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Ebola viral disease and pregnancy

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Abstract

Ebola viral disease's interaction with pregnancy is poorly understood and remains a particular challenge for medical and para-medical personnel responding to an outbreak. This review article is written with the benefit of hindsight and experience from the largest recorded Ebola outbreak in history. We have provided a broad overview of the issues that arise for pregnant women and for the professionals treating them during an Ebola outbreak. The discussion focuses on the specifics of Ebola infection in pregnancy and possible management strategies, including the delivery of an infected woman. We have also discussed the wider challenges posed to pregnant women and their carers during an epidemic, including the identification of suspected Ebola-infected pregnant women and the impact of the disease on pre-existing health services. This paper outlines current practices in the field, as well as highlighting the gaps in our knowledge and the paramount need to protect the health-care workers directly involved in the management of pregnant women.

Keywords

Ebola, Ebola viral disease, obstetrics, pregnancy, haemorrhagic fever, global health, epidemics, humanitarian, maternal medicine, maternal mortality

Introduction

Ebola virus disease (EVD) was first recognised in 1976, with multiple subsequent outbreaks confined to sub-Saharan Africa.[1] In 2014, an epidemic unique in both scale and distribution spread across a region of West Africa, and was transported to Europe and the United States of America. At the time of writing, total figures from this outbreak alone were estimated to be 25,515 infections, 10,572 deaths of which almost 500 have been health-care workers.[2]

While this article is focused on the pregnant patient, an infected pregnant woman is unlikely to be an isolated occurrence but part of a wider outbreak with generalised transmission within the community. As the current epidemic has evolved, reflection, evaluation and adaptation of control strategies have resulted in increasing knowledge and experience with this previously neglected disease. This is particularly the case for the management of the infected pregnant woman, with much of what is now practised resulting from field experience and ongoing multi-professional discussions.

It is conventional medical wisdom that one should assess the safety of their environment before responding to an emergency. This principle is a guiding force in the context of Ebola. Health-care workers and health facilities have paid a heavy price during this epidemic, and in turn the populations which they aimed to serve will suffer from the loss of their expertise, long after the epidemic is over. Maternity services have been particularly vulnerable to nosocomial Ebola infections.[3,4] It is therefore essential to discuss infection control and occupational safety as a priority in the management of pregnant women during an Ebola outbreak.

There has been no experience of managing a pregnant woman with Ebola in a resource-rich setting with access to high-dependency facilities. While appropriate for all clinicians to be familiar with the risk factors and symptomatology to consider the diagnosis during this epidemic, the priority should be to meet the needs of those who are directly affected by this epidemic. Treatment and management strategies for infected pregnant women in a Western setting have gained significant attention,[5–7] but these remain hypothetical at present and limitations remain in their transferability to most sub-Saharan contexts. In this setting there are technical, logistical and human resource constraints present. Pregnant women in this region are also most likely to receive their care in Ebola Management Centres (EMC) dedicated to the isolation and management of infected persons.

In this article, we aim to give a broad overview of the complex interaction between Ebola and pregnancy and possible management strategies.

Epidemiology

The burden of EVD in pregnant women remains uncertain due to the low numbers of patients affected in previous outbreaks and limitations in data collection during the current epidemic. In particular, numbers and rates of infected pregnant women and accurate survival rates are not yet available. However, in the two previously published case series, the estimated case fatality ratio (CFR) was approximately 90%.[8,9] While this has widely been used as a maternal mortality estimate, unpublished data from the current outbreak collected by Médecins sans Frontières (MSF) would suggest that the CFR is lower. The same case series reported a zero perinatal survival rate with all pregnancies ending in spontaneous miscarriage, stillbirth or neonatal death. The same observation has been made in all outbreaks, and so far in this epidemic there is no recorded case of a baby, born to an infected mother, surviving more than a few days.[10]

Clinical aspects of Ebola

EVD is a filovirus infection, thought to be transmitted to humans from an unknown animal reservoir. Current knowledge suggests that bats or non-human primates represent the most likely species involved in the occurrence of sporadic human outbreaks.[11,12] There are five identified species of EVD: Zaire ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus, Bundibugyo ebolavirus and Reston ebolavirus.[1] Zaire ebolavirus is the most lethal strain and is responsible for the current epidemic in West Africa.

