Maternal & perinatal outcome of fever in pregnancy in the context of dengue - A retrospective observational study

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Background & objectives: Pregnant women with dengue infection may be at increased risk of adverse maternal-foetal outcomes. This study was conducted to assess the maternal and perinatal outcomes in women who presented with fever and diagnosed to have dengue infection during pregnancy.

Methods: A retrospective observational study was conducted on pregnant women admitted with fever, in a tertiary referral centre in South India, during January 2015 to December 2018. We compared outcomes of women diagnosed with dengue with that of women without dengue. The study outcomes included pre-term birth, stillbirth, low-birth weight (LBW), maternal mortality and thrombocytopenia.

Results: During the study period, there were six maternal deaths following complications from dengue infection. Higher rates of thrombocytopenia (24.7% *vs.* 14.6%, *P*=0.02) were noted among those with recent dengue infection. The risk of still birth was 2.67 [95% confidence interval (CI) 1.09, 6.57], LBW [risk ratio (RR) 1.13, 95% CI 0.87, 1.45] and pre-term birth (RR 1.33, 95% CI 0.89, 1.97) among the cases.

Interpretation & conclusions: Occurrence of adverse maternal and foetal outcomes was increased in pregnant women with fever diagnosed with dengue infection. Future studies are needed to formulate the optimum monitoring and treatment strategies in pregnant women, where dengue can have additive adverse effects to other obstetric complications.

Key words Dengue infection - maternal mortality - pregnancy – pre-term birth stillbirth – thrombocytopenia

Dengue, caused by a mosquito-borne arboviral infection, is endemic to many countries across the world and poses major public health threat to various states in India[1-3]. Under the National Vector Borne Disease Control Programme, case detection, management and vector control remain as important strategies for prevention and transmission of dengue virus[4]. Most people with dengue virus infection develop a febrile illness which is usually self-limited. Rarely, they may progress to severe illness with rapid onset of symptoms due to leaky capillaries associated with reduced platelet count, bleeding and hepatic dysfunction. Treatment is usually symptomatic based on clinical manifestation, including fluid replacement and blood component therapy[3,4].

Pregnant women in endemic areas are prone to dengue infection and in recent years, concerns have been expressed regarding maternal and foetal consequences[5-10]. The changes associated with dengue infection such as increase in pro-inflammatory cytokines, capillary leakage due to increased vascular permeability, bleeding tendency secondary to thrombocytopenia and hepatic dysfunction can result in increased incidence of adverse pregnancy outcomes[11-13]. Earlier studies reported an increase in pre-term delivery, stillbirths and low-birth weight (LBW) in pregnancies complicated with dengue infection, while recent investigations suggested no or little increased risk[12]. We aimed to study the maternal and perinatal outcomes in pregnant women who presented with fever and diagnosed to have dengue infection and compared them against women who did not have dengue during pregnancy.

Material & Methods

This was a retrospective observational study conducted at the women and children hospital attached with the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India. Women admitted with fever during pregnancy and undergoing test for dengue infection during January 2015 to December 2018, were identified from admission registers maintained at the antenatal and labour wards, and the dengue report registers at the Microbiology department. The diagnosis of dengue was made using the clinical symptoms with confirmatory laboratory testing [either NS1 antigen or immunoglobulin M (IgM) antibody] as per the national guidelines laid down by the National Vector Diseases Control Programme of India 2008[4]. Those detected with dengue infection were considered as cases. The control group included pregnant women who were admitted with fever during the study period and tested negative for dengue. The study was approved by the Institute Ethics Committee and since the data were extracted from medical records, a waiver of consent was accorded (JIP/IEC/2019/169). All procedures performed in this study were done with the ethical standards set by the Scientific Advisory Committees and Institute Ethical Committees (IEC) - Human Studies, based on the 1964 Helsinki declaration and its later amendments as well as ethical guideline issued by the Indian Council of Medical Research.

The sample size was calculated using the nMaster2.0 software (CMC Vellore, India) based on the study by Friedman *et al*[14]. Using a two-sided alpha error of five per cent, power of 80 per cent and dengue positive to dengue negative case ratio of 1:4, a minimum of 55 pregnant women with dengue infection (dengue positive) and 220 pregnant women without dengue (dengue negative) were needed for the present study to detect a difference of about nine per cent in the occurrence of stillbirth between the groups. However, we included all pregnant women with fever who got admitted and tested positive on dengue serology during the study period.

