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CLINICAL CASE

Perinatal Dengue: A case Report

Dengue perinatal: Reporte de caso

Ramiro Manzano Núñez MD[a], James Alejandro Zapata MD[b], Herney A. García-Perdomo MD, MSc, EdD, PhD[c], Diego A. Gomez MD[c], Mónica A. Solís Velasco MD[c]

[a]Clinical Research Center, Fundacion Valle del Lili, Cali, Colombia
[b]Libre University, Cali, Colombia
[c]Del Valle University, Cali, Colombia

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Abstract

Introduction: Few reports are available about perinatal dengue, with controversial results in regards the risk of perinatal outcome. **Objective:** To report a case of perinatal dengue as a differential diagnosis with neonatal sepsis, which must be considered in endemic areas. **Clinical case:** Male newborn of a 23 year-old female, who presented a Non-Structural Protein 1 (NS1) antigen positive to dengue at 36 weeks of gestation and negative anti-dengue antibodies. At day six of the illness a healthy newborn was born. On the second day of life the neonate presented fever with no other pathological findings on the physical exam, associated with severe thrombocytopenia (17,900 platelets/uL), increased C-reactive protein, a positive NS1 antigen, and positive anti-dengue immunoglobulin G (IgG). He was treated with ampicillin and gentamicin according the Institution protocol of neonatal sepsis. The newborn showed clinical improvement, with hemodynamic stability and significant increase of platelets, receiving the medical discharge. **Conclusions:** Dengue in pregnancy produces the risk of adverse perinatal outcomes, particularly low birth weight and preterm delivery. Children of mothers diagnosed with dengue at the end of pregnancy should be observed closely with serial hemograms during child's first days of life, due to the high risk of vertical transmission.

Keywords:
Dengue;
Dengue virus;
Vertical transmission
Non-Structural Protein I Antigen

Correspondence:
Ramiro Manzano Núñez MD
ramiro.manzano@correounivalle.edu.co

Introduction

Dengue is a disease caused by the dengue virus (DENV), a member of the Flaviviridae family. It has 4 different serotypes (DENV 1-4) and is transmitted mainly to humans by the Aedes Aegypti mosquito. It is a global public health problem[1]. It is found in rural and urban zones and is estimated that 3.9 billion of people are at risk of getting infected in approximately 128 countries[1].

The incidence is higher in children and adolescents[2]. However, it is also presented in adults and pregnant women; so mother-to-fetus transmission, while infrequent, should be considered[3].

The onset of dengue in pregnancy has been reported in the literature since 1958. In Latin America, there are few descriptions of this condition. The first report was carried out in 1981 in Cuba, when 4 cases of newborns with positive Immunoglobulin M (IgM)[4] were observed in 52 women with dengue.

In 1994, Figueiredo et al.[5] described 10 cases of maternal dengue at the end of the pregnancy in which the presence of IgG in the newborn blood was confirmed. It was concluded that there was transference of antibodies to the fetus through the placenta, with no fetal abnormalities.

A retrospective study carried out in the French Guiana confirmed the mother-to-fetus transmission of the virus in 3% of newborns few days after delivery, and it was found that 40% of women with dengue had preterm birth[6].

In 2003, Restrepo et al.[7] performed a prospective cohort study in Colombia, in which 39 pregnant women with dengue and 39 without dengue were included in order to determine the adverse effects of the virus in pregnancy and newborns. It was noted that in the group of exposed women to the virus there was a higher risk of hemorrhagic manifestations without significant negative outcomes for newborns.

Some studies have proved that the infection by dengue in the pregnancy increases the adverse results in the newborn[8-11]. Systematic reviews of the literature have associated the dengue infection of pregnant women with preterm delivery. On the other hand, it has been described that most of cases of dengue infection during pregnancy do not carry a higher risk of adverse effects[13]. However, the consequences of the infection due to dengue in mothers and their fetuses cannot be affirmed certainly because of the limited number of comparative studies.

The reported cases in the literature show the importance of suspecting the disease in pregnant women, since even when the risk of vertical transmission is low[14], the prevalence of congenital infection could generate an important demand of health services in endemic areas of the disease.

In newborns, dnegue infection have a wide spectrum of presentation. The disease can rangefrom an asymptomatic infection[15], going through fever, exanthema, and thrombocytopenia[4,16], to cause a dengue shock syndrome[17], brain hemorrhage and death.

The diagnosis in the perinatal period is based on the clinical and laboratory findings. If counted on availability, it can be confirmed with RT-PCR for the virus or by the presence of antibodies in the newborns. The treatment, as well in other ages, is based on proper support, liquid handling, and management of complications[16].

The aim of this article is to report a case of perinatal dengue as a differential diagnosis of neonatal sepsis, that should be suspected in endemic areas.

Clinical case

We present a case of a male patient, son of a 23-year old woman in her third pregnancy with history of 2 miscarriages due to unknown causes. At 36 weeks of gestation, his mother seeked medical care in an obstetric emergency service due to fever and discomfort associated with epistaxis. She was found to have a generalized erythematosus exanthema with no evident signs of bleeding, no alteration in her vital signsand no other pathologic findings. In the first 24 hours, the blood test of the mother showed thrombocytopenia, positive viral antigen NS1 (Non-Structural Protein 1) and negative antibodies to dengue. The mother was hospitalized for observation.

