Typhoid fever during pregnancy: case report and review

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Summary: Typhoid fever, like many gastroenteric infections, is considered a particular risk during pregnancy because of reduced peristaltic activity in the gastrointestinal and biliary tracts and increased prevalence of biliary 'sludge' and concretions. Antibiotic resistance among salmonellae makes the choice of antibiotics for initial treatment of infection difficult before cultures and sensitivities are reported. Because of the potential risks of some antimicrobial agents for pregnancy, the selection of antibiotic therapy is further complicated.

Keywords: high-risk pregnancy, infectious diseases

Enteric fever caused by group D salmonellae, *Salmonella enterica* serotype typhi, is uncommon and unusual during pregnancy in the United States. Worldwide an estimated 22 million cases of typhoid fever occur each year with about 200,000 related deaths.¹ In the United States about 400 cases are reported to the CDC each year, most of whom are recent travellers.² Typhoid fever is recognized as a special risk for all travellers to and from South Asia: India, Pakistan and Bangladesh.^{2,3}

CASE REPORT

A 23-year-old gravida 2 para 1001 immigrant from Bangladesh at 18 weeks gestation by the date of her last menstrual period came to the emergency department complaining of severe epigastric pain and fever. She had arrived in the United States with her family three months before. Shortly after her arrival in the United States she experienced the onset of multiple episodes of epigastric and right upper quadrant pain and episodic fever progressing to sustained fever, with shaking chills and sweats. The epigastric pain was relieved by antacids and Tylenol but not on the day of admission. She denied diarrhoea but reported multiple episodes of nausea and vomiting, which she had attributed to her pregnancy. Her last bowel movement was two days before; there was no blood in the stool. She did not note a skin rash. She denied any uterine contractions or pelvic pain. She had not yet noted any fetal movement.

Her first child has Down's syndrome.

She denied any sick contacts but did relate multiple mosquito bites in Bangladesh. Her past medical and surgical history was non-contributory. She denied ever having had malaria or dengue fever.

On examination her oral temperature was 102.1°F. Her blood pressure was 112/69 mmHg, and her pulse was 100 and regular. She was weak and had severe epigastric and right

upper quadrant tenderness. The liver and spleen were not palpable. Bowel sounds were present. Ultrasound confirmed a viable fetus compatible with her dates and without signs of distress except for fetal tachycardia. The remainder of the physical examination was unremarkable.

Cultures of stool, blood and urine were obtained. The complete blood count had a haemoglobin of 112 gm/L, a white blood cell count of $11.2 \times 10^9/L$ with 76% neutrophils and platelet count of $194 \times 10^9/L$. Thick and thin malaria smears were negative for plasmodia. She was started on ceftriaxone 2 gm intravenously daily.

Over the next two days her temperature rose to 104 °F. Also the liver enzymes increased: aspartate aminotransferase from 1.84 to 9.94 $\mu\text{kat/L}$ and alanine transaminase from 1.04 to 4.29. Alkaline phosphatase was elevated at 3.47 $\mu\text{kat/L}$, consistent with pregnancy. Bilirubin, amylase and lipase did not change. The abdominal sonogram revealed thickening of the gallbladder wall but no stones.

By day 3 the following laboratory results were reported:

- (1) Stool and blood cultures $\times 2$ were positive for group D salmonellae sensitive to ceftriaxone;
- (2) There were negative serologies for dengue fever, hepatitis A, B and C, and TORCH pathogens.

The patient defervesced and repeat fetal ultrasounds were negative for signs of chorioamnionitis. The patient was discharged after 10 days of intravenous ceftriaxone therapy and had negative blood, stool and urine cultures on the day of discharge. Follow-up stool cultures continued to be negative for salmonellae.

She delivered a healthy female weighing 3700 g at 40 weeks gestation. Cultures of amniotic fluid, placenta and cord blood were negative for salmonellae. The patient's liver function tests had returned to normal by the time of her delivery.

DISCUSSION

Typhoid fever is the systemic infection with *S. enterica* serotype typhi, a human-specific pathogen highly adapted for

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persistence and transmission among human beings.⁴ The greatest burden of the disease is in regions of the developing world where crowding and poor sanitation and hygiene persist. Typhoid fever is usually spread by ingestion of food or water contaminated by gastrointestinal or urinary carriers excreting *S. enterica* serotype typhi. Although ingestion is the larger source of infection, contaminated injection devices, illicit and occasionally prescribed injectable drugs or fluids, and transplacental infection can occur.⁴⁻⁸

Ingestion of as few as 1000 organisms can result in infection. The reduction in peristaltic force and frequency normal for gestation combined with the use of acid-reducing medicaments because of gastroesophageal reflux symptoms make pregnancy a high-risk condition for gastrointestinal infections, including typhoid fever (Table 1).⁵⁻⁹ The incubation period from ingestion to the bacteraemic phase is usually 7–14 days. The immunological modulation of pregnancy combined with alterations in gastrointestinal tract motility may reduce the length of incubation, may reduce the inoculum necessary to initiate infection and may prolong the duration of clinical carriage of organisms.⁴⁻⁸

