GUIDELINES

Peripartum Infections: A Position Statement of the Indian Society of Critical Care Medicine

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Abstract

This position statement reviews the evidence and rationale for the management of severe peripartum infections with a special focus on tropical infections and is tailored for resource-limited settings.

Keywords: Dengue, Gram-negative sepsis, Malaria, Peripartum, Pregnancy, Scrub typhus, Tuberculosis, Viral infections.

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Highlights

- Maternal mortality due to severe peripartum infections is high, especially in resource-limited settings like India.
- This position statement is meant to provide insights into bedside management of severe peripartum infections and for decision-making to shift the patients to higher centres with clinical worsening.

Introduction

Peripartum infections pose significant risks to pregnant women and their unborn children. The incidence of infections in pregnancy has been steadily increasing globally. The literature available is scarce, making it crucial to address the specific challenges faced by the affected pregnant women. This Indian Society of Critical Care Medicine (ISCCM) position statement aims at providing a universal standard of care based on the available evidence which can be followed by Critical Care Physicians involved in the care of sick pregnant women due to peripartum infections and ensure the well-being of both the mothers and the infants.

Methodology

The ISCCM convened a meeting on 16 July 2023 to identify the writing group members and set the objectives for the position statement. The working group was formed by involving ten Critical Care Physicians with a special interest in Obstetric Critical Care from across the country. The group identified the following areas concerning peripartum infections, keeping in mind the issues relevant to the Indian subcontinent, where a review of the literature was needed and the problem areas that need to be addressed.

- Peripartum dengue infection.
- Peripartum malaria.
- Peripartum scrub typhus.
- Peripartum leptospirosis.
- Pulmonary and extrapulmonary tuberculosis.
- Viral pneumonias.
- Peripartum sepsis
- MDR and XDR infections.

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The writing group had a round table meeting and specific questions about each of the problems were identified by the group.

The questions identified to be answered for each of the areas are listed in the table below.

Peripartum dengue infection	• Assessment of severity • Fluid resuscitation • Indication for blood product support • Perioperative plan • Early warning signs and criteria for referral
Peripartum malaria	• Diagnosis and severity assessment • Choice of therapeutic agents • Indications for termination of pregnancy • Early warning signs (EWS) and Referral criteria
Peripartum scrub typhus	• Diagnosis and severity assessment • Therapy for scrub typhus • Monotherapy vs combination therapy • EWS and referral criteria
MDR and XDR infections	• Risk factors • Diagnostic criteria
Pulmonary and extrapulmonary tuberculosis	• Radiological diagnosis • Monitoring of antitubercular therapy (ATT) • Drug interactions
Viral pneumonia	• Severity assessment of hepatitis E infection • Severity assessment of viral pneumonia • Respiratory support • Early warning signs and referral criteria

Each member of the writing group was allocated specific areas and questions to be answered in 2 months' time period. The methodology for research and review of literature was defined. The search terms for each of the problem areas were set by the respective member answering the relevant questions. Multiple zoom meetings were convened in September to November 2023 to review the literature and discuss each of the recommendations among the core group. Thereafter a final draft including answers to each defined problem was made with specific recommendations. The final round was conducted through an email by circulating the draft recommendations to the other members of the writing group and a final version was arrived at by 1st December 2023.

Note

This writing group, in discussion with the ISCCM leadership, chose not to draft a position statement on puerperal sepsis, since established guidelines on the topic already exist.

Peripartum Dengue Infection

Dengue fever (DF) is a mosquito-borne viral infection, endemic in the tropical and subtropical regions and thereby posing a significant public health challenge.

Pregnant women have a high vulnerability to severe dengue infections and can transmit the virus to their infants before or during delivery.[1] Previous research indicates that dengue during pregnancy heightens the risk of maternal complications such as hemorrhage, preterm labor, reduced amniotic fluid (oligohydramnios), fetal death, and direct transmission of infection from the mother to the neonate, causing neonatal thrombocytopenia requiring platelet transfusion.[2,3] The symptomatology of dengue in pregnant women can overlap with the clinical presentation in hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Therefore, serological tests are essential to differentiate between these conditions.[4] Routinely, all three serological assays for the detection of specific antibodies including dengue IgM/IgG and NS1 antigen should be done since they may be detected during different phases of the disease, which will aid in reducing errors.

Severity Assessment of Dengue Infection in Pregnancy

- We cannot recommend any specific severity marker for dengue infection in pregnancy.
- We suggest using the same severity criteria as used for non-pregnant adults.

Rationale

Pregnant women infected with the dengue infection face increased risks of severe complications, including hemorrhagic fever and organ failure. Moreover, vertical transmission of the virus to the fetus can occur from the mother, to the fetus leading to adverse pregnancy outcomes such as fetal developmental abnormalities and preterm low birth weight babies. There are no separate severity assessment criteria for dengue available that are specific to peripartum females and therefore we suggest the same severity criteria as used for adults can be used.[5]

Fluid Resuscitation in Dengue Infection in a Pregnant Patient

- We cannot recommend any specific fluid resuscitation protocol for dengue infection in pregnancy.
- We suggest using the same fluid resuscitation protocol as used for non-pregnant adults.

Rationale

Fluid resuscitation is a critical aspect of managing severe dengue during pregnancy, as it helps in maintaining adequate organ perfusion and preventing complications associated with plasma leakage. The World Health Organization (WHO) provides guidelines for fluid resuscitation in severe dengue, which are generally applicable to pregnant women as well.[5] The key points to consider when administering fluid resuscitation to pregnant women with severe dengue are:

Assessment of fluid status: Evaluate the patient's clinical condition including vital signs, urine output, and lab investigations like hematocrit level, and platelet counts to assess the severity of plasma leakage and determine the likely need for fluid resuscitation.

