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Original Article

Implications for Maternal and Fetal Outcomes of Dengue Fever in Pregnancy

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ABSTRACT

Introduction: *Dengue fever, a mosquito-borne viral illness, poses a significant global health threat, with millions of cases reported annually. Pregnant women, with their altered immune status, are particularly vulnerable to the complications of dengue infection. This study on the maternal and fetal outcomes of dengue infection during pregnancy aims to comprehensively understand the associated risks, challenges, and potential interventions.* ***Methods & Materials:*** *This retrospective observational study was conducted in the Department of Obstetrics & Gynaecology at Northern International Medical College Hospital & Al Manar Hospital Limited, Dhaka, Bangladesh from May, 2022 to March, 2023. Eighty-two pregnant patients had laboratory-confirmed dengue virus infection. Among them, 54 and 15 had dengue without and with warning signs respectively, and 13 presented with severe dengue. Four of these patients delivered healthy infants with average birthweights, while one delivered a premature infant with low birthweight.* ***Results:*** *Within ten days following the surgery, patients passed away due to multiple organ failure. Obstetric hemorrhage was observed in five patients, four of whom (30.8%) had severe dengue. Preeclampsia developed in four patients, including two (15.4%) with severe dengue, while eclampsia occurred in one patient (7.7%) with severe dengue. Patients with other two illness categories either did not experience these problems or did so infrequently. Furthermore, there was no correlation between mild dengue and poor newborn outcomes, fetal discomfort.* ***Conclusion:*** *The study shows that a significant incidence of fetal distress, cesarean birth is linked to severe dengue during pregnancy.*

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INTRODUCTION

Dengue, one of the most significant arbovirus infections in humans, is a major global public health concern, particularly in tropical nations where the environment supports the growth and spread of Aedes aegypti, the disease's primary mosquito vector. Approximately 40% of the global population is at risk of contracting dengue, with the disease being endemic in over 100 countries. Dengue is caused by four distinct viral serotypes—DENV-1, DENV-2, DENV-3, and DENV-4—that can circulate independently, succeed one another, or coexist within populations. According to estimates from the World Health Organization (WHO), between 50 and 100 million dengue cases are reported globally each year[1,2]. Urbanization, inadequate city infrastructure, and population behaviors contribute significantly to the spread of dengue, creating ecological conditions that facilitate an increase in cases and the rising frequency of epidemics, typically occurring in cycles every 3–5 years[3]. In Bangladesh, the combination of climatic and socioeconomic factors, rapid population growth, and inadequate sanitation further exacerbates the spread of the disease. Additionally, the natural immunosuppression that occurs during pregnancy may increase the risk of severe infections, heightening fetal susceptibility to congenital infections and posing potential health risks to both the mother and fetus[4-7]. Viral infections during pregnancy increase the risk of complications for expectant mothers and are among the leading causes of fetal morbidity and mortality[8,9]. According to specific research, severe dengue during pregnancy is linked to fatalities in mothers, fetuses, and newborns. Additional adverse outcomes, such as low birth weight, preterm birth, miscarriage, fetal distress, and vertical transmission, have also been reported[10-14]. This study aimed to assess the extent of maternal, fetal, and infant complications associated with dengue infection during pregnancy in Bangladesh.

METHODS & MATERIALS

A retrospective analysis (Northern International Medical College Hospital & Al Manar Hospital Limited) was conducted on the medical records of 82 completed pregnancies (live births and pregnancy losses regardless of gestation time) from May, 2022 to March, 2023- all patients who developed laboratory-confirmed dengue while pregnant were included in the study cohort. Patients were categorized into three groups: dengue without warning signs, dengue with warning signs, and severe dengue[15]. Laboratory-confirmed dengue infection was defined by the detection of DENV NS1 antigen or IgM antibodies in acute or convalescent-phase samples. An infant was considered to be born during the maternal-fetal viremia period (MFVP) if the interval between the onset of maternal dengue symptoms and labor was ≤15 days[16].

