#### MATERNAL-FETAL MEDICINE



# Maternal and fetal outcomes of dengue fever in pregnancy: a large prospective and descriptive observational study

Rinnie Brar<sup>1</sup> · Pooja Sikka<sup>1</sup> · Vikas Suri<sup>2</sup> · Mini P. Singh<sup>3</sup> · Vanita Suri<sup>1</sup> · Ritin Mohindra<sup>2</sup> · Manisha Biswal<sup>4</sup>

Received: 12 October 2020 / Accepted: 27 November 2020 / Published online: 2 January 2021 © The Author(s), under exclusive licence to Springer-Verlag GmbH, DE part of Springer Nature 2021

# Abstract

**Purpose** The primary objective of the study was to assess maternal and fetal outcomes of pregnancies affected with dengue fever.

**Methods** This was a prospective, observational and descriptive study carried out over a period of 1 year. 216 pregnant women with fever were screened. Of these, 44 women tested positive for dengue (non-structural protein antigen 1 or dengue IgM antibodies in the sera). The clinical and laboratory characteristics of women with dengue were recorded. Maternal outcomes, pregnancy outcomes and fetal outcomes were studied.

**Results** Mean period of gestation was  $31.89 \pm 7.31$  weeks. Thrombocytopenia was seen in 23 (52.3%) women. Of 40 women, 10 (25%) developed post-partum haemorrhage. The incidence of maternal systemic complications was high: eight (18.2%) women developed acute kidney injury and two (4.5%) required haemodialysis support; eight (18.2%) women developed ARDS and seven (15.9%) women required ventilatory support; four (9.1%) women developed acute liver failure. 18 (40.9%) women had evidence of shock. Seven (15.9%) women died and another seven (15.9%) were classified as WHO maternal near-miss cases. Two (4.5%) pregnancies suffered from miscarriages, four (9%) from still births and two (4.5%) from neonatal deaths. Preterm babies were delivered in 15 (34.1%) and low birth weight babies in 13 (29.5%).

**Conclusions** Dengue in pregnancy adversely affects maternal and fetal outcomes with high maternal mortality of 15.9%. Prematurity and postpartum haemorrhage are significant risks to mother and baby. Vector control strategies should be implemented with vigour in affected areas.

Keywords Arbovirus · Dengue · Dengue fever · Infectious diseases · Pregnancy

Pooja Sikka drpoojasikka@yahoo.com

- <sup>1</sup> Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India
- <sup>2</sup> Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India
- <sup>3</sup> Department of Virology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India
- <sup>4</sup> Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India

# Introduction

Dengue fever a mosquito-borne febrile illness has rapidly emerged as the most common arboviral infection globally. It is caused by dengue virus, a single positive stranded RNA virus belonging to the family Flaviviridae. Dengue is transmitted by the bite of mosquito Aedes aegypti and Aedes albopictus. It is a major public health problem, especially in tropical and sub-tropical areas worldwide [1]. According to the World Health Organization (WHO), approximately 40% of the world's population (over 2.5 billion people) live in areas with high risk of contracting dengue infection [2]. The disease still has the potential to cause massive outbreaks in regions from where it has been previously eliminated, including areas of United States and Europe [3]. The ability of the virus to cause explosive outbreaks has led public health professionals across the globe to step up their efforts to control this disease.

A systematic review of pregnancy outcomes due to maternal dengue in 2016 described the complications of dengue in pregnancy, including increased rates of caesarean deliveries, pre-term births and low birth babies. However, the review could not establish whether maternal dengue is a risk factor for adverse pregnancy outcomes because majority of the literature available on the matter comprised of only small studies (19 case reports, 9 case series and 2 comparison studies) [4]. Since then, there has been no major advancement of research on the topic and literature search has exposed a dearth of well conducted prospective studies ascertaining the course of pregnancies with dengue. This is the first large prospective and descriptive study carried out at a tertiary care and referral hospital in India, which aimed to ascertain maternal outcomes associated with dengue, and the impact of dengue on pregnancy, fetal and neonatal outcomes.

