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CLINICAL CASES

Dengue in pregnancy and dengue neonatal: a case report

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Abstract

We present the case of a newborn whose mother was diagnosed with dengue 3 days before the resolution of the pregnancy. At birth, the product presented data of a systemic inflammatory response, so a picture of neonatal sepsis was suspected, receiving antimicrobial treatment without finding improvement, having a torpid clinical evolution, persisting with high-grade fever and adding thrombocytopenia and lymphopenia, which is why considering the history maternal dengue diagnostic tests were performed on the product, with positive results confirming the diagnosis of neonatal dengue, initiating supportive management with a favorable evolution.

Keywords: *Neonatal dengue. Sepsis. Thrombocytopenia. High-grade fever.*

Introduction

Dengue is a disease caused by infection with one of the four variants of the dengue virus (DENV), which is transmitted by mosquitoes, mainly Aedes aegypti. It should be noted that each variant has serotype-specific immunity[1]. During pregnancy, the infection, although rare, can manifest asymptomatically or present with severe symptoms and high morbidity[2]. Transmission to the newborn can be vertical or horizontal. Vertical transmission of dengue is rare, with an estimated prevalence of 1.6-10.5%. The incubation period varies from 3 to 25 days, most commonly being 5-8 days. This transmission usually occurs in endemic areas and occurs mainly when the mother is infected during the third trimester of pregnancy. The health implications of the maternal-fetal binomial have been documented since the early 2000s[2]. It should be noted that in Mexico there are no epidemiological studies that report the exact prevalence of neonatal dengue. Machain (Mexico, 2018) conducted a study of patients from Veracruz, Tabasco, and Tamaulipas with immunoglobulin M (IgM) or NS1 for dengue positive during pregnancy in 82 patients, 31 were during the last trimester and all those that were severe occurred between gestational week 34 and 36, of these last patients, five died. Of the reported newborns, only one was low birth weight and none developed symptoms during their hospital stay[3].

The antibody response to DENV infection is primarily directed at specific serotype determinants, but there is a substantial level of serotype E cross-reactive antibodies, with the precursor membrane (pre-M) and NS1 being the main viral proteins targeted. *In vitro*, specific antibodies to the E protein can mediate infection neutralization, complement-mediated direct lysis, or antibody-dependent

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cellular cytotoxicity of DENV-infected cells and block the binding of the virus to cell receptors[4].

Pre-M-specific antibodies only bind to virions that have not fully matured and have remaining pre-M protein uncleaved. NS1 is not found in the virion; Thus, NS1-specific antibodies are unable to neutralize viral infection, but they can direct complement-mediated lysis of infected cells. To date, the basis for neutralization of the virus by antibodies is not well understood[4].

Clinical manifestations

It is estimated that more than 390 million DENV infections occur each year and approximately 96 million are clinically evident. Clinically apparent dengue is more common among adults, while among children, most infections are usually asymptomatic or minimally symptomatic and may occur with persistent vomiting. Clinical accumulation of fluid (ascites, pleural effusion), bleeding from the mucous membranes, lethargy or restlessness, hepatomegaly > 2 cm concurrent increase in hematocrit with a rapid decrease in platelet count. Severe plasma leak causing: shock, fluid accumulation with respiratory distress. May also present with severe bleeding[4].

It is also feasible to present severe organ involvement through aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1000 units/L and deterioration of alertness. A primary DENV infection is defined as the first wild-type infection that an individual suffers from, while a secondary infection is the second wild-type infection caused by a different serotype of DENV. Secondary infections separated in time by more than 18 months represent the greatest risk of causing a serious clinical outcome[4].

The incubation period for DENV infection ranges from 3 to 14 days; symptoms usually develop 4-7 days after an infected mosquito bite. Phases of infection: there are three phases that can be observed in the context of a DENV infection: a febrile phase, a critical phase, and a recovery phase; however, the critical phase is not observed in all infection categories[4].

Within the 1997 WHO classification scheme, the three phases of infection occur in the context of dengue hemorrhagic fever and dengue shock syndrome; dengue fever (DF) includes febrile and recovery phases, but no critical phases. Within the WHO's 2009 classification scheme, the three phases of infection occur in the context of severe dengue and dengue with warning signs; dengue without warning signs includes febrile and recovery phases, but no critical phases[5].

