

Maternal and peri-natal outcomes of dengue fever with special emphasis on vertical transmission

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Abstract

Objectives: To investigate the maternal and peri-natal outcomes of dengue infection and frequency of dengue immunoglobulin G positivity in pregnant women along with pregnancy outcomes.

Method: The observational two-phase study was conducted from 2012 to 2015 in Lahore, Pakistan. In phase 1, pregnant women who had acute dengue fever were prospectively and retrospectively enrolled from 4 tertiary care hospitals. Demographic data, clinical/laboratory parameters and maternal/foetal outcomes were recorded for each subject. In the second phase, normal pregnant women with no current or past history of dengue fever were enrolled from Gynaecology Department of Shaikh Zayed Hospital, Lahore, to determine the frequency of dengue immunoglobulin G positivity and pregnancy outcome. Data was analysed using SPSS 20.

Results: Of the 12 subjects in phase 1, 10(83.3%) were prospective cases and 2(16.6%) were retrospective. The overall mean age was 26.3 ± 5.4 years, 7(58.3%) were in 2nd and 5(41.6%) were in 3rd trimester of pregnancy. Among the 4(33.3%) women at gestational age ≥ 33 weeks, 3(75%) had poor foetal outcome. In the second phase, there were 127 women with a mean age of 27.4 ± 4.3 years. Among them, 38(29.9%) women were in the 2nd and 89(70.1%) were in the 3rd trimester. Dengue immunoglobulin G positivity was found in 65(51.2%) cases, but poor maternal or foetal outcome was not found in such women.

Conclusion: Acute dengue fever at late term resulted in adverse foetal outcomes. Frequency of dengue immunoglobulin G positivity was high among pregnant women, but it was not associated with adverse outcomes.

Keywords: Acute dengue, Dengue IgG positivity, Pregnancy, Adverse outcomes. (JPMA 72: 658; 2022)

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Introduction

Dengue fever is one of the commonest mosquito-borne diseases, with an estimated 100 million infections resulting from it globally per year.^{1,2} Many factors like urbanisation, increase in population, air traveling and inadequate resources for dengue prevention, have contributed to the spread of dengue and it has been transformed into a major public health problem in the tropics.² Although dengue fever is now a worldwide health problem of major concern, around 75% of the world's population exposed to dengue virus resides in the Asia-Pacific region.³ Out of the 100 million infections occurring annually, 250,000 to 500,000 people suffer from severe disease, with the rest being mild, non-specific or even asymptomatic.^{1,2}

Dengue fever is caused by dengue virus which is a member of the genus *Flavivirus* of family *Flaviviridae*. Different age groups have been reported to be affected by dengue virus in different regions of the world. In Pakistan, dengue infection is more common in the adult

population (reason unknown) compared to other countries.⁴ According to a Pakistani study, 2,612 out of 11,283 (23.1%) dengue patients were aged 21-30 years.⁵ The high frequency of dengue infection in the adult population in Pakistan renders pregnant women at an increased risk.

Pregnancy increases the vulnerability for dengue fever both in terms of the health of the pregnant women and the fear of pregnancy outcome.^{3,6} Dengue in pregnancy can lead to more severe infection in mothers and mother-to-newborn transmission is also a predisposed risk.⁷ Studies on dengue fever and pregnancy have been conducted in Asian countries where dengue is endemic, but literature lacks data from Pakistan which is also a dengue-endemic country for more than a decade. Compared to non-pregnant woman, an increase in severe dengue has been reported in pregnant women in Brazil during the second and third trimesters.⁸ A small cohort study conducted in Brazil reported more maternal deaths in dengue-exposed pregnant women compared to those who were not exposed to dengue.⁹ Studies also reported foetal and neonatal complications like miscarriage, stillbirth, premature delivery, low birthweight (LBW) and perinatal infection.¹⁰⁻¹³