# Methods

# Study setting and design

This study was a hospital based prospective observational study, conducted over a period of 12 months from 1st July 2016 to 30th June 2017. The study was conducted in Post Graduate Institute of Medical Education and Research, a tertiary health care hospital in Chandigarh, which caters to the parent Union Territory and the neighbouring states of Punjab, Haryana, Himachal Pradesh, some parts of Uttar Pradesh and Jammu and Kashmir and is a major referral centre for high risk pregnancies. All pregnant women who presented to the obstetric emergency services of the institute with fever were screened for enrolment in the study.

A total of 216 pregnant women presented with fever, out of which every consecutive antenatal woman with dengue fever, diagnosed by the positivity of non-structural protein antigen 1 (NS1 antigen) or dengue IgM antibodies in the sera, irrespective of gestational age at presentation over the period of study were included in the study. A total of 44 women were diagnosed with dengue and were included in the study. The study was approved by the institutional ethics committee and institutional review board. Written informed consent was obtained from all the participating women.

# Patient management and data collection

Detailed medical history, examination and investigations were performed as per the standard institutional protocols followed in obstetric emergency department and data obtained were recorded on case record sheets. Demographic data, symptomatology, clinical findings and laboratory parameters, including complete blood counts, liver transaminase enzymes aspartate transaminase (AST) and alanine transaminase (ALT), renal function tests and coagulation profile (prothrombin time, activated partial thromboplastin time, international normalised ratio) were recorded. Further testing was done depending upon the clinical condition of patients. Women were managed according to the institute protocol and all necessary treatment and care was provided.

Maternal outcomes including any complications that developed, including shock, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) and acute liver failure were recorded. All deaths and WHO maternal near miss cases [5] were recorded in detail. Need for various supportive therapies, including intravenous fluids, blood and blood products, inotropes, ventilatory support and hemodialysis was also recorded. Women were discharged when assessed to be medically stable and by clinical judgement of their obstetric condition. The duration of hospital stay was noted for all women.

#### Follow up

All women were followed up prospectively with clinical and laboratory assessments till discharge from hospital after delivery. Out of the total 44 women, 1 was lost to follow-up, 2 did not deliver by the end of the study period and 1 died in the pregnant state with fetus undelivered. Hence, labour details were noted and neonatal outcomes were assessed for the remaining 40 women.

#### Laboratory testing

Dengue IgM antibodies (DENV IgM) were detected using ELISA (NIV, Pune) if presentation was more than 3–5 days after the onset of clinical symptoms and/or NS1 antigen assay (Pan Bio, Queensland, Australia) if the presentation was within 3–5 days after the onset of clinical symptoms. Complete blood counts were analysed in the Institute's emergency laboratory equipped with a Sysmex KX-21N automated hematology analyser from Sysmex Corporation, Kobe, Japan, which has a daily quality control check by the laboratory. Transaminases, serum urea and creatinine were analysed in the Institute's central laboratory equipped with a Cobas 8000 analyser from Roche Hitachi Corporation, Japan.

# Results

A total of 44 pregnant women tested positive for dengue over the course of study period. The mean age of women was  $24.5 \pm 0.71$  (range 18–37) years. Two (4.5%) women presented in the first trimester, 5 (11.4%) in the second trimester and 37 (84.1%) in the third trimester of their pregnancy. The mean period of gestation was  $31.89 \pm 7.31$  weeks. Thirty (68.2%) women were referred to our institute secondary to dengue, 11 (25%) women had their pregnancies booked at our institute and 3 (6.8%) women did not get their pregnancies booked at any health centre. Twenty-three (52.3%) women were primigravid women and 21 (47.7%) were multigravid women. Twenty-three (52.3%) women were primigravid women and 21 (47.7%) were multigravid women. Twelve (27.2%) women had anaemia, ten (22.7%) women had hypothyroidism, two (4.5%) had chronic hypertension and two (4.5%) had overt diabetes at the time of admission.

All 44 women reported fever. The median temperature at admission was 100.0 °F (range 99.9–104.2 °F). Other complaints that were most commonly reported were myalgias in 40 (90.9%) followed by arthralgias in 39 (88.6%) (Fig. 1). 22 (50%) women presented with warning signs on admission; these signs included vomiting (21/44, 47.5%), behavioural changes (4/44, 9.1%), difficulty in breathing (3/44, 6.8%), abdominal pain 3/44 (3/44, 6.8%), altered sensorium (2/44, 4.5%), seizures (1/44, 2.3%), jaundice (1/44, 2.3%) and loss of consciousness 1/44(1/44, 2.3%) in overlapping incidences.

