Update in
Anaesthesia

Update in obstetric maternal sepsis

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Summary

Sepsis remains one of the four main causes of maternal mortality. Common causes of severe sepsis & septic shock during pregnancy include pyelonephritis, infection during labour and peurpurium & respiratory infection. The Surviving Sepsis Campaign (SSC) is a global effort to improve the care of patients with sepsis and septic shock, first published in 2004. SSC is a multidisciplinary approach to treatment of sepsis based on 2 phases: Resuscitation phase & Management phase. In a critically ill pregnant woman, birth of the baby may be considered if it would be beneficial to the mother or the baby or to both.

Definitions:

- The World Health Organization (WHO) in 2017 has adopted the following definition of maternal sepsis: Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period.
- The international consensus conference has launched new definition for sepsis and septic shock:
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[5]
- Organ dysfunction can be identified as a change in total SOFA score (the Sequential Organ Failure Assessment - Table1) at least two points consequent to the infection.
- Multi-organ dysfunction syndrome : Presence of altered function of two or more organs in an acutely ill patient such that hemostasis cannot be maintained without intervention.[6,7,8]
- Systemic Inflammatory Response Syndrome - Table 2.[9]
- Septic Shock: Sepsis-induced hypotension persisting despite adequate fluid resuscitation.[5]

INTRODUCTION

Septic shock is a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities, identified by two main symptoms; Vasopressor requirement to maintain a mean arterial pressure of 65mmHg and serum lactate level greater than 2mmol/L (>18mg/dL) in the absence of hypovolemia.[9] A new study of Guo et al., demonstrates the role of IL-15 in the pathogenesis of septic shock being able to facilitate sepsis-induced systemic inflammation, hypothermia, acute organ injuries and death by maintaining the natural killer (NK) cell pool.[10]

Although it is rare in pregnancy accounting for 0.002-0.01% of deliveries, it is associated with hospital mortality rates >40%.Prognostic Indicators of Poor Outcome in Septic Shock include delay in initial diagnosis, pre-existing debilitating disease, poor response to massive intravenous fluid resuscitation, depressed cardiac output ,reduced oxygen extraction, high serum lactate (>4mmol/L) and multiple organ dysfunction syndrome.[4]

Pathophysiology of sepsis:

A simple explanation of the pathophysiology is given by the Society for Maternal-Fetal Medicine (SMFM)[11]: According to the recent definition, sepsis results from a dysregulated host response to infection resulting in any organ damage. As sepsis is associated with excessive inflammatory response, extravasation of albumin and fluid occur resulting in intravascular

Table1: Quick Sepsis- Related Organ Failure Assessment.[8]

qSOFA Criteria	Points
Respiratory rate≥22/minute	1
Change in mental status	1
Systolic blood pressure≤100mmHg	1

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Table 2: Definition of Systemic inflammatory response (SIR) in pregnancy.[9]

Temperature>38 or <36C measured on two occasions at least 4h apart.
Heart rate>100beats/minute measured on two occasions at least 4h apart.
Respiratory rate>20/minute measured on two occasions at least 4h apart
White cell count >17 or < 4x 109 /L or with >10% immature band forms measured on two occasions.

hypovolemia. The inflammatory mediators; cytokines is released leading to decreased systemic vascular resistance and increased cardiac output. However, Septic cardiomyopathy results in oedema of the cardiac muscle together with decreased compliance. The cardiomyopathy manifests as both systolic and diastolic dysfunction, increasing the risk of pulmonary oedema and hypotension.

Other signs of sepsis include ischemia and disseminated intravascular coagulation.

Risk factors for maternal sepsis

Risk factors for maternal sepsis include obesity, diabetes, impaired immunity, anaemia, vaginal discharge, history of pelvic infection, history of group B streptococcal infection , amniocentesis, cervical cerclage, prolonged spontaneous rupture of membranes, group A streptococcal (GAS)infection in close contacts, retained products of conception & Caesarean birth.[12]

Causes of Severe sepsis and septic shock in pregnancy & peurperium

Obstetric causes include retained product of conception (septic abortion, retained placenta), chorioamnionitis, endometritis pelvic abscess and wound infection.