Type of fluid: Use isotonic, balanced salt solutions, or Ringer's lactate as the primary fluid for resuscitation. Avoid the use of hypotonic solutions, such as half-normal saline, as they can exacerbate fluid shifts and worsen tissue edema.

Fluid rate: Administer fluids cautiously and adjust the fluid administration rate based on the patient's response. The goal is to maintain an adequate perfusion pressure while avoiding fluid overload, which can lead to respiratory distress and other complications. Start with a moderate rate, (e.g., 5–7 mL/kg/hour) and adjust according to the patient's clinical response.

Monitoring: Monitor the patient closely for signs of fluid overload, such as increased respiratory rate, crackles in the lungs, and decreasing oxygen saturation. Urine output, hematocrit levels, and platelet counts should be monitored regularly to assess the response to fluid resuscitation.

Hematocrit and platelet count trends: Rising hematocrit levels and falling platelet counts are indicators of plasma leakage. If hematocrit

levels rise significantly or platelet counts drop to a critical level, consider increasing the fluid rate cautiously to maintain organ perfusion. In patients who do not respond to fluid boluses of isotonic saline, we can consider administering colloids such as albumin for refractory shock on an individual basis.

Transfusions: Transfuse packed red blood cells if there is evidence of severe bleeding leading to hemodynamic instability. Platelet transfusions may be considered if severe thrombocytopenia (<20,000/mm^3) is present, especially in the context of bleeding.

Avoid overhydration: Be vigilant to avoid overhydration, especially in pregnant women, as excessive fluids can lead to pulmonary edema and compromise respiratory function.

Continuous monitoring: Continuously monitor the patient's clinical status, laboratory values, and fluid balance. Adjust fluid administration rates promptly based on the patient's response and evolving clinical condition.

It is crucial to tailor the fluid resuscitation strategy based on the individual patient's condition, considering the unique physiological changes and requirements associated with pregnancy.

Blood Product Support in Dengue Infection in a Pregnant Patient

- We cannot make any specific recommendation for transfusion of blood products for dengue-complicating pregnancy.
- We suggest the standard recommendations for platelet counts during neuraxial anesthesia be applicable for dengue-complicating pregnancy.

Rationale

Indications for blood product support in severe dengue in pregnancy typically revolve around managing complications related to severe bleeding and low platelet counts. The common indications for blood product support in pregnant females with severe dengue are:

- Severe Thrombocytopenia: Platelet counts dropping below a certain threshold, often 20000/mm^3, can necessitate platelet transfusions, especially if there is evidence of bleeding or a high risk of bleeding (e.g., invasive procedures).
- Active or Profuse Bleeding: Urgent packed red blood cells (PRBCs) transfusion may be required if there is active or profuse bleeding, to restore blood volume and prevent hemorrhagic shock.
- Hemorrhagic Shock: In cases where severe bleeding leads to hemodynamic instability and shock, transfusion of PRBCs is essential to maintain tissue perfusion and oxygenation.
- Platelet Dysfunction: Platelet dysfunction, indicated by prolonged bleeding time and abnormal platelet function tests, may require platelet transfusions to improve hemostasis.
- Severe Anemia: If severe dengue-related anemia is present, transfusion of PRBCs might be necessary to increase hemoglobin levels and improve oxygen-carrying capacity.
- Disseminated Intravascular Coagulation (DIC): Pregnant women with severe dengue may develop DIC, characterized by widespread activation of clotting factors and excessive bleeding. Blood products including single donor platelets and clotting factor concentrates, might be needed to manage this complication.
- Bleeding During Delivery: If a pregnant woman with severe dengue experiences significant bleeding during delivery, blood product support, including PRBCs and platelets, may be required to manage the bleeding and stabilize the patient.
- Surgical Procedures: If surgical interventions are necessary, such as caesarean section or other obstetric procedures, blood product support may be required to manage intraoperative and postoperative bleeding.
- Patient's Clinical Status: The overall clinical condition, including vital signs, lab results, and response to other treatments should be the basis for the decision to administer blood products. Close monitoring is essential to assess the need for blood product support.

Perioperative Plan for a Pregnant Lady with Dengue Infection

- We cannot recommend any specific perioperative plan for a pregnant woman with Dengue infection.
- We suggest platelet transfusions to be administered closer to the surgery.
- We suggest general anesthesia be preferred over regional anesthesia.

Rationale

The evidence for anesthesia management in pregnant dengue patients is mainly from isolated case reports, with no specific recommendations or guidelines available in the literature.[6,7] The risk of hemorrhage is the key concern in these patients, so platelet transfusions should be planned closer to the surgical time so as to minimize perioperative bleeding.[8] Considering the potential for spinal hematoma, general anesthesia is considered a safer choice compared to regional anesthesia.[9] No specific cutoff value for platelets has been recommended prior to delivery or caesarean section but as per the consensus, a threshold of 50,000 can be accepted as for other surgeries.

Early Warning Signs and Criteria for Transport for a Pregnant Lady with Dengue Infection

- We cannot recommend any specific early warning signs and criteria for transport for a pregnant woman with dengue infection
- We suggest using the same early warning signs and criteria for referral of a pregnant female with Dengue infection as used for non-pregnant adults.

Rationale

The warning signs that should alert us against a possible worse prognosis in a diagnosed dengue pregnant patient include:

- Abdominal pain or tenderness.
- Persistent vomiting.
- Clinical fluid accumulation.
- Mucosal bleed.
- Lethargy or restlessness.
- Liver enlargement >2 cm.
- Laboratory finding of increasing HCT concurrent with a rapid decrease in platelet count.

Transport

Transporting a pregnant woman with dengue infection requires specific considerations due to the potential complications associated with the disease including:

Severity of Symptoms

If the pregnant woman is experiencing severe symptoms such as persistent vomiting, severe abdominal pain, bleeding, or difficulty in breathing, immediate medical attention and transport to a hospital are necessary.