Zoonotic transmission is believed to transfer Ebola from the animal reservoir to the human host through hunting and meat consumption practices, while human-to-human transmission efficiently propagates EVD through mucosal contact with infected body fluids. The risk of transmission continues following death; hence, corpses remain at high risk and must be handled in accordance with full infection control procedures.[13]

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The incubation period is up to 21 days (median 5–9 days); however, transmission is only recognised from symptomatic patients.[11,14] Non-specific early symptoms (see Box 1) mimic other common infections such as malaria, typhoid or influenza, making accurate clinical diagnosis difficult. The combination of signs and symptoms used to identify those suspected of Ebola infection is referred to as the 'case definition'. Nucleic acid amplification testing (NAAT) is currently the gold standard diagnostic test and is performed in category 4 bio-safety facilities.[15] The low sensitivity of NAAT during the first 72 h of symptoms mandates that all negative tests during this period should be repeated.[16]

Treatment for EVD-infected patients is supportive with particular focus given to the replacement of electrolytes and fluids and the management of distressing symptoms. Limited access to further diagnostic tests frequently necessitates the empirical administration of anti-bacterial and anti-malarial treatment given the high incidence of these infections in Ebola-afflicted countries.[17] Iron supplementation is recommended for all pregnant women in some guidelines.[18]

Mortality rates from EVD in this epidemic are reported to be 50–70%.[19] Survival is most likely dependent on the adequacy of immune response,[20] as yet unrecognised host factors and the level of supportive care provided. Causes of death remain poorly understood but are likely to be due (in combination or alone) to a process of septic shock and multi-organ failure.[21]

There are currently no proven curative treatments for EVD, but several experimental therapies and vaccinations are currently at various stages of clinical trial. These include anti-viral drugs, monoclonal antibody cocktails and convalescent blood/plasma transfusion.[20,22–24] A number of pregnant women have received convalescent plasma and ethical approval has been obtained for the emergency administration of favipiravir, an antiviral drug.[25]

Vitally, an important aspect of EVD treatment is the recording and following-up of any potential contacts to an infected person. Without rigorous contact tracing, case finding and public health promotion, further cases will continue to go undetected and increase the spread of disease.[26] Contacts of a suspected case should be sensitively questioned about possible exposure and educated about seeking medical assistance if symptoms of early EVD develop.

Box 1. Signs and symptoms for suspecting Ebola infection.[16,43,44]

The case definition for suspected Ebola infection can change during the course of an outbreak, and may differ from that of future or previous outbreaks. It is applied in a defined geographical area where Ebola transmission is suspected. Below is an example adapted from case definitions used during the current outbreak by the WHO, CDC and MSF.

Fever + contact with a known case of Ebola

Or

Fever + at least three of the following:

Headaches	Loss of appetite
Lethargy	Myalgia or arthralgia
Dyspnoea	Vomiting
Dysphagia	Diarrhoea
Dyspepsia	Hiccups

Or

Any person with unexplained bleeding
(Some definitions also include spontaneous miscarriage +−fever)

Or

Any unexplained death

Ebola–pregnancy interaction

Pregnant women are not thought to be at a higher risk of contracting EVD from a physiological perspective; however, their attendance at hospital for antenatal appointments, and role as the caretaker in the family are both activities which may put them at higher risk of exposure, though epidemiological data for this epidemic have thus far demonstrated equal distribution of EVD between the sexes.[2] In the Ebola outbreak of Yambuku, Zaire 1976, pregnant women were disproportionately affected. This increased transmission was traced back to poor infection control practices at an antenatal clinic where vitamin injections were being administered rather than a biological consequence of pregnancy.[8]

Pregnant women with obstetric or early pregnancy complications pose a particular challenge to health-care workers who must decide on whether or not criteria for testing as a 'suspect' case of EVD[27] have been fulfilled. The management strategy for a woman who is suspected of having Ebola would normally be to isolate her, test her and treat medically until laboratory confirmation of her EVD status is received. For women with obstetric emergencies requiring prompt operative action, this is problematic as invasive procedures frequently place health-care workers at increased risk of exposure to body fluids and may therefore be deemed too dangerous to perform prior to the exclusion of EVD.[18,27]

The overlap between the symptoms of a woman presenting with pregnancy-related complications and EVD is further complicated by the poor condition of maternal healthcare[28] in the affected region. It is not uncommon for a woman to present to a health-care facility with late and multiple complications due to delays in recognising the need to seek help and due to the wider socio-economic environment of the population. For example, a woman with obstructed labour may attend not only with an undeliverable fetus, but also chorioamnionitis, bleeding and an intrauterine fetal death. Differentiating this complex presentation from a suspected Ebola case creates a practical and ethical dilemma, which cannot be rapidly overcome.

