

REVIEW



Dengue in Pregnancy: A Systemic Review and Meta-analysis of Maternal and Perinatal Outcomes

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ABSTRACT

Background: Dengue fever, a mosquito-borne viral infection, is a growing concern for maternal and fetal health in endemic regions, particularly in South Asia. Dengue infection during pregnancy poses serious risks, yet comprehensive data on its impact remains limited. **Objective:** This study aims to evaluate the maternal, fetal, and neonatal outcomes associated with dengue infection in pregnant women based on evidence from ten South Asian studies. **Methods:** A systematic analysis was conducted across ten studies involving 1,956 pregnant women with confirmed dengue infection through NS1 antigen and/or IgM antibody testing. The pooled prevalence of maternal and neonatal complications was calculated, with statistical significance determined at a p-value of <0.05. **Results:** Postpartum hemorrhage was the most prevalent maternal complication, affecting 3.02% of cases. Additionally, 1.02% of infected women required ICU admission, and the maternal mortality rate was 0.51%. Other maternal complications included hypertensive disorders (0.46%), acute kidney injury (0.41%), and acute respiratory distress syndrome (0.36%). Fetal and neonatal complications were also notable, with preterm birth occurring in 3.63% of cases, low birth weight in 2.76%, and NICU/SNCU admission in 2.15%. Adverse outcomes, such as stillbirth/intrauterine death (1.02%) and miscarriage (0.72%), were also observed, with 0.61% of cases showing evidence of vertical transmission. **Conclusion:** Dengue infection during pregnancy is associated with significant maternal and fetal/neonatal risks, including postpartum hemorrhage, preterm birth, and pregnancy loss. This analysis underscores the need for vigilant monitoring, early diagnosis, and intervention in pregnant women with dengue to improve outcomes.

Keywords: Dengue, Pregnancy, Maternal outcomes, Perinatal outcomes, Epidemiology.

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INTRODUCTION

Dengue fever is a febrile disease transmitted by mosquitoes, which has rapidly become the most

prevalent arboviral infection globally. This illness is caused by the dengue virus, a single-stranded RNA virus classified within the Flaviviridae family. The primary

vectors for the transmission of dengue are the *Aedes aegypti* and *Aedes albopictus* mosquitoes. The World Health Organization (WHO) estimates that around 40% of the global population, equating to more than 2.5 billion individuals, reside in regions with a heightened risk of contracting dengue infection [1,2]. This situation is particularly alarming as dengue has the potential to reignite significant outbreaks in areas where it was previously eradicated, including certain regions of the United States and Europe.

According to WHO criteria, dengue hemorrhagic fever (DHF) is defined by four key clinical features: the presence of fever or a recent history of fever lasting between 2 to 7 days, any hemorrhagic manifestations, thrombocytopenia (characterized by a platelet count of less than 100,000/mm³), and evidence indicating increased vascular permeability. Among the common mild hemorrhagic symptoms are the positive tourniquet test, cutaneous hemorrhages such as petechiae and hematomas, as well as epistaxis (nosebleeds) and gingival bleeding (gum bleeding). More severe forms of hemorrhage may include hematemesis (vomiting of blood), melena (dark, tarry stools), and cerebral hemorrhages, which are considered critical complications [3].

In the context of pregnancy, the implications of dengue fever are particularly concerning both the mother and the developing fetus, as both are at increased risk for severe bleeding complications. A systematic review conducted in 2016 highlighted several adverse pregnancy outcomes associated with maternal dengue infection, including elevated rates of cesarean deliveries, preterm births, and instances of low-birth-weight infants [4,5]. Severe dengue infections during pregnancy, while rare, can lead to maternal mortality. The associated perinatal outcomes may include various obstetric complications such as intrauterine growth restriction, chronic health conditions, developmental abnormalities, and low birth weight. Neonatal dengue can occur when the virus crosses the placenta, resulting in symptoms such as fever, rash, bleeding tendencies, and hepatomegaly (enlargement of the liver) [6].