Medical evaluation: A healthcare professional should assess the pregnant woman's condition to determine the severity of the infection and the need for hospitalization.

Hydration: If the pregnant woman is unable to drink fluids or is showing signs of severe dehydration (such as dizziness, rapid heartbeat, or sunken eyes), intravenous fluid administration might be necessary during transport.

Platelet count: Dengue fever can lead to a decrease in platelet count, which can cause bleeding. If the platelet count drops significantly, hospitalization might be necessary for close monitoring and transfusion if required.

Pregnancy complications: Pregnant women with dengue fever are at an increased risk of complications, including preterm delivery and low birth weight babies. Close monitoring and appropriate medical care are crucial to ensure the fetal well-being. Transport to an equipped hospital is mandated for cases with high risk.

Availability of medical facilities: If the pregnant woman is in an area where medical resources are limited, it might be advisable to transport her to a location with better medical facilities, especially if she is experiencing severe symptoms.

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Peripartum Malaria Infection

Severe malaria can cause an unacceptably high incidence of deaths, as has been documented in the successive editions of the World Malaria report.[1] In 2021, estimated malaria cases reported globally were 247 million with 619, 000 deaths, and from India alone, around one million cases reported annually. With the commencement of appropriate treatment early, malaria is potentially curable, but delays in treatment might result in serious consequences including death. Prompt effective treatment can prevent malaria transmission also.

Diagnosis and Severity Assessment

- We cannot recommend any severity markers for malaria infection specifically in pregnancy.
- We suggest using the same severity criteria in pregnant women with malaria infection, as used for non-pregnant adults.
- We suggest that all cases of suspected malaria should have a parasitological test such as microscopy or rapid detection test (RDT) for confirming the diagnosis.

Rationale

Although the likelihood of severe malarial disease in pregnant women is 3 times higher as compared with their non-pregnant counterparts and the mortality rate approaches 50%, no specific severity markers have been identified. Since the malaria presentation is similar in pregnancy and non-pregnant populations, thereby the same severity criteria can be used.

Parasitological diagnosis of malaria is routinely done by light microscopy or immune-chromatographic RDTs, which detect the parasite, genus, or species-specific antigens or enzymes. Nearly all cases of symptomatic malaria can be confirmed on examination of thick and thin blood films by a competent microscopist which will reveal the malarial parasites. If good quality malaria microscopy is not readily available or in *Plasmodium vivax malaria*-endemic regions, a combination RDT which allows detection of *P. vivax* (pLDH antigen from *P. vivax*) or pan-malarial antigens (Pan-pLDH or aldolase) is recommended.[2] Rapid detection tests for detecting PfHRP2 (*Plasmodium falciparum* Histidine Rich Protein 2) can even be useful for patients who have received incomplete antimalarial treatment or in whom blood films can be negative due to a recent dose of an artemisinin derivative.

Negative microscopic evidence for asexual parasites may be encountered in patients with severe infections due to sequestration and partial treatment, wherein confirmation may be done by repeat microscopy or RDT. But patients should be treated empirically if the clinical presentation indicates severe malaria and there is no alternative explanation for negative tests.[2]

Choice of Therapeutic Agents

- We suggest artemisinin-based combination therapy (ACT) in uncomplicated *falciparum malaria* for pregnant women with malaria; Artesunate + sulfadoxine-pyrimethamine and artesunate-pyronaridine are not recommended for use in the first trimester of pregnancy.
- We suggest intravenous artesunate for severe malaria, as used for non-pregnant adults.
- We suggest ACT-based combination drugs or chloroquine for *P. vivax*, and ovale. We suggest using a same therapeutic agent for severe malaria of all types.

Rationale

It is recommended to treat adults including infants, pregnant women in second and third trimesters, breastfeeding women, and children with uncomplicated *P. falciparum malaria* with the WHO-approved first-line ACT options including artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, di-hydroartemisinin + piperaquine and artesunate + sulfadoxine–pyrimethamine.[3,4] A meta-analysis of 7 studies, including 34,178 pregnancies, found no evidence of embryotoxicity or teratogenicity with ACT during the first trimester of pregnancy and suggested that artemether–lumefantrine was associated with fewer adverse pregnancy outcomes, superior tolerability, and antimalarial effectiveness than quinine and thereby should be considered the preferred treatment for uncomplicated *P. falciparum malaria* in the first trimester and if this combination is unavailable, other ACTs (other than artesunate–sulfadoxine–pyrimethamine) should be preferred to quinine.[5]

In areas with chloroquine-susceptible infections, adults and children with uncomplicated *P. vivax*, *ovale* malaria or *knowlesi* malaria should be treated with either chloroquine or ACT and in areas with chloroquine-resistant infections, with an ACT only. Only a single study conducted in Indonesia demonstrated resistance to chloroquine in *P. malariae*.[6] The blood stages of *P. ovale*, *P. malariae*, and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for *vivax* malaria.

Adults including pregnant women in all trimesters, lactating women, and infants and children with severe malaria should be treated with intravenous or intramuscular artesunate for at least 3 days. A 3-day or a 7-day oral ACT treatment after intravenous artesunate is recommended since there is a higher risk of recrudescence with Artesunate monotherapy.

Indications for Termination of Pregnancy

- We cannot recommend any specific indicators for termination of pregnancy in malaria.
- We suggest using the same indicators for termination as in non-malarial patients.

Rationale

Pregnant women have low antibody-mediated immunity, thereby more likely to develop severe malaria syndrome with hypoglycemia, respiratory distress, cerebral malaria, and a greater risk of spontaneous abortion, stillbirth, prematurity, and LBW, even in areas with low malaria transmission.[3,7–10] This applies to both *vivax* and *falciparum* malaria. Women with severe *vivax* malaria may need to be on weekly prophylaxis with chloroquine.

