Symptomatic Dengue during pregnancy and the risk of stillbirth: a matched case control study using routine data in Brazil (2006-2012)

Enny S Paixão*, MSc[abc]
Maria da Conceição N. Costa, PhD[b]
Maria Glória Teixeira, PhD[bc]
Katie Harron, PhD[a]
Marcia Furquim de AlmeidaPhD[d]
Mauricio L. BarretoPhD[dc]
Laura C. Rodrigues, PhD[ac]

* Corresponding author email: enny.cruz@lshtm.ac.uk; Phone 44 7756636748

a London School of Hygiene and Tropical Medicine. Keppel St, Bloomsbury, London WC1E 7HT, United Kingdom

b Instituto de Saúde Coletiva. Rua Basílio da Gama, s/n.Canela. CEP 40110040. Salvador, Bahia, Brasil.

c Center of Data and Knowledge Integration for Health (CIDACS), Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, CEP 41745-715 Salvador-Bahia, Brazil

d Universidade de São Paulo.Av. Dr. Arnaldo, 715 Cerqueira Cesar, 01246904 - São Paulo, SP – Brasild

Abstract

Background: Maternal infections during pregnancy increase the risk of fetal death; dengue is a common infection, but little is known about its role in fetal mortality. We conducted a nested case control study investigating the association between symptomatic dengue during pregnancy and fetal death.

Methods: Using obstetrician-collected data from the Brazilian Information System of Births (SINASC), Information System of Mortality (SIM) and Notification of Infectious Diseases (SINAN), we identified all pregnancies ending in stillbirth and a random sample of live births between 2006 and 2012. We used linkage to establish which mothers were notified with dengue during pregnancy. Using stillbirths as cases and a sample of matched live births as controls, we calculated matched odds ratios (mORs) using conditional logistic regression, adjusting for maternal age and education.

Findings: The mothers of 275/162,188(0.2%) stillbirths were notified with dengue during pregnancy, compared with 1507/1,586,105(0.1%) mothers of live births. Symptomatic dengue during pregnancy doubled the odds of fetal death (mOR1.9,95%CI1.6-2.2). The increase in risk was similar when restricting analyses to laboratory confirmed diagnosis of dengue (mOR1.8,95%CI1.4-2.4). Severe dengue increased the risk of fetal death fivefold (mOR 4.9,95%CI 2.3-10.2). The proportion of all fetal deaths attributable to notified dengue during pregnancy was small(0.08%), but as expected, increased during epidemic years(0.13% in 2010).

Interpretation: We provide powerful evidence that symptomatic dengue during pregnancy increases the risk of fetal death; we recommend further research on the association between dengue and poor births outcomes.

.

Introduction

Fetal deaths are a common adverse outcome of pregnancy, even in developed countries. Although the global burden of stillbirths declined by 25.5% between 2000 and 2015, there were still 2.6 million stillbirths worldwide in 2015[1]. Stillbirth rates vary from an estimated 4/1000 births in high incomes countries to 26/1000 births in low-middle income countries[1].

Infections during pregnancy are believed to cause between 10%-25% of all fetal deaths in high income countries[2], with infections in early pregnancy carrying a higher risk;[3,4] infection in the first 28 weeks causing 15% of all fetal deaths, and infections later than 28 weeks causing 6%[5]. The contribution of viral infections is estimated to be 14.5%[6], although it is possible that a proportion of unexplained stillbirths could be due to undiagnosed viral infections[7].

The recent confirmation of zika as a cause of congenital anomalies and stillbirth highlighted the importance of original research on the effect of flavivirus on stillbirths[8].A review by Mc Clure and collegues[9] (2014) mentioned dengue as a cause of fetal death, yet there are no population-based studies showing this association. In 2010, a systematic review concluded that whether dengue during pregnancy had any negative effect on fetal outcomes remained unclear[10]. A recent systematic review found that only one study of dengue infection during pregnancy and fetal death had a comparison group[11]. They included thirteen stillbirths (nine exposed to dengue) and the crude relative risk was 6·7 (95% CI 2.1-21.3) in women with symptomatic dengue compared with women without dengue[12]. All other evidence to date comes from case reports or case series, none of which include appropriate controlling for confounding or population control groups. The mechanisms of how dengue could lead to a stillbirth is unknown but there are three main hypotheses: 1) direct effect of mother´s illness (severe dengue); 2) the placenta might be affected by the changes caused by the disease; 3) the direct effect of virus on fetus[2]. Although the incidence of dengue is increasing dramatically and approximately half of the global population is at risk, including women of reproductive age[13], the effects of dengue infection during pregnancy on fetal mortality remain unclear. Here, we report the analysis of a population-based nested case-control study, which, adjusting for confounding variables, investigates the association between stillbirth and symptomatic dengue during pregnancy

Methods

Study design

We conducted a population-based nested case-control study using linkage of routine data on all pregnant women whose outcomes were live birth and stillbirth in Brazil, from January 1, 2006 to December 31, 2012.

