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REVIEW ARTICLE

Obstetric Sepsis: A Review Article

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Abstract

Introduction The World Health Organization defines obstetric (maternal) sepsis as organ failure caused by infection during pregnancy, childbirth, post-abortion or postpartum period. It is the third most prevalent reason for maternal death. According to statistics, sepsis caused 11 percent of maternal fatalities worldwide.

Discussion Physiological changes related to pregnancy may imitate the start of sepsis, which makes definitive diagnosis difficult. The definition of sepsis is gradually amended over decades. Various diagnostic tools and criteria are available.

Conclusion Prevention, early diagnosis, and appropriate management can reduce sepsis related maternal mortalities and morbidities. To reduce unnecessary maternal mortality, future policy development in the area of evaluation and care of obstetric sepsis is essential.

Keywords Obstetric sepsis · Septic shock · Pregnancy · Puerperium · Maternal · Mortality · Morbidity

Introduction

Obstetric sepsis is the leading cause of maternal death [1]. It contributes significantly to serious maternal morbidity all around the world, resulting in 11% of maternal mortality and ranking as the third most common primary cause of maternal death [2–4]. In 2017, an estimated 5.7 million women were impacted by sepsis during pregnancy, labour, and postpartum period [5]. Acute morbidities and long-term consequences such as pelvic inflammatory disorders, subsequent infertility, and persistent pelvic pain can occur in addition to maternal mortality [6]. It has been related to 1 million neonatal deaths around the world [7, 8]. Maternal-newborn attachment is also compromised by admission to hospital. Pregnancy-related physiological, mechanical, and immunological changes render women more vulnerable to infection [9].

This is a detailed overview and analysis of clinical advice aimed at defining sepsis, different diagnostic tools, and recent sepsis prevention and therapy measures.

Definition Sepsis is a Greek term that relates to the breakdown of pathogens. Between 460 and 370 BC, Hippocrates coined the term "Sepidon", which means "distortion, breakdown of a web structure" [10].

Due to improvements in sepsis epidemiology and management, a new definition of sepsis was proposed in 2016 by the critical care task force in the third international consensus [10, 11]. Definitions are as follows:

- Sepsis–The third international consensus in 2016 defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host immune response to infection" [11].
- Septic shock–"It is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone" [11].
- Multiorgan dysfunction syndrome–"Presence of altered function of two or more organs in an acutely ill patient such that haemostasis cannot be maintained without intervention" [11].

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- Maternal sepsis–It is defined by World health organisation as "life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period" [12].

Discussion

Pathophysiology of Sepsis

Sepsis is a complex disruption of the immune system's finely adjusted balance of inflammatory and anti-inflammatory mechanisms [13]. The complement and coagulation pathways are activated by pro- and anti-inflammatory molecule activation. This causes release of inflammatory mediators and pathogen-related molecules [14]. Damage-associated molecular patterns (DAMPs) are triggered by pathogens or host-derived danger signals after detecting molecule patterns like (PAMPs, such as lipids, or DNA sequences exo- and endotoxins). These chemicals activate receptor sites (TLR, toll-like receptors) on the surface of monocytes as well as (APCs) antigen-presenting cells, resulting in the gene transcription. It is involved in changed immunity, inflammation, cell metabolism, resulting in the clinical state of sepsis [15]. While both pro- and anti-inflammatory mechanisms are activated, inflammation leads to tissue damage.

Pregnancy-related physiological as well as immunological changes may limit the mother's ability to react to infection. Sepsis diagnosis may be delayed because of pregnancy-related physiological changes which resemble early sepsis. Maternal sepsis is attributed to the risk factors, pathogens responsible for infections are listed in Table 1, [16].