Severe malaria in pregnancy is associated with higher maternal and fetal complications, which may even require termination of pregnancy.[4] Severe malaria should be recognized early and is characterized by one or more of the following features:

- Impaired consciousness/coma.
- Repeated generalized convulsions.
- Renal failure (Serum creatinine >3 mg/dL).
- Jaundice (Serum bilirubin >3 mg/dL).
- Severe anemia (Hb <5 gm/dL).
- Pulmonary edema/acute respiratory distress syndrome.
- Hypoglycemia (Plasma glucose <40 mg/dL).
- Metabolic acidosis.
- Circulatory collapse/shock (Systolic BP <80 mm Hg/<50 mm Hg in children).
- Abnormal bleeding and disseminated intravascular coagulation (DIC).
- Hemoglobinuria.
- Hyperpyrexia (Temperature >106°F or >42°C).
- Hyperparasitemia (>5% parasitized RBCs).

Early Warning Signs and Referral Criteria

- We cannot recommend specific early warning signs in pregnant patients; warning signs can be extrapolated from the general population infected with malaria.
- We suggest keeping a low threshold for referring pregnant patients with severe malaria to higher centers.

Rationale

All the patients with the following symptoms should receive treatment at a higher center, where adequate facilities for managing complications are available:

Impaired consciousness/coma, convulsions, renal failure, and acute kidney injury (AKI), jaundice serum bilirubin >3, severe anemia (Hb <5 gm/dL), pulmonary edema/acute respiratory distress syndrome, hypoglycemia (plasma glucose <40 µ/dL), metabolic acidosis, circulatory collapse/shock (Systolic BP <80 mm Hg, <50 mm Hg in children), abnormal bleeding and DIC, hemoglobinuria, hyperpyrexia (temperature >106°F or >42°C), hyperparasitemia (>5% parasitized RBCs).

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Peripartum Scrub Typhus Infection

Diagnosis and Severity Assessment

- We suggest that the diagnosis of scrub typhus in pregnancy be based on the same clinical features and diagnostic methods as in non-pregnant patients.
- We suggest that the clinical features of scrub typhus may mimic other tropical illnesses and differentiating them through appropriate clinical evaluation and lab tests are essential.
- We suggest that the presence of an eschar is pathognomonic of scrub typhus infection, if detected.
- We suggest IgM as the preferred serological test for diagnosing the illness, preferably sent after the first week. Weil-Felix can also be used as an alternative test for the diagnosis
- We suggest that in the absence of any specific tool for assessing the severity of illness, evidence of one or more organ dysfunction could be considered as a marker of severe disease.

Rationale

Diagnosis of scrub typhus in pregnancy is very challenging. The dilemmas arise due to multiple factors including delay in diagnosis, delay in presentation, overlapping symptoms between pregnancy, scrub typhus, and other tropical diseases, lack of availability of commonly available tests in resource-limited settings, fallacies of the diagnostic tests, and low index of suspicion.[1]

The clinical features and diagnostic methods for diagnosing scrub typhus in pregnancy are similar as for non-pregnant patients and therefore, in the absence of a separate diagnostic criteria, most authors and studies use the Modified WHO criteria for the diagnosis of scrub typhus.[2,3] Clinical presentation of scrub typhus in pregnancy varies from mild, self-limiting to severe disease with clinical features varying from fever, exanthematous rash, myalgias, diffuse lymphadenopathy to hepato-splenomegaly.[3,4] Presence of an eschar is pathognomonic of scrub typhus infection, but reported in only 8–15% of patients. Gastrointestinal symptoms may be seen in about 25% of patients and these include abdominal pain, nausea, vomiting, hematemesis and diarrhea. Complications of scrub typhus include sepsis, shock, acute respiratory distress syndrome (ARDS), encephalopathy, acute kidney injury (AKI), and multiorgan failure. Fetal complications are also reported in patients developing scrub typhus during pregnancy mainly in the form of fetal demise, preterm delivery and small for gestational age.[3–6]

WHO Criteria for Diagnosis of Scrub Typhus (Adapted from Reference 3)

Clinical description: acute onset fever along with headache, sweating, conjunctival injection, with a dull macular popular rash over the trunks and extremities
Defervescence within 48 h following tetracycline initiation
Presence of a primary "punched out" skin ulcer (eschar), where the bite occurs.
Laboratory criteria for diagnosis: isolation of Orientia tsutsugamushi by inoculation of patient's blood in white mice
Serology detection scrub typhus IgM
1:100 or higher by EIA by ELISA
1:32 dilution or higher by Immunoperoxidase
1:10 dilution or higher by indirect Immunoflurescence
Case Classification
Suspected: A case that is compatible with the clinical profile
Confirmed: a suspected case with laboratory confirmation

Apart from the symptoms at presentation, diagnosis of scrub typhus will be based on an exposure history and confirmed serological testing. Serologic tests for *O. tsutsugamushi* include indirect fluorescent antibody (IFA) and immunoperoxidase assays, which are the preferred diagnostic tool with high sensitivity. The Weil-Felix test is less expensive, easy to perform, and can be done in low-resource settings but is relatively insensitive and non-specific due to cross-reactivity with various other clinical conditions.[1] Isolation of *O. tsutsugamushi* can be done in cell culture, in inoculated mice, or can be visualized in the spleens of infected mice by giemsa or diff-quick staining. Polymerase chain reaction amplification of blood, skin, or lymph node samples is useful, but not generally available in endemic parts of the world.[5,6]

Predictors of MODS and mortality in scrub typhus infections include a serum creatinine of >1.5 mg/dL, platelet count of <100,000/cu.mm, or transaminases (AST, ALT, or both) >500 U/L on admission.[7]

Therapy – Mono vs Combination

- We suggest using Azithromycin IV at a dose of 500 mg OD for 7 days for managing scrub typhus infections in pregnant women.
- We suggest against using doxycycline for treatment of scrub typhus in pregnancy.

