DENGUE IN PREGNANT WOMEN: A POTENTIAL THREAT TO MATERNAL-FETAL OUTCOMES?

https://doi.org/10.56238/sevened2024.037-033

Marcela Pereira Romão[1], Lara Zaccarelli Rubira[2] and Ethel Zimberg Chehter[3]

ABSTRACT

INTRODUCTION: Dengue is an acute febrile disease caused by the DENV virus and transmitted mainly by the Aedes mosquito. It is an endemic disease mainly in countries in Asia and America. The clinical course is usually divided into three phases: febrile, critical and recovery, with fever being the initial symptom, sometimes accompanied by anorexia, vomiting, diarrhea and maculopapular rash. The critical phase is characterized by increased capillary permeability, which results in hemorrhage, shock and organ dysfunction due to fluid accumulation, gradually reabsorbed in the recovery phase. The diagnosis of dengue is made based on the detection of the NS1 antigen; the genome, by RT-PCR; or IgM or IgG antibodies. Treatment is only symptomatic. During pregnancy, studies suggest that there is an increase in adverse maternal-fetal outcomes due to DENV infection, in addition to the challenging diagnosis, due to the physiological adaptations of pregnancy. In this context, this systematic review aims to analyze how dengue behaves in pregnant women and the outcome of the infection. METHOD: searches were performed in PubMed, using the keywords “dengue pregnancy”, in LILACS, using “dengue pregnancy” and “dengue embarazo”, and in Scielo, using “dengue pregnancy”. A total of 188, 18, 21 and 1 results were obtained, respectively, and after exclusion by title and abstract, and by full text, 32 articles were included. RESULT: of the maternal outcomes, severe thrombocytopenia and death were the most cited in the articles, followed by postpartum hemorrhage, more severe forms of the disease, need for cesarean section and preeclampsia. The most prevalent fetal repercussion was prematurity, in addition to stillbirths, neonatal deaths, low birth weight and oligohydramnios. DISCUSSION: The articles analyzed suggest that dengue during pregnancy increases the risk of severe forms of the disease, postpartum hemorrhage, maternal death, miscarriage, stillbirths, fetal growth restriction, prematurity, and oligohydramnios, especially in cases of infections acquired in the third trimester of pregnancy. Vertical transmission also increases at the end of pregnancy. CONCLUSION: This review highlights that dengue is especially relevant during pregnancy, with a significant negative impact on maternal and fetal outcomes. However, further studies are still needed for greater depth, since there is no consensus.

Keywords: Dengue. Pregnancy. Arbovirus disease. Fever.

[1] 5th-year student at FMABC University Center
[2] 5th year student at FMABC University Center
[3] Advisor
Doctor of Medicine from the FMABC University Center

INTRODUCTION

DEFINITION

Dengue is an acute infectious disease caused by an arbovirus and transmitted by arthropods, especially by the mosquito of the genus Aedes, mainly the species Ae. aegypti. The disease presents a systemic and dynamic picture, with a wide spectrum of clinical manifestations, which vary from uncomplicated cases with mild, spontaneous or induced presentations, such as thrombocytopenia, to complicated forms such as dengue hemorrhagic fever and dengue shock syndrome [1]. Furthermore, dengue can be considered a global public health problem, both due to its occurrence throughout the globe, in an endemic, sporadic or epidemic form, but also due to its significant epidemiological and economic impact [1, 2,3]. The dengue virus, DENV, belongs to the Flaviviridae family and the Flavivirus genus, and has four different serotypes (DENV 1-4), each with distinct genotypes and lineages [1, 2, 3].

Furthermore, the dengue virus is characterized by being enveloped with icosahedral symmetry, a diameter of approximately 50 nm, and having its genome composed of a single strand of positive-polarity RNA [3]. This RNA encodes a single polyprotein that is cleaved into the structural proteins of the capsid (C), membrane (M), and envelope (E), in addition to eight nonstructural proteins (NS). In this context, the structural glycoprotein E is related to cellular recognition and promotion of entry, while the NS proteins assist in the replication of the viral genome [3].

EPIDEMIOLOGY

Dengue is one of the main vector-borne diseases, representing a major public health problem worldwide, with approximately half of the world's population at risk of becoming infected with the virus, with estimates of 100 to 400 million new cases per year, according to WHO data from 2021 [3,4]. In 2019, the same institution mentioned declared dengue as one of the “top ten threats to global health” that year, which reiterates its relevance, seriousness, and potential impact on health [3]. Furthermore, dengue is considered endemic in more than 100 countries, predominantly in tropical and subtropical areas, such as Africa, the Americas, the Eastern Mediterranean, Southwest Asia, and the Eastern Pacific; of these, the Americas are one of the most severely affected and Asia accounts for approximately 70% of the global burden of the disease. [4]

In the global context, the incidence of dengue virus infection has grown significantly across the globe in recent decades, with an increase from 505,430 cases reported to the WHO in 2000 to 5.2 million in 2019. This increase in the number of cases and the worldwide

spread is related to rapid urbanization with the growth of urban and semi-urban areas, combined with inadequate infrastructure planning, which favors the mosquito's life cycle and makes it difficult to combat it, in addition to the large number of trips between continents, which favors the disease being transmitted to new environments. [3]

Regarding the most recent data, 2023 was the year with the highest number of dengue cases recorded in the Americas, with a total of 4,565,911 cases and 2,340 deaths [5]. This situation continued until 2024, when data from epidemiological weeks 1 to 5 showed a 157% increase in the number of cases compared to the same period in 2023 and a 225% increase compared to the average of the last 5 years [5]. Until epidemiological week 12, the trend of increasing cases in 2024 compared to the same period in 2023 continued [6].