This underscores the necessity for heightened awareness and preventive measures concerning dengue fever in pregnant populations, given the potential for significant health repercussions for both mothers and their unborn children.

METHODS

Search Strategy

A systematic search was conducted utilizing databases such as PubMed and Google Scholar, alongside various relevant articles. This analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7]. A comprehensive literature search was undertaken using the search terms “Dengue fever,” “Dengue virus,” “Dengue hemorrhagic fever,” “Dengue shock syndrome,” in conjunction with “Pregnancy,” “gestational,” or “maternal outcome.” The search imposed no language restrictions, and studies from all geographical regions were considered. Additionally, the reference lists of the included studies, along with pertinent literature, were scrutinized to identify further qualifying studies. After eliminating duplicate citations, the remaining articles were assessed for eligibility based on their titles and abstracts.

Inclusion criteria

Confirmed dengue fever in pregnancy
Geographic surveys to capture diversity
Both clinical and community assessments
Studies published in the last decade to ensure relevance

Exclusion criteria

Studies lacking adequate data on maternal and perinatal outcomes
The study focused only on non-pregnant or non-human populations
Studies with a small sample size may not yield robust results
Non-peer reviewed articles or research published before a specific date for up-to-date information
Studies not reporting specific maternal and perinatal outcomes associated with dengue in pregnancy

Study Selection

According to the inclusion criteria, the titles and abstracts of the shortlisted papers were meticulously evaluated. Data from each selected study were extracted and analyzed, revealing that dengue virus (DENV) infection during pregnancy is linked to a heightened risk of maternal mortality, stillbirth, and neonatal deaths when compared to pregnant women without DENV infection. The methodology employed in this analysis is presented below (Table 1, Figure 1).

Table 1: Search Methodology

Database	Search Date	Search Query	Results
Google Scholar	25 July 2024	((dengue[All Fields] AND pregnancy[All Fields]) AND (outcomes[All Fields] OR complications[All Fields]))	800
PUBMED	25 July 2024	(dengue[MeSH Terms] AND pregnancy[MeSH Terms] AND (maternal[All Fields] OR fetal[All Fields] OR neonatal[All Fields]) AND English[lang])	250
EMBASE	25 July 2024	dengue AND pregnancy AND (outcome OR complication) AND [english]/lim	100