Febrile phase: the febrile phase of DENV infection is characterized by sudden onset high fever (≥ 38.5°C) accompanied by headache, vomiting, myalgia, arthralgia, and transient macular rash in some cases. Children have a high fever but are usually less symptomatic than adults during the febrile phase. The febrile phase lasts 3-7 days, after which most patients recover without complications. Headache, eye pain (i.e., pain with eye movement), and joint pain occur in 60-70% of cases. The rash occurs in about half of the cases, being more common during the primary infection than during the secondary infection. When present, the rash usually occurs 2-5 days after the onset of fever[6-8].

In children, clinically significant bleeding rarely occurs, usually associated with prolonged, deep shock. It should be noted that there is not always significant thrombocytopenia when hemorrhagic manifestations occur and when it is present, the risk of bleeding increases. Physical examination may demonstrate conjunctival injection, pharyngeal erythema, lymphadenopathy, and hepatomegaly. Facial edema, petechiae (on the skin and/or palate), and bruising (particularly at venipuncture sites) may be observed[9,10].

A biphasic ("saddle") fever curve has been described in about 5% of cases; in these patients, acute febrile illness remits and then recurs about a day or two later; the second febrile phase lasts 1 or 2 days. Leukopenia and thrombocytopenia (≤ 100,000 cells/mm) are common[11,12] (Fig. 1). Serum aspartate transaminase (AST) concentrations are usually elevated and these elevations are usually moderate (2-5 times the upper limit of normal), but marked elevations (5-15 times the upper limit of normal) occasionally occur. Elevated liver enzymes are common in the febrile phase; synthetic liver dysfunction (i.e., elevated activated partial thromboplastin time) and fibrinogen decreases are not frequently identified.

Between days 3 and 7 of the disease, significant vascular leakage reduces intravascular volume and decreases organ perfusion. Corresponding clinical manifestations may include persistent vomiting, increasingly severe abdominal pain, painful hepatomegaly, development of pleural effusions and/or ascites, mucosal hemorrhage, and lethargy or restlessness; laboratory findings may include a high or increasing hematocrit level (≥ 20% from baseline) concurrent with a rapid decrease in platelet count[13-16] (Fig. 1).

Critical phase: The vast majority of infections that progress to a critical phase are the result of second DENV infections that occur more than 18 months after a first resolved infection. However, a subset of critical infections