Dengue infection during pregnancy carries the risk of

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various complications, including miscarriage, maternal mortality, preterm delivery, foetal anomalies, LBW, neonatal hospital admissions and foetal death.¹⁴ Some studies have also reported different rates of vertical transmission of dengue infection from mother to the newborn.^{14,15} Most of the studies done so far considered infants as exposed only if their mothers had symptomatic dengue infection during pregnancy. It was supposed that it may be possible that dengue immunoglobulin G (IgG)-positive pregnant women, without current or past history of dengue infection, may also have poor birth outcomes,¹⁶ as they had been exposed to the dengue virus. Keeping all these aspects in mind, the current study was planned to investigate maternal and perinatal outcomes of acute dengue infection, to determine the frequency of dengue IgG positivity in normal pregnant women, and to inspect poor foeto-maternal outcomes in IgG-positive mothers.

Patients and Methods

The observational two-phase study was conducted from 2012 to 2015 in Lahore, Pakistan. The first phase was a cohort, while the second phase had a cross-sectional design. After approval from the ethics review board of the Federal Postgraduate Institute, Sheikh Zayed Hospital, Lahore, the sample for phase-1 was raised using purposive sampling technique without calculating the sample size as the study was time-barred and all pregnant women with clinically diagnosed acute dengue fever were enrolled. Close liaison was maintained with the gynaecology departments of major public-sector tertiary care hospitals of Lahore and Rawalpindi/Islamabad and whenever a pregnant woman with acute dengue was located, the case was enrolled. The cases were enrolled from Shaikh Zayed Hospital, Jinnah Hospital and Mayo Hospital in Lahore, and Benazir Bhutto Hospital, Rawalpindi.

Those included in phase-1 were clinically confirmed dengue-positive pregnant women aged 18-35 years who were enrolled both prospectively and retrospectively. Pregnant women having dengue along with clinically confirmed chronic diseases, like hepatitis, kidney diseases, liver diseases and diabetes, were excluded. All cases were enrolled after obtaining written informed consent.

Grading of the severity of dengue infection was done according to the World Health Organisation (WHO) classification and case definitions.¹⁷

Demographic data, laboratory and clinical parameters, maternal and foetal outcomes were recorded on a predesigned proforma both prospectively and retrospectively from medical files and hospital records.

In phase-2, pregnant women aged 18-35 years without current or past history of dengue infection and registered at the antenatal clinic of Gynaecology and Obstetrics Department of Shaikh Zayed Hospital, Lahore, were enrolled using simple random sampling technique. The sample size was calculated using the frequency of ~50% of the dengue IgG seropositivity¹⁸ with 9% precision at a 95% confidence interval (CI) and 7% non-response rate.

Pregnant women who did not plan to have the delivery at Shaikh Zayed Hospital were excluded. After obtaining written informed consent, frequency of dengue IgG seropositivity was checked for which blood samples (2cc) were collected under aseptic conditions. Data regarding demographics, clinical parameters and pregnancy outcome were recorded on a predesigned proforma.

Dengue IgG antibodies were determined using enzyme-linked immunosorbent assay (ELISA) (Calbiotech, California, United States). Tests were performed according to the manufacturer's instructions. Assay format was indirect ELISA, and wells were coated with purified antigen. Dengue IgG antibodies, if present in patient's serum, bounded with the antigen. All the unbounded material was removed by washing and enzyme conjugate was added to the bind with antibody-antigen complex. After washing, substrate was added and plates were incubated at room temperature. Hydrolysis of the substrate by enzyme produced colour which was quantified after the addition of stop solution. Analysis of the assays was carried out on Anthox 2010 plate reader using softmax statistical package. Samples were assayed in duplicate and the average of two readings was taken for the calculation of results. Seropositivity of dengue IgG antibodies was considered to be an indicator of exposure to dengue virus.

Data were analysed using SPSS 20. Mean and standard deviations were calculated for quantitative variables, like age, and frequencies and percentages were calculated for gravidity, asymptomatic dengue infection and other similar variables. Chi-square test was applied to check for differences in outcome of delivery, birth weight, term of delivery etc, between women exposed to dengue infection (dengue IgG positive) and those who were not exposed (dengue IgG negative) to dengue infection.

