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SYSTEMATIC REVIEW

Maternal and foetal-neonatal outcomes of dengue virus infection during pregnancy

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Abstract

Objective: Given that women of reproductive age in dengue-endemic areas are at risk of infection, it is necessary to determine whether dengue virus (DENV) infection during pregnancy is associated with adverse outcomes. The aim of this systematic review and meta-analysis is to investigate the consequences of DENV infection in pregnancy on various maternal and foetal-neonatal outcomes.

Methods: A systematic literature search was undertaken using PubMed, Google Scholar, and Embase till December 2021. Mantel–Haenszel risk ratios were calculated to report overall effect size using random effect models. The pooled prevalence was computed using the random effect model. All statistical analyses were performed on MedCalc Software.

Result: We obtained data from 36 studies involving 39,632 DENV-infected pregnant women. DENV infection in pregnancy was associated with an increased risk of maternal mortality (OR = 4.14 [95% CI, 1.17–14.73]), stillbirth (OR = 2.71 [95% CI, 1.44–5.10]), and neonatal deaths (OR = 3.03 [95% CI, 1.17–7.83]) compared with pregnant women without DENV infection. There was no significant statistical association established between maternal DENV infection and the outcomes of preterm birth, maternal bleeding, low birth weight in neonates, and risk of miscarriage. Pooled prevalences were 14.9% for dengue shock syndrome, 14% for preterm birth, 13.8% for maternal bleeding, 10.1% for low birth weight, 6% for miscarriages, and 5.6% for stillbirth.

Conclusion: DENV infection in pregnant women may be associated with adverse outcomes such as maternal mortality, stillbirth, and neonatal mortality. Hence, pregnant women should be considered an at-risk population for dengue management programmes.

KEYWORDS
dengue virus, DENV, foetal outcomes, maternal, neonatal, pregnancy

INTRODUCTION

Dengue fever, an infectious disease spread by mosquitoes, is widespread in tropical and subtropical areas.[1] In 2010, it was estimated that 390 million dengue infections occurred worldwide, with 96 million presenting clinically and resulting in 21,000 deaths.[2] Dengue virus (DENV) infection has increased substantially in recent years, with the number of cases almost doubling within a decade from 2.4 million in 2010 to 4.2 million cases in 2019.[3] Explosive outbreaks and regional spread into new locations are a factor behind this recent huge increase in the incidence of dengue fever.[3]

DENV is part of the Flaviviridae family and consists of four antigenically and genetically distinctive serotypes: DENV 1, 2, 3, and 4.[4] *Aedes aegypti* and *Aedes albopictus*, which are both common in tropical and subtropical areas, are the primary vectors of transmission.[3] Typically, the incubation period for dengue fever ranges from 3 to 14 days,

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with an average incubation period of 5 to 7 days.[3] Dengue viral infection manifests clinically in a wide variety of ways, ranging from asymptomatic to life-threatening severe dengue or dengue shock syndrome (DSS).[2] Only 20% of DENV infections cause fever and other symptoms such as joint and muscle discomfort, skin rashes, nausea, and severe headaches, while the other 80% go unrecognised.[1] Although infection with one serotype of the DENV offers lifetime protection, secondary infection with heterologous serotypes or virulent strains enhances the risk of severe disease.[5]

Given that women of reproductive age in dengue-endemic areas are at risk of infection, it is necessary to determine whether dengue infection during pregnancy is associated with adverse foetal outcomes. Premature birth, low birth weight, stillbirth and miscarriage have been linked to maternal DENV infection during pregnancy, according to recent reports.[6] In a study by Tougma et al. on 121 pregnant women infected with DENV, premature birth was reported in about 10% of pregnancies, a similar recent report by Nujum et al. reported low birth weight in 18% of cases from a pool of 78 pregnant women infected with DENV.[7,8] The previous meta-analysis by Xiong et al. reported no significant association between maternal DENV infection and preterm birth, low birth weight, or miscarriage.[9] However, the result of their analysis was limited to few studies. Besides that, they had not included maternal bleeding, maternal mortality and neonatal mortality outcomes in their analysis. Several new studies have been published since the last meta-analysis, reporting the impact of DENV infection during pregnancy on various maternal and foetal-neonatal outcomes.

Hence, in this article, we aimed at conducting an updated systematic review and meta-analysis, using all evidence to date to investigate the consequences of DENV infection in pregnancy on various maternal and foetal-neonatal outcomes such as maternal mortality, preterm birth, miscarriages, maternal bleeding, stillbirth, low birth weight, and neonatal mortality.

