

DENGUE INFECTION IN PREGNANCY

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Abstract. While dengue infection is still on the increase in adults in Thailand, it also affects pregnant women, especially pregnant teenagers. This study was designed to investigate dengue infection during pregnancy. Seven cases of dengue infection in pregnant women were admitted to Ban Pong Hospital, Ratchaburi, Thailand, between 2008 and 2012. Dengue infection presented in all pregnancy trimesters. There were two severe cases: one was dengue hemorrhagic fever in the first trimester, and the second was at a critical stage of the infection during labor. There were three cases of abortion. These three cases included one complete, one incomplete, and one threatened abortion, with rising hematocrits of 22.8%, 17.1%, and 14.7%, respectively. Two out of the three teenage pregnancies experienced complete and threatened abortions, while the third abortion case was a threatened abortion pregnancy at the critical stage of infection during intrapartum. Leukopenia was identified in six out of seven women. Low baseline hematocrit and low maximum hematocrit were laboratory findings. Clinical management involved administration of intravenous fluids and antipyretics. Favorable outcomes can be obtained through early diagnosis and supportive treatment. The morbidity profile can be more serious in teenage pregnancies. Additional studies should be conducted to establish whether low baseline hematocrit, low percentages of rising hematocrit in pregnant women with dengue infection, and abortions (with a high degree of increasing hematocrit during the critical stage of the disease) are typical clinical signs.

Keywords: dengue infection, HELLP, pregnancy, teenage, Thailand

INTRODUCTION

Dengue infection is a major public health problem in tropical and subtropical countries. This mosquito-borne viral disease is a potential threat to 50-100 million people each year. Of those infected,

about 500,000 develop dengue hemorrhagic fever (DHF), and 22,000 die of the disease (Thisyakorn and Pengsaa, 2012). Dengue infection severity is variable, ranging from mild, non-specific febrile illnesses to classic dengue fever (DF) or DHF and dengue shock syndrome (DSS), which are more severe forms of the disease. DF, an acute febrile disease, frequently presents with headache, bone, joint and muscle pain, rash, and leukopenia. In contrast, DHF is characterized by four major clinical manifestations: high fever, hemorrhagic

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phenomena (often with hepatomegaly), and signs of circulatory failure in severe cases. DHF patients may develop hypovolemic shock (known as DSS) resulting from plasma leakage; this can be fatal (WHO, 1997; CDC, 2013). Currently, neither a vaccine nor specific antiviral therapy exists.

Dengue infection is most often encountered in children. However, more recently, dengue infection in Thailand has started to affect people over 10 years of age as well as adults. In Thailand, the modal age group affected by dengue has shifted from <10 years of age to 10-34 years of age. In 2012, 79,593 cases of dengue infection were reported in 76 Thai provinces. The highest proportion of cases by age group was found in 15-24 year olds (23.79%, $n=18,923$), followed by 10-14 year olds (21.59%, $n=17,182$), 7-9 year olds (11.85%, $n=9,432$), and 25-34 year olds (9.86%, $n=7,853$) (Department of Disease Control, 2012).

Dengue infection can appear in pregnant women at any time as well as in the immediate post-partum period (Waduge *et al*, 2006). These infections can have various complications, including maternal mortality, preterm delivery, fetal death, low birth weight, neonatal admissions, fetal anomalies, and spontaneous abortion. In East Sudan, dengue infection during pregnancy has poor maternal and prenatal outcomes (Ishag *et al*, 2010). In this Sudanese region (2008-2009), 17 (21.7%) maternal deaths, 14 (17.9%) of the 78 women with preterm deliveries, and 19 (24.3%) admissions of neonates to neonatal intensive care units were reported. Additionally, 19 (24.3%) women gave birth to low birth weight babies, and there were seven (8.9%) perinatal deaths.

Furthermore, because of the presence of various obstetrical indicators, eight (10.2%) patients were delivered by Caesarean section (Ishag *et al*, 2010).

During normal pregnancy, physiological changes to the cardiovascular system and blood increase the cardiac output, heart rate, and stroke volume while slightly decreasing the diastolic blood pressure (Ouzounian and Elkayam, 2012). These normal signs could be misinterpreted as plasma leakage and hypotensive shock caused by dengue infection. Some of the overlapping clinical and/or laboratory features of dengue infection in pregnancy can be confused with a diagnosis of pre-eclampsia, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count).

Despite the high prevalence of dengue infection in Thailand, there have been few reported cases of this infection in pregnant women. This study was conducted to investigate pregnancy-related dengue infection in an area of high prevalence.