Rationale

A large multicentric, randomized controlled trial of over 700 patients, showed that combination therapy with intravenous doxycycline and azithromycin was a better therapeutic option for the treatment of severe scrub typhus than monotherapy with either drug alone.[8] However, in pregnancy, tetracyclines are contraindicated and hence combination therapy is not recommended, and IV azithromycin for 7 days may be the only treatment option used in these patients at the earliest successfully.[3,4]

Early Warning Signs (EWS) and Referral Criteria

- We suggest using same EWS as used for infections in other critically ill scrub typhus patients, in the absence of a specific EWS for pregnant women.
- We suggest considering patients who have clinical or biochemical evidence of one or more organ dysfunctions to be referred to a tertiary care center for further care.

There are no specific warning signs or referral criteria for scrub typhus. However, it can be suggested that common EWS used for other infections can be used in the setting of scrub typhus. Furthermore, there are no clear studies to decide on the referral criteria for patients with scrub typhus. However, the study by Sivarajan et al., suggested thrombocytopenia, AKI, or biochemical evidence of hepatitis were predictors of mortality and MODS and all patients with these risk factors may be considered for referral to a higher center.[7]

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Peripartum Leptospira Infection

Leptospirosis in pregnancy is underreported since the clinical presentation mimics the symptoms of common obstetric complications such as acute fatty liver of pregnancy (AFLP), Pre-eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes and low platelets).

Epidemiology

- We suggest to include Leptospirosis in differentials for acute febrile illness in geographic areas where the disease is endemic, particularly when there is a high risk of exposure based on profession or certain environmental risk factors.

Rationale

Leptospirosis is a tropical disease with significant mortality and morbidity predominantly seen in the geographic area extending between the Tropic of Cancer and Tropic of Capricorn.[1] Exposure to rats and stagnant water is a significant risk factor for getting infected with leptospirosis. There are two patterns identified, rural and urban, with rural cases occurring predominantly in association with farming, while the urban variant primarily relates to poor disposal of sewage and rodent infestation.[2,3] Other potential risks for getting infected include professions bringing workers in contact with sewage water, veterinarians, recreational sports, after rainfall-related flooding, etc.[4,5] Most of the cases in India are reported from coastal areas possibly due to the presence of large river deltas prone to flooding and due to the warm and humid conditions which favor the survival of leptospires.[6]

Diagnosis

- We suggest that clinical features may often lead to suspecting leptospirosis as a possible diagnosis in pregnant women.
- We suggest that the presence of conjunctival suffusion and icterus may help differentiating leptospirosis from other tropical illness like dengue, scrub typhus, enteric fever, and chikungunya.
- We suggest differentiating leptospira infection from pregnancy-induced complications which can mimic leptospirosis.
- We suggest using polymerase chain reaction (PCR) in the first week and IgM enzyme-linked immunosorbent assay (IgM ELISA) or increasing titers of IgM from the second week onwards to confirm the diagnosis of leptospirosis.

Rationale

Most inferences for diagnosis of leptospirosis in pregnancy are drawn from literature emanating from non-pregnant patients. Leptospirosis may need to be differentiated from other causes of acute febrile illnesses like dengue, malaria, scrub typhus, enteric fever, and chikungunya or other reasons of sepsis. One of the differentiating features that may help in suspecting leptospirosis from other causes includes the presence of icterus or conjunctival suffusion. Besides this characteristic clinical feature, diagnosis, and differentiation from other differential diagnoses will need microbiological methods.[7] The presentation may mimic other infections including viral, bacterial, and parasitic, AFLP, pregnancy-induced hypertension, and HELLP syndrome.[2]

Depending on the phase of the illness, different tests can be used to confirm the diagnosis.[8] In the first week, PCR and blood culture may be the preferred investigation, but after the first week, the sensitivity and specificity of these tests decline, and in the second week urine samples for culture or PCR may be more useful. Blood cultures may not always be available or feasible. However, after the first week, serology may be the investigation of choice for diagnosis of leptospirosis with the microagglutination test (MAT) as the gold standard method. In the absence of MAT, IgM ELISA is the most commonly used serological method for diagnosing leptospirosis.[7] The disadvantages of the serological methods (the need for specialized labs, expertise and long turnaround time) led to the development of multiple rapid tests. The most commonly used technique is lateral flow assay-based immune chromatography (ICT) with fairly good concordance to IgM ELISA. The major fallacies of serology-based tests include false positive reports, particularly in endemic areas.[9] In patients with atypical symptoms, the diagnosis can be confirmed by demonstrating elevating titers with paired samples sent two weeks apart. A scoring system called modified Faine's criteria has been validated for the diagnosis of leptospirosis.

Treatment and Diagnosis

- We suggest antibiotics including penicillin, ceftriaxone, piperacillin-tazobactam, meropenem and azithromycin for the treatment of leptospirosis in pregnancy. Doxycycline is contraindicated in pregnancy.

Rationale

There are poor quality studies in literature with regards to treatment of leptospirosis. The antibiotics used in studies vary from penicillin, ceftriaxone, piperacillin-tazobactam and even meropenem to doxycycline and azithromycin, with a total duration of therapy around 7 days in most studies.[8,9] However, among all these drugs, doxycycline is a contraindication in pregnancy, due to its potential teratogenic effects on bone and teeth development of the fetus.

Indications for Termination

- We suggest that termination of pregnancy in leptospirosis be based on usual obstetric indications.

Rationale

Congenital anomalies are rare in pregnant ladies infected with leptospirosis, but in early pregnancy, there is a risk of spontaneous abortion.[10,11] As such, leptospiral infection, in itself, is not an indication for termination of pregnancy.