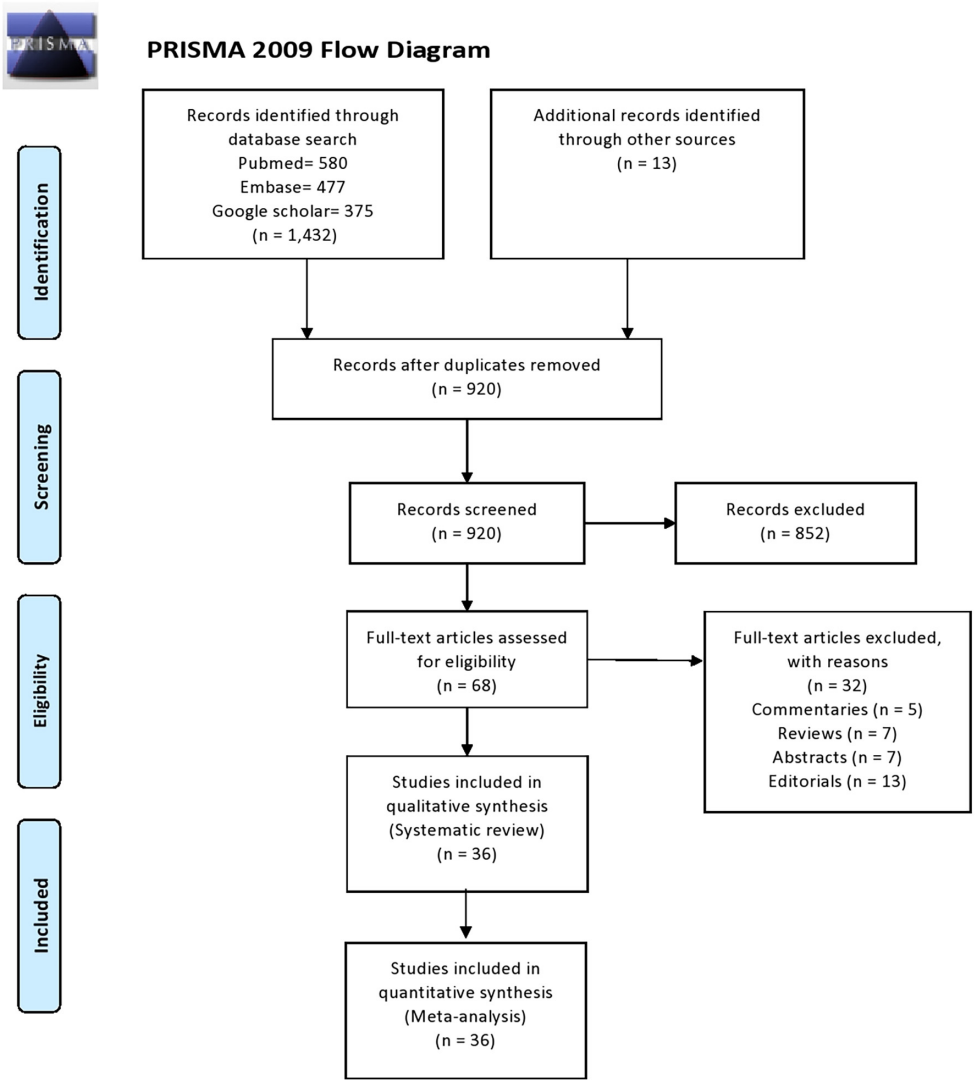

FIGURE 1 PRISMA flow diagram outlining the study selection process

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METHODS

This systematic review and meta-analysis was performed in compliance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards[10] (Figure 1).

Search strategy

A rigorous literature search was executed using PubMed, Google Scholar, and Embase till December 10, 2021. We linked Medical Subject Headings (MeSH) terms and keyword and succeeding search terms (([Dengue fever] or [Dengue virus] or [Dengue hemorrhagic fever] or [Dengue shock syndrome] AND [Pregnancy] or [gestational] or [maternal outcome] or [Premature Birth] or [low birth weight] or [miscarriages] or [Still birth] or [maternal bleeding] or [Post-partum hemorrhage] or [neonatal outcomes] or [Neonatal deaths] or [Maternal deaths])). Studies were included from all around the globe, with no language limitations. For more qualifying studies, we inspected the reference lists of the incorporated articles and the pertinent literature manually. Duplicate citations were eliminated and all remaining reports were reviewed by using their titles and abstracts to appraise eligibility.

Eligibility criteria

To be eligible for this meta-analysis, articles had to fulfil the following inclusion criteria: (a) cohort, case–control, or cross-sectional studies; (b) DENV infection diagnosis in pregnant women; (c) articles describing the maternal and/or foetal-neonatal outcomes, including maternal mortality, preterm birth, miscarriages, maternal bleeding, stillbirth, low birth weight, and neonatal mortality in DENV-infected pregnant mother; (d) studies with a sample size of ≥10 patients.

Exclusion criteria were: (a) no evidence regarding maternal or foetal-neonatal outcomes given in the article; (b) duplicate publication; (c) letters to the editor, case reports, commentaries, reviews, and posters. A comprehensive interpretation of the residual studies and data extraction were carried out in an Excel table.

Study selection and quality assessment

Two authors independently assessed the titles and abstracts of the shortlisted articles based on the inclusion criteria. Any disputes in study selection were addressed by negotiation and discussion with a third investigator (S.S.R.). Two investigators independently assessed the risk of bias and the quality of each study using the Newcastle-Ottawa Scale (NOS).[11] Each study was graded as: low bias risk (8–9 points), moderate bias risk (5–7 points), or significant bias risk (0–4 points).

Data extraction

Data for each study were extracted autonomously by two authors and cross-checked to eliminate errors. Numerous details were extracted from each study, including the first author's name, year of publication, the study's country of origin, study design, the total sample size, the number of pregnant women with DENV infection, dengue detection technique maternal mortality, percentage of women going into a stage of DSS, and data on various maternal and foeta-neonatal outcomes.

Statistical analysis

MedCalc® Statistical Software version 19.6.4 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) was used for all statistical analyses. The pooled prevalence and associated 95% confidence interval (CI) were calculated using the random effects model. Results for outcome analysis were presented as odds ratios with 95% CIs and pooled using the Mantel–Haenszel random-effects model. The I^2 statistics were used to assess the heterogeneity of effect size estimates across these studies with I^2 (low heterogeneity: $I^2 \leq 25\%$; moderate: 25%–50%; high >75%). Probability values <0.05 were considered statistically significant in all cases. A leave-one-out sensitivity analysis was also carried out to assess the effects of individual studies on the statistical results. Publication bias was explored using funnel plots, Egger's regression test, and Begg–Mazumdar's rank correlation test.

Grading quality of evidence

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group approach of grading the quality of evidence was incorporated for all the outcomes analysed.[12,13]

RESULTS

Characteristics of the included studies

Preliminary searches of different databases pulled up 1432 articles. After removing duplicates, 920 studies were assessed. After taking into account titles and abstracts, 852 articles were eliminated, leaving 68 articles for review and potential consideration in this study (Figure 1). Ultimately, 36 articles reporting on 39,632 DENV-infected pregnant women were included in this meta-analysis,[6–8,14–46] comprising 18 from Asia (mostly from India, $n = 12$), 15 from Latin America and 3 from Africa (Table 1).