Diagnosis

Sepsis screening options include manual methods as well as automated usage of an electronic generated health record to facilitate early detection of sepsis [17]. Screening of sepsis includes a variety of clinical variables like vital signs, signs of infection, systemic inflammatory response syndrome (SIRS) diagnosing criteria, and different scoring systems such as (qSOFA) quick Sequential Organ Failure or (SOFA) Sequential Organ Failure Assessment, (MEWS) Modified Early Warning or National early warning(NEWS) scores are used [18, 19].

In a meta-analysis of seven studies including 42,623 patients for predicting sepsis which is hospital acquired, with confidence interval of 95 per cent (SAUROC), the pooled area under the receiving operating curve (0.89 per cent), sensitivity (80–81 per cent), and specificity (80–81 per cent) were all positive [19, 20]. Machine learning has

Table 1 Maternal sepsis attributed risk factors and pathogens responsible for sepsis [16]

Maternal medical condition
1. Anaemia
2. Impaired glucose tolerance
3. Diabetes mellitus
4. Obesity
5. History of immunosuppressant medication
6. Disorders of immunosuppression
Maternal infections
1. Abnormal vaginal discharge
2. History of pelvic inflammatory diseases
3. History of infection with group B streptococcus
4. Urinary tract infections
5. Surgical site infection related to wounds
6. Other infection: cholecystitis, pyelonephritis, pancreatitis, appendicitis, gastroenteritis, meningitis, pneumonia
7. Breast infections
8. Intravenous access site infections
Obstetric interventions
1. Antenatal:
Amniocentesis
Cervical cerclage
2. Intrapartum:
Multiple vaginal examinations
Instrumental vaginal deliveries
Caesarean section
3. Postpartum:
Manual removal of the placenta
Perineal trauma/tear/lacerations
Wound hematoma or abscess formation
Obstetric condition
1. Prolonged rupture of membranes
2. Chorioamniotis
3. Intrauterine foetal death
4. Septic abortion
Pathogens responsible for sepsis
1. Gram positive cocci
Group A beta haemolytic streptococci
Group B streptococcus
Staphylococcus aureus
2. Gram negative
Escherichia coli
Klebsiella
3. Anaerobes:
Bacteroides
Pepto streptococcus
Clostridium
Pepto coccus

Table 1 (continued)

4. Viruses:
Influenza
Varicella
Hepatitis
Herpes simplex

a higher specificity (72 per cent) than screening methods including SOFA (0.78), SIRS (0.70), and (0.50) MEWS. [20] Different scoring systems and diagnostic criteria used for screening sepsis are enlisted in Table 2 [19, 20, 21].

Because physiological changes in pregnancy can affect variables in the above scoring system, obstetrically modified—SOFA and qSOFA scoring systems have been amended by SOMANCE (Society of obstetric medicine of Australia and New Zealand) for obstetric sepsis end organ dysfunction assessment [20]. Maternal clinical findings and laboratory investigations are enumerated in Table 3 [21, 22].

Management

Early detection and treatment remain the cornerstones of management. The Surviving Sepsis Campaign (SSC) International clinical practice guidelines (2004), which got updated periodically, are based on a "bundle" strategy to simplify sepsis management. A bundle is a collection of care elements that, when used together, have a greater impact on outcomes than used separately. In 2018, SSC updated the one-hour (GOLDEN HOUR) bundle [23].

The “golden one-hour bundle” of care includes following components:

1. Measurement of serum lactate levels.
2. If serum lactate level is more than 2 mmol/L, then recheck it.
3. Use of broad-spectrum antibiotics.
4. Send blood culture before use of antibiotics.
5. Use of intravenous crystalloid 30 mL/kg for hypotension or lactate level ≥ 4 mmol/L.
6. In case of hypotension, use a vasopressor to maintain mean arterial pressure more than 65 mmHg.

The Surviving Sepsis Campaign (SSC) International guidelines for sepsis and septic shock screening and management have been recently revised in 2021. The following is a summary of its screening and management [18].

