

What We Should Know about Cholera During Pregnancy

Cholera in pregnant Women in Lebanon applying the 4Rs care bundle: Readiness, Recognition, Response, and Reporting

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ABSTRACT

In the studies reviewed, evidence documenting the severity of cholera during pregnancy could not be determined, and no previous meta-analysis that estimates the extent to which cholera affects pregnancy outcomes, such as maternal, fetal, and neonatal deaths, was identified. In light of the scarcity of published evidence on the subject and the public health importance of addressing the needs of pregnant women with cholera, we try to apply team 4R to determine the risks of fetal demise and neonatal and maternal mortality in pregnant women with cholera.

Keywords: Pregnancy; Women; Cholera; Delivery; Prenatal ultrasound

INTRODUCTION

Cholera is an acute diarrheal disease caused by the bacterium *Vibrio cholerae* and transmitted through fecally-contaminated water or food, which affects children and adults.^[1] Around 20% of the infected individuals develop acute, watery diarrhea, and 10% to 20% of them develop severe watery diarrhea with vomiting.^[2] If these patients do

not receive prompt and adequate treatment, the massive loss of fluid and electrolytes can lead to severe dehydration and death within hours. The case-fatality rate in untreated cases with severe cholera may reach 70%.^[3,27] Rapid and intensive fluid therapy and supportive care should keep the case-fatality rate below the internationally-accepted threshold of 1%. WHO estimates the global disease burden to be 3 to 5 million cases and 100,000 to 100,300 deaths each year, occurring mostly in Asia and Africa, with periodic epidemics including the recent Haiti epidemic.^[4] The link between cholera in pregnancy and negative childbirth outcomes has been observed since the 19th century.^[5] The 2010–2011 cholera outbreak in Haiti suggested again that cholera negatively impacts on pregnancy outcomes.^[6] The experience of Médecins sans Frontières (MSF) treating pregnant women with cholera in Haiti underscored the need to better understand the extent that cholera affects pregnancy and pregnancy outcomes, as to inform treatment guidelines and set benchmarks for cholera-related pregnancy outcomes. However, the World Health Organization (WHO), which hosts the Global Task Force of Cholera Control, and the Center for Disease Control do not address cholera in pregnancy in their guidelines^[7–11].

OBJECTIVES

In the studies reviewed, evidence documenting the severity of cholera during pregnancy could not be determined, and no previous meta-analysis that estimates the extent to which cholera affects pregnancy outcomes, such as maternal, fetal, and neonatal deaths, was identified. In light of the scarcity of published evidence on the subject and the public health importance of addressing the needs of pregnant women with cholera, we try to apply team 4R to determine the risks of fetal demise and neonatal and maternal mortality in pregnant women with cholera in 1971, an article written by Dr J. Voelkel, a French military doctor, mentions the need to have “multipurpose mobile teams” for surveillance (in-between outbreaks), diagnosis and care of patients, hygiene, sanitation and other prevention actions (disinfection, vaccination, contacts chemoprophylaxis).

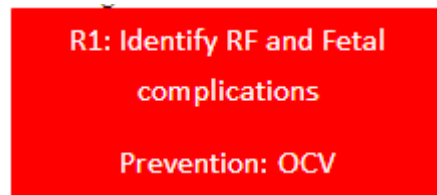


Figure2

Readiness **Figure2**

Identify risk factors

Risk factors that could influence pregnancy outcome: maternal nutritional status and anemia. The displacement of populations to inadequate and overcrowded camps can increase the risk of cholera transmission. Pregnant women are not at any greater risk of being infected by *Vibrio cholera*, nor developing symptoms than the general population. Cholera may affect women at any stage of pregnancy; pregnant woman early in pregnancy has comparable clinical illness and subsequent immune responses compared to non-pregnant women. Cholera in the third trimester was associated with significantly greater dehydration and stool output than in the second trimester, or in non-pregnant controls. No long-term complications of cholera when it is appropriately treated^[5,6]

