



A RETROSPECTIVE OBSERVATIONAL STUDY ON THE EFFECTS OF FEVER DURING PREGNANCY IN RELATION TO DENGUE

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ABSTRACT

Introduction: Pregnant women who have dengue may be more likely to experience negative maternal-fetal outcomes. The purpose of this study was to evaluate the maternal and perinatal outcomes in pregnant women who arrived with fever and were found to have dengue infection.

Methods: A retrospective clinical study was piloted at a tertiary care center in India. Pregnant women who were admitted with fever were the subjects. The various parameters evaluated were Thrombocytopenia, maternal death, “*Low Birth Weight (LBW)*”, stillbirth, and Preterm birth among the women with and without dengue. The values obtained were analysed for significance at less than 0.05.

Results: Among the 275 pregnant women who experienced fever throughout the study period, 122 (44.3%) were found to have dengue infection. The other 153 (55.6) (who tested negative for dengue) were included as controls. There was significant discrepancy between the groups for the Thrombocytopenia ($p=0.001$). Preterm birth rates were similar but higher among pregnant women with dengue illness than among controls. Stillbirth rates were higher in the dengue patients than controls (8.1% vs 5.2%). This was statistically significant ($p=0.05$).

Conclusions: Among pregnant women with fever who were also diagnosed with dengue infection, the likelihood of negative mother and neonates outcomes rose. Additional investigation is essential to develop the best monitoring and treatment plans for pregnant women because dengue can exacerbate existing obstetric difficulties.

Key words: Thrombocytopenia, Pregnancy, Dengue Infection, Stillbirth, Pre-Term Birth.

INTRODUCTION

Dengue is an arboviral virus that is transmitted by mosquitoes. It is endemic to many countries and poses a significant threat to the public health in various parts of India.¹⁻³ The National Program for the Prevention of Vector-Borne Diseases emphasizes the importance of medical care, case discovery, and vector control in its efforts to reduce the risk of dengue virus infection and transmission.⁴⁻⁶ The majority of people who get infected with the dengue virus get a feverish illness that usually clears up on its own after a few days. In extremely rare cases, they can progress into a dangerous illness marked by a rapid start of symptoms that include excessive bleeding, a low platelet count, and liver failure. These symptoms are brought on by capillaries that begin to leak suddenly. In accordance with the clinical signs, the treatment is typically symptomatic and may include fluid replacement as well as treatments involving blood components.³⁻⁷ In areas where the disease is endemic, pregnant women have an increased risk of catching dengue, and in recent years, concerns have been raised regarding the potential effects of the disease on both the mother and the fetus.⁵⁻¹⁰ The increased incidence of unfavorable pregnancy outcomes can be attributed to changes brought on by dengue infection, such as an increase in pro-inflammatory cytokines, capillary leakage brought on by increased vascular permeability, bleeding tendency brought on by thrombocytopenia, and hepatic dysfunction.¹¹⁻¹⁵ Earlier studies found an increased risk of preterm delivery, stillbirths, and “*Low Birth Weight (LBW)*” in pregnancies impacted by dengue sickness; however, more current research suggests there is little to no increased risk of these complications.¹⁶⁻²² The current research aims at contrasting the maternal and perinatal outcomes of pregnant women who presented with fever and were subsequently found to have dengue infection with those of pregnant women who did not contract the disease.

MATERIAL & METHODS

Study design & Study subjects

The research was piloted as retrospective clinical study at a tertiary care center. The study was carried form April 2020-May 2021 for a period of a year. The women admitted with fever during pregnancy and undergoing testing for dengue infection were identified using admission registers kept at the prenatal and labor wards as well as the dengue report registers at the Microbiology department. Cases were those who have been identified as having dengue infection. Pregnant women who were hospitalised with fever during the trial period and had dengue tests that came back negative made up the control group. The Institute Ethics Committee approved the study, and because the data were taken from medical records, a waiver of consent was granted. The ethical guidelines established by the Scientific Advisory Committees and Institute Ethical Committees (IEC) - Human Studies, based on Helsinki principles as well as the ethical guidelines published by the Indian Council of Medical Research, were followed during all procedures carried out in this study.

Sample size calculations

Based on the work by Sagili et al.,¹³ the sample size was determined. For the current study, a minimum of 55 pregnant women with dengue infection (dengue positive) and 220 pregnant women without dengue (dengue negative) were required in order to detect a difference of approximately 9% in the incidence of stillbirth between the groups using a two-sided alpha

error of 5%, power of 80%, and dengue positive to dengue negative case ratio of 1:4. However, any pregnant women with fever who were hospitalised and had a dengue serology test that was positive throughout the study period were also accounted for. and 275 women were identified to have fever.