Continuous variables were expressed as mean ± standard deviation (SD), while nominal variables were presented as percentages. Statistical analyses were conducted using SPSS Statistics version 22 for Windows, with significance set at $P \leq 0.05$. Normality was assessed using the Kolmogorov-Smirnov test, and homoscedasticity was evaluated using Levene's test. Data following a normal distribution and with homogeneous variances were analyzed using one-way ANOVA. For data that did not meet these assumptions, the nonparametric Kruskal-Wallis test was employed. The mean arterial pressure was calculated using the formula [(2 × diastolic) + systolic]/3 and analyzed by one-way ANOVA[17]. The participating medical institution approved the study.

RESULTS

The study included 82 patients with clinically and laboratory-confirmed DENV infections during pregnancy. Patient ages ranged from 16 to 36 years. Demographic, clinical, and laboratory data for patients categorized as having dengue without warning signs, dengue with warning signs, and severe dengue are summarized in **Table I**.

Table – I: Demographic, Clinical, and Laboratory Information for a Cohort of Pregnant Dengue Patients

Parameters	Disease Classification			*p*-value
	Dengue without Warning Signs (*n*=54)	Dengue with Warning Signs (*n*=15)	Severe Dengue (*n*=13)	
	Mean±SD			
General information				
Age (years)	26.7 ± 5.4	28.5 ± 5.4	26.2 ± 5.4	[a]≥0.05
Illness Onset (Weeks of gestation)	28.5 ± 6.1	28.7 ± 6.9	32.9 ± 5.5	[a]0.015
Time in Hospital (days)	6.1 ± 1.4	7.4 ± 2.3	9.9 ± 4.2	[b]0.009
Physiological Parameters[c]				
Arterial Pressure (mm Hg)	54.8 ±16.8	59.8 ± 15.4	72.1 ± 23.2	[b]0.013
Breathing Rate (Breaths per min.)	19.2 ±1.7	19.0 ± 0.8	20.1 ± 2.0	[b]≥0.05
Heart Rate (beats per min.)	91.6 ±4.4	89.5 ± 5.4	97.3 ± 15.8	[b]≥0.05
Blood Count [c,d]				
Coagulation Time: PT (sec) [12.1–15.0]	11.7 ± 1.9	12.6 ± 0.6	15.5 ± 3.6	[b]0.042

Coagulation Time: PPT (sec) [22.7–33.7]	31.8 ± 5.1	33.4 ± 3.4	51.6 ± 74.6	[b]≥0.05
Hematocrit (%) [38–47]	35.5 ± 2.0	36.3 ± 2.4	37.1 ± 11.8	[b]0.018
Hemoglobin (g/dl) [12–16]	10.9 ± 0.7	11.9 ± 0.7	12.0 ± 1.2	[a]0.001
Leukocytes (×1000) (per μl) [4–11]	4.2 ± 0.6	4.5 ± 0.8	5.8 ± 1.6	[b]0.001
Platelets (×1000) (per μl) [150–450]	124.0 ± 20.1	110.9 ± 15.4	86.4 ± 41.8	[b]≥0.05
Metabolic profile [c,d]				
Creatinine (mg/dL) [0.5–1.5]	1.0 ± 0.5	0.9 ± 0.5	1.2 ± 0.8	[b]≥0.05
Glucose (mg/dL) [60–120]	92.7 ± 12.3	97.4 ± 6.2	106.2 ± 21.0	[b]≥0.05
Urea (mg/dL) [15.0–38.0]	15.6 ± 8.3	14.7 ± 6.5	29.0 ± 20.9	[b]≥0.05
Hepatic profile [c,d]				
ALB (g/dl) [3.0–5.0]	3.2 ± 0.2	4.4 ± 5.5	4.7 ± 6.8	[b]0.000
ALT (IU/L) [10–40]	53.5 ± 44.1	63.5 ± 68.1	262.5 ± 328.3	[b]0.001
AST (IU/L) [9–48]	84.6 ± 62.4	105.9 ± 127.1	460.0 ± 709.8	[b]0.000
DB (mg/dl) [0.1–0.3]	0.2 ± 0.2	0.2 ± 0.2	1.2 ± 1.3	[b]0.000
IB (mg/dl) [0.1–0.4]	0.2 ± 0.2	0.3 ± 0.2	0.8 ± 0.7	[b]0.000
LDH (UI/L) [140–280]	161.9 ± 114.0	245.9 ± 190.4	737.1 ± 752.1	[b]0.000

