



## RESEARCH ARTICLE

# Clinical Characteristics and Obstetric Outcome of Symptomatic Dengue Infection in Pregnancy from a Tertiary Care Center in South India

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## Abstract

Dengue, the most prevalent mosquito-borne viral infection has a wide range of clinical presentation and the incidence is on the rise in the recent past. There is a concern that dengue infection in pregnancy might be associated with adverse maternal and perinatal outcome however there is paucity in the literature available. The aim of the present study was to analyze the outcome of dengue infection which required hospitalizations and were managed in a tertiary care center. A total of 52 pregnant women of confirmed dengue infection were studied for the severity of dengue, the clinical course and obstetric outcome. Out of 52 women, 34 (65.3%) had either severe dengue or some warning sign and there were 4 maternal deaths (7.7%). Thrombocytopenia was seen in 69.2% (n = 36) of women and 21.2% required platelet transfusions. Oligohydramnios was seen in 21.3% (n = 12) and 26.9% (n = 14) of women had PROM. The caesarean section rate was 44.2% (n = 22) and there were 2 stillbirths (3.8%). Adverse maternal and perinatal outcome was more in women with severe forms of dengue especially when they present near term gestation. Prompt diagnosis and appropriate supportive management are extremely important and avoiding interventions during the critical phase equally prevents maternal morbidity and mortality.

## Introduction

Dengue is the most common vector borne disease caused by family of flavivirus and is transmitted to human beings by *Aedes aegypti* mosquito. The incidence of dengue infection is rising worldwide with 20,000 deaths annually but the knowledge on maternal and

perinatal outcome remains unclear. Since it is an endemic disease, many tropical countries like India with more than 50% of world's population is at risk of dengue infection [1,2]. Not only the infection but also the deaths associated with dengue are on the rise. There are mainly four serotypes of dengue virus. Infection with one serotype confers lifelong immunity but repeat infections can occur with other serotypes. Such repeat infections are severe which increase the morbidity and mortality [3]. Dengue infection can be mild with or without warning signs or severe damage. Pregnancy is one of the vulnerable conditions for severe form of dengue infection which can substantially increase the maternal and fetal morbidity. Studies have shown that pregnancy does not seem to increase the incidence of dengue infection but it can cause devastating complications to the pregnant women [4,5]. There is an increased risk of spontaneous abortion, pre-term birth (PTB), oligohydramnios, and maternal hemorrhage, low birth weight (LBW) and increased caesarean section but there is paucity of data in pregnant women. Also, the maternal complications are not well understood. Various studies on the effect of dengue in pregnancy have produced varied results [6-8]. Severe forms of dengue infection are often got confused with disorders of pregnancy like preeclampsia (PE) and HELLP syndrome. Nevertheless, there could be rare manifestations of dengue infection which have been described in literature as case reports



**Citation:** Thiyagalingam S, Rengaraj S, Rajamanickam S (2020) Clinical Characteristics and Obstetric Outcome of Symptomatic Dengue Infection in Pregnancy from a Tertiary Care Center in South India. J Infect Dis Epidemiol 6:133. doi.org/10.23937/2474-3658/1510133

**Accepted:** June 11, 2020; **Published:** June 13, 2020

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can further complicate the clinical management. With rise in the epidemic of dengue, there is a need to study pregnancy outcome from different parts of the world which would help in formulating evidence based management guidelines. With this background, the present study was aimed at to assess the maternal and perinatal outcome among pregnant women infected with dengue virus from a tertiary care center, South India.

