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CASE REPORT

A premature newborn born to an adolescent girl with acute Ebola virus disease and malaria survives in a resource-limited setting in an Ebola treatment unit in DR Congo: "A case report"

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Key Clinical Message

In the acute phase of Ebola virus disease (EVD) premature neonatal survival is extremely rare. High mortality is related to prematurity, neonatal complications of Ebola, and precarious conditions of neonatal care in underresourced ETUs. This is a case of preterm neonatal survival in the setting of acute maternal EVD infection.

Abstract

This case describes rare preterm newborn survival in the setting of an Ebola treatment unit in Eastern DRC. The neonate was born vaginally to an acutely ill 17-year-old mother who was vaccinated against Ebola virus after being identified as a contact of her father, who was a confirmed case and who did not survive his infection. This woman was admitted to an Ebola treatment unit at 32 weeks of gestation and given monoclonal antibody treatment. She gave birth vaginally, succumbing to postpartum hemorrhage 14 h after delivery. This child survived despite compounding vulnerabilities of preterm birth and maternal Ebola infection. Despite a negative test for EVD, the neonate was given a single dose of monoclonal antibody therapy in the first days of life. We believe maternal vaccination and neonatal monoclonal antibody treatment contributed to the child's survival. The circumstances surrounding neonatal survival in this extremely resource-limited context must be analyzed and disseminated in order to increase rates of neonatal and maternal survival in future outbreaks. Maternal and neonatal health are critical aspects of outbreak response that have been understudied and underreported leaving clinicians severely underresourced to provide life-saving care in outbreak settings. Pregnancy and childbirth do not stop in times of disease outbreak, adequate equipment and trained staff required for quality neonatal care must be considered in future outbreak responses.

KEYWORDS

Democratic Republic of Congo, Ebola and pregnancy, limited resources, neonatal survival, preterm delivery

1 | INTRODUCTION

Discovered in 1976 in the Democratic Republic of the Congo (DRC), Ebola virus disease (EVD) is a serious, highly contagious disease transmitted to humans from wild animals and with human-to-human transmission through contact with bodily fluids.[1] As of August 22, 2022, the DRC has experienced 15 EVD outbreaks.[2] Without early and adequate treatment, infection is complicated by multisystem organ failure leading to death in less than 3 weeks.[3] From its discovery, until 2020, over 15,000 people have died due to EVD.[4] According to the World Health Organization (WHO), the average case fatality is around 50%.[5] In 2016, a review of 12 studies on maternal mortality in 108 cases of EVD found a case fatality rate of 84.3% with a neonatal survival of 0.9%.[6] The main obstetric complications are spontaneous abortion, premature rupture of membranes (PRM), preterm delivery, perinatal hemorrhage and intra-uterine growth retardation (IUGR). Pregnancy outcomes are generally unfavorable.[7] One study in West Africa reported two cases of neonatal survival but both died within the first 8 days of life after developing EVD.[8] In the DRC, during the tenth epidemic in 2018–2020, three cases of neonatal survival were reported in two different studies.[9]

In a context where healthcare is provided with limited resources, staff and evidence base for management of preterm babies born to mothers with active/acute Ebola infection, neonatal resuscitation remains a challenge and survival of premature infants born to mothers with EVD remains exceptional. This case study reports the clinical course of an infant born prematurely to a mother in the acute phase of Ebola viral infection.

2 | CASE PRESENTATION

On September 27, 2019 the Ebola treatment unit (ETU) in Mangina, North Kivu in DRC admitted a 17-year-old adolescent girl who was 32 weeks (approx. 7.5 months) pregnant, weighing 45 kg, confirmed to have EVD.

Her clinical symptoms included headaches, chills, fever, joint and abdominal pain, nausea, and dizziness. Seeking management for her symptoms, which began 7 days before her admission to the ETU, she visited a local health post where a diagnosis of malaria in pregnancy

was made. The local health post prescribed 6 days of antimalarial, mono-antibiotic, and antispasmodic therapy without symptomatic improvement, hence her transfer to the ETU.

The patient's obstetrical history included one living child delivered by cesarean section due to borderline pelvis. This was her second pregnancy. Her last menstrual cycle dated February 17, 2019. Four days before the onset of the symptoms detailed above, she was vaccinated against EVD by Ervebo®, recombinant vesicular stomatitis virus-Ebola Zaire (rVSV-ZEBOV). At the time of admission, fetal movement was present. Upon admission to the ETU she appeared in ill-health and was bedridden. She was not anemic nor did she show signs of jaundice. Her blood pressure was 126/62 mmHg, heart rate 98 beats/min, respiratory rate 22 breaths/min with a temperature of 38.5°C and arterial oxygen saturation (SaO_2) at 98% on free air.

