

A study on maternal and foetal prognosis and predictive factors for adverse outcome in pregnant patients with dengue in an endemic state of India

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ABSTRACT

Aims: Dengue fever is a major health problem with high morbidity and mortality especially during epidemic season; pregnant females being no exception. But, there is paucity of published data on dengue fever during pregnancy. Hence, this study was planned to study the clinical profile, maternal outcome and predictors of poor outcome in pregnant dengue patients. **Materials and Methods:** All pregnant females attending labour room of Tata Main Hospital, Jamshedpur from April 2016 to October 2020 with acute febrile illness caused by dengue virus at any gestational age were included in the study. Diagnosis of dengue was made by detection of NS1 antigen or dengue serology. A predesigned proforma was used to record materno-foetal outcomes and were analysed. **Results:** Dengue was the cause of fever in 7.1% febrile patients. Maternal complications included abortions (26%), abruptio (1.9%), postpartum haemorrhage (11.9%). Of all the pregnant dengue patients, five had severe dengue (SD) with high mortality (3/5; 60%). Fetal complications were intrauterine death (7.7%), preterm (42.3%). Thrombocytopenia and elevated transaminases were associated with adverse outcome. **Conclusions:** Dengue fever in pregnancy is associated with poor outcomes more in cases of SD rather than dengue fever. Pregnant females with high risk predictors should be identified and managed aggressively in intensive care units to improve outcomes.

Keywords: Dengue, pregnancy, postpartum hemorrhage

Introduction

Dengue has emerged as a worldwide problem; there has been an increase in the number of cases of patients suffering from dengue fever. Endemic areas are the worst hit. Approximately 40% of the population is at risk. Parallel to this, there is an upsurge in pregnant patients with dengue. Due to the paucity of studies on dengue little is known about the effects of pregnancy on course of dengue fever and effect of dengue fever on pregnancy and

developing foetus and it becomes a problem especially for the treating physician to deal with such patients. Only few studies have shown association of dengue with abortion and so the importance of this study and it can be included in trials to come to a conclusion.

Dengue, transmitted by infected Aedes mosquito, is caused by one of any of four distinct serotypes of family flaviviridae: DEN -1, DEN - 2, DEN-3, DEN -4. Among them DEN - 3, DEN-4 are Asian serotypes.

In 2008, the WHO classified dengue into dengue without warning signs (DWWS), dengue with warning signs (DWS), and severe dengue (SD).^[1-4]

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Aim and Objectives

Identification of predictors of poor outcome in pregnant dengue patients and risk stratification, to study the clinical profile, maternal and foetal outcome.

Study Design

It is a retrospective case only study done at Tata Main Hospital, Jamshedpur during a period of 4 years from April 2016 to October 2020. We included 57 patients who tested positive for the non-structural protein 1 (NS1) antigen or immunoglobulin M anti-dengue in the study population.

Informed consent and ethical committee clearance were waived owing to the retrospective observational nature of the study.

Demographic data, clinical and laboratory findings, and maternal and foetal outcomes were collected from each patient's electronic medical records.

Patients were classified according to WHO 2008 guidelines into dengue without warning signs (DWS-), dengue with warning signs (DWS+) and severe dengue.^[4]

Comparison between groups was made using Fischer exact test for categorical variables, whereas the *t* test or Mann-Whitney *U* test was used for continuous variables. $P < 0.05$ was considered statistically significant. category variables were reported as number (percentage); continuous variables were reported as mean \pm SD.

Results

Total number of pregnant patients with confirmed dengue was 57. This accounts for 7.1% of cases who came with fever. Distribution of these is shown in Figure 1. Demographic data, clinical profile and distribution according to WHO classification are shown in Table 1.

Pregnancy itself being a state of massive haemodynamic changes and infection with dengue increases morbidity and mortality.