## Materials and Methods

The present retrospective study analyzed data extracted from medical records of all pregnant women with dengue infection who were admitted to JIPMER, Puducherry, South INDIA from January 2014 to December 2018. As per the hospital protocol, written informed consent was taken from the patient/relative at the time of admission to undergo treatment or any procedure required for treatment. All pregnant women with H/O fever were investigated for UTI, dengue, enteric fever, malarial antigen and leptospira as per the institute policy. Both NS1 antigen and dengue specific antibody were tested for dengue infection. The laboratory confirmation of dengue infection was made when the woman was positive for either NS1 antigen or IgG/IgM antibody. The demographic details, obstetric risk factors, maternal and perinatal outcome were recorded. As per the revised WHO classification (2009), they were classified as dengue fever with or without warning signs and severe dengue and the pregnancy outcomes were expressed as percentages. The obstetric risk factors looked were oligohydramnios, premature rupture of membrane (PROM), preterm labour, ante partum hemorrhage and associated risk factors like preeclampsia and HELLP syndrome were studied. Other details like admission in intensive care, mode of delivery, post-partum hemorrhage (PPH), the need for blood transfusion and its details were also extracted. The perinatal outcomes which were looked include still birth, neonatal death and admission to neonatal intensive care unit.

## Results

There were totally 52 cases of pregnant women with dengue fever who were hospitalized during the study period. Majority (71.2%) of them were between 21 yrs to 30 yrs with mean age of  $24 \pm 3.2$  yrs. Out of 52 women, 53.8% (n = 38) were presented in third trimester, 23.1% (n = 12) of them presented before 28 weeks and two were referred after delivery and majority of them were multi parous (70%). Among those who were hospitalized with dengue 16 (30.8%) of them had severe form of dengue, 18 (34.6%) of them had dengue with warning signs and the most common warning sign was thrombocytopenia. The presentation was atypical in 2 of them who had neurological and respiratory abnormalities. The NS1 antigen was positive in 45.5% of cases whereas in 31.8% of cases both IgM antibody and NS1 antigen were positive (Table 1).

**Table 1:** Demographic and Clinical characteristics.

Characteristics	Number (n = 52)	Percentage (%)
Age in years (mean $\pm$ SD)	$24 \pm 3.2$ yrs	-
Gestational age in weeks (mean $\pm$ SD)	$35.4 \pm 1.4$ weeks	-
Oligohydramnios	12	23.1%
PROM*	14	26.9%
Previous caesarean section	12	23.1%
PE <sup>s</sup>	14	26.9%
Dengue fever without warning signs	18	34.6%
Dengue fever with warning signs	18	34.6%
Severe dengue	16	30.8%
NS1 Antigen positive	24	46.1%
Ig M antibody positive	12	23.0%
Both NS1 antigen and IgM antibody positive	16	30.8%

\*PROM: Premature rupture of membrane; <sup>s</sup>PE: Preeclampsia.

**Table 2:** Maternal outcome of women with dengue infection.

Characteristics	Number (n = 52)	Percentage (%)
Platelet $< 100 \times 10^9/L$	36	69.2%
ICU <sup>#</sup> care	24	46.2%
Abnormal LFT <sup>s</sup>	24	46.2%
Postpartum hemorrhage	13	25%
Platelet transfusion	11	21.2%
Preeclampsia with severe features	8	15.4%
Jaundice	6	11.5%
Maternal death	4	7.7%
Secondary infection	4	7.7%
MODS*	3	5.8%
Massive blood transfusion	2	3.8%
Encephalopathy	1	1.9%

<sup>#</sup>ICU: Intensive care unit; <sup>s</sup>LFT: Liver function unit; \*MODS: Multi organ dysfunction syndrome.

Thrombocytopenia (platelet  $< 100 \times 10^9/L$ ) was seen in 36 women (69.2%) and it was  $< 20,000$  in 7 women (13.6%). A total of 21.2% (n = 11) of them required platelet transfusion mainly in the peripartum period. Liver function test was abnormal in 24 women (46.2%) and all of them had mild transaminitis (raised ALT) and only 6 women had raised bilirubin. Severe preeclampsia was seen in 8 women (15.4%) among them HELLP syndrome was seen in six of them (Table 2).

