**Dengue during pregnancy and fetal adverse outcomes: a systematic review and meta-analysis**

Enny S Paixão\*, MSCa

Maria Glória Teixeira, PhDb

Maria da Conceição N. Costa, PhDb

Laura C. Rodrigues, PhDa

\* 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 Kindon

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

Summary

A systematic review and meta-analysis of the increase in risk of four adverse fetal outcomes (stillbirth, miscarriage, preterm birth and low birth weight) in women who had dengue during pregnancy. We included 16 articles in the qualitative analysis and 8 in the meta-analysis. Study designs, setting and quality of studies varied. Miscarriages were 3 times more frequent, still births 6 times more frequent, preterm births 1.7 more frequent and low birthweight 1,4 times more frequent in women who had dengue during pregnancy. All increases other than for low birthweight were statically significant. Presence of clinical symptoms appear to be necessary for an effect on fetal outcomes and severity of disease might be associated with risk.

If confirmed, it would be important to monitor pregnancies were dengue is diagnosed and to consider pregnant women in dengue control policies.

Abstract

Background: Little is known possible adverse effects of dengue during pregnancy on fetal outcomes. The objective of this systematic review and meta-analysis is to estimate the increase in risk of four adverse fetal outcomes (stillbirth, miscarriage, preterm birth and low birth weight) in women who had dengue during pregnancy.

Methods: We searched Medline, Embase, Global Health Library and Scopus for articles published before August 2015. We independent screened titles and abstracts to select the papers for inclusion and scored the quality of those included in meta-analyses. We estimated the increase in risk of adverse fetal outcomes using Mantel–Haenszel methods. Heterogeneity of odds ratio was assessed with the I2 statistic.

Findings: We included 16 articles in the qualitative analysis and 8 in the meta-analysis. Miscarriage was 3 times more frequent in women with dengue than without OR=3.5(95%CI:1.15-10.77); stillbirth risk was six times higher (RR=6.7;95%CI:2.1–21.3) among symptomatic dengue cases than women without dengue; preterm birth and low birth weight were the most common negative pregnancy outcomes; the OR for the association between dengue and preterm birth was 1.71 (95%CI:1.06-2.76) and for low birth weight was 1.4 (95%CI:0.9 -2.2).

Interpretation: There is some evidence that symptomatic dengue during pregnancy is associated with negative fetal outcomes. If confirmed, it would be important to monitor pregnancies were dengue is diagnosed and to consider pregnant women in dengue control policies.

Funding: National Council for Scientific and Technological Development–CNPq . The funders had no role in the study.

Introduction

Dengue, a vector borne disease, is endemic in over 100 countries (mainly in South American and Southeast Asia). The infection is spreading to new areas with outbreaks of increasing magnitude and severity.1 It is estimated that annually, 390 millions of people are infected and 96 million develop clinical symptoms.2 Most people with dengue either have no symptoms or have a mild influenza-like disease (fever, headache, retro-ocular pain, muscle and joint pain, nausea, vomiting and rash – dengue fever DF); a small proportion progresses to severe illness with rapid onset of capillary leakage accompanied by bleeding, thrombocytopenia and liver injury: dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS).3

There are four serotypes (DENV 1, DENV 2, DENV 3, DENV 4) of dengue virus. Infection with one serotype provides long immunity against that particular serotype; cross immunity to the other serotypes is temporary.3 The risk of severe dengue increases with subsequent infections.4 The complex pathogenesis of dengue disease is not completely understood, and it is not possible to predict accurately who will develop severe disease, but some risk factors for progression to severe disease have been described: age (mainly children),5-7 presence of chronic diseases,8-10 sequential infections;4 ethnicity (African ancestry is protective against DHF in admixed populations).11

There is no licensed vaccine and antiviral drugs are not effective. Treatment - mainly fluid replacement therapy and management of bleeding - is symptomatic and aims at clinical manifestations.12,13

Since women of reproductive age in endemic areas are at risk of dengue infection, it is necessary to establish whether there is an association between dengue during pregnancy and fetal adverse outcomes. In 2010, a systematic review on dengue in pregnancy and fetal outcomes was published. It reviewed 19 case reports, 9 cases series and two cohorts, and concluded that vertical transmission is possible; however the evidence was not sufficient to confirm that dengue during pregnancy increases the risk of adverse outcomes.14 The effects of this infection during pregnancy on fetal outcomes remain unclear.