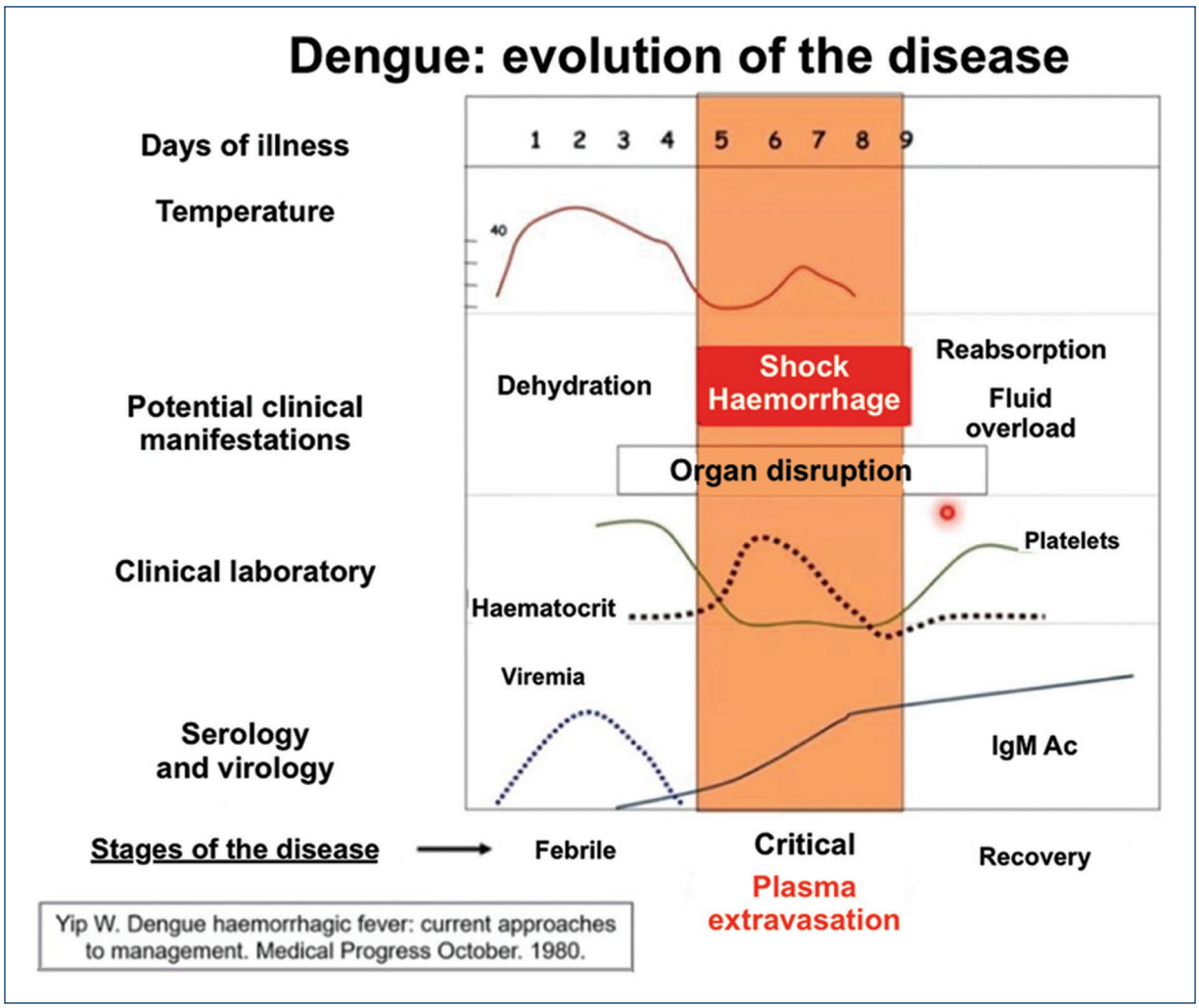

Figure 1. The image shows the natural evolution of the disease where first there is a febrile phase that lasts approximately 5 days and then presents changes in the blood count where the progressive decrease of the platelet count stands out, this being the critical stage of the disease.

occurs in children under 1 year of age, at the time when maternal antibodies are below protective levels and the child experiences a primary wild-type infection. The critical phase lasts 24-48 h. Initially, adequate circulation can be maintained by physiological compensation, resulting in a narrowing of pulse pressure (systolic pressure minus diastolic pressure ≤ 20 mmHg). In confirmed cases of dengue in the mother, most newborns do not show symptoms, but they may present with neonatal sepsis and present with fever, rash, irritability, and bleeding[17].

Presentation of the case

This is a full-term male newborn, son of a 21 year old woman, G1, P0, C1, A0. The mother received antenatal care at her local health center, with a total of 8 consultations, and underwent 3 reported ultrasounds with no obvious abnormalities. In addition, TdPA immunizations were administered during pregnancy, although immunization against influenza and COVID-19 was denied by the patient.

During pregnancy, the patient denied having presented threats of abortion, threat of pre-term delivery, pre-eclampsia, gestational diabetes, or other complications of pregnancy. She developed a urinary tract infection at 32 weeks of gestation, receiving unspecified antimicrobial treatment and finding improvement in symptoms. In addition, he presented cervicovaginitis on two occasions, which were managed with unspecified antimicrobial treatment with improvement of symptoms. Three days before the resolution of the pregnancy, the patient experienced headache, photophobia, myalgias,

Table 1. The values reported in the serial blood counts show the natural evolution of the disease where after the febrile stage a progressive decrease in platelet and leukocyte count begins, with an increase in hematocrit and an improvement in platelet count as well as in leukocytes from day 7 of the disease

Days of life	Platelets × 10^3	Hemoglobin (g/dL)	Hematocrit (%)	Leukocytes × 10^3	Neutrophils × 10^3	Lymphocytes × 10^3	Monocytes × 10^3	Eosinophils × 10^3
1	222	12.7	39.30	15100	8170	5770	920	180
5	32	14.9	46.50	1500	450	450	390	40
6	16	14.6	43.4	3900	1310	1950	530	80
7	130	11.8	36.10	11800	3000	6930	1560	220

arthralgias, and unquantified fever. She self-medicated with paracetamol, without finding improvement. 24 h after the onset of symptoms, they decide to go for evaluation at their health center, where dengue is probably diagnosed, given the typical manifestations and its location in an endemic area of Morelos. The patient was admitted to the General Hospital of Jojutla where she was kept under surveillance and laboratory studies were taken which reported: Leukopenia (4 thousand) and a decrease in platelets (150 thousand, previously 180 thousand) for which a polymerase chain reaction (PCR) test was performed for the detection of dengue. Given the clinical suspicion of the diagnosis and maternal complications, it was decided to terminate the pregnancy by cesarean section.