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TABLE 1 Baseline characteristics of the included studies

Study, year	Country	Study design	Dengue detection technique	Sample size	Dengue positive women (*n*)	Adverse foetal outcome	NOS
Adam, 2011[14]	Sudan	Retrospective study	—	—	78	Preterm birth, LBW	6
Agarwal, 2014[15]	India	Retrospective study	IgM and/or NS1 antigen	—	25	Preterm birth, LBW, miscarriage, still birth	6
Agarwal K, 2017[16]	India	Retrospective study	IgM and/or NS1 antigen	—	62	Preterm birth, miscarriage	7
Angarita, 2013[17]	Venezeula	Prospective observational study	IGM	30	7	Preterm birth, maternal bleeding	6
Barraso, 2010[18]	Cuba	Retrospective study	IgM /IgG	86	30	Preterm birth, LBW	6
Basurko, 2009[6]	French Guiana	Retrospective study	IGM/PCR	—	53	Preterm birth, LBW, maternal bleeding, still birth	7
Basurko, 2018[19]	French Guiana	Prospective observational study	IgM or NS1 antigen or PCR	292	73	Preterm birth, maternal bleeding, still birth	8
Brar, 2021[20]	India	Prospective observational study	IgM and/or NS1 antigen	—	44	Preterm birth, maternal bleeding	7
Carles, 2000[21]	French Guiana	Retrospective study	IgM/PCR/viral isolation	—	38	Preterm birth, still birth	6
Chansamouth, 2016[22]	Laos	Prospective observational study	IgM or NS1 antigen or PCR	304	76	Preterm birth, LBW, miscarriage, still birth, maternal mortality	7
Chitra, 2011[23]	India	Retrospective study	IgM and/or NS1 antigen	—	14	Preterm birth, Miscarriage	7
Dat, 2018[24]	Japan	Prospective observational study	IgM and/or NS1 antigen	—	20	Preterm birth, LBW, maternal bleeding, still birth	6
Feitoza, 2017[25]	Brazil	Retrospective study	gM or clinical/ epidemiological criterion	1000	200	Preterm birth, LBW, neonatal mortality	9
Friedman, 2014[26]	French Guiana	Retrospective study	IgM/PCR/viral isolation/ NS1 antigen	344	86	Preterm birth, LBW, still birth	9
Gehlot, 2017[27]	India	Prospective observational study	IgM and/or NS1 antigen	—	25	Preterm birth, LBW, miscarriage	6
Gupta, 2021[28]	India	Prospective observational study	IgM or NS1 antigen	88	35	Maternal mortality	7
Kallur, 2018[29]	India	Retrospective study	IgM and/or NS1 antigen	—	44	Preterm birth, still birth	5
Laoprasopwattana, 2015[30]	Thailand	Prospective observational study	IGM	96	4	Preterm birth	6
Leite, 2014[31]	Brazil	Prospective observational study	IgM /PCR	404	43	LBW	7
Mulyana, 2020[32]	Indonesia	Prospective observational study	IgM and/or NS1 antigen	—	41	Preterm birth, still birth	6
Naik, 2020[33]	India	Prospective observational study	IgM or NS1 antigen or PCR	42	6	Preterm birth, LBW, still birth, neonatal death	7
Nascimento, 2017[34]	Brazil	Retrospective study	IgM/PCR/viral isolation	7063	3898	Preterm birth, LBW	8
Nujum, 2019[8]	India	Prospective observational study	IgM or NS1 antigen	1272	74	Preterm birth, LBW, still birth	8

(Continues)

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TABLE 1 (Continued)

Study, year	Country	Study design	Dengue detection technique	Sample size	Dengue positive women (*n*)	Adverse foetal outcome	NOS
Ortiz-Mesina, 2019[35]	Mexico	Case control study	IgM or NS1 antigen or PCR	115	15	Preterm birth, still birth, miscarriage	7
Paixão, 2018[36]	Brazil	Retrospective study	IgM or NS1 antigen or PCR	14,440,229	16,224	Maternal mortality	8
Restrepo, 2003[37]	Colombia	Retrospective study	IGM	46	22	Preterm birth, LBW	6
Ribeiro, 2016[38]	Brazil	Retrospective study	IgM/PCR/viral isolation/ NS1 antigen	3,45,935	336	Preterm birth, LBW	7
Sharma, 2016[39]	India	Prospective observational study	IgM and/or NS1 antigen	—	16	Maternal bleeding	6
Singkibutr, 2020[40]	Thailand	Retrospective study	IgM or NS1 antigen	548	48	Preterm birth, LBW, miscarriage, maternal bleeding, maternal mortality, neonatal mortality	9
Singla, 2014[41]	India	Retrospective study	IgM and/or NS1 antigen	—	22	Preterm birth	7
Sondo, 2019[42]	Burkina Faso	Cross Sectional study	IgM/PCR/viral isolation	—	25	Preterm birth, still birth, maternal bleeding	6
Paixão, 2019[43]	Brazil	Retrospective study	IgM or NS1 antigen or PCR	1,67,38,000	17,673	Preterm birth, LBW	8
Tan, 2008[44]	Malaysia	Prospective observational study	IGM	2531	63	Preterm birth, LBW, maternal bleeding, neonatal mortality	7
Thiyagalingam, 2020[45]	India	Retrospective study	IgM and/or NS1 antigen	—	52	Maternal bleeding	6
Restrepo, 2004[46]	Colombia	Prospective observational study	IGM	78	39	Preterm birth, LBW, miscarriage, maternal bleeding	7
Tougma, 2020[7]	Burkina Faso	Retrospective study	—	424	121	Preterm birth, miscarriage, maternal bleeding, maternal mortality	8

Abbreviations: IgM, Immunoglobulin M; LBW, Low birth weight; NOS, Newcastle–Ottawa score; NS1, nonstructural protein 1; PCR, polymerase chain reaction.

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Maternal outcomes in pregnant women with DENV infection

The overall pooled random-effects estimate of DSS in DENV-infected pregnant women across 11 studies with a total of 418 participants was 14.9% (95% CI, 6.795–12.730). Statistical test results revealed moderate heterogeneity ($I^2 = 73\%$, $p < 0.0001$) (Figure 2a).

