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## Clinical management of dengue infection in pregnancy

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Dengue epidemics have become a serious concern in tropical and sub-tropical regions globally [1]. Several countries are also reporting a demographic shift of dengue from a disease that primarily occurs in children to one that increasingly affects adolescents and adults [1,2] and Sri Lanka is no exception. In 2017, during the worst dengue epidemic to be reported in Sri Lanka, the mean age of dengue patients was 29.7 years [4]. This transition is challenging early diagnosis and clinical management, and requires more standardized approaches to be extended to age groups beyond children. Delayed or misdiagnosed dengue infection with improper clinical management can lead to complications and even cause death [5].

Increasing number of pregnant women infected with dengue virus can have poor outcome without early identification of clinical disease and proper medical care. In fact, dengue haemorrhagic fever (DHF), the more severe form of dengue illness, was the leading cause of maternal deaths in the analysis of maternal mortality in Sri Lanka for the year 2017 [6]. It is also noted that a higher proportion of DHF occurs commonly among pregnant women than among non-pregnant women [7]. Furthermore, acute dengue illness during the third trimester is known to increase the risk of foetal compromise, inadvertently requiring higher chance of surgical interventions for delivery [8].

Although Sri Lanka has standardized the clinical management of dengue infection over the past several years with an overall reduction in the case fatality rate [9], maternal morbidity and mortality due to dengue had remained challenging. Therefore, a dedicated practice guideline on clinical management of dengue in pregnancy was considered an urgent need. A technical expert team was formed, with the Epidemiology Unit, Ministry of Health being the focal point, led by the President of the Sri Lanka Medical Association (2019), and including the Presidents of the Sri Lanka College of Obstetricians and Gynaecologists (2019) and Ceylon College of Physicians (2020), together with several other selected contributors. Based on clinical experience, expert reports, publications and opinion of practicing clinicians, comprehensive practice guidelines on clinical management of dengue in pregnancy were developed [10]. The key recommendations of this guideline are summarized below.

All pregnant women with acute onset of fever should be advised to get admitted to a hospital early, preferably at least by Day 2 of fever. Such patients,



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despite a normal full blood count (FBC) report (with normal white blood and platelet counts), should be managed in a hospital where specialist cover is available. Management of dengue in pregnancy should be through a multi-disciplinary team (MDT) approach, involving the obstetric team, internal medicine physician, neonatologist/paediatrician and intensivist. In a pregnant woman presenting late to hospital in shock (with a history of fever but afebrile at presentation with clear consciousness), dengue shock syndrome (DSS) should be considered early as a likely diagnosis. Usually, DSS is an extension of DHF state where excessive plasma leakage results in hypovolemic shock. However, in a pregnant woman with DSS, in addition to plasma leakage, bleeding (concealed or overt) is a common occurrence, which needs to be suspected and addressed early.

Significant physiological changes take place in all organ systems during pregnancy, labour and in the post-partum period [11]. Thorough understanding of these changes and application of that knowledge into clinical practice is important in the management of a pregnant dengue patient. We have highlighted below, several key changes and their relationship to dengue.

In the cardiovascular system, the heart rate which increases throughout gestation, peaks in the late third trimester with an upper limit not greater than 95 bpm. Pregnant dengue patients with a resting heart rate more than 100 bpm (without fever) are generally considered to have tachycardia and warrant further evaluation. Systemic vascular resistance (SVR) progressively drops by approximately 35-40% in the mid second trimester. Reduced SVR leads to low diastolic blood pressure (dBp). Diastolic blood pressure decreases more than systolic blood pressure (sBP) during pregnancy leading to increase in pulse pressure (wide PP). In a non-pregnant dengue patient PP  $\leq 20$  mmHg is defined as compensated shock. In the backdrop of wide PP during pregnancy narrowed PP of  $\leq 25$  mmHg indicates compensatory shock.

In pregnancy, the degree of change in blood pressure (BP) is influenced by the posture. Assumption of supine position can lower the venous return to the heart by 30-40% due to the compression on inferior vena cava by the gravid uterus leading to a substantial reduction in cardiac output and BP [12]. Blood pressure should be measured in complete left lateral or 15-30 degree left laterally tilted position during resuscitation of pregnant women with DHF. In a DHF patient with plasma leakage, postural hypotension is a feature of volume depletion (due to plasma leakage/bleeding or both) which may be incorrectly interpreted as supine hypotension syndrome.