The objective of this systematic review and meta-analysis is to investigate whether the published literature shows an increase in risk of four adverse fetal outcomes (stillbirth, miscarriage, preterm birth and low birth weight) in women who had dengue during pregnancy.

Methods

Search strategy and eligibility criteria

This study is being reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).15 We searched Medline, Embase, Scopus and Global Library to identify studies reporting fetal outcomes in women who have had dengue during that pregnancy. Databases were searched from August 2015, using the following approach: 1) Dengue terms: “Dengue”, “Dengue haemorrhagic Fever” AND 2) Pregnancy outcomes terms: “pregnancy outcomes”, “pregnancy complication”, “low birth weight”, “small for gestational age”, “intrauterine growth restriction”, “stillbirth”, “fetal death”, “preterm birth”, “preterm delivery”, “preterm labour”, “abortion”, “miscarriage”. We supplemented database searchers by screening bibliographies of the review article. The “explode” functions was used in dengue, pregnancy outcomes and pregnancy complications. No language restrictions were applied. All titles and abstracts of publications identified in the course of the primary search were reviewed for relevance and eligibility, after duplicates have been removed (full electronic search strategy for Medline; appendix 1).

Eligibility criteria were: original studies that report any fetal outcome of pregnant women who had dengue during gestational period. To avoid overlapping populations, if participants were included in more than one publication, the study with the largest sample size was included. Eligible study designs were case-control, cohort, cross sectional and unselected case-series (i.e., those in which participants were selected independently of outcome). Case reports, ecological studies, reviews, and vitro studies and studies without pregnancy outcome information were excluded.

Articles titles and abstracts were screened independently by two reviewers (ESP, MCNC) to select papers for full text screening. Full texts were independently assessed by the reviewers; in case of disagreement a third author was consulted (MGT) and a decision was agreed by consensus.

Exposure and outcomes

We studied four adverse fetal outcomes:

* miscarriage: non-viable product of conception less than 22 weeks;
* stillbirth: fetal death in utero at or after the 22nd week of gestation or weight more than 500g (or as defined by the study);
* preterm birth (PTB) live delivery before 37 weeks of gestation;
* low birth weight (LBW) birth weight less 2500g/ intrauterine growth restriction (IUGR): < 10th birthweight percentile for gestational age.

Dengue during pregnancy was defined by clinical criteria (symptoms of dengue) or/and laboratory criteria (positive test from one of the laboratory test- IgM detection by ELISA, viral RNA detection via PCR, NS-1 viral antigen or positive viral culture.

Data extraction and quality evaluation

A uniform tool was used to extract from eligible articles the following study characteristics: study design, year of publication, study location, period of study, authors, and population characteristics such as number of pregnancies, dengue diagnostic, and frequency of outcomes.

Two authors (ESP, LCR) independently scored the quality of the studies included in meta-analyses using the Newcastle-Ottawa scale (NOS).16 This was used for cohort and case-control studies and a modified version was used for case series studies and cross sectional studies. In this scale, cohort and case-controls studies are scored between zero and nine stars in nine questions covering three items (selection, comparability and outcome); cross sectional studies between zero and eight, and case series between zero and six. The final score was agreed between the two reviewers.

Statistical Analyses

When estimates were not presented in the papers, we provided estimates based on the data for each study. For stillbirths, PTBs and LBWs the denominator was the total number of pregnant women beyond 22nd week of gestation and for miscarriages, the denominator was all pregnancies; 95% confidence intervals (CI) were calculated using Poisson distribution.

In cohorts, case control and cross sectional studies, Odds Ratios (OR) were estimated afresh by comparing odds of fetal outcomes in pregnancies with and without dengue during pregnancy. We conducted meta-analysis for miscarriages, PTB and LBW/IUGR; we did not conduct a meta-analysis for stillbirths as this outcome was investigated in only one study with a comparison group. In one of the case series we used information provided by the study on frequency of preterm births among live births in the maternity hospital where the study was conducted to estimate the OR. This allowed us to include this study in the meta-analysis with the other studies that had a comparison group. To estimate the increase in risk of adverse fetal outcomes we used the Mantel–Haenszel methods, since the data are sparse in terms of event and study size as recommended 17. Heterogeneity of OR was assessed with the I2 statistic. We analysed the data with Stata version 14.0.