Non-Obstetric causes are appendicitis, bowel infarction, Pancreatitis and pneumonia (bacterial as staphylococcus or pneumococcus) or viral (H_1N1,influenza, Herpes).[4,11]

Corona virus is another newly identified disease, as a potential cause of sepsis during pregnancy in Middle East countries. Several authors concluded that MERS-CoV may pose serious health risks to both mothers and infants during pregnancy. They suggested that efforts to limit exposure of pregnant women to MERS-CoV should be strengthened.[13,14,15]

Clinical Features suggestive of sepsis

It's important to diagnose sepsis as early as possible as sepsis is a major hospital killer, so every minute delay in diagnosis delays recovery. It is recommended to use quick SOFA criteria to identify severe sepsis & septic shock. While only 1 in 4 infected patients have 2+ q SOFA points, they account for 3 out of 4 deaths.

Maternal and Perinatal Complications of Severe Sepsis and Septic Shock

The pregnancy-associated severe sepsis (PASS) is commonly complicated by many adverse maternal and perinatal complications. Many studies have reported a wide range of maternal morbidities affecting multiple organs, specially the respiratory system (pulmonary oedema and adult respiratory distress syndrome). The cardiovascular system complications was reported, commonly myocardial ischemia and left ventricular dysfunction. Patients admitted to ICU with SIRS had longer ICU stays and were more likely to develop organ failure; renal or central nervous system and disseminated intravascular coagulation. Multiple organ failure in septic mothers is associated with a high rate of maternal mortality.[2,4] Pregnant patients with acute infection can develop uterine contractions as a result of release of endotoxins complicated by preterm delivery. In addition, intrauterine infection is associated with neonatal hypoxia, sepsis or death.