Methodology

Conferring to the official recommendations established by the National Vector Diseases Control Plan of India 2008,¹⁴ the diagnosis of dengue was performed using the clinical symptoms along with confirmatory laboratory testing (either immunoglobulin M (IgM) antibodies or NS1 antigen). The specifics of the cases and controls were taken from the medical records and entered into a predesigned proforma. Demographic data, symptoms upon presentation, and clinical profile were all gathered. The information was gathered on microbiological tests, haematological and biochemical examinations, and treatment methods such blood product transfusions, the requirement for admission to an intensive care unit, and mechanical ventilation. Obstetric information was also gathered, including mode of delivery, gestational age, newborns weight and mother or neonatal morbidity.

The outcomes included preterm birth, stillbirth, and LBW children. Additional issues like miscarriage, premature preterm membrane rupturing, intrauterine growth restriction, transfusion requirements, rates of thrombocytopenia, etc., were also investigated.²⁴ On the basis of an ultrasonographic examination, ascites was diagnosed. The projected foetal weight lower than the 10th percentile for the gestational age was used to define "small for gestation age."²³ Preterm births were defined as those that occurred before 37 weeks of pregnancy,²⁵ and "Low Birth Weight (LBW)" was <2.5kgs regardless of gestational age.²⁶ Based on the viability of the pregnancy in the institution, a stillbirth was defined as a baby born ≥ 28 weeks of gestation or with a birth weight of 1kg.^{27,28} Pregnancy losses before the cut-off of gestational age for fetus viability or that of birth weight were considered a miscarriage in the study.

Statistical analysis

Data were examined statistically using STATA 15.0. (Stata Corp., College Station, Texas, USA). Observation were represented as percentages and means. Depending on whether the continuous variables had a normal distribution or not, the association between continuous variables and outcomes was assessed using the Student's t test or the Mann-Whitney U test. Depending on the frequency of the events, the association between categorical variables and results was evaluated using the Chi-squared test; the values obtained were analysed for significance at less than 0.05.

RESULTS

Among the 275 pregnant women who experienced fever throughout the study period, 122 (44.3%) were found to have dengue infection. The other 153 (55.6) (who tested negative for dengue) were included as controls. A total of 69 (56.6%) of those who tested positive for dengue had IgM antibody, and the remainder 53 (43.4%) showed NS1 antigen positivity. Table 1 compares baseline characteristics that were present at the time of presentation.

Table 1: Demographics

Variables	Case	Controls	P
Age (years)	25.3±4.1	26.39±4.56	0.124
Nulliparous	61(50%)	100(65.3%)	0.888
Systolic blood pressure	112.9±15.3 mm Hg	115.0±14.6 mm Hg	0.632
Diastolic blood pressure	74.0±11.2 mm Hg	75.1±8.3 mm Hg	0.354

In the patient group, ascites was found on ultrasound in 15 (12.2%) cases, compared to 20 (13.0%) in the control group (P=0.061); nevertheless, pleural effusion was found in two (2.4%) and 6 (9%) cases in both groups, respectively. Anemia was distributed equally among the two groups. Compared to controls, pregnant women with dengue had a higher incidence of thrombocytopenia. There was significant discrepancy between the groups for the Thrombocytopenia (p=0.001). **Table 2**

Eight of the ten maternal deaths within the patient group were caused by dengue shock syndrome, and 2 were by dengue hemorrhagic fever. There were no maternal deaths in the control group. Miscarriages were observed to be more in the control febrile subjects than those with dengue. Pre-term pre-mature rupture of membranes, Post-partum haemorrhage were similar in both groups. Preterm birth rates were similar but higher among pregnant women with dengue illness than among controls (32 (26.2%) vs 34 (22.22%)). Similarly Foetal growth restrictions were also higher in dengue subjects than the controls.

Complications, and other clinical findings for the study population are shown in **Table 2**.