Also in 2024, up to the time of this study, there were 2,573,293 probable cases of dengue, 1,456 deaths under investigation and 923 confirmed deaths. Regarding gender, the disease is more prevalent in women, who represent 55.4% of probable cases, while men total 44.6%. In terms of race, mixed race people account for 39.8% of cases, followed by white people (36.7%), no information (16.3%) and black people (5.7%). In terms of age, the infection is more common in the 20 to 29 age group, in both sexes, and more serious in the age group from 80 years old. Finally, the most affected states are the Federal District, Minas Gerais, Espirito Santo, Paraná and Goiás.. [6]

PATHOPHYSIOLOGY

An individual becomes infected with DENV through the bite of the Aedes aegypti mosquito, and from then on, the virus begins its life cycle within the human body, with viral entry and fixation, going through several stages until the release of mature DENV particles.

In its mature form, the virus can circulate freely in the plasma or inside monocytes/macrophages, cells for which DENV has tropism and are the largest sites of viral replication, as well as in striated muscle cells, smooth muscle cells, fibroblasts and local lymph nodes. In this scenario, general symptoms such as fever and malaise coincide with the period of viremia, a time when serum cytokine levels are high. High serum levels of interleukins, tumor necrosis factor, interferons and platelet activating factor are also observed. [7]

Regarding the immune response to dengue virus infection, dendritic cells are the connectors between the innate and adaptive immune responses during the invasion of viral particles. These cells present the target antigen to T cells, especially TCD8 and TCD4, as the starting point of the innate immune response [8].

In addition, the complement system is of great importance in blocking infection by the

virus in the initial phase of the innate immune response. However, the immune evasion of DENV can be facilitated by NS1, when it interacts with the respective complement components in different pathways of their activation. As a consequence, this alters the functionality of the complement components and generates inhibition of their response. Another mechanism involved is the production of interferons, which control viral replication in its initial phase, as the first line of defense. [8]

There is also a paradoxical immune response mechanism, which harms the infected individual and is responsible for the immunopathology of hemorrhagic dengue. This occurs after sequential infections by DENV, in which the antibodies previously produced by infection by another viral type do not neutralize the second infecting virus and amplify the infection, facilitating the penetration of macrophages by the new infecting type. This is the phenomenon of facilitation by antibodies of viral penetration into macrophages, which leads to their activation by lymphocytes and aggression by cytotoxic cells, resulting in the release of thromboplastin, initiating coagulation phenomena and the release of complement-activating proteases, causing cell lysis and shock [7].

In summary, hemorrhagic dengue is caused by an anomalous immune response, which involves leukocytes, cytokines and immune complexes, leading to increased permeability due to poor vascular endothelial function, without destruction of the endothelium, with extravasation of fluids into the interstitium, causing a drop in blood pressure and hemorrhagic manifestations, associated with thrombocytopenia [7].

Regarding antibody production, structural protein E defines the production of antibodies specific to the viral type through its epitopes, in addition to being vital for the binding of the virus to the membrane receptor and having the most important antigenic domains. Antibodies produced against NS1 promote viral lysis by fixing the complement; however, they are not capable of neutralizing viral particles, acting as mediators of cytotoxicity phenomena by lymphocytes, through their receptors for the Fc portion of immunoglobulins. Furthermore, the humoral response produced by plasma cells resulting from the activation of B lymphocytes is usually vigorous [7]. Finally, susceptibility to DENV is universal, that is, when an infection by the virus occurs, acquired immunity is permanent and long-lasting for a specific serotype (homologous). Furthermore, through the mechanism of cross-immunity (heterologous), the individual also acquires partial protection against infection caused by the other three DENV serotypes, but this lasts only two or three months after the first infection. This is because the NS1 protein shares its similar sequence in up to 70% of dengue serotypes and also shows similarities ranging from 40-50% with other flaviviruses [2, 3].

LIFE CYCLE

The main form of transmission of dengue to humans, in the urban cycle, is through the vector route, through the bite of infected female Ae. aegypti, in the human-vector-human cycle [2]. This begins when a mosquito bites a person infected with the virus, which initially generates an infestation of the epithelial cells of the mosquito's midgut, followed by rapid viral dissemination within the arthropod, reaching the salivary glands and other tissues, thus making the mosquito capable of transmitting DENV to uninfected humans through its bite, closing the human-vector-human cycle [9].

Also in relation to Ae. aegypti, it is a mosquito with opportunistic habits, which lives close to humans, mainly in urban areas and in regions with high population density, especially those with disorderly occupation that provide more breeding sites for females to lay eggs. In this context, the main breeding sites are water tanks, gallons and barrels, but also small reservoirs such as plant pots, clogged gutters, bottles, open-air garbage, among others. It is in these places, associated with clean, still water, that the female mosquito can lay her eggs, on the walls of the breeding sites, very close to the surface of the water [10].

Regarding mosquito activity, it is most active in the early morning and at dusk, which are the periods of greatest risk for bites and consequent transmission of the disease [5]. In general, females feed every 3-4 days, with hematophagy being important for the complete development of the eggs and their maturation in the ovaries [5, 10].

CLINICAL PICTURE

Dengue is, by definition, an acute, systemic and dynamic febrile disease, with a broad clinical spectrum. [1] There may be asymptomatic patients, but in general, it is a debilitating and self-limiting pathology, with a benign evolution in most cases. However, some may evolve into severe forms or even death. [2]

The evolution usually occurs in three clinical phases: febrile, critical and recovery. In the febrile phase, the first symptom is generally a fever above 38ºC, but this can vary from 39 to 40ºC, with an abrupt onset and duration of two to seven days. There may also be associated anorexia, nausea, vomiting and diarrhea, in addition to maculopapular rash, mainly on the face, trunk and limbs. After the febrile phase, most patients recover gradually. [2]

The critical phase begins with the decline of fever, between the third and seventh day. The warning signs, resulting from increased capillary permeability, can evolve into shock due to plasma leakage, severe hemorrhages and severe organ dysfunction. Some of the warning signs are: severe abdominal pain (reported or on physical examination),

continuous vomiting, fluid accumulation (ascites, pleural effusion, pericardial effusion), postural hypotension and/or fainting, lethargy and/or irritability, hepatomegaly greater than 2 cm below the costal margin, mucosal bleeding and progressive increase in hematocrit [2]. Thinking about the early identification of warning signs, it is essential to perform the snare test, even if dengue is suspected.

