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

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ABSTRACT

INTRODUCTION: Dengue is an acute febrile disease, caused by the DENV virus and transmitted mainly by mosquitoes of the genus Aedes. It is an endemic pathology mostly 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 the accumulation of fluid, which is gradually reabsorbed in the recovery phase. The diagnosis of dengue is made after the detection of the NS1 antigen; genome, by RT-PCR; or IgM or IgG antibodies. Treatment is symptomatic only. During pregnancy, studies suggest that there is an increase in adverse maternal-fetal outcomes in the face of DENV infection, in addition to challenging diagnosis, due to pregnancy physiological adaptations. In this context, this systematic review aims to analyze how dengue behaves in pregnant women and the outcome of the infection. METHODS: searches were performed in PubMed, with 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. RESULTS: 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 fever in pregnancy increases the risk of severe forms of the disease, postpartum hemorrhage, maternal death, miscarriage, stillbirths, fetal growth restriction, prematurity and oligohydramnios, especially in the face of infections acquired in the 3rd 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, more studies are still needed for further study, since there is no consensus.

Keywords: Dengue. Gestation. Arbovirus. Fever.

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INTRODUCTION

DEFINITION

Dengue is an acute infectious disease, caused by an arbovirus and transmitted by arthropods, especially by the mosquito of the genus Aedes, especially the species *Ae. aegypti*. The disease presents a systemic and dynamic picture, with a wide spectrum of clinical manifestations, ranging 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]. In addition, dengue can be considered a global public health problem, both because of its occurrence around the globe, endemic, sporadic or in the form of epidemics, but also because of its significant epidemiological and economic impact [1, 2,3].

The dengue virus, DENV, belongs to the family Flaviviridae and the genus Flavivirus, having four different serotypes (DENV 1-4), each having distinct genotypes and lineages [1, 2, 3].

In addition, the dengue virus is characterized by being enveloped with icosahedral symmetry, with 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), as well as eight non-structural proteins (NS). In this context, structural glycoprotein E is related to cell recognition and promotion of entry, while NS proteins aid in the replication of the viral genome [3].

EPIDEMIOLOGY

Dengue is one of the main vector-borne diseases, representing an important public health problem in the world, and about half of the world's population is 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 declared dengue as one of the "top ten threats to global health" that year, which reiterates its relevance, seriousness, and potential health impact [3]. In addition, dengue is considered endemic in more than 100 countries, with a predominance in tropical and subtropical areas, such as the regions of 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 corresponds to approximately 70% of the global burden of the disease. [4]

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

Regarding the most current data, the year 2023 was the year with the highest number of dengue cases recorded in the region of the Americas, with a total of 4,565,911 cases and 2,340 deaths [5]. This situation extended until 2024, in which data from epidemiological week 1 to 5 show a 157% increase in the number of cases compared to the same period in 2023 and 225% 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 was maintained [6].

Still in 2024, at the time of this study, there are 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 relation to race, browns are related to 39.8% of the cases, followed by white (36.7%), without information (16.3%) and blacks (5.7%). In terms of age, the infection is more prevalent in the age group of 20 to 29 years, in both sexes, and more severe in the age group from 80 years old. Finally, the most affected states are the Federal District, Minas Gerais, Espírito Santo, Paraná and Goiás. [6]

PATHOPHYSIOLOGY

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

In their mature form, viruses can circulate freely in plasma or inside monocytes/macrophages, cells for which DENV has tropism and are the largest sites of viral replication, as well as in striated, smooth muscle cells, fibroblasts and local lymph nodes. In this scenario, general symptoms such as fever and malaise coincide with the period of viremia, when serum levels of cytokines are elevated. High serum levels of

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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 innate and adaptive immune responses during the invasion of viral particles. These cells have the target antigen T cells, especially TCD8 and TCD4, as a starting point for the innate immune response [8].

