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Research Article

DENGUE INFECTIONS IN PREGNANCY: CASE SERIES FROM A TERTIARY CARE HOSPITAL OF NORTH INDIA

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ABSTRACT
Dengue is the most important, arthropod-borne viral illness in humans, transmitted by mosquito *Aedes agyptii*. Dengue Fever has a mortality rate of less than 1%. Dengue Hemorrhagic Fever when treated carefully has a mortality rate of 2-5%, however the mortality rate may go up to 50%, when it is not treated. Dengue during pregnancy increases the risk of hemorrhagic diathesis, thrombocytopenia, need for blood and blood component transfusion, preterm labour, preterm birth and intensive care unit admission of babies. This study was conducted to identify the feto-maternal outcome in pregnant women with dengue infection. The study was carried out among pregnant women who initially reported in outpatient clinic with symptoms of dengue and subsequently had their delivery at Hindu Rao hospital, from September 2013 to November 2014. Patients tested serologically positive for dengue IgM/IgG antibodies were included in the study and various obstetric and fetal consequences both during pregnancy and at birth were compiled. All the patients reported with high fever out of which 83.3% patients were in their third trimester. The principal maternal consequences observed were severe thrombocytopenia (33.3%), myalgia (41.7%), premature labour (50%), premature birth (25%) and postpartum haemorrhage (8.3%). Fetal consequences observed were prematurity (25%), acute fetal distress during labour (8.3%), low birth weight (41.7%) and admissions to Neonatal Intensive Care Unit (16.7%).

Keywords: *Dengue Fever, Pregnancy, Maternal Consequences, Fetal Consequences*

INTRODUCTION
Dengue is the most common arthropod-borne viral (arboviral) illness in humans, transmitted by mosquitoes *Aedes aegyptii*, which are widely distributed in subtropical and tropical regions of the globe including India (Shepherd, 2014). Dengue infection is caused by four closely related virus serotypes namely DENV-1, DENV-2, DENV-3 and DENV-4, belonging to genus Flavivirus and family Flaviviridae (Halstead, 2007). Infection with one serotype does not confer immunity to the remaining three serotypes. The first encounter of dengue fever i.e. primary dengue predisposes a person to more severe manifestations of the disease after infection with other serotypes i.e. secondary dengue (Gubler, 1998). Many patients with dengue experience a prodrome of chills, erythematous mottling of the skin and facial flushing, which may last for two to three days. Patients with dengue may also experience headache, retro-orbital pain, myalgias of lower back, arms and legs, arthralgias of the knees and shoulders, nausea and vomiting although diarrhea is rare, maculopapular or macular confluent rash over the face, thorax and flexor surfaces, with portions of skin sparing, weakness, altered taste sensation, anorexia, sore throat, hemorrhagic manifestations (e.g. petechiae, bleeding gums, epistaxis, menorrhagia, hematuria) and lymphadenopathy. Dengue Fever (DF) when complicated with Spontaneous bleeding and endothelial leak, is termed as Dengue Hemorrhagic Fever (DHF). Dengue fever (DF) is typically a self-limiting disease with a mortality rate of less than 1%. It has been found that DHF when treated has a mortality rate of 2-5%, but when it is left untreated; the mortality rate may go up to 50% and may result into Dengue Shock Syndrome (DSS). Common symptoms in impending Dengue Shock Syndrome (DSS) include abdominal pain, vomiting and restlessness. Patients also may have symptoms related to circulatory failure (Shepherd, 2014). Characteristic findings in dengue fever are thrombocytopenia (platelet count < 100 x 10^9 /L), leukopenia, and mild to moderate elevation of aspartate amino transferase and alanine aminot ransferase values (Azin, 2012). Patients with dengue hemorrhagic fever, may also have increased