Diagnosis of dengue was based on the positivity of dengue NS1 antigen or DENV IgM antibody as depicted in Table 1. Of the 27 women who demonstrated positivity for NS1 antigen, 24 (88.9%) presented within 5 days of symptom onset.

Three women had co-infections (6.8%) with other pathogens as well. One woman was diagnosed with co-existent

Table 1 Diagnostic testing of 44 pregnant women with dengue fever

	NS1 Ag positive	Dengue IgM antibody posi- tive
At admission		
Number of women (%)	27 (61.4%)	17 (38.6%)
At discharge		
Number of women (%)	6 (13.6%)	30 (68.2%)

pulmonary tuberculosis on the basis of microbiological examination of sputum smears. Two women had co-existent urinary tract infections on the basis of clinical and microbiological grounds with urine culture showing growth of *Escherichia coli* in both women.

Maternal outcomes have been listed in Table 2. The most common complication observed was maternal thrombocytopenia. Twenty-three (52.3%) women had platelet counts less than 100,000/ $\mu$ L and 19 (43.2%) of them had severe thrombocytopenia with platelet counts less than 50,000/ $\mu$ L. Eighteen (40.9%) women developed circulatory shock. Eight (18.2%) developed AKI and two of them required haemodialysis. Eight (18.2%) developed ARDS of which seven (15.9%) required ventilator support. Four (9.1%) women developed acute liver failure.

On follow-up, 2 (5%) of 40 women developed preeclampsia. Both had underlying chronic hypertension

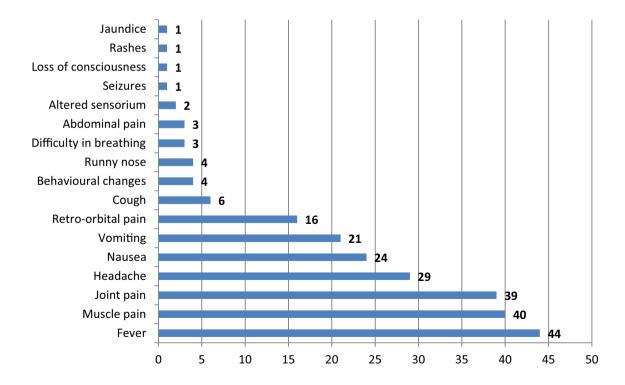


Fig. 1 Symptomatology of a cohort of 44 pregnant women with dengue fever at admission

**Table 2** Maternal outcomes of acohort of pregnant women withdengue fever

	Number of cases (%)
Preeclampsia $(n=40)^*$	2 (5%)
Preterm labour (28–36 weeks) $(n=40)^*$	12 (30%)
Latency between infection and delivery (in weeks) $(n=42)^*$	
<1 week	23 (54.7%)
1–3 weeks	2 (4.8%)
>3 weeks	17 (40.5%)
Labour outcomes $(n=40)^*$	
Vaginal deliveries, including instrumental vaginal deliveries	26 (65%)
Caesarean deliveries	14 (35%)
Indications of caesarean deliveries:	
a) Meconium stained liquor	2
b) Abruption	4
c) Fetal distress	6
d) Previous 2 caesareans in labour	1
e) Placenta praevia	1
Post-partum hemorrhage $(n=40)^*$	10 (25%)
Establishment of breastfeeding $(n=40)^*$	22 (55%)
Pyoperitoneum and puerperal sepsis $(n=40)$	2 (5%)
Post-partum antibiotics $(n=40)^*$	32 (80%)
Thrombocytopenia $(n = 44)^*$	23 (52.3%)
Shock $(n = 44)^*$	18 (40.9%)
Acute kidney injury $(n=44)^*$	8 (18.2%)
Acute respiratory distress syndrome $(n=44)^*$	8 (18.2%)
Acute liver failure $(n=44)^*$	4 (9.1%)
Maternal near miss $(n=44)^*$	7 (15.9%)
Maternal deaths $(n=44)^*$	7 (15.9%)

<sup>\*</sup>Out of total 44 women, 1 woman was lost to follow up, 1 woman died in the antenatal period and 2 women did not deliver by the end of study period

pre-pregnancy. Two (5%) women developed pyoperitoneum and severe puerperal sepsis in the post-partum period; one woman required pigtail drainage of pyoperitoneum and one woman required laparotomy and drainage of the collections. Both of them had delivered vaginally. Out of 40 women who delivered, 10 (25%) experienced post-partum hemorrhage. Of these, three women required Bakri balloon uterine tamponade, one woman required drainage of vulval hematoma, and the rest were managed with pharmacological methods. Out of total 44 women, 11 (25%) required platelet transfusions, 8 (18.2%) required packed red cell transfusions and 8 (18.2%) required fresh frozen plasma transfusions.

