

Perinatal Transmission of Dengue: A Report of 7 Cases

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Perinatal transmission of dengue virus was confirmed by the evidence of virus in fetal tissue, newborn serum, and placenta of pregnant women. Abortion, several different clinical findings, and placental inflammatory findings were documented. No association was seen between severity of maternal dengue and disease of the newborn. (*J Pediatr* 2013;163:1514-6).

Dengue, currently the most widespread human viral disease transmitted by mosquitoes, is endemic in many tropical countries. The dengue virus (DENV) is classified into 4 serotypes (1, 2, 3, and 4). Since 1948, the occurrence of dengue in pregnancy has been reported in the literature, mostly in case reports. The largest series comprised 38 cases in 2000 and 53 in 2009, both in French Guiana.¹ Maternal deaths attributed to dengue during pregnancy recently have been described in Brazil.² Perinatal transmission of DENV in pregnancy was confirmed either by DENV isolation or by the presence of specific IgM antibodies in newborns.³⁻⁵ We report 7 confirmed cases of DENV infection acquired through perinatal transmission.

Methods

From January 2008 to July 2010, 28 placentas and 7 ovular remnants from pregnant women with laboratory-confirmed dengue were analyzed by the pathology service of the University Hospital Antônio Pedro, Niterói, Rio de Janeiro, Brazil. This study was approved by the Ethics Committee of the Hospital Universitário Antônio Pedro, Universidade Federal Fluminense (CMM/HUAP No. 038).

Laboratory confirmation of dengue was defined as the presence of IgM by the method of IgM antibody capture enzyme-linked immunosorbent assay, by the presence of nucleic acid by reverse-transcription polymerase chain reaction in maternal or neonatal serum, or by immunohistochemistry in placental tissue.

Placentas and ovular remnants were analyzed by macroscopic examination after fixation in 10% formalin. Cleavage was performed, and 7 samples were retrieved from the placenta and annexes. Samples were subsequently stained with hematoxylin-eosin. The ovular membranes, umbilical cord, and placental tissue were analyzed histologically. Immunohistochemistry was conducted with the murine IgG2A monoclonal anti-DENV complex (MAB8705; clone D3-2H2-9-21; Millipore, Billerica, Massachusetts) diluted 1:300 in phosphate-buffered saline and incubated overnight.

Paraffinized liver tissue from a patient who died from DENV was used as the positive control for the immunohistochemical analysis. For the negative immunohistochemical control, 2 different procedures were incorporated: (1) paraffinized liver tissue from the patient who had died of dengue, suppressing the monoclonal antibody, the primary antibody of the incubation step, using only the diluent solution (bovine serum albumin) and (2) paraffin-embedded placental tissue of patients without infectious disease on which the full technique was performed (without the deletion of the MAB).^{6,7}

Results

Maternal, fetal, and neonatal clinical findings and outcomes are described. Perinatal transmission was confirmed in 7 cases. In 5 cases, the DENV infection was confirmed by immunohistochemistry by the presence of marking in the decidua or placenta villus. In 4 of these, villous stromal edema, excessive formation of syncytial knots, and chorangiosis were the main pathologic findings of placental hypoxia. DENV also was demonstrated in 1 case by immunohistochemistry in the epithelial cells of lung, ependymal, and kidney of the aborted fetus (**Figure**).

The time elapsed between the first day of maternal disease (D1) and date of birth or abortion ranged from 1 to 8 days, with an average of 3.4 days and median of 3 days. No newborn presented with asphyxia during delivery. Only 1 newborn presented with low birth weight. Maternal, fetal, and newborn clinical manifestations, laboratory findings, dengue diagnosis, and outcomes are illustrated in the **Table**.

Discussion

This report of perinatal transmission of dengue documents the presence of DENV in fetal tissue in which the pregnant

DENV	Dengue virus
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome

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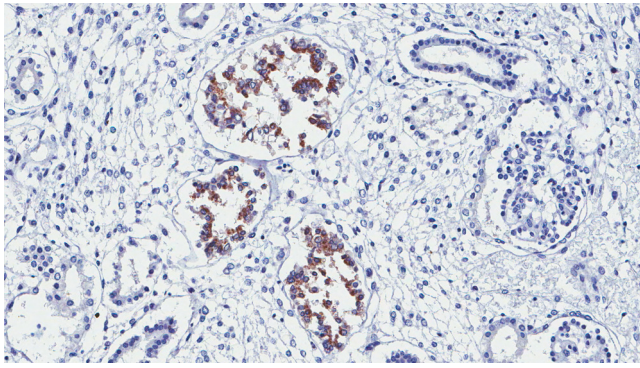


Figure. Microscopy kidney of aborted fetus. Glomerular and tubular structures expressing positive immunoreaction to DENV (20x).

women were diagnosed with dengue. DENV also was confirmed in the placenta and newborn serum.

