Retrospective comparative study on maternal, fetal, and neonatal outcomes of symptomatic dengue infection: A study in Teaching Hospital, Peradeniya, Sri Lanka

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Abstract

Introduction: Dengue fever is one of the most important mosquito-borne infections and is considered a major health problem in Sri Lanka. The impact of dengue fever on pregnancy is not very well studied owning to small study cohorts and methodical bias.

Objectives: This is a retrospective comparative study to assess the maternal, fetal, and neonatal outcomes in symptomatic dengue infection in pregnancy

Method: The maternal, neonatal, and fetal outcomes of a cohort of pregnant patients with serologically confirmed dengue fever (n=24) were compared with an age-matched group of healthy pregnant mothers without symptomatic dengue illness (n=72).

Results: There were no statistically significant differences in birth weight (p=0.229), prematurity (p=1.000), peripartum complications (p=0.439) and mode of delivery (p=0.246). Neonates born to mothers with dengue infection needed more premature baby unit (PBU) admissions (p<0.01), and a longer hospital stay (p<0.01). Two maternal deaths were due to multi-organ failure with dengue haemorrhagic fever and one symptomatic case of mother-to-child transmission of dengue infection was noted in the study

Conclusions: In this study there were no statistically significant differences in the fetal or neonatal outcomes between the dengue-exposed and un-exposed groups of pregnant mothers. However, 2 maternal deaths were reported in the exposed group of 24 compared to none in the non-exposed group of 72 which is statistically significant (p<0.001).

(Key words: Dengue, Pregnancy, Maternal, Fetal, Neonatal, Sri Lanka)

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Introduction

Dengue fever (DF) is one of the most important mosquito-borne infections which is endemic in Sri Lanka and has been currently recognized as one of the major health problems. The first confirmed case of DF dates back to 1962[1] and the first outbreak occurred in 1965[2]. Since then, there had been an exponential rise in the reported cases of DF. The largest outbreak occurred in 2017 when 161,000 suspected dengue cases were reported to the Epidemiology Unit, Ministry of Health in Sri Lanka[3]. Currently, there is little evidence that dengue infection behaves differently in pregnancy. A few studies have suggested that preterm labour, risk of abortion and miscarriage, low birth weight (LBW) and peripartum bleeding could be higher in pregnancies complicated with dengue fever[4-7]. There is a lack of comparative studies, which are especially important when studying a cohort of pregnant patients, as there are potential confounders in pregnancy which need rigorous adjustments from a matched control group.

Objectives

The main objective of the study was to compare the maternal, fetal and neonatal outcomes between pregnancies complicated with symptomatic dengue infection and healthy pregnant women.

Method

This was a retrospective comparative cohort study. All pregnant patients who were diagnosed to have serologically confirmed DF were selected retrospectively in 2017. An age-matched cohort of healthy pregnant females without symptomatic DF was selected as the control group. Comparisons were made between the study sample and the control

group with regard to maternal, fetal and neonatal outcomes.

Sample size: Convenient sampling method was used and the sample size comprised all pregnant females admitted to the Teaching Hospital, Peradeniya from 1st January to 31st December 2017 with serologically confirmed dengue fever.

Definitions of cases and controls: A *case* was defined as a pregnant female (positive urine human chorionic gonadotrophin (HCG) with a period of amenorrhoea confirmed with ultrasonography) with fever tested positive for either NS1 antigen or specific dengue IgM test. A *control* was defined as an age-matched pregnant patient with no documented history of an acute febrile illness or serologically confirmed dengue infection at any time during pregnancy who had progressed through pregnancy.

Outcome definitions: A *preterm birth* was one <37 weeks of gestation, including miscarriages. An infant with *low birth weight* was one born weighing <2,500g irrespective of gestational age. Definitions of live birth, stillbirth, and miscarriage used in this study were based on the French definitions[8]. A *stillbirt*h was defined as the birth of a dead infant who weighed 500g or was 22 weeks of gestational age. A *miscarriage* was defined as the birth of a dead fetus that was 22 weeks of gestational age and weighed 500g. None of the miscarriages included in this study were deliberately terminated pregnancies. *Gestational age* in this study was determined by ultrasound. Ultrasound information was missing in 5 cases, and gestational age was determined by the date of the last menstrual period (LMP) in two cases, by clinician estimate in two cases, and by both in one case.