- Screening of sepsis

a. Surviving Sepsis Campaign advises against using qSOFA as a single-screening test for sepsis or septic shock compared to SIRS, NEWS, or MEWS. All hospitals should have a performance improvement programme for sepsis, including sepsis screening for suspected patients.
b. Measure blood lactate levels in suspected patients of sepsis.

- SSC international guidelines (2021) for management of sepsis

1. Initial cardiopulmonary resuscitation management includes:
a. Management of sepsis is a medical emergency and should start immediately
b. Intravenous fluid management: At least 30 millilitre/kilogram of intravenous crystalloid fluid should be given within the initial three hours of sepsis-induced hypoperfusion.
c. Use of dynamic measures to monitor resuscitation such as serum lactate levels and capillary refill time.

2. Mean arterial pressure:

For adults with septic shock on vasopressors, an initial target mean arterial pressure (MAP) of 65 mmHg over higher MAP targets.

3. Admission to intensive care unit (ICU):

Sepsis or septic shock patients should be admitted to ICU within six hours.

4. Infection:

a. Continuous re-evaluation and search for alternate diagnosis for unconfirmed infections, and stop use of empiric antimicrobials if another cause of disease is suspected or confirmed.
b. Intravenous antimicrobials should be started as early as after recognition of sepsis and within 1 h for both with empiric broad-spectrum therapy with one or more antimicrobials to cover all suspected microorganisms (including bacterial/viruses or fungus). Empirical antibiotic regimen used in sepsis proposed by (ICMR) Indian

Table 2 Different scoring systems with detailed clinical parameters: [19–21]

Scoring system	Clinical parameters					Limitation
Systemic inflammatory response syndrome (SIRS)	A. Fever: (temperature > 38.3 °C) B. Temperature: < 36° C or > 38 °C C. $PaCO_2$: less than 32 mmHg D. Respiratory rate; more than 20 breaths/minute E. Heart rate: more than 90 beats/minute; F. Investigation: White blood cell count (WBC) > 12,000/cu mm OR WBC < 4,000/cu mm OR (band forms) immature WBC > 10%					1. High sensitivity 2. False positive
Sequential organ failure assessment score: (SOFA) Interpretation: Positive: ≥ 2	Score	1	2	3	4	Not validated in pregnancy
	Respiration With respiratory support: PaO_2/FiO_2 (mmHg)	< 400	< 300	< 200	< 100	
	Liver function assessment: serum Bilirubin (mg dL^{-1})	1.2–1.9	2–5.9	6–11.9	> 12	
	Coagulation Platelets × 103/mm^3	< 150	< 100	< 50	< 20	
	Cardiovascular system Maintain mean arterial pressure and use of vasopressor drugs(dose)	Mean arterial pressure (MAP) < 70 mmHg	Dopamine < 5.0 or dobutamine (any dose)1	Dopamine = 5.1–15.0 or adrenaline < 0.1 or nor adrenaline < 0.11	Dopamine > 15.0 or adrenaline > 0.1 or noradrenaline > 0.11	
	Central nervous system assessment: Glasgow Coma Score (GCS)	GCS 13–14	GCS 10–12	GCS 6–9	GCS < 6	
	Renal system Creatinine (mg dL-1)	1.2–1.9	2.0–3.4	3.5–4.9 > 5.0	> 5.0	
	Urine output (ml)	_	_	< 500	< 200	
Quick sequential organ failure assessment score (qSOFA) Interpretation: Positive: score ≥ 2 Negative: score < 2	A. Respiratory rate: more than 22 breaths/minute B. Systolic blood pressure: less than 100 mmHg C. Altered mental status (Glasgow Coma scale score < 15)					Poor sensitivity The Surviving Sepsis Campaign (2021) panel issued a recommendation against its use for screening alone

Table 2 (continued)