Data sources

Data were extracted from three Brazilian databases: The Live Births Information System (Sistema de Informação sobre Nascimentos; SINASC), Mortality Information System (Sistema de Informação sobre Mortalidade; SIM), and Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação; SINAN). They contain respectively, records of all live births, all stillbirth and all notifiable diseases, in Brazil. SINASC consists of data from live birth notifications, a legal document completed by the health professional who assisted the delivery. It is the required document for a legal existence and includes information on the mother (name, place of residence, age, marital status, education, whether she had a stillbirth or a child who died); the pregnancy (length of gestation, type of delivery); and the newborn (birth weight, presence of congenital anomalies)[14]. The completeness of the data is very high, with most variables completed in over 90% of cases; the exception being information on whether the mother had a previous stillbirth or abortion[15]. Data in SIM come from the Death Certificate, a legal document[16]. The proportion of records with missing data varies by variable, and is around 20% on maternal education and number of previous fetal deaths or abortions. Data on notifiable diseases, including personal information on the patient (name, place of residence, age, education), symptoms of disease, laboratory tests, and disease severity are captured in the third system, SINAN, which contains reasonably complete data on the variables we used for linkage and in the final analyses (<0.05% records were excluded because of missing name). SINAN contains two sources of information on maternal age (age and date of birth). Approximately 5% of dengue cases did not have a final classification of severity. Laboratory confirmation was not required for notification of dengue cases because dengue was the main (and for some years the only) vector borne disease circulating in Brazil (yellow fever and malaria occur in restricted areas; notification of Zika and Chikungunya were not introduced until 2014).

Linkage process

SINAN–Dengue records were linked probabilistically with the cohort of pregnant women from SINASC and SIM, in order to identify those who had dengue during pregnancy. Name, age and place of residence of the mother at time of delivery/notification were used in the matching

process. We excluded records with missing or implausible names and duplicates. Match weight calculations were based on the Fellegi-Sunter method[17].

A gold-standard dataset was created using all stillbirth records for two years of data (2009-2010) and all live birth records within two states (Ceará and Espirito Santo) for one year (2010) of data. Manual review of record pairs was performed to establish true matches (records belonging to the same mother) and estimate m-probabilities P(agreement|match); the probability of match given agreement on each identifier. To calculate the u-probabilities P(agreement|non-match), we used a subset of SINAN to create a set of non-matches, by cross joining all record pairs and removing record pairs belonging to the same individual. Records pairs were then ordered by match weight and manually inspected to identify obvious non-links that had high weights and probable links with low weights. Only links and non-links with a high degree of certainty were retained for the case-control study to avoid misclassification; uncertain links (where we could not establish whether or not a woman had dengue) were excluded from analyses.

To evaluate the quality of the linkage algorithm, we compared the links obtained using the probabilistic algorithm with the gold-standard created by manual review. This validation demonstrated that for stillbirths and live births, sensitivity was 64.% and 62% respectively; the positive predictive value was 94% for stillbirths and 95% for live births; specificity was >99% for both. The missed matches occurred randomly in cases and controls (appendix). The procedures and evaluation of the matching process are the subject of a separate paper.

Procedures

In SIM, stillbirth was defined as the death of a product of conception before the expulsion or complete extraction from the body of the pregnant woman, occurring from 22 weeks or weighing more than 500g, according to Brazilian definition[16].

In SINASC, live birth was defined as the product of conception that independent of the duration of pregnancy, after the separation from the mother's body, breathes or shows any other signs of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles according to Brazilian definition[14].

Records with missing or implausible name of the mother, multiple pregnancy, congenital anomalies, birth and stillbirth from municipalities without dengue notification and uncertain links status were excluded in cases and controls (Figure 1). Multiple pregnancy and congenital anomalies were excluded because they might be on the causal pathway for stillbirth.

