Maternal and Fetal Death after Dengue Infection: Insights on Dengue Diagnosis

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Abstract
Dengue virus infection in pregnancy has been associated with miscarriage, intrauterine fetal death, and secondary neonatal impairment, including prematurity and vertical transmission of the virus.

This study reports a fatal outcome due to confirmed dengue, resulting in maternal and fetal death. Dengue should be included in the differential diagnosis of HELLP syndrome in hyperendemic areas such as Brazil, and RT-PCR in paraffin-embedded tissue used to confirm the diagnostic, especially when these samples are the only available material.

Keywords
Dengue, Maternal death, Pregnancy, Pathology

Introduction
Dengue Virus (DENV) is an arthropod-borne virus belonging to the Flaviviridae family, genus Flavivirus and has four antigenically distinct serotypes (DENV 1-4). Brazil is considered hyperendemic for dengue, and all serotypes have been identified. The occurrence of dengue infection in pregnancy has been reported in the literature since 1948 and a recent systematic review [1] reported several cases of antenatal complications associated with dengue, including miscarriage, stillbirth, and premature deliveries. In 2013, seven laboratory confirmed cases (serology, RT-PCR, and immunohistochemistry) of vertical transmission were reported in Rio de Janeiro [2].

We report evidences of vertical transmission resulting in maternal and fetal death, in a dengue infected pregnant woman diagnosed after death.

Case Report and Investigation
Since 2009, after the reporting of 13 pregnant women with dengue in the state of Rio de Janeiro [3] an intensified surveillance of dengue in pregnant women had been recommended, and a guideline to the care and monitoring of infected pregnant women by healthcare workers was created along to the recommendation to the placenta pathological examinations of all suspected cases in the reference maternities of the state. In November 2010, a 23-year-old pregnant woman was admitted to a maternity in Rio de Janeiro, complaining of lower abdomen pain, vomiting and diarrhea. The symptoms had started at the same day and fever has not been reported. The fetal heartbeat was audible at the admission, but after lipothymy and maternal hypotension (BP = 120 × 80 mmHg at the moment of...
The fetal membranes, umbilical cord, chorionic plate, villi, intervillous space, and decidua basalis were examined under a light microscope.

For immunohistochemistry, the primary antibody MAB 8705 (Merck Chemicals) was used according to the manufacturer's instructions, and the Novolink™ Polymer Detection System and SIGMA FAST™3,3 kits were used in the staining reactions. Paraffin-embedded tissue sections from the livers of patients with a confirmed diagnosis of dengue virus infection who progressed to death as well as paraffin-embedded fetal tissues of the products of conception from infected patients were used as the positive controls for immunohistochemistry. For the negative controls for immunohistochemistry, paraffin-embedded tissue sections from the livers of patients who died due to dengue in which the primary monoclonal antibody used in the incubation step was omitted and only the diluent solution of Bovine Serum Albumin (BSA) were used together with paraffin-embedded placental samples from uninfected patients in which the primary monoclonal antibody was included.

For molecular diagnosis, the viral RNA was extracted from paraffin-embedded tissues using the PureLink FFPE RNA Isolation Kit (Invitrogen, Carlsbad, California, USA). The qualitative Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) described by Lanciotti [4] was performed for DENV detection and typing. This protocol detects the four serotypes in a semi-nested procedure, generating amplified products with specific molecular sizes (in bp) for each DENV serotype.

### Results

The histopathological analysis of the placenta showed areas of corioangiosis (abundance of blood vessels), edema of the villous stroma, and increase in the number of syncytial knots and reduced intervillous space (Figure 1). The immunostaining was positive in decidual cells (Figure 2). The infecting dengue serotype, DENV-2, was identified by RT-PCR detected virus only in the umbilical cord.

### Discussion and Conclusions

Maternal mortality is considered a serious public health problem worldwide, so that the etiological diagnosis for the cause of death is indispensable. Some diseases, specific to pregnancy such as HELLP syndrome, sepsis and bleeding syndromes can cause confounding to complication of Dengue disease. There have been descriptions of thrombocytopenia, liver insufficiency and hemorrhagic complications after childbirth in pregnant women with dengue infection, evidencing the importance of diagnosis distinction from the diseases that are common to pregnancy, such as the HELLP Syndrome in hyperendemic country [5].

Mother’s and fetus death were probably associated to shock, the most severe form of Dengue and which mimicked a usual obstetric complication. The abdominal pain,
be added to the differential diagnosis of pregnant women whose clinical manifestations are compatible to sepsis or HELLP syndrome [5]. In the event of maternal death, we suggest that immunohistochemistry and/or RT-PCR should be used to test placental tissue, especially in the absence of other materials, to elucidate the cause of death [6].

The hemodynamic changes experienced by the mother due to capillary leak syndrome as well as the vertical transmission of the virus would be responsible for the fetal morbidity.

In countries where DENV infection is endemic, serology testing, ELISA IgM and paired IgG or NS1 or RT-PCR should...
The placenta proved to be an organ that reflects well the inflammatory response, virus presence and the maternal hemodynamic alterations.

The presented case illustrates the histopathological alterations of placenta due to DENV infection and demonstrates DENV perinatal transmission by the presence of positive RT-PCR in the fetus umbilical cord and reinforces the importance of including DENV infections in differential diagnosis of syndromes occurring in pregnant women such as HELLP and sepsis.

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References