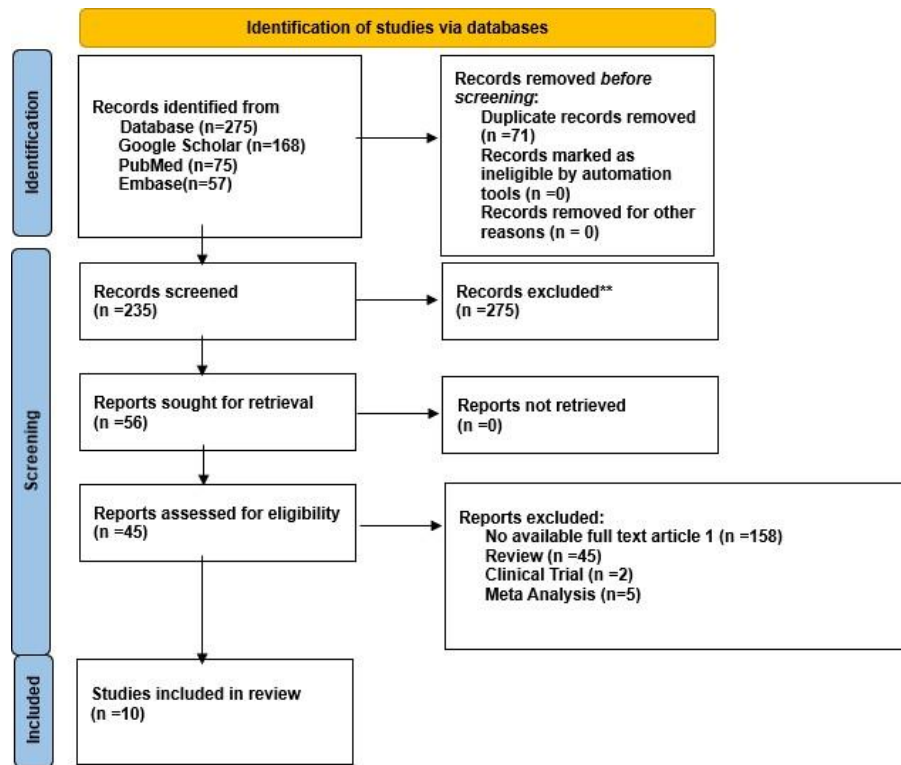


Figure 1: PRISMA Flowchart of the studies selected for the current study

Data Extraction

Data extraction was conducted independently by two authors, who subsequently cross-verified the information to minimize errors. A comprehensive set of details was collected from each study, including the name of the first author, the year of publication, the country where the study was conducted, the study design, total sample size, the number of pregnant women diagnosed with dengue virus (DENV) infection, the methods used for dengue detection, maternal mortality rates, the percentage of women experiencing dengue shock syndrome (DSS), and various maternal and fetal-neonatal outcomes.

Quality Assessment

Two independent reviewers evaluated the methodological quality of all included clinical trials following Cochrane Collaboration guidelines. Key aspects assessed included random sequence generation, allocation concealment, blinding of outcome assessment, completeness of outcome data, selective reporting, and potential sources of other biases.

Statistical analysis

Statistical analyses were conducted using SPP Statistical Software version 26. The pooled prevalence and corresponding 95% confidence intervals (CIs) were calculated employing a random effects model. For

outcome analyses, results were expressed as odds ratios with 95% CIs. A probability value of <0.05 was deemed statistically significant across all analyses. Additionally, a leave-one-out sensitivity analysis was performed to evaluate the influence of individual studies on the overall statistical outcomes.

RESULTS

Initial searches across various databases identified a total of 575 articles. Following the removal of

duplicates, 235 studies were eligible for assessment. After reviewing titles and abstracts, 275 articles were excluded, resulting in 45 articles remaining for further evaluation and potential inclusion in this study (Figure 1). Ultimately, 10 articles detailing data on 1,956 pregnant women infected with dengue virus (DENV) were incorporated into this meta-analysis, comprising 10 studies from Asia (predominantly from India, n = 5), Pakistan 2, Sri Lanka 2 and 1 from Bangladesh (Table 2).

Table 2: Baseline characteristics of the included studies

Study	Study design	Sample size	Dengue detection technique	Dengue positive women (n)	Adverse foetal outcome
Nallaperuma, (2024) Sri Lanka [8]	Retrospective study	687	IgM and/or NS1 antigen	115	Fetal adverse outcomes (n=9) Neonatal adverse outcomes (n=33) Transplacental transmission (n=2)
Sarkar, (2024) India [9]	Prospective observational study	40	IgM and/or NS1 antigen	40	ICU care (n=3) Platelet transfusion (n=9) CPAP (n=7) PPH (n=8) Abortion (n=7) Abruptio (n=2) Fetal distress (n=5) Oligohydramnios (n=2) Normal neonatal (n=4) SNCU admission (n=8) NICU admission (n=2)
Fatema Rahman, (2023), Bangladesh [10]	Prospective observational study	44	IgM and/or NS1 antigen		ICU admission (n=11) Maternal mortality (n=2) Still birth (n=6) NICU admission (n=6)
Dr. Kiranjeet Kaur, (2023) India [11]	Prospective observational study	100	IgM	100	IUGR (n=4) Fetal malformation (n=3) Meconium-stained amniotic fluid (n=9) Fetal distress (n=6) Prematurity (n=12) Low birth weight (n=35) ICU admission (n=6) Vertical transmission (n=7)
Chamara Dalugama, (2023) Sri Lanka [12]	Retrospective study	76	IgM and/or NS1 antigen	24	Pre-eclampsia (n=1) Puerperium – PPH (n=1) Puerperium – Sepsis (n=2) Maternal death (n=2) Oligohydramnios (n=2) Reduced fetal movement (n=1) CTG abnormalities (n=3)

