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# Culture-confirmed typhoid fever and pregnancy

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## KEYWORDS

Typhoid fever;  
Enteric fever;  
Women;  
Pregnancy;  
Complications

## Summary

**Background:** The relationship between pregnancy and typhoid fever is not well defined. The objective of this study was twofold: to assess the effect of the pregnant and postpartum host on typhoid disease expression, and to explore the relationship between typhoid fever and pregnancy outcome.

**Methods:** Over an 11-year period, all 181 adult women with blood culture-confirmed typhoid fever admitted to a university hospital in Karachi, Pakistan were studied; those with pregnancy-related disease were compared to the non-pregnant women. The relationship between typhoid fever and pregnancy outcome was evaluated by comparing 80 pregnant women with typhoid, with 194 randomly selected pregnant women without typhoid who were matched for age and study year.

**Results:** In adult females with bacteremic typhoid disease, a significant proportion was pregnancy-related (47%). These women were less likely to have other co-morbid illnesses (2% vs. 27%,  $p < 0.001$ ) and were almost exclusively treated with ampicillin/amoxicillin or third-generation cephalosporins, while the non-pregnant women with typhoid fever preferentially received quinolones. The mean duration of antimicrobial therapy was similar in both groups (14 days) but the non-pregnant group defervesced earlier (4.2 days vs. 5.6 days,  $p = 0.011$ ). Complications of typhoid fever were significantly more likely in the non-pregnant group (23% vs. 8%,  $p = 0.005$ ) and primarily involved lower gastrointestinal bleeding. On comparing the pregnant women with typhoid with randomly selected age-matched pregnant women without typhoid, there were no apparent effects of typhoid fever on pregnancy outcome as measured by gestational age at delivery, pregnancy complications, modes of delivery, neonate gender, birth weight, or birth Apgar scores.

**Conclusions:** While pregnancy is a risk factor for and effects typhoid disease expression, typhoid fever does not appear to affect pregnancy outcome.

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## Introduction

Typhoid, or enteric fever, is a distinctive acute systemic febrile infection caused by several serotypes of the Gram-negative bacillus *Salmonella* (primarily *Salmonella choleraesuis* serotypes typhi and paratyphi). Human carriers are the only known reservoir of the disease that is spread through contaminated food and water. Known global hotspots for typhoid fever include Mexico, Peru, Egypt, Indonesia, India, Pakistan and Nepal.

The hallmark of typhoid fever is a bacteremic illness associated with prolonged, persistent fever lasting 4–8 weeks in untreated patients. Complications include intestinal hemorrhage or perforation, pneumonia, myocarditis, hepatitis, acute cholecystitis and meningitis. Following an initial recovery, relapses occur in about 10–20% of untreated patients. The diagnosis is confirmed by isolation of the bacteria from a blood, urine, stool or bone marrow culture. Supportive laboratory findings include anemia, normal or decreased white blood cell count, diminished platelets, elevated aminotransferases (two or three times normal levels), and fecal leukocytes in patients with diarrhea. A two-week antibiotic course with chloramphenicol, ampicillin or trimethoprim–sulfamethoxazole was the mainstay of therapy until the emergence of multidrug-resistant strains in Asia where quinolones and third-generation cephalosporins are now gaining popularity.

Although the course and treatment of typhoid fever has been widely researched, the relationship of the disease with pregnancy is largely unknown. The aim of this study was twofold: (1) to assess the effect of the pregnant and postpartum host on typhoid disease expression, and (2) to explore the relationship between typhoid fever and pregnancy outcome.

## Patients and methods

The study was conducted at a 450-bed tertiary care university hospital located in the megacity of Karachi, Pakistan. Over an 11-year period (1989–1999) all adult female patients (age >14 years) with a clinical discharge diagnosis of typhoid fever were identified using the ICD-9-CM codes. Records of 307 patients were retrieved, of whom 133 (43%) were pregnant or postpartum (within 6 weeks of delivery). Of the 174 non-pregnant women with presumed typhoid, 96 (55%) had positive blood cultures, while 85 (64%) of the 133 pregnant or postpartum patients had culture-confirmed typhoid fever. To assess the effect of the pregnant and postpartum host on typhoid disease expression, the two groups with culture-confirmed typhoid fever were compared. The effects of typhoid fever on pregnancy outcome were explored by comparing 80 of the pregnant women with culture-confirmed typhoid, with 194 age-matched randomly selected pregnant women without typhoid taken from the over 40 000 patients admitted to obstetrics services. All the patients in the study were followed at the same institution during the entire duration of pregnancy and received the same standard of care throughout their pregnancy.