The most common complication was post-partum hemorrhage (PPH) which was seen in 13 women (25%). One of the patients had reactionary hemorrhage after caesarean section which required exploration under

**Table 3:** Details of maternal death & atypical dengue.

Timing of diagnosis	Type	Mode of delivery	Platelet (10 <sup>9</sup> /L)	Maternal complications			Transfusion	Duration of Stay	Fetal outcome
<b>Maternal death</b>									
Antenatal III trimester	Severe dengue	Caesarean delivery	1.97 lakh	PE <sup>#</sup>	DIC <sup>*</sup>	PPH <sup>x</sup>	8 platelets 4 FFP 12 cryo	6 days	LB <sup>§</sup>
Antenatal III trimester	Severe dengue	Low forceps delivery	17,000	PE with severe features	DIC <sup>*</sup>	PPH <sup>x</sup>	2 Packed cells 8 platelets 4FFP	1 day	SB <sup>^</sup>
Postpartum Day 1	Severe dengue	Caesarean delivery	23,000	HELLP syndrome	Metabolic acidosis	PPH <sup>x</sup>	9 platelets 1 Packed cell	3 days	LB <sup>§</sup>
Postpartum Day 2	Dengue with warning signs	Vaginal delivery	22,000	PE Abruptio placenta	DIC <sup>*</sup>	PPH <sup>x</sup>	8 platelets 6 cryo 2 Packed cells	3 days	SB <sup>^</sup>
<b>Atypical dengue</b>									
32 weeks	Dengue with warning signs	Vaginal delivery at term	< 15,000	B/L pleural effusion	Gall bladder edema	Nil	Nil	5 days	LB <sup>§</sup> SGA <sup>%</sup>
36 weeks	Dengue with warning signs	Caesarean section	17,000	Reactionary hemorrhage	Dengue encephalopathy	PE <sup>#</sup>	2 Packed cells 4 platelets	24 days	LB <sup>§</sup> SGA <sup>%</sup>

<sup>#</sup>PE: Preeclampsia; <sup>\*</sup>DIC: Disseminated intravascular coagulation; <sup>x</sup>PPH: Postpartum hemorrhage; <sup>§</sup>LB: Live born; <sup>^</sup>SB: Still born; <sup>%</sup>SGA: Small for gestational age.

anaesthesia. There were two patients who had massive PPH required massive transfusion and were managed medically and 8 women had hemorrhage during caesarean section. A total of 24 women required ICU care among them ventilatory support was needed in six women. Sepsis was present in 4 women and 3 women had multi organ dysfunction syndrome. There were 4 (7.7%) maternal deaths noted in our series and all of them had severe form of dengue. The details of the maternal deaths were given in [Table 3](#).

There were 2 atypical forms of dengue, one presented at 28 weeks with fever and primary respiratory problems in emergency medicine later she went on to develop massive pleural effusion, ascites and gall bladder edema. She was evaluated extensively and responded with supportive measures for dengue in addition to pleural fluid aspiration twice. She was discharged after a short period of hospital stay and she carried the pregnancy till term and had an uneventful peripartum period. The other patient presented with PPROM at 36 weeks, an emergency section was undertaken in view of monoamniotic twin. She presented with features of encephalopathy 48 hours later and had vomiting, dehydration and low BP. The low platelet count and raised AST which were associated with encephalopathy after delivery was confused with HELLP syndrome and Posterior reversible encephalopathy syndrome (PRES). There was

a transient H/O fever 2 days before admission which was not associated with any other specific symptoms and during evaluation she was found to have dengue infection. However the BP was normal and she responded well to supportive measures under intensive care monitoring and got discharged after 3 weeks of hospital stay.

There were no miscarriages or pre term deliveries observed in the present study and the mean gestational age at delivery was 35.4 ( $\pm$  1.4) weeks. Oligohydramnios with AFI of < 5 was seen in 14 women (26.9%) whereas FGR was seen in 23.1% (n = 12) of women. The caesarean section rate was 44.2% (n = 23) in the present study and 19.2% (n = 10) had operative vaginal deliveries. The most common indication for caesarean section was fetal distress (n = 11) followed by secondary arrest of dilation (n = 6).

