ORIGINAL ARTICLE

Dengue Infection in Pregnancy: Impact on Maternal and Fetal outcomes

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Abstract

Objective
To assess the impact of dengue infection during pregnancy on obstetric and fetal outcomes.

Methodology
A retrospective study was conducted by Department of Medicine at a tertiary care hospital in Karachi, Pakistan by reviewing patient records from 2009 – 2015.

Inclusion criteria were pregnant patients of any gestational age fulfilling WHO diagnostic criteria for dengue infection. Exclusion criteria were febrile pregnant patients positive for malaria parasite, immunological tests for malaria or with positive blood cultures, patients diagnosed with HELLP syndrome or other autoimmune disease and patients with drug-induced thrombocytopenia.

Frequencies and percentages were noted for maternal and fetal outcomes being studied.

Results
Our data shows that antenatal dengue infection has the potential to significantly impact maternal and fetal outcomes.Antepartum and postpartum hemorrhage each occurred in 5% of patients with acute antenatal dengue infection. Moreover, we note that counts may not be predictive of development of these complications, so extreme clinical vigilance is warranted. Oligohydroamnios occurred in 21% of our patients; this is likely to be a consequence of significant fluid shifts with dengue and hydration of the pregnant dengue patient is paramount. There may be an increased risk of fetal loss.

Conclusion
Obstetric complications such as antepartum hemorrhage, oligohydramnios and postpartum hemorrhage can occur with acute dengue infection during pregnancy. Preterm delivery necessitated by these can impact neonatal outcomes (eg low birth weight and APGAR scores). Acute dengue infection contracted during the 3rd trimester carries high risk of causing pregnancy morbidity. As platelet counts are not predictive of development of bleeding complications, a high index of suspicion and extreme clinical vigilance are warranted.

Keywords
dengue; pregnancy; pregnancy complications; hemorrhage; premature birth

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Introduction

Dengue is the commonest arbovirus infection.[1] 3.9 billion people are at risk.[2] Accurate estimates are hampered by underreporting and misclassification; currently 390 million dengue infections per year are estimated to occur.[3]

Since 1994, dengue fever has become a very significant infectious disease and public health issue in Pakistan; WHO reported the largest ever dengue epidemic from Pakistan in 2012.[4]

Only a few studies [5,6,7,8] have examined the impact of antenatal dengue infection on mothers and neonates, reporting increased risk of obstetric complications and adverse neonatal outcomes. While the literature includes some regional studies [5,6,7,8] to our knowledge, such data has been reported only once from Pakistan with18 patients surveyed.[9]

We conducted a retrospective review of records of patients with antenatal dengue infection to help elucidate the impact of dengue infection during pregnancy. Our aim was to acquire objective data to help formulate appropriate management strategies to help in counseling of patients.

The main objective was to assess the impact of dengue infection in pregnancy on obstetric and fetal outcomes.

Methodology

A retrospective study was conducted by Department of Medicine at a tertiary care hospital (200 beds, offering post-graduate training in medicine and gynaecology) by reviewing patient records from 2009 – 2015. Records were retrieved from medical record room using ICD codes (061, 065.4, 647.6X). A total of 844 files were reviewed; 19 pregnant patients were identified. (Figure 1)

Patients were followed till the end of their pregnancy for the outcome including gestational age at delivery, mode of del obstetric,

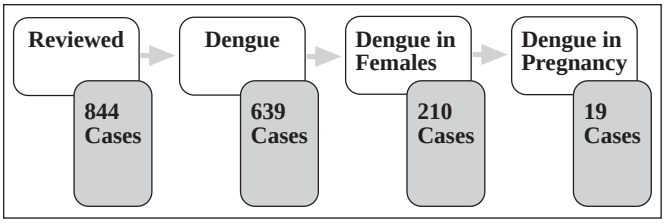

Fig 1. Number of cases identified with acute dengue in pregnancy

Inclusion criteria were pregnant patients of any gestational age fulfilling WHO diagnostic criteria for dengue infection for probable or confirmed dengue.[10]

WHO Diagnostic Criteria
Probable dengue
Live in/travel to dengue endemic area. Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leucopenia
- Any warning sign

Laboratory confirmed dengue

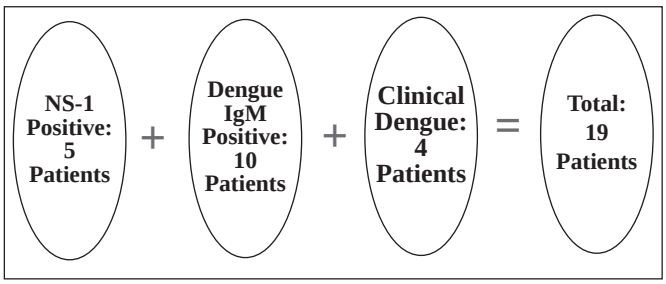

Fig 2. Criteria for identifying patients with acute dengue infection.