Dengue fever in the first trimester carries high risk of abortion. Out of 19 patients, 5 patients (26.3%) aborted and all were in the first 12 weeks of gestation, so percentage of abortion in the first 12 weeks was as high as 38.4%. Incidence of oligohydramnios was 19.2%. There was 1 patient of abruption placentae that account for 1.9% incidence. Postpartum haemorrhage is usually the main concern in managing these patients. It was seen in 5 (11.9%) patients. There were 3 (5.3%) deaths because of dengue. No case of preeclampsia because of dengue.

The developing foetus was also affected but 71.9% had normal outcome. Details are shown in Table 2.

Table 1: Age, trimester wise and clinical profile distribution of patients

CHARACTERISTICS	CATEGORY	n (%)
Age n (%)	20-30 years	45 (79%)
	30-40 years	12 (21%)
Trimester wise distribution n (%)	1 st	12 (21.1%)
	2 nd	8 (14%)
	3 rd	37 (64.9%)
Presenting complaint n (%)	Fever	100%
	Myalgia	46 (80.7%)
	Headache	36 (63.1%)
	Petechia	2 (3.5%)
	Abdominal pain	4 (7%)
	Vomiting	4 (7%)
Classification n (%)	DWS+	10 (17.5%)
	DWS-	38 (66%)
	SD	9 (15.7%)
Delivery n/42 (%)	Preterm	7 (2.7%)
	NVD	28 (75.7%)
	LSCS	8 (21.6%)
	Ventouse	1 (2.7%)

n - number of patients

Table 2: Maternal and fetal outcome. Fetal outcome and maternal outcome like oligohydramnios, abruption are calculated on (total - patients who had abortion) i.e., 52. outcome like PPH is calculated on total patients who delivered i.e., 42

MATERNAL OUTCOME	VARIABLE	n (%)
	Abortion (N/19)	5 (26.3%)
	Oligohydramnios (N/52)	10 (19.2%)
	Abruption (N/52)	1 (1.9%)
	PPH (N/42)	5 (11.9%)
	Maternal deaths (N/57)	3 (5.3%)
FETAL OUTCOME		
	Normal outcome	71.9%
	Preterm (N/52)	7 (13.5%)
	IUGR (N/52)	5 (9.6%)
	IUD (N/52)	2 (3.8%)

The most common complication in these patients is postpartum haemorrhage and preventing this by predicting it well in advance can prevent many deaths. Various factors were studied like gestational age at delivery, birth weight, platelet count, elevated liver enzymes, bleeding manifestation and caesarean section. Out of these platelet count and elevated liver enzymes had a positive correlation. In 4 patients who had postpartum haemorrhage (PPH) the average platelet count was 48,000 and in patients who did not had postpartum haemorrhage the average platelet count was 106,000 which was statistically significant ($P = 0.0007$). Similarly patients who had postpartum haemorrhage had higher liver enzymes level (AST/ALT > 40 IU/mL) ($P = 0.01$).

Thrombocytopenia can be used to predict maternal prognosis. Maximum (40.4%) patients had mild thrombocytopenia with

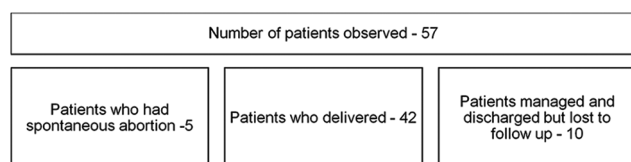


Figure 1: Distribution of patients

maximum complications like foetal distress requiring caesarean section (33%), PPH (33.3%) and maternal death were mostly in patients with severe thrombocytopenia.

As we compared patient with dengue with or without warning signs (33) and patient with severe disease (5). Patients with dengue without warning signs had less complications, one had PPH and no case of abruption, IUD and maternal death. While in cases of dengue with severe disease three cases (60%) had PPH, one (20%) had abruption, two (40%) had IUD and there were three (60%) maternal deaths.

Thus thrombocytopenia, raised liver enzymes and severity of disease can help identify patients who need intensive care.