Eight prospective and nine retrospective cohort studies plus one case–control study with a total of (how many??) individuals reported the effect of DENV infection on preterm birth. Compared to pregnant women without DENV infection, no significant association was found between DENV infection in pregnancy and preterm birth with pooled OR of 1.20 (95% CI, 0.93–1.56, $I^2 = 72.3\%$) (Figure 2b). The overall pooled random effects estimate on

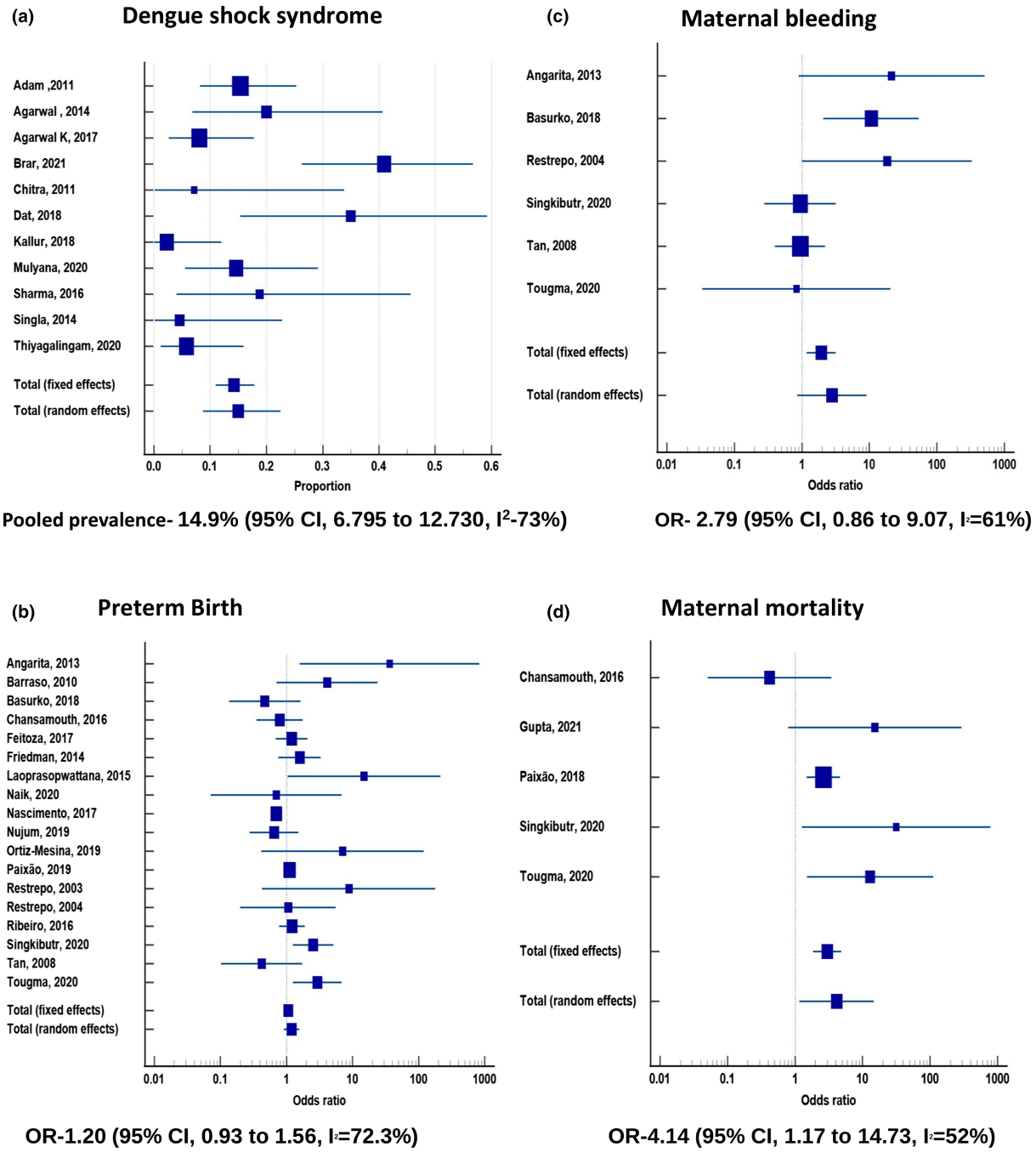

FIGURE 2 (a) Prevalence of dengue shock syndrome (DSS). (b) Association between dengue infection during pregnancy and preterm birth. (c) Association between dengue infection during pregnancy and maternal bleeding including post-partum haemorrhage. (d) Association between dengue infection during pregnancy and maternal mortality

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prevalence of preterm birth in DENV-infected pregnant women across 31 studies was 14% (95% CI, 11.97–16.53, $I^2 = 82.1\%$) (Figure S1a).

Four prospective and two retrospective cohort studies of 3896 participants in total reported the effect of DENV infection on maternal bleeding. Compared to pregnant women without DENV infection, no significant association was found between DENV infection in pregnancy and maternal bleeding including post-partum haemorrhage with pooled OR of 2.79 (95% CI, 0.86–9.07, $I^2 = 61\%$) (Figure 2c). The overall pooled random effects estimate on prevalence of maternal bleeding including post-partum haemorrhage birth in DENV-infected pregnant women across 12 studies was 13.8% (95% CI, 7.41–21.67, $I^2 = 82.7\%$) (Figure S1b).

Five prospective and three retrospective cohort studies with a total of (how many??) participants reported the effect of DENV infection on maternal mortality. Compared to pregnant women without DENV infection, DENV infection in pregnancy was associated with an increased risk of maternal mortality with pooled OR of 4.14 (95% CI, 1.17–14.73, $I^2 = 53\%$). Test statistics revealed moderate heterogeneity ($I^2 = 53\%$) (Figure 2d).