Fetal complications

Spontaneous abortion, preterm labor, and intra-uterine fetal death. Fetal death associated with cholera during pregnancy is approximately 8%. by trimester 1st trimester 6.2%, 2nd: trimester 9.1%, and 3rd: trimester 6.7%. The main risk factor identified for fetal death was severity of dehydration. The risk factors associated with fetal death during cholera in pregnancy were linked to the severity of the cholera episode: dehydration status on admission, number of stools passed, presence and number of vomiting episodes, number of liters of Ringer's lactate received during the treatment, and length of hospitalization. Risk factors for complicated pregnancy and childbirth, such as young or older age and the number of previous pregnancies and deliveries were not associated with negative outcome during cholera in pregnancy. This association may be explained by the possible mechanism where severe maternal dehydration leads to critical hypovolemia, which compromises placental and fetal perfusion and results in severe fetal hypoxia and acidosis (eventually leading to fetal death). Alternatively, the gastrointestinal loss of bicarbonate could directly contribute to maternal acidosis. Severe maternal acidosis also appears to be implicated in compromising fetal survival in pregnant women with diabetes type 1, as shown by the high fetal mortality ratio of 35% in pregnant women with ketoacidosis. Severe vomiting was another risk factor for fetal death, independent of the severity of dehydration. Changes in electrolytes in the amniotic fluid of pregnant women suffering from cholera have been described in the literature, but it remains unclear how these affect the fetus. Finally, cholera toxin seems unlikely to play an important role in fetal death since it is not-absorbed, although it is the primary driver of the secretory diarrhea that leads to the severe maternal dehydration associated with fetal demise.^[6]

Half of fetal deaths occurred prior to admission. Close supervision of the hydration status of pregnant women, as well as availability of high quality obstetric and neonatal services, can help prevent negative maternal, fetal and neonatal outcomes. **(Figure 1)** In addition, this strategy reinforces a woman-centered approach to patient care and helps protect her dignity. The association between cholera in pregnancy and negative fetal outcome has been described since the 19th century. However, there is limited published literature on the subject. ^[6]

Fetal lost mechanism

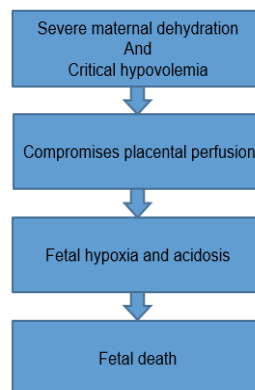


Figure.1

Prevention

WHO recommends the inclusion of oral cholera vaccines in cholera control programs in endemic areas. Pregnant women are a high-risk group for severe cholera and should be targeted by Killed oral cholera vaccines (OCV). OCV are not recommended for pregnant women though there is no evidence of harmful effects during pregnancy. The vaccines could be given in the third trimester of pregnancy. The ideal way to prevent fetal deaths due to cholera in pregnancy would be to prevent cholera. Currently available oral cholera vaccines are not contraindicated in pregnancy and have been recently shown to be safe. WHO suggests that pregnant women as an especially vulnerable group might be specifically targeted for vaccination in endemic areas. Currently there are three WHO pre-qualified oral cholera vaccines (OCV): Dukoral®, Shanchol™, and Euvichol-Plus®. All three vaccines require two doses for full protection. A multifaceted approach is key to control cholera, and to reduce deaths. A combination of surveillance, water, sanitation and hygiene, social mobilization, treatment, and oral cholera vaccines are used. ^[7,8]

The long-term solution for cholera control lies in economic development and universal access to safe drinking water and adequate sanitation. Actions targeting environmental conditions include the implementation of adapted long-term sustainable WASH solutions to ensure use of safe water, basic sanitation and good hygiene practices in cholera hotspots. The WASH solutions for cholera are aligned with those of the Sustainable Development Goals (SDG 6).^[9]

Community Engagement

Community Engagement means that people and communities are part of the process of developing and implementing programmes. Local culture practices and beliefs are central to promoting actions such as the adoption of protective hygiene measures such as handwashing with soap, safe preparation and storage of food and safe disposal of the feces of children. Community engagement continues throughout outbreak response with increased communication regarding potential risks, symptoms of cholera, precautions to take to avoid cholera, when and where to report cases and to seek immediate treatment when symptoms appear. The communities should be part of developing programs to address needs including where and when to seek treatment. Rapid access to treatment is essential during a cholera outbreak. Oral rehydration should be available in communities, in addition to larger treatment centres that can provide intravenous fluids and 24-hour care. With early and proper treatment, the case fatality rate should remain below 1%.^[10,11]

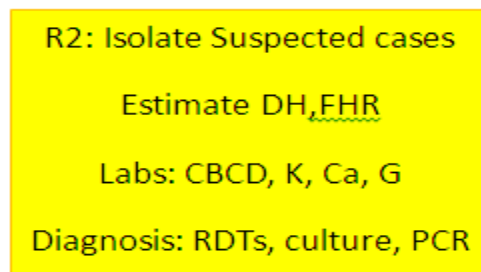


Figure 3

Recognition Figure3

A suspected cholera case is defined as any patient presenting with three or more liquid stools and/or vomiting episodes in the previous 24 hours. Estimating the degree of dehydration in pregnancy is difficult, in particular towards the end of pregnancy due to the increase in plasma volume: a pregnant woman can lose as much as 30–35% of blood volume during acute bleeding without changes in clinical status. Although the loss of volume through diarrhea and vomiting is different from bleeding, underestimation of the degree of dehydration in pregnancy is likely. ^[17,18]