Pathophysiology in pregnancy

Very little is known about the specific pathophysiology of EVD in pregnancy. Inferences have been made using knowledge gained through experience with other viral haemorrhagic fevers in particular Lassa Fever.[29,30] However, important differences remain between the two diseases and care should be taken not to assume that the rules for one can be applied to the other.

The Ebola virus is able to cross the placenta and infect the amniotic fluid and fetus.[24] Furthermore, after a woman has survived Ebola, and viraemia has resolved, the products of conception (POC) remain NAAT positive, frequently with results signifying high virus levels.[31] The significance of positive NAAT results from POC remains debated since this test does not provide information about virus viability. The technical barriers to performing Ebola virus culture have prevented this question from being adequately answered. In light of the knowledge that Ebola virus is able to survive for prolonged periods within decomposing human tissue, it remains prudent to treat the POC (including a full-term fetus) with full infection control precautions.

The length of time between resolution of maternal viraemia and expulsion of POC does not appear to affect the amount of virus present. MSF recorded a case of a woman in Guinea who miscarried after five months' gestation; over one month after her recovery from EVD, yet the fetus and other intra-uterine products remained highly positive on NAAT.[18]

Routine pregnancy testing was not standard practice for the majority of this epidemic to reduce the need for additional body fluid

exposure to health-care workers and also due to the perception that it would not change the initial management of the patient. At times of high work intensity (for example during the peak of the epidemic), non-essential tests were deemed to be inappropriate. Women who present as 'suspect' cases, with non-specific symptoms, pregnancy testing can be helpful in exploring other differential diagnoses. If pregnancy is suspected and not clinically obvious, then testing should be performed.[18] In surviving women of reproductive age, a pregnancy test prior to discharge is recommended so that delivery or termination can be planned.

It is well documented that the semen of men who survive Ebola continues to contain cultivable virus for at least three months following recovery.[32,33] Vaginal secretions in surviving women have continued to be positive for Ebola on NAAT; however, live virus has not yet been demonstrated.[18,33] While breast milk from lactating EVD survivors is also known to be NAAT and culture positive, the duration and degree of viral shedding are not established.[32] Current advice for women on when it is safe to re-establish breast feeding remains controversial.[18,34] This is particularly problematic in the African setting where breastfeeding is both culturally important and often safer than alternative options requiring access to clean water.

Principles of management

The presence of pregnant women inside an Ebola Treatment Centre tends to cause high levels of anxiety amongst the health-care workers as well as the other patients. However, the cornerstones of management do not differ from that of the general population. Importantly, recognition is given to the reality that no neonate has yet survived an infected pregnancy, therefore necessitating that the focus of management should be on maternal survival.

Current practice for Ebola confirmed pregnant women has been to manage the infection first, and the pregnancy after the woman has tested NAAT negative. The reasoning behind this is that the overall management of the pregnancy, regardless of gestation, will be delivery. It is considered safer to plan the delivery once viraemia has resolved to reduce the risk of EVD-associated disseminated intravascular coagulopathy (DIC), which may result in greater blood loss during and after delivery. Additionally, the health-care worker's contact with infected body fluids may be reduced.

As with all Ebola management, the safety of the health-care (and allied) workers should take priority in all decisions. Only appropriately trained personnel should enter the high-risk area. Training should focus on the donning and doffing of full personnel protective equipment (PPE) and knowledge of the limits of PPE. Staff should be familiar with decontamination procedures (e.g. usage of chlorine sprayers) and also comfortable, as well as competent, with any procedures that they perform. While inside the high-risk area one is both responsible for themselves and also the safety of their colleagues. In the context of managing a woman's delivery, where large amounts of potentially infective body fluids may be present, teamwork and good communication are crucial for ensuring the integrity of all staff members' PPE, preventing unnecessary risk-taking practices and assisting with procedures.

Pregnant women should be carefully counselled on the prospects of the pregnancy, and a careful history of fetal movements, bleeding and rupture of membranes should be taken. This should be repeated regularly during the admission. The vast majority of fetuses die prior to delivery permitting ultrasound or sonicaid confirmation; however, when not available, a reliable history of absent fetal movements would suffice. In the rare event of a confirmed ongoing pregnancy, the woman should be sensitively told of the likely poor outcome for the baby. If, having survived Ebola, she chooses to continue with the pregnancy she would need to be readmitted when labour begins. The option of termination of pregnancy may also be discussed with the patient at an appropriate time.