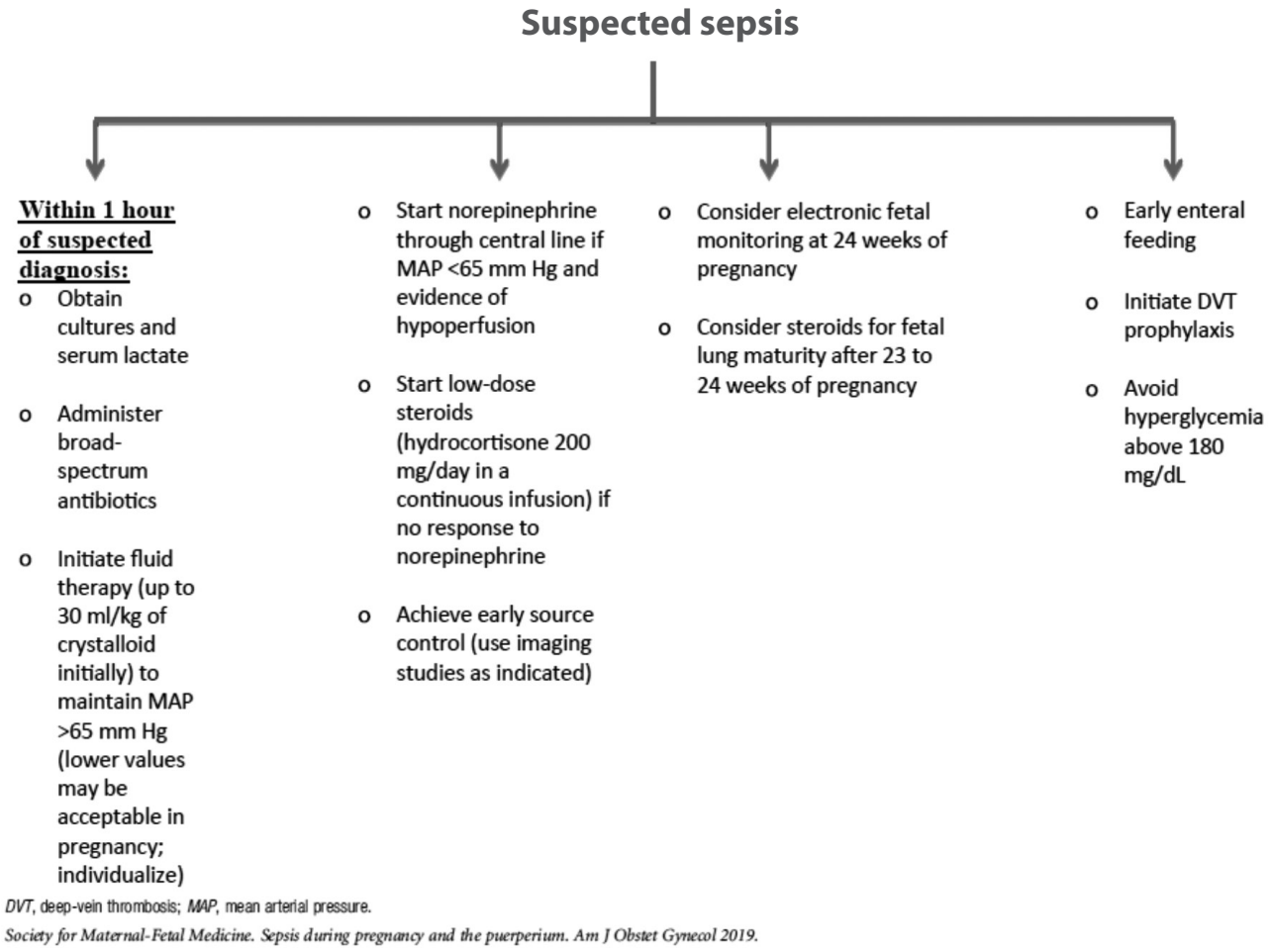
Septic shock management

The onset of sepsis may be insidious, with women appearing well before suddenly collapsing, hence the early identification of severe sepsis allows for prompt, appropriate management. (Figure 1)

Table 3: Clinical and Laboratory diagnosis of sepsis (modified from Barton[4], Singer[16] and Edward[1])

Clinical and laboratory diagnosis of sepsis	
Signs and Symptoms	**Laboratory Findings**
• Fever or Temperature instability(>38^{0}C or <36^{0}C)	• Leukocytosis or leukopenia
• Tachycardia (>110 beats/min)	• Positive culture from infection site and/or blood
• Tachypnea (>24 breaths/min)	• Hypoxemia
• Diaphoresis	• Thrombocytopenia
• Clammy or mottled skin	• Metabolic acidosis: Increased serum lactate, low arterial pH, increased base deficit
• Nausea or vomiting	• Elevated serum creatinine
• Hypotension or shock	• Elevated liver enzymes
• Oliguria or anuria	• Hyperglycemia in the absence of diabetes
• Pain (location based on site of infection)	• Disseminated intravascular coagulation
• Altered mental state (confusion, decreased alertness)	

Figure 1: Initial management of sepsis in pregnancy. Quoted from Plante et al., 2019[11]



DVT, deep-vein thrombosis; *MAP*, mean arterial pressure.

Society for Maternal-Fetal Medicine. Sepsis during pregnancy and the puerperium. Am J Obstet Gynecol 2019.

Two high profile campaigns, the Surviving Sepsis Campaign (SSC) and the Sepsis Six, have suggested "bundles" of care, though studies have shown that the tasks are rarely achieved. Neither of these care bundles has been specifically examined in pregnancy.[5, 19, 20]

Surviving Sepsis Campaign (SSC)

The Surviving Sepsis Campaign (SSC) is a global effort to improve the care of patients with sepsis and septic shock, first published in 2004.

– SSC is a multidisciplinary approach to treatment of sepsis based on 2 phases:
  - Resuscitation phase
  - Management phase.[20]

Early screening and management

The SSC recommend the following steps for early screening & management;

1. *Screening and Management of Infection:*

The first step in screening should be identification of infection according to signs and Symptoms. Once the patient is identified as having infection, cultures and blood samples are obtained as indicated ,followed by administering appropriate antibiotics.

2. *Screening for Organ Dysfunction and Management of Sepsis (formerly called Severe Sepsis):*

Patients with sepsis should be identified by the organ dysfunction criteria; the quick Sepsis-Related Organ Failure Assessment (q SOFA).