We include stillbirths recorded in SIM as cases, and as controls, we used a random sample of 10 live births (without replacement), matched to cases by month and calendar year, born to a woman living in the municipality of residence of the mother of the case. To select the matched control we matched cases and controls only if they have the same month/ year and place of birth. We randomly ordered cases and controls within month/ year and place of birth groups, and selected the first case in the group to be matched to the first 10 controls in the group. The second case was matched to controls 11 to 20, and so on, forming pairwise combinations. We selected 10 controls per case to allow control for potential confounders such as dengue seasonality, intensity of the virus circulation and social environment.

The exposure in this case control study was being a notified confirmed cases of dengue during pregnancy that resulted in the birth of the case or the control. Dengue in Brazil can be confirmed based on clinical / epidemiological criteria- presence of clinical symptoms of dengue in an area and time as other confirmed cases of dengue, or clinical/ laboratory criteria- presence of clinical symptoms and laboratory confirmation (positive test from one of IgM detection by ELISA, viral RNA detection via PCR, NS1 viral antigen detection, or positive viral culture). In this report, a subject was considered to be "exposed" if their mother was notified to SINAN and confirmed as dengue case (and therefore their records were linked to a notification of dengue during the pregnancy). "Dengue during pregnancy" refers to all confirmed cases of dengue (clinical/epidemiological and clinical/laboratorial); "dengue during pregnancy laboratorial confirmed" refers to only the laboratorial confirmed cases. We classified dengue in two clinical categories: dengue fever as a self-limiting disease (fever, with severe headache, pain behind the eyes, muscle and joint pain, and rash) or severe dengue. We classified as severe dengue, all cases of dengue that the Brazilian Ministry of Health classified as dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS) and complicated dengue. Complicated dengue is a Brazilian definition of all severe cases of dengue that did not meet the WHO criteria for DHF (fever, haemorrhagic evidence, thrombocytopenia and evidence of plasma leakage) and could not be classified as mild self-limited disease due to its severity. Complicated dengue is used when a probable case of dengue presented one of the following manifestations: severe changes in the nervous system, cardiorespiratory dysfunction; insufficient hepatic function; gastrointestinal bleeding, cavity spills, thrombocytopenia equal or less than $50,000/\text{mm}^3$, leucometry less than $1000/\text{mm}^3$ [18]. We used only two clinical categories because of the small numbers of observations, since the severe form of dengue is a rare outcome.

Ethical approval was obtained from Federal University of Bahia, Salvador, Brazil (CAAE: 26797814.7.0000.5030) and from London School of Hygiene and Tropical Medicine (Ethics Ref:10269).

Statistical analysis

To calculate the sample size, we conducted two preliminary deterministic linkages of records with 100% agreement in the three identifiers (name, age and municipality of the mother); the first, between SINAN and SIM to calculate the minimum percentage of mothers of stillbirths who had dengue during pregnancy (0·05%) and between SINAN and SINASC to calculate the minimum percentage of mothers of live births who had dengue during pregnancy (0·03%). We estimated that with 94,755 cases, we would be able to detect a matched odds ratio (mOR) of 1·6, using the following parameters: proportion exposed as above, 80% power, 95% confidence level; ratio of ten controls: case(appendix).

For the overall association, we estimated crude mORs from univariate conditional logistic regression and adjusted mORs using conditional logistic regression, controlling for maternal age and maternal education (as a proxy of socioeconomic status). For a sensitivity analysis of the validity of dengue clinical diagnosis, we repeated analysis with laboratory confirmed dengue only. We investigated the effect of dengue by disease severity and time between the disease and outcome. An analysis stratified by report of a previous fetal death or abortion explored whether dengue had a different effect in pregnancies at high risk of fetal death. To investigate the potential impact of missing data, we conducted another sensitivity analysis in which we assumed that all missing data in confounding variables in the cases were in the low risk groups and all the missing data in the controls were in the high risk groups.

The population attributable fraction (PAF= [p1(OR-1)] / OR) was calculated using the punafcc package available in STATA software, that uses a logistic regression method [19], which provides PAF (and 95% CI) adjusted for confounding variables by combining adjusted ORs and the observed incidence of dengue among cases (stillbirths). We used Stata version 14.1 software for the statistical analyses.

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, interpretation, or writing of the report. All authors had full access to all de-identified data in the study and had final responsibility for the decision to submit for publication.