Role of the funding source

The sponsor of this study had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors had access to the data and had final responsibility for the decision to submit for publication.

Results

Results of the search are presented in Figure 1. The primary search identified 664 papers; 387 were duplicates. After screening, 107 articles were reviewed to assess eligibility, and 91 were excluded because did not meet the inclusion criteria; 16 articles were included in the qualitative synthesis (five cohorts, one case-controls, one cross sectional, nine cases series), and eight in the meta-analysis (Figure 1). The studies characteristics are described in Table 1 and 2. The studies were published from 1994 to 2014, and conducted in ten countries (Brazil,18,19 Colombia,20 Cuba,21 French Guiana,22 India,23-25 Malaysia,26-27 Mexico,29 Sri Lanka ,30,31 Sudan,32 and Venezuela).33

Quality of the studies

We assessed the quality of the studies included in the meta-analysis using the modified Newcastle – Ottawa scale. The cohort conducted in French Guiana22 was awarded nine stars; the Malaysia case –control27 was awarded eight stars. Two prospective cohort studies that used only the laboratory criteria to define dengue during pregnancy18,26 was awarded seven stars (because they did not control for confounding factors). Restrepo and colleagues20 and Barroso and colleagues,21 (two small prospective cohort studies) and a cross sectional study33 were awarded six stars. The case- series19 with a comparison group was awarded five stars. Reasons for the classification for each study in appendix 2. All studies included in meta-analysis were assessed as including representativeness of the exposed cohort and adequateness of follow up.

Outcomes

Miscarriage as a potential adverse outcome associated with dengue during pregnancy was described in six case series,19,23,25,28,29,31 one case-control study, 27 and one cohort study.20 The miscarriage rates associated with dengue during pregnancy ranged from 3.8% (CI 95% 0-21) in Sri Lanka 31 to 16% (CI 95% 4.3 – 41) in India.23 The single study that controlled for confounding,27 in Malaysia, found recent dengue infection to be four times more frequent among miscarriage cases than controls after adjusting for maternal age, gestational age, parity and ethnicity (OR: 4.2 95% CI 1.2-14) [70]. We used two studies (case-control and cohort)20,27 to conduct the meta-analysis for miscarriage as a pregnancy outcome potentially associated with dengue pregnancy; the crude overall OR was 3.51 (95% CI 1.15-10.77 I2 =0) (Figure 2).

Stillbirths were investigated in four case series23,28-30 and one cohort study.22 Stillbirth rates among pregnant women who had have dengue varied between 4.7% (CI 95% 0.1-26) in India23 to 13% (CI 955 1.6 – 48) in Sri Lanka.30 In three of four case series, stillbirths occurred only in women who had severe dengue - DHF/DSS.28-30 In the cohort study, in French Guiana, the stillbirth rate was more than six times higher (RR: 6.7 95% CI 2.1 – 21.3) among symptomatic dengue cases than women without dengue.22 (This crude RR was estimated by us, based on data presented in the paper).

Preterm birth and low birth weight/intrauterine growth restriction were the most common negative pregnancy outcomes in pregnant women with dengue.18-23,25,26,28,30-33 There was a marked variation in preterm birth and low birth weight rates were between studies, even in studies conducted in the same country. In studies in Malaysia, for example, the proportion of PTB among women with dengue during pregnancy ranged from 3.1% 26 (CI 95% 0.3 – 11) to 26.6% (CI 95% 7.2 – 68).28 The proportion of LBW among women with dengue during pregnancy in studies in Brazil varied from zero18 to 58% (CI 95% 23- 120).19

The meta-analysis for preterm births included five studies (three cohort studies)20,22,26 one cross sectional study33 and one case series.19 The crude overall OR for the association between dengue during pregnancy and preterm birth was 1.71 (95% CI 1.06-2.76 I2 = 56.1%) (Figure 3).