Scoring system	Clinical parameters				Limitation
National clinical early warning signs: (NEWS) Scoring 0–20 Interpretation: High risk ≥ 7 Medium risk 5–6 Low risk ≤ 4	Seven clinical parameters: 1) Temperature 2) Heart rate 3) Respiratory rate 4) Blood pressure 5) Oxygen saturation 6) Any supplementary oxygen 7) Level of consciousness AVPU scale (AVPU: alert, voice, pain, unresponsive)				Low specificity
Modified early warning signs (MEWS) Interpretation: High risk ≥ 5 Medium risk 3–4 Low risk < 3	Six clinical parameters: 1) Level of consciousness 2) Temperature 3) Heart rate 4) Respiratory rate 5) Blood pressure 6) Urine output				
Obstetrically modified—Sequential organ failure assessment score: (SOFA) Interpretation: Positive > 2 Negative < 2	System parameters	Score 0	Score 1	Score 2	More studies are required for its validation
	Respiration PaO_2/FiO_2	≥ 400	300–400	< 300	
	Coagulation platelets(*10^6/l)	≥ 150	100–150	< 100	
	Liver Bilirubin (micromole/L)	≤ 20	20–32	> 32	
	Cardiovascular mean arterial pressure (mmHg)	≥ 70	< 70	Vasopressors required	
	Central nervous system	Alert	Responds to oral commands	Responds to painful stimuli	
	Renal Creatinine (micromol/L)	≤ 90	91–120	> 120	
Obstetrically modified- quick Sequential organ failure assessment score(qSOFA) Interpretation: Positive > 2 Negative < 2	Parameters	Score 0	Score 1		More studies are required for its validation
	Systolic blood pressure	≥ 90 mmHg	< 90 mmHg		
	Respiratory rate: (breaths/minute)	< 25	≥ 25		
	Altered mentation	alert	Not alert		

Table 3 Maternal clinical findings and laboratory investigation [21, 22]

Maternal clinical findings	Maternal laboratory findings
Vital signs 1. Temperature: Fever: temperature ≥ 38.0 °C Cold: temperature ≤ 36.0 °C 2. Tachycardia: heart rate ≥ 110 beats/minute 3. Tachypnoea: respiratory rate ≥ 24 breaths/minute 4. Oxygen saturation, PaO_2/FiO_2	Complete blood count and coagulation studies 1. Leucocytosis/leukopenia 2. Immature neutrophils 3. Thrombocytopenia, 4. Increased INR, PTT 5. Disseminated intravascular coagulation (DIC) 6. Raised serum lactate
General 1. Altered mental state (deranged Glasgow Coma scale score, confusion, decreased alertness,) 2. Nausea and vomiting 3. Pain (location based on site of infection)	Arterial blood gas studies (ABG) 1. Arterial pH: low 2. Base deficit: increased 3. Hypoxemia 4. Metabolic acidosis
Circulatory disturbances 1. Cold clammy or mottled skin 2. Diaphoresis 3. Decreased capillary refill 4. Hypotension 5. Shock	Culture from infection site or blood: positive Renal function test: Elevated serum creatinine and blood urea
Renal: Oliguria or anuria Foetal distress: 1. Foetal tachycardia 2. Foetal acidosis	Liver function test Elevated liver enzymes, bilirubin Serum electrolytes: Altered Serum sodium and potassium Blood glucose levels: Hyperglycaemia without history of diabetes

Table 4 Empirical antibiotic regimen in sepsis proposed by (ICMR) Indian Council of Medical Research 2019 [24]

Diagnosis	Preferred antibiotic regimen	Alternative antibiotic regimen
Sepsis or septic shock with unclear focus	Imipenem-cilastatin 500 mg IV 6 hourly or 1gm 8 hourly	Meropenem 1 gm IV 8 hourly or
	± Inj Amikacin 15 mg/kg IV per day	Cefoperazone–sulbactam 3 gm IV 12 hourly
	± Vancomycin 15 mg/kg IV 8–12 hourly	± Inj amikacin 15 mg/kg IV per day
	Teicoplanin 400 mg IV every 12 hourly for 3 doses followed by 400 mg IV per day	
	± Doxycycline100 mg IV 12 hourly ± Colistin 9 mu IV stat, then 4.5 mu IV 12 hourly or Polymyxin B 15–20 lakhs units IV stat, then 7.5–10 lakhs IV 12 hourly	± Vancomycin15 mg/kg IV 8–12 hourly or Teicoplanin 400 mg IV every 12 hourly for 3 doses followed by 400 mg IV per day

