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Madiha Hashmi

Aga Khan University, madiha.hashmi@aku.edu

Fazal Hameed Khan

Aga Khan University, fazal.hkhan@aku.edu

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SPECIAL ARTICLE

A review of critical care management of maternal sepsis

Madiha Hashmi*, Fazal Hameed Khan**

**Director Surgical ICU & Assistant Professor; **Professor
Department of Anesthesiology, Aga Khan University, Stadium Road, Karachi (Pakistan)*

Correspondence: Dr. Madiha Hashmi, Department of Anesthesiology, Aga Khan University, Stadium Road, P.O. Box 3500, Karachi-74800 (Pakistan); E-mail: hashmi_madiha@yahoo.ie

ABSTRACT

Sepsis is a leading cause of preventable maternal mortality in developing countries due to poverty, home deliveries by untrained persons in unhygienic conditions, limited access to healthcare facilities and lack of availability of antibiotics. Recent confidential enquiries into maternal deaths from the developed nations have revealed an increase in maternal mortality secondary to genital tract sepsis and provision of suboptimal critical care. Early recognition of critical illness in obstetric patients, involvement of intensive care teams earlier and provision of same standard of critical care to pregnant women as non-pregnant patients while being mindful of the altered maternal physiology and fetal wellbeing is necessary to improve outcome of this vulnerable population.

This article reviews the definitions and risk factors of maternal sepsis and describes the standards recommended for efficient delivery of maternal critical care and sepsis management.

Key words: Maternal sepsis; Puerperal sepsis; Critical care; Fetal monitoring; Resuscitation; Maternal mortality

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INTRODUCTION

Sepsis is responsible for causing more deaths globally than prostate cancer, breast cancer and HIV/AIDS combined¹ and is the one of the most common causes of mortality in the intensive care units.² In the developing world, 60-80% of childhood deaths are due to sepsis resulting in the death of over 6 million newborns and children every year along with over 100,000 cases of maternal sepsis³ The 8th report of The Confidential Enquiry into Maternal Deaths (CEMCH) published in March 2011 showed a decrease in the overall maternal mortality rate in UK from 13.95 to 11.39 per 100,000 deliveries but the report indicated an increase in deaths related to genital tract infections and sepsis was rated as the most common cause of direct maternal death.⁴

Admission rate of obstetric patients to general or surgical critical care units varies from 0.05-1.7% of total admissions in developed countries⁵ to about 11.6% in developing countries.⁶ Recent ICNARC (Intensive Care National Audit and Research Centre) Case Mix Programme (CMP) data showed that 11.4%

of women between the age of 16 years and 50 years who were admitted to adult general intensive care units in England, Wales and Northern Ireland were either pregnant or recently pregnant.⁷ Critically ill obstetric patients present a unique challenge to the intensivists due to altered maternal physiology and concerns regarding fetal safety and outcome. Early recognition of critical illness, involvement of intensive care teams earlier and provision of same standard of critical care to pregnant women as non-pregnant patients is necessary to improve survival of critically ill women in the peripartum period.⁸

The objective of this article is to review the definitions and underlying causes of maternal sepsis which is a re-emerging threat to maternal health and describe the standards recommended for efficient delivery of maternal critical care and sepsis management.

DEFINING MATERNAL SEPSIS

Globally 10% of maternal deaths are caused by sepsis, and the incidence is highest in Southeast Asia (13.2%) and Africa (10%)⁹. However, describing the

total burden of maternal sepsis is challenging for a number of reasons. Firstly there is a lack of a uniform definition of maternal sepsis. Secondly there is confusion whether to include maternal deaths resulting from genital tract sepsis only or to include maternal deaths resulting from all other sources of infection like urinary tract infections, respiratory tract infections, mastitis, malaria, hepatitis, dengue fever, HIV, and nosocomial infections.^{10,11} Thirdly there is gross underreporting of sepsis and maternal deaths in the developing countries where the burden of disease is the greatest due to lack of data of home deliveries and absence of postnatal follow-up after hospital discharge.¹²

