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Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease [Internet]. Geneva: World Health Organization; 2020 Feb.

Recommendations

Guiding principles

Equitable and respectful care should be provided. Women should be given the opportunity to make reproductive health choices regarding the continuation or termination of pregnancy after being presented with all the available options. Decisions should include careful consideration of the risks pertaining to EVD in pregnancy, and they should incorporate both a woman's personal values and individual situation. Women should be supported in the choices they make.

1. Treatment of pregnant women with acute Ebola virus disease

RECOMMENDATION #1: Clinical management for all pregnant women should include optimized supportive care.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #2: In the context of rigorous research or in accordance with the MEURI protocol, the use of the investigational therapies REGN-EB3 or mAb114 may be offered to pregnant women with EVD.	
Recommendation strength: strong.	Very low quality evidence.

Remarks

1. Optimized supportive care includes systematic assessment and re-assessment of patients with EVD, fluid resuscitation, electrolyte monitoring and correction, glucose monitoring and management, treatment of potential co-infections, and nutritional support. Symptomatic care, as well as prevention and management of complications, should always be provided (8).
2. Based on evidence from general adult populations, applying the principles of optimized supportive care to pregnant populations with EVD will likely decrease mortality and confer a beneficial impact on disease outcomes (8).
3. The use of fluid resuscitation in pregnant women with EVD, such as oral rehydration and parenteral administration of clinically appropriate fluids, has not been specifically evaluated. However, among adults with EVD, correction of intravascular depletion through adequate fluid resuscitation likely improves survival (8).
4. Where available, intensive critical care such as non-invasive ventilation, intubation with mechanical ventilation, central venous line insertion with vasopressor support, or renal replacement therapy will likely benefit pregnant women with EVD similar to that observed in adults with EVD.
5. The Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) expert panel recommends that "access to and use of investigational therapeutics under MEURI be carefully considered for each individual patient, including for vulnerable populations such as pregnant women and paediatric patients, as appropriate given the available data." In general, the expert panel recommends consideration of factors such as disease severity and risks/benefits of investigational therapy (including adverse effects in pregnant or paediatric populations) (6).

6. Pregnant women with acute EVD who are not treated with investigational or compassionate use agents experience very high (>95%) rates of spontaneous abortion, foetal or neonatal death.

* Further information regarding recommendations 1 and 2 can be found in the WHO publications: "Optimized Supportive Care for Ebola virus disease: Clinical management standard operating procedures" (8), "Notes for the record: Consultation on Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) for Ebola virus disease" (6), and "Guidance for managing ethical issues in infectious disease outbreaks" (51).

Summary of evidence and considerations

Optimized supportive care

In 2018, a multidisciplinary panel of international experts formulated evidence-based recommendations for delivering optimized supportive care to individuals with acute EVD. Recommendations were formulated based on the quality of evidence as well as benefits, harms, values, and preferences. The majority of recommendations, including rehydration therapy, systematic vital sign assessment, and biochemistry assessment were strongly recommended to all patients with suspected, probable or confirmed EVD as steps to reduce mortality and optimize care (7). These recommendations were adapted for the WHO guidance document "Optimized supportive care for Ebola virus disease" for adults and children (8).

Investigational therapies

Three published reports described investigational therapeutic use in pregnant women with acute EVD (3,9,10). During the 2014-2016 outbreak, van Griensven *et al.* conducted a non-randomized comparative study using convalescent plasma. Among 84 participants, eight pregnant women were treated with convalescent plasma in addition to supportive care. Mortality was 25% among pregnant women and 32% among non-pregnant individuals after receiving plasma treatment. Compared to historical controls with EVD, one of the two (50%) pregnant women died from EVD, but pregnancy in the control group was incompletely documented (3).

A pregnant woman with EVD was also treated with favipiravir in addition to supportive care during the 2014–2016 (9,10). The woman went into preterm labour and died from haemorrhagic shock. Her newborn child tested positive for EBOV and was treated with investigational therapies. The child became the first known survivor of congenitally-acquired EVD, and an examination at 12 months of age revealed normal development and a complete recovery from EVD (9,10).

The safety and efficacy of certain investigational therapeutics (ZMapp, Remdesivir, mAb114, REGN-EB3) are being evaluated in an ongoing randomized study. Pregnancy was not used as exclusion criteria in this study (11). Interim analyses noted improved outcomes resulting from treatments including REGN-EB3 or mAb114, and because of this, early termination of the trial was recommended. The efficacy of these treatments in pregnant women specifically is not yet known (12).

