Bangladesh J Obstet Gynaecol, 2019; Vol. 34(1): 36-42

Review Article

Dengue in Pregnancy

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Abstract:

Dengue fever during pregnancy is increasing day by day in Bangladesh. The knowledge of adverse effects on mother and neonate remains limited and there are also lack of management guideline in this regard. Mortality rate for severe dengue fever is 0.8–2.5%, and pregnancy should be considered as a coexisting risk factor for serious infection. However, the maternal and fetal outcomes not fully understood. Some review articles on outcomes of neonates born to mother with dengue fever was reported, and demonstrated that preterm birth and low birth weight were the most common adverse pregnancy outcomes; however, dengue fever was not significantly associated with these adverse outcomes, suggesting that symptomatic dengue fever may indicate risk. Other adverse effects such as stillbirth or postpartum hemorrhage (PPH) remain unclear. Therefore, we aimed to brief review of recent management guideline of OGSB about dengue fever in pregnancy.

Key words: *Dengue fever, Pregnancy, Maternal and fetal outcome.*

Introduction:

Dengue is one of the fastest growing emerging infectious disease in the world. Dengue Fever is a viral disease caused by any of 4 closely related serotypes of Flavivirus (RNA virus). Aedes mosquitoes, particularly A. aegyptiis a vector transmitting it to human[1]. Early detection and access to proper medical care reduces fatality from 20% to below 1%[2].The prevalence of dengue has grown dramatically around the world in recent decades. A vast majority of cases are asymptomatic and hence the actual number of dengue cases are under-reported and many cases are misclassified. One estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically with any severity of disease[3]. Another study on the prevalence of dengue, estimates that 3.9 billion people in 128 countries are at risk of infection with dengue viruses. Member States in three WHO regions regularly report the annual number of cases[4]. The number of cases reported increased from 2.2 million in 2010 to over 3.34 million in 2016. Although the full global burden of the disease is uncertain, the initiation of activities to record all dengue cases partly explains the sharp increase in the number of cases in recent years[5].

Dengue case burden in Bangladesh: Bangladesh first experience a large outbreak of Dengue in the year 2000 with 5551 cases with case fatality of 93. Aedes aegyptiis was identified as the main vector responsible for the epidemic, and Aedes albopictus was identified as a potential vector in Chittagong. According to WHO the worst outbreak occurred in 2002 with 6,232 cases and 58 deaths. The prevalent serotypes of dengue until 2000 in Bangladesh were: DENV1, DENV2 and DENV3, with the highest number of reported cases attributed to DENV-3.The containment of the disease was successfully handled afterword and was rewarding. Even between the year 2007 to 2011 very lower number of cases reported with no death record. From 2015 the incidence again started rising with few deaths. This is obviously a change in epidemiology of the disease. In 2019 it crossed 50,000. With increasing rate of adult dengue fever victims, the number of infected pregnant women has also been increased[6].

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Pathophysiology of Dengue Infection: After an infective mosquito bite, the virus replicates locally at the site of inoculation in the reticuloendothelial system or fibroblast or both. Primary dengue infection develops serum antibodies that can neutralize the homologous serotype[7]. In a secondary infection, the pre-existing heterologous antibodies form complexes with the new infecting virus serotype, but do not neutralize the new virus. Antibody-dependent infected monocytes act as antigen presenting cells (APCs) to induce release of lymphokines and other factors from activated T cells. Tumour Necrosis Factor IL-1² IL-2, IL-6, IL-8, Interferon (IFN)-³, RANTES etc[8] are the cytokines that are released from these cells. These cytokines along with complement breakdown products (C3a, C5a) are activated, increases vascular permeability of vascular endothelial cells leading to Dengue Shock Syndrome (DSS). Bleeding is a major problem in Dengue Hemorrhagic Fever (DHF) resulting from combination of vascular endothelial cell damage, thrombocytopenia, platelet dysfunction and blood clotting defects. The positive tourniquet test and petechiae are the common clinical manifestation of bleeding[9].

Clinical Presentation:

- Asymptomatic Infection: Majority of Dengue in Pregnancy may be asymptomatic or minimally symptomatic.
- Symptomatic Dengue Fever: The body temperature is usually between 39 °C and 40 °C (102° F to 104° F) and the fever may be biphasic, lasting 2-7 days in the majority of cases. Headache, Retro orbital pain, Myalgia and Arthralgia (break-bone fever) are also presenting symptom[10].
- Rash: First 2 to 3 days diffuse flushing or fleeting eruptions may be seen on the face, neck and chest. On third and fourth day a conspicuous rash petechiae surrounding scattered pale round areas of normal skin may appear over the dorsum of the feet, on the legs and on the hands and arms. Skin itching may be observed[11].