For the purpose of the study, pre-term delivery was defined as a delivery between 28 and 37 weeks of pregnancy.¹⁹ Term delivery was defined as a delivery after 37 and before 40 weeks of pregnancy. Post-term delivery was defined as a delivery after the 40th week of pregnancy. LBW was taken as <2.5kg (2500g) at the time

of delivery. Early neonatal death was defined as death of a live born infant occurring before 7 complete days from the time of birth, and late neonatal death was defined as death after 7 complete days of life but before 28 complete days of life.²⁰

Results

Of the 12 subjects in phase-1, 10(83.3%) were prospective cases enrolled in 2012-14 period, and 2(16.7%) were retrospective enrolled in 2015 (case number 5 and case number 8). The overall mean age was 26.3 ± 5.4 years, 7(58.3%) were in 2nd and 5(41.6%) were in 3rd trimester of pregnancy. Among the 4(33.3%) women at gestational age ≥ 33 weeks, 3(75%) had poor foetal outcome.

Overall, 2(16.7%) women had only positive dengue IgM antibodies, 7(58.3%) were positive for both dengue IgM and IgG antibodies, 2(16.7%) were only positive for dengue IgG antibodies. In terms of outcome, 3(25%) women, at gestational age 37 weeks (case 05), 34 weeks (case 06), and 33 weeks (case 10) had poor pregnancy outcome. There were 2(16.7%) neonatal deaths, 2(16.7%) preterm deliveries and 1(8.3%) LBW baby. The mean birth weight of the newborns was 2.85 ± 0.55 kg.

Newborn of case number 5, enrolled retrospectively, was a suspected case of acute dengue infection (vertical transmission), but left undiagnosed. At the time of delivery, the mother was a diagnosed case of dengue haemorrhagic fever (DHF) and had highly reactive dengue IgM (55.4) which was five times higher than the cut-off value of 11.0. Pelvic ultrasound findings showed that mother had hepato-splenomegaly with liver size 18.8cm and spleen size 16.7cm. Serial full blood counts of the newborn showed gradual decline in platelet counts,

and increase in serum glutamic pyruvic transaminase (SGPT) i.e. 94 U/L against normal range of 08-39 U/L. Blood culture and urine culture of the baby did not yield any bacterial or fungal infection. Biochemical tests showed that the newborn was a suspected case of acute dengue fever, but left undiagnosed and died on the 11th day of life.

Case 11 had severe dengue infection at 37th week of pregnancy. The patient was admitted in high dependency unit (HDU) for close monitoring of vital signs at 15-minute intervals. The patient was shifted to the labour room for Caesarean section (CS) during the active dengue infection period, but due to the refusal to provide consent by the patient and caregivers, CS was not done. After 8 days, on meeting the discharge criteria for dengue infection, the patient was discharged. Later on, the patient delivered a normal baby girl weighing 2,500g at 39+4 weeks of gestation. Dengue polymerase chain reaction (PCR) of the newborn was done and no virus was detected. At the time of delivery, no active virus was present in the mother's body (Table-1).

In phase-2, there were 127 women with a mean age of 27.4 ± 4.3 years. Among them, 38(29.9%) women were in the 2nd and 89(70.1%) were in the 3rd trimester. Within the sample, 87(68.5%) enrolled women were without history of any disease or risk factor 65(51.2%) were IgG-positive and 62(48.8%) were IgG-negative for dengue antibodies. Minimum gestational age at the time of delivery was 33+1 weeks and maximum was 41+1 weeks. Among the IgG-positive women, 23(35.4%) and 17(27.4%) among the IgG-negative women had co-morbidities/risk factors. Significant difference was not seen between the exposed and not-exposed pregnant women regarding

Table-1: Clinical and laboratory characteristics of pregnant women with symptomatic dengue infection.

