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Impacts of Dengue Virus During Pregnancy

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ABSTRACT

Introduction: Common infections during pregnancy that have long been recognized as congenitally and perinatally transmissible to newborns include the Dengue virus, and constitute a relevant target for current research into maternal-fetal interactions in viral infections during pregnancy. Objectives: The aim of this study was to characterize and discuss dengue-related complications in pregnant women. Material and Methods: The research was carried out through an electronic search of published scientific articles. The inclusion criteria were: original article, published in Portuguese and English, freely accessible, in full, on the subject, in electronic format and published in the last ten years (2014-2024) totaling 25 articles. Discussion: The number of dengue cases in pregnant women increased by 345.2% this year. Therefore, considering this increase in the number of pregnant women with dengue, coupled with the increased risk of severe forms in these women, a public health picture emerges that inspires differentiated care, since both maternal and perinatal prognosis are compromised in this disease. Final considerations: The diagnosis and treatment of dengue during pregnancy and the puerperium should be carried out as soon as possible.

Keywords: Dengue fever in pregnancy, high-risk pregnancy, viral infections during pregnancy.

1. INTRODUCTION

Dengue is a disease caused by a Flavivirus and is considered to be the most important arbovirus worldwide. The four serotypes of the virus (DENV1-4) are transmitted by mosquitoes of the genus Aedes (Stegomya), causing an acute febrile illness that can range from oligosymptomatic to severe forms, capable of causing death (WYLIE et.al, 2016).

According to Silva Jr (2022), the mosquito that transmits dengue originated in Egypt, Africa, and has been spreading across the tropical and subtropical regions of the planet since the 16th century, during the period of the Great Navigations. It is believed that the vector was introduced to the New World in the colonial period by slave ships. It was first described scientifically in 1762, when it was called Culex aegypti. The definitive name - Aedes aegypti - was established in 1818, after the genus Aedes was described. Reports from the Pan American Health Organization (PAHO) show that the first dengue epidemic on the American continent occurred in Peru at the beginning of the 19th century, with outbreaks in the Caribbean, the United States, Colombia and Venezuela.

In Brazil, the first reports of dengue date back to the end of the 19th century, in Curitiba (PR), and the beginning of the 20th century, in Niterói (RJ). At the beginning of the 20th century, the mosquito was already a problem, but not because of dengue - at the time, the main concern was the transmission of yellow fever. In 1955, Brazil eradicated Aedes aegypti as a result of measures to control yellow fever. At the end of the 1960s, the relaxation of the measures adopted led to the reintroduction of the vector into national territory. Today, the mosquito is found in all Brazilian states (SILVA JR, 2022).

According to data from the Ministry of Health, the first occurrence of the virus in the country, documented clinically and laboratorially, happened in 1981-1982, in Boa Vista (RR), caused by the DENV-1 and DENV-4 viruses. Years later, in 1986, there were epidemics in Rio de Janeiro and some capitals in the Northeast. Since then, dengue has been occurring in Brazil continuously (BRAZIL. MINISTÉRIO DA SAÚDE, 2024).

The Ministry of Health's arboviruses monitoring panel counts 5,968,224 probable cases of dengue and 3,910 confirmed deaths from the disease throughout 2024. There are still 2,970 deaths under investigation. The dengue incidence rate in Brazil is currently 2,939 cases per 100,000 inhabitants (BRAZIL. MINISTÉRIO DA SAÚDE, 2024).

The Ministry of Health has invested huge resources in the PNCD. In 2022, of the R$1,033,817,551.00 spent on dengue control, 85% was spent on vector surveillance and control. In 2023, these actions absorbed around R$790 million, basically in costs, the purchase of equipment and insecticides, maintenance and training of personnel and social communication actions (BRASIL. MINISTÉRIO DA SAÚDE, 2024).

Liang (2019) points to recent discussions on dengue control and the need for greater investment in appropriate methodologies, to raise awareness among the population about the need for behavioral changes aimed at controlling the vector; and in environmental management, including broadening the focus of rational vector control actions, to minimize the use of insecticides and thus ensure greater sustainability of actions.

In addition to the risks of dengue transmission throughout the population, dengue infection during pregnancy has been associated with the development of pre-eclampsia, eclampsia, hemorrhage and maternal deaths, but not with the occurrence of congenital malformations (BASURKO ET.AL, 2019).