Induction

As far as possible, oral drugs should be used in the high-risk area to reduce the need for invasive procedures and associated risk of sharps injury, and to limit the time a health-care worker needs to spend inside PPE. Where planned emptying of the uterus is to take place, at any stage of pregnancy, it is recommended to use mifepristone and/or misoprostol in accordance with local protocols.[18] Strict adherence to gestation-dependant dosage is required as surgical recourse in the event of uterine rupture or haemorrhage is not recommended, nor likely to be available. In some circumstances, it may be appropriate to consider uterine vacuum aspiration; however, this would require a skilled provider with exemplary infection control technique.[6] The use of oxytocin for induction or augmentation is not advisable, as it is unlikely that the patient could be appropriately monitored given the constraints of PPE and the West African EMC setting.[18] These recommendations may differ according to the specific setting and resources available.[35]

Delivery

In the event of a woman being in spontaneous labour or undergoing planned induction, the following is advised.[18]

All deliveries (at any gestation and whether during or after illness) should take place inside a high-risk area. Inside the EMC there should be a designated area for maternity, which provides both good access for the health-care workers and privacy for the woman. Communication devices such as walkie-talkies can be used to communicate with the woman from outside the high-risk area, for example to alert teams when delivery is imminent or if there is a complication.

Intravenous access should be gained at the earliest time, ideally prior to labour. This is to reduce the need to perform procedures on a potentially distressed patient, under stressful circumstances or in a haemorrhaging patient where venous access may be difficult.

Fetal monitoring is not required during labour as obstetric interventions are not advised for suspected fetal distress. Surgical delivery for the sake of the fetus is likely to be futile, given the probability of neonatal death; this would also be of particularly high risk to the health-care providers. Where surgery is considered for maternal reasons, a multi-disciplinary team should decide on the risks versus benefit ratio, ideally consulting with a medical ethical opinion.[6]

Vaginal examinations are not necessary and artificial rupture of membranes should be avoided to reduce the risk of body fluid exposure.

Spontaneous vaginal delivery should be anticipated. It is very likely that delivery will be of a small or pre-term infant; hence, obstruction is a particularly rare event in this circumstance. If an attendant is present at the time of delivery and chooses to assist, they should stand side-on to the patient to avoid any body fluid splash.

Episiotomies and other surgical interventions should not be performed. Vaginal tears should have pressure applied to stop bleeding, but not be sutured. The risk of EVD transmission by sharps injury is of disproportionate risk to the health-care worker.[18] Furthermore, surgery while wearing PPE is impractical due to poor vision, sensation and high operating temperatures.[27]

As presence at delivery cannot be guaranteed, and the major concern is post-partum haemorrhage (PPH), active management of the third stage is recommended (with the exception of assisted placental delivery). The woman should be given 600 μg of misoprostol and carefully counselled on taking the tablets orally after delivery. It must be ensured that she understands the instructions not to take misoprostol prior to delivery. If there is any suspicion of multiple pregnancy misoprostol should not be given until the placenta has been delivered.[36] This a practice previously used in remote settings to prevent and treat primary PPH.[37] In this instance, it is beneficial both as an oral uterotonic particularly since it can be self-administered whilst health-care staff are donning their PPE.

A 'Maternity Box (see Box 2)' should be prepared and brought to the area of expected delivery once labour has begun. A woman bleeding inside the EMC can be very difficult to manage given the constraints of PPE and high-risk area procedures. Associated DIC may exacerbate bleeding and limit the ability to gain prompt haemostatic control. Having the appropriate means and training in place at delivery reduces both the time-to-treatment interval and stress to the health-care provider. Having intravenous access and drugs ready prepared allows for fast and easy administration. Uterine fundal massage and insertion of a urinary catheter can also be safely performed and may assist resolving uterine atony. More invasive procedures, such as uterine exploration or balloon tamponade, are generally not advised. However, this will depend on the discretion and expertise of the health-care workers present as well as the specific situation and setting.[31]

The placenta and fetus should be treated with the same infection control precautions as any corpse in the high-risk area. There should be ready access to an appropriate disinfectant, absorbent pads and a child-size body bag for safe disposal.

In the unlikely event of a live birth, the baby must be assumed to be Ebola positive and highly contagious. The mother can nurse and breastfeed the baby, though she should be sensitively counselled on the high likelihood of neonatal death.