In addition, the complement system is of great relevance to block 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 its activation. As a consequence, this alters the functionality of the add-on components and inhibits 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 still a paradoxical immune response mechanism, which harms the infected individual and is responsible for the immunopathology of dengue hemorrhagic fever. This occurs after sequential DENV infections, in which the antibodies previously produced by infection by another viral type do not neutralize the second infecting virus and amplify the infection, making it easier for the new infecting type to penetrate macrophages. This is the phenomenon of facilitation by antibodies of viral penetration in macrophages, which leads to their activation by lymphocytes and aggression by cytotoxic cells, resulting in the release of thromboplastin, initiating coagulation phenomena and release of proteases that activate complement, causing cell lysis and shock [7].

In summary, dengue hemorrhagic fever 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 the production of antibodies, the 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. On the other hand, the antibodies produced against NS1 promote viral lysis by fixing the complement, however, they are not able to neutralize the viral particles, acting as mediators of cytotoxicity phenomena by lymphocytes, through their receptors for

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the Fe portion of immunoglobulins. In addition, 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 with the virus occurs, acquired immunity is permanent and long-lasting for a specific serotype (homologa). In addition, through the mechanism of cross-immunity (heterologous), the individual also acquires partial protection against the infection caused by the other three serotypes of DENV, 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 has similarities ranging from 40–50% to other flaviviruses [2, 3].

LIFE CYCLE

The main form of transmission of dengue to humans, in the urban cycle, is by the vector route, through the bite of infected *Ae. aegypti* females, in the human-vector-human cycle [2]. This is initiated 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 spread 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].

Still 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 disordered occupation that provides more breeding grounds for females to spawn. In this context, the main breeding sites are water tanks, jerry cans and barrels, but also small reservoirs such as potted plants, clogged gutters, bottles, open garbage, among others. It is in these places, associated with clean and still water, that the female mosquito can lay her eggs, on the wall of the breeding sites, very close to the surface of the water [10].

Regarding mosquito activity, it is more active in the early morning and at dusk, these being 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 eggs and their maturation in the ovaries [5, 10].

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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 course in most cases. However, some can progress to 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 usually fever above 38ºC, but this can vary from 39 to 40ºC, with an abrupt onset and lasting from two to seven days. There may also be associated anorexia, nausea, vomiting and diarrhea, in addition to maculopapular rash, especially in 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. Alarm signs, resulting from increased capillary permeability, can progress to shock due to plasma extravasation, severe hemorrhages, and severe organ dysfunction. Some of the alarm signs are: severe abdominal pain (referred to or on physical examination), continuous vomiting, fluid accumulation (ascites, pleural effusion, pericardial effusion), postural hypotension and/or lipothymia, lethargy and/or irritability, hepatomegaly greater than 2cm below the costal margin, mucosal bleeding and progressive increase in hematocrit [2]. Thinking about the early identification of alarm signs, it is essential to test the snare, even in the suspicion of dengue.

Thus, as mentioned above, without adequate management of the critical phase, patients progress to severe forms of dengue, marked by shock, fluid accumulation due to 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, usually between the 4th and 5th day of illness. Shock settles quickly and lasts quickly, so that the patient can die in 12 to 24 hours.

The third characteristic period of dengue 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 in the following 48 to 72 hours. As a result, there is an improvement in general condition and appetite, a decrease in gastrointestinal symptoms, hemodynamic stabilization, and an improvement in

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urine output. The rash may remain in 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 for the diagnosis of DENV and that genomic techniques be used with direct detection of the virus in mind. [1]

From the simple suspicion, it is necessary to collect a blood sample for diagnosis. Within 8 days (preferably 5) after the onset of symptoms, blood samples should be processed for NS1 detection, and for genome and serotype detection, by the RT-PCR technique. From 8 to 15 days after the beginning of the condition, the search for IgM is carried out, using the ELISA technique; and, after 15 days, the search for IgG. [1]

Non-structural protein 1 (NS1) is a highly conserved glycoprotein, present in high concentrations in the serum of patients infected with the virus and, therefore, can be identified soon after the onset of acute symptoms and before antibody positivity. It is a direct method for diagnosis.