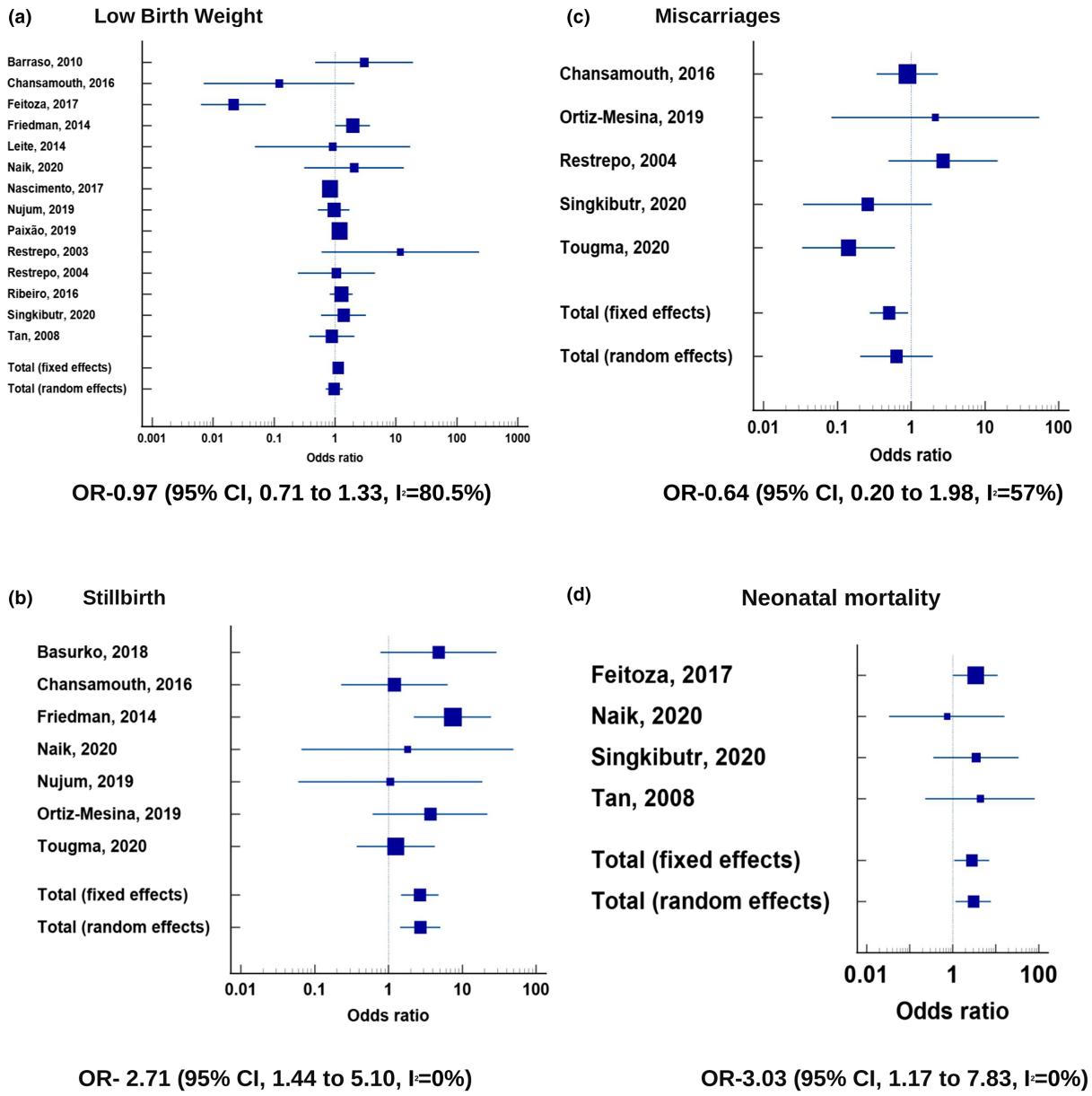

FIGURE 3 (a) Association between dengue infection during pregnancy and low birth weight. (b) Association between dengue infection during pregnancy and stillbirth. (c) Association between dengue infection during pregnancy and miscarriages. (d) Association between dengue infection during pregnancy and neonatal mortality

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Foetal and neonatal outcomes in pregnant women with DENV infection

Eight prospective and six retrospective cohort studies with a total of (how many??) individuals reported the effect of DENV infection on low birth weight. Compared to pregnant women without DENV infection, no significant association was found between DENV infection in pregnancy and low birth weight in neonates with pooled OR of 0.97 (95% CI, 0.71–1.33, $I^2 = 80.5\%$) (Figure 3a). The overall pooled random effects estimate on prevalence of low birth weight in neonates delivered by DENV-infected pregnant women across 19 studies was 10.1% (95% CI, 8.06–12.44, $I^2 = 84.1\%$) (Figure S1c).

Four prospective and two retrospective cohort studies plus one case–control study with a total of 2791 participants reported the effect of DENV infection on stillbirth. Compared to pregnant women without DENV infection, DENV infection in pregnancy was associated with an increased risk of stillbirth with a pooled OR of 2.71 (95% CI, 1.44–5.10). Statistical test results revealed low heterogeneity ($I^2 = 0\%$) (Figure 3b). The overall pooled random effects estimate on prevalence of stillbirth in DENV-infected pregnant women across 13 studies was 5.6% (95% CI, 3.35–8.43, $I^2 = 45.6\%$) (Figure S1d).

Two prospective and two retrospective cohort studies, plus one case–control study with a total of 1469 participants reported the effect of DENV infection on miscarriages. Compared to pregnant women without DENV infection, no significant association was found between DENV infection in pregnancy and miscarriages, with a pooled OR of 0.64 (95% CI, 0.20–1.98, $I^2 = 57\%$) (Figure 3c). The overall pooled random effects estimate on prevalence of miscarriages in DENV-infected pregnant women across 10 studies was 6.3% (95% CI, 3.66–9.62, $I^2 = 41.5\%$) (Figure S1e).

Two prospective and two retrospective cohort studies with a total of 4161 participants reported the effect of DENV infection on neonatal mortality. When compared with pregnant women without DENV infection, DENV infection in pregnancy was found to be associated with an increased risk of neonatal mortality with pooled OR of 3.03 (95% CI, 1.17–7.83). Test statistics results revealed low heterogeneity ($I^2 = 0\%$) (Figure 3d). Table 2 compiles all outcomes according to GRADE criteria for appraising the quality of evidence.

Sensitivity analysis

To determine the robustness of the data, sensitivity was estimated by systematically eliminating one study at a time. The pooled RR estimate for all the outcomes analysed in this study did not significantly change after elimination, indicating the robustness of the meta-analysis findings.

Risk of bias assessment

The NOS was used to assess the possibility of bias and evaluate the quality of the articles included.[12] With an average score of 6.9, 9 of the 36 studies were of excellent quality, while 27 were of moderate quality. Collectively, the evidence employed in these analyses was ascertained as being of moderate quality (Table 1).

Publication bias

Upon visual inspection the standard funnel plots for all the analyses done in this study were symmetric to a significant degree. Besides that, the Egger regression test and the Begg–Mazumdar rank correlation test were used to assess publication bias. A p-value <0.05 was considered significant in both tests, and the analysis was considered to have publication bias. No apparent publication bias concerning any of the analyses was detected (Table S1).