Exclusion criteria were febrile pregnant patients who tested positive for malaria parasite, immunological tests for malaria or with positive blood cultures, patients diagnosed with HELLP syndrome or other autoimmune cause for their symptoms and patients with drug-induced thrombocytopenia.

Clinical parameters of all patients were recorded in individual proforma by the investigators. Patients were followed till the end of their pregnancy for the final outcome including gestational age at delivery, mode of delivery, obstetric, fetal and neonatal complications and maternal and infant mortality (Table 1).

Data was collected from September 2016 to October 2016. It was entered and analyzed on SPSS Software (Version 21). Frequencies and percentages were noted for maternal and fetal outcomes being studied. Ethics review committee of our hospital studied the proposal and pro forma and issued approval (ERC Approval No: 45).

Results

A total of 19 pregnant patients were identified as per inclusion criteria (as shown above). General demographic features are shown in table 2. All patients had fever at the time of admission. Fever was the sole presenting feature in 6 (31.6%) patients. Mean fever noted was 102.6°F ± 1.3°F. Clinical features and laboratory parameters pertaining to dengue observed in our patients are shown in table 2.

Dengue-related non-obstetric bleeding occurred in 42%; one quarter of these were hemodynamically significant. 52.6% patients were given platelet transfusion. 1(5.2%) patient presented with severe hemorrhagic dengue and eclampsia. Oligohydroamnios was found at a frequency of 21%. 21% suffered preterm labor and 10.5% had premature rupture of membranes. 2 (10.5%) women with acute dengue in the first trimester suffered pregnancy loss. For details of maternal, fetal

Table 1: Maternal & Neonatal outcomes in patients with antenatal acute dengue infection

Maternal Outcomes	*Neonatal Outcomes*
• Antepartum Hemorrhage (APH)	• Intra-uterine growth restriction (IUGR)
• Pregnancy Loss	• Fetal Anomalies
• Oligohydroaminos	• Fetal Distress
• Pregnancy induced hypertension (PIH)	• Meconium Aspiration
• Preterm Labor	• Low APGAR (<7)
• Premature Rupture of Membrane (PROM)	• Prematurity
• Dengue related bleeding complication	• Low Birth Weight (LBW)
• Transfusion required	• Respiratory Distress Syndrome (RDS)
• C-section	• Neonatal Death
• Post partum Hemorrhage (PPH)	
• Maternal Mortality	

Table 2: Demographic, Clinical & Laboratory Parameters of Dengue

Demographic Features	n (%)
Age	
• Less than 20 Yrs	1 (5.3%)
• 20-30 Yrs	13 (68.4%)
• More than 30 Yrs	5 (26.3%)
Pregnancy Status	
• Primigravida	6 (31.6%)
• Multigravida	13 (68.4%)
Gestational Age at Presentation	
• First Trimester	6 (31.6%)
• Second Trimester	4 (21.1%)
• Third Trimester	9 (47.4%)
Clinical Features	
• Petechiae	2 (10.5%)
• Rash	3 (15.8%)
• Headache	6 (31.6%)
• Back Pain	3 (15.8%)
• Joint Pain	1 (5.3%)
• Nasal Bleed	3 (15.8%)
• Gum Bleed	3 (15.8%)
• Hematuria	1 (5.3%)
• GI Bleed	1 (5.3%)
• Intracranial Bleed	0 (0%)
• Pleural Effusion	5 (26.3%)
Laboratory Parameter	**Mean ± S.D**
• Hemoglobin (gm/dl)	10.8 ± 1.2
• Hematocrit (%)	29.9 ± 6.0
• Platelets Initial ($x10^9$/uL)	113.7 ±77.9
• ALT (IU/L)	132 ± 107.0

and neonatal outcomes see Tabe 3 & 4.