## Statistical analysis

Data were abstracted using a questionnaire containing information on the state of pregnancy, disease signs and

symptoms, relevant laboratory investigations, course of the illness, and response to treatment. In addition, various details of the pregnancy such as parity, outcome, complications, and details of delivery were also documented. Data were entered and analyzed using SPSS. Categorical data were compared using Chi-square tests while the independent sample *t*-test was used to compare means. Results of two-sided  $p < 0.05$  were considered significant.

## Results

### Effect of the pregnant and postpartum host on typhoid disease expression (Table 1)

Cases of typhoid fever were seen throughout the year with no seasonal pattern in either group of women with culture-confirmed disease. The average age in both groups was approximately 25 years. Overall, 71% of the 181 women with typhoid fever were infected with *S. typhi*. However, the proportion of pregnant or postpartum women with *S. typhi* (79%) was significantly higher than non-pregnant women (64%). While most cases of typhoid fever in pregnancy occurred in the second and third trimesters (75%), only two cases occurred in the postpartum host.

Only two pregnant women with typhoid fever had any comorbid illness, one had a history of malaria in the last three months while the other had had acute viral hepatitis in the preceding six months. By comparison, 26 (27%) of the non-pregnant women, a significantly higher number, presented with co-morbid illnesses. These included diabetes mellitus, hepatitis, asthma, pneumonia, malaria, thalassemia minor and tuberculosis. Prior use of antibiotics was observed in a total of 56% of all women with typhoid fever, and did not differ significantly between the pregnant and non-pregnant groups. The duration of fever prior to presentation was also similar in both groups. The symptoms of typhoid disease were assessed as upper gastrointestinal (nausea/vomiting), lower gastrointestinal (diarrhea/constipation), and cough. Pregnant women were significantly more likely to present with cough (36%), than non-pregnant women (21%), but were less likely to report upper gastrointestinal symptoms.

Of the investigations done, no significant differences were seen in the white blood cell or platelet counts. The mean hemoglobin level in the pregnant patients was 10.8 g/dl, significantly lower than the mean of 11.4 g/dl in the non-pregnant group. Serum transaminase levels were also more likely to be raised in the group with pregnancy-associated typhoid fever.

The most popular choice of antimicrobial therapy in the patients with pregnancy-associated typhoid was the third-generation cephalosporins (56%), while non-pregnant females with typhoid were predominantly treated with quinolones (58%). Only five pregnancy-related typhoid patients were given quinolones, three of whom were in their first trimester and had aborted (prior to antibiotic administration), and the remaining two were postpartum patients. Another popular choice for the women who were pregnant was ampicillin/amoxicillin, administered to 31% of them while only 9% in the non-pregnant group received this class of antibiotics. Antibiotic therapy was prescribed for two weeks in both groups. Fever after admission to hospital lasted