Totally 14 (27.3%) babies were shifted to NICU and there were 2 still births. The common indication for admission to NICU was for respiratory distress. Ten babies were born alive when the mother had acute febrile illness and three of them were positive for dengue infection. There was one baby with severe thrombocytopenia which required platelet transfusion.

## Discussion

Out of 52 women with dengue fever in pregnancy,

16 (30.8%) were diagnosed with severe dengue and all of them were in third trimester. There were two women with atypical presentation and both of them had uneventful outcome after appropriate supportive management. Dengue in pregnancy requires admission and prompt evaluation as the course is quiet unpredictable especially towards term. The number of cases diagnosed with dengue infection rises every year. In endemic areas like India, the sero positivity increases with age and young women are at increased risk of acquiring infection [9]. Even though pregnancy as such does not put the women at increased risk of acquiring dengue infection, when it occurs late in third trimester the severity is more [10]. Out of 52 women who were hospitalized with dengue majority (65.4%) of them were either severe dengue or with warning signs. This could be due to the fact that all women without warning signs would not have hospitalized and being a tertiary care center it catered all severe forms of dengue. In our case series majority of them presented in third trimester (73%) which is slightly more than other studies in the literature (57.4%) [8]. None of them presented in first trimester and 12 women had dengue infection between 14 to 28 weeks. The distribution of dengue fever is almost similar across trimesters in various studies but the hospitalizations are more in third trimester [7-9]. Fever in third trimester prompts pregnant women to seek health care could be the reason for more number of hospitalizations in third trimester. Severe forms of dengue and case fatality rate were also more in the third trimester than in earlier gestational age. The adverse outcome of dengue fever is also more when it occurs in the third trimester and more so when intervention is required during critical phase either due to PE or PROM. Oligohydramnios (23.1%) and PROM (26.9%) were the common obstetric complications and it was slightly lower than other studies. Various Indian (52%) and Brazilian (40%) studies have also shown an increased rate of oligohydramnios [6,11-13]. Even though the exact reason is not clearly understood it could be due to fever and dehydration associated with dengue fever of near term pregnancy. Hydration should be maintained adequately throughout the febrile phase and it is the key factor in the management of dengue fever to avoid complications. The mortality rate in the present series was 7.7% and all of them had severe forms of dengue. The mortality rate among pregnant women with dengue is generally high in various studies varies from 2.6% in a Columbia study to as high as 21.7% in a study from South Sudan [6,8,14,15]. The mortality rate is high in severe form of dengue and the most common cause of death is hemorrhage. The case fatality rate shown in a Brazilian study by Machado, et al. from Rio de Janeiro was 3 fold higher in women with severe dengue (OR 3.38; 95% CI 2.10-5.42) [15]. Severe dengue was associated with high maternal morbidity and mortality and all of them had clinical picture similar to that of severe pre-eclampsia/HELLP syndrome in the present study. This added to the

clinical dilemma and the intervention especially in the critical phase added to the morbidity and mortality of severe dengue. The mortality rate was more in pregnant women compared to non-pregnant women (18% vs. 3-5%) [6]. The exact reason for such high fatality rate has been reviewed in various studies include increased predisposition to severe dengue in pregnancy and the hemoconcentration associated with pregnancy as well dengue might lead to difficulty in diagnosing common clinical problems of pregnancy like PE. Moreover, there is a meta-analysis on the effect of infection in pregnancy showed the predisposition for the development of PE is more in women who had viral infection even though there is no direct relationship with dengue infection. Studies have shown the death rate among women with PE was 25% with dengue compared to 19% without dengue [6]. Infection with dengue has been associated with inflammatory damage of placental tissue similar to that of PE could also explains increased association with PE/HELLP syndrome [14,16,17]. There were no cases of abortion or neonatal deaths. Three of the neonates had dengue infection as majority of the women presented in third trimester. IgG antibodies will start elevated after a week following infection and it rises further. Usually the newborn is protected by the transplacental transfer of IgG antibodies. Various studies have shown that the protective effect of these maternal antibodies could cause severe dengue later in their life [18]. The fetal adverse effects are mainly due to endothelial damage and enhanced vascular permeability that occurs in placental bed [9,15].