MATERIALS AND METHODS

This descriptive retrospective study was conducted at Ban Pong Hospital, Ratchaburi, Thailand, which is a dengue endemic area. All hospitalized pregnant women with dengue infection were included in the study, which took place from 2008 Jan 1 to 2012 Dec 30. Diagnoses and classification of dengue infection as DF, DHF, and DSS were made according to WHO (1997) criteria. Maternal clinical signs, laboratory findings, pregnancy outcomes, and information concerning complications in mothers and fetuses were examined. The study was approved by

the Ethics Committee for research involving human subjects at Ban Pong Hospital (Registered N° R 2014-001). The patients provided written informed consent.

RESULTS

There were 11,690 deliveries and 2,829 dengue infections at Ban Pong Hospital during the five-year study period. The seven pregnancy-related dengue infection cases had no associated mortality. Three cases of dengue infection were teenagers (14, 16, and 19 years old), and four were adult pregnant women (27, 32, 33, and 34 years old). The women's ages, gestational ages, clinical manifestations, laboratory data and pregnancy outcomes for expectant mothers with dengue infection are shown in Table 1. Infection occurred in three women in the first trimester at 5, 10, and 12 weeks of gestational age, two women in the second trimester at 14 and 26 weeks, and two women in the third trimester at 33 and 38 weeks. There were two severe dengue cases: the first was DHF in the first trimester, and the second was when labor occurred at the critical stage of the infection. Both cases were teenaged women.

The clinical manifestations in all cases were fever (duration 3-5 days) and myalgia whereas bleeding episodes such as epistaxis and petechia were less common. Tourniquet tests were done in four cases, of which three cases were positive.

Complete blood counts in all seven cases revealed low white blood cell counts of 2,100, 4,900, 3,110, 6,700, 4,980, 1,680, and 3,500/ μ l of blood while the thrombocytopenia values were 74,100, 84,400, 95,800, 73,200, 26,100, 83,200, and 39,000 / μ l of

blood. Hematocrits were low baseline (35%, 35%, 29%, 35%, 30%, 35%, and 34%) and low maximum (43%, 41%, 33%, 37%, 32%, 37%, and 39%). The maximal percentages of rising hematocrit during the critical stage of the disease were 22.8%, 17.1%, 13.8%, 5.7%, 6.7%, 5.7%, and 14.7%. The first and the seventh cases had dengue virus-positive IgM rapid test results; the other cases were not tested.

Of the pregnancy outcomes of the four women who carried infants of 20 weeks or less gestation, two out of four had complete and incomplete spontaneous abortions, while one had a threatened abortion. All three abortion cases had high maximal rising hematocrit percentages during the critical stage of the disease: 22.8% (for the complete abortion), 17.1% (for the incomplete abortion), and 14.7% (for the threatened abortion). The times from onset of fever to abortion in the three cases were 8 weeks (for the complete abortion), 3 weeks (for the incomplete abortion) and 1 day (for the threatened abortion). Four out of seven cases, including the threatened abortion, progressed to normal deliveries with healthy full-term neonates.

Two of the three teenaged pregnant women with dengue infections had complete and threatened abortions; whereas, the other infection was intrapartum at the critical stage of infection, so a referral to a tertiary care hospital was necessary.

The clinical management of the pregnant women with dengue infection included supportive care, rest, intravenous fluids, and antipyretic medication. None of patients required platelets or other blood components except for one patient whose critical stage of infection occurred during intrapartum. Because she may have needed

a blood transfusion, she was referred to a tertiary care hospital.

DISCUSSION

From 2008 to 2012, dengue infection was present in both teenaged and adult pregnant women admitted to Ban Pong Hospital, Thailand. Three out of seven cases were teenaged pregnant women. Over the last decade, dengue infection has started to affect people over 10 years of age (Department of Disease Control, 2012). Concurrently, the number of teenage pregnancies in Thailand has increased (Prohmmo, 2007). At delivery, 94.7% of the Thai pregnant women had dengue HAI antibodies, and a mother's age was the only risk factor associated with dengue infection, because older mothers were significantly more likely to be seropositive than younger ones (Perret *et al*, 2005). The seropositivity rate for dengue infection increases with advancing maternal age, indicating that younger women are more at risk of contracting dengue infection during pregnancy. These three factors (older susceptible age group, higher numbers of teenage pregnancies, and low antibody seropositivity in younger women) are likely to have increased the numbers of pregnant women with dengue infection although teenagers tend to experience more severe effects than older women do.