Case No.	Age (years)	Gestational Age (weeks)	Dengue NS1/IgM/IgG	Dengue Classification	Maternal Outcome	Mode of Delivery	Time of Delivery	Foetal Outcome	Birth wt (Kg)/ Gender
1	23	29+3	IgM+/IgG+	DF	Normal	SVD	38+5	Normal	2.5/F
2	33	13	IgM+/IgG+	DF	Normal	SVD	39+6	Normal	2.8/F
3	18	20	IgM+/IgG+	DHF	Normal	LSCS	38+3	Normal	3.4/M
4	30	22	NS1+/IgG+	DF	Normal	SVD	37+3	Normal	2.8/M
5	25	37	IgM+/IgG+	DF	Normal	SVD	37+3	Death at 11th day	2.5/F
6	18	34	IgM+/IgG+	DHF	unconsciousness	SVD	34+3	Death within 24 hours (pre-term)	2.6/M
7	35	26	IgM+/IgG+	DHF	Normal	SVD	37+1	Normal	3.6/F
8	28	21	IgM+/IgG+	DF	Normal	LSCS	37+2	Normal	3.1/M
9	22	31+2	IgM+	DF	--	Lost	for	follow up	--
10	30	33+5	NS1+/IgM+	DHF	Normal	LSCS	34	Low birth weight (pre-term)	2.3/F
11	25	37	Very high IgG titer	Severe dengue	Normal	SVD	39+4	Normal	2.5/F
12	29	16	NS1+	Dengue without warning signs	Normal	SVD	40	Normal	3.8/M

DF: Dengue fever, DHF: Dengue haemorrhagic fever, SVD: Spontaneous vaginal delivery, LSCS: Lower segment Caesarean section, Ig: Immunoglobulin, NS: Nonstructural protein.

Table-2: Demographic and clinical characteristics of dengue immunoglobulin G (IgG) seropositive and seronegative pregnant women.

Maternal and new born characteristics	Dengue IgG positive (n = 65) Frequency (%)	Dengue IgG negative (n = 62) Frequency (%)	Chi square test result (p value)
Maternal age (years)			
18-23	11 (16.9%)	13 (21%)	0.852
23-29	37 (56.9%)	34 (54.8%)	
30-35	17 (26.2%)	15 (24.2%)	
Maternal gravidity			
1	30 (46.2%)	26 (41.9%)	0.08
3-Feb	23 (35.4%)	24 (38.7%)	
5-Apr	08 (12.3%)	12 (19.4%)	
>5	04 (6.2%)	-	
Co-morbidity or risk factor			
Anaemia	03 (4.6%)	02 (3.2%)	0.783
Eclampsia/pre-eclampsia	05 (7.7%)	02 (3.2%)	
History of miscarriage	03 (4.6%)	03 (4.8%)	
Previous Caesarean deliveries	12 (18.5%)	10 (16.1%)	
Mode of delivery			
Vaginal	15 (23.1%)	09 (14.5%)	0.238
Vaginal tear	15 (23.1%)	21 (33.9%)	
Caesarean	25 (38.5%)	27 (43.5%)	
Instrumental vaginal delivery	10 (15.3%)	05 (8.1%)	
Term of delivery			
Pre-term	11 (16.9%)	07 (11.3%)	0.576
Term	42 (64.6%)	45 (72.6%)	
Post-term	12 (18.5%)	10 (16.1%)	
Birth weight of baby (Kg)			
*(n=130)	16 (23.9%)	14 (22.2%)	0.615
1.5-2.5	47 (70.1%)	43 (68.3%)	
2.6-3.5	04 (6.0%)	06 (9.5%)	
> 3.5			

*There were 3 twin pregnancies.

outcome of labour, term of delivery and birth weight of the newborn (Table-2).

Discussion

The present study found that acute dengue infection at or near term was associated with adverse foetal outcomes. There was a high (51.2%) frequency of dengue IgG positivity among pregnant women, but it was not associated with poor maternal or foetal outcomes. Acute dengue infection results in a number of physiologic changes in the human body, some of which might lead to the initiation of early labour.¹⁶ The immune response generated by body against dengue infection can promote preterm delivery by inducing placental inflammation and trophoblast apoptosis, production of inflammatory cytokines and chemokines, or fever.²¹ Some of the cytokines and chemokines produced during dengue infection, including interleukin-6 (IL-6), IL-8 and IL-18, are also present in case of preterm delivery.²² It is also likely that the presence of fever resulting due to dengue infection could promote early labour, although the

evidence linking loss of foetus to febrile episode is mixed.^{23,24} Several mechanisms have been anticipated to explain increased maternal body temperature and foetal loss, including heat shock protein interaction causing harm to the placenta or foetus and stimulation of uterine contractions.²⁵

