



# Fever During Pregnancy: Etiology and Fetomaternal Outcomes

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## Abstract

**Purpose** Etiological spectrum of fever in pregnant women and its impact on fetomaternal outcomes were studied.

**Methods** This was a hospital-based prospective study, conducted over 12 months. All pregnant women with fever were screened and detailed etiological evaluation carried out. Maternal and foetal outcomes were noted.

**Results** One hundred and eighty-one pregnant women with fever were included. Common causes were dengue 44 (24.3%), hepatitis E 26 (14.4%) and urinary tract infection (UTI) 22 (12.2%). Mosquito-borne diseases accounted for the highest burden 61 (33.7%). Second most common were diseases transmitted by feco-oral route 46 (25.4%). Maternal deaths occurred in 29 (16%) patients. Common causes of death were hepatitis E infection in 9 of 26 (34.6%) cases, dengue in 7 of 44 (15.9%) and tuberculosis in 5 of 11 (45.5%) cases.

**Conclusion** Dengue, hepatitis E and UTI were the most common causes of fever during pregnancy. Most cases were caused by vector- and water-borne diseases and thus potentially preventable. Overall maternal mortality was 16%.

**Keywords** Maternal fever · Dengue · Hepatitis E · Urinary tract infection

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## Introduction

Most of the efforts to reduce maternal mortality in India have focussed on haemorrhage, hypertension and sepsis. There is little focus on the impact of infectious diseases on maternal, foetal and neonatal outcomes, which is demonstrated by the lack of well-conducted prospective studies in the literature.

Owing to the anatomical and physiological changes, certain infections such as urinary tract infections (UTI) are more common during pregnancy [1]. Infections like *Plasmodium falciparum* malaria, hepatitis E and H1N1 influenza are more severe in pregnancy due to changes in the immune system [2]. However, the contribution of these infections towards maternal mortality and near-miss morbidity is not clear. Therefore, they should be incorporated in the national maternal mortality data in greater detail. Only few studies have been conducted on the impact of fever on fetomaternal outcomes [3]. It is postulated that with the development of maternal death surveillance and response (MDSR) guidelines established by Government of India in 2017, more information will be available on the morbidity and mortality burden of these diseases [4].

Causes of fever during pregnancy and its course and outcomes should be studied in detail. This knowledge will

improve maternal and foetal management and pregnancy outcomes. This is particularly important in the countries like India which have an immense burden of infectious diseases. Hence, this study was designed to fill the gaps in knowledge on the etiological spectrum of fever in the antenatal period in Northern India and its impact on maternal and fetoneonatal outcomes.

## Methods

This was a hospital-based prospective study, conducted over a period of 12 months from 1 July 2016 to 30 June 2017. The study was conducted in Post Graduate Institute of Medical Education and Research, Chandigarh, a tertiary care centre in Northern India. The institute caters to the regions of Chandigarh, Punjab, Haryana, Himachal Pradesh and Jammu & Kashmir and is a major referral centre for high-risk pregnancies. The study was approved by institutional ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all subjects.

All pregnant women presenting with fever over the course of study period were screened. 216 women presented with fever, of whom, non-consenting women, women with history of pelvic instrumentation and women with history of ruptured membranes were excluded, and 181 patients were recruited in the study. Fever was defined as *a.m.* temperature of  $> 37.2^{\circ}\text{C}$  ( $98.9^{\circ}\text{F}$ ) or *p.m.* temperature of  $> 37.7^{\circ}\text{C}$  ( $99.9^{\circ}\text{F}$ ) [5, 6].

Detailed medical history, examination and investigations were performed, and all the data were recorded on case record sheets.

## Laboratory Investigations

All cases underwent investigations as per the standard protocol followed in obstetric emergency including haemoglobin, complete and differential blood counts, serum electrolytes, urea and creatinine, liver function tests. Samples for blood cultures were obtained and tested using automated blood culture systems (BD BACTEC™). A 10 ml of mid-stream urinary sample was obtained, and urine microscopic examination as well as culture by inoculation onto CLED medium was carried out. Additionally, investigations to elucidate the etiology of fever that were carried out in all patients as per Table 1.

Further testing was done depending on the clinical profile. Ziehl–Neelsen staining from early morning sputum smears or body fluid smears for acid fast bacillus testing was performed to diagnose tuberculosis. This was supported with Mycobacteria Growth Indicator Tube (MGIT) or polymerase chain reaction where clinical suspicion was high. Sputum culture was performed whenever lower respiratory tract infections were suspected. Chest X-ray using abdominal lead shield protection was added as an adjunct, wherever indicated. Nasopharyngeal swabs were tested with real-time polymerase chain reaction (RT-PCR) for pandemic H1N1 influenza testing as per CDC protocol, wherever indicated. Patients with suspected viral hepatitis were tested as per Table 2.

