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Original Research Article

Liver transaminase enzyme analysis as a predictor of poor maternal outcome in pregnant women with dengue

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ABSTRACT

Objective: To find out predictive value of elevated liver transaminases as a predictor of poor maternal outcome in pregnant women with dengue infection.
Study Design: Our study was a retrospective study, conducted in a tertiary care centre of North India from July 1 to December 31, 2021. Data of all the pregnant women with dengue infection during the above period was screened for maternal and fetal outcomes. Elevated liver transaminases in women who developed DHF, DSS and maternal mortality were the main outcome measures. Mode of delivery, obstetric complications, medical complications (Dengue Hemorrhagic Fever, Dengue shock syndrome and Acute Respiratory Distress Syndrome) and KFT for prediction of maternal mortality were the secondary outcome measures.
Statistical Analysis: The association of liver transaminases derangement with stage of dengue at diagnosis were analysed using Fisher's exact test. Data analysis was done with Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21. P value of less than 0.05 was considered statistically significant.
Result: A total of 35 women were included in the study. The mean age was 23.49 + 2.94 years. Acute respiratory distress syndrome, acute kidney injury, atonic PPH, and puerperal sepsis developed in 6(17.14%), 7(20%), 4(8.57%), and 10 (28.57%) women respectively. The maternal mortality rate was 25.71%. All women who developed DHF (3 women) and DSS (9 women) had altered liver enzymes. Alanine transaminase has very high sensitivity (100%) and specificity (76.92%) as a predictor of maternal mortality in pregnant women with dengue, ($p<0.05$). Similarly, serum creatinine levels at a value of more than 0.9 mg/dl had a sensitivity and specificity of 88.89% and 92.31%, respectively for predicting maternal mortality in pregnant women with dengue, ($p<0.05$). Conclusion: Elevated liver transaminases can be used as predictors of poor maternal outcome in pregnant women with dengue infection.

1. 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 stranded RNA virus belonging to the family Flaviviridae. Dengue is transmitted by the bite of Aedes aegypti and Aedes albopictus. It is a major public health problem, especially in tropical and subtropical 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 incidence of dengue cases in India has gradually increased

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in the last two decades.[3]

The burden of dengue in pregnancy on maternal ill health is not well understood. Dengue during pregnancy has been associated with poor maternal and fetal outcomes. During all three trimesters, physiological changes includes decreased in concentration of total bilirubin in pregnancy. Early signs of dengue hemorrhagic fever (DHF) like– may be masked by the physiological changes in pregnancy. Therefore, it may be difficult to pick altered hematological parameters and/or derangement of liver enzymes in the early course of disease, thus leading to misdiagnosis.[4,5] There is some evidence that the risk of severe dengue and of hospitalization due to dengue is higher among pregnant compared with non-pregnant women[6] and reported maternal deaths and other complications such as premature birth, abruption, hemorrhage, increased rate of caesarean section and still births as being associated with dengue.[7]

Against this background, the present study was planned to find out the significant association of liver transaminases in determining maternal outcome in patients suffering from dengue fever.

2. Materials and Methods

Our study is a retrospective study, data of all the pregnant women who were admitted to the obstetric ward of a tertiary care centre of North India from July 1 to December 31, 2021 was screened and cases of women who had dengue infection were analyzed for the outcome of pregnancy and dengue related complications.

As per hospital protocol, dengue was diagnosed by positivity of non-structural protein antigen 1 (NS1 antigen) or dengue IgM antibodies in the sera, irrespective of gestational age. NS1 antigen assay (Pan Bio, Queensland Australia) was done if the presentation was within 3-5 days after the onset of clinical symptoms and/or Dengue antibodies (DENV IgM) were detected using ELISA (NIV, Pune) if presentation was more than 5 days after the onset of clinical symptoms.

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 normalized ratio) were recorded.

Maternal outcomes like ICU/Ward stay, mode of delivery, gestational age at delivery, any obstetric complications, fetal condition and any dengue related complications like shock, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) and acute liver failure that developed during the course of hospital stay were recorded. All cases of maternal deaths during the course of hospitalization(treatment) were recorded in detail.

Statistical Analysis: The presentation of the Categorical variables was done in the form of number and percentage (%). The association of liver transaminases derangement with stage of dengue at diagnosis were analyzed using Fisher's exact test as at least one cell had an expected value of less than 5. Receiver operating characteristic curve was used to find cut off values of liver function test (LFT) and kidney function test (KFT) for predicting DHF/ Dengue Shock Syndrome (DSS) and maternal mortality. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

3. Results

A total of 35 pregnant women who were diagnosed with dengue infection were included in the study. The mean age of the women was 23.49 + 2.94years. Most women (71.43%), presented with fever at the time of admission. The median temperature at admission was 100.0 F (range 99.9 – 104.2 F). Other complaints were chills, breathlessness, headache, rigors, altered sensorium, jaundice, leaking per vaginum (Table 1). 17.15% women had poor GCS at admission (Table 2).