EWS and Referral Criteria

- We suggest using SPiRO score as a criterion to consider referral to a higher center in pregnant women with leptospirosis.

Rationale

A retrospective analysis of 402 patients in Northern Queensland showed good sensitivity and specificity of a 3-point scoring system to predict severity of leptospirosis.[12] The three clinical findings (systolic blood pressure >100 mm Hg, respiratory auscultation abnormalities, Oliguria), awarded one point each, were used to generate a three-point SPiRO score, with the risk of severity of disease rising with the progressively increasing SPiRO score.[12] Though this score is not validated in pregnant women, in the absence of any other scoring systems, extrapolating experience in non-pregnant patients may be considered. SPiRO score performed better as compared to qSOFA but there was no difference in predictive ability of the SPiRO score compared to the qNEWS score.

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Peripartum Pulmonary and Extrapulmonary Tuberculosis

Tuberculosis (TB), if left untreated in pregnancy, is a bigger hazard to pregnant women and the fetus than the problems with its treatment, therefore treatment is imperative.

Diagnosis

- We suggest that diagnosis of active TB disease is based on a combination of clinical presentation, chest radiograph, acid-fast bacilli on smear, culture, or pathologic data.

Rationale

Symptomatology of tuberculosis is typical including fatigue, tiredness, loss of weight, shortness of breath, chest pain, hemoptysis, and low-grade fever lasting for more than 3 weeks. The common sites of extrapulmonary TB are the pleura, lymph nodes, bones, meninges, and the urogenital tract. Genital TB usually presents with infertility, menstrual disorders, or pelvic pain.

Screening for TB using chest X-ray (CXR) should be done even among pregnant women with typical signs and symptoms. In symptomatic pregnant females, the Norwegian Institute of Public Health recommends that CXR should be a routine test for tuberculosis screening.[1] International Commission on Radiological Protection (ICRP) suggests that the threshold dose of radiation injury for fetal damage begins at 100 mGy, whereas the typical dose to the fetus/ embryo during chest X-ray is only 0.01 mGy.[2]

Treatment

- We suggest all 3 first-line antitubercular drugs including isoniazid, rifampicin, and ethambutol in pregnancy for 9 months.
- We suggest consideration of pyrazinamide as 4th drug for extra-pulmonary and HIV-related TB in pregnancy.
- We suggest treatment of latent TB infection should be considered in pregnancy if the woman contracted TB in the past two years owing to the high risk for active TB. If not, then treatment for latent TB should be deferred until 2–3 months postpartum.

Drug Interactions and Monitoring

- We suggest liver function tests before starting antitubercular therapy and continue liver function monitoring, especially with isoniazid treatment in pregnant females.
- We suggest that pyridoxine supplements should be received in pregnancy.

Postpartum and Breastfeeding

- We suggest that untreated active tubercular disease be considered a contraindication to breastfeeding.
- We suggest all infants born to mothers with TB during their pregnancy require evaluation for congenital TB.

Rationale

All four first-line medications used to treat TB including isoniazid, rifampin, ethambutol, and pyrazinamide are classified by the Federal Drug Administration (FDA) as category C.[3–5] However, pyrazinamide due to lack of evidence about its safety during pregnancy, its use is controversial in the United States.[3] Hepatotoxicity is a known complication of antitubercular therapy and thereby before starting therapy, it is mandatory to monitor

liver function tests.[3] But there is high incidence of hepatotoxicity with isoniazid treatment during pregnancy and in the early postpartum period, thereby requiring more stringent monitoring.[6] Pregnant women are more likely to be deficient in pyridoxine, therefore supplemental pyridoxine (vitamin B6) is considered a mandate to prevent neurotoxicity.[7,8]

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Peripartum Viral Infections

The common viral infections in pregnancy include influenza, varicella, hepatitis A to E, SARS caused by a coronavirus (COVID-19), and HIV-associated infections. The most common viral infections in pregnancy are the respiratory infections.

Severity Assessment of Viral Pneumonias in Pregnancy

- We cannot recommend any specific markers to assess the severity of viral pneumonia in pregnancy.
- We suggest a liberal policy for ICU admission for pregnant patients with viral pneumonia.

Rationale

Although the literature has shown high levels of association between severe viral pneumonia and pregnancy leading to higher mortality and maternal and fetal complications, specific factors could not be identified.[1] Viral pneumonia occurring in late pregnancy (3rd trimester) are usually associated with increased mortality. Pneumonia severity index (PSI) to define severity of illness in patients with community-acquired pneumonia (CAP) underestimates the need for hospitalization and ICU care in CAP during pregnancy.[1,2] The US Centers for Disease Control (CDC) suggest asthma and obesity as the common comorbid conditions associated with adverse outcomes, based on surveillance data.[3] The severity of influenza is higher in pregnancy as compared to non-pregnant women, but there is no difference in clinical symptomatology. The criteria for ICU admission in the pregnant CAP patient should be liberal considering physiologic alterations with high susceptibility to hypoxemia and potential for rapid progression and worsening of viral infections in pregnancy.[4] Since most of the studies show patients with antepartum pneumonia had positive findings on chest radiographs at admission or on repeat examination, pregnant women with persistent symptoms must have a chest radiograph, irrespective of the intrapartum period, to avoid delays in recognizing the CAP.[5] The ATS/IDSA guidelines recommend CXR (with an abdominal shield during pregnancy) along with an assessment of gas exchange (oximetry or arterial blood gas), and routine blood counts in all patients with suspected CAP.[6] The Advisory Committee on Immunization Practices recommends that all women who might get pregnant during influenza season receive the influenza and H1N1 virus vaccine safely in any trimester of pregnancy except for the first trimester.[7] A prospective meta-analysis of 21 studies on COVID-19 infection in pregnancy found that comorbidities including diabetes mellitus, hypertension, cardiovascular disease, HIV infection, pre-pregnancy underweight, and anemia were associated with severe COVID-19-related outcomes in pregnant women including higher maternal morbidities, and adverse birth outcomes.[8]

Respiratory Support in Viral Pneumonia in Pregnancy

- We suggest early proning for pregnant patients with moderate to severe ARDS, with close monitoring.
- We strongly suggest the early institution of ECMO for severe viral pneumonia in pregnancy.

