

Tuberculosis diagnosed during pregnancy: a prospective study from London

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Abstract

Background—A study was undertaken to characterise the presentation of tuberculosis in pregnancy and the difficulties in diagnosis in an area of the UK with a high incidence of tuberculosis.

Methods—A prospective case series was investigated at Northwick Park Hospital, a university affiliated district general hospital in Brent and Harrow health authority in north-west London which incorporates a regional infectious diseases unit. Patients diagnosed with tuberculosis over the study period were included if the onset of symptoms occurred during pregnancy.

Results—Thirteen patients were diagnosed during a 30 month period from December 1995 to May 1998 during which 9069 mothers were delivered, a prevalence of 143.3/100 000 deliveries. Symptoms began at a median of 22 weeks gestation (range 9–40 weeks). All patients were recent immigrants of Indian subcontinent or Somali origin and their median duration of residence in the UK was 31 months (range 1–72). Prevalence broken down for racial origin of mothers was 466.3/100 000 for mothers of black African origin and 239.1/100 000 for mothers of Indian origin. Nine of the 13 patients had extrapulmonary tuberculosis. Four patients with widely disseminated disease had a negative Mantoux response and five with localised disease had a strongly positive Mantoux response. HIV co-infection was absent. The median delay between the onset of symptoms and diagnosis was seven weeks (range 2–30). The response to standard treatment was excellent and all patients were cured.

Conclusions—Tuberculosis occurring in pregnancy is common in recent immigrants. Diagnosis during pregnancy is delayed because the disease is frequently extrapulmonary with few symptoms.

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changed considerably since 1961, this aspect of the disease needed to be reassessed.

In the light of reports from New York describing a resurgence of tuberculosis during pregnancy in association with HIV infection,⁴ we set out to gather prospectively a patient series to describe tuberculosis in pregnancy presenting in a British hospital where rates of tuberculosis are relatively high.

Methods

SETTING

Northwick Park is an 800 bed district general hospital which incorporates a 34 bed regional infectious diseases unit. The hospital serves a population of about 300 000 in the boroughs of Brent and Harrow. The notification rate of tuberculosis in Brent in 1993 was 47.2/100 000 population; the UK national rate was 10.1/100 000.¹¹ The hospital notifies about 150 patients annually with tuberculosis. The obstetric unit performs approximately 3300 deliveries/year.

SUBJECTS

Over a 30 month period from December 1995 to May 1998 we prospectively gathered all patients with tuberculosis in whom the symptoms had started during pregnancy. Where possible the diagnosis was confirmed by culture of *Mycobacterium tuberculosis* or demonstration of caseating granulomas in biopsy material. Otherwise, patients were diagnosed on clinical and radiographic evidence and response to treatment. Patients were considered to have developed tuberculosis during pregnancy if the diagnosis was made during pregnancy or soon after delivery if symptoms clearly began during pregnancy. Data recorded by the midwives gave accurate figures for the total number of deliveries and the racial origins of the mothers.

Results

Thirteen patients with tuberculosis during pregnancy were documented. Details of each case including presenting features and the basis on which the diagnosis was made are given in tables 1 and 2.

RACIAL ORIGIN OF PATIENTS

During the study period 9069 deliveries were performed, translating into an incidence of tuberculosis of 143.3/100 000 deliveries. The racial origins of the mothers were as follows: white European, 3963 (43.7%); black African, 1930 (21.3%); Indian, 1673 (18.4%); black Caribbean, 416 (4.6%); Pakistani, 346 (3.8%); other (Bangladeshi, Mediterranean, not stated,

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Recent publications^{1–8} have described case series of tuberculosis in pregnancy within various populations, but no data have been published from the UK since 1961.⁹ At that time the pattern of disease in London did not differ from that seen in matched populations of young women. A similar conclusion was reached later in New York.¹⁰ Because the demographics of tuberculosis in the UK have