All studies included in the meta-analysis required both serology and clinical symptoms for definition of dengue. However, among studies with preterm as an outcome, Tan (2008) and colleagues,26 defined exposure based only on serology for recent dengue infection (IgM positive) so some of the women with classified having had dengue during pregnancy had no clinical symptoms. The OR of preterm birth, in this study was less than one (0.42 95% CI 0.10 – 1.73), although the 95% CI include one (Figure 3). Sensitivity analysis excluding Tan (2008) and colleagues,26 found a OR= 2.50 (95% CI 1.43-4.34, I2 = 25.5%) (Figure 3). Sensitivity analysis excluding studies with quality assessment below six stars 19-21 and Tan (2008) and colleagues,26 found an OR of 2.36 (95% CI 1.24-4.5, I2 = 48.3%); in the only study with more than seven stars22 (once Tan (2008) and colleagues was excluded) the crude OR was 2.2 (95% CI 1.04 – 4.66).

Five cohort studies were included in the meta-analysis to estimate the association between low birth weight/intrauterine growth restriction and dengue during pregnancy, .18,20-22,26 The crude overall OR was 1.4 (95% CI 0.9 -2.2, I2 = 0). Two studies included women with dengue IgM serology but did not require presence of clinical symptoms;18,26 in these studies the ORs for the association with low birth weight/intrauterine growth restriction, were less than one (0.90 95% CI 0.38-2.08; 0.66 95% CI 0.03–12.4) (Figure 4). Excluding these studies, the OR for the association between dengue during pregnancy and low birth weight/intrauterine growth restriction was 1.84 (95% CI 1.04-3.25, I2 = 0) (Figure 4). Once the studies with no requirement for clinical symptoms were excluded,18,26 the crude OR in the only study with more than seven stars22 was 1.95 (1.00 – 3.75).

Other outcomes reported in the literature but not part of the objectives of this study included three cases of congenital mal formation,20 fetal distress,20,21 perinatal death,32 as well threat of premature delivery.21

Discussion

We systematically reviewed 16 studies of maternal dengue and adverse fetal outcomes (miscarriage, stillbirth, preterm birth and low birth weight). The evidence from these published studies suggests that symptomatic dengue during pregnancy is associated with negative fetal outcomes.

The association between dengue and negative fetal outcomes is biologically plausible: dengue leads to pathological changes such as increased production of pro inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor α (TNF-α)4 that can activate the uterus, through stimulation of production of uterine activation proteins. These can induce uterine contractions culminating in a preterm delivery.34,35 Disease symptoms for instance thrombocytopenia, plasma leakage or hemorrhagic tendency secondary to dengue hemorrhagic fever (DHF) could result in damage in placental circulation with consequences to fetus, including stillbirth.36,37 Endothelial damage and increased vascular permeability due to DHF may facilitate passage across the placental barrier and contribute to vertical transmission of dengue infection.31 Once the virus reaches the placental tissue, pathological changes might be produced such as villous stromal edema, increase the formation of syncytial knots and chorangiosis, result in hypoxia.38,39 The hypoxia itself could cause stillbirth, restrict fetal nutrition or initiate trophoblasts apoptosis leading to fetal growth restriction.40-42

Consistent with the previous systematic review,14 and on line with routine data, the most common fetal outcomes were preterm birth and low birth weight. The increase in risk of adverse fetal outcomes with dengue during pregnancy was highly variable across studies, expected given the heterogeneity of studies in terms of site, study design, and control of confounding. We pooled IUGR with LBW since LBW includes infants born preterm and infants with IUGR.43 It would be better to have used IUGR or small for gestational age than LBW (due to overlapping with PTB), but data were not available (only Barroso and colleagues21 had data on IUGR defined by Dueñas curves)44 . All the other remaining studies classified new-borns only according to whether LBW or normal weight.

Two studies classified women as having had dengue during pregnancy if they had positive IgM serology even if they did not have had clinical symptoms. These two studies did not show statistically significant associations between negative fetal outcomes and dengue. In one of these studies, 89% of the IgM positive women did not have dengue-clinical symptoms; in the other study, this was 63% .18,26 When these studies were excluded from the meta-analyses, the association between symptomatic dengue and both preterm birth and low birth weight became statistically significant. Also in three stillbirths were present only when women had severe dengue. This suggests that presence of clinical symptoms and severity of disease are related to the risk of negative fetal outcomes. It was not possible to explore this further in the meta-analysis as studies did not report severity of clinical symptoms. It is however likely that the severity of disease among women in different studies varied and this might have contributed to estimated variations in ORs.