According to the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO), severe cases of dengue fever increase the risk of maternal death by more than 400 times (FEBRASGO, 2024).

The aim of this study was to characterize and discuss dengue-related complications in pregnant women.

2. MATERIAL AND METHODS

The methodology used was a literature review. A literature review is a meticulous and comprehensive analysis of current publications in a particular area of knowledge. This type of research aims to put the investigator in direct contact with the existing literature on a subject.

The research was carried out by means of an electronic search for scientific articles published on the Scielo (Scientific Electronic Library Online) and Lilacs (Latin American Health Sciences Literature) and Pubmed websites. The health terminologies consulted in the Health Sciences Descriptors (DeCS/BIREME) were used: Dengue-related pregnancy complications, types of treatment and prevention.

The inclusion criteria were: original article, published in Portuguese and English, freely accessible, in full, on the subject, in electronic format and published in the last ten years (2014-2024) totaling 25 articles.

3. LITERATURE REVIEW

3.1 Types of Dengue and their incidence

Arboviruses are organized phylogenetically into six families (Togaviridae, Flaviviridae, Bunyaviridae, Reoviridae, Rhabdoviridae and Orthomyxoviridae) (KHAMIM et.al, 2015).

According to Ribeiro et.al (2017), as a virus whose genome is made up of RNA, DENV has high mutation rates, and its different types derived from this characteristic imply diverse pathogenic potential, with clinical manifestations of varying spectrum. DENV has four different serotypes, called DENV-1, DENV-2, DENV-3 and DENV-4.

The main vector of DENV in the urban cycle in Brazil is the Aedes aegypti mosquito, responsible for both epidemic outbreaks and endemic rates of this infection (KHAMIM et.al, 2015).

These four serotypes, in general, can cause the classic form or evolve into serious conditions such as dengue shock, hemorrhagic fever or direct involvement of various organs such as the liver, brain and heart (TEIXEIRA et.al. 2014).

The DEN1 virus is the one that most affects Brazilians and is seen as the most explosive of the four and can cause major epidemics in the short term. According to studies, DEN-3 is responsible for causing more severe forms of the disease, followed by DEN-2, DEN-4 and DEN-1 (BASURKO ET.AL, 2019).

FIGURE 1 shows the types of Dengue in schematic form. DENV-1, DENV-2, DENV-3 and DENV-4 with EDIII (circled) in red, green, blue and black respectively. EDIII provoke strong neutralizing antibodies specific to the serotype (antibodies in bold). Due to homology, especially in the domains (EDI/II and prM) in yellow, weakly neutralizing cross-reactive antibodies (antibodies in bold) and non-neutralizing enhancer antibodies (antibodies in dashed) are provoked en masse (BASURKO ET.AL, 2019).

The four serotypes are identical in 65% of their genome, but there may be some genetic variation even within each serotype. The pathophysiological responses to infection by each of the four serotypes differ in terms of immune status, making dengue a highly complex disease. However, despite these immunological differences, infection with any of the serotypes would result in the same clinical disease (WORLD HEALTH ORGANIZATION, 2019).

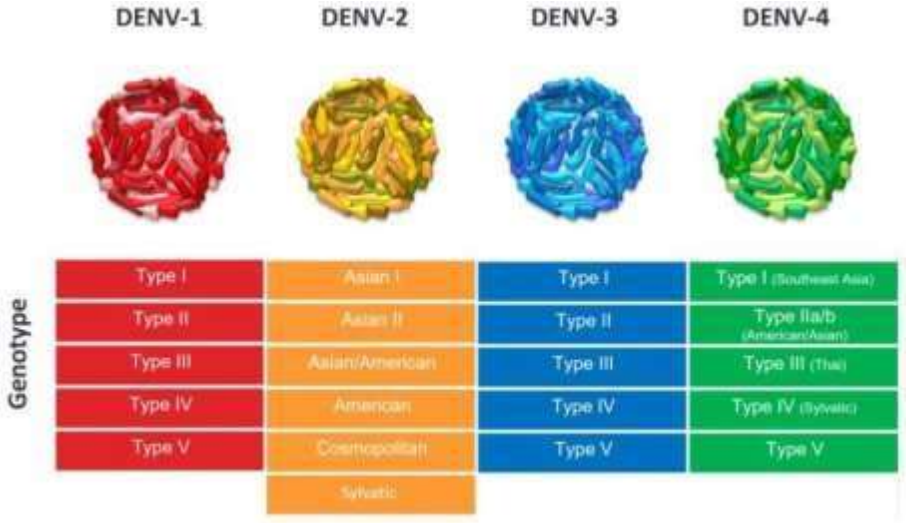

Figure 1. Dengue virus genotypes. Source: (WORLD HEALTH ORGANIZATION, 2019).