On the sixth day of disease (third afebrile) and having 37 weeks of gestation, she went into labor. A male newborn was born with APGAR 8/10 at minute, weight 6.7 lb (3.040 grams), height 19.2 in (49 cm), and cephalic perimeter 12.9 in (33 cm). The newborn did not present alterations in his neonatal adaptation and spent his first 24 hours of life with his mother.

During his second day of life, the newborn presented an axillary temperature of 101.3° F (38.5 °C) with other vital signs in normal ranges and with no other pathological findings in the physical examination. Regular check-ups showed a drop in platelets and a rise in C-reactive protein. Due to the maternal history of febrile syndrome, the newborn was hospitalized in the neonatal intermediate care unit. Antibiotics (Ampicillin and gentamicin) were initiated following the protocol of the institution for possible neonatal sepsis. Breastfeeding was continued and intravenous fluids were added for maintaining a proper support.

During his third day of life, the newborn presented a good general state, no new febrile peaks, with proper hemodynamic parameters, a slight drop in platelets

and the test for dengue reported positive antigen NS1 and positive anti dengue immunoglobulin G (IGg). On the fifth day of life, he presented a severe thrombocytopenia (17.900 platelets/uL) (Figure 1), and thus a close monitoring was initiated.

During the seventh day of life, the antibiotic treatment was suspended, as well intravenous fluids, andexclusive breastfeeding continued. The newborn showedclinical improvement with oral tolerance, hemodynamic stability, and a significant increase of platelets. On the eleventh day of life, he was discharged.

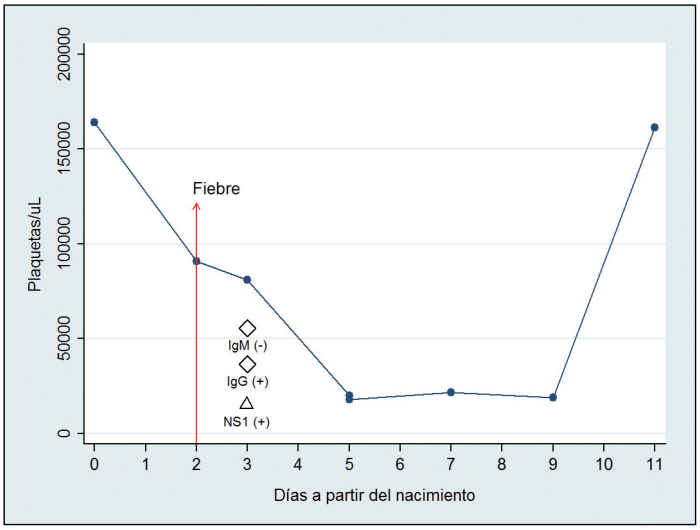

Figure 1. Laboratory values trends. Blue line: daily platelets values, Red Line: Fever onset. The newborn had dengue seropositivity on the third day of life.

Discussion

Currently, there is a growing concern on dengue cases in pregnant women due to the greater risk of complications in this population and the possible adverse perinatal outcomes caused by vertical transmission.

To date, the mechanism by which the mother's infection impact the fetal outcome is unknown. However, three mechanisms of disease that might be involved in the fetal implications were postulated: 1) hematogenous spread secondary to the maternal infection via placenta 2) virema that increases the risk of virus transmission due to the blood exchange during labor 3) severe presence of dengue in the mother that alter directly the placental function affecting the fetus without having a real viral infection[16].

It is known that the dengue infection causes the activation of an immunological response characterized by an increase of proinflammatory cytokines production as interleukins[4,12] and tumor necrosis factor-alpha[18,19]. These cytokines acts at an uterine level, stimulating the production of activating proteins of the utero, which in turn triggers the start of the uterine contraction ending up in the onset of labor[15,20]. Additionally, the thrombopenia and extravasation of liquids caused by dengue can lead to an injury of placental circulation and hypoxia with consequences to fetus as growth restriction and fetal death[21].

The risk of vertical transmission could be higher in pregnant women close to end of pregnancy, those with a symptomatic disease or with greater severity and with concomitant infections[9,14]. In the more severe cases, the possibility of transmitting the infection to fetus is higher due to endothelial damage and the consequential increase of the vascular permeability that open a passage for the virus thought the placenta[9,19]. In the reported case, the mother presented close to the end and during the febrile phase of the disease, which could have favored the transmission.

The clinical manifestations of the disease in the newborn and the infant could be variable and this hampers the prediction of the final outcome. The burden of more severe cases of the disease fall on infants[22]. In these patients, it is common to find lower values of platelets and hematocrit, compared to those found in prescholar and almost 51% of them will have platelet levels under 80.000 mm^3 [23]. For this reason, it has been recommended that newborns sons of mothers with dengue should be observed closely during their first week of life[16].