3. *Identification and Management of Initial Hypotension:*

Patients with infection and hypotension or a lactate level >4mmol/L, are given 30mL/kg crystalloid with reassessment of volume responsiveness and tissue perfusion.[9]

Resuscitation bundle

The Severe Sepsis Bundles are a series of evidence-based therapies that, when implemented together, will achieve better outcomes.[21]

The SSC guidelines established goals of care across various therapeutic modalities for sepsis. These guidelines included recommendations on initial resuscitation; diagnostic goals; timing and regimens of antibiotic administration; vasopressor and inotropic use; corticosteroids; sedation strategies; ventilation strategies; blood product administration; and preventive measures against ventilator-acquired pneumonia, stress ulcers, and deep vein thrombosis (DVT).[22]

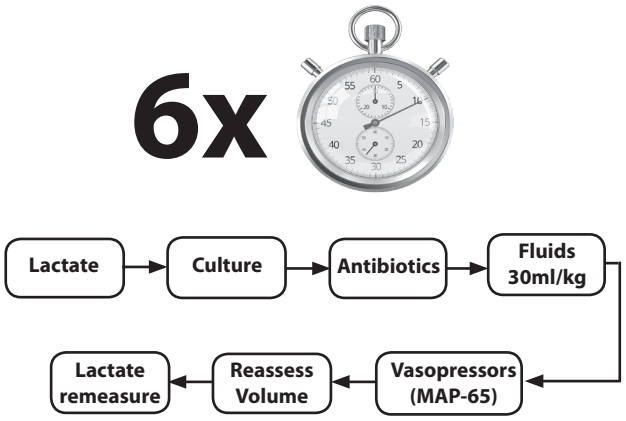


Figure 2: Resuscitation phase within 1st 6 hours

The international guidelines for management of sepsis and septic shock in 2016[23] emphasis that we should consider sepsis and septic shock as medical emergencies. Hence, the treatment and resuscitation should begin immediately. The evidence in the literature has demonstrated an association between compliance with bundles and improved survival in patients with sepsis and septic shock. The key elements in management according to SSC guidelines 2012, were divided into two bundles of care, the "resuscitation" and "management" bundle. The interventions are accomplished within 6hours and 24 hours, respectively.[22] The most important recent change in the revised SSC bundles, is that the 3-h and 6-h bundles have been combined into a single "hour-1 bundle".[24]

Initial Resuscitation Phase (first 6-h) - Figure 2:

1. Obtain blood cultures prior to antibiotic administration
2. Administer broad-spectrum antibiotic within one hour of recognition of severe sepsis
3. Measure serum lactate
4. In the event of hypotension and/or a serum lactate >4mmol/l deliver an initial minimum 30ml/kg of crystalloid or an equivalent.
5. Apply vasopressors (Norepinephrine) for hypotension that is not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65mmHg
6. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4mmol/l
   a. Achieve a central venous pressure (CVP) of ≥8mmHg
   b. Achieve a central venous oxygen saturation ($ScvO_2$) ≥ 70% or mixed venous oxygen saturation ($ScvO_2$) ≥ 65%.

During the initial resuscitation of severe sepsis, pregnant women should be in the left lateral position to avoid aortocaval compression.[11,24,25]

Tasks to be performed as soon as possible and scored over 24 hours:

Administer low-dose steroids per hospital policy

Maintain glucose higher than lower limit of normal, but less than 180mg/dl (8.3mmol/l)

Maintain inspiratory plateau pressures at less than 30cmH_2O for mechanically ventilate patients.[26]

Antimicrobial therapy

The new WHO guidance for treatment of maternal infections, recommends specific classes of antibiotics for the management of chorioamnionitis (ampicillin and gentamicin) and post-partum endometritis (clindamycin and gentamicin). However, they acknowledged that other simple, effective, and locally available antibiotics could be used as an alternative.[27]

In addition to antimicrobial therapy, the source of sepsis should be sought and dealt with.