During pregnancy there is reduction in pulmonary vascular resistance, increased pulmonary blood flow with normal mean pulmonary arterial pressure. Plasma colloid osmotic pressure is reduced by 10-20% due to reduced albumin level. The colloid osmotic pressure/pulmonary capillary wedge pressure gradient is reduced by about

30% making the pregnant women particularly susceptible to pulmonary oedema [12]. Pulmonary oedema will be precipitated if there is either a sudden increase in cardiac pre-load (such as rapid fluid bolus if given in DHF) or increased pulmonary capillary permeability (such as in pre-eclampsia). Hence, leaky capillary state as seen in DHF can easily precipitate pulmonary oedema particularly in a pre-eclamptic woman.

Plasma volume expands progressively until 30-34 weeks of gestation and then plateaus or decreases slightly until term. The total gain of plasma volume at term is 30-50% above that of non-pregnant women [12]. Likewise, the blood volume increases and reaches about 50% by 30th week of gestation with a similar increase in venous return and cardiac output until term. A pregnant woman with DHF may not show features of hypovolemia even with significant blood loss until late stages (i.e., hypotension will appear later than in a non-pregnant woman). Therefore, a blood transfusion should be considered in DHF even with a normal blood loss during delivery (400-500 ml of blood loss).

Maternal hypotension and compression of the aorta by the gravid uterus lead to a reduction of utero-placental blood flow [13]. Foetal distress may be an early indication of maternal haemodynamic decompensation in pregnancy with DHF having capillary plasma leaking. In such patients, early adjustment of fluid resuscitation is important before considering termination of pregnancy by intervention.

Red blood cell (RBC) mass steadily rises up to levels 20-30% higher by the end of pregnancy [12]. However, the increase in RBC mass is smaller than the increment in plasma volume which contributes to the physiological anaemia of pregnancy (normal haemoglobin of 10.5-13.5 g/dl and haematocrit of 32-34%). A haematocrit of 38-40% in a pregnant woman may indicate leaking in DHF (haematocrit rise towards 20%) which may be within the normal range in a non-pregnant woman.

Pregnancy is associated with leucocytosis. White blood cell count (WBC) ranges from 9,000-15,000 cells/ $\mu$ l, while further rise may occur during labour up to 25,000 cells/ $\mu$ l [14]. A WBC count of less than 5000 cells/ $\mu$ l (leukopenia) classically seen in dengue infection may not be seen in febrile pregnant dengue patients. Observing a downward trend of WBC count is important even in the absence of leukopenia. Cell mediated immunity is also suppressed to prevent rejection of foetus, making pregnant women more susceptible to viral infections such as dengue [14].

A mild decrease in platelet counts, from pre-pregnant levels, occurs in women during uncomplicated pregnancy (gestational thrombocytopenia, GT) during the 2<sup>nd</sup> trimester and more commonly in 3<sup>rd</sup> trimester. Platelet counts seldom drop to less than  $80 \times 10^9/L$  in GT. Pregnant women with a recent history of fever returning from an endemic area with a platelet count less than  $100 \times 10^9/L$  should be

investigated for dengue. Also, in pre-eclampsia and HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low Platelets) thrombocytopenia is a common feature [15]. Dengue should be excluded before termination of pregnancy in HELLP syndrome with a recent history of fever.

Glomerular Filtration Rate (GFR) increases as much as 50-85% in pregnancy [12]. Renal plasma flow increases up to 80% as compared with non-pregnant levels. In dengue shock syndrome (DSS) with pregnancy despite intravascular volume depletion a normal urine output may persist. As such, urine output may not be a reliable marker of the degree of shock in a pregnant woman with DSS.

Normal pregnancy is a prothrombotic state (hypercoagulable state). Compared with non-pregnant women, pregnant women have a marked increase in several coagulation factors, reduced fibrinolysis and increased platelet reactivity [14]. The activated partial thromboplastin time (APTT) and prothrombin time (PT) are slightly shortened, and INR is usually less than 1 in pregnancy. Fibrinogen levels in normal pregnancy are 3-5 g/l, which are much higher than in non-pregnant women. On the contrary, reduced platelets in pregnancy with dengue increases the risk of bleeding with the formation of an unstable clot. Consumption coagulopathy can develop easily, especially in the presence of a placental abruption. Bleeding is an important complication in pregnant dengue patients. If the patient delivers during the critical phase of DHF, bleeding is likely to be due to oozing from raw uterine surface which should be considered significant. Surgical maneuvers including caesarean sections should be avoided, particularly during plasma leakage in DHF as it can result in severe life-threatening bleeding.