Tzanck smear was performed from vesicles wherever patients presented with fever and vesicular rash. RT-PCR for chikungunya was performed wherever indicated, RT-PCR and IgM antibodies if presentation was within 1 week of onset of symptoms, and IgM antibodies (SD Bioline, Korea) if presentation was more than 1 week after symptom onset.

Neuro-imaging, cardio-imaging and abdominal imaging were performed wherever required based on the clinical

**Table 1** Investigations to elucidate the specific etiology of fever carried out in all women

Etiology	Investigation
Malaria	Peripheral blood thin smears examined for malarial parasites on 3 successive days and rapid immune-chromatographic tests for malarial antigen (based on the detection of histidine-rich protein 2 from <i>Plasmodium falciparum</i> and parasite-specific lactate dehydrogenase (pLDH) (Nicholas Piramal, India, and SD Bioline, Korea) performed to diagnose malaria infection and causative species of <i>Plasmodium</i>
Dengue	Dengue IgM antibodies were detected using ELISA (NIV, Pune) if presentation was more than 3–5 days after the onset of clinical symptoms and/or NS1 antigen assay (Pan Bio, Queensland, Australia) if the presentation was within 3–5 days within onset of clinical symptoms
Enteric fever	Blood was cultured to detect <i>Salmonella typhi</i> as well as paratyphi A and Widal tube agglutination test performed for serological diagnosis of enteric fever
Leptospira	IgM ELISA (SD Bioline, Korea) or microscopic agglutination test (MAT)
Scrub typhus	PCR for scrub typhus (if presentation was within 10 to 15 days of onset of symptoms) and IgM ELISA (InBios, Fullers laboratories, USA) if fever was more than 7 days

**Table 2** Evaluation of patients with suspected viral hepatitis

Hepatitis A infection	IgM anti-HAV enhanced chemiluminescence method using Vitros EciQ (Ortho-clinical diagnostics VITROSTM, Johnson and Johnson, USA). Hepatitis C was diagnosed by anti-HCV testing by enhanced chemiluminescence method using VitrosEciQ (Ortho Clinical Diagnostics, Johnson & Johnson, USA); anti-HEV IgM testing using ELISA (DSI, Italy) was used to diagnose acute hepatitis E infection
Hepatitis B infection	HBsAg detection was done by enhanced chemiluminescence method using Vitros EciQ (Ortho-clinical diagnostics VITROSTM, Johnson and Johnson, USA) to diagnose hepatitis B infection and further testing by RT-PCR assay (Roche Molecular Systems, Branchburg, NJ, USA) for viral load assessment in positive cases, and specimens were tested for anti-HBc total, anti-HBc IgM and hepatitis B e antigen (HBeAg) and anti-HBe antibody to assess the stage of infection
Hepatitis C infection	anti-HCV testing by enhanced chemiluminescence method using VitrosEciQ (Ortho Clinical Diagnostics, Johnson & Johnson, USA)
Hepatitis E infection	Anti-HEV IgM testing using ELISA (DSI, Italy)

assessment of each patient. Ultrasound for foetal assessment was performed by obstetric consultants in the department of obstetrics and gynaecology of the Institute. Dating, foetal weight, malformations, liquor and bio-physical profile were assessed.

All women were managed according to the institute protocol. Supportive management, anti-pyretics and specific anti-microbial therapy according to laboratory investigations were prescribed. Women were reviewed again after discharge from hospital. Further, all women were followed up till delivery and maternal and fetoneonatal outcomes were noted.

## Results

The study included 181 pregnant women with fever. Etiology of fever and maternal outcomes were assessed for all 181 patients. Out of total 181, 175 (96.7%) patients were given a specific diagnosis, of whom 156 patients had laboratory evidence of disease and 19 were clinically diagnosed (upper respiratory tract infection (URTI) = 11, gastroenteritis = 8). A specific diagnosis could not be reached in 6 (3.3%) patients (Table 3). Details of the 11 (6.1%) patients with recurrent episodes of fever are listed in Table 4.