One study highlighted which of the Dengue subtypes have the highest incidence (FIGURE 2). It was observed that the DENV 1 type has the highest rate (53%), followed by type 2 (26%) (WORLD HEALTH ORGANIZATION, 2019).

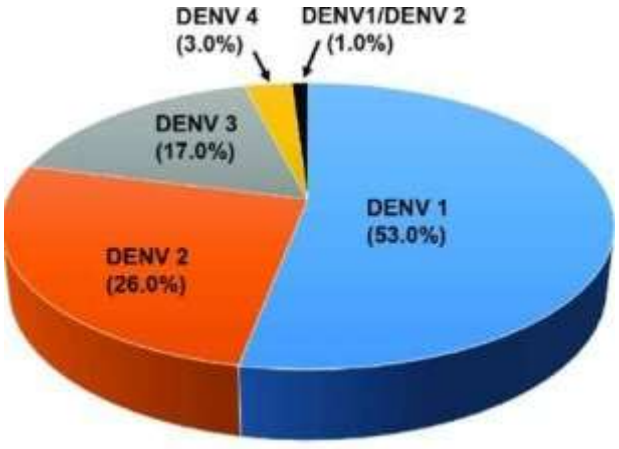

Figure 2. Distribution of dengue cases by serotypes in the study population.

Source: (WORLD HEALTH ORGANIZATION, 2019).

The global spread and increase in frequency and magnitude of dengue epidemics over the last 50 years underline the urgent need for effective surveillance, prevention and control tools (TEIXEIRA et.al. 2014).

These mosquitoes are found mainly in: Asia, Africa and South America (see map) (FIGURE 3).

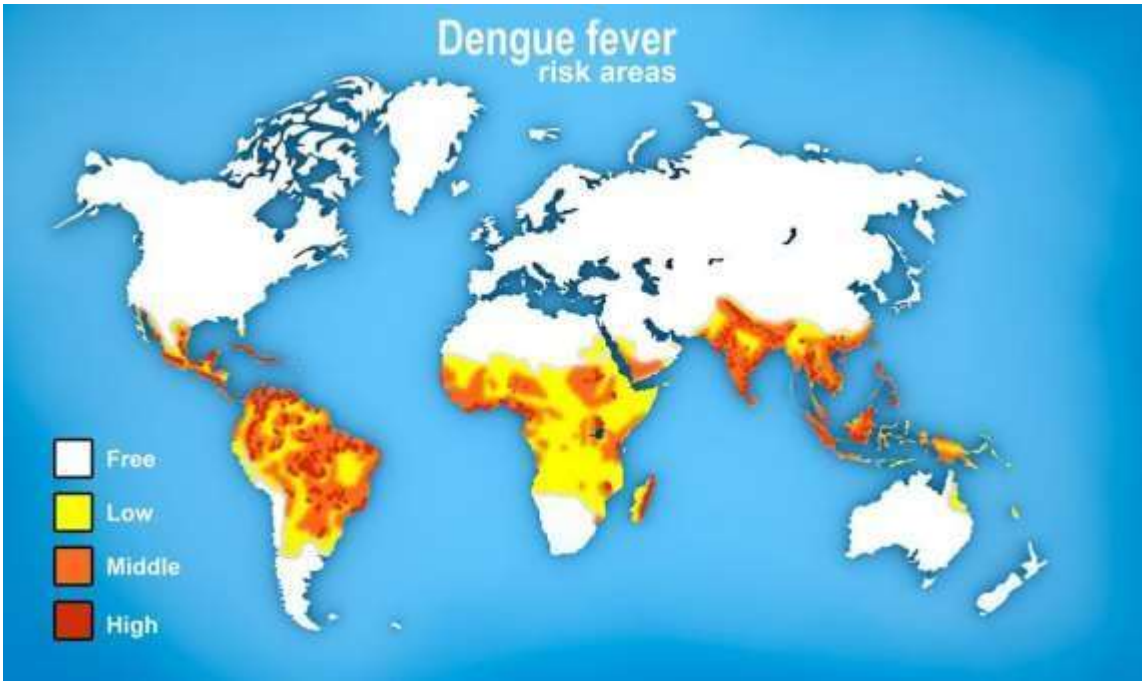

Figure 3. Risk of Dengue contamination in the world population. Source: (WORLD HEALTH ORGANIZATION, 2019).