Post-natal care

Any woman who has survived delivery following EVD infection must be carefully counselled on post-natal care. Where possible, a lactation-suppressing drug should be administered (e.g. cabergoline). If this is not feasible, a breast pump should be provided with clear instructions on safe disposal of the infected milk, and how to employ a weaning technique with the aim of ceasing lactation.

In the African setting, discharged patients are given supplies to assist them with re-entry into their community. This includes medicines, nutritional supplements and clothing. Previously, only men received a three-month supply of condoms to reduce the risk of sexual transmission; however, given that Ebola virus has also been detected in vaginal swabs, this should apply to both sexes. Post-natal women should also receive hygiene pads and iron supplements.[18]

Box 2. Example of EMC maternity box contents.[18]

2 × Large bore cannula, 2 × small size cannula (in case of difficult veins)
2 × Plaster to fix cannula
2 × IV fluid giving set
2 × Saline flush for cannula
3 × 21 gauge needle
1 × 10 ml syringe
1 × Urinary catheter and bag
1 × Ringer's Lactate (1 Litre)
1 × Ringer's Lactate (1 Litre) + 40 iu Oxytocin
1 × Syringe with 10 iu Oxytocin
1 × Syringe with 0.2 mg Ergometrine
Paracetamol
Sanitary pads/diapers
Specimen swabs for NAAT check of POC

If not already in delivery area/with patient:
Misoprostol 600 μm (three tablets)
Iodine solution
Tourniquet
Safety sharps bin
Absorbable pads

To be asked for only in event of live birth or retained placenta:
Delivery kit (two clamps and scissors)

As with all stages of Ebola management, counselling and effective communication are paramount. The surviving pregnant woman is very likely to be recently bereaved, not only from the current pregnancy, but often with deaths of close family members including other children and her partner. Returning home she may suffer stigma, social isolation and economic hardship. She is, however, also a rare beacon of hope for a traumatised community, and with the right support is able to act as an ambassador for the ongoing response.[38]

Family planning

All women of reproductive age should be offered effective contraception at the time of discharge from an EMC, including those who have delivered during the course of their illness. This is both to allow time for them to recover from their recent illness, and also in recognition of the gross lack of safe maternity services in the most affected region. Women being discharged fall into a unique group where both their negative Ebola status (hence safe for health-care workers to insert contraceptive devices) is known, as well as that they are known to not be pregnant and are therefore suitable for most contraceptive options.[39]

Wider implications

Ebola is a disease that spreads great fear amongst the affected (and unaffected) populations. The deaths of health-care workers have impacted greatly on a health-care system that was already under-resourced and vulnerable. The nature of how Ebola is spread, and its particular difficulties in pregnancy have led to women being refused access to emergency obstetric care.[3] Furthermore, women and local communities have become fearful of hospitals which were associated with Ebola cases, and occasionally as amplification centres of disease due to poor infection control procedures.[40]

These knock-on effects of the epidemic have resulted in a dearth of maternity care, and projections of maternal mortality rates reaching up to 1 in 7 pregnant women dying during childbirth[41] in the three worst affected countries. It is clear that for pregnant women in an Ebola epidemic the greatest risk appears not to be Ebola but the wider impact of the epidemic on their access to safe services. This cannot be ignored, and for future epidemics a contingency plan should be in place from the outset. Further knowledge is required to develop triaging systems that incorporate the wider obstetric picture and an emphasis on risk of exposure as well as symptoms. Unfortunately, the reality is that women with obstetric complications will continue to pose specific challenges to health-care providers in this or similar settings.

It could be argued that given these barriers to care, pregnancy itself has become a life-threatening condition in the Ebola epidemic setting. It is therefore of high importance that adequate access to family planning be available as a life-saving intervention.[39] The United Nation's Populations Fund has estimated that 1.2 million women in the affected region could be lacking access to family planning, and has projected that 120,000 women could die from childbirth-related complications over the next year as a result of the loss in health care.[42]

Conclusions

While the current Ebola epidemic is not yet over, much has already been learnt during this sad event in human history on how to help pregnant women infected survive both Ebola and delivery, while protecting those caring for them. There is still much to learn, and as the epidemic continues to develop so should our management strategies adapt to meet the new realities in the field.

The difficulties faced by pregnant women living within the epidemic area are complex and multi-factorial. It will take years to rebuild the

health-care system and the trust of the population. Re-established services need to be prepared for future shocks so that they are resilient enough to maintain life-saving maternity services.

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