[2] Considering that the detection of NS1 is quite specific, but not so sensitive, negative samples for this antigen cannot be considered negative for dengue, and must be confirmed by the detection of IgM and IgG. [1]. In addition, thinking about potential differential diagnoses, all negative samples for dengue are screened for zika virus and then for chikungunya. [1] Other indirect diagnostic methods include: demonstration of seroconversion in antibody titers by hemagglutination (HI) inhibition; 4x change in the titer of the plaque reduction neutralization test (PRNT), in paired samples, the first being collected from the 6th day of symptom onset and the second 15 days after the first; or anatomopathological, with histopathological and search for viral antigens 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 mosquito reproduction, in addition to the use of insecticides and repellents, composed of N,N-diethyl-3-methylbenzamide (DEET), which is very effective against the mosquito. Vector control is based on the assumption that

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by reducing the concentration below the entomological threshold, transmission can be delayed [9].

Dengue control in the country faces difficulties and challenges such as: bureaucracies 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 even favors the accumulation of water in peridomiciliary environments. In addition, in order for the population to avoid the accumulation of standing water at home, it is necessary to carry out periodic epidemiological surveillance and raise awareness among residents about the importance of this measure. Because of these challenges, despite robust government investment, a reduction in vector density that could reduce the spread of the disease has not been noted in recent years. [1]

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

Several live attenuated vaccines have been developed using the recombinant DNA technique, including the tetraviral attenuated dengue virus vaccine (DENVax), the recombinant mutant vaccine DENV-4, 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. It is the Qdanga vaccine, manufactured by the pharmaceutical company Takeda, which is made with attenuated technology and even became recommended by the WHO in October 2023, for places with a 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% in the prevention of severe cases. The vaccination schedule involves two doses, with an interval of three months between them, and the priority, throughout 2024, includes large municipalities, with high transmissibility in the last 10 years,

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and a resident population equal to or greater than 100 thousand inhabitants. Furthermore, the focus of the Brazilian Ministry of Health, in 2024, is to vaccinate children and adolescents aged 10 to 14 years, 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]

With regard to treatment, there is no therapy specifically aimed at dengue. Therapy is only symptomatic, and hospitalization is necessary in more severe cases in order to replace fluids and enable blood transfusion, if necessary. [1]

Thus, 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, alarm signs, comorbidities, social risk and special clinical conditions, in addition to negative snare test, and can receive outpatient follow-up, in this way. [2]

Group B involves spontaneous (petechiae) or induced (positive snare test) bleeding, but no alarm signs. Also within stage B, specific groups include: breastfeeding 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 diseases) and individuals at social risk. Group B should be monitored in health units with observation beds until the test results come out and clinical reassessment is carried out. [2]

Group C, in turn, has some alarm sign, but does not show signs of severity, and should be monitored in a hospital bed until stabilization. Patients in group C should be initially treated in any health service, regardless of complexity, and rapid intravenous hydration and follow-up in a hospital bed until stabilization and conditions for discharge should be performed for at least 48 hours. If there is no clinical and laboratory improvement, the conduction should be the same as in group D. [2]

Group D is defined by the presence of signs of shock and respiratory distress, as well as severe organic impairment and severe hemorrhagic manifestations. Thus, it is necessary to follow up in an ICU bed until stabilization, for at least 48 hours, followed by the stay in an inpatient bed. [2]

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DENGUE AND PREGNANCY

With regard to dengue, which belongs to the same family as Zika virus, the WHO and the Pan American Health Organization recommend that strict observation is necessary in relation to the risks to the mother and the fetus. In the meantime, the risks of obstetric bleeding are highlighted, so pregnant women with this condition should always be questioned about the presence of fever or history of fever in the last 7 days. According to a study carried out in Brazil, dengue lethality in pregnant women is higher than that of non-pregnant women of childbearing age, especially in the 3rd trimester of pregnancy. In addition, 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 proper supervision and management during childbirth. In 7.2 to 7.9% of cases, there may be problems during labor, sometimes with the need to progress to cesarean section, in case of severe dengue or other complications. [14]