Data from the epidemiological bulletin published by the Ministry of Health (FIGURE 4) show that in 2023, from epidemiological week (EW) 1 to EW 35, 1,530,940 probable cases of dengue were recorded in the country, with an incidence coefficient of

753.9 cases/100,000 inhabitants. These figures represent a 16.5% increase in the number of cases compared to the same period last year.

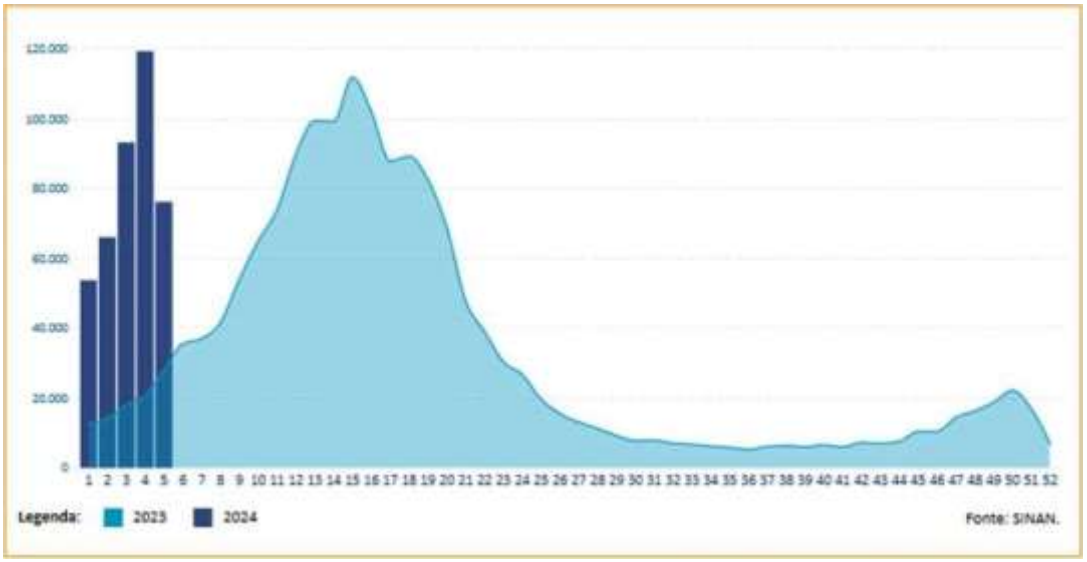

Figure 4. Number of probable dengue cases per epidemiological week. Source: Brazil. Ministry of Health. Emergency Operations Center (COE). Number of probable dengue cases per epidemiological week, Brazil, 2023 and 2024. Weekly Report. Weekly. Issue no. 02. SE 01 to 07/2024.

3.2 Dengue during pregnancy

Pregnancy, in addition to being a physiological process, is a condition characterized by major adaptations in maternal endocrine and metabolic homeostasis, necessary to accommodate the fetoplacental unit. Unfortunately, all these systemic, cellular and molecular changes in maternal physiology also make the mother and fetus more prone to adverse outcomes, including numerous changes resulting from viral infections (MORAES, 2016).

Some population groups are more susceptible to complications and progression to the most severe forms of dengue, including pregnant and puerperal women, especially up to 14 days postpartum, due to the slow return of physiological changes to pre-pregnancy standards (VIANA & BARRETO, 2024).

Comparing the recorded frequency of these diagnoses in the epidemiological weeks from 01 to 06/2023 with the same weeks in 2024, it was found that the number of dengue cases in pregnant women increased by 345.2% this year. Therefore, considering this increase in the number of pregnant women

with dengue, coupled with the increased risk of severe forms in these women, a public health picture emerges that inspires differentiated care, since both maternal and perinatal prognosis are compromised in this disease. On the maternal side, the increased risk of morbidity and mortality is based on the potential occurrence of severe forms, such as shock, bleeding and death (BRASIL. MINISTÉRIO DA SAÚDE, 2024).