**Table 1** Culture-proven typhoid fever in a cohort of 181 adult women admitted to a tertiary care hospital (1988–1999)

Variable	Study groups		<i>p</i> Value ( $\chi^2$ or <i>t</i> -test)
	Pregnancy-related typhoid fever ( <i>N</i> = 85)	Non-pregnant with typhoid fever ( <i>N</i> = 96)	
Age in years (mean $\pm$ SD)	25.8 $\pm$ 4.9	24.3 $\pm$ 6.4	0.077
Typhoid serotype			
<i>S. typhi</i>	67 (79%)	61 (64%)	0.032
<i>S. paratyphi</i>	18 (21%)	35 (36%)	
Fever duration prior to admission (mean $\pm$ SD)	12.4 $\pm$ 12.5	14.2 $\pm$ 16.8	0.419
History of prior antibiotic use	42 (49%)	59 (61%)	0.122
History of co-morbid illness	2 (2%)	26 (27%)	<0.001
Symptoms			
Nausea/vomiting	44 (52%)	69 (72%)	0.017
Diarrhea/constipation	32 (38%)	38 (40%)	0.833
Cough	31 (36%)	20 (21%)	0.020
Investigations			
Hemoglobin mg/dl (mean $\pm$ SD)	10.8 $\pm$ 1.4	11.4 $\pm$ 1.6	0.018
White cell count $\times 10^3$ /ml (mean $\pm$ SD)	7.3 $\pm$ 2.1	7.6 $\pm$ 4.0	0.494
Platelets $\times 10^3$ /ml (mean $\pm$ SD)	207 $\pm$ 75	223 $\pm$ 96	0.285
Raised transaminases	22/32 (69%)	26/61 (43%)	0.017
Antibiotics used			
Ampicillin/amoxicillin	26 (31%)	9 (9%)	<0.001
Third-generation cephalosporin	48 (56%)	17 (18%)	
Quinolone	5 (6%)	56 (58%)	
Other	2 (2%)	14 (15%)	
Mean duration of antibiotics (mean $\pm$ SD)	14.1 $\pm$ 3.5	13.1 $\pm$ 5.6	0.186
Duration of fever after admission	5.6 $\pm$ 3.9	4.2 $\pm$ 2.7	0.011
Relapse of typhoid	2/80 (3%)	1/95 (1%)	0.460
Complications of typhoid	6/80 (8%)	22 (23%)	0.005

an average of 5.6 days in women with pregnancy-related typhoid, significantly longer than the 4.2 days in those who were not pregnant. While relapse rates were similar in both groups, complications of typhoid fever were significantly higher in non-pregnant women (23% versus 8%,  $p = 0.005$ ). Complications in the pregnancy-related group included three cases of lower gastrointestinal bleeding and single cases of sepsis, sepsis with disseminated intravascular coagulation, and cholecystitis. Lower gastrointestinal bleeding was also the most common complication in the non-pregnant group, observed in 13 women. Other complications included sepsis, liver abscess, psychosis, myocarditis and pancreatitis. There were no fatalities in either group.

### Effect of typhoid disease on pregnancy outcome (Table 2)

Of the 85 pregnancy-associated typhoid fever cases, the five that had had first trimester abortions (3) or were postpartum (2) were excluded from the comparison with the age-matched randomly selected group of 194 pregnant women without typhoid fever. Both groups were similar in their gravid status. No significant differences were seen between the two groups in complications of pregnancy, modes of delivery, and details of the live born. There were more

females born to the pregnant women with typhoid but this difference was not statistically significant.

### Discussion

Given that 47% (85/181) of all adult women with culture-confirmed typhoid fever admitted to the hospital in the 11-year study period were pregnant or postpartum, pregnancy seems to exert some effect on the presentation and course of typhoid fever.

This raises the issue that amongst women with typhoid, pregnancy status should be assessed prior to embarking on antimicrobial therapy that may include quinolones. Olu-buyide too, in a review of postmortem typhoid cases recognized pregnancy as a distinct risk group for typhoid in adult patients.<sup>1</sup>

Interestingly, pregnant women were more likely to be infected with *S. typhi* than *S. paratyphi*, raising the issue of increased virulence of *S. typhi* compared to *S. paratyphi* in this susceptible population. In a sample of 114 adults (with twice as many males as females) with culture-confirmed typhoid fever, admitted to the same study hospital between 1993 and 1997, 64% was due to *S. typhi* and 34% was due to *S. paratyphi*; this is similar to the distribution in the non-pregnant women with typhoid (unpublished data, personal