In the management of DHF in pregnancy, timely and appropriate intervention should be considered based on 2 principles; a) the trimester of pregnancy (whether in late third trimester – patient in partus/immediate post-partum or not), b) phase of DHF (whether in febrile, critical or convalescent phase). During the early febrile phase of DHF, irrespective of the trimester of pregnancy, general principles of management should be considered with appropriate febrile phase monitoring to identify early leaking. Clinical accumulation of fluid in the peritoneal and pleural spaces is a late finding in DHF patients, which is further hindered by the presence of the gravid uterus. Therefore, performing repeated interval ultrasonography (USS) of the chest and abdomen for evidence of plasma leakage into the third space is an important investigation in pregnant febrile patients suspected of DHF.

Fluid management in the critical phase (leaking phase) of DHF is of utmost importance. Once it begins, plasma leaking gradually increases, reaches a peak usually around 24 hours (around the middle of the critical phase). A high rate of leaking does not persist for more than a few hours and then it slows down. In most DHF patients, the leak is not significant enough to cause haemodynamic instability leading to shock. Therefore, they would not

require much adjustment of fluids. However, in some patients, the leak can be significant enough to cause haemodynamic instability. Identification of such patients and adjusting fluid therapy will prevent them from developing shock. The total fluid quota (TFQ) calculated based on pre-pregnant body weight required during the leaking phase should be manipulated according to the patient's haemodynamic status, haematocrit and urine output (UOP) as too much fluid would lead to fluid overload and too little fluid may cause shock. The amount of fluid can be gradually increased during the critical phase, depending on need, but should be gradually reduced during the latter part of the critical phase (towards the end of leaking). If the haematocrit continues to increase, or if the patient's haemodynamic parameter/s become abnormal, it is indicative of significant reduction of intravascular volume requiring the administration of colloidal solution (10% Dextran-40 in normal saline) provided adequate crystalloids have already been given. Delayed treatment of intravascular hypovolaemia can result in prolonged shock, leading to organ failure with a high mortality. If the patient is haemodynamically stable (non-shock DHF), the TFQ should spread over 48 hours. In a haemodynamically unstable patient (i.e. presenting in shock – DSS), TFQ can be given over 24-36 hours. It is important to recognize the features indicating adequate fluid therapy/resuscitation in DHF. Clinically, improvement of general well-being/good orientation and mental state, warm peripheries with capillary refill time (CRFT)  $\leq 2$  sec, and good urine output are feature of adequate fluid therapy.

In the late third trimester, particularly if a woman is in labour, the outcome of DHF can be unfavourable unless the delivery is planned properly. Therefore, in view of possible high mortality as a consequence of emergency delivery it is advisable to follow certain principles. Induction of labour or elective caesarean section during the critical phase of the illness should be avoided as far as possible. If premature labour occurs during critical phase, it is advisable to delay the delivery until the leaking resolves by using tocolytic drugs such as nifedipine. If delivery is mandatory, induction of labour or a caesarean section may be considered during the early febrile phase of the illness before the onset of critical phase, when the platelet count is above  $130 \times 10^9/L$ . During the critical phase, vaginal delivery or caesarean section should be considered if the mother's life is at risk or if the patient develops spontaneous labour.

During pregnancy, early bleeding should be anticipated if the patient has been on non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and steroids. The threshold for blood transfusion is low with dengue in pregnancy. Treatment of bleeding is volume replacement with blood. In pregnant women with anaemia having a low haemoglobin (Hb  $\leq 8g/dl$ ) e.g. iron deficiency, thalassemia minor, with dengue, blood transfusion should be considered early. With dengue, the risk of post-partum

haemorrhage (PPH) is higher in instrumental delivery and surgical interventions. Fever during the post-partum period due to acquired dengue infection may be misdiagnosed as puerperal sepsis. Newborns with mothers who had dengue just before or at delivery should be closely monitored and investigated in hospital for up to a week in view of the risk of vertical transmission.