Common infections during pregnancy that have long been recognized as congenitally and perinatally transmissible to newborns include the Dengue virus, and are a relevant target for current research into maternal-fetal interactions in viral infections during pregnancy (KARIYAWASAM et.al 2020).

Tauil (2021) highlights the compromised perinatal prognosis, the most frequently observed complications being prematurity, intrauterine growth restriction and fetal death. It should be noted that there has still been no progress regarding the specific treatment of dengue or vaccines that can be used safely during pregnancy

(KARIYAWASAM et.al 2020).

Objectively speaking, accessible prophylaxis to avoid the deleterious effects of dengue during the pregnancy-puerperal cycle is based on behavioral, personal and community attitudes, which must be continually remembered, reinforced and passed on to people. In practice, it has been observed that the dissemination of these guidelines to pregnant and postpartum women fails, even considering that they are the same for avoiding infection by all arboviruses (VIANA & BARRETO, 2024).

These failures are frequent and range from those aimed at controlling mosquito breeding sites to the use of appropriate clothing and repellents.

If prophylactic measures fail, it will be necessary to properly organize care units for pregnant and postpartum women up to the 14th day postpartum, still in the early stages of the disease, in order to avoid cases of severe dengue, which are responsible for the deaths that result from it. In addition to reception, screening with risk classification is of paramount importance, as it enables priority and timely treatment for cases with alarm signs and for severe cases (KARIYAWASAM et.al 2020).

Vouga et.al (2019) cites that among the possible reasons for the high lethality rate is the delay in caring for pregnant women with dengue. This delay can be caused by both the professional making the diagnosis and the woman seeking care. Thus, in the presence of fever associated with at least two other symptoms, such as myalgia, rash, retro-orbital pain, nausea, vomiting and diarrhea, dengue should be considered suspected.

Undoubtedly, assertive and rapid care, following the appropriate principles that guide clinical and obstetric care for these women, makes it possible to reduce potential harm to maternal and perinatal health (VIANA & BARRETO, 2024).

3.2.1 Influence of dengue on maternal and perinatal prognosis

According to Moraes (2016), all dengue serotypes increase the production of pro- inflammatory chemokines, promote thrombocytopenia and increase vascular permeability, pathophysiological phenomena responsible for various maternal health problems.

According to Mate et al (2018), as a result of compromised vascular permeability, there is a greater risk of shock, thrombocytopenia and hemorrhagic phenomena, aggravated by the increase in pro-inflammatory chemokines. The literature has shown that pregnant women are considered a risk group and are more likely to progress to more severe forms of the disease and die.

The risk of obstetric bleeding in pregnant women with dengue is associated with the physiological adaptations of pregnancy, which can make it difficult to identify the clinical manifestations of the disease correctly and early. Increased capillary permeability in pregnant women is a functional adaptation, but it is clearly exacerbated in dengue. This fact alerts us to the greater risk of pregnant and postpartum women with dengue developing acute pulmonary edema when they are included in a hyperhydration regime, which is part of the treatment for the disease (KARIYAWASAM et.al 2020).

3.2.2 Clinical diagnosis

The clinical diagnosis of dengue is extremely important, indicating that, in the face of a suspicious clinical picture, laboratory diagnosis becomes crucial, allowing for early therapeutic management (TEIXEIRA et.al. 2014).

According to Bhatt et.al (2014), in pregnant women, the snare test and blood count should be carried out. The snare test is a screening test that should be carried out on all patients with suspected dengue who do not have spontaneous bleeding. It is a way of looking for hidden hemorrhagic manifestations.

A positive loop test has the function of assessing the presence of induced bleeding and, whenever positive, the case should be considered in the classification of dengue in staging group B or higher (BHATT et.al, 2014),

To perform the loop test, a square measuring 2.5 x 2.5 cm should be drawn on the forearm and then follow these steps: Assess the person's blood pressure with the sphygmomanometer; Re-inflate the sphygmomanometer cuff to the average value between the maximum and minimum pressure (TEIXEIRA et.al. 2014).