Using a predesigned proforma, the details of the cases and controls were extracted from the medical records. Information was collected on demographic details, symptoms at presentation and clinical profile. Details of microbiological testing, haematological and biochemical investigations and treatment modalities such as transfusion of blood products, need for intensive care admission and mechanical ventilation were retrieved. Obstetric details such as gestational age at delivery, mode of delivery and neonatal outcomes including birthweight and neonatal and maternal morbidity were also collected.

Outcomes of interest were pre-term birth, stillbirth and LBW babies. Other complications such as miscarriage, pre-term premature rupture of membranes, intrauterine growth restriction, need for transfusion, rates of thrombocytopenia, *etc*., were also studied. The diagnosis of ascites was done on ultrasonographic examination. Small for gestation age was defined as the estimated foetal weight <10th percentile for the gestational age[13]. Pre-term birth was defined as those delivering before completion of 37 wk of pregnancy[15] and LBW as defined as birth weight <2500 g irrespective of gestational age[16]. Based on the viability of the foetus in the institution, stillbirth was defined as a baby born with no signs of life at or after 28 wk of gestational age or with a birth weight of 1000 g[17,18] and the pregnancy losses before the cut-off of gestational age for foetal viability or that of birth weight were considered a miscarriage in the study.

Statistical analysis: Data was analyzed using STATA 15.0 (Stata Corp., College Station, Texas, USA). While summary statistics for continuous variables were expressed either as mean with standard deviation or median with range, findings on categorical variables were presented as frequencies and percentages. Association between continuous variables with outcomes were tested with Student's t test or Mann-Whitney U test depending on the normality distribution

of the variables or otherwise. Association of categorical variables with outcomes was assessed, depending on the frequency of the events, using Chi-squared test (if the frequency of the vents were more than 5) or Fisher's exact test (when the frequency of the events was <5); *P* values of < 0.05 was considered statistically significant.

Results

During the study period, of the 408 pregnant women with fever, 91 women (22.3%) diagnosed as having dengue infection were included as cases, and the remaining 317 (dengue negative) were included as controls. Among those tested positive for dengue, 59 (64.8%) had IgM antibody and the remaining (32, 35.2%) were positive for NS1 antigen. Baseline characteristics at the time of presentation were compared and are shown in Table I. Ascites on ultrasound examination was noted in 11 (12%) among the patient group compared to 19 (6%) among controls (*P*=0.056); whereas pleural effusion was observed in one (1.1%) and five (1.6%) in both the groups, respectively.

Six maternal deaths were recorded among patient group, with five of them due to dengue shock syndrome and one due to dengue haemorrhagic fever. No maternal death occurred in the control group. Thrombocytopaenia occurred more among pregnant women with dengue compared to controls. Requirement of platelet transfusion (n=8, 8.7% *vs*. n=13, 4.2%, *P*=0.084) and packed red cell transfusion (n=13, 14.1% *vs*. n=42, 13.4%, *P*=0.861) were similar in both the groups. Table II shows obstetrics complications, labour and delivery characteristics among the study population.

Foetal and neonatal outcomes in the study population is shown in Table III. The proportion of pregnant women experiencing pre-term birth was higher among those who had dengue infection compared to the controls (32.1% *vs*. 22.7%) as was the findings on stillbirth (9.1% *vs*. 3.4%). Occurrence of LBW and small for gestational age babies were lower among pregnant women with dengue than among the controls. The risk of stillbirth was 2.67 [95% confidence interval (CI) 1.09, 6.57] times higher among the cases than the controls. Risk of LBW (risk ratio 1.13, 95% CI 0.87, 1.45) and pre-term birth (Risk ratio 1.33, 95% CI 0.89, 1.97) was similar among cases and controls.

Discussion

Earlier studies reported varying range of occurrence of adverse perinatal events in women developing dengue in pregnancy[5-10,12,14,19,20]. In 2008, Tan *et al*[20] in a study from Malaysia reported no difference in pregnancy outcomes between women who experienced dengue while pregnant and those who did not. The same group of authors subsequently in a prospective study observed the risk of miscarriage [adjusted odds ratio (OR) 4.2] to be increased among those who developed dengue infection during pregnancy. A systematic review by Paixão *et al*[12] highlighted about the increased risk of various foetal adverse outcomes, such as the risks of LBW (OR=1.41) and pre-term birth (OR=1.71); the review considered data from 292 women with dengue infection during pregnancy.