Table 1 Presentation, gestation at onset of symptoms, and time to diagnosis

Case	Site of disease	Clinical presentation	Gestation at onset of symptoms	Time to diagnosis
1	Pulmonary	Fever, weight loss. Travelled to India for treatment	4 weeks	4 weeks
2	Pulmonary	Cough and fever	40 weeks	8 weeks
3	Pulmonary and laryngeal	Cough and fever	3 weeks	26 weeks
4	Pulmonary	Contact of child who had pulmonary tuberculosis	Diagnosed at 30 weeks	
5	Pulmonary and cerebral tuberculomas	Seizures. History of fever and weight loss late in pregnancy	36 weeks	17 weeks
6	Pleural	Night sweats and pleural effusion	10 weeks	2 weeks
7	Miliary	Fever and abdominal distension. Also cough and dyspnoea. Presented cachectic and severely unwell	18 weeks	4 weeks
8	Miliary	Bell's palsy treated with steroids, developed dyspnoea	30 weeks	4 weeks
9	Miliary and TBM	Impaired cognitive state	13 weeks	4 weeks
10	Peritoneal	Presented with abdominal pain, distension and diagnosis of possible appendicitis	27 weeks	6 weeks
11	Ileocaecal	Failure to gain weight in pregnancy, lower abdominal pain	16 weeks	30 weeks
12	Peritoneal	Abdominal distension and altered bowel habit	23 weeks	9 weeks
13	Tibial osteomyelitis	Discharging sinus. Investigated after delivery	24 weeks	26 weeks

any other racial group), 741 (8.2%). All the women in the study were born outside the UK and all were either of Somali (n = 9) or Indian (n = 4) origin. They had lived in the UK a median of 31 months (range 1–72).

Although the number of Somalis among the black African mothers was not recorded, even if all these mothers were Somali this would equate to a prevalence of 466.3/100 000 deliveries for mothers of Somali origin. A total of 1673 mothers were of Indian origin, equating to a prevalence of 239.1/100 000 deliveries.

SKIN RESPONSE TO TUBERCULIN

Tuberculin testing was performed in nine patients. Anergy to tuberculin occurred in four tested patients in whom tuberculosis was disseminated and in five tested patients who had more localised disease the tuberculin response was strongly positive. All had more than 10 mm skin induration in response to one unit of tuberculin. As is apparent from table 2, this was frequently of diagnostic value.

HIV STATUS

Ten of the 13 patients were tested for antibodies to HIV 1 and 2. All were HIV negative. Of the three who were untested, none had risk factors for HIV infection and none had clinical features suspicious of HIV infection.

CLINICAL PATTERN OF DISEASE

Only three patients had disease confined to the lung parenchyma. Two patients presenting with respiratory disease were found on investigation to have disease elsewhere; patient 3 was found at bronchoscopy to have laryngeal tuberculomas and patient 5 had cerebral tuberculomas on CT brain scan. Three patients had disseminated miliary disease and, in total, seven had disease outside the thorax.

DURATION OF SYMPTOMS BEFORE DIAGNOSIS

In some patients there was a considerable time lapse between the onset of symptoms and a diagnosis of tuberculosis being made. Patient 1 only presented on return to the UK and patient

Table 2 Diagnosis and outcome of pregnancy

Case	Site of disease	Basis of diagnosis	Outcome of pregnancy
1	Pulmonary	Positive Mantoux. Sputum smear and culture positive	Therapeutic abortion at 12 weeks in India
2	Pulmonary	Sputum smear and culture positive	Full term normal delivery
3	Pulmonary and laryngeal	Positive Mantoux. Bronchoscopy; laryngeal tuberculomas, lavage smear and culture positive	Normal delivery 38 weeks
4	Pulmonary	Chest radiographic changes. Bronchoscopy, smear negative culture positive	Full term normal delivery
5	Pulmonary and cerebral tuberculomas	Positive Mantoux. Chest radiograph and CT head scan appearances. Bronchoscopy; smear negative culture positive	Normal delivery 36 weeks
6	Pleural	Positive Mantoux. Granulomas in pleural biopsy	Full term normal delivery
7	Miliary	Miliary changes on chest radiograph. Ascitic fluid culture positive	Spontaneous abortion at 22 weeks. 4 days after presentation.
8	Miliary	Miliary shadowing on chest radiograph. Gastric washings culture positive	Normal delivery 37 weeks
9	Miliary and TBM	Miliary shadowing on chest radiograph. CSF smear negative culture positive	Delivered at 38 weeks
10	Peritoneal	Peritoneal studding on laparotomy. Ascitic fluid culture positive	Normal delivery 34 weeks
11	Ileocaecal	Characteristic barium follow through changes. Response to treatment	Full term normal delivery
12	Peritoneal	Lymphocytic ascites smear negative culture positive	Full term normal delivery
13	Tibial osteomyelitis	Positive Mantoux. Wound swabs smear negative culture positive	Full term normal delivery