According to Mate et.al (2018), despite its limitations in severe cases and in obese patients, the snare test is indirect evidence of capillary fragility, the basis of dehydration to varying degrees, a reduction in the blood's figurative elements and an elevated hematocrit.

The blood count provides important information such as the indirect attack on the bone marrow by viral action, with a reduction in the blood's figurative elements (notably thrombocytopenia) and an elevated hematocrit resulting from the liquid extravasation that occurs in response to increased capillary permeability (TEIXEIRA et.al. 2014).

3.2.3 Laboratory diagnosis

When talking about laboratory resources to support the care of pregnant women who have recently given birth up to the 14th postpartum day with dengue, two aspects are considered. The first deals with the etiological diagnosis of the infection and the second deals with laboratory resources to measure the extent of the severity of the clinical picture of the disease (VIANA & BARRETO, 2024).

According to Moraes (2016), for the etiological laboratory diagnosis of dengue in its initial phase, the most suitable tests are those that identify specific viral particles, such as non-structural glycoprotein 1 (NS1) or viral RNA in the blood.

In the acute phase, which occurs in the first three to seven days after the onset of symptoms, serum viral RNA would be the best test, using reverse transcription polymerase chain reaction (RT-PCR) as the most accurate test for dengue diagnosis, but unfortunately still not very accessible for rapid diagnostic response by the Unified Health System (SUS), since many regions still depend on samples being sent to official centralized laboratories (TEIXEIRA et.al. 2014).

3.2.4 Clinical management

Allgoewer et.al (2021) mentions that pregnant women with dengue should be treated according to the clinical phase of the disease and its particularities. Systematizing, grouping and stratifying certain organic alterations that occur in pregnant women with dengue makes it easier to approach and draw up clinical care protocols that can be followed in the most remote communities in the country. The first stratification is based on clinical manifestations and their severity, allowing pregnant women with the same clinical manifestations and possible complications to be grouped together.

3.2.5 Clinical management according to the severity classification for pregnant and postpartum women with dengue fever

The criteria for dengue fever severity are identified through anamnesis, physical examination and blood count, as well as early recognition of warning signs and signs of severity. This defines the staging of the disease (Groups A, B, C and D), which will guide therapeutic interventions for pregnant women in each specific group (BHATT et.al, 2014).

According to the Centers for Disease Control and Prevention (2024), once the severity criteria have been established, therapeutic interventions for pregnant and postpartum women up to the 14th postpartum day, according to the clinical staging of the disease, should be promptly instituted. Both pregnant women and women who have recently given birth need constant monitoring, regardless of severity, but at rates appropriate to each stage. Teststo confirm dengue fever are mandatory for pregnant women, but they are not essential for starting treatment at any stage of the disease.

Generally speaking, as there is no antiviral treatment for dengue, treatment will most often consist of rest, fluid intake or infusion to prevent dehydration and the use of analgesics and antipyretics such as paracetamol or dipyrone, when necessary. The use of acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) is contraindicated, as they can aggravate bleeding (VIANA & BARRETO, 2024).

According to Lo (2018), in some situations, it is not possible to provide outpatient care for pregnant women and postpartum women until the 14th postpartum day, requiring hospitalization as a priority. These conditions are summarized below: - Inability to follow up or return to the health unit due to clinical or social conditions; - Comorbidities that are decompensated or difficult to control, such as diabetes mellitus, severe heart disease, hypertension, heart failure, use of anticoagulants or antiplatelet agents, asthmatic crisis and sickle cell anemia; - Other clinical or social situations, at the team's discretion.

3.2.6 Prenatal, obstetric and puerperal care line

Assuming that the available dengue vaccine is restricted to pregnant and breastfeeding women because it contains live attenuated viruses, it is imperative that alternatives are sought to prevent this infection during prenatal care. Regardless of the options to be adopted, these guidelines are mandatory during the pregnant woman's prenatal visit (BHATT et.al, 2014).

Regular prenatal care does not differ if a particular community or region is in a period of peak dengue epidemic. The only differences are related to the emphasis given to guidelines for preventing the disease and providing information that allows pregnant women to promptly identify the signs and symptoms of dengue and the need to seek medical assistance when they are present (VIANA & BARRETO, 2024).

One of the obstetrician's main concerns when caring for pregnant and postpartum women (up to the 14th postpartum day) with dengue is to ensure that clinical management complies with the criteria set out in the Clinical Management section (BASURKO ET.AL, 2019).