This literature review has some limitations: among the 16 studies reviewed, 56% were case series, and in the studies with comparison groups, sample sizes were relatively small. This may have led to publication bias and consequently outcomes might have been overestimated. This was the first meta-analysis of fetal outcomes and dengue in pregnancy; it has some limitations. First, there were few studies and many were of imperfect methodology. The majority were assessed as less than seven starts. Second, most studies did not control for confounding nor stratified by gestational age. In the two studies that controlled for confounding22,27 the adjusted measure was stronger than the crude measure, indicating that at least in those settings any confounding was negative confounding. Despite these limitations, this systematic review and meta-analysis consistently showed an association between symptomatic dengue in pregnancy and each of the four adverse fetal outcomes.

We recommend that further epidemiological studies be conducted, with larger sample sizes, adequate comparison groups and controlling for confounding. There are many opportunities for this to be done, mainly in South America and Southeast of Asia, where dengue incidence have been increasing and explosive outbreaks occurs frequently. If this association between dengue in pregnancy and negative fetal outcomes is confirmed, recommendation should be made for close monitoring of pregnancies were dengue is diagnosed and for strategies for dengue control to include pregnant women as a at risk population.

Conflicts of interest

We declare that we have no conflicts of interest.

References

1. WHO. Dengue and severe dengue. Fact Sheet No117 Updat. Sept. 2014. <http://www.who.int/mediacentre/factsheets/fs117/en/> (accessed Jul, 205).
2. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature 2013; **496**: 504–07.
3. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet 1998; **352**: 971–77.
4. Halstead SB. Dengue. Lancet 2007; **370**:1644–52.
5. Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin. Microbiol. Rev* 1998; 11: 480–96.
6. Guzmán MG, Kourí G. Dengue: an update. Lancet Infect Dis. 2002;2(1):33–42.
7. Guzman MG, Halstead SB, Artsob H, et al. Dengue: a continuing global threat. Nat Rev Microbiol 2010; **12**:8–16.
8. Figueiredo MAA, Rodrigues LC, Barreto ML, et al. Allergies and diabetes as risk factors for dengue hemorrhagic fever: results of a case control study. PLoS Negl Trop Dis. 2010;4 : (6):e699.
9. Pang J, Salim A, Lee VJ, et al. Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study. PLoS Negl Trop Dis. 2012;6(5):e1641.
10. Teixeira MG, Paixão ES, Costa MCN, et al. Arterial Hypertension and Skin Allergy Are Risk Factors for Progression from Dengue to Dengue Hemorrhagic Fever: A Case Control Study. PLoS Negl Trop Dis. 2015 21;9(5):e0003812.
11. Blanton RE, Silva LK, Morato VG. Genetic ancestry and income are associated with dengue hemorrhagic fever in a highly admixed population’, Eur. J. Hum. Genet. EJHG 2008; **16**: 762–65.
12. WHO. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: [World Health Organization](http://www.who.int/publications/guidelines/en/); 2009.
13. Nhan NT, Phuong CXT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour’, Clin. Infect. Dis 2001; **32**: 204–13.
14. Pouliot SH, Xiong X, Harville E, et al. Maternal dengue and pregnancy outcomes: a systematic review. Obstet. Gynecol. Surv 2010; **65**: 107–18.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7):e1000097.
16. Wells GA, Shea B, O’Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2008 <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp> (accessed Aug 2015).
17. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration,* 2011. http://[www.cochrane-handbook.org](http://www.cochrane-handbook.org) (accessed Sep 2015).
18. 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**: 16–21.
19. Alvarenga CF, Silami VG, Brasil P, Boechat MEH, Coelho J, Nogueira RMR. Dengue during pregnancy: a study of thirteen cases. Am J Infect Dis 2009; 5: 6.