					Doppler abnormalities (n=1) PBU admission (n=3) Low birthweight (n= 6)
Sagili, (2022) India [13]	Retrospective study	408	IgM and/or NS1 antigen	91	Miscarriage (n=3) Pre-term premature rupture of membranes (n=12) Oligohydramnios (n=5) Foetal growth restriction (n=8) Labour, induced (n=13) Caesarean section rate (n=32) Pre-term birth <37 wk (n=25) Post-partum haemorrhage (n=2) Fetal adverse outcomes (n=9) Neonatal adverse outcomes among live births (n=33) Transplacental transmission (n=2)
Naz S, (2022) Pakistan [14]	Prospective observational study	139	IgM and/or NS1 antigen	65	Poor fetal outcome (n=3)
Brar, (2021) India [15]	Prospective observational study	216	IgM and/or NS1 antigen	44	Thrombocytopenia (n=23) Post-partum hemorrhage (n=10) Acute kidney injury (n=8) ARDS (n=7) Acute liver failure (n=4) Maternal Mortality (n=6) Miscarriages (n=2) preterm babies (n=15) Low birth weight babies (n=13) Neonatal deaths (n=2) Still Birth (n=4)
Ruchika Garg, (2021), India [16]	Prospective observational study	196	IgM and/or NS1 antigen	196	Moderate-to-severe oligohydramnios (n=41) PPH (n=35) Abruptio (n=23) Preterm labor (n=46) Preeclampsia (n=7) Eclampsia (n=1) Miscarriage (n=2) Preterm (n=44) Fetal distress (n=21) Stillborn (n=5) Intrauterine death (n=3) NICU admissions (n=23)
Maryam Shoaib, (2021) Pakistan [17]	Prospective observational study	50	NS1, IgM or IgG test	50	Postpartum hemorrhage (n=3) Intrauterine fetal death (n=2) Dengue encephalitis (n=1) Vertical transmission survive (n=1)

This comprehensive analysis included 10 studies from South Asian countries with a total sample size of

1,956 pregnant women with dengue infection. The diagnosis was confirmed through NS1 antigen and/or

IgM antibody testing across all studies. The results demonstrated significant maternal and fetal/neonatal complications associated with dengue infection during pregnancy.

Maternal Outcomes

Among the maternal complications, postpartum hemorrhage was the most prevalent, affecting 3.02% (n=59) of cases. Critical care requirements were substantial, with 1.02% (n=20) of patients requiring ICU admission. The maternal mortality rate was 0.51% (n=10),

indicating the potential severity of dengue infection during pregnancy. Other significant maternal complications included hypertensive disorders of pregnancy (pre-eclampsia/eclampsia) in 0.46% (n=9) of cases. Evidence of organ dysfunction was observed in several cases, including acute kidney injury (0.41%, n=8), acute respiratory distress syndrome (0.36%, n=7), and acute liver failure (0.20%, n=4). Less common but serious complications included sepsis (0.10%, n=2) and dengue encephalitis (0.05%, n=1) (Table 3).