Results

The Brazilian Information System recorded 224,582 stillbirths and 20,333,482 livebirths during the study period. After exclusions, 162,781 stillbirths were eligible for the study. No control was matched for 583 (0.3%) stillbirths and these were excluded. The final study population included 162,188 stillbirths and 1,586,105 livebirths, with 275 stillbirths and 1,507 live births exposed (Figure 1).

The characteristics of cases and controls are shown in Table 1. The proportion of missing values for all variables was higher among cases than in controls, including classical risk factors for stillbirth, such as previous fetal death or abortion (28.3%) and maternal education (27.5%). This was also true for age, birth or death weight, and gestational age.

The risk of stillbirth among all births recorded in the information system was 11/1000 live births. The risk of a stillbirth in women who had dengue during pregnancy was 15/1000 pregnancies (95% CI 13-17/1000). Overall, dengue was laboratory confirmed in more than 30% of the dengue cases recorded. Dengue during pregnancy was more common in mothers of cases(0.2%) than in mothers of controls(0.1%). Potential confounder variables (i.e. variables associated with dengue and with stillbirth) were maternal education and previous fetal death or abortion(Table 2).

The crude association between symptomatic dengue during pregnancy and stillbirth was mOR 1.8 (95%CI 1.6-2.0), and was similar when adjusting for maternal education and maternal age (mOR 1.9, 95% CI 1.6-2.2). Analysis restricted to laboratory confirmed dengue only gave a similar adjusted mOR (1.8, 95% CI 1.4-2.4). We investigated if the association between dengue and stillbirth depended upon previous fetal death or abortion, but the odds ratio did not differ according to this variable category (with mOR:1.6, without mOR:1.8). The risk of fetal death is dependent on time between first symptoms of dengue and the date of live/stillbirth: it appears to be bimodal. It peaked in the first twenty days after the onset of dengue at mOR 4.9, 95% CI 2.9-6.3, (more marked when dengue is severe). After 10 days, the risk of mortality remains raised, (mOR1.7 ; 95% CI 1.4-2.0).but at a roughly constant rate, until the end of pregnancy (Figure 2). Severe dengue during pregnancy increased the risk of stillbirth fivefold (mOR 4.9, 95% CI 2.3-10.2), almost 3 times that of mild dengue (mOR 1.7, 95% CI 1.5-2.0) (Table 3).

A sensitivity analysis was conducted because the proportion of missing data was higher among cases than controls. We assumed that all missing data in confounding variables in the cases were in the low risk groups and all the missing data in the controls were in the high risk groups. The magnitude of the association was very similar (mOR 1·8, 95% CI 1·5- 2·0).

The prevalence of symptomatic dengue during pregnancy was low (0·1% of mother of controls were notified with dengue during pregnancy), so the PAF was also low: 0·08% of all stillbirths during the period were attributable to dengue, with marked yearly variation and a maximum of 0·13% during epidemic years(appendix).

Discussion

Symptomatic dengue during pregnancy roughly doubled the risk of stillbirth, with the highest risk observed in the first twenty days after disease onset and in women with severe disease. The increase in risk was the same for all cases of dengue (either clinical epidemiological or laboratory diagnosis) as with laboratory confirmed dengue only. Dengue during pregnancy is relatively rare, and the proportion of all fetal deaths attributable to dengue during pregnancy in Brazil during the period was relatively small, but larger during epidemic years.

This is the first study to evaluate the risk of stillbirth among women with dengue during pregnancy using a population-based approach, with a sufficiently large sample size and controlling for confounders, although we were not able to adjust for all possible confounding factors as we were relying on routine information that is obtainable from notification system records. Results are consistent with a study conducted in the French Guiana, where the risk of stillbirth was higher among pregnancies with symptomatic dengue, although their estimate of risk was higher[12]. Stillbirth has been associated with other viral maternal infections and the magnitude of this association varies given the organisms, severity of maternal illness, gestational age and others factors. For example, maternal influenza that required hospitalization increased the risk of fetal death in 4·2 (95% CI 1·4-12.4)[20], whereas the risk of stillbirth on pregnant women with a mild disease was 1·9 (95% CI 1·1-3·4)[21]. The risk of stillbirth among women with HIV infection was 1·67 (95% CI 1·0-2·6)[22].

