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Review

Dengue virus infection during pregnancy increased the risk of adverse fetal outcomes? An updated meta-analysis

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ABSTRACT

Objective: To evaluate the effect of maternal dengue virus (DENV) infection during pregnancy in premature birth, low birth weight, miscarriage and stillbirth.

Methods: Systematic electronic literature searches were conducted including PubMed, Medline, Embase, Web of science, Scopus and the Cochrane Library database, up until July 5, 2017. Effect sizes were estimated by using the relative risk (RR) or odds ratio (OR) with theirs corresponding 95% confidence interval (CI). Subgroup analyses were conducted for study design (prospective or retrospective) and clinical symptom of participants (symptomatic or asymptomatic). Statistical analysis was conducted by STATA 12.0.

Results: The initial systematic literature searches identified 1048 studies. After screening, fourteen studies were included. The pooled results did not suggest maternal DENV infection might increase the risk of adverse fetal outcomes with a pooled RR of 0.96 (95% CI: 0.85–1.09, I^2 = 49.6%) for premature birth, RR of 0.99 (95%CI: 0.87–1.12, I^2 = 35.1%) for low birth weight, OR of 1.77 (95% CI: 0.99–3.15, I^2 = 17.5%) for miscarriage and RR of 3.42 (95% CI: 0.76–15.49, I^2 = 54.8%) for stillbirth. Subgroup analysis of studies in symptomatic participants still did not indicate DENV infection appeared to be a risk factor for premature birth, low birth weight and miscarriage with pooled effect size of 0.99 (95% CI: 0.87–1.13, I^2 = 49.3%), 1.22 (95% CI: 0.827–1.80, I^2 = 55.1%) and 1.19 (95% CI: 0.56–2.55, I^2 = 4.7%), respectively.

Conclusions: Current evidence did not suggest that maternal DENV infection during pregnancy might increase the risk of premature birth, low birth weight, miscarriage and stillbirth.

1. Introduction

Dengue is one of the most important mosquito-borne viral diseases and the incidence of dengue has risen in these decades worldwide [1]. Dengue is a threat to health and a burden on health services and economies in most tropical and subtropics countries in the world [2]. The World Health Organization (WHO) estimates that 50–100 million dengue infections occur each year [3]. Dengue infection was caused by 4 serotypes of dengue virus (DENV) and primarily transmitted by *Aedes aegypti* or *Aedes Albopictus* [4]. Infected by DENV, the individuals may appear fever, body aches, leukopenia, and other symptoms of acute viral infection. However, the outcomes of DENV infection are various and range from asymptomatic, to mild and hospitalization. Most participants who became infected by DENV were either asymptomatic or minimally symptomatic [5].

DENV infection is generally encountered in children and adolescents [6], but adults can also be infected [7–9]. Although a small proportion of dengue infections will present complications, pregnant women seem to be more likely to present more severe forms of dengue infection than general population [10]. Recent evidence suggests that maternal DENV infection during pregnancy may affect the fetal outcomes, such as premature birth, low birth weight and miscarriage [11–14]. For example, Adam and colleagues [14] reported the preterm birth rate of 78 laboratory confirmed dengue cases in Sudan was 18% and the rate of low birth weight was 24%. Since most of related studies were case reports and case series and because of the lack of comparative studies, it is still controversial whether maternal DENV infection is a risk factor for adverse pregnancy outcomes [15]. A meta-analysis conducted by Paixão and colleagues [16] indicated that symptomatic dengue during pregnancy might be a risk factor for fetal adverse outcomes with a pooled OR of 2.50 (95% CI: 1.44–4.34) and 1.84 (95% CI: 1.04–3.25) for premature birth and low birth weight, respectively.

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However, there were two limits in this study. This study failed to include two comparative articles [17,18] in the meta-analysis. Furthermore, the authors used Mantel and Haenszel method to calculate the pooled effect size when the heterogeneity between studies was statistically significant. The two limits may confuse the association between maternal DENV infection during pregnancy and fetal outcomes. Hence, we conducted an updated meta-analysis, with a summary of all published studies, to evaluate the effect of maternal DENV infection during pregnancy in premature birth, low birth weight, miscarriage and stillbirth.

2. Methods

This meta-analysis is conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19].

2.1. Literature search

Systematic electronic literature searches were conducted including PubMed, Medline, Embase, Web of science, Scopus and the Cochrane Library database, up to July 5, 2017. The searches were limited to human studies without language restriction. We used the following keywords separately and in combinations: “dengue,” “dengue hemorrhagic fever,” “pregnancy,” “preterm birth,” “abortion,” “low birth weight,” and “miscarriage.” Additional references were identified by manual searching of the reference lists of review articles and selected articles.