Thus, as mentioned above, without adequate management of the critical phase, patients progress to severe forms of dengue, marked by shock, fluid accumulation resulting from plasma extravasation, respiratory distress, severe bleeding and signs of organ dysfunction in the heart, lungs, kidneys, liver and central nervous system. Dengue shock syndrome (DSS) occurs when a critical volume of plasma is lost due to extravasation, generally between the 4th and 5th day of illness. Shock sets in quickly and lasts for a short time, so that the patient may die within 12 to 24 hours.

The third characteristic period of dengue fever is called the “recovery phase” and occurs 24 to 48 hours after the critical phase, with the gradual reabsorption of the fluid that had leaked into the extravascular compartment, and this process persists for the next 48 to 72 hours. This leads to an improvement in the general condition and appetite, a decrease in gastrointestinal symptoms, hemodynamic stabilization, and an improvement in urinary output. The rash may persist during this phase, and there may also be bradycardia and changes in the electrocardiogram. [2]

DIAGNOSIS

The World Health Organization (WHO) suggests that serological methods be used to diagnose DENV and that genomic techniques be used to directly detect the virus. [1]

Based on simple suspicion, a blood sample must be collected for diagnosis. Within 8 days (preferably 5) after the onset of symptoms, blood samples must be processed for NS1 detection, and for genome and serotype detection, using the RT-PCR technique. From 8 to 15 days after the onset of symptoms, IgM is searched for using the ELISA technique; and, after 15 days, IgG is searched for. [1]

Non-structural protein 1 (NS1) is a highly conserved glycoprotein, present in high concentrations in the serum of patients infected by the virus and, because of this, it can be identified soon after the onset of acute symptoms and before antibody positivity. This is a direct method for diagnosis. [2] Given that NS1 detection is quite specific but not very sensitive, samples negative for this antigen cannot be considered negative for dengue, and should be confirmed by detection of IgM and IgG. [1]. Furthermore, considering potential differential diagnoses, all samples negative for dengue are screened for Zika virus and,

later, for chikungunya. [1] Other indirect diagnostic methods include: demonstration of seroconversion in antibody titers by hemagglutination inhibition (HI); 4x change in plaque reduction neutralization test (PRNT) titer, in paired samples, the first collected from the 6th day after the onset of symptoms and the second 15 days after the first; or anatomopathological, with histopathological and viral antigen testing by immunohistochemistry (IHC), no more than 48 hours after death. [2]

PREVENTION AND TREATMENT

Vector control, in an attempt to reduce the spread of Aedes aegypti, can be done by avoiding the accumulation of water, which favors the reproduction of the mosquito, in addition to the use of insecticides and repellents, composed of N,N-diethyl-3-methylbenzamide (DEET), which is highly effective against the mosquito. Vector control is based on the assumption that, by reducing the concentration below the entomological threshold, transmission can be delayed [9].

Dengue control in the country faces difficulties and challenges such as: bureaucracy imposed by shared responsibilities and favoring the spread of the mosquito, in the face of deforestation, precarious basic sanitation and climate change. Unsatisfactory basic sanitation also favors the accumulation of water in peridomestic environments. In addition, in order for the population to avoid the accumulation of stagnant water in homes, periodic epidemiological surveillance and awareness of residents about the importance of this measure are necessary. Due to these challenges, despite robust government investment, there has been no reduction in vector density that could reduce the spread of the disease in recent years. [1]

The development of vaccines for dengue is quite challenging, considering that protection against a given serotype will generate long-term homologous protection, but will only provide heterologous protection in the short term, for approximately 2 years, and may even trigger the worsening of the disease during a second heterotypic infection [8]. Furthermore, the immune response adapted to the virus is not fully understood, especially because there is no accessible animal model that mirrors human immune responses after infection. [9]

Several live attenuated vaccines have been developed using the DNA technique recombinant, including the attenuated dengue virus tetraviral vaccine (DENVax), the recombinant mutant DENV-4 vaccine, with a deletion of 30 nucleotides (rDEN4Δ30), and the tetravalent dengue vaccine, with chimeric yellow fever virus 17D (CYD-TDV). In the latter, the infectious component of the DNA of the yellow fever vaccine was modified to

incorporate the structural genes of dengue. [12]

Brazil was the first country in the world to make a dengue vaccine available in the universal public system. This is the Qdanga vaccine, manufactured by the pharmaceutical company Takeda, which is made with attenuated technology and was even recommended by the WHO in October 2023, for places with high burden and transmission of the disease. Preliminary studies have shown efficacy in protecting against the four dengue serotypes in children - the results indicated an 80.2% reduction in contamination and 90.4% prevention of severe cases. The vaccination schedule involves two doses, with a three-month interval between them, and the priority, throughout 2024, includes large cities, with high transmissibility in the last 10 years, and a resident population equal to or greater than 100,000 inhabitants. Furthermore, the focus of the Brazilian Ministry of Health, in 2024, is to vaccinate children and adolescents aged 10 to 14, due to the higher number of hospitalizations due to dengue in this age group. [13] The vaccine has already been incorporated into the Immunization Program (PNI). [12]

Regarding treatment, there is no therapy specifically aimed at dengue. Therapy is solely symptomatic, with hospitalization being necessary in more severe cases, in order to replace fluids and allow blood transfusion, if necessary. [1]