Data collection: All the bed head tickets of the pregnant patients admitted or transferred to the University Medical Unit, Teaching Hospital Peradeniya with an acute febrile illness with serologically confirmed DF were collected from the medical record room. All relevant data were transcribed into standardized data entry forms. A semi-structured data collection form was used to extract all relevant information on the antenatal, perinatal and immediate post-natal period. If the patient was discharged prior to delivery, her delivery details were sought by contacting her via telephone or mail or by searching the admission registry based on the tentative date of delivery. All information regarding antenatal, perinatal and postnatal periods was extracted. Information on neonatal outcome was obtained from the baby's BHT and transcribed into standardized data entry forms.

The control group was obtained by randomly selecting a cohort of patients admitted for confinement, who were not having fever or a history of fever during the pregnancy period. The matching for age, locality and follow-up at the same institution was done and was included in the study. Data were extracted from the bed head ticket, national partogram, and neonatal examination format.

Ethical issues: Institutional Ethics Review Committee (IERC) of the Faculty of Medicine, University of Peradeniya approved the study on 22 May 2020 (No. 2019/EC/52) and Institutional approval from the Director of the hospital was obtained to access the records of the deceased patients.

Statistical analysis: Continuous variables are presented as mean and standard deviation (SD), and categorical variables are presented as percentages. Statistical analyses were performed using the Stata statistical software. Results were considered significant when $p<0.05$. The normality of all measurements was tested using the Shapiro-Wilk test. Fisher's exact test was used to compare the distributions

Results

The fetal and neonatal outcomes of 24 pregnant women with serologically confirmed DF were compared with those of 72 healthy (unexposed) age-matched pregnant women. There were no statistically significant differences in perinatal complications such as oligohydramnios, Doppler abnormalities, placental abruption, preterm delivery, preeclampsia, miscarriages or intrauterine death between the exposed and unexposed groups of pregnant mothers to symptomatic dengue infection. The mode of delivery was not statistically different in the two groups as well as the mode of anaesthesia used in caesarean section. No significant differences were observed in the incidence of post-delivery haemorrhage, puerperal sepsis, and the use of blood products in the puerperal period between the two groups. There was no significant difference in the birth weight of the neonates of the exposed and unexposed groups (p= 0.229). One-minute and five-minute Apgar scores were not statistically different in the two groups. The neonates in the exposed group needed more premature baby unit (PBU) admissions (p=0.04). The exposed group had a longer stay in the hospital following delivery which is statistically significant (p=0.004) compared to the unexposed group. The study characteristics of each fetal and neonatal outcome of pregnancy are shown in table 1.

Table 1: ***Study characteristics of each fetal and neonatal outcome of pregnancy***

Maternal, fetal and neonatal outcome		Number of observations		p-value of Fishers exact test
		Cases	Controls	
Maternal outcome				
Preterm delivery	Yes	0	01	1
	No	24	71	
PIH / Pre-eclampsia	Yes	01	01	0.439
	No	23	71	
Miscarriage / IUD	Yes	0	02	1
	No	24	70	
Mode of delivery	Normal vaginal delivery	09	41	0.246
	Assisted vaginal delivery	01	04	
	Elective caesarean section	06	15	
	Emergency caesarean section	08	12	
Mode of anaesthesia used for caesarean section	Spinal anaesthesia	12	24	0.168
	General anaesthesia	02	03	
	Not relevant	10	45	
Puerperium - PPH	Yes	01	02	1
	No	23	69	
Puerperium - Sepsis	Yes	02	0	0.062
	No	22	71	
Duration of stay	1 - 3 days	08	29	0.001
	4 - 6 days	10	35	
	>6 days	06	07	
Mortality	Survived	22	72	<0.001
	Died	02	0	
Fetal outcome				
Oligohydramnios	Yes	02	04	0.638
	No	22	68	
Reduced fetal movement	Yes	01	04	1
	No	23	67	
CTG abnormalities	Yes	03	08	1
	No	21	64	
Doppler abnormalities	Yes	01	01	0.439
	No	23	71	
Neonatal outcome				
Birthweight	-3 SD	01	02	0.229
	-3 SD to -2 SD	05	07	
	-2 SD to -1 SD	04	24	
	-1 SD to 2 SD	14	39	
Apgar score	0-3	02	01	1
	4-6	0	01	
	7-10	22	70	
PBU admission	Yes	03	01	0.04
	No	19	70	