A spectrum of dengue clinical presentations was observed in newborns, from asymptomatic (cases 2 and 6) to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) (cases 3 and 4, respectively), as has been previously described.^{4,8} In 3 cases, the newborns were mildly symptomatic (cases 2, 6, and 7), showing only a nonspecific laboratory change such as leukopenia, thrombocytopenia, or hemoconcentration that did not correspond to the mother's severity of dengue. No instances of premature birth occurred, possibly because of the onset of maternal infection between 37 and 39 weeks of pregnancy. However, abortion occurred in 1 case of infection during the first trimester of pregnancy (12th week), confirming recent findings.⁹

Infants who developed DHF or DSS (cases 3 and 4) and the single case of abortion (case 5) had a severe inflammatory response and premature detachment of the placenta, reflecting a more severe course of the disease. However, there was no relationship between severity of newborn/fetal outcome and the mother's clinical presentation of dengue. DENV was identified in all but 2 cases of neonatal infection, with IgM present in the serum after 1 day of maternal disease. These findings indicate that neonatal DENV infection occurred during the incubation period of the mother's disease.

A period of 1 to 8 days between the first day of mother's illness and childbirth was sufficient to cause DENV perinatal transmission and harm to the fetus. This finding suggests that the virus itself might be the major factor responsible for the injury of the concept in pregnant DENV-infected women. However, it is not known whether subneutralizing levels of maternally derived anti-DENV IgG serotypes enhanced DENV-2 infection in neonatal Fc receptor-bearing cells and therefore contributed to severity of the newborn diseases.

The most severe clinical newborn cases (3 and 4) responded favorably to intensive care and antibiotic therapy. In the cases of neonatal DHF/DSS (cases 3 and 4), an association of severity with neonatal bacterial infection cannot be excluded. The differentiation of dengue in the neonatal period from neonatal bacterial sepsis is difficult, and in this context, specific

Table. Maternal, fetal, and neonatal clinical findings and outcomes

Case	Maternal findings				Fetal and newborn findings								
	Mother age, y	GA at child birth	Signs of illness	Clinical syndrome	Time, d*	Mode of delivery	Maternal outcome	PCRs/ELISA-IgM†	Clinical findings of newborn	Laboratory findings	Admitted in ICU	Antibiotic therapy	Newborn outcome
1	34	39	Yes	DHF	8	Cesarean	Discharge	DENV2	Hepatomegaly, respiratory distress, jaundice	Thrombocytopenia, lymphocytosis, increased liver enzymes	Yes	No	Discharge
2	23	39	No	DF	1	Cesarean	Discharge	IgM positive	Low birth weight	Thrombocytopenia, lymphocytosis	No	No	Discharge
3	26	39	No	DF	3	Cesarean	Discharge	DENV2	Rash, fever, acrocyanosis, jaundice, bleeding from puncture sites, hepatomegaly, ascites, pleural effusion	Thrombocytopenia, negative blood cultures	Yes	Yes	Discharge
4	22	39	Yes	DHF	1	Vaginal	Discharge	IgM Pos	Petechiae, fever, jaundice, acrocyanosis, slow perfusion, shock	Thrombocytopenia, negative blood cultures	Yes	Yes	Discharge
5	32	12	No	DF	3	Abortion	Discharge	‡	Abortion	-	-	-	-
6	34	37	Yes	DHF	6	Vaginal	Discharge	DENV2	None	Normal	No	No	Discharge
7	17	38	Yes	DSS	2	Vaginal	Death	DENV2	Abdominal distension	Leukopenia, thrombocytopenia, increased serum hepatic enzymes levels, negative blood cultures	Yes	Yes	Discharge

DF, dengue fever; ELISA, enzyme-linked immunosorbent assay; GA, gestational age in weeks; ICU, intensive care unit; PCR, polymerase chain reaction.

*Time elapsed between the first day of mother's illness and childbirth.

†Newborn serum.

‡Immunohistochemistry positive in placental tissue for DENV.

treatment for bacterial sepsis may have contributed to a better prognosis of severe neonatal disease.^{4,10} Dengue should be included in the differential diagnosis of neonatal sepsis in hyperendemic areas such as Brazil, as well as for children of pregnant women who visit areas where dengue is endemic. ■

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