Therefore, treatment is based on adequate volume replacement, considering the staging between groups A, B, C and D, according to the clinical picture [2]. Group A is characterized by the absence of spontaneous hemorrhagic manifestations, warning signs, comorbidities, social risk and special clinical conditions, in addition to a negative lasso test, and can receive outpatient follow-up. [2]

Group B involves spontaneous skin bleeding (petechiae) or induced bleeding (positive lasso test), but without warning signs. Also within stage B, specific groups include: lactating women, pregnant women and adults over 65 years of age, people with comorbidities (such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease and liver disease) and individuals with social risk. Group B should be monitored in health units with observation beds until the test results are available and a clinical reassessment is performed. [2]

Group C, in turn, has some warning signs, but does not show signs of severity, and should be monitored in an inpatient bed until stabilization. Patients in group C should initially be treated in any health service, regardless of complexity, and should be given rapid intravenous hydration and monitored in an inpatient bed until stabilization and conditions for discharge, for at least 48 hours. If there is no clinical and laboratory improvement, the management should be the same as for group D. [2]

Group D is defined by the presence of signs of shock and respiratory distress, in addition to severe organic impairment and severe hemorrhagic manifestations. Therefore, monitoring in an ICU bed is necessary until stabilization, for at least 48 hours, followed by remaining in an inpatient bed. [2]

DENGUE AND PREGNANCY

With regard to dengue, which belongs to the same family as the Zika virus, the WHO and the Pan American Health Organization recommend that strict monitoring of the risks to the mother and the fetus is necessary. In this context, the risks of obstetric bleeding are noteworthy, so pregnant women with this condition should always be questioned about the presence of fever or a history of fever in the last 7 days. According to a study conducted in Brazil, the mortality rate due to dengue in pregnant women is higher than that of non-pregnant women of childbearing age, especially in the 3rd trimester of pregnancy. Furthermore, some other Brazilian studies show that pregnant women with symptomatic infections have a higher risk of fetal death and premature birth. [2]

According to a review study published in January 2023, in order to assess the severity of dengue in pregnant women, it is necessary to pay attention to the patient's immune response, since the results may be worse in those with previous diseases or immunosuppressive conditions, such as systemic lupus erythematosus, even increasing the risk of severe dengue. The results are also influenced by access to timely diagnosis and regular prenatal care, for faster identification, treatment and control of dengue. Dengue also increases the risk of bleeding, which results in the need for supervision and adequate management during childbirth. In 7.2 to 7.9% of cases, there may be problems during labor, sometimes requiring progression to cesarean section, in cases of severe dengue or other complications. [14]

The DENV virus can cross the placenta and affect fetal circulation, which is more likely when the infection is acquired shortly before birth. Higher levels of maternal viremia increase the risk of vertical transmission, which occurs in 1 to 6% of cases. However, it is worth noting that, in the case of vaccination or even previous infection, the fetus may receive protection due to maternal antibodies, which reduce the likelihood and impact of vertical transmission. Vertical transmission may also vary according to the viral strains, the geographic region and the prevalence of dengue in the population. [14]

Regarding perinatal outcomes, this same review showed that there may be harm to fetal growth and newborn development, sometimes including intrauterine growth restriction (IUGR), increasing the risk of chronic diseases and low birth weight. Although rare, gestational dengue can result in fetal mortality, which is directly proportional to complications such as organ failure

and increased bleeding. Breastfeeding is not contraindicated in mothers with dengue fever, because there is no viral transmission through milk, and breastfeeding provides nutrients and antibodies essential for protecting the baby. [14]

A systematic review published in June 2022 analyzed 36 studies and established that DENV infection during pregnancy is associated with an increased risk of maternal mortality, stillbirths, and neonatal deaths. However, there was no statistical association between infection and preterm birth, maternal bleeding, low birth weight, and spontaneous abortion. [15]

A retrospective observational study conducted at a tertiary referral center in southern India between January 2015 and December 2018 compared adverse outcomes between pregnant women diagnosed with dengue and women hospitalized due to a fever but with a negative dengue test. During the study period, there were six maternal deaths resulting from complications of the infection, five of them due to shock syndrome and one due to hemorrhagic fever, and no deaths in the control group. [16]

Therefore, these analyses allow us to infer that there is an increase in adverse maternal and fetal outcomes in pregnant women diagnosed with dengue. Pregnancy complications can be explained by the fact that physiological changes during pregnancy, such as the procoagulant state and hemodilution, can delay the increase in hematocrit or thrombocytopenia during dengue infection. Furthermore, pregnancy complications, such as hemolysis, HELLP syndrome and preeclampsia, can make it difficult to recognize infectious complications caused by DENV. Proinflammatory mediators resulting from the infection, such as interleukin-6 and tumor necrosis factor alpha, can cause uterine contractions and premature birth, while thrombocytopenia and hemorrhagic tendency can lead to placental dysfunction and hypoxia, affecting fetal nutrition, with consequent growth restriction or even neonatal death in more severe cases.. [16]

JUSTIFICATIVE

This systematic review is justified by its purpose of studying maternal and fetal outcomes in the face of dengue virus infection during pregnancy. As stated above, some studies have shown that there is a relationship between contamination by the DENV virus during pregnancy and potential complications, such as low birth weight and maternal mortality. However, there are disagreements between the articles regarding the implications that have statistical significance when comparing infected and healthy pregnant women. Thus, the literature is not very well defined regarding the incidence and prognosis of infection during pregnancy. Because of this, the present study is relevant, even to enable

the development of new strategies aimed at preventing negative outcomes and ensuring maternal and fetal well-being. It is worth noting that, in a context of re-emergence of the dengue virus, including in Brazil, this planning is especially necessary..

