



Dengue infection in pregnancy and transplacental transfer of anti-dengue antibodies in Northeast, Brazil



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ABSTRACT

Background: Dengue affects nearly 400 million people annually worldwide and considered one of the most serious health threats in tropical and subtropical countries.

Objective: To analyze the occurrence of dengue infection among the parturient who have formed the baseline of an ongoing birth cohort study in the city of Recife, Northeast of Brazil.

Study design: From March 2011 to May 2012, we recruited 417 parturients with low-risk pregnancies at maternity ward who agreed to a follow-up of their babies. Dengue infection was accessed through DENV RT-PCR and anti-dengue antibodies (IgM and IgG). The prevalence of IgG antibodies in the parturients and their concepts were determined. The concordance among the pairs was tested using Kappa. The association of recent infection (IgM and/or DENV RT-PCR positive) with the maternal characteristics and clinical features of the neonates was analyzed through logistic regression.

Results: The prevalence of IgG antibodies in the maternal and cord blood samples was 95.1% (95% CI: 92.6–96.9%) and 95.8% (95% CI: 93.4–97.5%), respectively, with high agreement between maternal-cord pairs (Kappa = 0.93). The prevalence of recent infection was 10.6% (95% CI: 7.9–14.2%) in the parturients. Reported fever during pregnancy was associated to recent infection ($p = 0.023$).

Conclusion: The data draw attention for the high frequency of anti-dengue antibodies in the women studied and for the high occurrence of infection during pregnancy in this region of Brazil. There is a need for further studies to better characterize dengue infection in pregnant women.

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1. Background

Dengue affects nearly 400 million people annually worldwide and is currently considered as one of the most serious health threats in tropical and subtropical countries [1]. In the Americas, where

Abbreviations: DENV, dengue virus; RT-PCR, real-time polymerase chain reaction; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; ELISA, enzyme-linked immunosorbent assay; MAC-ELISA, immunoglobulin M antibody capture enzyme linked immunosorbent assay; Ig G, immunoglobulin G; IgM, immunoglobulin M; RNA, ribonucleic acid; SINAN, National Disease Notification System.

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there is co-circulation of the four dengue virus serotypes (DENV 1–4), approximately 70% of the cases were reported in Brazil [2,3].

The clinical spectrum of infection is broad and ranges from asymptomatic infection or undifferentiated fever to severe forms such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) [4]. In pregnant women, dengue infection has been related to greater risk of severe cases [5], maternal complications such as miscarriages [6] and increased bleeding during delivery [7], and neonatal complications such as preterm birth and low birth weight [8]. Anti-dengue maternal antibodies transferred via placenta are also implicated in the development of DHF in infants having primary dengue infection [9–11].

The Northeast region of Brazil has been responsible for approximately one third of the cases in the country [12]. Population-based surveys conducted in this region have also shown the high prevalence of anti-dengue antibodies in the population [13,14]. However, the burden of infection in pregnant women and their offspring is still unknown in the region. For that reason, a birth cohort study was

implemented to investigate the incidence of dengue infection and kinetics of anti-dengue maternal antibodies transferred to children during the first years of life in the city of Recife, an area of intense co-circulation of dengue virus in this region [13,15].

2. Objective

This paper analyzes the occurrence of dengue infection and transplacental transfer of anti-dengue antibodies among the parturients and their infants enrolled in this birth cohort study.

3. Study design

The participants were recruited at the time of admission for delivery at the Instituto de Medicina Integral Prof. Fernando Figueira, a publicly funded teaching hospital located in Recife, between March 2011 and May 2012. A total of 934 women classified as having low-risk pregnancies were admitted in the study period.

Recife is a larger urban center in Pernambuco state and has a population of around 1.5 million inhabitants [16] and an approximate number of 22,000 births per year [17]. The introduction of dengue virus in Recife was reported in the early 1980s, and studies indicate the intense transmission of DENV in the population [13,18]. The four DENV serotypes currently co-circulate in the region [19]. The reported dengue incidence during recruitment was 487 cases per 100,000 inhabitants per year in Recife [20]. Routine yellow fever vaccination is not recommended in this setting since it is considered a non-endemic area [21].

3.1. Inclusion criteria

Women with low-risk pregnancies living in Recife, who agreed to participate and to have their infants followed for at least one year in this cohort study.