A male product of 40 SDG per Capurro was obtained through the abdomen, who cried and breathed at birth presenting a weak cry and a heart rate > 100 beats/min, with a report of meconium-stained fluid. The product had a weight of 3700 g height: 52 cm APGAR: 8/8, at 10 min of life the product presents data of respiratory distress at the expense of: discrete intercostal retraction, discrete nasal flaring, and respiratory whine receiving a Silverman score of 3, so it was decided to transfer him to the neonatal intensive care unit (NICU) where a chest X-ray was taken, which showed evidence of horizontal costal arches and an increase in intercostal spaces, in addition to a predominant nodular infiltrate in the right lung. An umbilical catheter was placed in an intrahepatic position and laboratory studies were taken, identifying in the blood count a hemoglobin of 12.7 g/dL, a hematocrit of 39.3%, a leukocyte count of 15.1 (94.1% neutrophils, 38.2% lymphocytes, 6.1% monocytes, 1.2% eosinophils, 0.4% basophils) and platelets of 222 thousand. Cord blood gases reported: a pH of 7.3, PCO_2 of 47 mm Hg, pO_2 of 10 mm Hg, lactate of 2.6 mmol/L, DB - 3.3 mmol/L, and HCO_3 of 23.1 mmol/L.

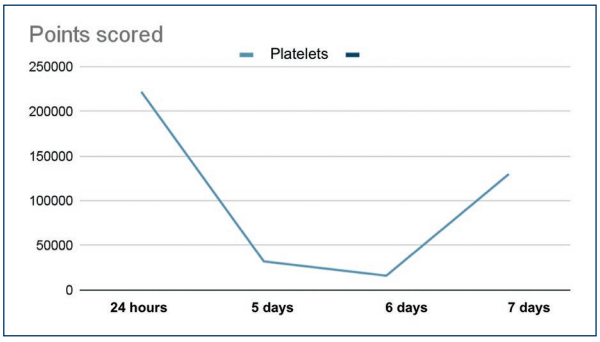

Figure 2. The graph shows a downward curve of the platelet count in the newborn during the course of the disease in which a clear decrease in the platelet count can be seen that becomes more pronounced between days 5 and 6 of the disease with a significant increase in the platelet count from day 7 of the disease evidencing the recovery stage.

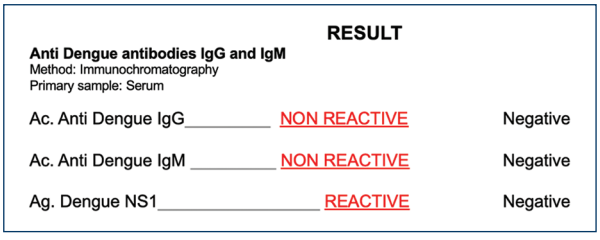

Figure 3. The report of the diagnostic test performed on the newborn whose result was positive for dengue when Ag. NS1 was positive and is shown. NS1 is one of the 7 non-structural proteins of the dengue virus that are thought to be involved in viral replication, so a positive result for NS1, with negative immunoglobulin M (IgM) and IgG indicates recent infection, probably with a disease time of < 5 days.

The product was admitted to the NICU with the diagnosis of "full-term newborn (40 weeks of gestation) with high weight for gestational age, meconium aspiration

syndrome and child of a mother with dengue without alarm data". Antimicrobial treatment with ampicillin and amikacin was initiated due to meconium aspiration and the patient was kept fasting receiving supplemental oxygen through nasal CPAP due to the persistence of respiratory distress that did not improve with supplemental oxygen supply through nasal tips.