Allgoewer et.al (2021) mentions that it is important to note that hydration of pregnant women is the most effective therapeutic strategy in preventing and controlling the most severe clinical forms. If venous hydration is necessary, care must be taken to prevent the physiological changes in the mother's body, such as increased general and pulmonary capillary permeability, from being aggravated by dengue.

In this scenario, the risk of acute pulmonary edema during hydration is a possibility. To this end, it is necessary to monitor the pregnant woman's vital signs during liquid infusion, especially heart and respiratory rate, respiratory auscultation, pulse quality, jugular turgor, diuresis and level of consciousness (KARIYAWASAM et.al 2020).

In Dengue virus infections in pregnant women, obstetric management must also take into account the likelihood of complications, especially hemorrhagic complications. In this sense, a fundamental demand for these pregnant women is hydration, the shortest way to correct the effects of fluid leakage into the interstitium, potentially also helping to correct thrombocytopenia (VIANA & BARRETO, 2024).

Generally speaking, after the start of clinical management, the obstetrician's role is more expectant in managing these cases, restricting themselves to assessing maternal well-being (seeking to comply with all clinical care guidelines) and fetal well-being (VIANA & BARRETO, 2024).

(2023), all the complications and situations that occur in pregnant women with dengue, such as pre-eclampsia, placental abruption, the use of antiplatelet or anticoagulant drugs and preterm labor, need to be better studied. Most of the time, current protocols are based on common sense, aiming for the most logical course of action, most of which is still not backed up by research with definitive results.

In the case of pregnant or parturient women with dengue who require prolonged hospitalization, it is necessary to encourage walking as a strategy to prevent venous thromboembolism, the occurrence of which, already increased in pregnancy, tends to worsen in cases of altered coagulability present in dengue. Although hemorrhagic phenomena are the most common in dengue, cases of thrombosis can result from hemoconcentration and blood hyperviscosity. To alleviate this situation, physiotherapeutic measures, lower limb massage and compressive or pneumatic stockings should be considered if the pregnant woman is confined to bed (as occurs in more severe cases in intensive care units) (BHATT et.al, 2014).

According to Moraes (2016), another variable of concern when caring for pregnant women with dengue is the use of aspirin for secondary prevention of pre- eclampsia or to avoid thromboembolic phenomena. During the acute phase of dengue, the

use of this medication should be suspended. Although there have been no studies on the appropriateness of resuming this medication throughout the pregnancy, it is common sense that ASA can be reintroduced one week after remission of the disease, in the expectation that the protective benefits have been maintained during the interruption of prophylaxis and will be re-established with its return. More complicated is when platelet antiaggregants (ASA or clopidogrel) are used as part of therapy for diseases with a high thromboembolic risk (e.g. conjunctive diseases and acquired thrombophilias).

In these cases, the tendency is also to discontinue the drug in the acute phase of dengue, but the pregnant woman should be hospitalized for daily monitoring.

For pregnant women with severe pre-eclampsia or signs of failure to inhibit preterm labor up to 32 weeks, magnesium sulfate offers proven maternal protection and perinatal neuroprotection (MORAES, 2016),

Kariyawasam et.al (2020) describe that although there are doubts about the safety of using magnesium sulfate in cases of pregnant women with dengue fever and a risk of hemorrhage or shock, considering the risk versus benefit of its use in the clinical scenario of severe pre-eclampsia or the need for fetal neuroprotection, the use of this medication is suggested. Of course, this pregnant woman should be in a hospital environment and calcium gluconate should be immediately available.

Although there is a lack of controlled studies on fetal assessment in pregnant women with dengue, it seems reasonable for them to have their fetal vitality measured by electronic means such as ultrasound and cardiotocography (KARIYAWASAM et.al 2020).

4. FINAL CONSIDERATIONS

The diagnosis and treatment of dengue in pregnancy and the puerperium should be carried out as soon as possible.

To prevent Aedes aegypti from entering homes, it is recommended that fine mesh screens (metal or plastic) be placed on windows and doors.

The use of bed nets helps, but with limitations, since Aedes aegypti has preferentially diurnal habits, combining with high levels of daylight and higher temperatures.

Measures such as the use of insecticides or natural environmental repellents at home are parallel strategies with varying percentages of effectiveness.

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