Another reason is misclassification of the cause of the maternal deaths as 'indirect cause' instead of sepsis being the 'direct cause' of maternal death in countries where endemic diseases like HIV, malaria and tuberculosis are highly prevalent or in the presence of significant comorbid diseases.¹³

World Health Organization (WHO) defines Puerperal Sepsis as, "*infection of the genital tract occurring at any time between the onset of rupture of membranes or labour and the 42nd day postpartum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, abnormal smell/foul odour of discharge and delay in the rate of reduction of the size of the uterus*".¹⁴

International Classification of Diseases (ICD-10) defines 'Puerperal Sepsis' as, "*temperature rise above 38.08°C (100.48°F) maintained over 24 hrs or recurring during the period from the end of the first to the end of the 10th day after childbirth or abortion*".

American College of Chest Physicians and the Society of Critical Care Medicine attempted to standardize definitions¹⁵ for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock in 1992 (Table 1) which were later elaborated at an international sepsis definition conference in 2001.¹⁶ Onset of labour and rupture of membranes triggers symptoms of SIRS even without the presence of an infection and may mask a serious infection.

RISK FACTORS OF SEPSIS DURING PREGNANCY

Pregnant women are highly susceptible to infection because the maternal immune response is down-regulated to protect the immunologically distinct foetus¹⁷ and there is loss of the protective physiological barriers against bacterial infection with the onset of labour.¹¹

The surgical site and the endometrium is exposed to pathogens during Cesarean section, increasing the risk of severe infections five to 20-fold in women who undergo operative delivery as compared to women who deliver naturally.¹⁸ Increased incidence of caesarian sections and obesity are two most important factors contributing to increased maternal mortality due to sepsis in UK.¹⁹

Poverty, home deliveries by untrained persons in unhygienic conditions, limited access to healthcare facilities and lack of availability of antibiotics are the most important factors that increase the risk of maternal sepsis in developing countries.²⁰ HIV-related infections are the main cause of maternal mortality in sub-Saharan and southern Africa.²¹

Table 1: Definitions related to sepsis [15]

SIRS	Sepsis	Severe Sepsis	Septic shock
Two of the following <ul style="list-style-type: none"> • Heart rate ≥ 90 bpm • Respiratory rate ≥ 20 bpm or $\text{PaCO}_2 \leq 32$ mmHg • Temperature $\geq 38^\circ\text{C}$ or $\leq 36^\circ\text{C}$ • WBC ≥ 12000 or ≤ 4000 cells/μL or $\geq 10\%$ immature forms 	SIRS with a suspected or documented source of infection	Sepsis associated with organ dysfunction i.e. <ul style="list-style-type: none"> • Decreased GCS • Decreased urine output $<0.5\text{ml/kg/hr}$ for > 2 hrs • Creatinine > 2 mg/dl • Bilirubin > 2 mg/dl • INR > 1.5 • Acute Lung Injury with $\text{PaO}_2/\text{FiO}_2 < 300$ • Plasma C-reactive Protein > 2 SD above normal • Serum Lactate > 4 mmol/L 	Organ dysfunction despite adequate fluid resuscitation

Table 2: Risk factors for severe maternal morbidity and mortality from sepsis [13]

High income countries	Low income countries
Cesarean section	Poverty
Emergency Cesarean section	Unhygienic birth conditions
Prolonged rupture of membranes	Lack of skilled birth assistants
Retained products of conception	Long distance to healthcare facility
Early labour	Unavailable medical supplies
Multiple vaginal examinations (>5)	Young age
Obesity	Primiparity
Diabetes	Anemia
Anemia	HIV, Tuberculosis, Malaria
Low socioeconomic status	Failure to recognize severity
Winter months	
Failure to recognize severity	

Invasive streptococcal infections are responsible for most cases of severe sepsis world over.^{22, 23} Hypervirulent strains of gram-positive *Streptococcus pyogenes* or group A streptococcus (GAS) were responsible for 45% of direct maternal deaths from genital tract sepsis in the UK in the triennium 2006-2008.⁴ GAS resides in the human nasopharynx and is transmitted during influenza outbreaks via the respiratory tract or the perineum gets contaminated directly when proper hand hygiene is not observed resulting in genital tract infection.²⁴

IMPACT OF CARDIORESPIRATORY CHANGES OF PREGNANCY ON MATERNAL CRITICAL CARE

Physiological changes of pregnancy help adapt the mother to the requirements of the foetus and the placenta. The hormone progesterone is a potent smooth-muscle relaxant and respiratory stimulant and is responsible for most of these maternal adaptations that return to normal approximately 6 weeks after delivery.²⁵ These cardiorespiratory adaptations of pregnancy have a significant impact on critical care management of the mother.

