

DENGUE IN PREGNANCY

Surasith Chaithongwongwatthana

Division of Infectious Diseases, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Abstract. Pregnant women living in an endemic area or travel to tropical countries have a risk of dengue infection. When compared to non-pregnant women, pregnant women are at increased risk of dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), and death. Dengue diseases during pregnancy are found to be associated with a higher risk of cesarean delivery, preeclampsia, preterm birth, and low birthweight infant. Vertical transmission of the virus causing symptomatic diseases in the newborn has been reported. Physiologic changes during pregnancy and some obstetric complications may mask or resemble clinical or laboratory features of dengue leading to misdiagnosis and delayed treatment. Early recognition of dengue during pregnancy and its consequences as well as prompt management would result in a better outcome. In endemic countries, dengue infection should be considered in pregnant women presenting with febrile illness. Hospitalization, close clinical and laboratory monitoring and fluid therapy are recommended in the management of dengue in pregnancy. Vaccination among women in reproductive age in endemic countries prior to pregnancy may be an effective method to prevent dengue disease during pregnancy.

Keywords: dengue, pregnancy, severe dengue

INTRODUCTION

Dengue is a systemic infection caused by dengue virus. It is a major public health problem in more than 100 endemic countries, including Thailand. Globally, this mosquito-borne viral infection was estimated to cause 58.4 million annual symptomatic cases and about 10,000 deaths per year (Stanaway *et al*, 2016). Poorly planned urbanization providing an environment for *Aedes* mosquito proliferation and international travel facilitate the global spread of dengue virus in the recent decades (Messina *et al*, 2014). The virus has four immunologically distinct serotypes, and infection by any of the four serotypes results in a wide range of clinical manifestations from

asymptomatic to severe and life-threatening dengue shock syndrome (DSS) (Guzman *et al*, 2016). Disease severity is largely associated with the host immune response. The phenomenon called antibody-dependent enhancement promotes clinically severe dengue, especially in individuals with monotypic immunity during secondary heterotypic infection.

Reports on dengue disease in Thailand between 2000 and 2011 demonstrated a shift in age group predominance of dengue disease from younger towards older individuals over 15 years of age (Limkittikul *et al*, 2014). During 2003-2013, the number of symptomatic dengue infections among the Thai population was reported to be between 20,000 and 80,000 cases each year with a total of 782 deaths (Kaewnorkkao *et al*, 2015). The mortality had the highest rate in cases complicated with DSS and was associated with age more than 15 years old. Unusual bleeding, ageing, co-morbidity, and waning immunity are related to an increased risk of the complications of dengue disease and fatality among adult and elderly patients (Tantawichien, 2015).

Correspondence: Surasith Chaithongwongwatthana, MD, Division of Infectious Diseases, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok 10330, Thailand.
Tel: +66 (0) 2256 4000; Fax: +66 (0) 2250 1333
E-mail: iamsurasith@gmail.com

Pregnant women living in an endemic area or traveling to tropical countries are also at risk to acquire a dengue infection. Dengue seroprevalence that represents evidence of previous dengue infection among Thai pregnant women has been reported to be between 94.7% and 97.3% (Watanaveeradej *et al*, 2003; Perret *et al*, 2005; Pengsaa *et al*, 2006; Khamim *et al*, 2015). Interestingly, more than 90% of the women had past infection with more than one serotype (Perret *et al*, 2005; Khamim *et al*, 2015). A hospital-based prospective study (Chansamouth *et al*, 2016) conducted in two central hospitals in Vientiane, Lao PDR found that dengue was the most common infection among pregnant women hospitalized due to fever. Severe diseases and poor pregnancy outcomes were reported in these cases.

This narrative review presents updated evidences on the effect of pregnancy on dengue infection as well as on the impact of the disease on pregnancy outcomes. The clinical management of dengue during pregnancy is described.