TABLE 2 Grade criteria for appraising the quality of evidence

Outcome	Number of studies	Sample size	OR	95% CI	Heterogeneity (I^2) (%)	Grade
Maternal outcome						
Preterm birth	18	1,71,15,329	1.20	0.93 to 1.56	72.3	Moderate ⨁⨁⨁O
Maternal bleeding including post-partum haemorrhage	6	3896	2.79	0.86 to 9.07	61	Low ⨁⨁OO
Maternal mortality	5	1,44,57,817	4.14	1.17 to 14.73	53	Moderate ⨁⨁⨁O
Foetal and neonatal outcomes						
Low birth weight	14	1,71,14,548	0.97	0.76 to 1.33	80.5	Moderate ⨁⨁⨁O
Stillbirth	7	2791	2.71	1.44 to 5.10	0	Moderate ⨁⨁⨁O
Miscarriages	5	1582	0.64	0.20 to 1.98	57	Moderate ⨁⨁⨁O
Neonatal mortality	4	4161	3.03	1.17 to 7.83	0	Low ⨁⨁OO

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DISCUSSION

In this systematic review and meta-analysis, we compiled all available evidence by utilising data of 39,632 DENV-infected pregnant women from 36 articles to determine the effect of DENV infection in pregnancy on maternal and foetal-neonatal outcomes. According to our analysis, DENV infection in pregnancy is associated with an increased risk of maternal mortality with a pooled OR of 4.14 (95% CI, 1.17–14.73), stillbirth with a pooled OR of 2.71 (95% CI, 1.44–5.10), and neonatal deaths with a pooled OR of 3.03 (95% CI, 1.17–7.83) compared to pregnancies without DENV infection. There was no significant statistical association between maternal DENV infection and the outcomes of preterm birth, maternal bleeding, low birth weight in neonates, or risk of miscarriage.

The previous meta-analysis by Xiong et al. reported no significant association between maternal DENV infection and risk of stillbirth with a pooled RR of 3.42 (95% CI: 0.76–15.49).[9] Besides, it did not analyse maternal or neonatal mortality outcomes. We found a significant association between maternal DENV infection and stillbirth, maternal, and neonatal mortality. As reported by Xiong et al., our analysis also showed no increased risk of preterm birth, low birth weight, and miscarriage in DENV-infected pregnant women.

Although the pathological mechanism behind the effect of DENV infection in pregnancy is poorly understood, a few mechanisms have been proposed. DENV infection causes pathological alterations, including upregulation of pro-inflammatory cytokines such interleukin 6, interleukin 8, and TNF-5, which can alter the normal gestational physiology.[47,48] Clinical manifestations such as thrombocytopenia, plasma leakage, or a tendency to bleed could impair placental circulation, resulting in complications for the foetus.[49,50] Severe dengue infection can lead to endothelial damage and an increase in vascular permeability, and this can allow the DENV to slip through the placental barrier and contribute to vertical transmission.[51] Rebeiro et al. reported the presence of viral antigen in the placenta of 19 of 25 pregnant women infected with DENV. Histopathological characteristics such as deciduitis, choriodeciduitis, intervillositis, focal and multifocal villitis, and multifocal necrotizing villitis were observed in these patients under a light microscope.[52] Furthermore, oedema of the villous stroma, pre-infarction regions, chorangiosis, and infarcted sites were all detected as pathological alterations due to hypoxia.[52] The significance of haemodynamic alterations in pregnant women during DENV infection is highlighted by these findings and these changes including hypoxia could potentially be responsible for increased risk of adverse maternal and foetal-neonatal outcomes including stillbirth observed in DENV infection in pregnancy.[53,54]

In this meta-analysis, we also estimated pooled prevalences of maternal and foetal-neonatal outcomes. These were 14% for preterm birth, 13.8% for maternal bleeding, 10.1% for low birth weight, 6% for miscarriages, and 5.6% for stillbirth. Although these findings may suggest a higher incidence of these outcomes in DENV infection in pregnancy, except for stillbirth, no outcome was significant compared to pregnant women without DENV infection as evidenced by our primary analysis. Another important finding was a higher prevalence of DSS with a pooled estimate of about 14.9% in pregnant women. This is higher than what is observed in the general population infected with dengue; which is about 5% of patients going into the stage of DSS.[55] There may be a bias in result of DSS analysis since women are more likely to be admitted for illness, which may enhance its presumed incidence in pregnant women. Despite this, continuous monitoring of these patients might be necessary to prevent both maternal and foetal consequences.

This article has a few strengths. To correlate the effect of DENV infection on maternal and foetal-neonatal outcomes in pregnancy more consistently and accurately, we conducted a systematic review and meta-analysis of 37 indexed studies published to date with the inclusion of larger studies which were not available at the time of the previous meta-analysis leading more robustness of result in our study with a larger sample size. Another strength is that the GRADE method was used to assess the certainty of evidence. However, there are certain limitations to our meta-analysis. First, DENV exposure can have variable levels of impact at different gestational ages. As the timeframe of pregnancy complications was not adequately described in individual articles, we were not able to analyse the risk of DENV infection on various maternal and foetal-neonatal outcomes according to first-, second-, or third-trimester infection. Second, as some articles had greater weight in the pooling than others, the results might be biased towards those studies. Another limitation was that studies coming from the same centres may have common patients in different studies. Lastly, we could not register the current review in PROSPERO. We tried to prospectively register our review but chose not to because due to the growing number of COVID-19-related articles it would have taken too long.

In this field of interest, additional epidemiological research with bigger sample sizes, appropriate comparator groups, and confounding control are required, especially from regions where dengue outbreaks are common, such as Latin America, India, and Southeast Asia.

CONCLUSION

Our meta-analysis shows an increased risk of stillbirth, maternal mortality, and neonatal mortality due to DENV infection during pregnancy. Moreover, there is an increased risk of DSS in maternal DENV infection during pregnancy. Hence, pregnant women with dengue infection should be targeted by dengue management programmes to prevent complications and ensure the well-being of both mother and foetus.