Antimicrobial choices and its considerations

- Co-amoxiclav: Does not cover MRSA or Pseudomonas and may increase risk of neonatal necrotizing enterocolitis. It is commonly avoided in pregnancy
- Metronidazole: Only covers anaerobes
- Clindamycin: Covers most streptococci and staphylococci including MRSA.
- Teicoplanin or linezolid : Covers MRSA.
- Piperacillin-tazobactam (Tazocin) or meropenem : covers all except MRSA
- Gentamycin (3-5mg/kg single dose): Does not affect renal function if given once.
- cefuroxime or cefotaxime and metronidazole; with clarithromycin or clindamycin and gentamicin as alternatives in those with penicillin allergy
- In critically unwell patients, piperacillin-tazobactem or meropenem or ciprofloxacin and gentamicin, may be preferred.[9,28]

The study of Patil and Jambulingappa in 2015 suggested the use of combination of ceftriaxone, sulbactam and disodium edetate (EDTA) for the treatment of multi-drug resistant MDR septicaemia associated with extended spectrum beta lactamse (ESBL) and metallo-beta lactamase (MBL) producing microbes.[29]

Fluid therapy

The Surviving Sepsis Campaign recommends an initial bolus of 30mL/kg of balanced crystalloids for initial resuscitation and maintenance volume replacement in patients with sepsis and septic shock.

When the patient require substantial amounts of crystalloids , balanced crystalloids or albumin can be given, while hydroxyethyl starches (HESs) and gelatin are not recommended for intravascular volume replacement in those patients.[23] After initial fluid resuscitation, further fluid therapy should be guided by dynamic measures of preload; by using either pulse-pressure variation or passive leg raising.

Measurement of pulse-pressure variation is accomplished by analyzing the waveform of an arterial line, but it is reliable only in sedated individuals receiving positive-pressure ventilation, while passive leg raising to 30-45 can be used in spontaneously breathing patient. On

the other hand, some authors do not recommend static measures of preload (central venous pressure or pulmonary artery occlusion pressure), being poor predictors of fluid responsiveness. About 50% of hypotensive septic patients do not respond to fluid challenge, and are better treated by vasopressors.[10] Aggressive fluid administration to all patients without assessment of their response, may result in pulmonary and cerebral edema, cerebral together with increased intra-abdominal pressure and increased mortality in sepsis.[30]

Role of corticosteroids:

The indication of corticoids in septic patients is subject of controversy in the literature. The Surviving Sepsis Campaign 2012 & 2016[31, 23] recommended administration of intravenous infusion of hydrocortisone at a dose of 200mg per day. Hydrocortisone should be reserved only for septic patients with refractory shock (those who remain hypotensive following initial fluid resuscitation and vasopressors). Patients receiving corticosteroids should be cautiously monitored for hyperglycemia and hypernatremia. Corticoids are usually given within the first seven days of treatment and should be interrupted as soon as the patient shows signs of clinical improvement. A systematic review of Annane et al suggested that treatment with a long course of low-dose corticosteroids significantly reduced 28-day mortality.[32] Another benefit of corticosteroids infusion in the case of sepsis in pregnant women is the need for corticoid to accelerate fetal lung maturation due to the risk of premature birth.

Deep venous thrombosis prophylaxis:

Prevention of DVT is essential in septic pregnant patients as both pregnancy and sepsis are associated with hypercoagulability.[33, 34] Methods of prophylaxis are the use of compression stockings, intermittent lower limb compression, and low molecular weight or unfractionated heparin.[31]

SSC recommend against the use of antithrombin for the treatment of sepsis and septic shock, but recommend the use of heparin as two systematic reviews showed increased survival when heparin is used for patients with sepsis without an increase in major bleeding.[23, 35]

Vasoactive Drugs

SSC 2016 strongly recommend norepinephrine as the first choice vasopressor. Vasopressin or epinephrine to norepinephrine to norepinephrine for raising MAP to target.

Dopamine can be used as an alternative vasopressor to norepinephrine only in patients with low risk of tachyarrhythmias and bradycardia. However, low dose dopamine is not recommended for renal protection. Dobutamine can be used in patients with persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.[36-38]

The role of intravenous immunoglobulin (IVIG):

IVIG is recommended for severe invasive streptococcal or staphylococcal infection if other therapies have failed because of its immunomodulatory effect. High dose IVIG has been used in pregnant women and is effective in exotoxic shock caused by streptococci and staphylococci.[28]

Delivery decision:

The decision of delivering the fetus or continuing the pregnancy is influenced by patient's condition, gestational age, fetal status, presence of chorioamnionitis, and labour.