Council of Medical Research in 2019 is described in Table 4, [24].

c. In high-risk multidrug resistant infection, two antibiotics should be used to give gram negative coverage.
d. Accepted pharmacokinetic/pharmacodynamic principles, as well as particular pharmaceutical characteristics, should be used to optimise antimicrobial dosage approaches.
e. Identify and eliminate sources of infection such as specific anatomical sites or intravenous access to curtail sources of infection.
f. Daily evaluation to decrease the need of antibiotics over using fixed durations should be done.
g. Clinical evaluation and procalcitonin measurement are used for further continuation of antibiotics.

5. Haemodynamic management:

a. Intravenous crystalloids are recommended as first-line fluid for resuscitation over gelatine and starch.
b. Norepinephrine is used as the first-line vasopressor of choice over other agents.
c. Other vasopressors like vasopressin, epinephrine can be added in order with inadequate MAP with norepinephrine.
d. In septic shock with cardiac dysfunction and persistent hypoperfusion, dobutamine can be added to norepinephrine. In such cases, invasive monitoring of arterial blood pressure should be done meticulously.

6. Ventilation:

a. In a sepsis-induced acute respiratory distress syndrome (ARDS), use a low tidal volume (6 mL/kg) over a high tidal volume (> 10 mL/kg) ventilation strategy.
b. In severe ARDS an upper limit goal for plateau pressures of 30 cm H2O, over higher plateau pressure, higher positive end expiratory pressure (PEEP) and low tidal volume and use of prone ventilation for greater than 12 h daily with intermittent neuromuscular blocking agents (NMBA) infusions.

7. Additional therapy:

a. Use a restrictive blood transfusion strategy.
b. Intravenous hydrocortisone should be reserved for septic refractory shock at a dose of 200 mg per day.
c. Use of prophylaxis for stress ulcer in patients who have a high risk of gastrointestinal tract bleeding.
d. For venous thromboprophylaxis low molecular weight heparin is preferred.
e. Initiating insulin therapy: at a blood glucose level of (≥ 180 mg/dL), 10 mmol/L use of insulin is advised.
f. Sodium bicarbonate treatment is recommended in septic shock with severe metabolic acidemia (pH 7.2) and acute kidney injury (AKI) grade 2 or 3.
g. Initiation of parenteral nutrition within 72 h if indicated

8. Goals and follow-up: long-term duration:

a. Prognosis of illness, treatment options and palliative care should be discussed with patients' relatives within 72 h of admission.
b. Refer appropriately for psycho-social and economic support.
c. At the time of discharge give a written summary of treatment and advice follow-up with clinicians for managing new and long-term consequences.

- Obstetric management in obstetric sepsis: [25]

a. It is crucial to first stabilise the mother, after which the foetal health will improve.
b. Various factors influence the decision to deliver the foetus or continue the pregnancy, including the patient's clinical parameters, foetus lung maturity and gestational age, the stage of labour, any existence of uterine infection like chorioamnionitis.
c. After a period of viability for the foetus, foetal parameters should be assessed regularly.
d. Continuous electronic foetal monitoring is advised.
e. If the source of infection is outside the uterus, efforts should be focused on treating maternal sepsis and extending pregnancies that are far from term.
f. If the sepsis is caused by uterine infections, the foetus must be delivered. If delivery is imminent, corticosteroids should be given if the gestational age is less than 36 weeks.
g. Eliminate the source of infection such as retained products of infection or intra-abdominal or pelvic pus by medical or surgical procedure.
h. Maternal sepsis exerts significant influence on neonatal mortality. These antenatal infections cause prematurity, pneumonia, respiratory distress syndrome (RDS), neonatal sepsis and long-term neurologic impairment in infants.