The DENV virus has the ability to cross the placenta and affect the fetal circulation, which is more likely when the infection is acquired right before delivery. 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 case of vaccination or even previous infection, the fetus can receive protection due to maternal antibodies, which reduce the probability and impact of vertical transmission. Vertical transmission can also vary according to the viral strains, geographic region, and the prevalence of dengue in the population. [14]

Regarding perinatal outcomes, this same review showed that there may be impairment to fetal growth and development of the newborn, sometimes even with intrauterine growth restriction (IUGR), increasing the risk of chronic diseases and low birth weight. Although rare, gestational dengue can lead to fetal mortality, which is directly proportional to complications such as organ failure and increased bleeding. Breastfeeding is not contraindicated in mothers with dengue, because there is no viral transmission

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through milk, in addition to the practice of breastfeeding providing essential nutrients and antibodies for the protection of the baby. [14]

A systematic review, published in June 2022, analyzed 36 studies and established that DENV infection in pregnancy is linked to 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 miscarriage. [15]

A retrospective observational study, conducted at a tertiary referral center in southern India, between January 2015 and December 2018, compared the adverse outcomes between pregnant women diagnosed with dengue and women hospitalized due to a febrile condition but tested negative for dengue. During the study period, there were six maternal deaths due to 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 because the physiological changes of pregnancy, such as the procoagulant state and hemodilution, can delay the increase in hematocrit or thrombocytopenia during dengue infection. In addition, pregnancy complications, such as hemolysis, HELLP syndrome, and preeclampsia, may hinder the recognition of infectious complications caused by DENV. The pro-inflammatory mediators resulting from the infection, such as interleukin-6 and tumor necrosis factor alpha, can generate 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]

JUSTIFICATION

This systematic review is justified because it proposes to study 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 among the articles regarding the implications that have statistical significance when comparing infected pregnant women 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,

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even to enable the thought of new strategies aimed at preventing negative outcomes and ensuring maternal and fetal well-being. It is worth mentioning that, in a context of reemergence 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, focusing on obstetric complications and their clinical importance, as well as neonatal outcomes, compared to uninfected pregnant women.

SPECIFIC OBJECTIVES

- To investigate the risk factors associated with dengue infection in pregnant women, including demographic characteristics, exposure to mosquito vectors, and past 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 assess neonatal outcomes in infants 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-fetal health and reducing the burden of the disease in endemic areas.

METHOD

Four concomitant searches were carried out. The first of them, executed from PubMed (https://pubmed.ncbi.nlm.nih.gov/), used, as keywords, "dengue pregnancy" and obtained 188 results, on April 8, 9 and 10, 2024. The second and third were carried out in the LILACS database (https://lilacs.bvsalud.org/), using the keywords "dengue pregnancy", at first, and "dengue embarazo", a posteriori. In them, 18 and 21 articles were found, respectively, on April 10, 2024. The fourth search, finally, was made 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.

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The exclusion of articles that would not be included in the work was initially carried out based on the title and abstract. To this end, the studies obtained in the four studies were equally divided between the two main researchers. The inclusion criteria were: texts that addressed pregnant women and dengue (although not exclusively), taking into account the question of the study (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 involved: articles that did not answer the question of the study, analysis only of dengue seroprevalence in pregnancy (epidemiological study), studies carried out in rats, focus only on the clinical management of infection in pregnant women (without addressing the infectious repercussion itself), focus only on vertical transmission or neonatal repercussions, and analysis only of serological markers or vaccination in pregnant women. Therefore, of the 188 articles reached in the PubMed search, 152 were excluded, a priori, and 36 were included. In the searches carried out in LILACS, the 18 articles found with the keywords "dengue pregnancy" were also included in the 21 results obtained with "dengue pregnancy", so that, of these 21, 16 were excluded and 5 were included. The only article obtained from Scielo was excluded.