OBJECTIVES

GENERAL OBJECTIVE

- To investigate the relationship between dengue infection in pregnant women and maternal-fetal outcomes, with a focus on obstetric complications and their clinical importance, in addition to neonatal outcomes, in comparison with uninfected pregnant women.

SPECIFIC OBJECTIVES

- To investigate the risk factors associated with dengue infection in pregnant women, including demographic characteristics, exposure to the mosquito vector and previous medical history.
- To analyze obstetric outcomes in pregnant women infected with dengue, including complications during pregnancy, maternal death, thrombocytopenia and postpartum hemorrhage and miscarriage.
- To evaluate neonatal outcomes in babies born to dengue-infected mothers, including prematurity, low birth weight, stillbirths and neonatal complications. - Provide evidence-based recommendations for the prevention, diagnosis and management of dengue in pregnant women, with the aim of protecting maternal and fetal health and reducing the burden of the disease in endemic areas.

METHOD

Four simultaneous searches were performed. The first, performed using PubMed (https://pubmed.ncbi.nlm.nih.gov/), used the keywords “dengue pregnancy” and obtained 188 results on April 8, 9, and 10, 2024. The second and third searches were performed in the LILACS database (https://lilacs.bvsalud.org/), using the keywords “dengue pregnancy” initially and “dengue embarazo” subsequently. In these searches, 18 and 21 articles were found, respectively, on April 10, 2024. The fourth search, finally, was carried out in Scielo (https://www.scielo.br/), with the keywords “dengue pregnancy”, obtaining only 1 article as a result, also on April 10, 2024. These four searches used articles published between 2020 and 2024 as a filter.

The exclusion of articles that would not be included in the work was initially carried

out based on the title and abstract. For this purpose, the works obtained in the four searches were equally divided between the two main researchers. The inclusion criteria were: texts that addressed pregnant women and dengue (although not exclusively), meeting the question of the work (how dengue behaves in pregnant women and what is the outcome of this infection), articles written in English, Portuguese or Spanish and studies of women at any gestational age. The exclusion criteria included: articles that did not answer the study question, analysis only of dengue seroprevalence during pregnancy (epidemiological study), studies conducted on rats, focus only on the clinical management of the infection in pregnant women (without addressing the infectious repercussions per se), focus only on vertical transmission or neonatal repercussions, and analysis only of serological markers or vaccination in pregnant women. Therefore, of the 188 articles found in the PubMed search, 152 were excluded a priori and 36 were included. In the searches performed in LILACS, the 18 articles found with the keywords “dengue pregnancy” were also included in the 21 results obtained with “dengue embarazo”, so that of these 21, 16 were excluded and 5 were included. The only article obtained in Scielo was excluded.

The exclusion was then based on the full text. Thus, of the 35 articles initially included in the PubMed search, 8 were excluded because they were paid for and one because it did not meet the objectives of the study. The result was 27 articles included in this database. The 5 texts included from the LILACS search were maintained, on the other hand. Thus, in the end, 32 articles were obtained for a more detailed study.

These 32 articles were finally divided again between the two main researchers for analysis, with the most relevant information described in a summary table. Such data were subdivided into: identification of the article (DOI, year, location and type of article); population studied (number of patients, predominant age, race, trimester of pregnancy, comorbidities and co-infection), clinical and laboratory findings and outcomes (maternal outcome, fetal outcome and treatment in pregnant women).

RESULTS

Of the 32 articles included in the study, 6 were published in 2020, 6 in 2021, 8 in 2022, 10 in 2023 and 2 in 2024.

Regarding the place of origin, there was a predominance of articles from India, with 9 in total. In addition, 7 multicenter articles were found, two of which specified the locations: one used data from Asia, Latin America and Africa, while the other referred only to Southwest Asia (Brunei, Myanmar, Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand and Vietnam). There were also 4 Brazilian articles, three of

which detailed the states of origin: Paraná, Recife and Ceará, in addition to 3 articles from Mexico and 2 from Indonesia. Finally, one article was found from each of the following countries: Burkina Faso, Peru, Sri Lanka, Nigeria, Australia and Pakistan, while one article did not specify its country of origin.

From the point of view of the study design, there was a predominance of case reports, with 9 in total. In addition, 8 reviews, 7 retrospective studies, 6 prospective studies, one meta-analysis and one observational study with two phases (the first cohort and the second cross-sectional) were found.

The number of patients studied ranged from one, in 7 of the 9 case reports found, to 2,121,582, in a retrospective study. 9 articles did not specify the number of patients involved. Furthermore, one article was found with each of the following samples: 3, 4, 41, 57, 62, 91, 136, 181, 216, 424, 780, 1,006, 27,605, 39,632 and 94,832. It is worth mentioning that not all patients included in the articles were, in fact, diagnosed with dengue, since this varied according to the study design.

With regard to age, there was a predominance of women between 20 and 39 years old, which coincides with the fertile period. For example, the Brazilian retrospective study that studied 2,121,582 women determined that 70.3% of dengue cases were concentrated between 20 and 39 years old. [17] Six articles outlined the mean ages, which were: 24.5 with a standard deviation (SD) of 0.71 (range 18 to 37 years); 26 in phase 1 (range 18 to 35 years) and 27.4 years in phase 2 (with the same range); 26.5 years, with an SD of 3.6; 27.1 with an SD of 6.23 (range 16 to 49 years); 28.6 with an SD of 2.88 (range 18 to 37 years); 29 (range 15 to 49 years). Regarding the variation in outcomes according to age group, only two studies were able to establish a relationship: one of them found that all age groups increase the risk of hospitalization, compared with the period between 10 and 19 years. This study used a sample of 16% pregnant women and 19.8% non-pregnant women aged 10 to 19 years; 48.6% pregnant women and 26.7% non-pregnant women aged 20 to 29 years; 27% pregnant women and 27.7% non-pregnant women aged 30 to 39 years; 8.4% pregnant women and 25.8% non-pregnant women aged 40 to 49 years. [18] The other study found a higher risk of adverse effects between the ages of 26 and 35 years, based on a sample with 42.28% of patients aged 16 to 25 years; 47.74% aged 26 to 35 years; and 9.98% aged 36 to 49 years. [19] Ten studies did not specify the ages of the patients studied.