At 24 h of life, nasal CPAP was removed and nasal prongs were progressed due to improvement of the ventilatory pattern, presenting adequate tolerance, and PCR test results for dengue were collected from the mother, which reported positive NS1 with DENV-3 serotype. The product presented adequate clinical evolution, however, on the 5th day of life the newborn presented a fever quantified up to 39°C, so new blood biometry was taken that reported: hemoglobin of 14.9 g/dL, a hematocrit of 46.5%, a leukocyte count of 1500, (29.9% neutrophils, 29.9% lymphocytes, 26% monocytes, 2.4% eosinophils, 11.8% basophils, platelets of 32 thousand and liver function tests that reported ALT/TGP: 38.0 U/L, serum albumin: 3.10 g/dL evidencing a decrease in platelet count (Table 1) so it was decided to perform a specific PCR test for dengue and water support was started at 110 mL/kg/day with dynamic management of intravenous fluids and thermal control with paracetamol and starting management with vitamin K. The patient continued to be feverish, irritable, but remained without bleeding data. 24 h later, new control laboratory studies were taken which reported hemoglobin of 14.6 g/dL, a hematocrit of 43.4%, a leukocyte count of 3900, (33.7% neutrophils, 50.1% lymphocytes, 13.5% monocytes, 2.1% eosinophils, 0.6% basophils,) platelets of 16 thousand (Fig. 2). TP: 14.62, APTT: 64.09, INR: 1.09, so it was decided to transfuse platelets and fresh plasma, on the 7th day of life the PCR report for dengue was collected, identifying reactive Ag. NS1 confirming the infection in the neonate (Fig. 3).

Discussion

This clinical case presents a complex scenario in which maternal dengue during pregnancy conditions complications in the pregnant woman, causing the resolution of the pregnancy urgently through the abdominal route, associating neonatal complications, in particular a meconium aspiration syndrome and a clinical picture that initially suggested neonatal sepsis. Although the diagnosis of dengue in the mother was clinical, the clinical picture of the newborn was larval in the first hours of life, representing a real challenge for the diagnosis since, as previously described, vertical transmission is rare, once the newborn began with a picture of persistent high-grade fever, complementary laboratory studies were repeated, evidencing the development of thrombocytopenia In addition, it was possible to collect the result of the confirmatory tests for dengue carried out on the mother, which yielded a positive result, so diagnostic tests were carried out on the newborn, thus confirming the diagnosis. Another of the challenges identified in this clinical condition was the adequate water management of the newborn since, as described, there is no evidence or guidelines that guide the most appropriate water management in these patients, having opted in this case to carry out a dynamic water management similar to that of any other newborn, carrying out fluid increases of 12.5 mL/kg/day every 24 h maintaining strict control of water balance and diuresis, another challenge during the course of the disease in the newborn was the risk of developing bleeding data, so it was decided to initiate management with Vitamin K and once a thrombocytopenia of 16,000 was identified, it was decided to transfuse platelets. A transfontanelar ultrasound was performed where hemorrhage at this level was ruled out. It should be noted that at no time was there any data of bleeding at another level. Temperature management was carried out with alternating paracetamol and metamizole, thus achieving adequate thermal control.

The relationship between maternal dengue infection and the risk of meconium aspiration syndrome in the newborn is a question that requires further investigation. Dengue is a mosquito-borne disease that affects people of all ages, but the focus on neonatal dengue is focused on newborns who acquire the virus during birth or shortly after birth. Although neonatal dengue is rare, it is important to understand its clinical characteristics, diagnosis, and management to ensure adequate care and prevent complications, it should be noted that the management of the patient with dengue involves a high intake of fluids which, so far, has not been fully studied in the newborn, making it a real challenge for the treating physician.

Clinical characteristics in the newborn

Neonatal dengue presents variably and can be asymptomatic or have symptoms ranging from mild to severe. Typical symptoms of dengue in neonates may include:

- Fever may be one of the first signs of infection in neonates, although body temperature may not rise significantly. Irritability and inconsolable crying.
- Poor diet or difficulty sucking, vomiting and diarrhea, respiratory symptoms, hemorrhagic manifestations:

thrombocytopenia and hemorrhagic manifestations, such as petechiae, bleeding gums, or nose, can occur in severe cases.

Diagnosis

Diagnosing neonatal dengue can be challenging due to the variety of symptoms that can be mistaken for other neonatal conditions. Diagnosis is based on a combination of clinical criteria and laboratory tests.