Britez et al. reported a series of 10 neonates that developed the disease, and whose mothers were diagnosed with dengue in the peripartum. All the newborn presented fever and 90% presented moderate to severe thrombocytopenia. The antigen NS1 was positive in nine cases and the IgM in four. On average, the symptoms initiated on the sixth day of birth. In the presented case, there was an antigen positive NS1 and the thrombocytopenia emerged on fifth day of disease.

Additionally, it has been reported that the hemorrhagic manifestations of the disease are more frequent in infants[24] and that the more severe cases are presented between 4-7 months of age, stage in which the risk of seizures and liver damage is greater[22,25]. In the reported case, the newborn presented severe thrombocytopenia but did not have hemorrhagic manifestations.

The degree of severity of disease could be explained following the hypothesis of Guzmán and Halstead[26]. This hypothesis describes that severe disease in newborn and infants with primary infection is produced by a phenomenon known as antibody-dependent enhancement (ADE) of monocytes and macrophages that are infected thought Fc receptors by the immune complexes formed between the DENV and non-neutralizing antibodies. The infection eliminates the innate immu-

ne response, facilitates the intracellular infection, and increases the response of cytokines and chemokines, which in turn amplify the disease and increasethe risk of Dengue shock syndrome[26].

Approximately, 135 arboviruses that causes disease in human have been identified[27]. From these, Zika virus (ZIKV) and Chikungunya (CHIKV) have acquired significant relevance for their rapid spread and for the greater risk of causing severe neonatal and fetal complications, mainly microcephaly[28]. The symptoms of the three infections (Dengue, ZIKV y CHIV) are similar. The diagnosis in the first days of life is complex since the clinical presentation can be confounded with other causes of neonatal sepsis. Calvo et al.[29] reported 8 cases of pediatric patients with suspected of dengue or chikungunya in order to compare the presumptive diagnosis based on the clinical findings with the differential diagnosis performed through laboratory tests. In this series 8 cases were included, 7 of them were newborns. All the patients had a confirmed diagnosis of dengue infection, chikungunya or simultaneous infection. The most common symptoms were skin rash, hypoactivity, and hyperoxia and there were no specific signs that allowed to do a differential diagnosis between the infections.

In order to establish a diagnosis in the mothers and neonates, virus behavior and immune response to the disease must be taken into account. During the viremic stage, that goes from 3 to 5 days of disease, the virus and its antigens in the blood (ex: glycoprotein NS1) can be isolated. In the primary infection, the IgM antibodies rise in the 3 to 5 days of the disease, reaching its peak in the second week and being undetectable 2-3 months after the infection. The IgG is detectable at the end of the first week and starts to increase onwards. On the other hand, in the secondary infection, the IgG antibodies can be identified even from the acute phase, while the IgM levels are lower than in the primary infection which increase the number of false negatives[26].

The seroconversion of IgM or IgG is the serological standard test to confirm the infection. Additionally, the genome or viral antigens detection confirms the diagnosis, especially in the window period that occurs before the third day of the disease when the IgM is negative[26]. In our case report, the diagnosis of the pregnant woman and the neonate was confirmed by the detection of antigen NS1 in the first and third day of disease, respectively.

It is assumed that the newborn coursed with a dengue primary infection, which indicates that IgG in blood is of maternal origin. However, the infection was confirmed for the presence of the antigen in the blood which is a reflection of the replication and viral viability in the pediatric patient.

The principal concern when a neonate presents fever in the second day of life is neonatal sepsis. S. agalactiae and E. coli are some of the causes of early sepsis; these are acquired by contamination of the amniotic liquid or by exposition to the mothers genital tract during delivery[30,31]. In this case, the patient received empiric antibiotics because of the perceived increased risk of sepsis However, all of the mentioned etiologic agents were never isolated in blood.

The newborn presented an increase of PCR. It is important to mention that PCR in the neonatal period is a marker with a high sensitivity but with a low specificity to diagnose a severe bacterial infection[32]. Furthermore, PCR also could increase in other non-infectious condition that involves an increased inflammatory response[33].

Other diagnosis for neonates with fever include systemic infections caused by bacteria (e.g. congenital syphilis), virus (e.g. herpes simplex virus, enterovirus, cytomegalovirus, influenza, and respiratory syncytial virus), parasites (e.g. malaria and toxoplasmosis), and fungi (e.g. candidiasis)[34]. However, many of these diseases have typical clinical presentations that our patient did not present.

One of the approaches to prevent the dengue infection is the vector control that transmits it. In the congenital dengue case, the main goal would be to avoid the maternal infection using the same tools that are used in the general population. These includes eradicating the possible hatcheries, avoiding having standing water and using insecticides to decrease the A. aegypti population, among others[26].

Conclusion

In the presented case, the infection was self-limiting and there were no severe maternal-fetal outcomes. However, the maternal infection caused by dengue could have a higher risk of adverse perinatal results, especially preterm delivery and low birth weight. So in the areas of high endemicity of dengue the disease should be suspected in pregnant women that present with febrile syndrome and compatible symptomatology. In cases of the mothers diagnosed with dengue, their children should be carefully observed, performing a serial hemogram in the first days of life given the risk of congenital transmission.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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