Blood volume increases progressively by up to 50%, so the mother can lose up to 30% of her blood volume before her vital signs change. In the event of significant maternal hypotension, placenta experiences vasoconstriction unlike other vital organs resulting in placental hypoperfusion, fetal hypoxia and acidosis. Fetal distress may be the first sign of maternal haemodynamic instability. Maternal systolic blood pressure should be maintained at 90

mmHg to ensure adequate placental perfusion, however the haemodynamic targets should be re-set in view of the altered physiological variables,²⁶ as shown in Table 3. After 20 weeks gestation the gravid uterus can cause aortocaval compression, decreasing uterine perfusion and venous return to the heart. Ensuring adequate lateral maternal tilt or manual displacement of the uterus are simple but effective maneuvers to prevent aortocaval compression and the resulting hypotension.

Table 3: Changes in physiological variables during late pregnancy (Clinical Physiology in Obstetrics, 3rd edn. Oxford: Blackwell Science;1998)

Parameter	Value change
Systolic arterial pressure	- 5 mmHg
Mean arterial pressure	-15 mmHg
Diastolic arterial pressure	-15 mmHg
Central venous pressure	No change
Pulmonary capillary wedge pressure	No change
pressure	+15%
Heart rate	+30%
Stroke volume	+45%
Cardiac output	-15%
Systemic vascular resistance	
Tidal volume	+40%
Respiratory rate	+10%
Minute volume	+50%
Oxygen consumption	+20%
pH	No change
PaO2	+10 mmHg
PaCO2	-10 mmHg
HCO3	-4 mmol/l
Total blood volume	+40%
Haematocrit	-0.06
Plasma albumin	-5 g/l
Oncotic pressure	-3 mmHg

As the uterus expands out of the pelvis during pregnancy, the diaphragm elevates limiting the lung expansion. Residual volume and functional residual capacity are reduced resulting in decreased reserve when respiratory decompensation occurs. Tidal volume, minute ventilation and oxygen consumption increase to cope with the increased metabolic demands. Maintaining a maternal PaO₂ > 60 mmHg will help ensure adequate foetal oxygenation. Although changes in anatomy and lung compliance don't make mechanical ventilation

difficult in pregnant women, the lung protective strategies recommended for managing adult respiratory distress syndrome (ARDS) may be more difficult to implement.²⁷ Low tidal volumes make it difficult to maintain the increased ventilatory demands of pregnancy and higher tidal volumes and alveolar plateau pressures up to 35 cm H₂O may be necessary. Permissive hypercapnoea may cause fetal respiratory acidosis that will reduce the ability of foetal haemoglobin to bind oxygen. Prone positioning recommended for severe ARDS has not been investigated during pregnancy. Upper airway oedema makes the airway management potentially difficult and delayed gastric emptying increases the risk of pulmonary aspiration

DRUG SAFETY IN PREGNANCY

Vasopressors cause vasoconstriction in all vessels therefore while selecting a vasopressor it is important to select an agent that preserves uteroplacental perfusion. However vasopressors have diverse effects on fetoplacental circulation and the underlying pharmacodynamic mechanisms and their clinical implications are unclear.²⁸ Ephedrine crosses the placenta and may cause fetal tachycardia and acidosis. It should only be used as a bolus agent for short-lived hypotension. Phenylephrine may cause more uteroplacental vasoconstriction but is associated with less fetal acidosis, better neonatal outcomes and is more suitable when continuous infusions are indicated.²⁹ Dopamine is commonly used in pregnant women with sepsis, although both dopamine and dobutamine decrease uterine blood flow. Vasopressin may cause uterine contractions so it should be used cautiously in the third trimester. Epinephrine and norepinephrine can also cause vasoconstriction of the maternal and placental vasculature especially in hypoxic women and are best avoided.²⁵