7 presented at an advanced stage of disease. Reasons for delay in diagnosis in the remaining 11 cases varied and are discussed below. This delay ranged from two to 30 weeks with a median of seven weeks.

SENSITIVITY OF ISOLATES, TREATMENT AND OUTCOME

All 11 isolates of *Mycobacterium tuberculosis* from these patients were fully sensitive to the four first line antituberculous agents (rifampicin, isoniazid, pyrazinamide and ethambutol). Patients were treated for nine or 12 months using all four of these drugs for two months and then rifampicin and isoniazid for the remaining period of treatment. Treatment was prolonged beyond the recommended six months because many of the patients had complicated disease and, in several cases, compliance was uncertain. In all patients we observed a normal response to treatment. Patient 1 chose to terminate her pregnancy abroad. Patient 7 had a spontaneous abortion at 22 weeks gestation, four days after presenting critically ill with disseminated tuberculosis.

Discussion

This is the first British series of patients developing tuberculosis in pregnancy to be reported since 1961. Unlike the earlier UK studies in which the patients were predominantly of white European descent, all our patients were recent immigrants to Britain. Most recent publications come from the developed world where the risk factors for patients developing tuberculosis were HIV co-infection or social deprivation. A few reports are from immigrant non-white populations^{3 7 8} but, in general, clinical data on tuberculosis in pregnancy in immigrants are lacking. This is a significant deficiency in our understanding of tuberculosis since immigration status is the major epidemiological factor in the UK. The 1993 national survey of tuberculosis in England and Wales produced incidence estimates for different ethnic groups of 4.3/100 000 for whites compared with 114.7/100 000 and 135.2/100 000, respectively, for subjects of Indian or black African origin.¹² Furthermore, there is a strong association with duration of residence in the UK. Data from the same 1993 survey show that, for adults aged 15–34 years born outside the UK, the incidence of tuberculosis after 15 years in residence was 53/100 000 compared with 440/100 000 for immigrants resident for less than five years.¹²

It is of interest to consider whether the very high incidence of tuberculosis in our study reflects the background incidence in this group, or whether pregnancy is an independent risk factor for developing tuberculosis. The question of pregnancy as a risk factor for tuberculosis has been debated since the earliest days of medicine. Hippocrates believed that pregnancy had a beneficial effect on the outcome of tuberculosis and this was the view generally held until the middle of the last century. In 1850 Grissolle reported a series of patients whose tuberculosis worsened during the course of their confinement.¹³ This view

then held sway until the large case series of the 1940/50s, prior to the advent of effective antituberculosis drugs. These studies failed to show either a beneficial or detrimental effect of pregnancy on tuberculosis.^{9 10 14 15} With these data the argument appeared to be settled, at least among women in developed countries. These data may not necessarily be applicable to different racial groups and studies both in the developing world and larger studies within immigrant populations such as ours are clearly indicated.