20. Restrepo BN, Isaza DM, Salazar CL, et al. Dengue y embarazo en Antioquia, Colombia’. Revista Facultad Nacional de Salud Pública 2004; 22 No. 1.
21. Barroso LR, Betancourt ID, Saeta YF, Navarro MM, Guerra GD. Repercusión del dengue serotipo 3 sobre el embarazo y producto de la concepción. Rev. Cuba. Obstet. Ginecol 2010; **36**: 42–50.
22. Friedman EE, Dallah F, Harville EW, et al. Symptomatic dengue infection during pregnancy and infant outcomes: a retrospective cohort study. [PLoS Negl Trop Dis.](http://www.ncbi.nlm.nih.gov/pubmed/25299383) 2014 **9**;8(10):e3226.
23. Agrawal P, Garg R, Srivastava S, Verma U, Rani. Pregnancy Outcome in Women with Dengue Infection in Northern India. Indian Journal of Clinical Practice 2014; 24: 11.
24. Malhotra N, Chanana C, Kumar S. Dengue infection in pregnancy. Int. J. Gynecol. Obstet. 2006; **94**: 131–32.
25. Chitra TV, Panicker S. Maternal and fetal outcome of dengue fever in pregnancy. [J Vector Borne Dis.](http://www.ncbi.nlm.nih.gov/pubmed/22297282) 2011;**48**(4):210-3.
26. Tan PC, Rajasingam G, Devi S, Omar SZ. Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet. Gynecol. 2008; **111**(5):1111-17.
27. Tan PC, Soe MZ, Lay KS, Wang SM, Sekaran SD, Omar SZ. Dengue infection and miscarriage: a prospective case control study. PLoS Negl Trop Dis 2012; **6** (5) e1637.
28. Ismail NAM, Kampan N, Mahdy ZA, Jamil MA, Razi ZRM. Dengue in pregnancy. [Southeast Asian J Trop Med Public Health](http://www.ncbi.nlm.nih.gov/pubmed/?term=Dengue+in+pregnancy++ismail) 2006; **37**(4):681-3.
29. Sastré AJ, González MA. Fiebre de Dengue y Embarazo estudio de 21 casos en Tabasco, México. Univ Med 2009; **50**: 433–43.
30. Kariyawasam S, Senanayake H. Dengue infections during pregnancy: case series from a tertiary care hospital in Sri Lanka. J. Infect. Dev. Ctries 2010; **4**(11): 767–75.
31. Waduge R, Malavige GN, Pradeepan M, Wijeyaratne CN, Fernando S, Seneviratne SL. Dengue infections during pregnancy: a case series from Sri Lanka and review of the literature. J. Clin. Virol 2006; **37**(1): 27–33.
32. Adam I, Jumaa AM, Elbashir HM, Karsany MS. Research Maternal and perinatal outcomes of dengue in PortSudan, Eastern Sudan. Parity 2010; **2**: 2–3.
33. Angarita LCR, Angarita SV, Correa M, Odreman MI. Transmisión perinatal del virus dengue en el binomio madre-hijo. Arch Venez Pueric Pediatr 2003; **76**(3): 99–104.
34. Christiaens I, Zaragoza DB, Guilbert L, Robertson SA, Mitchell BF, Olson DM. Inflammatory processes in preterm and term parturition. J. Reprod. Immunol. 2008; **79**(1): 50–57.
35. Bahar AM, Ghalib HW, Moosa RA, Zaki ZMS, Thomas C, Nabri OA. Maternal serum interleukin-6, interleukin-8, tumor necrosis factor-alpha and interferon-gamma in preterm labor. Acta Obstet. Gynecol. Scand. 2003; **82**(6):543–49.
36. Srikiatkhachorn A. Plasma leakage in dengue haemorrhagic fever. Thromb. Haemost 2009; **102**: 1042–49.
37. Andersen AMN, Vastrup P, Wohlfahrt J, Andersen PK, Olsen J, Melbye M. Fever in pregnancy and risk of fetal death: a cohort study’, Lancet 2002; 360: 1552–56.
38. 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): 1514–16.
39. Ribeiro CF, Silami VG, Brasil P, Nogueira RMR. Sickle-cell erythrocytes in the placentas of dengue-infected women. Int. J. Infect. Dis 2012; **16**(1): 72.
40. Miller J, Turan S, Baschat AA, Fetal growth restriction. Semin. Perinatol 2008; **32**(4): 274–80.
41. Sharp AN, Heazell AE, Crocker IP, Mor G. Placental apoptosis in health and disease. Am. J. Reprod. Immunol 2010; **64**(3): 159–69.
42. Heazell AEP, Sharp AN, Baker PN, Crocker IP. Intra-uterine growth restriction is associated with increased apoptosis and altered expression of proteins in the p53 pathway in villous trophoblast. Apoptosis Int. J. Program. Cell Death 2011; **16**(2): 135–44.
43. Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob. Health 2013; **1**(1): 26–36.
44. Gomez ED. Patrones antropométricos en el recién nacido’, in Patrones antropométricos en el recién nacido, Editorial de Ciencias Medicas, 1990.