Discussion

With an outbreak of dengue infection in recent years, total number of dengue patients admitted in hospital during the study period were 2402 out of which 57 were pregnant females. With such huge burden of cases more research is required to understand the impact of the disease.

Dengue infection and risk of miscarriage

Vertical transmissions to the foetus and pregnancy losses in relation to dengue illness have been reported but the relationship of dengue to miscarriage is unknown. Studying this aspect is particularly helpful in predicting risk of abortion in patients with early pregnancy travelling to endemic areas.

In our study the incidence of abortion was 26.3% and in another study by Tan et al it was 20%.^[5] In another study at AFMC, Pune they have reported all or none phenomenon and observed abortion in all cases in first trimester.^[6] Other studies have also reported^[7-9] and it was clear that there is increased risk of abortion specially in first 12 weeks.

Thrombocytopenia

Thrombocytopenia in dengue has an acute onset and high mortality rate in left untreated. The severity of thrombocytopenia correlates well with severity of dengue infection and risk of bleeding as observed in many studies. The mechanism involves bone marrow suppression, attenuation of megakaryocyte maturation and increased peripheral platelet destruction.^[10] Thrombocytopenia is transient, and spontaneous recovery is mostly observed.^[11]

Table 3: Distribution of patients on basis of degree of thrombocytopenia and its impact on various maternal outcomes

	MILD	MODERATE	SEVERE
TOTAL n (%)	23 (40.4%)	17 (29.8%)	6 (10.5%)
Mode of delivery			
LSCS n (%)	4 (17.4%)	2 (11.8%)	2 (33.3%)
Vaginal delivery n (%)	20 (86.9%)	11 (64.7%)	4 (66.7%)
Abortion n (%)	1 (4.3%)	4 (23.5%)	0
Postpartum haemorrhage n (%)	1 (4.3%)	2 (11.8%)	2 (33.3%)
Death n (%)	1 (4.3%)	1 (5.9%)	1 (16.7%)

Incidence of thrombocytopenia in our study is 96.5%. We found that twenty three patients had mild thrombocytopenia, seventeen had moderate and six had severe thrombocytopenia.

Patients with moderate and severe thrombocytopenia had maximum effect on pregnancy like spontaneous miscarriage, postpartum haemorrhage, foetal distress, requirement of LSCS and maternal mortality as shown in Table 3.

Thus degree of thrombocytopenia can be a predictor of complications. Further larger studies are required to find a correlation between the variables. Only few studies have covered this aspect as a study in Indonesia where they found that severe thrombocytopenia is associated with maternal mortality and IUFD.^[12]

Maternal death and dengue

The cause of maternal deaths in dengue is not clear, one possible explanation is that the clinical aspects of the disease may be different during pregnancy in a way that increases the susceptibility to dengue haemorrhagic fever. Another hypothesis is that physiological changes during pregnancy such as haemoconcentration and the difficulty in distinguishing between severe dengue and common obstetric conditions may have led to misdiagnosis and delay in treatment.

This is the clinical profile of patients who died due to dengue is given in the Table 4. All the patients were in third trimester. Platelet count in all three patients were low and liver function was deranged. Time between onset of symptoms and death was less than 6 days in all. First patient died because of PPH and the other two because of multiorgan failure.

Maternal mortality in our study was 5.3%.