- Anaesthesia for surgical intervention in obstetric sepsis [26]

a. In women with sepsis, general anaesthesia is preferred for surgical intervention over regional (epidural/spinal) anaesthesia due to risk of hypotension, meningitis, and intracranial bleeding.
b. Multispeciality team (obstetrician, anaesthetist, neonatologist and intensivist) approach: all should participate in the decision-making process.
c. Induction and maintenance drugs can aggravate haemodynamic instability in septic patients, however etomidate, ketamine and rocuronium can be used safely.

- Postoperative care and transfer to intensive care unit (ICU): [17]

a. Analgesics: Non-steroidal anti-inflammatory medications are contraindicated due to altered kidney and liver functions. Paracetamol and opioids can be given as analgesics.
b. Depending upon the severity of sepsis, the critical care team, in consultation with the obstetric and anaesthetist consultant, should consider transfer to the ICU.
c. Indications to transfer to critical care are as follows: haemodynamically unstable patients with need of vasopressor and ventilator support, altered conscious level, multiple organ failure, hypothermia or acute renal failure with need of haemodialysis.

d. In refractory obstetric sepsis, use of extracorporeal membrane oxygenation (ECMO) is becoming more frequent.

Recommendations for Prevention

Recommendations for prevention and treatment of obstetric sepsis proposed by World health organisations (WHO) in 2016 are summarised below [27].

1. Perineal/pubic shaving and vaginal washing with chlorhexidine during labour are not advised.
2. In low-risk women, routine digital vaginal examinations at four-hour intervals are indicated for assessing the active initial stage of labour.
3. Administration of antibiotics are recommended in following conditions
   A. Colonisation of Group B Streptococcus for GBS infection prevention in newborns.
   B. Manual removal of placenta.
   C. (PPROM) Preterm and prelabour rupture of membranes.
   D. Perineal tear: Third/fourth degree
   E. Elective or emergency caesarean section.
   F. Operative vaginal delivery: use of vacuum or forceps [5].
4. Administration of antibiotics are not recommended in following conditions
   A. To reduce infection in second or third trimester
   B. Preterm labour with intact amniotic membranes
   C. Meconium-stained amniotic fluid.
   D. Prelabour (at/near term) rupture of membranes
   E. Episiotomy
   F. Vaginal birth without complications
5. Before a caesarean section, vaginal cleaning with povidone-iodine is advised.
6. Skin preparation with alcohol-based chlorhexidine gluconate is advised before caesarean section (elective or emergency). Prior to a caesarean section, the manner of applying alcohol-based chlorhexidine gluconate should be based mostly on the directions for usage, the clinician's preference and experience [28].
7. Prophylactic antibiotics, such as a single dosage of cephalosporin (first-generation) or penicillin, should be given before taking skin incision instead of giving after umbilical cord clamping during caesarean delivery.
8. For the treatment of chorioamnionitis, a basic antibiotic regimen such as ampicillin and gentamicin once in a day is indicated.
9. In postpartum endometritis, a combination of gentamicin and clindamycin is indicated as a first-line antibiotic.

Conclusion

Early detection and treatment of sepsis is difficult due to physiological, anatomical, and immunological changes related to pregnancy. Reduced sepsis-related morbidity and death can be achieved by preventing, diagnosing, and treating sepsis early. To recognise the sepsis-related signs and treat the infection successfully, health staff must be sufficiently trained and skilled. The latest sepsis recommendations apply to the whole adult population, with the exception of pregnant patients. Although new recommendations for risk stratifying pregnant patients have been developed, they must be validated. More studies are needed to complete validation, which will help in the identification and treatment of sepsis in order to enhance maternal and foetal outcomes.

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Conflict of interest All authors declare that they have no conflict of interest.

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