In cases of confirmed maternal dengue, delivery care is carried out under usual conditions, but precautions are taken to avoid contamination by blood and fluids. A series of diagnostic tests and evaluations are performed on both the newborn and the mother.

Diagnostic tests and evaluations

1. Confirmation of the diagnosis in the newborn: a PCR for dengue and specific IgM for dengue of cord blood or the newborn is requested in the first 48 h of life. IgM dosing for dengue may need to be repeated later, as its titers may not be detected initially.
2. Clinical evaluation: a complete blood count with lamina, C-reactive protein, procalcitonin, and blood culture is performed after 6 h of life.
3. Attention to warning signs: thrombocytopenia of < 100,000 and an increase in hematocrit of 20% are considered as warning signs. Leukopenia may also be observed, indicating severity in this age group[17].

Hospitalization of the newborn

- The hospitalization sector is adapted according to the clinical situation, guaranteeing isolation, control, and strict and permanent monitoring.
- Even if there are no clinical manifestations, the patient is admitted to an area that ensures isolation, with constant monitoring. In asymptomatic cases, it is not necessary to separate the newborn from the mother, as long as the clinic allows it and adequate controls are maintained in the co-housing.
- Vector isolation with mosquito nets and tulle is implemented, ensuring that there are no vectors (mosquitoes) in the area before patient admission.

Treatment

- Treatment is adjusted to the clinical situation of the newborn.
- In asymptomatic cases, the risk and benefit of initiating breastfeeding are evaluated, considering that some authors suggest the possibility of transmission of the disease through milk.
- In situations of shock, the protocol for the treatment of shock in the neonatal period is followed. Volume replacement is adapted to the clinical situation, starting with a physiological solution at 10 mL/kg of weight in 30 min to 1 h. Sudden changes in osmolarity and flow due to the high risk of intracranial bleeding are avoided.

Evolution and discharge

If the newborn with dengue remains separated from his mother and is asymptomatic in the first 7 days, control and follow-up can continue in mother-child accommodation, maintaining the aforementioned isolation measures.

- The initiation of breastfeeding is allowed according to the evolution of the maternal disease.
- After 15 days, the patient is discharged home with home monitoring by the health team[17].

Management of neonatal dengue focuses on supporting and treating symptoms. Measures may include:

- Hydration: maintaining hydration is crucial, especially if the newborn has a fever and vomiting. Intravenous fluids may be needed in severe cases.
- Fever management: safe and suitable antipyretics for the neonate can be used to control fever.
- Platelet transfusions: in cases of severe thrombocytopenia or bleeding manifestations, transfusions of platelets and other blood products may be given as needed.

Prognosis

The prognosis of neonatal dengue varies depending on the severity of the infection and how quickly treatment is started. In general, most neonates recover completely with proper management. However, in severe cases, neonatal dengue can be life-threatening, underscoring the importance of medical care.

Transmission mechanism

Vertical transmission of dengue can occur in several ways:

- Intrauterine: during pregnancy, the DENV can cross the placenta and reach the fetus. This route of infection can occur at any stage of pregnancy, although it

is generally considered uncommon. During delivery: If the mother has dengue and gives birth to a baby, there is a chance that the newborn may become infected during delivery, especially if the baby comes into contact with blood or maternal body fluids contaminated with the virus.

- Breastfeeding: although transmission of dengue through breast milk is rare, the virus has been documented to be excreted in breast milk. This raises the possibility that a newborn may become infected if fed breast milk from a mother with active dengue. However, breastfeeding is not considered a common route of infection for neonatal dengue[17].

Clinical manifestations of neonatal dengue transmitted vertically:

- The diagnosis of vertically transmitted neonatal dengue is based on a combination of clinical criteria and laboratory tests, such as PCR or reverse transcription-PCR tests to detect dengue viral RNA in newborn blood samples and serological tests to detect IgM and IgG antibodies. The management of vertically transmitted neonatal dengue is similar to that of acquired neonatal dengue after birth. It focuses on symptom support and treatment, including hydration, fever care, and monitoring for bleeding manifestations. In severe cases, transfusions of platelets and other blood products may be necessary[17].

Conclusion

Mother-to-child transmission of dengue is a rare but important route of infection. Neonatal top-down dengue can present with a variety of symptoms, and its diagnosis and management require careful clinical evaluation and laboratory testing.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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