Two patients in the exposed group of 24 died due to dengue haemorrhagic fever (DHF) compared to none in the 72 patients in the unexposed group. This was statistically significant ($p<0.0001$). A 32-year-old previously healthy primigravida at 33 weeks of gestation was admitted in compensated shock in DHF. Pregnancy was complicated with placental abruption leading to an emergency caesarean section. DHF was complicated with fulminant liver failure, acute kidney injury and disseminated intravascular coagulation (DIC) and the patient succumbed on the day of admission. The baby was admitted to PBU and recovered without complications. The second patient is a 24-year-old primigravida admitted at 39 weeks of gestation. She underwent an emergency caesarean section due to fetal distress. She developed fever on postpartum day 3 and was serologically confirmed as DF. On day 4, she was found to have plasma leak and the disease course was complicated with acute kidney injury and fulminant liver failure resulting in death on day 5 postpartum. Neonate had an uneventful recovery.

One neonate born to a pregnant mother with symptomatic dengue during the delivery at 37 weeks of POA developed fever and thrombocytopenia and dengue was confirmed on day 1 with a positive NS1 antigen in the neonate confirming the possible transplacental transfer of the dengue infection from mother to child. He had an uneventful recovery.

Discussion

Our comparative study found that maternal dengue infection had no statistically significant impact on LBW. A larger comparative study is needed to confirm or refute the finding. A few studies demonstrated higher incidence of LBW among mothers who were infected with dengue during pregnancy[9,10]. Postulations were made that it could be due to damage to the fetoplacental unit by the virus and this was supported by the demonstration of viral antigens in the placental tissue[11,12]. Other studies demonstrated that maternal dengue infection had no statistically significant impact on the birth weight of the newborn[13,14].

Our study found no statistically significant impact on prematurity, preterm delivery or preterm labour. Some studies have shown an increased incidence of premature labour and preterm birth[4]. High fever and high circulatory levels of cytokines and chemokines were attributed to preterm rupture of membranes leading to preterm labour[8, 15-18]. Importantly, all this evidence is coming from descriptive studies from tropical countries where dengue is endemic and we believe that there could be many confounders leading to prematurity and pre-term labour in a pregnancy cohort in a tropical country and there is a need for larger retrospective or prospective cohort studies to clarify this association

Oligohydramnios is a reported prenatal complication (43%-52%) of dengue illness in a few studies[19,20]. However, in our study there was no significant difference between the two groups. High fever, viraemia and fetal infection were postulated in some studies as risk factors of fetal loss in dengue infection[21-25]. In our study there was no significant difference in miscarriage between the exposed and non-exposed pregnant groups. Although the exposed pregnant cohort showed a statistically significant difference with regard to the duration of postpartum stay and PBU admissions, there were no significant differences in postpartum complications such as puerperal sepsis, bleeding or infection. The significantly prolonged hospital-stay of the study group compared to the control group could be attributed to 2 reasons: (1) Neonates born to mothers with dengue infection needed more PBU admissions and hence maternal hospital stay was prolonged. (2) In maternal cases who had dengue during the peripartum period, patient discharge was mainly decided by the recovery from dengue.

In the dengue exposed group of 24 there were 2 maternal deaths giving a mortality rate of 8.3% and both were cases of DHF complicated with multi-organ failure. Maternal deaths were reported in 6-18% of pregnant dengue patients in some studies and all had multi-organ failure and DIC[26,27]. We reported one case of maternal-fetal transmission in this study. The neonate was having fever and investigations revealed thrombocytopenia and positive dengue serology (IgM). Since we have not routinely screened for dengue in all neonates born to exposed mothers, we could have missed asymptomatic cases of maternal-fetal transmission. A systematic review of 30 articles reported 12-64% cases of vertical transmission among pregnant dengue patients[28].

There were some limitations. This comparative analysis was done using retrospective data from bed head tickets and some data were missing from patient records which affected the comparison. Data in BHTs were documented at different times by different health care professionals and there could have been interpersonal variations in the observations. In the comparative study, matching was done for age, but extended matching was not carried out for socio-demographic factors which could have introduced confounders in the comparison. All the pregnant patients serologically confirmed with DF during the study period in Teaching Hospital Peradeniya were included in the study using a convenient sampling method. But the analysis could have been more generalizable if more patients from multiple centres were recruited.

Conclusions

In this study there were no statistically significant differences in the fetal or neonatal outcomes between the dengue-exposed and un-exposed groups of pregnant mothers. However, 2 maternal deaths were reported in the exposed group of 24 compared to none in the non-exposed group of 72 which is statistically significant ($p<0.001$).

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