Additionally, the WHO convened an expert panel regarding investigational therapeutics using the MEURI ethical framework. The panel recommended that among vulnerable populations such as pregnant women, investigational therapeutics should be considered, and that until evidence suggests otherwise, pregnant women should be offered similar treatments to the non-pregnant population. Given that very few infants born to women with EVD survive, teratogenic effects were considered secondary to the mother's health; however, risks and benefits should be highlighted in informed consent procedures (6).

2. Induced abortion and induction of labour in women with acute EVD

RECOMMENDATION #3: Labour should not be induced for foetal indications in pregnant women with acute EVD.	
Recommendation strength: strong.	Very low quality evidence.

Remarks

1. There is insufficient evidence to determine if induced abortion or induction of labour impacts maternal outcomes of acute EVD. No recommendation can be made.
2. Pregnant women with acute EVD or following recovery (with conception before EVD) who undergo an induced, incomplete, or spontaneous abortion should be provided with post-abortion care as described in the WHO guidelines "Safe abortion: technical and policy guidance for health systems" (13). Women should be provided instructions on how to handle potentially infectious specimens (such as products of conception) using Ebola-specific IPC measures and personal protective equipment (PPE).
3. Pregnant women recovering from EVD should be provided with counselling and necessary information pertaining to the risks of EVD that affect pregnancy outcomes, such as the risk for persistent infectivity of pregnancy-related fluids and tissues after EVD recovery. This information is necessary for women to make an informed decision regarding their choice to continue the pregnancy or undergo induced abortion.
4. Health authorities should take steps to expand access to all relevant reproductive options to women during an Ebola outbreak including safe abortion and contraceptive access. Health authorities should also ensure that access to reproductive options are not limited by a woman's socioeconomic, cultural, racial, or religious status (55).
5. Women who have recovered from EVD but who wish to terminate a pregnancy should receive accurate information about their options and have access to safe abortion and post-abortion care (13,45). They should be supported in the choices they make regarding continuation or termination of pregnancy.
6. Pregnant women who have recovered from EVD (with conception prior to EVD) may choose to proceed with an induced abortion. Due to the risk of viral persistence in pregnancy-related fluids and tissues, medical abortion (use of medications including misoprostol +/− mifepristone when possible) is preferred to surgical abortion (use of trans-cervical procedures), as surgical abortion may increase risk of EBOV transmission due to the invasiveness of the procedure.
7. Follow-up after an uncomplicated medical abortion using mifepristone and misoprostol is not required for obstetric indications. If only misoprostol is used, a follow-up visit is

   recommended to assess for completion of the abortion. Follow-up visits can be used to monitor symptoms, recovery, and assess the need for contraceptive services (45).
8. Induced abortions should be performed and managed at ETCs or healthcare facilities that are able to follow standard precautions in addition to Ebola-specific IPC measures, and that have the capability to provide obstetric care. Women who proceed with an induced abortion should stay at the facility in which the operation was performed until the abortion is completed due to the potential risk of infection from pregnancy-related fluids and tissues.
9. PPE (e.g. double gloves, face mask, gown or coverall and apron, head cover, eye protection (goggles or face shield) and boots (53)) in addition to standard precautions

(52) should be used when handling pregnancy-related fluids and tissues from women with acute EVD or following recovery (if conception was prior to EVD), given the potential for disease transmission (53,54).

10. Products of conception should be tested for EBOV using reverse transcriptase polymerase chain reaction (RT-PCR), and should be handled and disposed of using PPE in accordance with established recommendations (52).
11. Women discharged from ETCs should receive Ebola-specific advice and counselling related to pregnancy, abortion, post-abortion care, breastfeeding, and sexual transmission.
12. Engagement from multiple stakeholders such as national authorities, epidemic response, UNFPA, UNAIDS and WHO is recommended to provide adequate sexual and reproductive healthcare within the context of Ebola.

Summary of evidence and considerations

One study found that uterine evacuation of pregnant women with acute Lassa fever was associated with improved survival from viral haemorrhagic fever (14). There were no studies of women with acute EVD undergoing induced abortion, though two studies included outcome data from four women who underwent induced abortion after recovering from EVD (15,16). The first was a retrospective cohort investigation by Henwood *et al* from 2014–2015 including 13 pregnant women with laboratory-confirmed EVD, one of which underwent induced abortion on the day of her discharge from the ETC (15). Similarly, in another retrospective cohort study of 77 pregnant women with laboratory-confirmed EVD, Caluwaerts *et al* reported results from three women who underwent induced abortion after recovering from EVD (16), but other evidence of induced abortion during acute EVD was limited to unpublished individual case reports and were not included.