The average age of patients was  $28.6 \pm 2.88$  (range: 18–37) years with 147 (81.3%) cases presenting in the 3rd trimester of pregnancy (Table 4). Most (80 (44.2%)) women had residence in Chandigarh tricity area, 32 (17.7%) were from Punjab and 26 (14.4%) from Haryana. Twenty-five (13.8%) women were unbooked.

Seventeen (9.4%) patients had received antibiotics before presentation, and all were empirical in nature. All antibiotics were penicillins (co-amoxycylav, cephalosporins, piperacillin–tazobactam) except 1 patient who had been started on chloroquine empirically.

As a group, mosquito-borne diseases were responsible for the highest burden accounting for 61 (33.7%) cases. This included dengue in 44 (24.3%), malaria in 11 (6.1%) and chikungunya fever in 6 (3.3%). The second most common group

were diseases transmitted by feco-oral route accounting for 46 (25.4%) cases. This included hepatitis E in 26 (14.4%), gastroenteritis in 8 (4.3%), hepatitis A in 6 (3.3%), typhoid in 5 (2.7%) and liver abscess in 1 (0.6%) patient.

Dengue was the most common cause of fever followed by hepatitis E and UTI (Table 5). Of 44 patients with dengue, 27 (61%) demonstrated positivity for NS1 antigen and out of these, 24 (89%) presented within 5 days of symptom onset. Seventeen (39%) patients had IgM positivity at admission. Twenty-two (50%) patients had dengue with warning signs (WHO definition), while 14 (31.8%) patients had severe dengue (WHO definition) at admission; of these, 7 patients died and 7 were classified as maternal near-miss cases (WHO MNM criteria). There were 2 miscarriages, 4 still births, 15 pre-term births, 13 low birth weight babies and 2 neonatal deaths.

Twenty-two patients had UTI of whom 12 (46%) had pyelonephritis. Twelve patients had urine culture positivity for *Escherichia coli*, 6 for *Klebsiella spp*, 1 for *Pseudomonas aeruginosa* and 1 for *Proteus mirabilis*. Both urine and blood cultures were positive in 2 patients (1 = *Escherichia coli*, 1 = *Klebsiella spp*). All patients were treated with appropriate antibiotics based on culture and sensitivity reports and safety of antibiotic use in pregnancy. Most commonly used antibiotics were nitrofurantoin, ceftriaxone and piperacillin–tazobactam. Four patients required drainage of pyonephrosis/perinephric collections. Five women developed oligohydramnios, 9 had pre-term births, 9 low birth weight babies and 1 still birth.

Thirty-six (19.9%) patients had febrile jaundice, of whom 26 (14.4%) had hepatitis E, 6 (3.3%) had hepatitis A, 2 (1.2%) had malaria, 1 (0.6%) had cholangitis and 1 (0.6%) had liver abscess. A high rate of poor pregnancy outcomes was noted in women with hepatitis E infection evidenced by 9 (34.6%) maternal deaths, 8 (30%) still births, 10 (38%) pre-term births, 13 (50%) low birth weight babies and 1 miscarriage.

Overall, 29 (16%) patients died. Of the 152 (84%) women were discharged alive, 33 (18.2%) were near miss. Common causes of death were hepatitis E infection in