As can be seen in Table 5 risk of pregnant patients dying due to dengue is five times more than non-pregnant patients. In other studies maternal mortality was 4%,^[13] 21.7%.^[14] Other studies found that dengue increased the risk of maternal death by 3 times.^[15] and dengue haemorrhagic fever increased the risk of maternal death by 450 times when compared to mortality of pregnant women without dengue.^[15-17]

Table 4: Clinical profile of patients with postpartum haemorrhage

Gest. age	Gravida	Platelet Count Day 1/max. fall	AST/ALT Day1 (max. rise)	Disease classification	ASS. COND.	Blood loss	Transfusion	Mode of delivery
38	G3P1L1A1	100000/38000	90/91 (1523/47)	Severe disease	Abruption	1000	8 Plat., 36 FFP, 18 PC	NVD;
33	G1P0L0	52000	16/66	Severe disease	Falciparum malaria	1000	2 PC	NVD
38	G2P1L1	22000	56/60	Severe dengue		1600	nil	LSCS; DIED
38	G1 P0L0	80000/49000	436/295	Severe dengue			nil	LSCS ; DIED
39	G1P0L0	40000	122/75	Severe dengue	IUD	20000	25 plat., 2 pc	VD of IUD baby, DIED

Other maternal outcome-

Dengue infection had other grave impact on pregnancy like decreased liquor, abruption, intrauterine death and postpartum haemorrhage.

Oligohydramnios is an ominous sign as this can lead to intrauterine death, pulmonary hypoplasia, nursery admission and prolong hospital stay. Exact cause is not known but it can be due to dehydration related to fever during dengue infection. Maintaining hydration for such patients is important.

Amniotic fluid index (AFI) and gestational age graph was used and oligohydramnios was taken as AFI less than fifth percentile. The incidence of oligohydramnios in our study was 17.9%. This was high as compared to other studies in which incidence was 8%.^[18]

Sudden catastrophic event like abruption can further complicate the already at risk pregnancy. In our study there was one case of abruption, incidence being 1.7% as compared to 0.5 – 1% in general population. In other studies incidence of antepartum haemorrhage was 4%.^[18]

Postpartum haemorrhage-

The pathogenesis of bleeding in dengue is multifactorial. There are various papers on how dengue causes coagulation abnormalities, one is by Bridget A. Wills *et. al.* in which he has found that dengue virus can directly activate plasminogen *in vitro*. Rather than causing true disseminated intravascular coagulation, it can activate fibrinolysis primarily, degrading fibrinogen directly and promoting secondary activation of procoagulant homeostatic mechanisms. There is decrease in plasma levels of coagulation proteins and also accounts for bleeding tendencies in patients infected with dengue virus.

In our study, five patients (8.7%) had PPH which was high as compared to general average of 2- 4%. In other studies it was 20%.^[13]

As we can see in Table 6 five patients had postpartum haemorrhage. All were in third trimester. First patient came at term in labour with fever (101 degree) for last 3 days. She had mild abruption and delivered vaginally. Lab reports showed moderate thrombocytopenia and mildly raised LFT. She had postpartum haemorrhage which was mild. Her condition deteriorated on 3rd day of delivery when her platelet (38,000) kept falling and

Table 5: Predictive factors for postpartum haemorrhage

	PPH (n=5)	NO PPH (n=42)	P
Gestational age at delivery	37.2±2.387	31.31±8.588	0.1372
Birth weight (kg±SD)	2.34±0.723	2.74±0.510	0.1193
Platelet count (x 10 ³)	48.6±19.59	106.243±34.319	0.0007**
Elevated liver enzymes (>40/40) n (%)	4 (80.00%)	15 (35.71%)	0.01
Caesarean section n (%)	2 (40.00%)	6 (14.29%)	0.148

**P is significant at 0.01 level

Table 6: Category of disease as a predictor for maternal and fetal outcome

	Patients with or without warning sign	Severe disease
Total	33	5
PPH	1 (3%)	3 (60%)
Abruption	0	1 (20%)
IUD	0	2 (40%)
Mortality	0	3 (60%)

LFT (AST/ALT – 1523/478) and creatinine were deranged and went into multiorgan failure and dengue severe disease. Her INR – 1.57 and aptt- 133 sec. she received 18 PC, 36 FFP, 8 platelet and recovered after 14 days of ccu stay.

The second patient had concomitant infection with falciparum malaria. She had moderate thrombocytopenia, mildly raised LFT, crepts in chest. Falcigo was started for malaria. She had PPH at the time of delivery and recovered well and discharged.