EFFECT OF PREGNANCY ON DENGUE

The clinical manifestations and outcome of dengue in pregnant women were found to be similar to those of non-pregnant women (Waduge *et al*, 2006). However, a more recent study demonstrated that pregnant women were at increased risk of developing severe dengue [dengue hemorrhagic fever (DHF) and DSS] and mortality when compared with non-pregnant women (Machado *et al*, 2013). Advanced gestational age was associated with severe dengue. Women in the third trimester of pregnancy were four times more likely to have DHF/DSS when compared to those in the first trimester [odds ratios (OR) = 3.98; 95%CI: 1.36-12.65].

The overlapping clinical or laboratory features of dengue with both physiologic change during pregnancy and some more common obstetric complications may cause misdiagnosis, delayed diagnosis, or delayed treatment. For example, an increase in blood volume leading to a lower baseline hematocrit level during the second-

half of pregnancy may cause plasma leakage unrecognized by clinicians. When a pregnant woman has thrombocytopenia as well as increased liver enzymes, most obstetricians will consider HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, an entity of preeclampsia, rather than DHF. For terminating HELLP syndrome, cesarean section may need to be performed, and this can lead to massive hemorrhage in a misdiagnosed case of DHF. For early recognition of dengue disease in pregnancy, clinicians need awareness of clinical and laboratory manifestations of dengue when dealing with the pregnant woman who presents with fever (Waduge *et al*, 2006; WHO, 2012).

IMPACT OF DENGUE ON PREGNANCY OUTCOMES

A systematic review of 30 published observational studies, mostly case reports or case series, found that the women with dengue infection during pregnancy had high rates of cesarean delivery, preeclampsia, and preterm birth (Pouliot *et al*, 2010). In addition, a higher risk of low birthweight among the infants born to women with dengue infections during pregnancy was demonstrated.

Increasing risks of preterm birth and low birthweight among infants born to women with symptomatic dengue infection during pregnancy were also reported in a retrospective cohort study (Friedman *et al*, 2014). The adjusted OR of preterm birth and low birthweight were 3.34 (95%CI: 1.13-9.89) and 2.23 (95%CI: 1.01-4.90), respectively.

A recent systematic review (Paixao *et al*, 2016) identified and included 16 studies that were case-control, cohort, cross-sectional studies, or unselected case series with a total of 6,071 pregnant women including 292 cases who were exposed to dengue during pregnancy. Similar to the prior reports, the most common adverse pregnancy outcomes for women with dengue infection during pregnancy were preterm birth and low birthweight. The meta-analysis showed that women with clinical dengue symptoms had an increased risk of preterm birth (OR = 2.50; 95%

CI: 1.44-4.34) and low birthweight (OR = 1.84; 95 %CI: 1.04-3.25). Likewise, dengue infection during pregnancy was found to be associated with a higher risk of miscarriage (OR = 3.51; 95% CI: 1.15-10.77).

Vertical transmission of dengue virus during *in utero* or at parturition has been reported in the literature (Tan *et al*, 2008; Pouliot *et al*, 2010). The rate of transmission is inconclusive; however, the risk of vertical transmission is potentially related to the severity and timing of maternal infection (Pouliot *et al*, 2010). Maternal infection with symptoms during the peripartum period was found to increase risk of vertical transmission and symptomatic disease in the newborn (Pouliot *et al*, 2010; Arragain *et al*, 2016). Time interval from maternal symptoms to neonatal onset of fever was reported to be between 5 to 13 days (mean 7 days) (Pouliot *et al*, 2010). Most of the newborns who had vertically-transmitted dengue infections exhibited symptoms. Common clinical manifestations included fever, thrombocytopenia, and hepatomegaly. Documented complications in the infected newborns included pleural effusion, hemorrhage, circulatory failure, and death (Pouliot *et al*, 2010).

MANAGEMENT OF DENGUE DURING PREGNANCY

As previously mentioned, one of the keys to success in the management of dengue during pregnancy is early recognition of the infection and its consequences. A high index of suspicion of dengue is needed when clinicians deal with pregnant women presenting with acute febrile illness who live in or with recent travel to a dengue-endemic area (WHO, 2012). Women are probable to be dengue fever when they have a febrile illness together with two or more of the following manifestations (WHO, 2012; RCPT, 2015):

- nausea, vomiting;
- rash;
- aches and pains: headache, retro-orbital pain, myalgia, arthralgia;
- hemorrhagic manifestations: petechiae, epistaxis, positive tourniquet test; and

- leukopenia, neutropenia, and atypical lymphocyte findings.