Table 1: Distribution of symptoms and signs of study subjects

Symptoms	Frequency	Percentage
Chills	10	28.57%
Fever	25	71.43%
Breathlessness	7	20.00%
Headache	2	5.71%
Rigor	3	8.57%
Absent FM	1	2.86%
Moderate anemia	1	2.86%
Leaking per vaginum	4	11.43%
Atonic PPH	1	2.86%
Body pains	1	2.86%
Cough	1	2.86%
Epistaxis	1	2.86%
Nose bleed	1	2.86%
Jaundice	1	2.86%

24 (68.58%) women presented in 3^{rd} trimester, out of which 3 (8.57%) had maternal death. 9 women presented in the puerperium period, out of which 5 (14.2%) had maternal death (Table 3).

Total of 9(25.71%) were diagnosed with DSS at admission (Table 4). Mortality and maternal near miss was significantly more among women with DSS than among women with dengue fever. A total of 9 women (25.71%) had maternal mortality out of which 8 women (22.8%) presented with DSS, most of them expired within 72 hours

Table 2:

Signs		
Poor GCS with shock	6	17.15%
Paraparesis	1	2.86%
APE	1	2.86%
Altered sensorium	1	2.86%
Tachypnoea	1	2.86%
Wound infection	1	2.86%
Maternal tachycardia	1	2.86%

Table 3: Maternal outcomes among the study women

Pregnancy length at diagnosis (weeks+days)	**Number of women (%)**	**Stage of dengue at diagnosis**	**Mode of delivery**	**Maternal outcome**
<14	1(2.86)	Dengue fever: 1/1	Missed abortion	Full recovery
14-27+6	1(2.86)	Dengue fever: 1/1	FTNVD	Full recovery
28-36+6	12(34.29)	Dengue fever:6/12 DHF: 3/12 DSS: 3/12	1 LSCS 9 NVD 2 In- utero death	Maternal mortality: 2/12 Infective endocarditis: 1/12 Full recovery: 9/12
>=37	12(34.29)	Dengue fever: 12/12	2 LSCS 10 NVD	Maternal mortality: 1/12 Full recovery: 11/12
Post natal	9(25.71)	Dengue fever: 3/9 DSS: 6/9	5 NVD 4 LSCS	Maternal mortality: 5/9 Full recovery: 4/9

of admission, 3 women came with DHF, all of them required admission in obstetric critical care unit and were discharged after full recovery.

16 (45.71%) women developed thrombocytopenia with a platelet count of <100000. 6 women (17.15%) with DSS and 2 women (5.71%) with DHF required platelet transfusion (Table 5).

One woman had missed abortion, and was medically managed. Most of the maternal complications includes acute respiratory distress syndrome (17.14%), acute kidney injury (20%), preterm rupture of membranes (11.42%), preterm labour (14.28%), thrombocytopenia (45.71%), atonic PPH (8.57%), puerperal sepsis (28.57%) and wound gape (8.57%).

Fetal complications were still births (11.43%), NICU admission (22.85%), neonatal sepsis and neonatal mortality. 2 cases (5.71%) of neonatal death were recorded at day 7 and day 10 respectively, cause of both the deaths was neonatal sepsis.

Predictive value of liver and kidney function tests was calculated for prediction of maternal mortality and severity of dengue (DHF/DSS). ALT value of more than 65 IU/L had a sensitivity of 100% and 91.67% in predicting maternal mortality and development of DHF/DSS, respectively (Tables 6 and 7).

4. Discussion

This retrospective study was done in a tertiary care centre in North India over a period of 6 months. 35 women who tested positive for dengue infection were included in the study and were analyzed for maternal and fetal outcome. Most patients in our study were in the third trimester of pregnancy at the time of diagnosis. This is similar to results published by other studies.[8–13] This is likely because women at early gestations and dengue are managed in medicine ward, while those at later gestations are managed in obstetric ward.

Our study has demonstrated a high rate of adverse maternal outcomes for pregnant women with dengue. 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 turns 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 a frequent cause of death in dengue.[14] Most of the cases of dengue deaths (8 women) in our study were accompanied with MODS (Multi-Organ Failure). 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.[15] In our study also, we found that all women who died had both these features.