Dengue infection can appear at any time during pregnancy and the intrapartum period. In Sri Lanka (2000-2004), 26 patients were reported with dengue-associated pregnancies. One (3.8%), 2 (7.7%), and 20 (77%) presented in the first, second, and third trimesters, respectively, as well as 3 (11.5%) in the immediate post-

partum period (Waduge *et al*, 2006). In the present study, the dengue infections occurred mainly during the first trimester. The clinical signs and symptoms experienced by the seven pregnant women with dengue infection (fever of 3-5 days duration, myalgia, nausea and vomiting, epistaxis, and petechiae) were similar to those of non-pregnant women with this infection.

Leukopenia was identified in all the cases except for Case 4, who was 38 weeks pregnant and had a normal white blood cell count during the intrapartum period (Table 1). During the febrile phase of dengue fever in non-pregnant women, a leukopenia (white blood cell count below 5,000/ μ l) indicates that the fever will likely dissipate within the next 24 hours and that the patient is entering into the critical stage of the disease (CDC, 2013); however, in normal pregnancy, a modest leukocytosis is observed. The normal white blood cell count ranges during the first, second, and third pregnancy trimesters and in non-pregnant adults were 5.7-13.6, 5.6-14.8, 5.9-16.9, and 3.5-9.1 ($\times 10^3$ / μ l), respectively (Abbassi-Ghanavati *et al*, 2009). Therefore, pregnant women presenting with febrile illness after travelling to or living within a dengue-endemic area who have significantly decreased white blood cell counts (leukopenia) compared with those of normal pregnancies warrant further investigation. Careful monitoring of infection indicators in pregnant women suspected of having dengue infections is essential.

Thrombocytopenia was present in all the case studies. Assuming that the earliest abnormality found in a complete blood count is a progressive decrease in the total white cell count followed by progressive thrombocytopenia, an obstetrician should

Table 1
Dengue infection in pregnant women.

Case number	1	2	3	4	5	6	7
Diagnosis (WHO, 1997)	DHF	DF	DF	DF	DF	DF	DF
Age (years)	14	32	33	16	34	27	19
Gestational age (weeks)	12	14	33	38	26	5	10
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Duration of fever (days)	5	3	3	3	3	3	5
Tourniquet test	No data	Positive	Positive	No data	No data	Positive	Negative
Petechiae	No	No	No	Yes	Yes	Yes	No
Epistaxis	No	No	Yes	No	Yes	No	No
Nausea/Vomiting	Yes	No	Yes	Yes	No	Yes	Yes
Myalgia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
White blood cell (μ l) min	2,100	4,900	3,110	6,700	4,980	1,680	3,500
Platelet count (μ l) min	74,100	84,400	95,800	73,200	26,100	83,200	39,000
Hematocrit (%)							
max	43	41	33	37	32	37	39
min (baseline)	35	35	29	35	30	35	34
Rising hematocrit (%)	22.8	17.1	13.8	5.7	6.7	5.7	14.7
Serological IgM rapid test	Positive	No data	No data	No data	No data	No data	Positive
Blood component transfusion	None	None	None	No data	None	None	None
Outcome of pregnancy	Complete abortion	Incomplete abortion	Normal labor: healthy baby	Referral	Normal labor: healthy baby	Normal Labor: healthy baby	Threatened abortion/ Normal labor: healthy baby
Duration from diagnosis to outcome of pregnancy (weeks)	8	3	7	Referral	12	35	1 day/ 30 weeks

DF, Dengue fever; DHF, Dengue hemorrhagic fever.

be alert to the likelihood of dengue infection.

Among the seven reported cases, low baseline hematocrit and low maximum hematocrit were present. Three out of four cases with pregnancies of 20 weeks or less had complete ($n=1$), incomplete ($n=1$) spontaneous abortions, and a threatened abortion ($n=1$); these cases had high maximal rising hematocrit values during the critical stage of the disease (22.8%, 17.1%, and 14.7%, respectively). By comparison, the other cases (with no abortion) all had low maximal rising hematocrit percentages during the critical stage of the infection. However, access to a larger data set is necessary to confirm whether these findings are generally applicable to pregnancies of 20 weeks or less.