Table 3: Maternal outcomes in pregnant women with DENV infection

Complication	Total Cases	Percentage (of 1,956)
Postpartum Hemorrhage (PPH)	59	3.02%
ICU Admission	20	1.02%
Maternal Mortality	10	0.51%
Pre-eclampsia/Eclampsia	9	0.46%
Acute Kidney Injury	8	0.41%
ARDS	7	0.36%
Acute Liver Failure	4	0.20%
Sepsis	2	0.10%
Dengue Encephalitis	1	0.05%

Fetal and Neonatal Outcomes

The impact on fetal and neonatal outcomes was notable. Preterm birth emerged as the most frequent complication, occurring in 3.63% (n=71) of cases. Low birth weight was observed in 2.76% (n=54) of newborns, and 2.15% (n=42) required NICU/SNCU admission. Oligohydramnios was documented in 2.56% (n=50) of cases, and fetal distress was observed in 1.64% (n=32) of pregnancies. The pregnancy loss rate was significant,

with stillbirth/intrauterine death occurring in 1.02% (n=20) of cases and miscarriage/abortion in 0.72% (n=14). Vertical transmission of dengue virus was confirmed in 0.61% (n=12) of cases. Growth-related complications included IUGR/fetal growth restriction in 0.61% (n=12) of cases. Other notable findings included meconium-stained amniotic fluid in 0.46% (n=9) of cases and fetal malformation in 0.15% (n=3) of cases (Table 4).

Table 4: Foetal and neonatal outcomes in pregnant women with DENV infection

Complication	Total Cases	Percentage (of 1,956)
Low Birth Weight	54	2.76%
Preterm Birth	71	3.63%
NICU/SNCU Admission	42	2.15%
Fetal Distress	32	1.64%
Oligohydramnios	50	2.56%
Stillbirth/IUD	20	1.02%
Vertical Transmission	12	0.61%
IUGR/Fetal Growth Restriction	12	0.61%
Fetal Malformation	3	0.15%
Miscarriage/Abortion	14	0.72%
Meconium-stained Amniotic Fluid	9	0.46%

DISCUSSION

This comprehensive analysis of 10 studies from

South Asian countries, encompassing 1,956 pregnant women with dengue infection, provides significant

insights into the maternal and fetal outcomes of dengue during pregnancy. The study's findings align with the growing body of literature that underscores the risks posed by dengue infection to pregnant women and their unborn children, particularly in regions where dengue is endemic.

Maternal Outcomes

Among the maternal outcomes, postpartum hemorrhage was found to be the most common complication, occurring in 3.02% of cases. This is consistent with studies that have observed an increased risk of hemorrhagic complications in pregnant women with dengue infection due to thrombocytopenia, a common manifestation in severe cases of dengue. Monocytopenia on pregnancy is profound, as it heightens the risk of bleeding complications, which may become life-threatening if not managed promptly. In severe cases, this can lead to extensive postpartum hemorrhage requiring blood transfusions or surgical interventions. Another critical outcome was the need for intensive care, with 1.02% of dengue-infected pregnant women requiring ICU admission. The severity of dengue in some pregnant women often leads to multi-organ involvement, as evidenced by cases of acute kidney injury (0.41%), acute respiratory distress syndrome (ARDS) (0.36%), and acute liver failure (0.20%). This requirement for critical care and high dependency on specialized care facilities has been echoed in other studies. According to a systematic review by Xie *et al.*, patients with severe dengue infection during pregnancy were more likely to need ICU admission due to complications such as hemodynamic instability and organ dysfunction.

Hypertensive including pre-eclampsia and eclampsia, were also noted among dengue-infected pregnant women, though at a relatively low rate of 0.46%. The exact mechanism by which dengue may exacerbate or precipitate hypertensive disorders is not fully understood. However, it is speculated that the virus's impact on endothelial cells and inflammatory mediators may contribute to the pathogenesis of pre-eclampsia in these patients. The presence of hypertensives adds another layer of risk, as pre-eclampsia and eclampsia can result in maternal and fetal complications if left unmanaged. Other severe but less common maternal complications included sepsis (0.10%) and dengue encephalitis (0.05%), both of which have been linked to higher mortality rates in other studies. These complications, although rare, underscore the severity of dengue in certain cases and underscore the need for vigilant

monitoring and prompt intervention in pregnant women diagnosed with the infection.