We found high incidence of atonic PPH (8.57%) in our study, which was similar to study conducted by Rinnie Brar et al.[16] Post- partum hemorrhage, due to dengue associated thrombocytopenia is a significant concern in

Table 4: Clinical details of cases of dengue shock syndrome

Case	Maternal age (years)	Pregnancy length at diagnosis (weeks+days)	Clinical presentation	Delivery outcome
1	19	35+5	Chills, Fever, Rigor, Body pains	MSBIUD F/B NVD followed by Atonic PPH
2	28	31	Chills, Fever, Poor GCS, Paraparesis	In- utero death
3	24	Post op day 11	Fever, APE	PTLSCS
4	21	Post natal day 3	Breathlessness, Altered sensorium, Tachypnoea	FTIUD F/B NVD
5	19	Post natal day 3	Fever, Shock	FTNVD
6	26	Post op day 8	Poor GCS, Wound infection	FTLSCS
7	22	Post op day 6	Fever, Poor GCS	PTLSCS I/V/O TRIPLETS
8	25	35+6	Fever, Poor GCS, Epistaxis, Nose bleed	In- utero death
9	26	Post natal day 21	Fever, Poor GCS, Jaundice, Pneumothorax	FTIUD F/B NVD

Table 5: Platelet count among the study group women

Platelet count, cell/mL	Number of women (%)	Underwent platelet transfusion
<50000	9(25.71)	5
50000 to 100000	7(20)	3
>100000 to 150000	4(11.43)	1
>150000	15(42.86)	-

Table 6: Derangement of liver and kidney function tests for prediction of DHF/DSS and maternal mortality.(DHF/DSS)

Variables	Serum bilirubin (mg/dL)	AST(U/L)	ALT(U/L)	Blood urea (mg/dL)	Serum creatinine (mg/dL)
Area under the ROC curve (AUC)	0.975	0.986	0.899	0.87	0.813
Standard Error	0.0209	0.016	0.0627	0.0821	0.0871
95% Confidence interval	0.856 to 1.000	0.874 to 1.000	0.749 to 0.975	0.713 to 0.959	0.646 to 0.925
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.0003
Cut off	>1	>149	>65	>50	>0.8
Sensitivity (95% CI)	91.67% (61.5 - 99.8%)	91.67% (61.5 - 99.8%)	91.67% (61.5 - 99.8%)	75% (42.8 - 94.5%)	75% (42.8 - 94.5%)
Specificity (95% CI)	95.65% (78.1 - 99.9%)	100% (85.2 - 100.0%)	82.61% (61.2 - 95.0%)	100% (85.2 - 100.0%)	86.96% (66.4 - 97.2%)
PPV (95% CI)	91.7% (61.5 - 99.8%)	100% (71.5 - 100.0%)	73.3% (44.9 - 92.2%)	100% (66.4 - 100.0%)	75% (42.8 - 94.5%)
NPV (95% CI)	95.7% (78.1 - 99.9%)	95.8% (78.9 - 99.9%)	95% (75.1 - 99.9%)	88.5%(69.8 - 97.6%)	87% (66.4 - 97.2%)
Diagnostic accuracy	94.29%	97.14%	85.71%	91.43%	82.86%

pregnant women with reported rates of 2.2-30%.[9,10,17,18] Balloon tamponade, intensive monitoring and management, accompanied with blood products transfusion is required to manage such cases.

Antibiotic prophylaxis was given to 75% women in our study. Despite that, puerperal sepsis was encountered in 10 women (28.57%), out of which 8 developed MODS and expired. 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. Differentiation between the two can be made easier using serum procalcitonin levels.[19] However, serum procalcitonin levels cannot be used reliably in cases of kidney injury and sound clinical judgement is needed in these cases.[20]

Pre-mature rupture of membranes was seen in four women (11.43%). Four women (11.43%) developed pre-eclampsia, out of which 2 women (5.71%) developed Ante-partum eclampsia. Both of these women developed MODS and died. Several case reports have highlighted the occurance of pre-eclampsia and eclampsia in pregnant

Table 7: Maternal mortality

Variables	Serum bilirubin (mg/dL)	AST(U/L)	ALT(U/L)	Blood urea (mg/dL)	Serum creatinine (mg/dL)
Area under the ROC curve (AUC)	0.872	0.85	0.897	0.85	0.944
Standard Error	0.0624	0.11	0.0523	0.106	0.0386
95% Confidence interval	0.715 to 0.960	0.689 to 0.948	0.748 to 0.974	0.689 to 0.948	0.811 to 0.993
P value	<0.0001	0.0014	<0.0001	0.001	<0.0001
Cut off	>1	>149	>65	>60	>0.9
Sensitivity (95% CI)	88.89% (51.8 - 99.7%)	88.89%(51.8 - 99.7%)	100%(66.4 - 100.0%)	77.78%(40.0 - 97.2%)	88.89%(51.8 - 99.7%)
Specificity (95% CI)	84.62% (65.1 - 95.6%)	88.46%(69.8 - 97.6%)	76.92%(56.4 - 91.0%)	96.15%(80.4 - 99.9%)	92.31%(74.9 - 99.1%)
PPV (95% CI)	66.7% (34.9 - 90.1%)	72.7%(39.0 - 94.0%)	60%(32.3 - 83.7%)	87.5%(47.3 - 99.7%)	80%(44.4 - 97.5%)
NPV (95% CI)	95.7% (78.1 - 99.9%)	95.8% (78.9 - 99.9%)	100% (83.2 - 100.0%)	92.6% (75.7 - 99.1%)	96% (79.6 - 99.9%)
Diagnostic accuracy	85.71%	88.57%	82.86%	91.43%	91.43%

women with dengue infection.[21–25]

