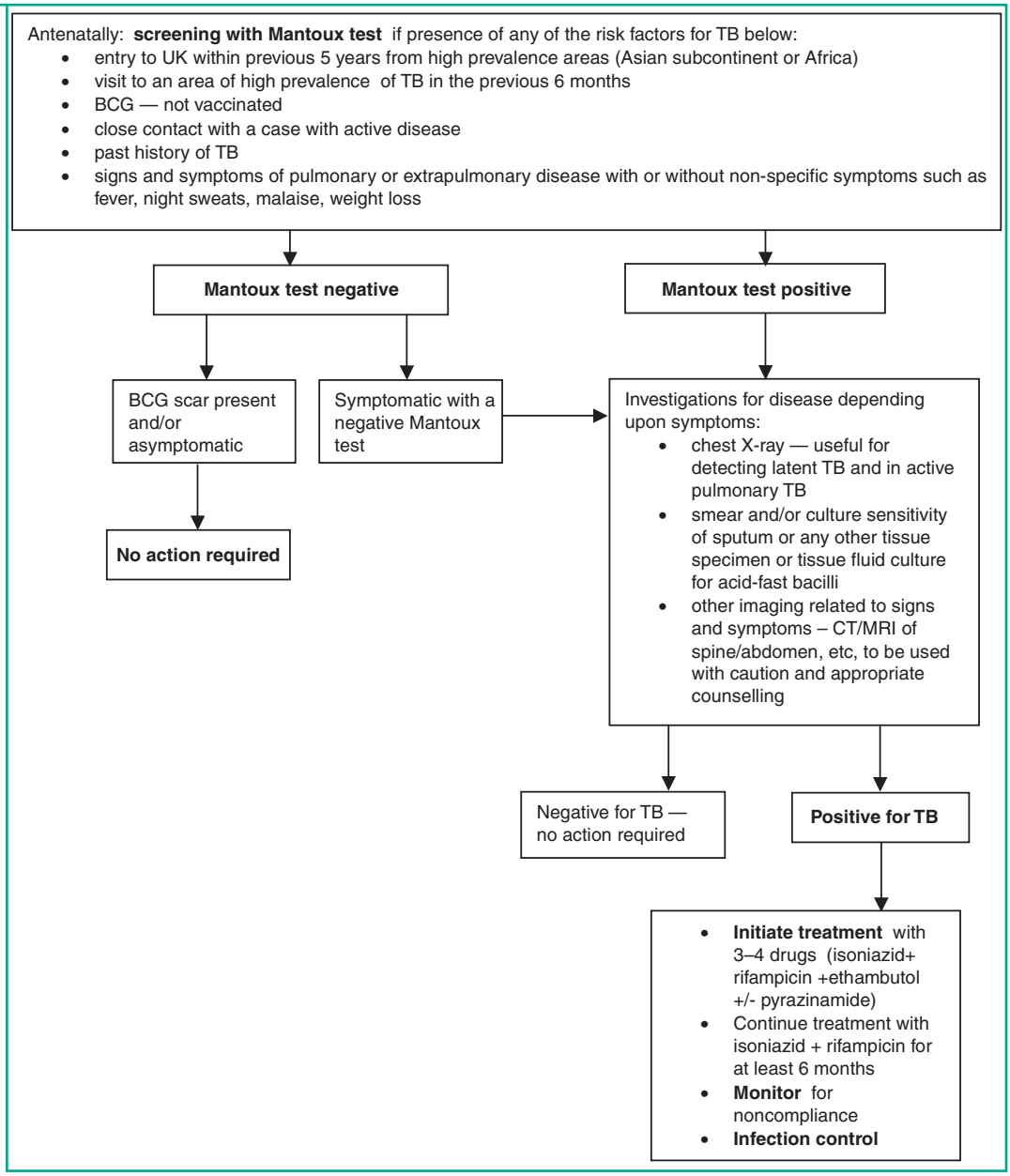
If TB is diagnosed postnatally, with the mother being sputum positive for acid-fast bacilli within the 2 weeks following delivery, there is a potential risk of transmission of the disease to the newborn. Infants with a mother who has had less than 2 weeks of treatment and who is sputum positive for acid-fast bacilli should be given prophylactic isoniazid (5 mg/kg) and pyridoxine (vitamin B6) (5–14 mg/kg)[20] and have a tuberculin test at 6–12 weeks. If this is negative then a bacille Calmette–Guérin (BCG) can be given and the chemoprophylaxis stopped. If the tuberculin test is positive then extended treatment should be given for a total of 6 months.[20] The BCG vaccine is not recommended for the babies of mothers who are HIV-positive until they have been shown to be HIV-negative. Contact tracing and screening involves all close family members or other individuals who have had close contact and is done by history, examination, tuberculin testing and chest X-ray. Contacts who are ill should be thoroughly investigated for TB.