**Table 2** Effect of typhoid fever on pregnancy

Variable	Study group		p Value ( $\chi^2$ or <i>t</i> -test)
	Pregnant with typhoid fever (N = 80)	Pregnant without typhoid fever (N = 194)	
Age in years (mean $\pm$ SD)	25.8 $\pm$ 4.9	26.2 $\pm$ 4.9	0.595
Gravid	2.4 $\pm$ 1.4	2.2 $\pm$ 1.8	0.478
Gestational age at delivery in weeks (mean $\pm$ SD)	38.1 $\pm$ 2.7	38.1 $\pm$ 3.4	0.942
Pregnancy complications			
None	69 (86%)	159 (82%)	0.319
Spotting	3 (4%)	11 (6%)	
Miscarriage	5 (6%)	19 (10%)	
Premature delivery	5 (6%)	5 (3%)	
Pregnancy outcome			
Abortion/still birth	4/60 (7%)	28/192 (15%)	0.108
Live birth	56/60 (93%)	164/192 (85%)	
Mode of delivery			
Spontaneous vaginal	46/54 (85%)	124/165 (75%)	0.125
Cesarean section	8/54 (15%)	41/165 (25%)	
Gender of infant			
Male	18/50 (36%)	80/165 (48%)	0.120
Female	32/50 (64%)	85/165 (52%)	
Birth weight in kg (mean $\pm$ SD)	2.9 $\pm$ 0.6	3.0 $\pm$ 0.5	0.125
Birth Apgar scores			
1 minute	7.8 $\pm$ 1.1	5.6 $\pm$ 1.5	0.122
5 minutes	8.9 $\pm$ 1.3	8.7 $\pm$ 1.6	0.467

communication with Dr Rumina Hassan, Department of Microbiology, Aga Khan University Hospital, Karachi, Pakistan).

Presenting symptoms among patients with typhoid differed between the groups. While pregnant women with typhoid were more likely to present with cough, non-pregnant patients reported nausea/vomiting more often than their pregnant counterparts did. Although nausea and vomiting are often associated with the first trimester of pregnancy, the majority of the pregnant patients (75%) presented in their second and third trimesters.

The antibiotics used to treat typhoid fever were markedly different in women who were pregnant compared to those who were not. The most popular choices of antibiotics for the pregnant patients were third-generation cephalosporins and ampicillin/amoxicillin, while quinolones, widely believed to be the drugs of choice for typhoid fever, were preferentially used in the non-pregnant group. The latter are often avoided in pregnancy due to the potential risk of toxicity to fetal skeletal structures. However, ciprofloxacin has recently been advocated as a safe drug to use in pregnancy by Koul et al., who based this recommendation on a case series of seven pregnant patients treated with the drug, all of whom safely delivered healthy babies.<sup>2</sup> Oral ciprofloxacin produces more rapid and reliable resolution of fever than does parenteral ceftriaxone,<sup>3</sup> and this fact, coupled with reports of increased multidrug resistance in typhoid fever, as high as 100% in Rawalpindi, Pakistan,<sup>4</sup> and 96% in Bangalore, India,<sup>5</sup> has led to an increased use of fluoroquinolones. However, in the present study only five patients in the pregnant category

received fluoroquinolones, of whom two were postpartum and three presented after spontaneous abortions in the first trimester. The shorter time to defervescence in the non-pregnant typhoid patient may, in part, be due to the preferential use of quinolones in this group.

The fact that non-pregnant women with typhoid were more likely to develop complications invokes the hypothesis that disease complications are related to host immunity and less likely to occur with the immunological changes associated with pregnancy. Pregnancy is associated with a strong skewing towards T-helper 2 cytokine pattern, which enables the survival of the fetus<sup>6</sup> and this may give protection against typhoid-related intestinal hemorrhage and perforation. To the best of our knowledge, the specific risk factors that predispose to complications of typhoid disease in adults have not been clearly elucidated and this is an area that needs more work.

It has previously been suggested that typhoid fever may have an adverse effect on the outcome of pregnancy. A case series of five pregnancies complicated by typhoid fever conducted in Mexico in 1994 did document one abortion and one preterm delivery resulting in neonatal death.<sup>7</sup> The authors suggested proper diagnosis and early treatment as the cornerstones of preventing such outcomes. The data presented here, however, show no significant differences in complications of pregnancy, outcomes, and markers of neonatal well being between pregnant women who developed typhoid fever and randomly selected pregnant women who did not have the disease.

## Conclusion

This study suggests that while pregnancy is an important risk factor for acquiring typhoid in adults and appears to modify disease expression, the disease itself may not affect pregnancy or its outcome in any significant way. However, these findings should be verified prospectively given the inherent biases associated with our retrospective study at a tertiary care institution where only the sicker pregnant women would be expected to seek care.

*Conflict of interest:* No conflict of interest to declare.

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