hematocrit level secondary to plasma extravasation and/or third-space fluid loss, hypoproteinemia, prolonged prothrombin time, prolonged activated partial thromboplastin time, decreased fibrinogen and increased amount of fibrin split products (Chuang, 2013). Patients with high fever and vomiting experience moderate dehydration and oral rehydration therapy is recommended for them. Patients who develop signs of DHF and DSS require closer and regular observation. Admission for intravenous fluid administration is indicated for patients who develop signs of dehydration, such as tachycardia, prolonged capillary refill time, cool or mottled skin, diminished pulse amplitude, altered mental status, decreased urine output, rising hematocrit, narrowed pulse pressure and hypotension (Springer, 2012). Concern regarding women who are pregnant becoming infected with dengue has seen a sharp rise in recent years due to an overall increase in the number of adolescent and adult infections (Goh, 1995). Dengue in pregnancy increases the risk of haemorrhage for both mother as well as the baby. There is also an increased risk of preterm labour and delivery, vertical transmission and thrombocytopenia in neonate and intrauterine fatal demise. It is important to differentiate infection from HELLP syndrome, characterised by elevated liver enzymes, homolysis and low platelet count. The presence of dengue in obstetric patient may affect the decision regarding mode of delivery due to potential risk of haemorrhage and hence it assumes great importance (Narayana, 2014). This study calculates the feto-maternal consequences in women who had symptomatic dengue infection during pregnancy and were admitted at our hospital.

MATERIALS AND METHODS

The study was conducted on pregnant women who reported to the Out Patient Clinic or Emergency of Department of Obstetrics and Gynaecology, Hindu Rao Hospital, New Delhi with clinical features resembling dengue infection. The study was conducted between September 2013 and November 2014. The patients who tested positive for dengue viral specific antibodies i.e. IgM/IgG or NS 1 antigen were included in the study. All relevant data in terms of demography, clinical and laboratory parameters were maintained carefully, while the patients were undergoing treatment. The patients were followed up on regular basis for any change in the clinical and laboratory parameters. The patients were classified according to the WHO classification given in Table 1 (WHO, 2011):-

Table 1: WHO Classification of Dengue Fever and Severity of DHF

DF/DHF	Grade	Signs and symptoms	Laboratory
DF		Fever with two of the following :- ● Headache ● Retro-orbital pain ● Myalgia ● Arthralgia/bone pain ● Rash ● Hemorrhagic manifestations ● No evidence of plasma leakage.	• Leucopenia (WBC ≤ 5000 cells/mm^3) • Thrombocytopenia (Platelet count ‹ 150000 cells /mm^2) • Rising Hematocrit (5% - 10%) • No evidence of Plasma Loss
DHF	I	Fever and hemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage	Thrombocytopenia ‹100,000 cells /mm^3; HCT rise≥ 20 %
DHF	II	As in Grade I plus spontaneous bleeding	Thrombocytopenia ‹100,000 cells /mm^3; HCT rise≥ 20 %
DHF #	III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (≤ 20 mm Hg), Hypotension, Restlessness	Thrombocytopenia ‹100,000 cells /mm^3; HCT rise≥ 20 %
DHF #	IV	As in grade III plus profound shock with undetectable BP and pulse.	Thrombocytopenia ‹100,000 cells /mm^3; HCT rise≥ 20 %

DHF# - Dengue Shock Syndrome
(Source: http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/)

RESULTS

A total of twelve serologically diagnosed antenatal women were included in the present study. The detailed feto-maternal outcome of the patients was compiled. The clinical and laboratory findings are tabulated in Table 2.

Table 2: Clinical and Laboratory Parameters with Feto-maternal outcomes

Patient	Age (years)	Gestational age (weeks)	NS1 antigen	Dengue IgM/IgG	Platelet count	Hematocrit	Presenting complaints	Pleural Effusion/ascites	Severity	Blood/Platelet Transfusion	Obstetric outcome	Fetal Outcome
1	23	33	+	IgM + IgG -	60 x10^3	31.9 %	Fever, Malena, Myalgia, threatened preterm	Nil	DF	2 units platelets	Term Vaginal delivery	3.1kg Apgar 8,9,10
2	30	35+5	+	IgM + IgG -	120 x 10^3	35%	Fever, Headache, Myalgia,	Nil	DF	Nil	Term vaginal delivery	2.7 kg Apgar 7,9,9
3	19	13	-	IgM + IgG +	20x 10^3	33.3 %	Fever, Headache, Myalgia,	Nil	DF	2 units platelets	Term vaginal delivery	2.8kg Apgar 8,9,9
4	30	38	+	IgM + IgG -	89x 10^3	34.5 %	Fever, Arthralgia Petechial rash	Nil	DF	Nil	Term vaginal delivery	3.1kg Apgar 9,9,9
5	28	32+6	+	IgM + IgG -	20 x 10^3	35 %	Fever, Headache, Arthralgia Preterm Labor	+/+	DHF1	7 units platelets	Preterm LSCS at 35+5 weeks MSL with fetal distress	2.4 kg Apgar 7,8,9
6	30	Post-natal	-	IgM + IgG +	20 x10 ^{3}	34%	Fever, increased Bleeding p/v on PNC day 6	Ascitis +	DHF2	3 units platelets	Delivered at maternity centre at term,	2.5 kg Cried Immediately