Of the 40 women who delivered, 26 (65%) delivered vaginally and 14 (35%) delivered by caesarean delivery. Out of the 14 caesarean sections, 1 was performed under regional anaesthesia after recovery from dengue fever when haematological and biochemical parameters had returned to normal and 13 were performed under general anaesthesia. There were no anaesthetic complications. Indications of caesarean deliveries are mentioned

in Table 2. The mortality rate was similar among women who delivered vaginally (3 of 26) and those who delivered via caesarean delivery (3 of 14) (P = 0.698).

A total of seven (15.9%) women died and seven women were WHO maternal near-miss women. Demographic details, clinical findings, laboratory findings and fetoneonatal outcomes of women who experienced death and of those who became WHO maternal near miss have been listed in Tables 3 and 4, respectively. All women who succumbed to the disease had body temperatures between 100-102 °F, platelet count less than 100,000/µL, deranged liver transaminases > 2 times the upper limit of normal for our laboratory. There was no period of latency between presentation with dengue fever and onset of labour in these women. Among the seven cases of maternal deaths, there were five women who presented at gestations beyond the age of fetal viability (>28 weeks), and all of these women had live births with no neonatal complications. Fetal and neonatal outcomes have been listed in Table 5. Both neonatal deaths occurred in the neonatal intensive care unit.

Neonatal outcome	LB, 3 kg	Death in antenatal period	LB, 2.4 kg	SB, 500 g	SB, 500 g
Duration of stay (days)	45	-	×	24	Few hours
Post partum compli- cations/ Cause of death	Puerperal sepsis with pyoperi- toneum, MODS/ Refrac- tory septic shock	Death in antenatal period/ Severe ARDS	MODS/ Severe ARDS, AKI	MODS/ Severe ARDS, AKI, Refrac- tory shock	MODS/ multiple seizures, Refrac- tory shock, Severe
Mode of delivery	CS	Death in ante- natal period	Vaginal	Vaginal	Vaginal
POG at delivery (weeks)	38	Death in ante- natal period	35	24	24
Blood and product transfu- sions	Yes	No	No	Yes	No
IgM antibody	+	I	+	I	+
Antigen	1	+	I	+	I
ITT	78	50	84	86	76
ALT (IU/L)	85	290	150	624	273
AST (IU/L)	183	376	133	284	155
Serum creati- nine (mg/dL)	1.8	1.1	1.1	2.5	1.4
Platelet count (/ µL)	31,000	5000	68,000	62,000	8000
Tempera- ture (°F)	101	100	101.6	101.2	100
POG (weeks)	38	37	35	24	24
Gravida status	G2P0A1	G2P1L1	GIP0	G3P2L2	GIP0
Age (years)	29	22	19	37	28
		7	3	4	Ś

Age (years)	Gravida POG status (weeks	POG (weeks)	Gravida POG Tempera- Platelet status (weeks) ture (°F) count (/ µL)	Tempera- Platelet Serum ture (°F) count (/ creati- µL) nine (mg/dL	Serum creati- nine (mg/dL)	AST (IU/L)	ALT (IU/L)	PTI NS1 Antig	en	IgM antibody	Blood and product transfu- sions	POG at delivery (weeks)	Mode of Post delivery partu comp catio Caus deatl	Post partum compli- cations/ Cause of death	Duration Neonatal of stay outcome (days)	Neonatal outcome
6 32	G3P2L2 36	36	100	97,000 3.1	3.1	380	373	56 +	+	1	Yes	36	CS	PPH, MODS/ AKI, ALF, Coagu- lopathy	10	LB, 2.3 kg
25	GIPO	38	100.4	89,000 2.4	2.4	10,547	3521	33 +	+	I	Yes	38	CS	PPH, MODS	5	LB, 2.7 kg

#### Discussion

It has been reported that dengue is the most common cause of fever in pregnancy [6]. Therefore, our study aimed to describe in detail its maternal, pregnancy and fetal outcomes. Most women in our study were in the third trimester of pregnancy at the time of diagnosis. This is similar to results published by other studies [7–12]. This is likely because women at early gestations and dengue are managed by internists at most hospitals, while those at later gestations are managed by obstetricians due to obstetric concerns like labour.