Clinical manifestation:

Clinical suspicion: any pregnant patient who present with severe acute watery diarrhea, abdominal discomfort and muscle cramping due to loss of potassium and calcium are common. Rapid maternal peripheral pulse can be rapid and it may become difficult to palpate as blood pressure drops. ^[20]

Diagnosis

Rapid tests should be performed then confirmed by stool culture. Cholera cases are detected based on clinical suspicion in patients who present with severe acute watery diarrhea. The suspicion is then confirmed by identifying *V. cholera* in stool samples from affected patients. Detection can be facilitated using rapid diagnostic tests (RDTs), where one or more positive samples triggers a cholera alert. The samples are sent to a laboratory for confirmation by culture or PCR. Local capacity to detect (diagnose) and monitor (collect, compile, and analyses data) cholera occurrence, is central to an effective surveillance system and to planning control measures.

**Figure 4**

Response Figure 4

Most people infected with *V. cholera* do not develop any symptoms, although the bacteria are present in their feces for 1-10 days after infection and are shed back into the environment, potentially infecting other people.^[19]

Isolation

Pregnant patients should be isolated to avoid the spread of cholera in hospitals and other general health facilities. Cholera isolation unit for pregnant women, needs to be established within the hospital compound. Following standard isolation procedures, the unit is separated from the rest of the hospital and has independent water and sanitation facilities. The unit comprise a delivery room and an operating theatre for emergency surgical obstetric interventions^[21]

Patients and admission criteria: The isolation unit is open to all pregnant women with suspected cholera. Association of pregnancy with cholera is classified as a complication, and therefore hospitalization is offered to all pregnant women with cholera, regardless of their level of dehydration. Other cholera treatment centers in the region is advised to refer pregnant women with suspected cholera to this unit^[22]

Volume repletion

Aggressive volume repletion is the mainstay of treatment for cholera. Administration of appropriate rehydration therapy reduces the mortality of severe cholera from over 10 percent to less than 0.5 percent. Intravenous fluid replacement is privileged because pregnant women are more likely to experience nausea and vomiting and therefore have difficulty drinking enough fluids to replace the losses immediately. Throughout their hospitalization the dehydration status of each patient is closely monitored clinically, including the measurement of blood pressure and pulse rate.

Protect the fetus by maintaining maternal systolic blood pressure (MSBP) above 90 mmHg to ensure adequate uterine blood flow. Treatment of clinical hypoglycaemia and hypokalaemia. To mitigate the potential effects of severe vomiting on the fetus patients are routinely given glucose at admission, based on empirical observation of several severe hypoglycaemia cases in adults during early stages of the outbreak. Systematic measurement of glucose level at admission, followed by management (if needed) based on laboratory findings, might be more appropriate.

Intense fluid replacement to avoid hypovolemic episodes. could potentially lead to complications due to fluid overload, especially in case of severe maternal anemia. However, close monitoring of rehydration among anemic women is of particular importance. Weigh the pregnant patient on admission, administer a bolus as for a 60 kg adult (2 liters in 30 minutes). Once stable, measure the patient's weight if possible to adjust the fluid volume for the remainder of the IV infusion. If the patient is vomiting frequently or is otherwise unable to retain ORS, on-going fluid losses can be replaced via the IV route (add at least 250 ml of RL for each stool).^[17,18,22]

Discharge criteria: Patients remained hospitalized until they fully recovered from cholera and completed treatment for any obstetrical complications. Before discharge, all patients receive a cholera health education session.

Zinc is an important adjunctive therapy, which also reduces the duration of diarrhea and may prevent future episodes of other causes of acute watery diarrhea^[19,21]

Cholera Kits

To ensure efficient and effective deployment of necessary materials for the investigation and confirmation of cholera outbreaks, as well as the treatment of cholera patients, WHO has developed a set of cholera kits.

In 2016, after consultation with implementing partners, WHO revised the cholera kits to better meet field needs.

There are 6 kits:

1 for investigation

1 with supplies for laboratory confirmation

3 for treatment at each of the community, peripheral and central levels

1 support kit with logistical materials including solar lamps, fencing, water bladders and taps.