3. Infection prevention and control measures for pregnant women with EVD

RECOMMENDATION #4: Invasive procedures should not be performed for foetal indications in pregnant women with acute EVD.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #5: All pregnant women with acute EVD should be managed using both standard precautions and Ebola-specific IPC measures.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #6: All pregnant women who have recovered from EVD (with conception prior to EVD) should be enabled and encouraged to attend frequent Antenatal Care (ANC). If there is no risk of exposure to pregnancy-related fluids during the ANC visit, only standard precautions are required. Complications associated with childbirth and pregnancy should be managed at ETCs and Ebola IPC measures should be used in addition to standard precautions.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #7: Among women who become pregnant after EVD (with conception after acute EVD), standard IPC precautions should be used.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #8: Surgically removing foetal tissue from the uterus following maternal demise from EVD (occasionally termed 'post-mortem caesarean') may pose a	

risk of transmission to contacts and should be strongly discouraged.

Recommendation strength: strong.	Very low quality evidence.

Remarks

1. Although the actual risk of EVD transmission from pregnant women following recovery is unclear, there is evidence that Ebola RNA can remain detectable in amniotic fluid, placental tissue, foetal tissue, and vaginal secretions. This evidence enables WHO to make strong recommendations regarding the necessity of Ebola-specific IPC measures for pregnant women who have recovered from EVD (with conception prior to EVD) in situations with potential for pregnancy-related fluid or tissue exposure. However, if the pregnancy was conceived after EVD, there is no known risk of EVD transmission with exposure to pregnancy-related fluids and tissues, and therefore only standard precautions are necessary.
2. Effective IPC measures require a hierarchy of engineering, environmental and administrative controls in order to block viral spread in healthcare facilitates. In addition to PPE, IPC includes, but is not limited to, barrier nursing, hand hygiene, and waste management (56).
3. EVD transmission has been linked to traditional funeral ceremonies. Similarly, there is likely a high risk of transmission from post-mortem caesareans for pregnant women who have died from EVD. Guidelines on how to conduct safe and dignified burials for patients with suspected or confirmed EVD should be followed in the event of a maternal death from EVD, including the recommendation that only trained personnel should handle human remains, handling should be minimal, and cultural and religious considerations should be taken into account (46).
4. Actions (such as an invasive procedure) should not be taken in the event of foetal distress in pregnant women with acute EVD. As such, foetal monitoring during labour is not necessary.

* Further information regarding recommendations 5, 6, and 7 can be found in the WHO publications: "Interim guidance: Interim infection prevention and control guidance for care of patients with suspected or confirmed filovirus haemorrhagic fever in healthcare settings, with focus on Ebola" (53), "Interim guidance: Clinical care for survivors of Ebola virus disease" (54), and "Standard precautions in health care. Aide-memoir" (52). Further information regarding recommendation 8 can be found in the WHO publication "Interim guidance: How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease" (46).

4. Infection prevention and control for breastfeeding women in the context of EVD

RECOMMENDATION #9: Breastfeeding should be stopped if acute EVD is suspected or confirmed in a lactating woman or in a breastfeeding child. The child should be separated from the breastfeeding woman and provided a breastmilk substitute as needed.

Recommendation strength: strong.	Very low quality evidence.

RECOMMENDATION #10: Children without confirmed EBOV infection who are exposed to the breastmilk of women with confirmed EVD should be considered contacts. The child should stop breastfeeding and should undergo close monitoring for signs and symptoms of EVD for 21 days. The child should be given a breastmilk substitute as needed. Post-exposure prophylaxis for EVD can be considered for children exposed to the

breastmilk of EBOV-infected women on a case-by-case basis and in accordance with existing research protocols.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #11: If a lactating woman and her breastfeeding child are both diagnosed with EVD, breastfeeding should be discontinued, the pair should be separated, and appropriate breastmilk substitutes should be provided. However, if the child is under six months of age and does not have safe and appropriate breastmilk substitutes, or the child cannot be adequately cared for, then the option to not separate and continue breastfeeding can be considered.	
Recommendation strength: strong.	Very low quality evidence.
RECOMMENDATION #12: A woman who has recovered from EVD, cleared viremia, and wants to continue breastfeeding should wait until she has had two consecutive negative RT-PCR breastmilk tests for EBOV by, separated by 24 hours. During this time, the child should be given a breastmilk substitute.	
Recommendation strength: strong.	Very low quality evidence.