Diagnosis: Tourniquet test positive and leucopenia (WBC <5000/cumm) have positive predictive value of 83%

Dengue Hemorrhagic Fever (DHF): Patients present with high continuous fever for 2-7 days, hemorrhagic manifestations, tourniquet test positive, petechiae, epistaxis, heamatemesis, P/V bleeding , enlarged liver and shock.

Laboratory evidences of plasma leakage are rising hematocrit >20%, pleural effusion, ascites, hypoalbuminaemia (serum albumin < 3.5 gm% or <4gm% in obese patients), platelet count< 100,000 cells/mm3.

Dengue Shock Syndrome (DSS): When DHF manifests circulatory failure with one or more of the following features which develop as a result of significant loss of plasma, abnormal haemostasis and hypovolemic shock[12].The clinical features of DSS are delayed capillary refill, rapid & weak pulse, lethargy, restlessness, cold clammy skin , undetectable pulse and blood presure, thrombocytopenia ,rising hematocrit and haemoconcentration[13].

Two hallmarks of (DHF/DSS) are plasma leakage & abnormal hemostasis that may lead to severe complications and death[14].

The gestational age and the phase of dengue are important factors in determining the management of dengue in pregnancy. If dengue virus infect a pregnant woman the patient is then catagorized as moderate dengue class and should manage as per guideline.

Effects of Pregnancy on Dengue: Impact on physiology of pregnancy are cardiovascular – tachycardia, lower blood pressure, hematological – lower HcT at 3rd trimester. HCO3 level is lowered.

Some physiological changes in pregnancy may make the diagnosis and assessment of plasma leakage challenging like elevation of HcT in dengue is masked by hemodilution especially in the 2nd and 3rd trimester[15]. Serial HcT measurement is crucial for disease monitoring in pregnancy. The detection of third space fluid accumulation is difficult due to the presence of gravid uterus. Baseline blood pressure is often lower and pulse pressure wider. Baseline heart rate may be higher.

Impact of dengue on pregnancy and delivery are early abortion (3%-13%) , embryopathy specially neural tube defect, antepartum haemorrhage (APH),preterm birth (3%-33%), low-birth weight (9%-16%), IUGR, fetal distress [16], IUD or still birth (4.7%-13%.) ,increased incidence of caesarean deliveries and Post Partum Haemorrhage (PPH).

Other complications of pregnancy, often misdiagnosed are severe pre eclampsia (PE) , HELLP syndrome, abruptio placental or concealed haemorrhage[17].Severe bleeding may complicate delivery and/or surgical procedures performed during the critical phase[18].

Risk of vertical transmission: The risk of vertical transmission is well established among women with dengue during the perinatal period due to disruption of placental barrier and prolong viremia.

New born complications are Fever, Hepatomegaly, Thrombocytopenia and Circulatory insufficiency

Causes of Maternal death: Severe Antepartum Hemorrhage (APH), severe Post-Partum Hemorrhage (PPH), Dengue Shock Syndrome (DSS) and Multi Organ Failure (MOF) [19]

Causes of Fetal death: Fetal distress, fetal circulatory insufficiency and fetal coagulopathy.

Stepwise approaches of management of Dengue in pregnancy: History taking and overall assessment followed by clinical examination and diagnosis of dengue phase and severity, management decision, disease notification, hospital admission and urgent referral are the steps of management of dengue in pregnancy.

Laboratory Investigations

Dengue virus infection needs early laboratory confirmation of clinical diagnosis because some patients progress within short period from mild to severe form and sometimes death may occur.

Urgent laboratory tests are:

- Dengue NS1 antigen can be detected within 3 to 4 days of fever.
- Dengue IgM and IgG may be detected after day 5 of fever.
- Dengue 1-4 serotype virus detection by RT-PCR.

Other tests are: Nucleic Acid Detection by reverse transcriptase polymerase chain reaction (RT-PCR) is the confirmatory diagnosis within <5 days of illness. Dengue virus Isolation from serum, plasma and leucocytes is the most definitive test for dengue virus infection.

Disease Monitoring Tests: CBC should be done on first consultation of the patient to have the baseline information. Leucopenia is common in DF, has an important diagnostic implication in early period. The change in total white cell count to Ã5000 cells/mm3 and ratio of neutrophils to lymphocyte count is useful to predict the critical period of plasma leakage. This finding precedes thrombocytopenia or rising haematocrit. These changes are seen in both DF and DHF[20].