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REFERENCES

1. Wilder-Smith A, Ooi EE, Horstick O, Willis B. Dengue. Lancet. 2019; 393(10169):350–63. https://doi.org/10.1016/S0140-6736(18)32560-1
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013; 496(7446):504–7. https://doi.org/10.1038/nature12060
3. World Health Organization. Dengue and severe dengue. [2021 Dec 15]. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
4. Weaver SC, Vasilakis N. Molecular evolution of dengue viruses: contributions of phylogenetics to understanding the history and epidemiology of the preeminent arboviral disease. Infect Genet Evol. 2009; 9(4):523–40. https://doi.org/10.1016/j.meegid.2009.02.003
5. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clin Epidemiol. 2013;5:299–309. https://doi.org/10.2147/CLEP.S34440
6. Basurko C, Carles G, Youssef M, Guindi WE. Maternal and fetal consequences of dengue fever during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):29–32. https://doi.org/10.1016/j.ejogrb.2009.06.028
7. Tougma SA, Zoungrana/Yaméogo WN, Dahourou DL, Salou IA, Campaore TR, et al. Dengue virus infection and pregnancy outcomes during the 2017 outbreak in Ouagadougou, Burkina Faso: a retrospective cohort study. PLoS One. 2020;15(9):e0238431. https://doi.org/10.1371/journal.pone.0238431
8. Nujum ZT, Nirmala C, Vijayakumar K, Saboora Beegum M, Jyothi R. Incidence and outcomes of dengue in a cohort of pregnant women from an endemic region of India: obesity could be a potential risk for adverse outcomes. Trans R Soc Trop Med Hyg. 2019;113(5):242–51. https://doi.org/10.1093/trstmh/trz003
9. Xiong YQ, Mo Y, Shi TL, Zhu L, Chen Q. Dengue virus infection during pregnancy increased the risk of adverse fetal outcomes? An updated meta-analysis. J Clin Virol. 2017;94:42–9. https://doi.org/10.1016/j.jcv.2017.07.008
10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
11. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Cited May 20, 2022. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. https://doi.org/10.1136/bmj.328.7454.1490
13. Castellini G, Bruschettini M, Gianola S, Gluud C, Moja L. Assessing imprecision in Cochrane systematic reviews: a comparison of GRADE and trial sequential analysis. Syst Rev. 2018;7(1):110. https://doi.org/10.1186/s13643-018-0770-1
14. Adam I, Jumaa AM, Elbashir HM, Karsany MS. Maternal and perinatal outcomes of dengue in PortSudan, eastern Sudan. Virol J. 2010;7: 153. https://doi.org/10.1186/1743-422X-7-153
15. Agrawal P, Garg R, Srivastava S, Verma U. Pregnancy outcome in women with Dengue infection in northern India. Ind J Clin Pract. 2014;24(11):1053–6.
16. Agarwal K, Malik S, Mittal P. A retrospective analysis of the symptoms and course of dengue infection during pregnancy. Int J Gynaecol Obstet. 2017;139(1):4–8. https://doi.org/10.1002/ijgo.12245
17. Angarita LCR, Angarita SV, Correa M, Odreman MI. Transmisión perinatal del virus dengue en el binomiomadre-hijo. Arch Venez Pueric Pediatr. 2003;76:99–104.
18. 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.
19. Basurko C, Everhard S, Matheus S, et al. A prospective matched study on symptomatic dengue in pregnancy. PLoS One. 2018;13(10): e0202005. https://doi.org/10.1371/journal.pone.0202005
20. Brar R, Sikka P, Suri V, Singh MP, Suri V, Mohindra R, et al. Maternal and fetal outcomes of dengue fever in pregnancy: a large prospective and descriptive observational study. Arch Gynecol Obstet. 2021; 304(1):91–100. https://doi.org/10.1007/s00404-020-05930-7
21. Carles G, Talarmin A, Peneau C, Bertsch M. Dengue et grossesse. Etude de 38 cas en Guyane française [Dengue fever and pregnancy. A study of 38 cases in French Guiana]. J Gynecol Obstet Biol Reprod (Paris). 2000;29(8):758–62.
22. Chansamouth V, Thammasack S, Phetsouvanh R, Keoluangkot V, Moore CE, Blacksell SD, et al. The Aetiologies and impact of fever in pregnant inpatients in Vientiane, Laos. PLoS Negl Trop Dis. 2016; 10(4):e0004577. https://doi.org/10.1371/journal.pntd.0004577
23. Chitra TV, Panicker S. Maternal and fetal outcome of dengue fever in pregnancy. J Vector Borne Dis. 2011;48(4):210–3.
24. Tien Dat T, Kotani T, Yamamoto E, Shibata K, Moriyama Y, Tsuda H, et al. Dengue fever during pregnancy. Nagoya J Med Sci. 2018;80(2):241–7. https://doi.org/10.18999/nagjms.80.2.241
25. Feitoza HAC, Koifman S, Koifman RJ, Saraceni V. Dengue infection during pregnancy and adverse maternal, fetal, and infant health outcomes in Rio Branco, Acre State, Brazil, 2007-2012. Os efeitos maternos, fetais e infantis decorrentes da infecção por dengue durante a gestação em Rio Branco, Acre, Brasil, 2007–2012. Cad Saude Publica. 2017;33(5):e00178915. https://doi.org/10.1590/0102-311X00178915
26. Friedman EE, Dallah F, Harville EW, et al. Symptomatic Dengue infection during pregnancy and infant outcomes: a retrospective cohort study. PLoS Negl Trop Dis. 2014;8(10):e3226. https://doi.org/10.1371/journal.pntd.0003226
27. Gehlot H, Yadav OP, Sharma S, Nagar GG, Yadav A, Gupta PP. A study of dengue fever in pregnancy and its maternal and fetal prognosis. Int J Reprod Contracept Obstet Gynecol. 2017;6:3414–7.
28. Gupta A, Jain P, Venkatesh V, Agarwal A, Reddy DH, Jain A. Prevalence of dengue, chikungunya, and zika viruses in febrile pregnant women: an observational study at a tertiary Care Hospital in North India. Am J Trop Med Hyg. 2021;106(1):tpmd210584. https://doi.org/10.4269/ajtmh.21-0584
29. Kallur SD, Surapaneni T, Boorugu HK, Aziz N, Gala AR, Donnuri S. Need for guidelines for the combined management of pregnancy and dengue: a retrospective study from an Indian tertiary care maternity hospital. Trop Doct. 2019;49(1):7–9. https://doi.org/10.1177/0049475518800638
30. Laoprasopwattana K, Suntharasaj T, Petmanee P, Suddeaugrai O, Geater A. Chikungunya and dengue virus infections during pregnancy: seroprevalence, seroincidence and maternal-fetal transmission, southern Thailand, 2009-2010. Epidemiol Infect. 2016;144(2):381–8. https://doi.org/10.1017/S0950268815001065
31. 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. https://doi.org/10.1016/j.jcv.2014.02.009
32. Mulyana RS, Pangkahila ES, Pemayun TGA. Maternal and neonatal outcomes during Dengue infection outbreak at a tertiary National Hospital in endemic area of Indonesia. Korean J Fam Med. 2020; 41(3):161–6. https://doi.org/10.4082/kjfm.18.0154
33. Naik S, Robinson ML, Alexander M, Chandanwale A, Sambarey P, Kinikar A, et al. Intensified short symptom screening program for Dengue infection during pregnancy, India. Emerg Infect Dis. 2020; 26(4):738–43. https://doi.org/10.3201/eid2604.191476
34. Nascimento LB, Siqueira CM, Coelho GE, Siqueira JB Jr. Symptomatic dengue infection during pregnancy and livebirth outcomes in Brazil, 2007-13: a retrospective observational cohort study. Lancet Infect Dis. 2017;17(9):949–56. https://doi.org/10.1016/S1473-3099(17)30169-X
35. Ortiz-Mesina JJ, Caballero-Hoyos JR, Trujillo X, Ortiz-Mesina M. Complicaciones obstétricas del dengue y la chikungunya en la paciente