Opioids, benzodiazepines, propofol and barbiturates are relatively safe in pregnancy, even though they easily cross the placenta. The newborn may experience withdrawal effects if any of these therapies have been used for more than a few hours before delivery but infusions of these agents in an intensive care setting are justified even if the women delivers while still receiving them. These agents also cross into breast milk and may cause considerable sedation in newborns, especially those born prematurely. Fentanyl may be a better choice of opioid because oral absorption is low but high-dose infusions could still cause respiratory depression in the newborn.²⁵

LEVELS OF MATERNAL CRITICAL CARE

Four levels of care are recommended for pregnant or recently pregnant woman,³⁰ depending on the organ support and level of monitoring required, and independent of the diagnosis.

Level 0 or normal ward care:

- For the care of low risk woman.

Level 1 or additional monitoring or step down from higher level of care:

- Neuraxial analgesia
- Risk of haemorrhage
- Oxytocin infusion
- Remifentanyl infusion
- Mild pre-eclampsia on oral anti-hypertensives/ fluid restriction
- Chronic medical condition at risk of deterioration such as congenital heart disease or diabetes requiring insulin infusion.

Level 2 or single organ support:

Basic Respiratory Support (BRS)

- 50% or more oxygen via face-mask to maintain oxygen saturation
- Non-invasive ventilation (CPAP or BiPAP)

Basic Cardiovascular Support (BCVS)

- Infusion of anti-hypertensives (labetalol or hydralazine) to control blood pressure in pre-eclampsia
- Arterial line used for pressure monitoring or sampling
- CVP line used for fluid management and CVP monitoring to guide therapy

Advanced Cardiovascular Support (ACVS)

- Simultaneous use of at least two intravenous, anti-arrhythmic/antihypertensive/vasoactive drugs
- Need to measure and treat cardiac output

Neurological Support

- Magnesium infusion to control seizures (not prophylaxis)

Hepatic support

Acute fulminant hepatic failure, e.g. from HELLP syndrome or acute fatty liver, such that transplantation is being considered

Level 3 or advanced respiratory support alone or support of 2 or more organ systems as above

Advanced Respiratory Support

- Invasive mechanical ventilation

Support of two or more organ systems

- Support of two or more organ systems—Renal support and BRS; BRS/BCVS and an additional organ supported

FETAL MONITORING IN INTENSIVE CARE UNIT

Organ support and multiple drugs required by the mother during critical illness may adversely affect the fetal wellbeing. In order to ensure adequate placental perfusion and oxygenation and avoid premature labour it is important to monitor the fetus in the intensive care unit along with the maternal monitoring.

1. ULTRASOUND

Abdominal ultrasound is a non-invasive technique that is widely available in the intensive care units. It helps assess

- Fetal viability and position.
- Placenta location and abruption status.
- Amniotic fluid volume.
- Uterine artery blood flow.

2. CTG MONITORING

Cardiotocography (CTG) or electronic foetal monitoring (EFM) is a technique for assessing fetal wellbeing during labour. Following standard terminologies are used to interpret a CTG trace.³¹

- Baseline foetal heart rate (FHR) is determined over a period of 5-10 minutes and is 110-160 beats per minute (bpm).
- Baseline variability is the minor fluctuation in baseline FHR (6-25 bpm) assessed in one minute segments of the trace.
- Accelerations are transient increases in FHR of 15 bpm or more above the baseline and lasting 15 seconds.
- Decelerations are transient episodes of decrease of FHR below the baseline of more than 15 bpm lasting at least 15 seconds. Decelerations indicate an abnormal CTG. Late decelerations are a sign of utero-placental insufficiency and warrant prompt attention.

Close collaboration between intensivists and the obstetricians is required for interpretation and clinical management response to an abnormal CTG.