Thrombocytopenia is observed in some patients with DF. Mild thrombocytopenia of 100000 to 150000 cells/mm3 is common and about half of all DF patients have platelet count below 100000 cells/mm3.A sudden drop in platelet count to below 100000 occurs before the onset of shock or subsidence of fever. The level of platelet count is correlated with severity of DHF[21].

Haematocrit: Slight increase may be due to high fever, anorexia and vomiting which occur in 10% of cases. A sudden rise in haematocrit is observed simultaneously or shortly after the drop in platelet count. Haemoconcentration or rising haematocrit by 20% from the baseline, e.g. from haematocrit of 35% to > 42% is objective evidence of leakage of plasma. It should be noted that the level of haematocrit may be affected by early volume replacement and by bleeding[22].

Biochemical Tests: Serum AST (SGOT) and ALT (SGPT levels are frequently elevated with DF and DHF. AST and ALT levels are significantly higher at 5 to 15 times in patients with DHF. Commonly AST is increased more than ALT in these cases.

In Special Cases: Hyponatremia is frequently observed in DHF and is more severe in shock. Hypocalcemia has been observed in DHF. Metabolic acidosis is frequently found in cases of prolonged shock. Blood urea nitrogen is also elevated in prolonged shock.

Coagulation Profile: Coagulation failure may occur in DSS. Activated Partial Thromboplastin Time (APTT) and Prothrombin time are prolonged in about half and one third of DHF respectively. Thrombin time is also prolonged in severe cases[23].

Fetal well-being evaluation: USG of pregnancy profile which includes gestational age, Fetal Heart Rate (FHR), fetal weight , fetal presentation ,AFI , placental position and maturation. Cardiotocography (CTG) and Biophysical profile should also be done for fetal monitoring.

Management: Patients can be divided in two groups for management purpose.

1. Suspected Dengue in pregnant women: Monitoring is important by baseline CBC on D1/D2 of fever, dengue NSI within day 3 to 4 of fever. If WBC count is normal, repeat CBC after 24 hours and compare it with further fall in platelets,rise in PCV because10% rise is considered as significant[24]

Treatment: Paracetamol 500-650 mg 6 hourly but not to exceed 4 grams in 24 hours. Warn the patient that fever may not settle with this dose, sponging for fever. No NSAID or Aspirin, oral intake encouraged like ORS, coconut water, dal, juice, soup, apart from routine food. Target is at least 3 liters of fluid intake per day. If nausea or vomiting of pregnancy restrict oral intake then IV fluid is infused. Normal saline but no plain dextrose, 100 cc/ hour is infused. Dengue Progress Chart (DPC) should be maintained.

2. Moderate Dengue fever with warning sign: No clinical improvement or worsening of the situation just before or during the transition to afebrile phase. Other warning signs are abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding like epistaxis, black stool, haematemesis, excessive p/v bleeding, pale, cold and clammy hands and feet, less or no urine output for 4-6 hours, lethargy, restlessness, liver enlargement > 2cm, APH, IUGR with fetal distress, intrauterine death (IUD) and (PPH)[25].

Treatment: Monitor vitals like BP/P/Pulse pressure, Capillary Refill hourly. Catheterization and maintenance of intake output chart are most important. Intense fluid resuscitation by Normal saline at the bolus dose of 10ml/kg/hour for 2 hours followed by 5ml/Kg/hour as a maintenance and monitored by urine output and pulse pressure. Induction of labour or planned surgery in this phase should be avoided.

DF with shock on admission : These patients need institutional management and ICU setup. Timely fluid infusion with management of any warning symptom practically prevents further complication. Before transferring the patient need to draw blood for CBC, HCT, blood group, SGOT, SGPT, electrolytes, blood sugar etc[26]. Fluid bolus given as (NS) 10ml /kg over 15 minutes before transfer. Second bolus as 10ml/kg for next 1 hour during transfer. All reports, fluid bolus details for reference for further treatment needs to hand over.

3. Obstetrical Management

Early pregnancy management: Dengue in early pregnancy should be managed very carefully. It is very important to keep in mind that intervention can be life threatening for the mother and fetus[27]. Medical termination of pregnancy and induction of abortion should be avoided .Amniocentesis, chorionic villous sampling and cordocentesis are discouraged.

Labour and delivery management: It is the most crucial point of management of pregnant woman with Dengue virus infection. They should be managed properly during the labour and delivery. Important points to be remembered are -

- Hospital delivery
- Blood available
- Multi disciplinary approaches
- Team of skilled Obstetrician, Physician, Anesthesiologist, Neonatologist, ICU Specialists are available.
- No planed induction of labour or elective caesarean section.
- During the critical phase unless to save mother's life, Lower Segment Caesarean Section (LSCS) or induction of labour needs to be avoided.
- External cephalic version or internal podalic version should be avoided during the critical phase.
- Episiotomy or instrumental delivery should not be done.