Fetal and Neonatal Outcomes

Dengue infection during pregnancy has profound implications for fetal and neonatal outcomes. The present analysis revealed that preterm birth was the most frequent neonatal complication, affecting 3.63% of cases. Preterm birth has been consistently linked to dengue infection, with a previous study by Carles *et al.* reporting similar findings. The preterm delivery rate may be attributed to complications such as pre-eclampsia, hemorrhage, and infection, all of which can contribute to early labor induction or cesarean delivery. Low birth weight was another prominent finding, observed in 2.76% of cases. Low birth weight is a significant indicator of neonatal health and is often associated with delayed growth and development in infants. Dengue infection during pregnancy, particularly in cases where maternal nutrition and immunity are compromised, has been shown to contribute to fetal growth restriction, which can manifest as low birth weight. In this study, intrauterine growth restriction (IUGR) or fetal growth restriction was documented in 0.61% of cases. Growth restriction is concerning, as it may lead to long-term developmental delays and health issues in the affected infants.

Another notable finding was the 1.64% incidence of fetal distress, which could be attributed to the maternal systemic effects of dengue, including high-grade fever and dehydration. Maternal fever has been recognized as a risk factor for fetal distress in multiple studies. In addition, oligohydramnios, seen in 2.56% of cases, tribute to fetal distress, as decreased amniotic fluid can compromise fetal movement and development. This connection highlights the need for close monitoring of amniotic fluid levels in pregnant women diagnosed with dengue. The study also recorded a significant pregnancy loss rate, with stillbirth/intrauterine death occurring in 1.02% of cases and miscarriage/abortion in 0.72% of cases. These findings are consistent with previous reports of adverse pregnancy outcomes associated with dengue. In a study by Basurko *et al.*, high rates of fetal loss were reported among pregnant women with severe dengue infection. Vertical transmission of the dengue virus was confirmed in 0.61% in this analysis. Although rare, vertical transmission remains a serious concern as it can result in neonatal dengue, which presents with fever, rash, and hepatomegaly shortly after birth. Neonatal dengue carries a high risk of mortality, particularly in preterm and low-birth-weight infants who may have

underdeveloped immune systems. Meconium-stained amniotic fluid was observed in 0.46% of cases, which, although a minor finding, may indicate fetal stress [18]. The mechanism by which dengue infection contributes to fetal stress is not entirely understood but may relate to maternal fever and dehydration. Fetal malformation, albeit rare (0.15%), was another complication noted in this analysis. Although malformations are uncommon in dengue, some studies have suggested that maternal infections during early pregnancy could disrupt fetal development.

Implications and Future Research

The findings of this study under the importance of timely diagnosis and intervention for dengue infection in pregnant women. Early detection through NS1 antigen and IgM antibody testing, as implemented in the studies reviewed, is essential to manage maternal and fetal risks effectively. Since dengue poses substantial health risks to both mother and fetus, there is a pressing need for more standardized protocols and guidelines for managing dengue in pregnancy. Despite these findings, there are notable gaps in the literature regarding the trimester-specific effects of dengue infection, long-term neonatal outcomes, and the efficacy of preventive measures like vaccination in pregnant women. Future research should focus on these areas, as well as on the development of targeted treatment protocols for pregnant women with dengue, which might include antiviral agents and immunotherapies. The creation of dengue vaccination strategies specifically tailored for women of childbearing age in endemic regions could also be explored as a preventive approach.

CONCLUSION

Dengue infection during pregnancy is associated with significant maternal and fetal/neonatal risks, including postpartum hemorrhage, preterm birth, and pregnancy loss. This analysis underscores the need for vigilant monitoring, early diagnosis, and intervention in pregnant women with dengue to improve outcomes. Further research is warranted to develop standardized protocols for managing dengue in pregnancy and to explore preventive measures in endemic areas.

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