Rationale

Proning: Proning remains a proven fruitful intervention for improving oxygenation in patients with severe refractory hypoxemia due to ARDS, associated with H1N1 influenza or COVID-19 infections.[9] Studies have demonstrated mortality benefits with early proning and should be considered in pregnant women also with the benefits of relieving aortocaval compression from the gravid uterus, and diaphragmatic compression from abdominal contents if performed correctly. Literature supports proning in pregnancy with no alteration of maternal hemodynamics or any major adverse events but proning requires careful attention during pregnancy due to the specific physiologic alterations and the technical challenges due to the gravid abdomen.[9,10] An RCT on 33 patients concluded that the prone position improved oxygen saturation and was safe and comfortable in pregnant females.[11] In a case series of thirteen pregnant-prone patients with COVID-19 during their hospitalization, no maternal hemodynamic instability, worsening oxygenation or ventilation, or fetal intolerance was observed, and thereby, no termination of prone positioning sessions was required. In one patient, uterine contractions started while proning which led to supine repositioning, subsequently, the contractions resolved and the patient was maintained prone without any further issues. Continuous fetal monitoring in a prone position was difficult and sometimes not possible, which mandated an earlier return to the supine position.[12]

Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation appears to be an effective and safe therapy for the temporary support of lungs in pregnant women with severe viral pneumonia. A systematic review of 90

publications on 97 pregnant patients, with adult respiratory distress syndrome (ARDS) as the most common respiratory indication (91.9%), reported up to 90.7% maternal survival and 83.3% survival in neonates.[13] In another meta-analysis of studies on the use of ECMO in pregnant and postpartum women with ARDS secondary to H1N1 infection, the pooled estimate of the survival rate was 74.6%.[14] Literature reports high survival rates with ECLS in pregnant and postpartum women and relatively low major complications even in COVID-19-related severe respiratory failure.[15,16]

Severity Assessment of Hepatitis E Infection in Pregnancy

- We cannot recommend any specific severity markers for hepatitis E infection (HEV) in pregnancy.
- We suggest considering the high viral load of HEV and the infection occurring in late pregnancy as a poor prognostic marker.

Rationale

There are global reports of hepatitis E-related acute liver failure worldwide, but more common in endemic areas including the Indian subcontinent, Southeast Asia, and China, mainly attributable to poor hygiene and sanitation. Hepatitis E in pregnant women results in fulminant hepatitis usually due to interplay between immunological and hormonal balance with higher viral load, higher interleukin levels, lower CD4/CD8 cells ratio, low cytokines, reduced estrogen and progesterone receptor expression and increased levels of steroid hormones. In late pregnancy, there is an increased risk of acute liver failure, fetal loss, and high mortality, up to 20–25% in third trimester. A systematic review reported up to 7 times increased odds of death during pregnancy in the presence of HEV infection.[17] There are no specific severity markers for hepatitis E infection in pregnancy. The infection occurring in later pregnancy itself is a poor prognostic marker and a high viral load of HEV could be one of the severity markers of infection during pregnancy.[18]

EWS and Referral Criteria for Pregnant Patients with Viral Infections

- We suggest that any pregnant women diagnosed with viral infections with any of the EWS or qSOFA score of >2 be shifted to a tertiary care center at the earliest.
- We suggest that any pregnant women diagnosed with viral infections, without high-risk symptoms or EWS, but with comorbidities like obesity, asthma, or obstetric issues like twin pregnancy, and pre-term labor be shifted to a tertiary care center.

Rationale

Early warning signs for pregnant patients with viral infections include (Maternal EWS)[18]

- Systolic BP <90 or >160 mm of Hg/Diastolic BP >100 mm of Hg.
- Heart rate <50 or >120/min.
- Respiratory rate <10 or >30/min.
- Oxygen saturation on room air <94%.
- Oliguria.
- Shortness of breath.
- Difficulty in speaking.
- Pain or pressure in the chest while coughing.
- Postural hypotension.
- Maternal confusion, dizziness or confused state, agitation, unresponsiveness.
- Worsening of influenza-like symptoms or recurrence of symptoms once settled.
- A known patient with preeclampsia reported a non-remitting headache or shortness of breath.

Or

Quick Sequential Organ Failure Assessment tool (qSOFA) (2 out of 3)

- Systolic BP <100 mm Hg.
- Respiratory rate >22.
- Altered level of consciousness.

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Peripartum Sepsis

Peripartum sepsis is one of the five major causes of maternal deaths globally, accounting for around 10–15% maternal deaths.[1]

Diagnosis

- We suggest that suspicion of peripartum sepsis should be high in any pregnant patient post-delivery or abortion, presenting with high-grade fever with systemic signs of infection.
- We suggest using ultrasonography, beyond routine investigations for diagnosis of peripartum infections.

Rationale

Patients presenting with peripartum sepsis usually present with vague symptoms like fever along with pain abdomen, uterine tenderness, bleeding, foul-smelling discharge, or incisional site findings like erythema, redness, warmth, local site pain, or discharge.[2] With signs typically appearing 4–7 days post-surgery, high suspicion should be kept with even minimal symptoms in the first 24 hours. In all patients, evaluation should include a complete blood count along with swab cultures. Typical lab findings include leukocytosis with neutrophilia with a leftward shift but the lab workup may be inconclusive, especially in endometriosis which is usually a clinical diagnosis. Ultrasound is mandatory to look for retained products of conception post-delivery or abortion.[3]

Treatment

- We suggest initiating broad-spectrum antibiotics empirically for patients with peripartum sepsis, which can be narrowed down with the availability of cultures or clinical stability.
- We strongly suggest immediate surgical removal of conception products, if retained.