3.2. Data collection

Data collection was carried out before or after delivery. Parturients were interviewed by trained nurses using a standardized questionnaire. Sociodemographic (age, marital status, schooling, race, and individual and family income) and prenatal information (YF vaccination, report of dengue fever, fever episodes, infectious events as urinary tract infections, and/or sexually transmitted diseases) were obtained. Maternal blood sample collections were performed before or right after delivery while umbilical cord blood samples were obtained immediately after birth.

3.3. Laboratory methods

Serum samples were separated and stored into cryovials at -70°C . All samples were screened for detection of DENV-specific IgG and IgM antibodies. Anti-dengue IgG indirect ELISA (PanBio, Brisbane, Australia) and anti-dengue IgM-capture ELISA (PanBio and Focus Diagnostics, Cypress, CA, USA) were performed following the recommended guidelines and results were interpreted according to the manufacturer's instructions. All samples were tested by a technician who was blinded to the results of each commercial kit.

Umbilical cord samples that showed positive or equivocal IgM results by Panbio were retested using an in-house IgM-capture ELISA (MAC-ELISA) performed according to the protocol described by Kuno et al. [22], with minor modifications.

Reverse transcriptase-polymerase chain reaction (RT-PCR) for detection of DENV serotypes was performed in the paired maternal-cord samples from parturients that reported fever in the seven

days preceding the delivery. RT-PCR was carried out following a standardized protocol described elsewhere [15,23]. Viral RNA was extracted from serum samples using QIAquick PCR purification kits (Qiagen, Valencia, CA). Negative and positive controls were included in all the steps.

3.4. Case definition

Anti-dengue IgG-positive results in the parturients were interpreted as previous infection, whereas the detection of anti-dengue IgG antibodies in the cord samples was interpreted as transplacental transferred anti-dengue antibodies. IgG antibody indeterminate results were interpreted as negative.

IgM antibody detection through ELISA is the most simple way to identify recent dengue infections due to its relatively short time window of measurement after infection ($\cong 6$ months) [24]. However, false-positive results can occur [25]. Therefore, the IgM antibody status of the parturient was defined based on the results of two different ELISA commercial kits: Panbio and Focus. Samples that met the following criteria were considered as a recent dengue infection case: IgM-positive results by both PanBio and Focus; positive result by Focus and equivocal result by PanBio; or RT-PCR positive result.

3.5. Sample size calculation

The number of parturients recruited ($n = 417$) is enough to estimate a dengue infection prevalence rate of 10% and approximate error of 2.9%.

3.6. Data analysis

The data analysis was performed using Epi-info 3.5.3 and STATA 10. The baseline characteristics of the participants were summarized using descriptive statistics. The prevalence of infection and the respective 95% confidence intervals (95% CI) were estimated. The agreement between the maternal and cord anti-dengue IgG antibodies was assessed using Kappa test.

The association between dengue infection and sociodemographic and clinical data of the parturients was analyzed using logistic regression. Crude and adjusted odds ratios were used as the effect measure. The level of significance was 5%.

4. Results

Fig. 1 shows the flowchart of the participant's recruitment. Among the 934 women who met the inclusion criteria, 417 were recruited. Two parturients were transferred to another maternity, and 415 were included in this study. Of these, 405 maternal and 380 umbilical cord samples were collected, obtaining 376 maternal-cord pairs.

The age of participants ranged from 13 to 43 years (median, 22 years). Most were mixed race (79.7%), had completed high school or university (57.1%), and had no paid work (56.9%). Gestational age ranged from 37 to 42 weeks (median, 39 weeks), and the majority had vaginal delivery (94.4%). Only 2.2% reported dengue fever during pregnancy, and 23.1% reported fever during the current pregnancy. Most of the parturients had no yellow fever vaccination (Table 1).

Table 2 shows the prevalence of dengue infection according to laboratorial tests. The prevalence of previous infection (IgG positive) was 95.1% (95% CI: 92.6–96.9%) in maternal samples, whereas the prevalence of anti-dengue IgG in the cord samples was 95.8% (95% CI: 93.4–97.5%). The frequencies of anti-dengue IgM were similar by both ELISA Panbio and Focus tests in the maternal samples (14.6% and 16.3%).

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