Remarks

1. The recommendation to discontinue breastfeeding in the event that both the breastfeeding woman and the breastfed child have acute EVD is based off a hypothetical risk of viral 'boosting' between two infected individuals. This viral boosting could theoretically increase disease severity through additional viremic exposure. Evidence to directly support this recommendation is lacking.
2. Infants younger than 6 months of age should be provided with a breastmilk substitute (eg, ready-to-use infant formula) that is acceptable, feasible, affordable, sustainable, and safe. Infants and young children between 6 months and 23 months of age should be provided with a ready-to use infant formula or ultra-high temperature full-cream (or whole) cow's milk along with complementary feeding (this food can be supplemented with micronutrient powders if the nutrient content is expected to be inadequate).
3. Rapid testing of breast milk of women with recovered EVD, who would like to continue to breastfeed, should be prioritized.
4. Women's choices related to stopping breastfeeding, or continuing after EVD recovery and testing of breast-milk, should be respected and supported by health care workers to facilitate the choice.

Summary of evidence and considerations

Disease transmission

Among studies describing the role of IPC measures at time of childbirth for EVD-positive women, multiple lapses in IPC measures likely contributed to the transmission of EBOV from pregnant women to others. These included inadequate and improper use of PPE such as using contaminated material for multiple patients, point of care exposure from patients with unrecognized EVD, and lack of proper isolation procedures (17–19). Contacts who subsequently contracted EVD after lapses in IPC measures included healthcare workers and caregivers (18), and other patients at health-care facilities (19).

In Sierra Leone, investigators performed contact tracing of a pregnant woman with EVD after she presented in labour. She delivered via caesarean at a general hospital and developed EVD symptoms two days following delivery. She died shortly after and a post-mortem buccal swab confirmed the diagnosis of EVD. The infant developed symptoms at three days of life and died

confirmed the diagnosis of EVD. The infant developed symptoms at three days of life and died seven days later. Investigators identified 46 individuals who had contact with the pregnant woman during her stay at the health-care facilities, and among these individuals, six contracted laboratory-confirmed EVD. In this study, investigators revealed that the nurses, hospital cleaning staff and caregivers did not have access to recommended PPE. Other potential contributors to the high risk of exposure from this case included a lack of recognition of EVD infection, exposure from infected bodily fluids, and lack of isolation precautions (18).

Similarly, Connolly and Young performed contact tracing on a pregnant woman with undiagnosed EBOV who delivered in a maternity ward in 2014. Investigators identified multiple lapses in IPC measures that likely contributed to EVD infection for two maternity ward patients and their infants. One of the maternity patients who contracted EVD was delivered by the same nurse as the index patient; PPE used by the nurse was both incomplete and contaminated from the index patient. Further, the maternity patient's delivery suite was the same as the index case and was not cleaned between deliveries. The second maternity patient was likely infected because of a lack of standard precaution procedures, as she was placed next to the index case during her delivery and subsequent haemorrhage (20).

Detectable EBOV RNA has been identified in amniotic fluid (21,22), placental tissue (21,23,24), foetal tissue (17, 21, 25, 26,27), vaginal secretions (28), and even in pregnant women with mild or unrecognized disease (17,27).

Viral persistence in pregnancy-related fluids and tissues

Persistence of EBOV has been documented in pregnancy-related fluids and tissues after clearance of the virus from blood has occurred (17,21) (Table 1). EBOV was successfully isolated from a foetal tissue sample in a woman who delivered a stillborn foetus one month after being exposed to EVD (17). Similarly, a woman from Sierra Leone delivered a stillborn foetus who tested positive for EBOV RNA, yet denied EVD or exposure to it. Her blood was EBOV RNA negative, IgM antibody negative, and IgG antibody positive for EBOV (27).

In reproductive tract specimens from non-pregnant individuals, EBOV RNA was detected up to 36 days following symptom onset for EVD (29), but all samples from menstrual blood in non-pregnant women tested negative (30).

Ebola in breastmilk

EBOV RNA has been detected in the breastmilk of women with acute and convalescent EVD up to 26 days after symptom onset (31,32), as well as in women with asymptomatic EVD (33,34) (Table 1). Two lactating women were evaluated after their infants died from laboratory-confirmed EVD. EBOV RNA was detected in their breastmilk by RT-PCR despite negative testing in blood (33,34).