It was then decided to exclude 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 they did not meet the objectives of the study. The result of 27 articles included in this database was then reached. 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 to be analyzed, with the description of the most relevant information in a file table. These data were subdivided into: article identification (DOI, year, place, and type of article); study population (number of patients, predominant age, skin color, trimester of pregnancy, comorbidities, and co-infection), clinical and laboratory status, and outcomes (maternal outcome, fetal outcome, and treatment in pregnant women).

RESULT

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 all. In addition, 7 multicenter articles were found, two of which specified the localities: one

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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 detail 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 all. In addition, we found 8 reviews, 7 retrospective studies, 6 prospective studies, one meta-analysis, and one two-phase observational study (the first cohort and the second cross-sectional).

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. In addition, 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.

Regarding age, there was a predominance of women between 20 and 39 years of age, which coincides with the fertile period. As an example, the Brazilian retrospective study that studied 2,121,582 women defined that 70.3% of dengue cases were concentrated between 20 and 39 years of age. [17] 6 articles outlined the mean ages, as follows: 24.5 with standard deviation (SD) of 0.71 (range from 18 to 37 years); 26 in phase 1 (range from 18 to 35 years) and 27.4 years in phase 2 (with the same range); 26.5 years, with SD of 3.6; 27.1 with an SD of 6.23 (range 16 to 49 years); 28.6 with SD of 2.88 (range 18 to 37 years); 29 (range from 15 to 49 years). Regarding the variation in outcomes according to age group, only 2 studies were able to establish a relationship: one of them found that all age groups increase the risk of hospitalization, compared to the period between 10 and 19 years. This study used a sample of 16% pregnant women and 19.8% non-pregnant women between 10 and 19 years old; 48.6% pregnant and 26.7% non-pregnant, aged 20 to 29 years; 27% pregnant and 27.7% non-pregnant, aged 30 to 39 years; 8.4% pregnant and 25.8% non-pregnant, between 40 and 49 years old. [18] The other study found a higher risk of adverse effects between 26 and 35 years of age, based on a sample of 42.28% of

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patients between 16 and 25 years of age; 47.74% from 26 to 35 years old; and 9.98% from 36 to 49 years old. [19] 10 studies did not specify the ages of the patients studied.

Only 4 of the 32 articles included detailed the color of the patients. In the retrospective cohort study that included 27,605 patients with confirmed dengue, 949 (3.49%) pregnant and 26,656 non-pregnant, 20,082 (72.3%) were white, 689 (72.6%) pregnant and 19,393 (72.8%) non-pregnant, i.e., there was no significant difference between the groups in terms of color. Another 6,307 were black, of whom 216 (22.8%) were pregnant and 6091 (22.9%) were not. [17] The prospective study conducted in Recife, Brazil, analyzed blood samples from 780 women who were admitted to the maternity hospital at 27 weeks or more of gestation, were 15 years of age or older, and had an 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 conducted 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% unknown race and 11% missing from the system. Also according to this same study, 32.2% of dengue cases occurred in whites and 43.3% in browns. [17] In addition, 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 carried out in India, for example, the mean was 31.89 weeks, with a standard deviation of 7.31, with 2 pregnant women in the 1st trimester (4.5%); 5 in the 2nd quarter (11.4%) and 37 in the 3rd quarter (84.1%) [22]. Two articles identified a higher risk of poor outcomes in the 3rd trimester of pregnancy - in one of them, the index corresponded to 34.78% of cases, followed by the 2nd quarter, 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 trimester 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 to be of childbearing age and to have been notified with dengue [17]. In addition, one of the case reports approached a woman on the 8th postnatal day, with dengue-induced fulminant hepatitis. [23]