Often, there are cases where false diagnosis of dengue is present, due to false serologic positivity for NS1 antigen or IgM antibody, where clinical features are absent [13]. We screened only those women for inclusion in our study who presented with fever, thereby reducing the number of false positive cases due to serologic positivity solely, which could have confounded the results of our study. Symptoms of dengue observed in our study were similar to symptoms observed in other studies on pregnant and non-pregnant women with dengue [14–16] with myalgia and arthralgias present in more than 90% of women.

There was one case with co-existent pulmonary tuberculosis. She presented with low grade fever for 2 weeks. On evaluation, dengue NS1Ag was positive. However, her symptoms did not abate even after 2 weeks. On further work up, her sputum smear was positive for acid fast bacilli and she was diagnosed with pulmonary tuberculosis. Here, the NS1Ag positivity could be false positive, however, she demonstrated seroconversion after 1 week testing positive for DENV IgM antibodies confirming that she had dengue fever.

Half the women presented with warning signs of severe dengue at admission. Severe thrombocytopenia, which is a feature of dengue hemorrhagic fever was present in 43.2% of the women in our study. Previous studies have demonstrated rates of thrombocytopenia in pregnant women with dengue between 48–100%. [8, 10, 14, 17]

Our study has demonstrated a high rate of adverse maternal outcomes for pregnant women with dengue, as 31.8% women had severe maternal outcomes (maternal near miss cases + maternal deaths). Dengue infection causes activation of immune system to release of cytokines and chemokines, endothelial cell autophagy and T cell apoptosis; all of these factors lead to endothelial cell dysfunction, which in turn leads to plasma leakage, contraction of intravascular volume and third space fluid loss. Depletion of intravascular volume leads to features of shock and hypoperfusion of various organs, instituting a cascade of hypoxic injury in various organ systems leading to shock and multi-organ dysfunction, which is

	) status	(weeks)	perature (°F)	r tated (/ puL)	Serum creati- nine (mg/ dL)	AST (IU/L)	ALI (IU/L)	Antigen	ng nati- body	Blood and product transfu- sions	POG at delivery (weeks)	Mode of delivery	Post partum compli- cations	Dura- tion of stay (days)	Neonatal outcome	MNM criteria
1 32 Maior interv	1 32 G4P1L1A2 30 100.4 9000 0.43 140 64 100 – + Maior interventions: Bakri halloon interine tannonade backed red cell and platelet transfusions ionotrone infusions	30 30 alloon ute	100.4	9000 Share of the state	0.43 ed red cel	140 I and nateld	64 et transfisei	100 – ans ionotrom	+ fisions	Yes	37	Vaginal	Hdd	15	LB, 2.9 kg	Cardio- vascular (shock), Coagu- lation*
2 24	G4P1L1A2	35	104	140,000 0.72	0.72	1090	340	100 -	+	Yes	36	CS (abrup- tion)	Puer- peral sepsis	20	LB, 2 kg	Cardio- vascular (Shock)
Major interv 3 29	Major interventions: Pigtail drainage for pyoperitoneum, ionotropes' infusions 3 29 G3P2L1 32 11 120,000 0.7 236 Mission interventional ANY / 2000 1000 1000	drainage fo 32	or pyoperit 11	120,000	notropes' i 0.7	infusions 236	128	- 68	+	No	32	Vaginal	ARDS	Ś	LB, 1.96 kg	Res- piratory (ARDS)
1 28 4 28	GIPILI GIPILI	(11011 111 Vas	100 100	25,000	1.8	528 (Total bili- rubin: 6.2 mg/ d1)	166	93 +	I	Yes	35	CS (fetal dis- tress)	Hdd	52	LB, 1.8 kg, NICU stay	Liver, coagu- lation*
Major interv 5 30	Major interventions: Bakri balloon uterine tamponade, packed red cell and platelet transfusions         5       30       G2P1L1       35       102       5000       0.5       81       34       8	aalloon ute 35	erine tampc 102	onade, pack 5000	ed red cel 0.5	ll and platele 81	et transfusi 34	ons 86 +	I	Yes	38	CS (fetal dis- tress)	I	17	LB, 2.5 kg	Coagula- tion*
Major interv 6 21	Major interventions: platelet transfusions 6 21 G1P0 31 1(	t transtusio 31	ons 103	36,000	2.8	237	318	- 26	+	Yes	32	CS (abrup- tion)	I	٢	LB, 1.5 kg, NICU stay	Coagula- tion*
Major interventions 7 25 G3F Interventions: none	Major interventions: platelet transfusions725G3P2L13810Interventions: none	t transfusio 38	ons 102	48,000	1.8	47	124	93 +	I	No	39	Vaginal	I	٢	LB, 3.2 kg	Coagula- tion*