Physiological changes in pregnancy such as being in a procoagulant state and the haemodilution may delay the manifestation of severe diseases following dengue infection, such as haematocrit increase or thrombocytopenia. Moreover, pregnancy-related complications such as haemolysis elevated liver enzymes low platelet (HELLP) syndrome or preeclampsia can make early recognition of dengue complications difficult[12]. In dengue infection, pro-inflammatory mediators such as interleukin-6 and tumour necrosis factor-∝ can result in uterine contractions and pre-term birth[21]. Furthermore, thrombocytopaenia resulting in increased bleeding tendency and increased endothelial permeability can result in pathological changes in the placenta evidenced by stromal oedema, syncytial knots and chorangiosis, resulting in dysfunction and hypoxia. These changes, in turn, can negatively affect transfer of nutrients to the growing foetus in the womb across placenta, which can cause foetal growth restriction or in severe cases, can lead to stillbirth[21,22]. In the present study, occurrence of stillbirth was significantly higher among those who had dengue infection during pregnancy compared to those pregnant women who had fever but not due to dengue, whereas pre-term birth or foetal growth restriction, even though occurred in higher proportion in pregnant women with dengue, were not significantly different compared to controls.

Being a hospital record based study, the present investigation focused on pregnant women presenting to hospital with fever. Those who had a miscarriage or milder symptoms who may not have reached the hospital at the time of dengue infection may have been excluded from the study affecting the strength of association of dengue infection with various outcomes. Even though all women who presented with fever and had undergone dengue testing were included, we could

Table I. The baseline characteristics of the study population

Variable	Patients n (%)	Controls n (%)	P
Age, yr[#]	24.7±3.8	25.2±4.1	0.289
Nulliparous	53 (57.0)	177 (56.2)	0.891
Systolic blood pressure, mm Hg[#]	112.4±16.3	113.3±16.9	0.641
Diastolic blood pressure, mm Hg[#]	73.1±10.8	74.4±11.9	0.340
Ascites	11 (12.0)	19 (6.0)	0.056
Pleural effusion	1 (1.1)	5 (1.6)	0.726
Anaemia[*]	72 (79.1)	247 (77.91)	0.957
Thrombocytopenia[**]	23 (24.73)	46 (14.60)	0.022

[*]Anaemia defined as haemoglobin level <11 g/dl; [**]Thrombocytopenia defined as a platelet count <1.5 lacs per mm^3; [#]Mean±SD. SD, standard deviation

Table II. The obstetrics complications, labour and delivery characteristics of the study population

Variable	Patients n (%)	Controls n (%)	P
Miscarriage	3 (3.2)	23 (7.3)	0.155
Pre-term pre-mature rupture of membranes	12 (13.6)	40 (13.6)	1.000
Oligohydramnios	5 (5.7)	10 (3.4)	0.330
Foetal growth restriction	8 (9.1)	19 (6.4)	0.385
Labour, induced	13 (17.8)	65 (23.5)	0.301
Gestational age at delivery, weeks, mean±SD	36.0±5.6	35.5±7.1	0.791
Caesarean section rate	32 (41.6)	127 (46.4)	0.986
Pre-term birth <37 wk	25 (32.1)	63 (22.7)	0.089
Post-partum haemorrhage	2 (2.5)	6 (2.0)	0.767

SD, standard deviation

Table III. The foetal and neonatal outcomes in the study population

Variable	Patients (n=88)$^\$$, n (%)	Controls (n=294), n (%)$^\$$	P
Birth weight (g), mean±SD	2442.8±720.0	2574.4±690.4	0.130
Still birth	8 (9.1)	10 (3.4)	0.007
Small for gestational age (weight <10th centile)	29 (32.9)	131 (44.6)	0.055
Low birth weight (<2500 g)	41 (46.5)	163 (55.4)	0.166
NICU admission[##]	30 (37.5)	82 (28.9)	0.141
Neonatal death[##]	2 (2.5)	7 (2.5)	1.000

$^\$$After excluding the miscarriages (patients, n=3; controls, n=23), [##]Among the live born after excluding the still born (patients, n=80; controls, n=284). NICU, neonatal intensive care unit; SD, standard deviation

not complete the recruitment based on 1:4 ratio (case : control), which can be considered as another limitation of the study. The lower event rates and the low number of controls precluded us from performing multivariate analysis for studying the association of various factors with adverse pregnancy outcomes.

Dengue, an endemic arbovirus infection in many Indian States and the subcontinent, poses a challenging public health problem, particularly when it occurs during pregnancy as it can lead to both maternal and foetal morbidity as well as mortality. In this investigation, occurrence of maternal mortality, stillbirths, pre-term birth and thrombocytopaenia were found to be high among pregnant women with dengue compared to the control. Larger prospective multicentric studies are required to assess the strength of association between dengue infection and various adverse pregnancy

outcomes, which would help formulate appropriate monitoring and treatment strategies.

Conflicts of Interest: None.

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