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Only 5 of the 32 articles detailed the comorbidities of the women included. In one of them, 5.3% 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; hematological diseases, in 0.6% pregnant and 0.4% non-pregnant; liver diseases, in 0.2% pregnant and 0.5% non-pregnant. In addition, 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 diseases; 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 with other agents, in the prospective study conducted in Recife, of the 780 patients studied, 16.6% had recent or active arbovirus infection, 2.3% (3) with active/recent dengue infection, 41.5% (54) with ZIKV infection, 53.1% (69) with CHIKV and 3.1% (4) with active/recent double 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 of the review studies 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 positive IgM 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 37.7ºC, 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), 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

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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 gingival bleeding (1). Regarding the sensory system, the estimated prevalence of behavioral alteration 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 (prevalence also 2.3% [22]). There were also reports of asymptomatic pregnant women in 2 studies and of one pregnant woman with uterine contractions.

From the laboratory point of view, the most prevalent alteration was thrombocytopenia, described in 10 articles. In addition, 4 reported increased AST and AST, denoting changes in liver function, 2 described leukopenia, 2 reported leukocytosis, and 2 reported anemia (here considering hemoglobin below 10mg/dL). One study addressed an increase in bilirubins and another an increase in LDH. According to an Indian retrospective study, dengue patients in late pregnancy had lower platelet counts (92,564.10 ± 388 vs 110,777.78 ± 340) (p value = 0.435). AST and AST were also higher in patients with dengue in late pregnancy (149.03/156.77), with a significant difference for AST (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 that ranged from 29.3% to 96.5% of the patients, depending on the study evaluated [29, 30]. Also having been cited in 12 different articles, the evolution to death was a very significant and worrying outcome, ranging from 0.2% of pregnant women in a retrospective SINAN study with 2,121,582 women of childbearing age to 15.9% in a prospective Indian study with 216 pregnant women with fever, of which 44 were positive for dengue [22]. However, one study placed this outcome as unusual, being more related to delay in diagnosis, insufficient medical attention, or consequences, including organ failure or significant bleeding [14]. Of equal frequency in the surveys, spontaneous abortion was repeatedly mentioned and related mainly 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]

Also in this context, postpartum hemorrhage was found in 10 articles with an oscillation of 2.5% to 25% of cases; Subsequently, the need for cesarean delivery was

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reported in 8 studies, some of them in the emergency context. Then, the severe forms of dengue were addressed in 7 studies, showing that pregnant women have a higher risk when compared to non-pregnant women [18], a higher relationship with the 3rd trimester and with DENV 4 [31]. Other less common outcomes were: preeclampsia (cited in 5 studies), placental abruption (4), dengue with alarm signs (verified in 4 articles and having a greater impact at the beginning of pregnancy [28]), dengue hemorrhagic fever (3), dengue fever with complications (1), ICU admission (3), shock (3), fulminant liver failure (2), acute renal failure (2), acute respiratory distress syndrome (3), vaginal hemorrhage (2), generalized clonic tonic seizure (2), delivery with dystocia (2), HELP syndrome (1), gestational diabetes mellitus (1), DIC (1), threatened miscarriage (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 about it. Among them, prematurity was mentioned 12 times and is shown to be 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, stillbirth was 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 Pakistan article; and low birth weight, which was described in 8 different studies, with a prevalence of 29.5% [22]. In addition, oligohydramnios 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 subsequent infection (66.7% vs. 17.9%) [28]. Regarding the transmission rate, this was discussed in 5 articles, with data that converge to a higher incidence when the virus is acquired in the third trimester, especially 15 days before delivery. Finally, less prevalent manifestations were: fetal growth restriction (mentioned 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, they have only been reported in one small study.