Low baseline hematocrit and rising hematocrits during pregnancy may be affected by plasma leakage or normal physiological changes in the cardiovascular system. For example, an increase of 40%-50% in plasma volume, which is relatively greater than the accompanying 20%-30% increase in red blood cell mass, results in hemodilution and decreased hematocrit (Ouzounian and Elkayam, 2012). Hence, the criterion for a diagnosis of anemia in pregnancy is a hematocrit of <30%, 33%, and 30% in the first, second, and third trimester, respectively; these values are lower than those of normal adult females (Abbassi-Ghanavati *et al*, 2009).

Having an enlarged gravid uterus makes it difficult to evaluate the clinical signs of plasma leakage such as pleural effusion and ascites. Therefore, routine abdominal and chest ultrasound examinations to detect free fluid in abdominal or thoracic cavities should be considered for pregnant women with dengue infection.

All cases in the present study except the one who was intrapartum and at the critical stage of the disease were managed by supportive care, rest, intravenous fluids and antipyretic medication similar to recent reports in which good clinical outcomes were obtained (Malhotra *et al*, 2006; Carroll *et al*, 2007; Ishag *et al*, 2010). Three cases of teenaged pregnant women with dengue infection had poor outcomes; two experienced spontaneous abortions, and one full-term pregnancy experienced labor during the critical stage of the disease. While the four pregnant women (>20 years old) with dengue infection had three normal deliveries and full term healthy neonates, there was only one case of incomplete abortion. This is not the first report of dengue infection associated with spontaneous abortion, or of the increased risk of such abortions occurring during the first trimester (Waduge *et al*, 2006; Tan *et al*, 2012).

Fever with thrombocytopenia during pregnancy, especially during the intrapartum period, can cause massive bleeding; therefore, obstetricians have to be extremely careful with cases presenting with these clinical signs. DHF and DSS are associated with fatality rates ranging from 2.9%-22% (Morta *et al*, 2012; Machado *et al*, 2013). These fatality rate differences probably result from differences in the ways these diseases are managed (Ishag *et al*, 2010; Pouliot *et al*, 2010). Hence, accurate and rapid diagnosis of DF, DHF, and DSS in pregnant women is very important; however, hemodilution in normal pregnancy can conceal the classical features of hemoconcentration associated plasma leakage in DHF. Ultrasound detection of free fluid in the chest or abdomen may precede clinical detection of DHF.

Pregnant women with severe dengue infection must be differentiated from those with HELLP syndrome, preeclampsia or eclampsia. Laboratory findings for severe dengue infection and HELLP syndrome overlap with thrombocytopenia and elevated liver enzymes whereas laboratory findings supporting a diagnosis of HELLP syndrome include hemolysis of peripheral blood smears, serum lactate dehydrogenase ≥ 600 IU/l and proteinuria. However, in pregnancy, proteinuria is the only one criterion used to diagnose preeclampsia. In 2013, the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy modified (in recognition of the syndromic nature of preeclampsia) the dependence of the diagnosis on proteinuria. In the absence of proteinuria, preeclampsia should be diagnosed as hypertension in association with thrombocytopenia (platelet count less than $100,000/\mu\text{l}$), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances (American College of Obstetricians and Gynecologists, 2013). In cases where proteinuria is absent, similar clinical and laboratory findings of thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, and new-onset cerebral or visual disturbances in severe preeclampsia and severe dengue infection in pregnant women may be found. Therefore, a history of fever and hypertension that predates pregnancy may

be helpful for arriving at a provisional diagnosis while the definite diagnosis of dengue infection should be confirmed serologically.

In the cases described herein, the dengue infections in the pregnant women were managed by supportive care, rest, administration of intravenous fluids, and antipyretic medication. None of the patients required platelets or other blood components except one patient who had the critical stage of the infection during intrapartum and was, therefore, referred to a tertiary care hospital because of the possibility of needing a blood transfusion. The handbook for clinical management of dengue (WHO and TDR, 2012) advises that clinicians need to maintain a high index of suspicion when dealing with pregnant women who present with febrile illness after travelling to or living in dengue-endemic areas. Early admission to hospital for close monitoring is desirable, particularly for pregnant women close to full-term and labor while the treatment of choice is medically conservative with obstetrical management of dengue disease (WHO and TDR, 2012).

Dengue infection occurs during all trimesters and the morbidity levels associated with it can be more serious in teenage pregnancies. Favorable outcomes can be obtained by early diagnosis and supportive treatment. Leukopenia was observed in most of the pregnant women with dengue infection. Further studies should be conducted to determine whether the low baseline hematocrits and low rising hematocrits (or abortions associated with increasing hematocrits during the critical stage of the disease) that we observed in pregnant women with dengue infection are typical clinical signs.

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