Rationale

The most common pathogens implicated in puerperal sepsis are the vaginal or reproductive tract along with urinary tract flora that are disseminated peri-procedurally. Antibiotic choices for these infections should be based on the knowledge of the genital tract microbiological profile, the local antibiogram, and the severity of the infection. In very sick ICU patients, antimicrobial coverage should be with a broad-spectrum antibiotic.[4] Empirical therapy may include beta-lactam, and carbapenems along with a gram-positive and anaerobic coverage. Breastfeeding should be a consideration for these patients and drugs excreted in breastmilk should be withheld. In case of non-improving status even after 96 hours, the probable diagnosis of pelvic abscess or infected hematoma should be considered.[5]

If there are retained products of conception in imaging, evacuation should be done on urgent basis followed by broad-spectrum antibiotics.[6] Necrotizing fasciitis is also a surgical emergency that cannot be treated with antibiotics alone. Surgical intervention should be followed by antibiotics, common regimen recommended being vancomycin and piperacillin-tazobactam with clindamycin, used for its antitoxin activity.[7]

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Peripartum Multidrug Resistant (MDR)/ Extended Drug Resistant (XDR) Infections

Pregnancy being an immune-suppressed state, pregnant women are prone to drug-resistant infections and sepsis is one of the leading causes of mortality among the obstetric population.

Risk Factors for MDR

- We suggest that in pregnant women with sepsis, risk factors should be considered for *gram-negative* and *gram-positive* multidrug resistant organisms (MDRO) along with clinical examination.

Rationale

Critically ill patients with puerperal sepsis should be assessed for probabilities of multidrug resistance for prompt and appropriate therapy. It is important to elicit a history of comorbid conditions like diabetes mellitus, cardiac diseases (valvular and nonvalvular), immunosuppressed states, prior episodes of infections and antibiotic history, and other medical diseases in the antepartum period like pre-eclampsia, jaundice, and any other pre-existing systemic diseases. Low-middle-income countries have a high incidence of puerperal sepsis caused by MDR infections as shown

in Studies from Uganda and Ethiopia.[1,2] It is predicted that actual data of resistant infections in these resource-limited setups may be much higher than reported due to constraints in the infrastructure of health care setups. Therefore, it is imperative to understand the risk factors and diagnosis of multidrug resistance in the obstetric group of patients which will help in early diagnosis and prompt appropriate treatment of MDR sepsis.

Among *gram-negative bacteria* (GNB), *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, *Enterobacteriaceae* (*E.coli* and *Klebsiella*) have emerged as major MDR/XDR organisms and a few newer ones like *Stenotrophomonas maltophila, Burkholderia pseudomallei* are also on the rise. Risk factors for *gram-negative* MDROs include antibiotic exposure within the preceding 90 days, history of recurrent pelvic/genitourinary infections, endometritis, uncontrolled diabetes mellitus, underlying immunocompromised state, history of steroids intake, prior hospital admission for at least 2 days in the preceding 90 days, nursing home resident, indwelling catheter (central venous, arterial, or urinary), tube feeding, mechanical ventilation, hepatic failure, and long-term hemodialysis.[3–5]

The risk factors postulated for major gram-positive MDROs including *methicillin-resistant Staphylococcus aureus* (MRSA) and *vancomycin-resistant enterococcos* (VRE) include recent prolonged hospitalization or admission to nursing homes, recent antibiotic use, MRSA colonization, intensive care admission, invasive procedures, HIV infection, open wounds, hemodialysis, and discharge with long-term central venous access or long-term indwelling urinary catheter.

Diagnosis of MDROs

- We suggest that the diagnosis for MDR/XDR infections in pregnant women should be established by both clinical and laboratory-based methods for the most accurate results and therapy.
- We suggest that cultures of relevant body fluids/specimens or blood should be done in all cases of suspected/proven sepsis and septic shock in pregnant women aimed at the identification and susceptibility of the organisms.
- We suggest considering rapid diagnostic tests in puerperal sepsis, as appropriate and feasible.

Rationale

Early timely diagnosis and administration of appropriate antibiotics within 1 hour of diagnosis are the keys to the best outcome in sepsis and septic shock.[6] The conventional culture sensitivity methods from samples like blood, tracheal secretions, urine, and other body fluids or specimens continue to remain the standard way for isolation of bacteria and identification of species but few newly emerging resistance mechanisms may be missing in these technology-based tests.[7] Therefore, the diagnosis of MDR sepsis should be equitably based on both clinical assessment and laboratory tests. The common RDTs include matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), light scattering technology, fluorescent in situ hybridization (FISH), FISH combined with time-lapse microscopy, molecular detection based on NAATs and microarrays, lateral flow immunoassay for rapid detection of resistance enzymes (LFIA), nucleic acid amplification and T2 magnetic resonance (T2MR) nano-diagnostic system will help in faster identification of organisms and to know the exact mechanism of resistance to antimicrobial agents which can aid in planning target specific therapy.[7]

Conclusion

Protecting pregnant females from the adverse effects of peripartum infections is a collective responsibility that demands collaborative efforts from healthcare professionals, researchers, policymakers, and communities. By investing in research, education, and healthcare infrastructure, we can mitigate the impact of deadly infections on pregnant women and the fetus, ensuring healthier outcomes for both mothers and their newborns. This position statement advocates for comprehensive strategies that prioritize the well-being of pregnant females, underscoring the urgency of addressing peripartum infections in the context of maternal and child health.

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