Her abdomen was enlarged by a gravid uterus with a large longitudinal axis and a large upper end with a median sub-umbilical scar. Fetal heart tones were undetectable due to lack of appropriate equipment. The ETU was not equipped with a Doppler or ultrasound machine. On the day of admission the patient began to experience uterine contractions of low intensity spaced 10 min apart. Fetal presentation was cephalic, mobile, and in position II. The vulva was clean, cervix medial, 50% effaced, and dilated 2 cm. A borderline pelvis was noted upon physical examination. We confirmed a diagnosis of malaria (*Plasmodium falciparum*) by the rapid diagnostic test (RDT) and EVD through real-time polymerase chain reaction (RT-PCR) analysis for Ebola virus nucleoprotein with cycle threshold (Ct) values of glycoprotein (GP) 23.7 and nucleoprotein (NP) 19.3 by the GeneXpert® (Cepheid, Sunnyvale, CA, USA). We treated the patient with artesunate, ceftriaxone, albendazole, paracetamol, oral rehydration solution, multivitamins and omeprazole. There was no stock of dexamethasone to support fetal lung development so we were unable to treat the patient with steroids in preparation for preterm delivery. Initiated by the PALM trial,[10] all admitted patients were entitled to receive one of the only two available monoclonal antibody treatments, neutralizing monoclonal antibody (mAb114), Ebanga® (Ansuvimab, Ridgepack Biotherapeutics, USA) and a neutralizing monoclonal composed of three antibodies, Regeneron® (REGN-EB3). Allocation was done by randomization.[11] Our patient was allocated mAb114 by one time intravenous infusion of 50 mg/kg/h.

On Day 3 of admission, she showed signs of breast tension, bilateral galactorrhea with absence of active fetal movements. We suspected fetal death in utero but were unable to confirm without ultrasound equipment. Her general condition was deteriorating. She developed a fever of 38.9°C and repeat RT-PCR showed Ct values of GP 22.0 and NP 16.9 for Ebola virus, indicating a high viral load. At 2 p.m. on the same day, the patient had effective uterine contractions, cervical effacement at 80% and dilation of 4 cm. The presentation of the fetus was cephalic and fixed. At 9 p.m., after spontaneous rupture of membranes, she gave birth by vaginal delivery to a premature female with Appearance-Pulse-Grimace-Activity-Respiration (APGAR) scores of 3/5/7 at 1, 5 and 10 min after birth, weighing 1850 g, head circumference of 29 cm, length of 45 cm without apparent malformations. Her mother died of postpartum hemorrhage 14 h after delivery.

The newborn's suckling, swallowing, Moro and grasping reflexes were positive. She had a temperature of 35.6°C, heart rate of 122 beats/min, respiratory rate of 56 breaths/min with an SaO_2 of 96% on free air. Blood work revealed hypoglycemia at 17 mg/dL, hemoglobin 12 g/dL, hypo-albuminemia at 2.9 g/dL, transaminases elevation with aspartate aminotransferase (ASAT) at 71 U/L, hyperkalemia at 5.8 mEq/L, without evidence of hemolysis or related clinical signs. The newborn was given intravenous cefotaxime 100 mg twice daily for 7 days, ampicillin 100 mg thrice daily for 7 days, gentamycin 10 mg daily for 3 days, metronidazole 100 mg thrice daily for 7 days, glucose 10% 20 mL bolus and then a continuous infusion of 120 mL 10% glucose + 1.4 mg KCl + 1 mL magnesium and 2 mg calcium gluconate over 24 h and vitamin K1 1 mg daily intramuscularly for 2 days. The mother's adnexal swab was RT-PCR positive but the newborn's venous whole and buccal swab were negative. However, the newborn could not be transferred to a health center with a neonatal care nursery because she was born to an Ebola positive mother. Protocol prescribed that any child born to an EVD positive mother should receive one of the two available monoclonal antibody treatments, despite negative RT-PCR results.[10,11] Thirteen hours after birth the newborn was given 22.5 mL of Regeneron® (REGN-EB3) by randomization, which was administered in a one-time IV dose of 150 mg/kg. The newborn did not receive breastmilk and received parenteral nutrition with glucose 10% at a rate of 80 mL/kg and 5 mL/kg of milk (ready-to-use infant formula) eight times per day with a gradual increase of 5 mL/kg/day, which she tolerated well.

In the absence of an incubator or heating lamp, we set up a makeshift heating system by wrapping cotton blankets over a hot water bottle. At 1 m above her bed, we installed four 100 Watt electric bulbs to heat the ambient area which could drop to 15°C in the ETU. We introduced a variation of Kangaroo care without direct skin-to-skin contact. Instead, Kangaroo care providers were lightly covered with the *personal protective equipment* (PPE); this was practiced three times a day for 2–3 h for the first 10 days by EVD survivors who worked in the ETU. Her

evolution was without particularities, and she was discharged after 14 days to the health post nursery outside the Ebola high-risk zone. At 45 days of life, her weight was 3850 g. She was healthy and developing normally at our last follow-up visit at the age of 3 years and 7 months on 23 April 2023.