											vaginally	
7	20	32	+	IgM + IgG -	65x10^3	30.2 %	Fever, Headache, threatened preterm labor	Nil	DF	Nil	Term , vaginally	2.6kg Apgar 9,9,9
8	28	36+3	+	IgM + IgG -	40x10^3	30 %	Fever, HeadacheArthralgia Preterm Labor	Nil	DF	1 unit platelets 1 unit fresh blood	Preterm 36+5, VBAC	2.1kg Apgar 8,10,10
9	25	39+4	-	IgM + IgG +	20 x 10^3	12.6 % Patient severly anemic, Hb 4.8	Fever, HeadacheArthralgia Myalgia	Nil	DF	2 units platelets 4 units packed cells	Term vaginal delivery	2kg shifted to NICU i/v/o RDS
10	23	41	-	IgM + IgG -	50x10^3	30%	Fever, Myalgia, Labor pains	Nil	DF	nil	Vaginal delivery	2.5kg Apgar 9,9,9
11	28	32	-	IgM + IgG -	40x10^3	31%	Fever, Headache Preterm labor	Nil	DF	2 units platelets	Preterm delivery	1.7kg Apgar 7,8,9 shifted to NICU
12	25	32	-	IgM + IgG -	100x10^3	37%	Fever, threatened preterm labor	Nil	DF	Nil	Vaginal delivery at 36 +1	2.4kg Apgar 8,9,9

The patients included in our study were in the age group of 19-30 years. Ten patients (83.3%) presented in the third trimester, one in second trimester (8.3%) and one patient (8.3%) presented in immediate postnatal period. Fever was the presenting complaint in all patients, seven patients (58.3%) complained of headache and myalgia was reported by five (41.7%) patients. Arthralgia was reported in four (33.3%) patients and six patients (50%) presented with threatened preterm labour. Haemorrhagic manifestations namely petechial rash, increased vaginal bleeding and malena were reported by one patient (8.3%) each. Clinical manifestation of plasma leakage i.e. pleural effusion and ascitis were seen in one (8.3%) and two patients (16.7%) respectively. Ten patients (83.3%) were classified as DF, one patient (8.3%) each was identified as DHF1 AND DHF2 respectively. Admission in intensive care unit was not required by any patient.

Platelet count ranged between 20 to 120 x 10^3µL and hematocrit ranged between 12.6% to 37%. It is pertinent to mention that majority of the patients were moderately anemic, despite that the hematocrit

value was in the normal range, depicting a relative rise in the level. Five patients (41.7%) did not require blood and blood components while transfusions were individualised in the rest of the seven patients (58.3%). One patient (8.3%) had emergency caesarean section in view of meconium stained liquor while other patients delivered vaginally. Two low birth weight neonates (16.7%) required admission in Neonatal Intensive Care Unit due to respiratory distress and prematurity. The result of the study has been tabulated in Table 3 as under:-.