Only 4 of the 32 articles included detailed the race of the patients. In the retrospective cohort study that included 27,605 patients with confirmed dengue, of whom 949 (3.49%) were pregnant and 26,656 were non-pregnant, 20,082 (72.3%) were white, of

whom 689 (72.6%) were pregnant and 19,393 (72.8%) were non-pregnant, that is, there was no significant difference between the groups in terms of race. Another 6,307 were black, of whom 216 (22.8%) were pregnant and 6,091 (22.9%) were not. [17] The prospective study carried out in Recife, Brazil, analyzed blood samples from 780 women who were admitted to the maternity ward at 27 weeks or more of gestation, were 15 years of age or older and had some obstetric complication. Of these patients studied, 480 (61.7%) were of mixed race, 157 (20.2%) were white, 141 (18.1%) were black, and 2 did not specify. [20] The Brazilian retrospective study carried out with 2,121,582 women of childbearing age was divided into: 26.9% white women, 3.9% black, 0.9% yellow, 33.5% brown, 0.3% indigenous, 23.5% of unknown race and 11% omitted in the system. Also according to this same study, 32.2% of dengue cases occurred in whites and 43.3% in mixed race. [17] Furthermore, the prospective study carried out with 1006 Nigerian women defined that they were all black[17].

In terms of gestational age, there is a clear predominance of patients in the 3rd trimester of pregnancy. In a prospective study conducted in India, for example, the average was 31.89 weeks, with a standard deviation of 7.31, being: 2 pregnant women in the 1st trimester (4.5%); 5 in the 2nd trimester (11.4%) and 37 in the 3rd trimester (84.1%) [22]. Two articles identified a higher risk of poor outcomes in the 3rd trimester of pregnancy - in one of them, the rate corresponded to 34.78% of cases, followed by the 2nd trimester, with 25.78% [19] In another, with a distribution of 4.9% of pregnant women in the 1st trimester of pregnancy, 17.1% in the 2nd and 78% in the 3rd, of the 6 maternal deaths, 1 occurred in the 1st trimester and 5 in the 3rd. [19] However, 12 articles did not specify the gestational age of the patients studied. It is also worth mentioning that, in one of the studies, there was a predominance of non-pregnant women (51%), since the inclusion criterion was being of childbearing age and having been notified with dengue [17]. Furthermore, one of the case reports addressed a woman on the 8th postnatal day, with fulminant hepatitis induced by dengue. [23]

Only 5 of the 32 articles detailed the comorbidities of the women included. In one of them, 5.3% of pregnant women and 4.8% of non-pregnant women had at least one comorbidity. Diabetes Mellitus was present in 1.7% of pregnant women and 1.1% of non-pregnant women; hematologic diseases, in 0.6% of pregnant women and 0.4% of non-pregnant women; liver diseases, in 0.2% of pregnant women and 0.5% of non-pregnant women. Furthermore, 0.3% of both groups had chronic kidney disease, 2.6% of pregnant women and 3% of non-pregnant women had hypertension, 0.3% of pregnant women and 0.5% of non-pregnant women had acid-peptic disease; and 0.4% of pregnant women and

0.5% of non-pregnant women had autoimmune diseases. This same study found that diabetes mellitus increased the risk of hospitalization. [18] In another study, of the 216 pregnant women with fever included, 12 (27.2%) had anemia, 10 (22.7%) had hypothyroidism, 2 (4.5%) had hypertension, and 2 (4.5%) had diabetes mellitus. [22] Regarding the case reports, only one of them detailed the patient's previous comorbidities: gestational diabetes mellitus. [24]

Regarding co-infection by other agents, in a prospective study conducted in Recife, of the 780 patients studied, 16.6% had recent or active arbovirus infection, of which 2.3% (3) had active/recent dengue infection, 41.5% (54) had ZIKV infection, 53.1% (69) had CHIKV infection, and 3.1% (4) had active/recent dual infection (CHIKV and ZIKV). [20]. A prospective study conducted in Mexico revealed 11 co-infections with DENV and CHIKV, 3 with DENV and ZIKV, 2 with ZIKV and CHIKV, and 2 with DENV, ZIKV, and CHIKV. [25] One review study reported a co-infection with dengue and malaria [26], while a case report conducted in Fortaleza described a co-infection with dengue and chikungunya [27]. A prospective Nigerian study found significant co-infections with ZIKV, DENV, and CHIKV, comprising 24.5% of all IgM-positive infections. Among the co-infections, 67.3% included CHIKV and DENV and 18.4% ZIKV and CHIKV. [21]

From a clinical point of view, the most common symptom was fever, cited in 19 studies, with a duration ranging from 2 days to 2 months. According to a prospective Indian study, the median was 37.7°C, and fever was present in 100% of the patients included [22]. Other very common signs and symptoms were: headache (cited in 11 studies), myalgia (verified in 10 articles, with an estimated prevalence of 90.9% [22] in the Indian study), arthralgia (9, with a prevalence of 88.6% [22]), vomiting (6, with a prevalence of 47.5% [22]). Retro-orbital pain (5), exanthema (skin rash) (5), jaundice (3, with an estimated prevalence of 2.3% [22]), hypertension (3, considering blood pressure greater than or equal to 140x100mmHg), tachycardia (3, considering heart rate greater than 100bpm), asthenia (2), dyspnea (2, with a prevalence of 6.8% [22]), abdominal pain (3), petechiae (2), ascites and fluid thrill (2), edema and weight gain (2), conjunctivitis (1), rash (1), hypotension (1, considering blood pressure less than or equal to 90x60mmHg), splenomegaly (1), chest pain (1), and gum bleeding (1). Regarding the sensory system, the estimated prevalence of behavioral changes was 9.1% [22], with 2 studies reporting seizures (with an estimated prevalence of 2.3% [22]), and one article reporting each of the following conditions: encephalopathy and loss of consciousness (also prevalence of 2.3% [22]). There were also reports of asymptomatic pregnant women in 2 studies and of one pregnant woman with uterine contractions.