**Table 3** Etiology of fever among pregnant women

Cause	n = 181 (%)	Positive laboratory results/clinical diagnosis
<i>Viral diseases</i>		
Dengue	44 (24.3)	27 (61%) were NS1 antigen positive, 17 (39%) = IgM antibody positive
Hepatitis E	26 (14.4)	26 (100%) were anti-HEV IgM antibody ELISA positive
Hepatitis A	6 (3.3)	6 (100%) were anti-HAV IgM antibody ELISA positive
Chikungunya	6 (3.3)	6 (100%) were IgM antibodies positive on immunochromatography
Chicken pox	5 (2.7)	5 (100%) had vesicular rash Tzanck smear depicted acanthocytes and syncytial giant cells; clinical judgement
H1N1 influenza	3 (1.7)	3 (100%) RT-PCR positive from nasopharyngeal swabs
Acute Hepatitis B infection	1 (0.6)	Clinical diagnosis; deranged liver function tests; high titre positivity to anti-HBc; and negativity to HBeAg and hepatitis A, C and E markers
<i>Bacterial diseases</i>		
UTI	22 (12.1)	22 (100%) had urine culture positive ( <i>Escherichia coli</i> , <i>Klebsiella spp</i> , <i>Proteus mirabilis</i> and <i>Pseudomonas aeruginosa</i> ); 2 had blood culture positivity ( <i>Escherichia coli</i> )
Tuberculosis	11 (6.1)	7 patients had pulmonary tuberculosis diagnosed by sputum ZN staining ± sputum for MGIT ± chest X-ray findings; 1 patient had spinal tuberculosis diagnosed clinically adjuncted by MRI findings; 1 patient had miliary tuberculosis with sputum AFB positive; and 2 patients had tubercular meningitis with suggestive neuro-imaging and CSF positive for AFB ± MGIT
Scrub typhus	6 (3.3)	PCR positivity in 3 (50%) patients, IgM positivity in 5 (83.3%) patients
Typhoid	5 (2.7)	5 (100%) = <i>Salmonella typhi</i> septicaemia demonstrated on blood culture
Leptospirosis	1 (0.6)	Positive IgM ELISA
<i>Others</i>		
Malaria	11 (6.1)	9 (82%) had <i>Plasmodium vivax</i> on peripheral blood smear/RDT, 1 (9%) had <i>Plasmodium falciparum</i> positive blood smear/RDT, and 1 (9%) had co-infection with both <i>Plasmodium vivax</i> and <i>falciparum</i>
URTI	11 (6.1)	11 (100%) based on clinical diagnosis with positive history and examination; no evidence of lower respiratory tract infection and no evidence of bacterial septicaemia; and H1N1 not tested as CDC criteria not met for testing
Gastroenteritis	8 (4.3)	8 (100%) based on clinical diagnosis with positive history; stool routine examination normal, stool and blood cultures negative
Pneumonia	6 (3.3)	6 (100%) based on chest X-ray findings, positive sputum culture; 4 (67%), <i>Klebsiella spp</i> , 2 (33%), <i>streptococcus pneumoniae</i> ; and 2 (33%), blood culture positive
Parotitis	1 (0.6)	Diagnosed based on clinical and ultrasonography findings
Cholecystitis-cholangitis	1 (0.6)	Described in Table 2
Liver abscess	1 (0.6)	Radiological diagnosis in patient with febrile jaundice; required pig tail drainage of empyema
Unclear diagnosis	6 (3.3)	

AFB acid fast bacillus, CDC centre for disease control, CSF cerebrospinal fluid, MGIT mycobacteria growth indicator tube, RDT rapid diagnostic tests, URTI upper respiratory tract infection, UTI urinary tract infection

**Table 4** Causes of recurrent fever among pregnant women

Etiology	n = 11	Details
Unevaluated	4	History suggestive of URTI
Recurrent UTI	2	Both the previous episodes had urine culture positivity for <i>Escherichia coli</i> . Ultrasonography revealed small lower calyceal calculi
Tuberculosis	4	1 = spinal tuberculosis, 1 = lymph node tuberculosis, 2 = pulmonary tuberculosis; all 4 patients were on anti-tubercular therapy (continuation phase regimen) at the present febrile episode
Recurrent cholecystitis-cholangitis	1	The diagnosis was confirmed on magnetic resonance cholangio-pancreaticography (MRCP) and required ERCP (Endoscopic retrograde cholangio-pancreaticography) and stenting to decompress the bile duct; the present febrile episode had the same etiology with blockage of the previous stent and required PTBD

PTBD percutaneous trans-hepatic biliary drainage, URTI upper respiratory tract infection, UTI urinary tract infection

**Table 5** Demographic features, clinical profile and maternal outcomes of pregnant women with fever by three most common aetiologies