**Table1: Characteristics of studies included in meta-analyses**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author; Year; Country** | **Study design** | **No of pregnant women admitted with dengue** | **Prevalence (%) of fetal outcomes in women with dengue** | **Other findings and comments** | **Score-NOS scale** |
| Friedman and colleagues, 2014  French Guiana22 | Retrospective Cohort | 86 exposed dengue case  258 unexposed records were used.  Exposed: pregnant with laboratory confirmed of symptomatic dengue.  Unexposed: pregnant women without dengue symptoms or received a negative dengue test if febrile. | PTB: 17% (IC 9 - 30);  LBW: 19.8% (IC 11.5 – 31.6)  Stillbirth**1**: 10% (IC 4.7 – 19.8)  Miscarriage were excluded | This study used retrospective data from a maternity.  PTB\*: OR=3.34 (1.13, 9.89)  LBW: OR=2.23 (1.01, 4.9)  Adjustment: maternal ethnicity, maternal age, maternal gravidity maternal anemia, interpregnancy interval  \*considering dengue cases before 37 weeks of gestation | 9 |
| Leite and colleagues 2014  Brazil18 | Prospective Cohort study | 43 IgM positive  361 IgM negative  IgM-positive-recent infection | LBW: none  Just LBW were measure | This study was conducted between women recruited at the time of delivery, involving women without report febrile illness in pregnancy. | 7 |
| Tan and colleagues 2008  Malaysia26 | Prospective cohort | 63 IgM positive  2468 IgM negative  IgM-positive-recent infection | PTB: 3.1% (IC 0.3 - 11);  LBW: 9.5% (IC 3.5 – 20.7) | This study was conducted between women recruited at the time of delivery. No difference was found among fetal outcomes between the two groups. 88.9% infected pregnant women did not report a febrile illness in pregnancy. | 7 |
| Restrepo and colleagues 2004  Colombia20 | Prospective cohort | 39 exposed 39 unexposed  Exposed: pregnant women that met the clinical criteria for dengue from PAHO. Laboratory confirmed.  Unexposed: pregnant women without febrile syndrome | PTB: 8.1% (IC 1.7 – 23)  LBW: 10.8% (IC 3 – 27.7)  Miscarriage: 5.1% (IC 0.6 -18)  Stillbirth do not occurred. | No difference was found among fetal outcomes between dengue group and non-infected group except for fetal distress. There were 3 malformation cases. Only study that reported malformation cases. | 6 |
| Barroso and colleagues 2009  Cuba21 | Prospective cohort | 30 dengue cases  56 controls  Dengue infection confirmed serologically IgM. | IGR2: 10% (IC 2.0- 29)  No preterm birth was observed. | 30 pregnancy women with dengue were identified in Santiago in 2006. There were threat of premature delivery in 4 dengue patients, and 3 cases of acute fetal distress. | 6 |
| Tan and colleagues 2012  Malaysia27 | Case-control | 115 miscarriage 296 controls  Miscarriage (case): non-viable product of conception less than 22 weeks.  Control: viable pregnancies matched for maternal and gestational age at the same hospital.  Dengue was tested using IgM and NS1 antigen. | 6 dengue cases among cases  5 dengue cases among controls | This study was conducted with women who went to a hospital diagnosed with miscarriage.  Miscarriage  OR= 4.2 (1.2, 14)  Adjustment: maternal age, gestational age, parity, maternal ethnicity. | 8 |
| Angarita and colleagues 2013  Venezuela33 | Cross sectional | 7 dengue cases  23 without dengue  Pregnant women were serologically tested for dengue;  Were included in the study pregnant women in third trimester | PTB: 42.8% (IC 8.8 – 125) | This study was conducted between women recruited at the time of delivery. There were 2 pregnant women with dengue shock and fetal distress. | 6 |
| Alvarenga and colleagues  2009  Brazil19 | Case-series | 13 dengue cases  Laboratory confirmed | PTB: 58% (IC 23 – 120)  LBW: 50% (IC 18 – 100)  Miscarriage: 7.6% (IC 0.2 – 42) | Study of all serologically diagnosed pregnant women admitted during 2002. | 5 |