Finally, regarding the treatment performed on pregnant women infected with the dengue virus, only 12 articles highlighted what was done. It is worth noting that among

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these, most 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, followed by the 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 time, 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 postpartum balloon to control bleeding, Mg sulfate to prevent eclampsia, Nifedipine and Hydralazine to control blood pressure, and the association of benzodiazepine, sulfate and Nifedipine for seizures were necessary. Finally, ursodeoxycholic acid and vitamin B12 were mentioned in only 1 article, while ICU admission was required 4 times.

DISCUSSION

From the results obtained in this research, it is noted that there is a growing concern regarding the behavior of dengue infection in pregnant women, which is evident by the number of articles found. [4]

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

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

Regarding the clinical presentation, it is known that pregnancy itself can make the diagnosis of dengue difficult, because the infection can overlap or even compensate for the physiological changes of pregnancy. [18] In addition, 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

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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 tie test.

From the laboratory point of view, thrombocytopenia is more common in pregnant women than in other sectors of the population, and has been described in several articles analyzed. Another very prevalent alteration is the increase in liver enzymes (AST and TGP). In this sense, the differentiation of dengue infection from HELLP syndrome can be quite challenging, since it 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 or even maternal death, as was evident in many of the articles contemplated. Death is usually due to the activation of the immune system, with consequent release of cytokines/chemokines, autophagy of endothelial cells, and apoptosis of T cells. Thus, it can progress to intravascular volume depletion, shock, organic hypoperfusion, and multi-organ dysfunction syndrome. [23]

In this regard, maternal outcomes seem to be worse in the 3rd trimester of pregnancy, since 2 of the studies analyzed reported a higher progression to death in this period. It is worth mentioning, in this context, that the diagnosis can be even more difficult in advanced stages of pregnancy, due to the increase in plasma volume by 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]. In addition, pregnancy itself involves a reduction in the inflammatory response, with immunological changes, to improve fetal tolerance and, thus, can increase the risk of infectious complications [34].

In terms of fetal repercussions, some studies have detected a relationship between dengue infection and 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, as much as there is no consensus in this regard, until further clarification, it is interesting to adequately monitor fetal growth, paying special attention to low 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 preferential one. However, the American College of Obstetrics and Gynecology (ACOG) recommends that platelet transfusions be

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performed to keep them above 50,000 before major surgeries (such as cesarean section) and above 70,000 for epidural and spinal anesthesia. This is to reduce the risk of postpartum hemorrhage. [33]

It is essential to pay attention to symptoms that are at first benign, such as fever, and to actually investigate dengue even in asymptomatic or oligosymptomatic pregnant women, especially in endemic areas [23]. In addition, it is interesting that sentinel maternity hospitals be created to monitor vertical transmission and potential maternal-fetal adverse outcomes of DENV infection, based on clinical and laboratory screening [20], since there is still no consensus on this matter.

CONCLUSION

Dengue in pregnant women represents 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 hemorrhages, and even maternal death. In addition, there is also a relationship with adverse impacts on fetal development, such as prematurity, oligohydramnios, and fetal death. The complexity of dengue in pregnant women is amplified by the difficulty in differential diagnosis of symptoms, which can often be disguised by physiological changes during pregnancy.

In this regard, it is interesting to establish a national guideline for the management of dengue in pregnant women, since many health professionals are not familiar 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. Additionally, it is crucial to implement robust preventive measures, such as effective control of the *Ae. aegypti* mosquito and educational programs targeting pregnant women in endemic areas.

This systematic review stands out for having brought together articles of different nationalities and clinical designs, allowing 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 the women included in the analyzed articles actually had dengue or were pregnant, since this varied according to the objectives and methodologies of the studies. In addition, some studies were carried out only in hospitals, which may have overestimated the complications resulting from the infection, while others were affected by

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the omission of data from the notification forms sent to SINAN, in view of the suspicion of 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. Thus, continuous research is crucial to expand and deepen knowledge about the effects of dengue infection on pregnancy and to develop effective prevention and clinical management strategies, and further studies are needed to elucidate issues that have not yet been fully clarified by this review.

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