In an adult contact, if the tuberculin test is positive and they are immunocompromised or they have HIV infection and have not had a BCG, chemoprophylaxis with isoniazid is given.
In children, a positive tuberculin test is suggestive of infection and treatment is given. A negative tuberculin test is repeated in 6 weeks and if it is still negative then a BCG is given; if it turns positive it suggests active infection and this needs treatment.

Breastfeeding

Breastfeeding is recognised as the healthiest way to feed a baby.[40] Antituberculous drugs cross into the breast milk but the amounts are too small to

Figure 4
Flow chart for management of TB in pregnancy



produce toxicity.[41,42] Women taking isoniazid should also take pyridoxine supplementation (14–25 mg/day).[41,42] There are no reports of any adverse effects among infants of nursing mothers receiving anti-TB drugs.[40,41] If a breastfeeding mother becomes acutely ill with TB, breastfeeding may have to be interrupted and breast milk expressed to prevent development of mastitis.[40,42]

The role of the BCG vaccine

The BCG vaccine contains a live attenuated strain of the bacillus derived from *M. bovis*. No harmful effects on the fetus have been observed from BCG during pregnancy but, as it is a live attenuated vaccine, it should be avoided in pregnancy, particularly in the first trimester, and wherever possible delayed until after delivery.[43] Breastfeeding is not a contraindication to the BCG. It should be given to all neonates and infants who live in an area with an annual TB incidence of >40 per 100 000 people or with a parent or grandparent from a country where the incidence is >40 per 100 000 population or family history of TB in the previous 5 years.[44] It is effective in preventing severe disease in infants and young children. The BCG is not recommended for babies of mothers who are HIV-positive until they have been shown to be HIV-negative, or if a member of the household has suspected or active TB.[45]

Multidrug-resistant TB in pregnancy

The overall incidence of MDR-TB in UK remains low[18] (~1% of all TB cases tested) but it is associated with a high mortality rate in the general population. There is a lack of evidence-based information in pregnancy.[46] Management of these cases should be individualised. Multidrug-resistant TB develops if there is non-compliance with the treatment initially. It must be treated with second-line antituberculous drugs and for a period of 2 years.

Conclusion

Tuberculosis in pregnancy is more likely to be seen in areas with a higher incidence of TB and in ethnic minority women. It should be suspected in women with these background risk factors in the presence of non-specific signs and symptoms and/or the presence of clinical features suggesting pulmonary or extrapulmonary disease. Tuberculin skin testing is a valuable screening test in pregnancy and should be carried out if latent TB is suspected. Chest X-ray with shielding is essential and safe in all TB suspects. Pregnancy does not affect the course of TB; however, delay in treatment or untreated TB increases maternal morbidities and has the potential to cause increased incidence of preterm labour and growth restriction and can be transmitted to the newborn. First-line antituberculous drugs such as isoniazid, rifampicin and ethambutol can be used safely in pregnancy and while breastfeeding. Co-infection with HIV increases maternal mortality rates. It is beyond the scope of this review to discuss MDR-TB and TB with HIV in cases of pregnancy.

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