In the present study, pregnant women who were at or near term showed foetal complications, which is consistent with other studies. Perrett et al. concluded that newborns suffered from serious dengue infection only when the mother is at or near term with insufficient time for the maternal production of protective antibodies.²⁶ In the same study most of the cases of prematurity, intrauterine deaths and miscarriages were related to hyperpyrexia.²⁶ In the present study, infants born to mothers suffering from acute dengue infection had LBW and were also preterm, suggesting that LBW was due to a shorter duration of gestation rather than impaired foetal growth in-utero.

In the present study, there were 2(16.7%) neonatal deaths and 2(16.7%) preterm deliveries. In an Indian study 2/16(12%) women had preterm deliveries.²⁷ Preterm births were reported by three studies¹⁴⁻¹⁶ from French Guiana as 9.6%, 14.9% and 22%, respectively. There were six neonatal intensive care unit (NICU) admissions (37%), three intrauterine deaths (IUDs) (18%), and one neonatal death (6%) in an Indian study.²⁷ Basurko et al. reported neonatal death rate of 1.9%¹⁵ which is similar to the present study.

Accurate and timely diagnosis of acute symptomatic dengue infection is of extreme importance in case of pregnant women and newborns. During the data collection process of the present study, it was noticed that newborns of mothers with acute dengue were not routinely screened for transmission of dengue from mother to the newborn. Another wrong clinical practice, during data collection before 2015, was to discharge patients if only IgG antibodies test was positive and dengue nonstructural protein1 (NS1) and IgM tests were negative. In that situation, the patient was not considered to be a case of acute dengue fever. However, according to Centers for Disease Control and Prevention (CDC) guidelines,²⁸ manifestation of a fourfold or greater increase in IgG antibody titers in acute and convalescent paired serum samples is a confirmation of acute dengue infection. Consideration shall be given to this in routine

diagnosis of acute dengue in order to avoid missed diagnosis. Further, as antibodies are detected later, PCR has become a primary tool to detect dengue virus early in the course of the illness, but unfortunately it is not available for routine diagnosis of dengue in Pakistan.

In most studies, infants were considered to be exposed only if their mothers had symptomatic dengue infection during pregnancy.¹⁶ Frequency of dengue IgG seropositivity among pregnant women in the current study was 51.2% (65/127). These results are slightly higher than a study conducted in Brazil which reported that 53.9% subjects had dengue IgG antibodies among 505 recruited mothers, of whom 100 had previous history of dengue fever and 184(45.4%) were dengue IgG seropositive.²⁹ In a study conducted in Malaysia, 35.8% pregnant women were found to be dengue IgG seropositive.³⁰ In the present study, dengue IgG seropositivity was not associated with adverse foetal outcomes. These findings are consistent with the Malaysian study which reported that dengue IgG seropositivity had no harmful effect on obstetric and neonatal outcome.³⁰ However, this much high frequency of dengue IgG seropositivity is alarming as it can lead to severe secondary dengue infection in pregnant women which can lead to adverse foeto-maternal outcomes. Further studies with larger sample size can provide more insight.

Limitations of the current study are that in phase-1 some pregnant females were enrolled retrospectively. Dengue PCR tests of all mothers and newborns were not performed due to non-availability of dengue PCR facility at the participating hospitals.

Conclusion

Transmission of dengue virus should be suspected in newborns of mothers suffering from acute dengue infection, especially at or near term. In dengue-endemic areas, newborns of dengue-positive mothers shall be screened for acute dengue infection. Frequency of dengue IgG seropositivity was high among pregnant women which can lead to severe secondary dengue infection in mothers. In dengue-endemic areas, pregnant women should be advised to strictly practise preventive measures to avoid severe secondary dengue infection.

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