Premature labour: Delivery awaited, till acute infection resolves. Tocolytics may be given. Inj. Steroid I/V given for the lung maturation of fetus.

Inevitable delivery during critical phase: If delivery is inevitable, bleeding should be anticipated and closely monitored. Fresh whole blood/fresh packed red cells should be administered as soon as possible if significant bleeding occurs. If blood loss can be quantified it should be replaced immediately. Waiting for blood loss to exceed 500ml before replacement, as in postpartum hemorrhage is not encouraged.

Prophylactic platelet transfusion is NOT recommended unless delivery is inevitable in coming 6 hours or Platelet count is between 50000 to >75000/ mm^3 for operative delivery[28]. Active Management of third stage of labour (AMTSL).Misoprostol may be

given for PPH prophylaxis or treatment. Prophylactic balloon tamponade given if delivery occur in critical phase of dengue. Prophylactic Inj. Tranexamic acid 1 gm in 10ml administered slowly with a second dose of 1 gm IV if bleeding continues after 30 min. Intramuscular injections or skin prick for blood sugar monitoring should be avoided

In case of fetal compromise priority should be given to the mother's life and decision making should involve the multidisciplinary team. Counseling the family on the probable outcome is essential.

Newborn care: Early cord clamping is advised and cord blood is sent for CBC, NSI antigent test, Dengue antibody test, Blood grouping and Rh typing.

Post-partum care : Newborn of mother with dengue just before or at delivery, should be closely monitored in hospital in view of the risk of vertical transmission. Severe fetal or neonatal dengue illness and death may occur when time is insufficient for the production of protective maternal antibodies[29].Breast feeding encouraged and allowed. Stable pulse, blood pressure and breathing rate, normal temperature , no evidence of external or internal bleeding, return of appetite, no vomiting, no abdominal pain ,good urinary output, stable hematocrit at baseline level, convalescent confluent petechial rash or itching, especially on the extremities are the sign of recovery.

Discharge criteria : She must be afebrile for 48 hours without antipyretics, stable hematocrit for at least 24 hours with baseline value of around 38-40 % .When baseline value is not known, rising trend in platelet count above 50000/mm3, no dyspnea or respiratory distress attributable to pleural effusion, no ascites, no or minimal visible bleeding[30], fully recovered organ dysfunction, no excessive P/V bleeding, stable maternal & fetal condition are the criteria to discharge the patient from the hospital.

Ten Points to be remembered

1. No NSAID (Ibuprofen/Diclofenac) for fever. Only Paracetamol can be given. Daily dose should not exceed 4 gram.
2. Resuscitation: Normal saline 0.9% should be used for initial resuscitation. Plain Dextrose solution NOT to be used. Colloids can be given only after 2 fluid boluses in patients with shock has been infused.
3. Fresh blood transfusion (BT) is only indicated if there is overt blood loss nearing 500 cc. No overt bleeding but drop in HCT without clinical improvement despite adequate fluid replacement is also indication of BT.
4. Prophylactic platelet transfusion is not recommended unless delivery is inevitable in coming 6 hours and platelet count should between 50000/CC and 75000/cc for operative delivery.
5. There is no role of IV immunoglobulin or prophylactic antibiotics.
6. Inj. steroid advised I/V for lung maturation of fetus.
7. Operative delivery for obstetric indications only.
8. AVOID Planned INDUCTION or surgery. The presence of wounds or trauma during the critical phase of dengue with marked thrombocytopenia, and plasma leak creates a substantial risk of severe hemorrhage.
9. Delivery should take place in a hospital where facility for blood/blood components transfusion, a team of skilled obstetricians and a neonatologist are available with ICU and NICU support.
10. Tocolytics and measures to postpone labor to a suitable time may be considered during the critical phase of dengue illness.

Conclusion:

The clinical presentation of dengue in pregnancy is slight different than non-pregnant adults. A high index of clinical suspicion is essential in any pregnant woman with fever during epidemic. The gestational age at presentation of dengue fever appeared to be significant[31] prognostic factor. Early onset or late onset in pregnancy appeared to have a bad prognosis. Conservative treatment should be given unless there are complications. Early diagnosis and treatment helps to prevent complications, maternal and fetal mortality and morbidities[32].Awareness about clinical and laboratory manifestations of dengue in pregnancy helps its early recognition and institution of appropriate treatment to prevent maternal and fetal mortality and morbidity.

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