There are three levels of management delays that may result in an adverse clinical outcome in dengue infection during pregnancy: (1) delay in presentation to the health care system resulting in delayed admission and hence delayed identification and institution of fluids, (2) delay in appropriate management and resuscitation in hospitalized patients, and (3) delay in discontinuing fluid therapy towards the end of the critical phase resulting in fluid overload. Common primary causes of death reported in pregnant women with dengue infection are prolonged shock as a consequence of delayed/inadequate fluid therapy leading to multi-organ failure, and massive bleeding or fluid overload leading to pulmonary oedema/heart failure, or a combination of these conditions. These comprehensive clinical practice guidelines developed through technical consensus has been disseminated to all clinical healthcare settings in Sri Lanka. Favourable improvement is expected through better understanding of the physiological changes in body systems during pregnancy, and application of that knowledge into clinical practice in the management of acute dengue infections through a multi-disciplinary team approach. A series of clinical training programmes coupled with an ongoing public education campaign on early health seeking for pregnant women with fever is expected to further strengthen this initiative to ensure wider utilization of these guidelines.

## References

1. World Health Organization, Regional Office for South-East Asia. (2011). *Comprehensive Guideline for Prevention and Control of Dengue and Dengue Haemorrhagic Fever*. Revised and expanded edition. WHO Regional Publication SEARO. 2011. 196 p. <https://apps.who.int/iris/handle/10665/204894>
2. Bhatia R, Dash AP, Sunyoto T. Changing epidemiology of dengue. *WHO South-East Asia J Public Health* 2013; 2(March): 23-7.
3. Tanayapong S, Pengsaa K. Changing epidemiology of dengue patients in Ratchaburi. *Asian Biomed* 7(4): 561-6.
4. Tissera HA, Jayamanne B, Raut R, Janaki S, Tozan Y,

- Samaraweera PC, et al. Severe Dengue Epidemic, Sri Lanka, 2017. *Emerg Infect Dis*. 2020; 26(4): 682-691. <https://dx.doi.org/10.3201/eid2604.190435>
5. Tantawichien T. Dengue fever and dengue hemorrhagic fever in adults. *Southeast Asian J Trop Med Public Health*. 2015; 46 Suppl 1: 79-98.
6. Wijesinghe PS, Jayaratne K, Peiris D. National Maternal Death Surveillance and Response: Sri Lankan scenario. *Ceylon Medical Journal* 2019; 64(1): 1-3. DOI: <http://doi.org/10.4038/cmj.v64i1.8822>
7. Machado CR, Machado ES, Rohloff RD, Azevedo M, Campos DP, de Oliveira RB, Brasil P. Is pregnancy associated with severe dengue? A review of data from the Rio de Janeiro surveillance information system. *PLoS Neglected Tropical Diseases* 2013; 7(5): e2217. <https://doi.org/10.1371/journal.pntd.0002217>
8. Machain-Williams C, Raga E, Baak-Baak CM, et al. Maternal, Fetal, and Neonatal Outcomes in Pregnant Dengue Patients in Mexico. *Biomed Research International* 2018; 2018: 9643083. DOI: 10.1155/2018/9643083.
9. Tissera H, Pannila-Hetti N, Samaraweera P, Weeraman J, Palihawadana P, Amarasinghe A. Sustainable dengue prevention and control through a comprehensive integrated approach: the Sri Lankan perspective. *WHO South-East Asia J Public Health* 2016; 5: 106-12.
10. National Guidelines on Clinical Management of Dengue Infection in Pregnancy. Epidemiology Unit of Ministry of Health and Sri Lanka Medical Association, 2019. [https://www.epid.gov.lk/web/images/pdf/DHF/Action\\_Plan/clinicalmanagementofdengueinfectioninpregnancy.pdf](https://www.epid.gov.lk/web/images/pdf/DHF/Action_Plan/clinicalmanagementofdengueinfectioninpregnancy.pdf)
11. Bhatia P, Chhabra S. Physiological and anatomical changes of pregnancy: Implications for anaesthesia. *Indian J Anaesth* 2018; 62: 651-7.
12. Hussein W, Lafayette RA. Renal function in normal and disordered pregnancy. *Current Opinion in Nephrology and Hypertension* 2014; 23(1): 46-53.
13. Humphries A, Mirjalili SA, Tarr GP, Thompson JMD, Stone P. Hemodynamic changes in women with symptoms of supine hypotensive syndrome. *Acta Obstet Gynecol Scand*. 2019; 00: 1-6.
14. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish A. K. Physiological changes in hematological parameters during pregnancy. *Indian Journal of Hematology and Blood Transfusion: an official Journal of Indian Society of Hematology and Blood Transfusion* 2012; 28(3): 144-6. <https://doi.org/10.1007/s12288-012-0175-6>
15. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: Clinical issues and management. A Review. *BMC Pregnancy Childbirth* 9, 8 (2009). <https://doi.org/10.1186/1471-2393-9-8>

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