Table 2: Complications, and other clinical findings

Variables	Case	Controls	P
Anaemia	7 (61.4%)	132 (86.2)	0.852
Ascites	15 (12.2%)	20 (13.0%)	0.061
Caesarean section rate	41 (33.6%)	76 (49.6%)	0.845
Foetal growth restriction	8 (9.1%)	19 (6.4%)	0.385
Gestational age at delivery, weeks	36.1±4.2	35.6±5.6	0.658
Labour, induced	13 (17.8%)	65 (23.5%)	0.301
Miscarriage	4 (3.2%)	18 (11.7%)	0.065
Oligohydramnios	6 (4.9%)	8 (5.2%)	0.259
Pleural effusion	2 (2.4%)	6 (9%)	0.645
Post-partum haemorrhage	3 (2.4%)	7 (4.5%)	0.747
Pre-term birth <37 wk	32 (26.2%)	34 (22.22%)	0.125
Pre-term pre-mature rupture of	12 (13.6%)	40 (13.6%)	1.01

membranes			
Thrombocytopenia	25 (20.4)	12 (7.8%)	0.001

Table 3 displays the fetal and neonatal outcomes in the study population. Stillbirth rates were higher in the dengue patients than controls (8.1% vs 5.2%). This was statistically significant. Contrary to expected pregnant dengue patients had lower rates of LBW and small for gestational age newborns than controls. Neonatal death was reported in 3 and 4 infants in the case and the control groups. Mean birth weight was similar but slightly higher for the dengue patients. **Table 3**

Table 3: The foetal and neonatal outcomes

Variables	Case	Controls	P
Birth weight (kg), mean±SD	2.52±0.56	2.33±0.642	0.11
Low birth weight (<2500 g)	57 (46.7%)	75 (49%)	0.125
Neonatal death	3 (2.44%)	4 (2.6%)	1.000
Small for gestational age (weight <10 th centile)	30 (24.5%)	88 (57.5%)	0.061
Still birth	10 (8.1%)	8 (5.2%)	0.05

DISCUSSION

In earlier research, it was found that females who contracted dengue at the time of pregnancy experienced a variety of unfavorable perinatal events.¹⁵⁻²⁷ Tan et al.,³⁰ in a Malaysian study from 2008 found no difference in pregnancy outcomes between pregnant women who experienced dengue and those who did not. The same group of scientists later discovered, in a prospective research, that women who contracted dengue virus while pregnant had a higher chance of miscarriage (adjusted odds ratio (OR) 4.2). A comprehensive study by Paixo et al.,²² looked at data from 292 pregnant dengue infected women and found that there was an elevated risk of multiple poor outcomes for the fetus, including the chances of LBW (OR=1.41) and preterm birth (OR=1.71).

The onset of serious disorders following dengue infection, such as a rise in hemoglobin concentration or thrombocytopenia, may be delayed by physiological changes in pregnancy, such as being in a procoagulant condition and hemodilution. Early detection of dengue complications might also be challenging due to pregnancy-related issues.^{13,22} Pro-inflammatory mediators associated with dengue infection, such as interleukin-6 and tumour necrosis factor, can cause uterine contractions and preterm birth.³¹ Moreover, thrombocytopenia can lead to pathological alterations in the placenta that are shown by stromal oedema, syncytial knots, and chorangiosis, which cause dysfunction and hypoxia and increase bleeding tendency and endothelial permeability. These modifications, in turn, may have a negative impact on the way nutrients pass the placenta to the developing fetus in the womb, which may result in fetal growth restriction or, in extreme circumstances, stillbirth.^{31,32} In the current study, stillbirth rates were significantly greater among pregnant

women with dengue infection than among pregnant women who had fever but not a dengue infection. However, preterm birth rates or foetal growth restriction rates were higher in pregnant women with dengue infection but did not differ significantly from controls. Contrary to expected pregnant dengue patients had lower rates of LBW and small for gestational age newborns than controls. Neonatal death was reported in 3 and 4 infants in the case and the control groups. These observations are similar to study by Sagili et al.¹³

The current investigation, which was based on an examination of hospital records for a period of 1 year, concentrated on pregnant women who presented to hospitals with fever. The study's exclusion of those with miscarriages or weaker symptoms who might not have made it to the hospital at the time of dengue infection may have weakened the correlation between dengue infection and various outcomes. In the study multivariate analysis to examine the associations of various factors with unfavorable pregnancy outcomes was not undertaken due to the lower event rates and the small number of controls.

CONCLUSION

A severe public health issue, dengue is an endemic arbovirus infection that affects several Indian States and the subcontinent. When it affects pregnant women, it can result in both maternal and fetal morbidity as well as mortality. In this study, it was discovered that dengue infected pregnant women had a higher incidence of maternal mortality, stillbirths, preterm birth, and thrombocytopenia than the control group. To determine the degree to which dengue infection is associated with a variety of unfavourable pregnancy outcomes, larger prospective multicentric studies are required. This information would be used to develop effective monitoring and treatment techniques.

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