3 | DISCUSSION

This case of neonatal survival of a premature infant born in the acute phase of EVD during the DRC's tenth epidemic in a context of limited resources remains exceptional. During maternal infection with EVD, pregnancies usually result in either spontaneous abortion or fetal death in utero. In this case, malaria co-infection cannot be ruled out as a contributing factor to premature delivery. The newborn did not show clinical signs of malaria infection and was not tested. In case of Ebola infection, if newborns are born alive, most die within 3 weeks of life.[12] In a review of five studies of EVD (1978-2010), 15 infants born to EVD positive mothers all died within 19 days of birth.[13] These unfavorable outcomes have multifactorial causes. Factors contributing to mortality are related to the high concentration of virus particles in the placenta and amniotic fluid, a delay in the synthesis of maternal immunoglobulins (IgG) which occurs from the sixth day after onset of Ebola symptoms,[14] the limited passage of maternal antibodies (IgG) to the fetus, which only starts in the 13th week of gestation,[15] and late gestational development of fetal antibody synthesis, which begins around the twentieth week.[14] Recently, three cases of neonatal survival during the active phase of EVD have been reported, including one during the Guinea epidemic and who has born with positive RT-PCR and two others born with negative RT-PCR tests during the tenth epidemic in DRC.[16,17] Our patient is therefore the fourth documented case of survival of newborns born in the active phase of EVD, the third case born in the active phase of EVD with negative RT-PCR and who did not develop the infection during hospitalization, and the first case of survival of a premature newborn born in highly precarious conditions, with no incubator or other necessary resuscitation equipment and who did not develop another neonatal infection afterward.

In this case, we believe maternal vaccination and EVD specific monoclonal treatment administered to her mother a few days before delivery were possibly sufficient to protect the fetus from intra-uterine infection. However, an additional effect of transfer of maternal antibodies for EVD to the fetus cannot be excluded either. This study remains limited due to a logistical problem, anti-Ebola antibodies were not measured in the newborn. According to the literature, some infants who had negative RT-PCR at birth became positive within 5 days of life.[8] For this infant, compliance with infection prevention and control (IPC) measures during and after birth, administration of monoclonal antibodies to her mother during pregnancy and to her in the first days of life along with early management of prematurity, may have contributed to prevention of Ebola virus infection and neonatal survival. This case challenges current assumptions that vertical mother to child transmission of EVD is systematic. The results of this case and those of two other neonates in one study,[17] born in the active phase of EVD with negative RT-PCR and whose mothers also received monoclonal antibodies before delivery, further support our hypothesis.

The absence of neonatal infection at the time of passage through the genital tract also remains unique, as risk of infection during vaginal birth in the active phase of EVD remains very high. Further research may shed more light on how vertical mother-to-child transmission of EV infection can be prevented in newborns born to mothers with EVD.

4 | CONCLUSION

Neonatal survival of a premature infant born to a mother in the acute phase of EVD with concurrent malarial infection remains rare but possible, even in a context of limited resources. The establishment of appropriate conditions for adequate management of obstetrical and neonatal emergencies is essential for all ETUs.

AUTHOR CONTRIBUTIONS

Prince Imani-Musimwa: Conceptualization; investigation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing. **Emilie Grant:** Investigation; methodology; validation; writing – original draft; writing – review and editing. **Micheline Feza-Malira:** Investigation; writing – original draft. **Placide Mbala-Kingebeni:** Validation; writing – original draft; writing – review and editing. **Gisèle Buhoro-Baabo:** Investigation; writing – original draft. **Espérence Zawadi-Endanda:** Investigation; writing – original draft. **Rigo Fraterne-Muhayangabo:** Conceptualization; investigation; writing – original draft. **Inès Claris-Mwatsi:** Investigation; writing – original draft. **Zacharie Tsongo-Kibendelwa:** Validation; writing – original draft. **Olivier Nyakio-Ngeleza:** Supervision; writing – original draft. **Sihali Juakali-Kyolov:** Methodology; writing – original draft. **Stanis Wembonyama-Okitosho:** Writing – review and editing. **Dieudonné Sengey-Mushengezi-Amani:** Validation; writing – review and editing. **Daniel Mukadi-Bamuleka:** Validation; writing – review and editing. **Mija Ververs:** Conceptualization; investigation; methodology;

project administration; supervision; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

No competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed for the current study are available from the corresponding author upon request.

ETHICS STATEMENT

This is a case report study, so no ethical approval was required.

CONSENT

The patient's father provided written informed consent for publication of this case report.

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