	Total ( <i>n</i> = 181) <i>n</i> (%)	Dengue ( <i>n</i> = 44) <i>n</i> (%)	Hepatitis <i>E</i> ( <i>n</i> = 26) <i>n</i> (%)	UTI ( <i>n</i> = 22) <i>n</i> (%)
Primigravida #	80 (44.2)	17 (38.6)	11 (42.3)	13 (59)
Gestational age (weeks)*	30 (6–40)	31 (10–40)	31 (12–39)	29 (6–39)
Duration of fever (days)*	6 (2–60)	4 (2–10)	7 (3–14)	6 (2–30)
Temperature at admission (°F)*	101.4 (99–104)	100.6 (99–102)	100.3 (99–104)	100.8 (99.6–103)
Haemoglobin (g/dL)**	10 (5–16)	11 (7.3–14.2)	11 (7.6–13.6)	10.3 (6.8–13.3)
Total leucocyte count (per $\mu$ L)**	11,900 (2400–41,300)	8350 (3200–24,000)	14,650 (3200–34,400)	18,900 (4400–29,200)
Platelet count (lacs/ $\mu$ L)**	1.7 (0.1–8.3)	0.97 (0.05–3.8)	1.85 (0.49–3.2)	2.1 (0.6–8.3)
Creatinine (mg/dL)**	0.6 (0.2–28)	0.6 (0.2–28)	0.7 (0.4–20)	0.65 (0.3–6.8)
AST (IU/L)**	79 (15–10,547)	78 (26–10,547)	537 (51–7775)	48 (15–224)
ALT (IU/L)**	54 (5–5083)	54 (15–3521)	568 (100–5083)	48 (5–278)
PTI (%)**	100 (10–100)	100 (33–100)	65 (19–86)	100 (56–100)
ARDS #	28 (15.5)	8 (18.2)	2 (7.6)	0
AKI #	41 (22.6)	8 (18.2)	6 (23.1)	5 (22.8)
ALF #	40 (22.1)	4 (9.1)	21 (80.7)	1 (4.5)
Encephalopathy#	34 (18.8)	5 (11.4)	8 (30.7)	0
WHO maternal near miss #	33 (18.2)	7 (16)	9 (34.6)	4 (18.2)
Duration of hospital stay (days)*	7 (1–52)	9 (1–52)	7 (1–12)	8 (1–27)
Maternal death#	29 (16)	7 (16)	6 (23.1)	0

AKI Acute kidney injury, ALF acute liver failure, ALT alanine transaminase, ARDS acute respiratory distress syndrome, AST aspartate transaminase, PTI prothrombin index, LSCS lower segment caesarean section, UTI urinary tract infection

#Percentage; denominator = *n* (Dengue = 44, Hepatitis *E* = 26, UTI = 22)

\*Average (minimum value–maximum value)

\*\*Median (minimum value–maximum value)

9 of 26 (34.6%) cases, dengue in 7 of 44 (15.9%) cases and tuberculosis in 5 of 11 (45.5%) cases. Other causes of death were gastroenteritis, H1N1 infection and pneumonia in 2 patients each and hepatitis A and scrub typhus in 1 patient each. Pregnancy and fetoneonatal outcomes were assessed for 167 cases. Of the remaining 14 patients, 3 were lost to follow-up, 4 did not go into labour till the end of study period and 7 maternal deaths were recorded with undelivered foetus (Table 6). Maternal complications and predictors of maternal mortality are listed in Tables 7 and 8, respectively.

## Discussion

This study spanned a full year and thus covered all seasons. Since many febrile illnesses are seasonal, coverage of a full year removes this bias and reflects the true incidence of various causes of fever in our population. Diseases with strong seasonal variations were the most common causes of fever in pregnant women. As a group, mosquito-borne diseases and those transmitted by the feco-oral route were the most common. Thus, most cases of fever in pregnancy are preventable. This suggests that strengthening of the public health

**Table 6** Pregnancy outcomes of women with fever

Outcomes	Frequency <i>n</i> (%)*
Miscarriage ( <i>n</i> = 167)	7 (4.1)
Pre-term births ( <i>n</i> = 167)	72 (43.1)
Oligohydramnios (on ultrasonography) ( <i>n</i> = 150, cases in late 2nd and 3rd trimester only, where ultrasonography was possible)	43 (28.7)
Still births ( <i>n</i> = 167)	20 (11.9)
Low birth weight babies ( <i>n</i> = 160, 167 minus 7 abortions excluded)	75 (46.9)
Requirement of Neonatal ICU (NICU) care ( <i>n</i> = 160, 167 minus 7 abortions excluded)	31 (22.1)
Neonatal death ( <i>n</i> = 160, 167 minus 7 abortions excluded)	9 (6.4)

\*overlapping incidences

**Table 7** Complications developing in the mother

Complication	Number	%	Common etiology	Significant association
Acute respiratory distress syndrome	28	15.5	Dengue (8 patients), pneumonia and tuberculosis (5 patients each)	83.3% of total pneumonia cases (5/6), 66.7% of total H1N1 cases (2/3)
Acute kidney injury	41	22.7	Dengue (8 patients), Hepatitis E (6 patients)	66.7% of total H1N1 cases (2/3)
Liver failure	40	22.1	Hepatitis E (21 patients)	80.8% of total hepatitis E cases (21/26), 66.7% of total hepatitis A cases (4/6), 66.7% of total H1N1 cases (2/3)
Encephalitis	34	18.8	Hepatitis E (8 patients)	50% of total hepatitis A cases (3/6), 30.8% of total hepatitis E cases (8/26)
Severe sepsis	75	41.4	Dengue (18 patients), hepatitis E (15 patients)	83.3% of total pneumonia cases (5/6), 54.5% of total tuberculosis cases (6/11), 66.7% of total H1N1 cases (2/3)