From a laboratory perspective, the most prevalent alteration was thrombocytopenia, described in 10 articles. Furthermore, 4 reported an increase in TGO and TGP, indicating alterations in liver function, 2 described leukopenia, 2 reported leukocytosis, and 2 referenced anemia (here considering hemoglobin below 10mg/dL). One study addressed an increase in bilirubin and another, an increase in LDH. According to a retrospective Indian study, patients with dengue fever in late pregnancy had a lower platelet count (92,564.10 ± 388 vs 110,777.78 ± 340) (p-value = 0.435). TGO and TGP were also higher in patients with dengue fever at the end of pregnancy (149.03/156.77), with a significant difference for TGP (p-value = 0.048) [28].

Regarding maternal outcomes, the occurrence of thrombocytopenia was very frequent and cited in 12 of the 32 articles, with a prevalence ranging from 29.3% to 96.5% of patients, depending on the study evaluated [29, 30]. Also cited in 12 different articles, the progression to death was a very significant and worrying outcome, which affected from 0.2% of pregnant women in a retrospective study of SINAN with 2,121,582 women of childbearing age to 15.9% in an Indian prospective study with 216 pregnant women with fever, of which 44 were positive for dengue fever [22]. However, one study considered this outcome to be uncommon, being more related to delayed diagnosis, insufficient medical care, or consequences, including organ failure or significant bleeding [14]. Spontaneous abortion was also frequently cited in the studies and was mainly related to earlier gestational ages, exemplified by a retrospective Indian article, in which the prevalence reached 71.4% in pregnant women with dengue before 12 weeks of gestational age. [28] In this context, postpartum hemorrhage was found in 10 articles with a range of 2.5% to 25% of cases; next, the need for cesarean delivery was reported in 8 studies, some of them in the emergency context. Next, severe forms of dengue were addressed in 7 studies, showing that pregnant women have a higher risk when compared to non-pregnant women [18], with a greater relationship with the 3rd trimester and with DENV 4 [31]. Other less common outcomes were: pre-eclampsia (cited in 5 studies), placental abruption (4), dengue with warning signs (verified in 4 articles and having a greater impact at the beginning of pregnancy [28]), dengue hemorrhagic fever (3), dengue with complications (1), ICU admission (3), shock (3), fulminant hepatic failure (2), acute renal failure (2), acute respiratory distress syndrome (3), vaginal hemorrhage (2), generalized tonic-clonic seizure (2), labor with dystocia (2), HELP syndrome (1), gestational diabetes mellitus (1), DIC (1), threatened abortion (1), complications (1), encephalopathy (1), pregnancy-induced hypertension (1), severe postpartum sepsis (1), and hemophagocytic syndrome (1).

From the point of view of fetal outcomes, it is worth noting that only 20 articles

provided information on this subject. Among them, prematurity was cited 12 times and was the most common outcome, ranging from 5.1% of cases, when the virus is acquired after 24 weeks of gestational age, to 42.3% in a retrospective Indian study [30]. In this context, stillbirths were also another frequent repercussion, having been addressed in 11 different studies, with a prevalence of 10.3% after 24 weeks of gestation [28]. These data were followed by neonatal deaths, which were detailed in 7 articles, with a maximum occurrence of 16.7% in a 2022 article from Pakistan; and by low birth weight, which was described in 8 different studies, with a prevalence of 29.5% [22]. Oligoamnios was another frequent finding, which was evidenced in 5 different studies and was shown to be more relevant when dengue infection occurs before 24 weeks when compared to later infection (66.7% x 17.9%) [28]. Regarding the transmission rate, this was discussed in 5 articles, with data converging on a higher incidence when the virus is acquired in the third trimester, mainly 15 days before delivery. Finally, less prevalent manifestations were: fetal growth restriction (cited in 4 articles, with 55.6% of cases before 24 weeks [28]), need for ICU admission (2 studies), need for mechanical ventilation (1), asphyxia (1), encephalitis (1), poor general condition at birth (1), severe neonatal infection (1) and neurodevelopmental disorders (2). Congenital malformations are not consistently associated and have only been reported in one small study.

Finally, regarding the treatment given to pregnant women infected with the dengue virus, only 12 articles highlighted what was done. It is worth noting that among these, the majority were case reports, totaling 8, followed by 3 reviews and 1 prospective study. In this context, supportive measures such as fluid replacement therapy, use of analgesics such as Paracetamol, and careful observation were the most adopted measures, being described in 8 different studies, accompanied by transfusion of platelet concentrate, which was detailed in 7 articles. In this scenario, blood transfusion, fresh frozen plasma, and cryoprecipitate were also used, 4, 2, and 1 times, respectively. Corticosteroids were addressed in 7 texts, with their use varying between methylprednisolone, prednisolone, and dexamethasone; antibiotic use was mentioned twice. For specific cases, measures such as a postpartum balloon to control bleeding, Mg sulfate to prevent eclampsia, Nifedipine, and Hydralazine to control blood pressure, and the combination of benzodiazepine, sulfate, and Nifedipine for convulsions were necessary. Finally, ursodeoxycholic acid and vitamin B12 were mentioned in only 1 article, while ICU admission was necessary 4 times.