Discussion

Dengue has become prevalent in Pakistan. Being a disease that has become endemic to Pakistan relatively recently, there is a need to elucidate and document impact of antenatal infection on pregnancy and child birth. While a handful of studies have reported on such outcomes[5,6,8] only one group has reported such data from Pakistan on 18 patients.[9]

We examined maternal and neonatal outcomes in 19 patients. We found increased obstetric and non-obstetric bleeding in mothers with acute dengue infection, increased risk of premature birth, poor APGAR scores and low birth weight in neonates. Antepartum hemorrhage occurred in 5%. Maqsud reported antepartum hemorrhage in 16% and Agrawal reported it in 32%.[6,9] While all patients in the former study presented with acute dengue in the 3rd trimester, 8/19 of our patients contracted dengue before 20 weeks' gestation. Post-partum haemorrhage also occurred in a small percentage in our study in contrast to previously reported19%-32% [5,6,9] In our group, both antepartum and post partum hemorrhage occurred in the same patient (who had contracted dengue infection at 33 weeks' gestation) and had a platelet count nadir of 85,000/ul. Agrawal[6] reported counts of 14000-82,000 in patients developing antepartum or post partum hemorrhage, suggesting that only the counts may not be predictive of development of these complications.

Non-obstetric bleeding complications attributable to dengue occurred in 42% of our patients. One-fourth of these were hemodynamically significant. Several authors have reported bleeding complications in frequencies ranging from 11-56%.[5-9] Basurko[8] reported a retroperitoneal hematoma in one patient; Sharma[5] reported rectal sheath hematoma in one patient and dengue-shock syndrome in three; Agrawal[6] reported dengue shock syndrome in 20%; Maqsud[9] reported massive epistaxis and recalcitrant bleed from site of C-section leading to death in one patient. Cases of PPH have been reported in the absence of any other bleeding manifestations.[5]

In our study, 10/19(52.6%) patients were given platelet transfusion, frequencies of 62.6% and 89% have been reported.[5,9]

One patient (5.2%), a primigravida with twin pregnancy, presented with eclampsia; she had contracted dengue infection at 33 weeks' gestation and needed immediate emergency Caesarean section. We found no reported association of antenatal dengue infection with pregnancy-induced hypertension. However, several groups[5,6] have noted the possible diagnostic dilemma between acute dengue infection and HELLP syndrome as both conditions are associated with low platelets and transaminitis. Oligohydroamnios is another complication believed to be strongly associated with acute dengue and Sharma[5] have postulated that this may be partly because of dehydration in dengue. We found oligohydroamnios in 21% of our patients. Other groups have reported a significantly higher frequency of oligohydroamnios- 43 – 52%.[5,6]

Pregnancy loss (including abortion and intrauterine death) was observed in 2/19 (10.5%) of our patients while frequencies of 6-25% have been reported by other groups.[5-8,11] Both fetal losses in our study occurred in women who presented with acute dengue in the first trimester. Kariyawasam and Senanayake[7] have postulated that endothelial damage due to dengue infection plays acausative role in adverse fetal outcomes.

Preterm labor occurred in 21%(4/19) of our patients.1 patient had acute dengue in the 2nd trimester while the other 3 contracted it in the 3rd trimester. 2 of these 4 preterm neonates were completely healthy; 1 developed respiratory distress and the 4th case was a twin delivery with both neonates having low

Table 3: Maternal and fetal outcomes recorded for each patient

Age	Parity	Gestational Age at Presentation	Gestational Age at Delivery	Mode of Delivery Complications	Obstetrics Outcomes	Neonatal
22Y	M	3rd trimester	Pre term	C Section	None	Healthy baby
33Y	M	3rd trimester	Term	C Section	None	Healthy baby
23Y	P	3rd trimester	Term	Spontaneous Vaginal	None	Healthy baby
18Y	M	2nd trimester	Pre term	C Section	Breech Presentation	Healthy baby
35Y	M	1st trimester	-	-	Missed Abortion	-
33Y	M	1st trimester	Term	C Section	None	Healthy baby
28Y	P	3rd trimester	Term	C Section	Oligohydroaminos	Healthy baby
30Y	M	3rd trimester	Term	C Section	None	Healthy baby
33Y	M	2nd trimester	Term	C Section	PROM	Healthy baby
22Y	P	3rd trimester	Term	Operative Vaginal	PROM	Healthy baby
25Y	M	3rd trimester	Pre term	C Section	APH, PPH	RDS
30Y	M	1st trimester	Lost to F/U	-	-	-
29Y	M	1st trimester	Term	C Section	None	Healthy baby
27Y	M	3rd trimester	Term	Operative Vaginal	Oligohydroaminos	Healthy baby
24Y	P	1st trimester	Term	C Section	Fetal Distress	Meconium Aspiration
30Y	M	1st trimester	Term	Spontaneous Vaginal	Twin Pregnancy, Intrauterine Death of one fetus	Healthy baby
23Y	P	2nd trimester	Term	C Section	Oligohydroaminos, Breech Presentation	Healthy baby
23Y	P	3rd trimester	Pre term	C Section	Twin Pregnancy, Eclampsia, Maternal Death after 1 week of delivery	Premature, LBW (1.9 & 1.5 kg)
33Y	M	3rd trimester	Term	Spontaneous Vaginal	Oligohydroaminos	Healthy baby