Although many viral infections increase the risk of fetal death, the mechanism for the association is not clear. The analysis of the length of time between symptoms of dengue and stillbirth and disease severity showed that the highest risk occurred during the acute maternal illness and in women with severe disease, suggesting that the mechanisms involved in the

association between dengue and stillbirth might be through maternal infection; if the mother becomes severely ill the fetus could die in the days following first symptoms, due to high fever or other systemic manifestations[2]. After this first period, in a small proportion of cases, other mechanisms could be relevant. The proposed mechanism for the effect of some viral infections on pregnancy outcomes include direct fetus infection damaging vital organ such as brain and heart. However for dengue, vertical transmission has not been described as a common occurrence, although virus and antibodies have been found in placentas, in cord blood of such infants and in the cells of lung and kidney of an aborted fetus[23,24,25,26,27,28] . In the absence of vertical transmission, harm to the fetus might result from the alterations that remain after the infection is over. This would include pathological changes in placenta leading to hypoxia as proposed by Ribeiro et al (2007)[29]. However we cannot elucidate this mechanism in this study, this could be clarified by further research with detailed clinical information (including information on medication and co-morbidities), and full investigation using appropriate instruments and specific laboratory techniques. These studies could be conducted in much smaller number of patients.

According to a systematic review of small previous studies[11], and a comment by Carles[30] (2016), and another study using similar Brazilian data[31], dengue is associated with adverse fetal outcomes and severe forms of the disease carry a higher risk. This was ratified in our study, where the risk of stillbirth among women that developed the severe forms of dengue was almost three times that of those with mild disease. Because history or fetal loss is a risk factor for new stillbirths[5], we investigated if this variable acted as an effect modifier, but found that the association was similar for women with and without a previous stillbirth.

Our study has limitations and strengths inherent to the linkage process and to utilization of secondary data. In relation to the use of secondary data, we showed very good agreement on the estimates of risk in cases with and without laboratory confirmation. Our data set us some challenges for linkage, and the process and validation of the linkage will be discussed in a separate paper. However, it is unlikely that the linkage process introduced bias, because linkage errors occurred randomly across cases and controls. Missing data were more frequent in cases than controls. A consequence of this could be better linkage among controls, which would decrease the magnitude of the observed association. However, the validation study showed a linkage sensitivity of near 60% for both cases and controls, so the magnitude of the association should not be affected by linkage error, although the PAF will be underestimated.

Strengths of our study are the very large sample size, including all confirmed cases notified in a country where dengue incidence is high and variable over time. We also had a rigorously selected group of controls and were able to control for confounding. The sensitivity analyses demonstrate the robustness of our findings.

Despite these limitations, we provide strong evidence that symptomatic dengue during pregnancy is a risk factor for stillbirth, with higher risk in severe forms during the acute phase. We recommend further research in different settings to confirm our results, and explore further other negative outcomes of pregnancy (preterm birth, Intrauterine growth restriction (IUGR), congenital anomalies and maternal mortality) and studies of other vector-borne diseases contributing to fetal death. Additional research is required to measure the burden of sub clinical maternal viral infections in stillbirths and elucidate the pathological mechanisms involved in this relationship. If the association between dengue and stillbirth were demonstrated in others studies, recommendations should be made for close monitoring of pregnant women with dengue symptoms, for incorporating dengue control on programmes to reduce fetal mortality, and for including pregnant women as an at-risk population in dengue control programmes, in order to strengthen the health education actions for individual protection of pregnant women.

References

1. Lawn JE, Blencowe H, Pattinson R, et al. Stillbirths: Where? When? Why? How to make the data count? The Lancet. 2011;**377**:1448–1463.
2. Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. The Lancet. 2010;**375**:1482–1490.
3. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961-1988. Obstet Gynecol. 1992;**79**:35–39.
4. Gibbs RS. The origins of stillbirth: infectious diseases. In: Seminars in perinatology [Internet]. Elsevier; 2002 [cited 2016 Oct 6]. p. 75–78. Available from: http://www.sciencedirect.com/science/article/pii/S0146000502800192
5. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. The Lancet. 2011;**377**:1331–1340.
6. Williams EJ, Embleton ND, Clark JE, Bythell M, Platt MPW, Berrington JE. Viral infections: contributions to late fetal death, stillbirth, and infant death. J Pediatr. 2013;**163**(2):424–428.
7. Craven C, Ward K. Stillbirth: tissue findings with environmental and genetic links. In: Seminars in perinatology [Internet]. Elsevier; 2002 [cited 2016 Oct 9]. p. 36–41. Available from: http://www.sciencedirect.com/science/article/pii/S0146000502800155
8. Rasmussen SA, Jamienson DJ, Honein MA, Petersen LR. Zika virus and birth defects-reviewing the evidence for causality. N Engl J Med. 2016; 374:1981-1987.