[a] One-way ANOVA test. [b] Nonparametric Kruskal-Wallis test, [c] determined during the acute-phase of illness, and [d] normal ranges are provided in square brackets. ALB: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, DB: direct bilirubin, IB: indirect bilirubin, LDH: lactate dehydrogenase, PT: Prothrombin time, and PPT: Prothrombin partial time.

The most common symptoms observed in patients with nonsevere dengue were fever, myalgia, arthralgia, headache, and nausea (**Table II**). These symptoms, along with fluid accumulation (peripheral edema, pleural effusion, and/or ascites), were also prevalent among patients with severe dengue. Obstetric hemorrhage was noted in five patients, four of whom (30.8%) had severe dengue. Preeclampsia developed in four patients, including two (15.4%) with severe dengue, while eclampsia occurred in one (7.7%) patient with severe dengue.

Table – II: Symptoms Reported of Pregnant Dengue Patients

Symptoms	Disease Classification		
	Dengue without Warning Signs (*n*=54)	Dengue with Warning Signs (*n* = 15)	Severe Dengue (*n*=13)
	n(%)		
Abdominal pain	8 (28.3)	1 (6.7)	7 (53.8)
Arthralgia	44 (81.5)	13 (86.7)	9 (69.2)
Cough/diarrhea/conjunctivitis	8 (14.8)	5 (33.3)	2 (15.4)
Eclampsia	0 (0)	0 (0)	1 (7.7)
Edema/pleural effusion/ascites	5 (9.2)	0 (0)	9 (69.2)
Exanthema	19 (35.2)	1 (6.7)	4 (30.8)
Fever	54 (100.0)	15 (100.0)	13 (100.0)
Gingivorrhagia	0 (0)	8 (53.3)	3 (23.1)
Headache	35 (64.8)	14 (93.3)	10 (76.9)
Hepatomegaly/visceral damage	0 (0)	0 (0)	3 (23.1)
Hyporexia	8 (14.8)	3 (20.0)	4 (30.8)
Multiple organ failure	0 (0)	0 (0)	5 (38.5)
Myalgia	45 (83.3)	13 (86.7)	8 (61.5)
Nausea	23 (42.6)	9 (60.0)	8 (61.5)
Obstetric hemorrhage	1 (1.9)	0 (0)	4 (30.8)
Oral intolerance	17 (31.5)	1 (6.7)	4 (30.8)
Petechiae	14 (25.9)	3 (20)	5 (38.5)
Pneumonia	0 (0)	0 (0)	1 (7.7)
Preeclampsia	1 (1.9)	1 (6.7)	2 (15.4)
Rash	4 (7.4)	0 (0)	0 (0)
Retroocular pain	4 (7.4)	5 (33.3)	6 (46.2)
Shock	0 (0)	0 (0)	3 (23.1)

Four pregnancies were full-term and infants were within the normal weight range (within range of 2500 to 4000 gm). Symptoms characteristic of dengue were observed in any of the infants from birth until hospital discharge. Two infants were born during the maternal-fetal viremia period (MFVP), while three infants were delivered outside of this period.