Table 3: Analysis of the Study Results

(A) **DEMOGRAPHIC DETAILS**			
S No	**Parameter**	**Result**	**Percentage (%)**
1.	Age	19-30 years	-
	Mean	25.5 years	-
2.	**Gestational at Age at Diagnosis**		
	<12 Wks	Nil	-
	12-24 Wks	1	8.3
	24-37 Wks	7	58.3
	>37 Wks	3	25
	PNC	1	8.3
(B)	**LABORATORY PARAMETERS**		
1.	**NS1 Antigen**		
	Positive	6	50
	Negative	6	50
2.	**Dengue IgM antibody**		
	positive	12	100
	negative	Nil	-
3.	**Dengue IgG antibody**		
	positive	2	16.7
	negative	10	83.3
4.	**Platelet Count**		
	$\leq 20 \times 10^3$	4	33.3
	20 to $\leq 50 \times 10^3$	3	25
	50 to $\leq 100 \times 10^3$	4	33.3
	$\geq 100 \times 10^3$	1	8.3
5.	**Hematocrit**		
	$\leq$ 34%	5	41.7
	>34	7	58.3
(C)	**CLINICAL DETAILS**		
1.	Fever	12	100
		7	58.3
		4	33.3
4.	Hemorrahgic Diathesis	3	25
5.	Myalgia	5	41.7
6.	Ascitis/Pleural effusion	2	16.7
7.	Preterm labor	6	50
(D)	**MATERNAL OUTCOME**		
1.	Transfusions	7	67.7
2.	Vaginal delivery	11	91.7
3.	LSCS (MSL with FD)	1	8.3
4.	PPH	1	8.3
5.	Preterm birth	4	33.3

6.	Mortality	Nil	-
(E)	**FETAL OUTCOME**		
1.	Birth weight		
	<2.5 kg	5	41.7
	≥ 2.5 kg	7	58.3
2.	NICU admission	2	16.7
3.	IUD	Nil	-
4.	Neonatal demise	Nil	-

It is important to consider dengue as one of the differential diagnosis in pregnant women with febrile illness. In our study Dengue serology IgM was positive in all the cases, NS1 antigen was positive in 50 % cases and both IgM and NS1antigen were positive in six cases (50 %). In a study conducted by Agarwal P et al in 2014 wherein 25 patients were included, dengue serology IgM was positive in 20 cases (80%), NS1antigen positive in 17 cases(68%) and both IgM and NS1antigen positive in 14 cases (56%).

In our study it was found that 10 out of 12 patients (83.3%) were in third trimester. Similar results were seen in a study conducted by Kariyawasam *et al.,* in 2010 where 13 out of 15 patients (86.6%) were in third trimester. A study by Ismail NA *et al.,* in 2006 also found that 50% of the patients reported were in their third trimester.

Fever was presenting complaint in all patients and myalgia was reported by five patients (41.7%) in our study. In a study conducted at De Soya maternity Hospital, Srilanka in 2010 by S Kariyawasam *et al.,* in 2010 fever was the presenting complaint in all the 15 patients where as myalgia was seen in eight patients (53.3%).

Basurko C *et al.,* conducted a retrospective study in 2009 and found that out of total 53 patients considered, 41% had preterm labor and 9.6 % had premature birth. In our study 50% of the patients had preterm labor and 4 patients (33.3%) had premature birth. In a study conducted by Agarwal P *et al.,* in 2014, 52 % of the patients had preterm labor.

In our study severe thrombocytopenia (≤ 20x 10^3/µl) was seen in 33.3% of patients whereas in a study conducted by Agarwal P *et al.,* in 2014, 36% had severe thrombocytopenia. Platelet count of ≤ 20 x 10^3/µl was found in 46.6 % patients, in a study conducted by S Kariyawasam *et al.,* in 2010.

Postpartum hemorrhage was seen in 8.3% cases in our study whereas in studies conducted by Basurko C *et al.,* in 2009 and Agarwal P *et al.,* in 2014 it was found to be 10% and 32% respectively.

In our study five (41.7%) babies were low birth weight whereas 52 % cases were found to be low birth weight in a study by Agarwal P *et al.,* in 2014. Fetal distress during labor was found in one patient (8.3%) whereas it was seen in 7.5 % cases in a study by Basurko C *et al.,* and 16% cases in study conducted by Agarwal P *et al.,* in 2014.

Conclusion

Dengue should be considered as one of the differential diagnosis in pregnant women with febrile illness especially in endemic areas. Pregnant women with dengue may have severe maternal and perinatal outcomes. Early detection and immediate treatment can minimise the risk to both mother as well as to the foetus. The principal maternal consequences observed are; severe thrombocytopenia, myalgia, premature labour, premature birth and postpartum haemorrhage. Fetal consequences observed are prematurity, acute fetal distress during labour, low birth weight and admission to Neonatal Intensive Care Unit. Due to these feto-maternal complications such patients should be managed in a tertiary care centre to minimise feto-maternal morbidity and mortality.

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