**Table 8** Predictors of maternal mortality

	<i>p</i> value
<i>Findings at admission</i>	
Duration of fever > 7 days	0.002
Dyspnoea	0.031
Seizures	0.000
Altered sensorium	0.000
Mean arterial pressure $\leq$ 65 mmHg	0.000
Respiratory rate > 24/min	0.000
O <sub>2</sub> saturation < 90%	0.000
Glasgow coma scale (GCS) < 15	0.000
<i>Laboratory investigations</i>	
Total leucocyte count < 4000/ $\mu$ L	0.048
Platelet count < 1lac/ $\mu$ L	0.020
Serum creatinine $\geq$ 1.5 mg/dL	0.018
AST > 3 times upper limit of normal	0.024
ALT > 3 times upper limit of normal	0.024
INR > 1.2	0.000
<i>Final diagnosis</i>	
H1N1 influenza	0.016
Tuberculosis	0.006

infrastructure can effectively reduce the incidence of fever and improve maternal and foetal outcomes. Use of mosquito nets and supply of potable water are likely to prevent febrile illness in a majority of cases. The overall maternal mortality was 16%. Our institute being a referral centre gets sicker patients which is likely the cause for a high maternal mortality.

Dengue was overall the most common cause of fever among pregnant women being responsible for almost a quarter of patients. Other common aetiologies were hepatitis E infection and UTI. Previous studies from tropics have found malaria to be the commonest cause of fever in pregnancy [7–9]. In our study, dengue was by far the commonest vector-borne disease with malaria forming only 6.1% cases. Dengue was associated with significant morbidity and mortality. 15.9% patients died, and another

15.9% were classified as maternal near-miss cases. This suggests that dengue is more severe in pregnant patients [10–12]. Potential referral of sicker patients to a tertiary care centre could confound the results. With an increasing annual incidence of dengue nation-wide, and observations of adverse maternal and foetal outcomes of pregnancy, seasonal preventive measures should be instituted and referral and management protocols standardized for optimal and timely management of pregnant women with dengue.

Hepatitis E was the second most frequent cause of fever during pregnancy, which is understandable as India is hyper-endemic to hepatitis E virus [13]. This is again a preventable condition. In our study, a high rate of maternal and foetal complications was recorded with a maternal mortality of 23.1%. Poor maternal–foetal outcomes with hepatitis E infection in pregnant women have been well reported with high case fatality rates, and foetal complications include still births, miscarriages and risks of vertical transmission [14, 15]. Hepatitis A and hepatitis B were less common and encountered in 3.3% and 0.6% patients, respectively. No patient with hepatitis C was seen.

UTI was found to be the third most frequent cause. There were no maternal deaths, but adverse foetal outcomes including pre-term births and low birth weight babies were seen. Adverse pregnancy outcomes in pregnant women with UTI have similarly been previously reported [16]. This suggests the need for promotion of screening urine cultures during pregnancy to detect asymptomatic bacteriuria and use of bacterial sensitivity guided antibiotic use in pregnant women with UTI.

Both pulmonary tuberculosis and extra-pulmonary tuberculosis were encountered, and all patients were treated with modified DOTS regimen anti-tubercular therapy. Studies have found that with early initiation of therapy, pregnancy does not adversely affect tuberculosis [17]. However, our patients commonly had adverse outcomes, likely because they were referred at a late stage. There is resurgence in the cases of scrub typhus in the country, and we encountered 6 patients with scrub typhus during pregnancy.

The strengths of our study include its large sample size and the thorough investigative process that was carried out with only 3 cases remained undiagnosed. Important limitations of this study include the hospital-based nature of this study, and hence, this study does not evaluate the profile of pregnant women with fever in the community. Also, ours is a regional referral and training centre; therefore, it is likely that a large number of complicated patients are referred to our institute and may not be representative of true complication rates in the community.

To conclude, dengue, hepatitis E and UTI were the most common causes of fever during pregnancy. Most cases were caused by vector- and water-borne diseases and are potentially preventable. The maternal mortality rate was high at 16%. Common causes of death were hepatitis E infection, dengue and tuberculosis.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** The study was approved by the Institutional Ethics Committee, PGIMER, Chandigarh Vide Numbers INT/IEC/2017/1116 dated 21.10. 2017. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed Consent** Written informed consent was obtained from all subjects.

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