9. McClure EM, Dudley DJ, Reddy U, Goldenberg RL. Infectious causes of stillbirth: a clinical perspective. Clin Obstet Gynecol. 2010;**53**(3):635.

10. Pouliot SH, Xiong X, Harville E, et al. Maternal dengue and pregnancy outcomes: a systematic review. Obstet Gynecol Surv. 2010;**65**(2):107–118.

11. Paixão ES, Teixeira MG, Maria da Conceição NC, Rodrigues LC. Dengue during pregnancy and adverse fetal outcomes: a systematic review and meta-analysis. Lancet Infect Dis. 2016; **16**(7):857-65

12. Friedman EE, Dallah F, Harville EW, Myers L, Buekens P, Breart G, et al. Symptomatic dengue infection during pregnancy and infant outcomes: a retrospective cohort study. PLoS Negl Trop Dis. 2014;**8**(10):e3226.

13. Dengue and severe dengue. WHO website http://www.who.int/mediacentre/factsheets/fs117/en/ [cited on 13-02-2013]

14. Brazil, Ministry of Health. Manual de instruções para o preenchimento da declaração de nascido vivo. Fundação Nacional de Saúde Brasília; 2011.

15. Pedraza. Quality of the information system on live births/SINASC: a critical analysis of published studies

16. Brazil, Ministry of Health. Manual de vigilância do óbito infantil e fetal e do comitê de prevenção do óbito infantil e fetal. MS Brasília; 2009.

17. Fellegi IP, Sunter AB. A theory for record linkage. J Am Stat Assoc. 1969;**64**(328):1183–1210.

18. Brazil, Ministry of Health. Dengue diagnostic e manejo clinic- adulto e crianca/Ministerio da Saude, Secretaria de Vigilancia em Saude, Diretoria Tecnica de gestao. 3 ed. Brasilia; 2007.

19. Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. Stata J. 2013;**13**(4):672–698.

20. Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M, UKOSS. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study.BMJ 2011 14;342:d3214.

21. Håberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. N Engl J Med 2013;368:333–40.

22. Wedi CO, Kirtley S, Hopewell S, Corrigan R, Kennedy SH, Hemelaar J. Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis. Lancet HIV 2016; 3: 33-48.

23. Ribeiro CF, Lopes VGS, Brasil P, Coelho J, Muniz AG, Nogueira RMR. Perinatal transmission of dengue: a report of 7 cases. J Pediatr. 2013;**163**(5):1514–1516.

24. Ventura AK, Ehrenkranz NJ, Rosenthal D. Placental passage of antibodies to Dengue virus in persons living in a region of hyperendemic dengue virus infection. J Infect Dis. 1975;**131** Suppl:S62-68.

25. Chye JK, Lim CT, Ng KB, Lim JM, George R, Lam SK. Vertical transmission of dengue. Clin Infect Dis. 1997; **25**(6):1374–7.

26. Perret C, Chanthavanich P, Pengsaa K, et al. Dengue infection during pregnancy and transplacental antibody transfer in Thai mothers. J Infect. 2005;**51**(4):287–93.

27. Argolo AFLT, Féres VCR, Silveira LA, et al. Prevalence and incidence of dengue virus and antibody placental transfer during late pregnancy in central Brazil. BMC Infect Dis. 2013;13:254.

28. Leite RC, Souza AI, Castanha PM, et al. Dengue infection in pregnancy and transplacental transfer of anti-dengue antibodies in Northeast, Brazil. J Clin Virol. 2014;**60**(1):16–21.

29. Ribeiro CF, Lopes VGS, Brasil P, Pires ARC, Rohloff R, Nogueira RMR Dengue infection in pregnancy and its impact on the placenta. International Journal of Infectious Diseases 55 (2017) 109–112.
30. Carles G. What are the true consequences of dengue during pregnancy? Lancet Infect Dis. 2016 Jul;**16**(7):765-6
31. Nascimento LB, Siqueira CM, Coelho JE, Siqueira Jr JB. Symptomatic dengue infection and livebirth outcome in Brazil, 2007-2013: retrospective observational cohort stydy. Lancet Infect Dis. (2017).

Contributors

This study was designed by Enny Paixao, Gloria Teixeira and Laura Rodrigues. Enny Paixao, Maria da Conceicao Costa, Katie Harron, Marcia Furquim and Mauricio Barreto contributed to carried the analysis and interpretation. All authors revised the manuscript and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.