DISCUSSION

This retrospective study included 82 pregnant women with symptomatic dengue. As one of the largest studies of its kind, it highlights a strong association between severe dengue and

an increased incidence of fetal distress and cesarean deliveries. Other studies have similarly demonstrated that dengue is linked to a higher rate of cesarean births[10,12,16].

One (1.2%) patient, a 29-year-old woman, delivered a low birth weight (LBW) infant. Other studies have also reported an association between maternal dengue and LBW, though at considerably higher rates than those observed in this study[12,14,10,18-19]. Instead of intrauterine growth restriction, preterm delivery was blamed for a large number of the previously stated LBW cases. In this study, only one patient delivered a premature infant. In contrast, a study from Brazil reported that 22 out of 336 (6.5%) infants born to dengue-infected mothers were low birth weight (LBW)[14]. The incidence of LBW was significantly higher among infants born during the maternal-fetal viremia period (MFVP) compared to those born outside this period (22.0% vs. 4.4%, respectively). In our study, five infants were born during the MFVP, and all had normal birth weights. Therefore, one possible explanation for the low incidence of LBW in our study is that only a small number of infants were delivered during the MFVP.

Dengue with or without warning signs was not associated with any apparent adverse maternal outcomes aside from symptoms typical of nonsevere dengue in the general population. Four (2.9%) cases of preeclampsia and two (1.5%) cases of obstetric hemorrhage occurred among the 138 patients with nonsevere dengue, but these rates are not higher than that observed during normal pregnancy[20,21]. The rates of eclampsia and preeclampsia in this study are significantly higher than those typically observed in normal pregnancies[20,21]. Several case reports have documented the occurrence of preeclampsia and eclampsia in pregnant patients with dengue fever (DF) and dengue hemorrhagic fever (DHF)[17,22-25]. Hemorrhage during labor was reported in five out of 53 (9.3%) pregnant DF patients in French Guiana[12].

None of the patients in our study developed dengue symptoms during the first trimester. Patients with nonsevere dengue became symptomatic during the second or third trimesters. A similar trend has been observed in other studies. In French Guiana, three of 53 (5.7%) patients developed dengue in the first trimester, with the remaining 94.3% becoming symptomatic in the second or third trimesters[12]. The reasons for the onset of illness typically occurring in mid to late pregnancy remain unclear. Several studies have reported maternal-to-fetal transmission of DENV[24,26,27]. In a review by Pouliot et al., vertical transmission rates were assessed from 19 case reports and nine case series. Of 25 infants in case reports, 16 (64.0%) were infected in utero, while 18 of 143 (12.6%) infants in case series acquired the virus. Among the 34 DENV-positive infants, 29 (85.3%) were symptomatic. In contrast, no neonates of this study exhibited dengue symptoms. Some infants, particularly those born to mothers having dengue in the final days of pregnancy, may have developed

symptoms after discharge, but we could not access post-discharge health records. No studies found evidence of maternal-to-fetal DENV transmission[17,28].

ALT and AST levels were elevated in the majority of patients across all three disease categories, with levels typically higher in those with severe dengue compared to nonsevere cases. Similar findings were reported in Sri Lanka, where raised ALT and AST levels were observed in 60% of pregnant DF patients and 100% of pregnant DHF patients[10]. Abnormal hepatic function is also commonly seen in nonpregnant dengue patients[29-33]. Platelet counts were reduced in nearly all patients in our cohort, a finding consistent with other studies of pregnant dengue patients[12,10,22]. It was also observed that platelet counts are often reduced in nonpregnant dengue patients[29,33].

CONCLUSION

We used one of the most significant cohorts for a study of this kind to examine the effects of dengue during pregnancy on the mother, fetus, and neonate. We provide data indicating that severe dengue in pregnant women is linked to cesarean birth, and fetal distress. Aside from the general population exhibiting dengue-like symptoms, nonsevere dengue did not appear to be linked to any evident adverse effects for mothers, fetuses, or newborns.

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Conflict of Interest

The authors declare no conflict of interest.

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