Laboratory testing to confirm the diagnosis includes the detection of dengue virus genomic sequences by PCR or demonstration of dengue virus antigen by non-specific protein of dengue virus (dengue NS1) or serological tests. Detection of serum anti-dengue antibody (anti-DEN) IgM or a rise in anti-DEN IgG titer of ≥ 2 times and convalescent IgG ≥ 100 units are considered as having recent dengue infection (RCPT, 2015).

After dengue fever is suspected and diagnosed, the pregnant woman should be admitted to the hospital early for close monitoring and supportive management (WHO, 2012). Acetaminophen (10 mg/kg every six hours, maximum 3 g/day) is recommended to reduce the fever and pains, but the patient should be informed that these symptoms might not be alleviated. In the woman using baby aspirin for prevention of preeclampsia, the drug should be withheld. Other NSAIDs and anti-platelet agents should also be avoided. Fluid and electrolyte balance has to be monitored and maintained. If the woman cannot tolerate oral fluid replacement, intravenous isotonic solutions should be started in the same manner as a non-pregnant woman. However, excessive fluid replacement should be avoided (WHO, 2012).

During admission, the woman should be monitored for the warning signs of severe dengue infection that lead to severe plasma leakage, severe hemorrhage, and severe organ impairment (WHO, 2012; Tantawichien, 2015). The warning signs include abdominal pain, persistent vomiting, clinical fluid accumulation (oliguria with respiratory distress), spontaneous mucosal bleeding (epistaxis, bleeding per gum), retinal hemorrhage, alteration of consciousness (either lethargy or restlessness), liver enlargement and tenderness, as well as hemoconcentration with rapid decrease in platelet count. Judicious volume replacement by intravenous fluid therapy in the patient with these warning signs or signs of dehydration may modify the course and the severity of disease (WHO, 2012). Parameters

that should be monitored include vital signs (1-4 hourly), urine output (4-6 hourly), hematocrit (6-12 hourly), blood glucose, renal function tests, liver function tests, and coagulation profile. Fetal monitoring is needed in the late second or third trimester of pregnancy. Maternal monitoring for detection of DHF/DSS should be performed until the woman is out of the critical phase. In the convalescent phase, the patient appetite returns, and their general condition improves. Laboratory findings show the platelet count and hematocrit both returning to baseline level.

There is no indication for termination of pregnancy in a pregnant woman with dengue infection. In some instances, administration of tocolytic agents may be considered in the pregnant woman who is in labor during the critical phase of dengue disease (WHO, 2012). If delivery is inevitable, blood and blood products should be prepared, and the delivery should take place in a hospital where skilled obstetricians and neonatologists are available. Platelet transfusion is indicated when the platelet count is $<50,000/\text{mm}^3$ during labor (RCPT, 2015) and should be initiated during or at delivery (WHO, 2012). Transfusion of packed red cells should be administered if indicated. Interventions to prevent postpartum hemorrhage should be commenced immediately after delivery. The newborn whose mothers had dengue just before or at delivery should be closely observed to determine whether vertically transmitted dengue infection is apparent (Pouliot *et al*, 2010; Arragain *et al*, 2016).

PREVENTIVE MEASURES

Vector control has been used for prevention and control dengue in most endemic countries for decades. However, the global dengue burden and spreading of both the virus and the mosquito have demonstrated the failure of this preventive measure (Guzman *et al*, 2016). Development of safe and effective dengue vaccines might be the most effective means to control dengue disease (Thisyakorn and Thisyakorn, 2015). To date, a live attenuated (recombinant) tetravalent vaccine (CYD-TDV) has been registered in several countries (WHO, 2016). To maximize the public health impact

and cost-effectiveness, the populations targeted for vaccination should have a seroprevalence of dengue of approximately 70% or greater (WHO, 2016). Because the registered dengue vaccine is a live attenuated vaccine, use in pregnant women is not recommended. Vaccination among women of reproductive age in endemic countries prior to pregnancy may be an effective measure to prevent dengue disease during pregnancy.

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