Two patients who had LSCS died and both had PPH intraoperatively. The profile and investigations are given in table. Both had stormy course in postoperative period and coagulation deteriorated rapidly platelet count -49000, apt -125, fibrinogen 120. They went into severe dengue and expired on day 3 and 4 day postoperatively.

Another patient with PPH was a term patient with IUD, she had severe thrombocytopenia (40,000) and raised LFT. She had PPH and had multiple transfusion but died of multiorgan failure.

Now we can see that PPH is catastrophic event in patients with dengue infection. Tolerance to blood loss in these patients is less as compared to normal patients. Injury to internal organs because of PPH add to the effect of dengue. Thus preventing PPH is of utmost importance and we can do this by predicting it.

We tried to find out various predictive factors for postpartum haemorrhage. As seen in Table 7. Among them low platelet count and elevated liver enzymes had P value < 0.05 and had significant correlation. Although liver is not a primary target of dengue, hepatic involvement has been detected ranging from elevated transaminase levels to acute fulminant hepatitis leading to hepatic failure.^[19]

Foetal outcome –

Dengue also affected the developing foetus. We studied various aspects as preterm birth, intrauterine growth retardation, intrauterine death and intrapartum stillbirth.

Complications of preterm birth are the single largest direct cause of neonatal deaths, responsible for 35% of the world's 3.1 million deaths a year, and the second most common cause of under-5 deaths after pneumonia.

The incidence of preterm delivery in our study was 42.3%. In an Indian study at Bengaluru by Pavanaganga *et al.* preterm delivery rate in dengue infected pregnant patients was 33%.^[20] Others have shown 17%,^[21] 22%.^[22] Yet another study by Basurko *et al.*^[23] it was as low as 4.3%.

There were 2 cases (7.7%) of intrauterine death in my study. Profile of both the patients are given in Table 8. First patient had severe dengue and was in shock. She was diagnosed with IUD at admission. Second patient had dengue with warning signs. Baby had intrapartum asphyxia. Both patients had low platelet count and raised LFT. So we can see that stillbirth occurred in patients with severe disease and those with warning signs. In a study in India incidence was 25%,^[24] 3.8% by Basurko C,^[7] 4.9% in a study in Indonesia.^[12]

Sharma *et al.*^[25] reported an increase in the incidence of foetal neural tube malformation in women who had dengue in the first quarter of pregnancy, but such an association has been demonstrated following other febrile illnesses, due to pyrexia rather than to any teratogenic effect of the virus *per se*.^[26]

Table 7: Predictive factors for postpartum haemorrhage

	PPH (n=5)	No PPH (n=42)	P
Gestational age at delivery	37.2±2.387	31.31±8.588	0.1372
Birth weight (kg±SD)	2.34±0.723	2.74±0.510	0.1193
Platelet count (×10 ³)	48.6±19.59	106.243±34.319	0.0007**
Elevated liver enzymes (>40/40) n (%)	4 (80.00%)	15 (35.71%)	0.01
Caesarian section n (%)	2 (40.00%)	6 (14.29%)	0.148

**P=0.01 level

Table 8: Profile of patients with IUD

Parity	Gestational Stage age	Plat. count	LFT (AST/ALT)	FDP/INR
G1P0L0	32 Severe dengue	1,20,000	104/64	1600/3.28
G2P0L0	39 Dengue + WS	40,000	75/122	30/1.2

Conclusion

This paper helps to get an insight of effect of dengue on pregnancy and shows us how important it is for the primary health workers to identify dengue symptoms and timely managing these patients. It helps to prognosticate the patients about the risk involved.

Identifying patients with high-risk factors, predicting PPH and properly treating these patients in intensive care unit is of utmost importance. So need of the hour is to predict and save lives.

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Conflicts of interest

There are no conflicts of interest.

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