**Table 2: Characteristics of case series included in qualitative analyses.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Author; Year; Country** | **No of pregnant women with dengue** | **Pregnancy outcomes** | **Other findings and comments** |
| Kariyawasam; Senanayake, 2010  Sri Lanka30 | 15 dengue cases  Laboratory confirmed | PTB: 6.6% (IC 0.1 -37)  LBW: 6.6% (IC 0.1 – 37)  Stillbirth3: 13% (IC 1.6 – 48) | Study of all serologically diagnosed pregnant women treated for dengue in 2009. Both fetal death were from women who had DSS. There was one born preterm and low birth weight (classified as iatrogenic due to pre-eclampsia). |
| Adam and colleagues 2010  Sudan32 | 78 dengue cases  Laboratory confirmed | PTB: 18% (IC 10 – 30)  LBW: 24% (IC 14.6 – 38) | Retrospective analysis of all pregnancy women with confirmed dengue infection admitted in two maternity during the study period 2008-2009.  There were 7 perinatal death. |
| Ismail and colleagues 2006  Malaysia28 | 16 clinical and/or laboratory dengue cases | PTB: 26.6% (IC 7.2 – 68)  Miscarriage: 6.2% (IC 0.1 – 34)  Stillbirth4: 6.6% (IC 0.1 – 37) | Retrospective study of all pregnancy women with dengue admitted in the maternity, between 2000 and 2004.  Dengue was defined as an acute febrile illness with two or more clinical manifestation and only 50% was serologically positive. There were 4 follow-up lost. |
| Waduge and colleagues 2006  Sri Lanka31 | 26 dengue cases  Laboratory confirmed | PTB: 4% (IC 0.1- 22)  LBW: 16% (4.3 – 41)  Miscarriage: 3.8% (IC 0 – 21) | All hospitalized pregnancy with confirmed dengue infections were included. |
| Malhotra and colleagues, 2005  India24 | 8 dengue cases  Laboratory confirmed | No adverse fetal outcomes observed. | None of neonates born infected. There was one neonatal death due to arthrogyposis congenital. |
| Chitra; Panicker, 2011  India25 | 14 dengue cases  Laboratory confirmed | PTB: 15% (IC 2 – 55)  Miscarriage: 7% (0.2 – 39) | Retrospective analysis of all pregnancy women with dengue infection admitted in the maternity (2009-2010).  There was one co-infection with malaria, this case had congenital anomaly and was medical terminated. The average birth weight was 2.44Kg however they did not mention how many babies were below 2.5Kg. There were 2 follow-up lost. |
| Agrawal and colleagues 2014 India23 | 25 dengue cases  Laboratory confirmed | PTB: 80% (IC 19.6 – 129)  LBW: 52% (IC 26 – 93)  Stillbirth3: 4.7% (IC 0.1 – 26)  Miscarriage: 16% (4.3 – 40) | Retrospective analysis of all pregnancy women with confirmed dengue infection admitted in the maternity during the study period. |
| Sastre; Gonzalez, 2009  Mexico29 | 21 dengue cases  Laboratory confirmed | Miscarriage: 4.7% (IC 0.1 – 26)  Stillbirth4: 5% (IC 0.1 – 26) | Retrospective analysis of all pregnancy women with confirmed dengue infection admitted in the maternity during the study period 2005-2007. |

1. Stillbirth- birth dead weighed ≥500g or 22 weeks of gestation;
2. IGR-less than minimum weight corresponding to their gestational age;
3. Stillbirth – without definition in the article occurred after 22 weeks;
4. Stillbirth – without definition in the article without information about gestational age;