Of 25 infants who were breastfed by mothers with EVD, 68% developed presumed or laboratory-confirmed EVD, with a mortality rate of 82%. Eight infants were breastfed by EVD-positive women but did not become ill (31–38). Other studies of four breastfed infants did not identify if the mother or infant developed EVD first (31,33,34). However, Bower *et al* (35) found that of 14 mothers who clearly acquired EVD prior to their breastfed infants, 86% (n=12) of the exposed infants contracted EVD, with EVD status proving to be the greatest risk. Breastfeeding alone was not identified as a risk factor for EVD transmission.

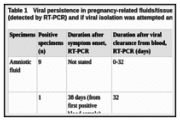

Table 1

Viral persistence in pregnancy-related fluids/tissues and breastmilk, of Ebola virus RNA (detected by RT-PCR) and if viral isolation was attempted and successful

viral isolation was attempted and successful.

5. Use of rVSV-ZEBOV-GP Ebola vaccine in pregnant women

RECOMMENDATION #13: Pregnant and breastfeeding women should be offered vaccination with the prequalified Ervebo (Merck) live-replicating rVSV-ZEBOV-GP vaccine during an active Zaire EBOV outbreak in affected areas, in the context of rigorous research or in accordance with a compassionate use protocol. Vaccination should occur with informed consent and in compliance with good clinical practice.	
Recommendation strength: conditional.	Very low quality evidence

Remarks

1. The WHO prequalified the injectable Ebola vaccine Ervebo (manufactured by Merck) in November 2019 after the vaccine was deemed compliant with WHO standards for quality, safety and efficacy. This decision followed the European Medicines Agency (EMA) announcement recommending a conditional marketing authorization for the rVSV-ZEBOV-GP vaccine.
2. The Strategic Advisory Group of Experts (SAGE), the principal advisory group to WHO on vaccinations, recommends that pregnant and lactating women be included in research within the framework of clinical trial vaccine protocols. SAGE notes that protocols must include provisions for safety monitoring and documentation of EVD cases among vaccinated individuals, as well as follow-up of pregnant women and their offspring.
3. The MEURI expert panel recommends that “access to and use of investigational therapeutics under MEURI be carefully considered for each individual patient, including for vulnerable populations such as pregnant women and paediatric patients, as appropriate given the available data”. In general, the expert panel recommends that factors including disease severity, available information on risks and benefits for the investigational therapy (including any available information on adverse effects in pregnancy or paediatrics) be considered (6).
4. There are no available studies that have determined the efficacy of rVSV-ZEBOV-GP vaccine in pregnant women; however, the vaccine is considered to have very good efficacy in the general population.

Summary of evidence and considerations

In 2015, Samai *et al* conducted a randomized, phase 2/3 trial to evaluate the safety and efficacy of the rVSV-ZEBOV vaccine among 8,651 healthcare and frontline Ebola response workers. Participants in the immediate vaccination cohort (n=4,319) were compared to participants in whom vaccination was delayed until 8-24 weeks after enrolment (n=4,332). Although pregnancy was part of the exclusion criteria and testing was required for women of reproductive age, 43 vaccinated women became pregnant during the study timeframe. Researchers were unable to assess the efficacy of rVSV-ZEBOV among pregnant women or among study participants because none developed laboratory-confirmed EVD, and exposure after enrolment was not detailed in the study (44).

In 2018, Edmunds and Jarvis performed an analysis of vaccinating pregnant women with rVSV-ZEBOV based on available data. The authors identified 11 studies, seven of which were randomized controlled trials and four were cohort studies, in the Democratic Republic of Congo, Gabon, Guinea, Kenya, Liberia, Sierra Leone, Spain and the United States of America. There were 98 pregnancies in the vaccinated group with 93 known pregnancy outcomes, of which 67% had a live birth and 27% had a pregnancy loss (2). Data on spontaneous abortions, induced

had a live birth and 27% had a pregnancy loss (2). Data on spontaneous abortions, induced abortions, and preterm births were available for 41 vaccinated pregnant women, of which 10% experienced a spontaneous abortion, 6% had a induced abortion, and 2% had a preterm birth (2).

One study provided comparison information for pregnant women who were vaccinated or unvaccinated. In this, 60 unvaccinated women were pregnant or became pregnant during the trial (with outcome data available for 46), compared to 43 vaccinated women (with outcome data available for 40), and a pregnancy loss rate of 43% among the vaccinated women and 44% among the unvaccinated women (44).

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