13653156, 2022, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tmi.13783 by CAPES, Wiley Online Library on [10/05/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

embarazada: estudio de casos y controles. Rev Med Inst Mex Seguro Soc. 2019;57(3):162–9.
36. Paixao ES, Harron K, Campbell O, et al. Dengue in pregnancy and maternal mortality: a cohort analysis using routine data. Sci Rep. 2018;8(1):9938. https://doi.org/10.1038/s41598-018-28387-w
37. Restrepo BN, Isaza DM, Salazar CL, Ramírez JL, Upegui GE, Ospina M, et al. Dengue en el embarazo: efectos en el feto y el recién nacido [Prenatal and postnatal effects of dengue infection during pregnancy]. Biomedica. 2003;23(4):416–23.
38. Ribeiro CF, Lopes VG, Brasil P, et al. Dengue during pregnancy: association with low birth weight and prematurity. Rev Inst Med Trop Sao Paulo. 2016;58:8. https://doi.org/10.1590/S1678-9946201658008
39. Sharma S, Jain S, Rajaram S. Spectrum of maternofetal outcomes during dengue infection in pregnancy: an insight. Infect Dis Obstet Gynecol. 2016;2016:5046091. https://doi.org/10.1155/2016/5046091
40. Singkibutr T, Wuttikonsammakit P, Chamnan P. Effects of dengue infection on maternal and neonatal outcomes in Thai pregnant women: a retrospective cohort study. J Med Assoc Thai. 2020;103:155–62.
41. Singla N, Arora S, Goel P, Chander J, Huria A. Dengue in pregnancy: an under-reported illness, with special reference to other existing co-infections. Asian Pac J Trop Med. 2015;8(3):206–8. https://doi.org/10.1016/S1995-7645(14)60316-3
42. Sondo KA, Ouattara A, Diendéré EA, et al. Dengue infection during pregnancy in Burkina Faso: a cross-sectional study. BMC Infect Dis. 2019;19(1):997. https://doi.org/10.1186/s12879-019-4587-x
43. Paixão ES, Campbell OM, Teixeira MG, et al. Dengue during pregnancy and live birth outcomes: a cohort of linked data from Brazil. BMJ Open. 2019;9(7):e023529. https://doi.org/10.1136/bmjopen-2018-023529
44. Tan PC, Rajasingam G, Devi S, Omar SZ. Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet Gynecol. 2008;111(5):1111–7. https://doi.org/10.1097/AOG.0b013e31816a49fc
45. Thiyagalingam S, Rengaraj S, Rajamanickkam S. Clinical characteristics and obstetric outcome of symptomatic Dengue infection in pregnancy from a tertiary Care Center in South India. J Infect Dis Epidemiol. 2020;6:133. https://doi.org/10.23937/2474-3658/1510133
46. Restrepo BN, Isaza DM, Salazar CL, Ramírez JL, Ramírez RE, Upegui GE, et al. Dengue y embarazo en Antioquia, Colombia. Rev. Fac. Nac. Salud Pública [Internet]. 2009;22(1):8-14. https://revistas.udea.edu.co/index.php/fnsp/article/view/702
47. Halstead SB. Dengue. Lancet. 2007;370(9599):1644–52. https://doi.org/10.1016/S0140-6736(07)61687-0
48. 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;82:543–9.
49. Srikiatkhachorn A. Plasma leakage in dengue haemorrhagic fever. Thromb Haemost. 2009;102(1042–49):39–1049.
50. 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;360:1552–6.
51. 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. https://doi.org/10.1016/j.jcv.2006.06.002
52. Ribeiro CF, Lopes VGS, Brasil P, Pires ARC, Rohloff R, Nogueira RMR. Dengue infection in pregnancy and its impact on the placenta. Int J Infect Dis. 2017;55:109–12. https://doi.org/10.1016/j.ijid.2017.01.002
53. Miller J, Turan S, Baschat AA. Fetal growth restriction. Semin Perinatol. 2008;32(4):274–80. https://doi.org/10.1053/j.semperi.2008.04.010
54. Sharp AN, Heazell AE, Crocker IP, Mor G. Placental apoptosis in health and disease. Am J Reprod Immunol. 2010;64(3):159–69. https://doi.org/10.1111/j.1600-0897.2010.00837.x
55. Ranjit S, Kissoon N. Dengue hemorrhagic fever and shock syndromes. Pediatr Crit Care Med. 2011;12(1):90–100. https://doi.org/10.1097/PCC.0b013e3181e911a7

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