The onset of bacteraemia is accompanied by malaise, vague abdominal discomfort, cough, myalgia and fever usually without rigors: a syndrome easily mistaken for a viral illness at its onset, or cholecystitis. The fever intensifies so that by the second week the temperature is high (39–40°C) and sustained. The blanching erythematous 'rose spot' rash is reported in only 5–30% of all cases. The hallmark of typhoid infection is persistent high fever and hyperthermia; early in gestation this may have adverse fetal effects. Serious complications occur in 10–15% of all patients and are more likely in patients who have been ill for more than two weeks (Table 2).^{4,9}

Typhoid fever during pregnancy can be complicated by uteroplacental infection, miscarriage and vertical intrauterine transmission leading to neonatal typhoid.^{4,5} Fortunately early diagnosis and antimicrobial therapy have made these outcomes less common. Gastrointestinal complications – bleeding and perforation of necrotic Peyer's patches – may be fostered by delayed diagnosis and treatment in underdeveloped regions. Perforation occurs in 1–3% of hospital inpatients. Confusion and obtundation may obscure intestinal perforation and are often accompanied by septic shock.⁴⁻⁹ Recent case reports and case series have illustrated the rarity of maternal and fetal complications in adequately treated patients.⁵⁻⁹

Blood cultures are essential for diagnosis, although bone marrow culture is more sensitive. Stool or rectal swab cultures are less reliable earlier in the course, but the rate of positive cultures increases with duration of the illness. Management of

Table 2 Pregnancy effects on the course of typhoid fever

I. Confusion with other more common infections
A. Cholecystitis
B. Urinary tract infections
C. Viral illness
II. Protracted febrile course and prolonged asymptomatic carriage of salmonella
A. Reduced biliary and gastroenteric motility favours slow clearance of bacteria
B. Presence of cholelithiasis/biliary sludge
C. Late and postpartum relapse
III. Uteroplacental infection with chorioamnionitis and fetal/neonatal infection

a febrile pregnant patient from a region with endemic typhoid fever should begin with prompt collection of blood, stool and urine cultures, as well as studies to exclude other possible pathogens such as malaria smears, serologies for endemic viral and bacterial pathogens (*Brucella*, chikungunya, dengue, HIV), and studies for coexisting risk factors such as intestinal parasites (amoeba, schistosomes) and haemoglobinopathies.¹⁰

The recurrent illness is usually less severe. Because of the changes in gallbladder and biliary motility and increased bone marrow activity induced by gestation, the risk of relapse is probably greater during pregnancy, especially in untreated or inadequately treated patients.⁵⁻¹¹ Repetitive stool cultures following successful antibiotic treatment of pregnant patients is essential in order to monitor persistent shedding of the bacteria and the risk of relapse.

Widespread use of antibiotics to treat a variety of gastrointestinal infections has resulted in the emergence of antimicrobial resistance among all salmonellae. By the 1990s *S. enterica* serotype typhi had developed resistance to all of the first-line drugs then in use: chloramphenicol, trimethoprim, sulfamethoxazole and ampicillin.⁴⁻¹² In 2009 there are increasingly frequent reports of resistance to fluoroquinolones and to second- and third-generation cephalosporins. However, in some areas of Asia, strains of *S. enterica* serotype typhi susceptible to the old first line antibiotics have reemerged.⁴ For acutely ill patients empiric antibiotic therapy with a quinolone or cephalosporin combined with an aminoglycoside may be desired and can be changed when culture and sensitivity results are available.

PREVENTION FOR TRAVELLERS

Pregnant patients travelling to high-risk typhoid areas should maintain strict hygiene for food and water. Boiled or reliable safe bottled water for drinking needs reinforcement! Consumption of raw, uncooked and cooked but cold foods should be discouraged. Exceptions include fresh fruit peeled or washed and cut using safe water and cutlery, fresh vegetables stir fried or scalded, and fresh meat and eggs cooked and served well done and hot. Freshly baked bread, chapatis and pastry without fillings should be safe. Unpasteurized milk and milk products are suspect for several pathogens – *Listeria*, *Brucella*, bovine tuberculosis and *Salmonella*.

Two effective vaccines for typhoid fever are available.² The oral live attenuated bacterial vaccine (Ty21a) requires four doses, 48 hours apart, without simultaneous consumption of antibiotic or antimicrobial medication. Because of the diminution of gastrointestinal motility that occurs early in gestation

Table 1 Risk factors for typhoid fever during pregnancy

I. Decreased gastrointestinal motility
A. Delayed gastric emptying
B. Oesophageal reflux resulting in the use of acid-reducing or neutralizing medication
C. Dilation of gallbladder
1. Increase in biliary sludge
D. Constipation
II. Increased production of red blood cell mass
A. Increased bone marrow activity and blood supply
III. Modulation of cell-mediated immunity
IV. Alterations in olfactory and gustatory sense
A. Changes in appetite and food selection: pica
B. Nausea and vomiting of pregnancy

and the frequent nausea and vomiting with symptomatic gastro-esophageal reflux requiring acid reduction therapy, we do not recommend the oral Ty21a vaccine for pregnant patients. Some patients with reduced gastrointestinal motility or immunodeficiency may develop a diarrhoeal syndrome with the live bacteria vaccine. The Vi capsular polysaccharide vaccine provides effective immunity for two years with a single dose. It is safe to use during pregnancy since it is a bacterial component and not a live vaccine. However, the duration of protection is relatively short; hence frequent travellers or long-term residents in high-risk areas need boosters every third year.

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