Dengue is characterized by rapid platelet destruction. In the present study almost 50% of patients had severe thrombocytopenia and 22.7% required platelet transfusion where Nidhi, et al. had shown almost 50% of them required platelet transfusion [9]. In an asymptomatic patient platelet transfusion is not mandatory unless intervention is required. The cut off point for platelet transfusion was < 50,000 for operative delivery and < 75,000 for regional delivery. Two of the women who were referred also had thrombocytopenia and tachycardia after caesarean section and was found to be dengue infection later. The commonest form of liver dysfunction as seen in many studies is mild transaminitis as evidenced by elevation of both Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT). The extent and severity of liver dysfunction is more in severe forms of dengue compared to other types. In the present study it was 75% in women with severe dengue, 55% and 11.1% with and without warning symptoms respectively which was in concordance with literature. Some of the studies have shown a higher prevalence of transaminitis (90-100%) in women with severe dengue [8,11,13,16].

Early diagnosis, prompt supportive management and adequate hydration can reduce fatality from dengue infection. Following dengue infection, only dengue



antigen used to be positive for the initial few days, followed by IgM antibodies will start rising after a week. Late presentation with dengue specific antibodies will put the women at risk of developing complications. Early diagnosis of dengue in initial stages will reduce its morbidity and mortality.

Induction of labour has no role in improving the obstetric outcome in dengue infection unlike preeclampsia. But when women presents little late in dengue with thrombocytopenia especially in third trimester the clinical dilemma arises for termination of pregnancy especially in the presence of hypertension. Moreover, dengue infection per se can be associated with mild elevation of liver enzymes which further complicates the clinical situation. The diagnosis of HELLP syndrome can be easily presumed when there is a blood pressure of 140/90 or more, proteinuria with thrombocytopenia and/or elevated liver enzymes. However one third of HELLP syndrome can have normal blood pressure. Thorough understanding of underlying clinical situation is mandatory and even if termination is required in view of severe PE the underlying hemodynamic abnormality has to be corrected before operative interventions. Oligohydramnios is other situation which might warrant delivery especially in third trimester. There was high rate of caesarean section in the present series (44.2%) compared to other studies and it was done mainly for fetal distress [6,9,12,13,16]. Antipyretics and maintaining euvoemia are extremely important. It is better to avoid induction of labour for oligohydramnios as well thorough assessment to rule out PE/HELLP syndrome during febrile and critical phase of dengue as operative delivery may further complicate the clinical condition and increases maternal mortality.

Sepsis in pregnancy is an important cause of morbidity and mortality. Co-infection with dengue has been reported in previous studies. Singla, et al. had showed there was a co infection with malaria and enteric fever [9]. There were four cases of secondary infection in women with severe dengue in the present series.

## Conclusion

Dengue in pregnancy needs early diagnosis and appropriate treatment. Even though dengue fever has a favourable outcome in pregnancy, severe forms of dengue are associated with adverse maternal and fetal outcome despite appropriate measures. Managing a pregnant woman with dengue is quite challenging and our knowledge on maternal and perinatal outcome is limited. The present study has shown that adverse maternal outcome is more in women with severe forms of dengue especially close to term when intervention was required for obstetric indications. At community level general preventive measures like mosquito nets/repellants use, avoiding travel to endemic areas, awareness and education about dengue fever play a major role however, maintaining euvoemia and antipyretic man-

agement are the two important principles of management of dengue fever. Obstetric interventions are best avoided in the critical phase as it is invariably associated with adverse maternal outcome.

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