Number (%)
2 (4.5%)
8 (18.2%)
4 (10%)
4 (10%)
1 (2.5%)
15 (37.5%)
13 (32.5%)
5 (12.5%)
3 (7.5%)
2 (5%)

 Table 5
 Fetal and neonatal consequences of the cohort of pregnant women with dengue fever

a frequent cause of death in dengue [18], as also seen in our study. Multiorgan dysfunction syndrome particularly ARDS and AKI, were accompanying factors in most cases of dengue deaths in our study and they have been shown to be strong predictors of mortality in non-pregnant patients with dengue [19]. Therefore, organ dysfunction in pregnant women with dengue requires vigilant monitoring and intensive management in ICU, to salvage such women. Elevated serum transaminases and creatinine levels have also been found as independent predictors of mortality in non-pregnant dengue patients [20]. In our study also, we found that all women who died had both these features. Further studies are needed to determine predictors of mortality in pregnant dengue women.

In our study, rate of caesarean deliveries in pregnant women with dengue was 35%. This is similar to the rate of caesarean delivery in pregnant women without dengue at our institute in 2017, which was 41.3%. In a previous study also, it has been shown that there is no increase in caesarean section rates in dengue positive pregnant women [21]. There were no anaesthetic complications noted in our study. Although, in our study, only one patient had caesarean delivery under regional analgesia, that too after recovery from dengue fever, safety of regional anaesthetic techniques in cases of mild thrombocytopenia has been reported [22].

We found high incidences of post-partum hemorrhage, post-partum sepsis, shock, AKI, ARDS and acute liver failure in our study. Post-partum hemorrhage, due to dengue associated thrombocytopenia is a significant concern in pregnant women with reported rates of 2.2–30% [7, 8, 14, 23]. We found a post-partum hemorrhage rate of 25%. Active management of the third stage of labour, intensive monitoring and management, accompanied with blood and products' transfusion is required to manage such cases. Rates of AKI, ARDS, and acute liver failure in our study on pregnant women are similar to those found in studies on non-pregnant patients [24]. No other study till date has evaluated organ system dysfunctions in pregnant women with dengue.

80% women received post-partum prophylactic antibiotics in our study. Despite that, puerperal sepsis was encountered in eight women, out of which two women developed pyoperitoneum. One woman required laparotomy and drainage of pyoperitoneum; however, she developed MODS and succumbed on post-partum day 42. The second case of pyoperitoneum required pigtail drainage and was a maternal near miss case. It remains debatable whether dengue is a risk factor for puerperal sepsis. Overlapping features of dengue and puerperal sepsis such as fever, hematologic and biochemical abnormalities make differentiation between the two difficult. Also, because of frequent institution of prophylactic antibiotics in the post-partum period, cultures often return sterile. Differentiation between the two can be made easier using serum procalcitonin levels [25]. However, serum procalcitonin levels cannot be used reliably in cases of kidney injury and sound clinical judgement is needed in these cases [26].

In our study, we had two cases in the first trimester and both of them suffered from miscarriages. A prospective case control study from 2012 studying the relationship between dengue infection and miscarriage found that, even after adjustment for confounding factors, there is a positive relationship between dengue and miscarriage [27]. However, updated meta-analyses from 2017 demonstrated that dengue infection in pregnant women did not increase the risk of adverse fetal outcomes, including miscarriage and preterm births [28]. We found 11.4% rate of still births. Rates of still births in previous studies have been reported from 3.8 to 13.1% [7, 8, 14, 23]. However, further research is needed to establish whether these increased rates of fetal loss are secondary to the effects of hyperthermia or to dengue virus and its effects.