Generally, in a critically ill pregnant woman, birth of the baby may be considered if it would be beneficial to the mother or the baby or to both. During the intrapartum period, continuous electronic fetal monitoring is recommended. Attempting delivery of unstable mother maternal increases the maternal and fetal mortality rates unless the source of infection is intrauterine. A decision on the timing and mode of birth should be made by a senior obstetrician following discussion with the woman if her condition allows.[39]

Potential Indicators of Delivery are either maternal or foetal causes. Maternal causes are Intrauterine infection, DIC, hepatic/renal problems, heart Failure, compartmental syndrome, multifetal gestation and ARDS. While foetal factors include foetal demise and gestational age with viable fetus.[4]

Newborn complications from maternal sepsis:

Maternal sepsis has a significant impact on neonatal mortality resulting in over one million infection-related neonatal deaths every year.[40] The resultant Intra-amniotic infections cause neonatal sepsis, pneumonia and respiratory distress and long-term neurologic impairment in infants.[41]

Neonatal sepsis is a major complication that may result in death or major disability for 39% of those affected even with timely antimicrobial treatment.[42]

Anesthesia for delivery in sepsis:

South Australian guidelines recommend against Epidural/spinal anaesthesia in women with sepsis and suggest that general anaesthetic is usually preferred for caesarean section. If preterm delivery is anticipated the use of antenatal corticosteroids for fetal lung maturity in the woman with sepsis can be considered.[43]

The decision process should involve a multidisciplinary team discussion among obstetrician, neonatologist, microbiologist, intensivist and anaesthetist. If surgical intervention is mandatory, the anaesthetist has to make the decision on regional or general anaesthesia. However, the decision to perform the surgery under regional or general anaesthesia must be individualized considering the risk–benefit ratio.[44]

Regional anaesthesia

Neuraxial block, is usually contraindicated in septic patients, as Septic hypotensive patients may not tolerate the sympathetic block and vasodilatation associated with spinal anaesthesia. There may be associated coagulopathy or thrombocytopaenia. The risk of epidural abscess or meningitis is very small in patients treated with antibiotics but it should be considered in these cases.

General anaesthesia

General anaesthesia is highly likely to be required in a septic parturient. Induction and maintenance agents in patients with sepsis may increase their hemodynamic instability and should be

chosen with care. Ketamine and etomidate can be used safely in such cases and the use of a rapid-acting nondepolarizing agent, such as rocuronium, should be considered. Invasive monitoring including Intra – arterial pressure, CVP, and cardiac output monitoring are helpful, especially for the postoperative phase. The oxytocin bolus should be administered slowly by infusion over 5 min to avoid haemodynamic instability. The decision to extubate or transfer to critical care is judged by severity of sepsis and the altered physiology of pregnancy. After operation, oxygen is recommended to meet the increased demand. Analgesia should be maintained with paracetamol and opioids .Non-steroidal anti-inflammatory drugs are contraindicated because septic patients have deranged renal function and coagulation profile.[45]

Postoperative care and transfer to critical care:

The decision & timing of transfer to intensive care should be decided by the critical care team in conjunction with the obstetric consultant and the consultant obstetric anaesthetist.

Transfer to critical care is needed if the patient is hemodynamically unstable and needs vasopressor support, mechanical ventilation is needed for pulmonary oedema, or altered conscious level, hemodialysis, multiple organ failure or hypothermia.[46]

Maternal sepsis in low-income countries

The WHO meeting in 2018, announced that the global mortality rate shown in many studies is around 55%, and 60% in cases of septic shock. Meanwhile, in some African countries mortality from sepsis may reach 100%.[47] Meanwhile, maternal mortality attributable to sepsis approach 33% in low-income countries,[39] as these countries lack sufficient clean water, soap and clean birth-kits.

The health system of LMIC has limited access to timely diagnosis of septic shock (e.g. serum lactate level is not available) and shortage of health care professionals. The previous factors contributes to increase maternal sepsis.[48]

The WHO meeting recommended increasing awareness of the medical personnel of the preventive measures, early home visits and postnatal care of the newborn, in order to prevent maternal and neonatal sepsis.[49]

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