Table 4: Maternal & Neonatal Outcomes in Dengue

Maternal Outcomes	n (%)	Neonatal Outcomes	n (%)
Antepartum Hemorrhage (APH)	1 (5.2%)	Intra-uterine growth restriction (IUGR)	0 (0%)
Post partum Hemorrhage (PPH)	1 (5.2%)	Fetal Anomalies	0 (0%)
Dengue related bleeding complication	8 (42%)	Fetal Distress	1 (5.2%)
Platelet Transfusion	10 (52.6%)	Meconium Aspiration	1 (5.2%)
Oligohydroaminos	4 (21%)	Respiratory Distress Syndrome (RDS)	1 (5.2%)
Pregnancy induced hypertension (PIH)	1 (5.2%)	Low APGAR (<7)	2 (10.5%)
Preterm Labor	4 (21%)	Low Birth Weight (LBW)	2 (10.5%)
Pregnancy Loss	2 (10.5%)	Prematurity	4 (21%)
Premature Rupture of Membrane (PROM)	2 (10.5%)	Neonatal Death	0 (0%)
C-section	12 (63.1%)		
Maternal Mortality	1 (5.2%)		

birth weight. It is worth noting that there were no major maternal complications in the 2 healthy preterm neonates. However, the preterm neonates who had above-mentioned adverse effects had mothers with severe complications, namely antepartum hemorrhage in one and eclampsia in the other. Studies have reported a variable rate (9-68%) of preterm labor.[5,6,8,9,11]

Premature rupture of membranes occurred in 10.5% (2/19) of our patients; 1 had contracted dengue in the 2nd trimester and the other in the 3rdtrimester. Both neonates were healthy. One other study[6] found a frequency of 4%.

C-Section was done in 63.1% (12/19) of our patients; only 2 of these could be ascribed to complications caused by acute dengue- the remainder were for obstetric indications unrelated to dengue infection. Maqsud[9] reported C-section rate of 77.7% and Agarawal[6] reported it in 32%.

Fetal and neonatal outcomes were examined. We did not find any cases of intra-uterine growth restriction (IUGR) or fetal anomalies. One study reported fetal anomalies in 13.6% ; none of the studies we reviewed specifically examined intrauterine growth restriction.

In our study one neonate had fetal distress along with meconium aspiration. Basurko reported fetal distress in 7.5% neonates[8] while Sharma reported meconium aspiration in 6%.[5]

Respiratory distress syndrome occurred in 1 neonate (5.2%) whose mother had antepartum as well as postpartum hemorrhage while Ismail *et al* reported it in 12.5%.[11] Low APGAR was also observed in 10.5% neonates. We did not find any other study reporting on APGAR scores. Low Birth Weight (LBW) occurred in 10.5% neonates. Two other studies reported LBW in 22% and 52% respectively.[6] Prematurity was found in 21% neonates while other studies have reported prematurity from 13-37%.[5,6,8,11] No neonatal death occurred in our study but other studies have reported it in 1.9-20%.[5,6,8]

The strengths of our study are that it adds to the very meagre data available from our country. We have attempted to document most obstetric and neonatal outcomes. The weakness of our data lies in its retrospective nature. Also, neonates were not specifically investigated to determine vertical transmission of acute dengue.

Conclusion

Antenatal dengue infection has the potential to adversely affect outcomes, especially when contracted in the 3rdtrimester.Attention must be paid to providing adequate fluid resuscitation. Bleeding complications bear no correlation to platelet counts.

Funding/Conflict of interest

This study does not have any source of funding. No conflict of interest exists for any investigators and none is declared.

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