We report one case of fetal malformation. The woman was referred to us at 22 weeks of POG due to fetal hydrocephalus. She contracted dengue infection at 40 weeks POG. Though maternal dengue related hyperthermia has been postulated to be associated with fetal neural tube effects [29], this case's findings are purely incidental as hydrocephalus had developed much earlier.

The rates of fetal adverse outcomes in our study were high with 10% FGR, 37.5% pre-term births and 32.5% low birth weight babies. Two metanalyses on adverse fetal outcomes in pregnancies with dengue reveal conflicting results regarding the association of dengue with preterm births and low weight births [28, 30]. Till concrete evidence is available, it is reasonable to perform sequential fetal growth monitoring in pregnant women with dengue to screen for FGR and still births, and to keep neonatal facilities when such women are admitted in anticipation of preterm births and low weight births. Due to the non-availability of fetal samples for serological reporting, it is not possible for us to comment on the perinatal transmission of dengue.

This study was hospital-based and hence, this study does not evaluate the profile of pregnant women with dengue in the community. Ours is the largest referral centre of the region catering to four large north Indian states and receives a high load of high risk and complicated pregnancies. Therefore, the complication rate may not be representative of the true complication rates in the community.

# Conclusions

Dengue in pregnancy adversely affects maternal and fetal outcomes with high maternal mortality of 15.9%. Preterm labour and postpartum haemorrhage can cause significant morbidity to the baby and mother. Because of such morbidity and mortality rates, vector control strategies should be implemented with vigour in affected areas.

Authors' contributions RB: Protocol development, data collection and management, data analysis, manuscript writing. PS: Protocol development, data collection and management, data analysis, manuscript editing. VS: Protocol development, data analysis. MPS: Protocol development, data analysis. VS: Protocol development, data analysis. RM: Data analysis. MB: Protocol development, data analysis.

Funding No funding sources.

Availability of data On request.

#### **Compliance with ethical standards**

**Ethical approval** The study was approved by the Institutional Ethics Committee, PGIMER, Chandigarh vide number INT/IEC/2017/1116.

Conflict of interest None.

# References

- Guo C, Zhou Z, Wen Z, Liu Y, Zeng C, Xiao D et al (2017) Global epidemiology of dengue outbreaks in 1990–2015: a systematic review and meta-analysis. Front Cell Infect Microbiol 7:317
- Fact sheet: Neglected tropical diseases: Dengue. World Health Organisation. http://origin.searo.who.int/entity/vector\_borne \_tropical\_diseases/data/data\_factsheet/en/. Accessed 17 September 2020.
- 3. Lambrechts L, Scott TW, Gubler D (2010) Consequences of the expanding global distribution of *Aedes albopictus* for the dengue virus transmission. PLoS Negl Trop Dis 4:e646
- Pouliot SH, Xiong X, Harville E, Paz-Soldan V, Tomashek KM, Breart G et al (2010) Maternal dengue and pregnancy outcomes: a systematic review. Obstet Gynecol Surv 65:107–118
- 5. Pattinson R, Say L, Souza JP, van den Broek N, Rooney C, WHO Working Group on Maternal Mortality and Morbidity

Classifications (2009) WHO maternal death and near-miss classifications. Bull World Health Organ 87:734–734