Each treatment kit provides enough material to treat 100 patients. The revised cholera kits are designed to help prepare for a potential cholera outbreak and to support the first month of the initial response^[25]

Antibiotic therapy

Mass administration of antibiotics is not recommended, as it has no proven effect on the spread of cholera may contribute to antimicrobial resistance. Give Systematic antibiotic therapy: A dose of antibiotic will be given to all pregnant women, regardless of the stage of pregnancy or the degree of dehydration. All patients received oral antibiotics (erythromycin), in order to reduce the purging rate, shorten its duration and reduce the excretion of *Vibrio cholera* in the stool, shortens the duration of diarrhoea, thus the period during which the pregnant woman could become dehydrated; reduces the duration of vibrio excretion in stools which will facilitate their admission to a maternity ward in the event of serious obstetrical complications (after 48 hours of antibiotic therapy). Azithromycin PO (1 g single dose) is the antibiotic of choice, alternative antibiotic therapy Doxycycline PO 300 mg single dose^[26]

Obstetrical evaluation

Once the patient's state of dehydration has been evaluated and the SBP stabilized, take a history to determine if there has been any bleeding, pain, contractions, loss of foetal movements. Check for these signs daily to determine if there has been any intervening change^[18]

Hypoglycaemia and hypokalaemia: If the mother presents with clinical signs of hypoglycaemia or hypokalaemia, then appropriate therapy should be given. There is no evidence that systematically adding glucose or potassium to rehydration fluid is beneficial for the foetus.

Hypoglycaemia: Due to dehydration and vomiting (i.e., not eating) give ORS and stimulate to eat. Check foetal heart tones every 30 minutes. Check foetal heart tones every 30 minutes.

Then perform a simple obstetrical evaluation:

1. Estimate the gestational age by measuring the fundal height and bed side ultrasound.
2. Listen for foetal heartbeat or NST.^[16,17,18]

Managing a normal delivery

Wait as long as possible before, assisting in the rupture of membranes just prior to delivery. Avoid positioning the patient on her back: as pregnancy progresses, the increasing weight and positional rotation of the uterus will compress the inferior vena cava reducing blood flow to the heart and decreasing cardiac output.^[22]

Special obstetrical cases^[23]

- 1- Intra-uterine foetal death: does not require an emergency transfer to the Delivery Suite (DS).
- 2- Spontaneous abortion: there is no urgency to transfer the patient to a maternity ward in the absence of persistent significant bleeding. Perform a bed side ultrasound to verify if expulsion is complete and evacuate the uterus in the OR if the expulsion was incomplete.
- 3- Threatened premature delivery: abdominal muscle cramping due to loss of potassium and calcium are common and should be differentiated from uterine contractions.
 - a- Between 26 and 34 weeks of gestation:
 - If the cervix is dilated, perform tocolysis, and lung maturation. Prior to transfer, stabilize the patient haemodynamically with RL (SBP > 90).
 - If the cervix is closed, the contractions will likely stop as cholera resolves. If contractions persist after rehydration is completed, transfer to a maternity unit for possible treatment of premature labour.
 - b- Allow the labour to continue if gestational age is > 34 weeks, intra-uterine foetal death, or the life of the mother is in danger (e.g. severe pre-eclampsia), or labour has progressed too far.^[5,6,7,8,20,22]

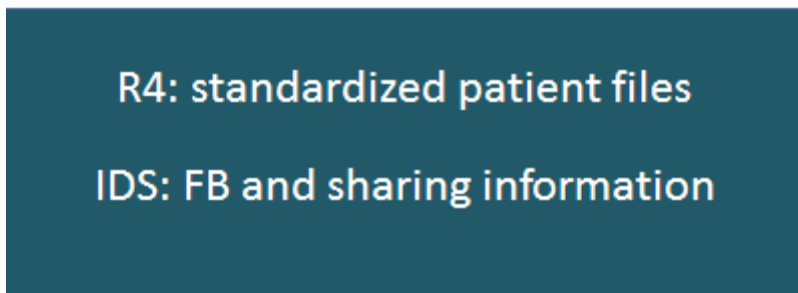


Figure 5

Review Figure 5

Clinicians treating cholera patients are encouraged to document the pregnancy outcomes and any adaptation of treatment protocols, which might contribute to the understanding and treatment of these neglected patients, many cases are not being recorded due to limitations in surveillance systems and fear of impact on trade and tourism. Cholera surveillance should be part of an integrated disease surveillance system that includes feedback at the local level and information-sharing at the global level. Under the International Health Regulations, notification of all cases of cholera is no longer mandatory. However, public health events involving cholera must always be assessed

against the criteria provided in the regulations to determine whether there is a need for official notification. A standard cholera patient file and, upon admission, recorded demographic data and information related to pregnancy, cholera episode (estimation of dehydration status, blood pressure, pulse rate, temperature at admission, time of onset), number of stool and vomiting episodes, amount of fluid and any medication received, and fetal status monitoring. Relevant events during hospitalization, such as miscarriage, delivery and procedures undertaken, are also reported. At discharge, the outcome of the patient and the pregnancy are recorded^[13,14,15,18]

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