That a group of patients who, because they are pregnant, are under regular medical review can have symptoms of tuberculosis for a median of seven weeks before a diagnosis is made is clearly a cause for concern. We identified a variety of reasons for this delay. Firstly, symptoms were often non-specific—for example, lethargy, alteration in bowel habit, or failure to gain weight appropriately—and these were interpreted as usual symptoms commonly occurring in pregnancy. Secondly, the tuberculosis in these patients was commonly extrapulmonary; cough was often absent. Finally, there was an understandable tendency to defer radiological investigations during pregnancy. Useful data for comparison on duration of symptoms before diagnosis of tuberculosis are lacking in the literature. Previous studies have focused on hospitalised patients with pulmonary disease.^{16 17} A recent study of 203 patients in Missouri found a median time lapse of only six days between admission and onset of treatment but information on duration of symptoms was not given. Interestingly, the delay was less for patients from ethnic minorities in this study, probably reflecting a higher index of suspicion in the attending physician.¹⁸

The lack of specific symptoms when tuberculosis occurs in pregnancy is in keeping with previous studies. Up to 20% of pregnant women with tuberculosis have been found to be asymptomatic.⁵ In one study a group of pregnant patients with pulmonary tuberculosis were matched to non-pregnant women with pulmonary tuberculosis and found to be significantly more likely to be asymptomatic at time of diagnosis.³ In another, pregnant patients with tuberculosis were significantly more likely to have non-specific symptoms and also to experience a delay in obtaining a chest radiograph than non-pregnant women with tuberculosis.⁷ Infant and maternal mortality from untreated active tuberculosis are between 30% and 40%.¹⁰ A recent study¹⁵ comparing outcomes in patients who started treatment early and late in pregnancy found a significant increase in obstetric morbidity and perinatal mortality in patients whose treatment was started late in pregnancy.

The high proportion of extrapulmonary tuberculosis in this series is intriguing and also partly explains the delay in diagnosis. Previous series of tuberculosis in pregnancy showed no excess of extrapulmonary disease. Ten of 16 patients in a New York study had pulmonary tuberculosis⁴ despite the known link between HIV infection and extrapulmonary disease.¹⁹ Nine of 10 patients in Kentucky had pulmo-

nary tuberculosis,²⁰ and all 27 patients whose tuberculosis occurred during pregnancy or up to one year after delivery in Denver during the late 1970s had pulmonary tuberculosis.⁵ Twenty five patients collected over 66 months in Mexico City during the early 1990s included 12 patients with extrapulmonary disease, most of which were renal.⁸ In the UK, however, there is a well established link between extrapulmonary tuberculosis and immigrants. The MRC 1983 survey found 66% of immigrants from India and 63% of immigrants from Bangladesh/Pakistan to have extrapulmonary disease.²¹ The bias of our population towards recent immigrants may partly explain the frequency of extrapulmonary disease seen. It is interesting to note that, in the three series published from places where patients were predominantly recent immigrants or non-whites, all reported frequent extrapulmonary disease. In these reports the ratio of extrapulmonary to pulmonary cases was 2:5, 3:1, and 12:13, respectively.^{3 7 8}

In New York, where the resurgence of tuberculosis was linked to HIV co-infection, the development of tuberculosis in pregnancy was similarly related to HIV. Among a total of 16 patients with tuberculosis in pregnancy over seven years, the incidence of tuberculosis increased from 12.4/100 000 deliveries between 1985 and 1990 to 94.8/100 000 deliveries between 1990 and 1992.⁴ Eleven of the patients were tested for HIV and seven were seropositive. The overall tuberculosis notification rate in New York in 1992 was 50.2/100 000.²² Although both the tuberculosis notification rate among UK immigrants and our estimates of the incidence among pregnant immigrants are much higher than the New York rates, a significant impact from HIV on tuberculosis in the UK has not been found.²³

The most recent guidelines from the British Thoracic Society on control and prevention of tuberculosis make no specific recommendations regarding pregnancy.²⁴ From our experience it is likely that pregnant women from ethnic minority groups in the UK are at an especially high risk of developing tuberculosis. Furthermore, because of the predominance of extrapulmonary disease and the non-specific symptomatology in these patients, a high index of suspicion for tuberculosis is needed when such patients develop symptoms.

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