- Chansamouth V, Thammasack S, Phetsouvanh R, Keoluangkot V, Moore CE, Blacksell SD et al (2016) The aetiologies and impact of fever in pregnant inpatients in vientiane. Laos PLoS Negl Trop Dis 10:e0004577
- Tien Dat T, Kotani T, Yamamoto E, Shibata K, Moriyama Y, Tsuda H et al (2018) Dengue fever during pregnancy. Nagoya J Med Sci 80:241–247
- Basurko C, Carles G, Youssef M, Guindi WEL (2009) Maternal and fetal consequences of dengue fever during pregnancy. Eur J Obstet Gynecol Reprod Biol 147:29–32
- Yang J, Zhang J, Deng Q, Wang J, Chen Y, Liu X et al (2017) Investigation on prenatal dengue infections in a dengue outbreak in Guangzhou City, China. Infec Dis 49:315–317
- Kariyawasam S, Senanayake H (2010) Dengue infections during pregnancy: case series from a tertiary care hospital in Sri Lanka. J Infect Dev Ctries 4:767–775
- Chitra TV, Panicker S (2011) Maternal and fetal outcome of dengue fever in pregnancy. J Vector Borne Dis 48:210–213
- Basurko C, Everhard S, Matheus S, Restrepo M, Hilderal H, Lambert V et al (2018) A Prospective matched study on symptomatic dengue in pregnancy. PLoS ONE 13:e0202005
- Matusali G, Colavita F, Carletti F, Lalle E, Bordi L, Vairo F et al (2020) Performance of rapid tests in the management of dengue fever imported cases in Lazio, Italy 2014–2019. Int J Infect Dis 99:193–198
- Sondo KA, Ouattara A, Diendere EA, Diallo I, Zoungrana J, Zemane G et al (2019) Dengue infection during pregnancy in Burkina Faso: a cross-sectional study. BMC Infect Dis 19:997
- Tavakolipoor P, Schmidt-Chanasit J, Burchard GD, Jordan S (2016) Clinical features and laboratory findings of dengue fever in German travellers: a single-centre, retrospective analysis. Travel Med Infect Dis 14:39–44
- 16. Guzman MG, Harris E (2015) Dengue Lancet 385:453-465
- Machain-Williams C, Raga E, Baak-Baak CM, Kiem S, Blitvich BJ, Ramos C (2018) Maternal, fetal, and neonatal outcomes in pregnant dengue patients in Mexico. Biomed Res Int 2018:9643083
- Martina BE (2014) Dengue pathogenesis: a disease driven by the host response. Sci Prog 97:197–214
- Padyana M, Karanth S, Vaidya S, Gopaldas JA (2019) Clinical profile and outcome of dengue fever in multidisciplinary intensive care unit of a Tertiary level Hospital in India. Indian J Crit Care Med 23:270–273
- Saroch A, Arya V, Sinha N, Taneja RS, Sahai P, Mahajan RK (2017) Clinical and laboratory factors associated with mortality in dengue. Trop Doct 47:141–145
- Tan PC, Rajasingam G, Devi S, Omar SZ (2008) Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet Gynecol 111:1111–1117
- Choi S, Brull R (2009) Neuraxial techniques in obstetric and nonobstetric patients with common bleeding diatheses. Anesth Analg 109:648–660
- Carles G, Talarmin A, Peneau C, Bertsch M (2000) Dengue fever and pregnancy. A study of 38 cases in French Guiana. J Gynecol Obstet Biol Reprod 29:758–762
- Juneja D, Nasa P, Singh O, Javeri Y, Uniyal B, Dang R (2011) Clinical profile, intensive care unit course, and outcome of patients admitted in intensive care unit with dengue. J Crit Care 26:449–452
- Chen CM, Chan KS, Chao HC, Lai CC (2016) Diagnostic performance of procalcitonin for bacteremia in patients with severe dengue infection in the intensive care unit. J Infect 73:93–95
- Nakamura Y, Murai A, Mizunuma M, Ohta D, Kawano Y, Matsumoto N et al (2015) Potential use of procalcitonin as biomarker

for bacterial sepsis in patients with or without acute kidney injury. J Infect Chemother 21:257–263

- 27. Tan PC, Soe MZ, Lay KS, Sm W, Sekaran SD, Omar SZ (2012) Dengue infection and miscarriage: a prospective case control study. PLoS Negl Trop Dis 6:e1637
- Xiong YQ, Mo Y, Shi TL, Zhu L, Chen Q (2017) Dengue virus infection during pregnancy increased the risk of adverse fetal outcomes? An updated meta-analysis. J Clin Virol 94:42–49
- 29. Edwards MJ (2006) Review: hyperthermia and fever during pregnancy. Birth Defects Res A Clin Mol Teratol 76:507–516
- Paixao ES, Teixeira MG, Costa MCN, Rodrigues LC (2016) Dengue during pregnancy and adverse fetal outcomes: a systemic review and meta-analysis. Lancet Infect Dis 16:857–865

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.