One patient was referred to our institute on post-operative day 3 of cesarean done in view of ante-partum eclampsia. Patient was in shock and emergency laparotomy was done in view of rectus sheath hematoma. Multiple blood products transfusion were done, inspite of that she developed ischemic brain injury and died. One woman who presented to us in the early third trimester (29+3 weeks) developed infective endocarditis which was diagnosed on echocardiography. She was managed in medicine ICU. In our study, there were two cases of co-infection with enteric fever, one case had co-infection with hepatitis A virus and one with hepatitis E virus.

In our study, there were 7 women (20%) had caesarean section. 3 women (13.04%) had caesarean in our hospital, all were done for maternal indications. 4 women were referred to our institute post caesarean. All of them were in poor general condition, we could save one of them whereas three had maternal mortality. In our study, the rate of caesarean section was not high as compared to the normal women, whereas a number of case series report increase rate of caesarean delivery in women with dengue.[7] 16 (45.71%) women developed thrombocytopenia with a platelet count of <100000, of which 5 had a platelet count of <50,000. 8 out of these 16 women required platelet transfusion out of which 6 had DSS and 2 had DHF. In one patient with dengue fever platelet were arranged for cesarean section. The need for platelet transfusion is more in pregnant women with dengue as seen in the other studies also.[26,27]

During the study period there were a total of 90 maternal deaths at our centre out of which 9 deaths (10%) were due to dengue. Dengue fever is typically a self-limited disease with mortality rate of less than 1% in general population (WHO). We found a maternal mortality rate of 25.71% which was much higher as compared to non-pregnant patients. Out of 9 patients who had maternal mortality 7 patients were referred to our hospital in poor general condition and expired within 72 hours of admission.

Liver transaminases were deranged in 16(69.57%) patients with dengue fever, whereas all the patients who had DHF and DSS had deranged liver enzymes. Elevated transaminases and creatinine levels have also been found as independent predictors of mortality in non-pregnant dengue patients.[15] In our study also, we found that sensitivity of ALT at a value of 65IU/L was 100% for prediction of maternal mortality. Diagnostic accuracy of deranged kidney functions was 91.43% for the prediction of maternal mortality at the cut off value of 60 mg/dl and 0.9 mg/dl for serum blood urea and creatinine, respectively. Our results were similar to the study conducted by Rinnie Brar et al.[16]

We found still birth rate of 11.42% which was similar to the study conducted by Rinnie Brar et al.[16] Rates of still birth in previous studies have been reported from 3.8 to 13.1%.[7,8,15,17] In a study conducted in Mexico by Carlos et al[21] no association was found between dengue and fetal or prenatal death. The rates of fetal adverse outcome in our study were high with 7 women (20%) had pre-term births, 8 babies (22.8%) required NICU admissions, 10 women (28.5%) delivered LBW babies, and two (5.71%) neonatal deaths. There were 2 cases of neonatal death at day 7 and day 10 respectively. The cause of both the deaths was meningitis due to neonatal sepsis. Two meta-analyses on adverse fetal outcomes in pregnancies with dengue reveal conflicting results regarding the association of dengue with pre-term births and low birth weight.[28,29] Till concreate 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 in anticipation of preterm births and low birth weights. Due to non-availability of fetal samples for serological reporting, it is not possible for us to comment on perinatal transmission of dengue.

A similar study was done in our hospital by Agarwal K et al. in 2015,[26] for the same duration of time (6 months). 62 cases with dengue infection were reported whereas in our study 35 cases were reported highlighting the limitation of hospital admission admist prevailing covid-19 pandemic. The caesarean rate in our study was less as compared to the previous study.[26]

All the women admitted or diagnosed with dengue were included in the study and were followed for maternal outcomes. The women admitted under other specialities were not included in this study. According to our institutional protocol, dengue in early pregnancy is managed under medicine department. This study was hospital-based and hence, this study does not evaluate the burden of dengue in pregnancy as only women who were admitted in the hospital were included in the study. Ours is the one of the largest referral centre of North India and hence it 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.

5. Conclusion

Dengue in pregnancy adversely affects maternal and fetal outcomes with high maternal mortality. Deranged liver and kidney function tests are predictors of poor maternal outcomes in pregnant women with dengue infection.

6. Source of Funding

None.

7. Conflict of Interest

None.

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