DISCUSSION

Based on the results obtained in this research, it is clear that there is a growing

concern regarding the behavior of dengue infection in pregnant women, which is evident from the number of articles found. [4]

Regarding the public included in the articles studied, it is not possible to establish a relationship between the color and age of patients with the highest profile of involvement or with the worst outcomes due to dengue infection, since few studies included this data. Co-infections, mainly by Zika virus and chikungunya, seem to be relatively common in the context of dengue infection, but it is also difficult to establish a conclusion, given the scarcity of data.

Regarding previous comorbidities, it is assumed that pregnant women with underlying health problems, such as diabetes, hypertension, or immunological diseases, are more likely to develop severe dengue. [32] However, since few articles detail the comorbidities of the public included, this analysis does not allow us to reach any conclusion in this regard.

Regarding clinical presentation, it is known that pregnancy itself can make it difficult to diagnose dengue because the infection can overlap or even compensate for the physiological changes of pregnancy. [18] Furthermore, although some studies have cited fever, headache, myalgia, and arthralgia in the clinical presentation of pregnant women, it is known that the characteristic clinical picture of dengue is less evident in pregnant women than in the rest of the population. [18] In this sense, it is worth noting that none of the 32 articles analyzed cited the positive loop test.

From a laboratory point of view, thrombocytopenia is more common in pregnant women than in other sectors of the population, having been described in several articles analyzed. Another very prevalent change is the increase in liver enzymes (AST and ALT). In this sense, differentiating dengue infection from HELLP syndrome can be quite challenging, since the latter is characterized by hemolysis, elevated liver enzymes, and thrombocytopenia, and may coincide with the clinical presentation of dengue. [23]

There may be progression to postpartum hemorrhage, severe forms of dengue fever, or even maternal death, as was evident in many of the articles reviewed. Death generally occurs due to activation of the immune system, with consequent release of cytokines/chemokines, autophagy of endothelial cells, and apoptosis of T cells. This causes plasma leakage, contraction of intravascular volume, and loss of fluid to the third space. Thus, it may progress to intravascular volume depletion, shock, organ hypoperfusion, and multiple organ dysfunction syndrome. [23]

In this regard, maternal outcomes appear to be worse in the 3rd trimester of pregnancy, since 2 of the studies analyzed reported a greater progression to death in this

period. It is worth mentioning, in this context, that diagnosis may be even more difficult in advanced stages of pregnancy, due to the increase in plasma volume of approximately 40% at the end of the 3rd trimester, with resulting dilutional anemia, which masks the hemoconcentration characteristic of dengue [33] and may underestimate the infectious load [29]. Furthermore, pregnancy itself involves a reduction in the inflammatory response, with immunological changes, to improve fetal tolerance and, thus, may increase the risk of infectious complications.[34].

In terms of fetal repercussions, some studies have detected a relationship between dengue infection and an increased risk of miscarriages and stillbirths, but it is not known whether fetal loss is secondary to hyperthermia or to the action of the DENV virus itself. It is also noted that several articles have reported an association with fetal growth restriction, prematurity, and low birth weight. Thus, although there is no consensus on this subject until further clarification is made, it is important to adequately monitor fetal growth, paying special attention to low birth weight and prematurity. [26] On the other hand, there appears to be no relationship between the action of DENV and fetal malformations.

Regarding the mode of delivery, there is no preferred method. However, the American College of Obstetrics and Gynecology (ACOG) recommends that platelet transfusions be performed to maintain platelet counts above 50,000 before major surgeries (such as cesarean section) and above 70,000 for epidural and spinal anesthesia. This is done to reduce the risk of postpartum hemorrhage. [33] It is essential to pay attention to symptoms that are initially benign, such as fever, and to investigate dengue even in asymptomatic or oligosymptomatic pregnant women, especially in endemic areas [23]. In addition, it is interesting that sentinel maternity units be created to monitor vertical transmission and potential adverse maternal-fetal outcomes of DENV infection, based on clinical and laboratory screening [20], since there is still no consensus on this subject..

CONCLUSION

Dengue fever in pregnant women is a significant concern due to the potential risks to both the mother and the fetus. Dengue virus infection during pregnancy can lead to serious complications, including thrombocytopenia, severe hemorrhage, and even maternal death. In addition, it has also been associated with adverse impacts on fetal development, such as prematurity, oligohydramnios, and fetal death. The complexity of dengue fever in pregnant women is compounded by the difficulty in differentially diagnosing symptoms, which can often be masked by physiological changes during pregnancy. In this sense, it is interesting that a national guideline be established for the management of dengue fever in pregnant

women since many health professionals are unfamiliar with the potential complications associated with it. Optimal management involves early diagnosis, appropriate serological testing, careful monitoring of fluid and hemodynamic status, and prevention of progression to more severe forms of the disease. In addition, it is crucial to implement robust preventive measures, such as effective control of the Ae. aegypti and educational programs aimed at pregnant women in endemic areas.

This systematic review stands out for having brought together articles from different countries and clinical designs, allowing for a deeper understanding of the maternal-fetal repercussions of dengue, which have not yet been fully elucidated. However, it has some limitations, since not all women included in the articles analyzed had dengue or were pregnant, as this varied according to the objectives and methodologies of the studies. Furthermore, some studies were conducted only in hospitals, which may have overestimated the complications resulting from the infection, while others were affected by the omission of data from the notification forms sent to SINAN, in the face of suspected DENV infection.

In short, addressing the challenges posed by dengue in pregnant women requires a multidisciplinary and collaborative approach between health professionals, researchers, and public health authorities. Therefore, continued research is crucial to expand and deepen knowledge about the effects of dengue infection in pregnancy and to develop effective prevention and clinical management strategies, with further studies being needed to elucidate issues not yet fully clarified by this review.

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