2.2. Inclusion and exclusion criteria

Studies were screened for eligibility if they met the following criteria: (1) reported the adverse fetal outcomes (premature birth, or low birth weight, or miscarriage, or stillbirth) of DENV pregnancy infection; (2) reported corresponding effect estimates or sufficient data for their calculation; (3) cohort study, case-control study, or cross-sectional study design which provide effective control group; and (4) DENV infection was detected during pregnancy. Studies were excluded if they were: (1) review articles, case reports, case series, editorials, opinions; and (2) without effective control groups to calculate effect estimates.

2.3. Data selection and extraction

Citations were merged in Endnote (version X7) to facilitate management and data extraction. Two authors independently evaluated all retrieved articles by title, abstract, and full text according to the above inclusion and exclusion criteria. Any disagreement was resolved by consensus. We used a uniform questionnaire, which was developed before searching the literature, to extract information from each eligible study. Extracted information included: first author, publication year, country of origin, study design, dengue detection method, symptomatic or asymptomatic, number of dengue infected participants with or without adverse fetal outcomes (premature birth, or low birth weight, or miscarriage, or stillbirth), corresponding RRs or ORs, and 95% CI values, and statistical adjustments for confounding factors. When data were reported from overlapping study samples (e.g., multiple publications from the same study), the most recent and comprehensive report was considered.

2.4. Quality assessment

The quality of case control and cohort studies was assessed by the Newcastle–Ottawa Scale (NOS) [20,21]. In this scale, studies are scored across three categories: selection of subjects, comparability of study groups, and assessment of outcome/exposure. The rating system was used to indicate the quality of a study, with a maximum score of nine. Studies were graded on an ordinal scoring scale, where higher scores representing studies of higher quality. We defined a study as high quality when the NOS score was not less than six.

2.5. Statistical analysis

Relative risk (RR) was selected as the effect size when only cohort study was included in pooled analysis. When pooled analysis included cohort study, case-control study and cross-sectional study, a pooled odds ratio (OR) was calculated. Inter-study heterogeneity was estimated by the I^2 statistic, and significant heterogeneity was defined as $I^2 \geq 50\%$. Pooled results and corresponding 95% CIs were calculated with a fixed effects model (Mantel and Haenszel method) when heterogeneity was not significant ($I^2 < 50\%$); otherwise, a random-effects model (DerSimonian and Laird method) was applied. Subgroup analyses were conducted for study design (prospective or retrospective) and clinical symptom of participants (symptomatic or asymptomatic). Sensitivity analyses by sequentially removing individual eligible studies were used to evaluate whether any single study dominated the results of the meta-analyses. Sensitivity analyses were also conducted by removing the low quality studies (NOS score less than six) from the analysis. A meta-regression analysis was performed to explore potential inter-study heterogeneity. Finally, publication bias was assessed by visual inspection of funnel plots and Egger’s linear regression [22]. Statistical analyses were conducted using STATA 12.0 (Stata Corp LP, College Station, TX).

3. Results

Description of included studies

The initial systematic literature searches identified 1048 studies. Most ineligible studies were excluded based on the information in the title or abstract. After screening, fourteen studies [17,18,23–34] were assessed for eligibility and were included in this meta-analysis. The selection process was shown in Fig. 1. The main characteristics of included studies were described in Table 1. Eleven studies reported [17,23,25–29,31–34] the impact of DENV infection on the risk of premature birth and ten studies reported [17,23,25–30,33,34] the impact of DENV infection on the risk of low birth weight. Five studies [18,24,26,29,32] and two studies [28,29] reported the association between maternal DENV infection during pregnancy and miscarriage and stillbirth, respectively. Eight studies [17,18,23,26,27,30,33,34] were conducted in Latin America and three studies [24,25,29] were conducted in Asia. Data of the study conducted by Baudin and colleagues [32] was obtained from the authors by e-mail. At the same time, we treated this study [32] as a retrospective comparative study, since the authors retrospectively analyzed the association between DENV infection in blood samples of pregnant women and the following fetal outcomes. The quality of most included studies was high, but NOS score of two cohort studies [26,27] and one case-control study [18] were less than six (Table 1).

3.1. Association between maternal DENV infection and premature birth

Eleven studies [17,23,25–29,31–34], including two prospective cohort studies, eight retrospective cohort studies, and one cross-sectional study, with a total of 357983 participants, reported the impact of DENV infection on risk of premature birth. The pooled results indicated that there was no significant association between DENV infection and premature birth with RR of 0.96 (95% CI: 0.85–1.09, $I^2 = 49.6\%$) (Fig. 2). In addition, subgroup analyses showed that when only nine symptomatic studies [17,23,26–29,31,32,34] were included, the DENV infection still did not appear to be a risk factor for premature birth with RR of 0.99 (95% CI: 0.87–1.13, $I^2 = 49.3\%$). The pooled RRs of two prospective studies [25,29] and nine retrospective studies [17,23,26–28,31–34] were 0.64 (95% CI: 0.34–1.21, $I^2 = 0.0\%$) and