CURRENT RECOMMENDATION FOR SEPSIS MANAGEMENT

Management of pregnant patients in sepsis is not different from the management of other septic patients as long as the altered maternal physiology and wellbeing of the fetus are considered. The normal physiological adaptations seen in pregnancy make early detection of sepsis difficult on one hand and may exacerbate the organ dysfunction associated with sepsis on the other hand. Use of modified early obstetric warning score (MEOWS) leads to timely recognition of an obstetric patient becoming critically ill³² and The Royal College of Obstetrics and Gynaecology³³ endorses the use of evidence-based recommendations of the Surviving Sepsis Campaign (SSC) to manage severe maternal sepsis.

Following are the treatment and intervention bundles for early goal directed therapy [34].

Initiate the following after recognition of severe sepsis and septic shock and complete within 3 hours:

- Obtain blood culture specimens before antibiotic administration.
- Obtain serum lactate level.
- Administer broad-spectrum antibiotic (don't delay more than 45 min for blood cultures).
- Initiate 30 mL/kg isotonic crystalloid fluids for hypotension or lactate level of 4 mmol/L or greater (may use albumin as part of initial fluid resuscitation in patients requiring substantial amounts of crystalloids; avoid hydroxyethyl starches).
- Goals are to achieve a mean arterial pressure (MAP) of 65 mm Hg and urine output >0.5 mL/kg/hr.

Within 6 hours of recognition of severe sepsis or septic shock:

- Infuse vasopressors (for hypotension that doesn't respond to initial fluid resuscitation or for abnormally low diastolic blood pressure) to maintain MAP of 65 mm Hg or greater. Intravenous norepinephrine is the vasopressor of choice.
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate of 4 mmol/L or more, measure CVP and aim for a target of 8-12 mm Hg; measure ScvO₂ and target ScvO₂ or SvO₂ >70% or 65%, respectively.
- Re-measure lactate if initial level was elevated.

Two recent trials have challenged the effectiveness of SSC recommendations. The preliminary results of the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial were released at the European Society of Intensive Care Medicine (ESICM) annual meeting in Barcelona in September 2014 and failed to show benefit of early goal-directed therapy. The results of this trial came within a year after the Protocolized Care for Early Septic Shock (ProCESS) trial released similar findings.³⁵

Based on the conclusions of the ProCESS and ARISE trials, the SSC Executive Committee issued the following statement;

- Central venous pressure (CVP) and central venous oxygen saturation (ScvO₂) monitoring as part of an early resuscitation strategy does not confer survival benefit in patients with septic shock who received timely antibiotics and fluid resuscitation compared with controls.
- CVP and ScvO₂ monitoring in all patients who have lactate levels >4 mmol/L and/or persistent hypotension after initial fluid challenge and who have received timely antibiotics is not supported by robust scientific evidence.
- Results of the ProCESS and ARISE trials did not demonstrate adverse outcome in the group that utilized CVP and ScvO₂ as end points for resuscitation.
- In light of the evidence from the ProCESS and ARISE trials, the SSC guidelines committee will review the evidence and re-assess the guidelines and if required issue a focused update.
- The current SSC bundles will not change till such time that the new guidelines are introduced.
- When revised bundles become available, they will be posted on the SSC website and the SSC data collection tool will be modified appropriately.
- The 3-hour SSC bundle will not be affected by this process.

Till SSC issues a focused update, management of the pregnant septic patients should continue as per the SSC recommendation, specially the first three hours bundle.

Hand hygiene and intravaginal application of antiseptics are the two main strategies described in the current literature to prevent puerperal sepsis, in addition to the prophylactic use of antibiotics during elective and emergency caesarian sections.³⁶

MATERNAL RESUSCITATION

If cardiac arrest happens in a pregnant woman after 20 weeks gestation, manual displacement of the uterus prevents aortocaval compression, increases venous return, cardiac output and uteroplacental perfusion.

If initial resuscitation fails to revive the mother following a cardiac arrest and the foetus is of greater than 24 weeks gestation, emergency caesarian section to deliver the foetus within 5 minutes of cardiac arrest facilitates maternal and foetal survival.

Therapeutic hypothermia for 12-24 hours may be considered after return of spontaneous circulation to improve neurological outcome.³³

CONCLUSIONS

Sepsis remains a leading cause of preventable maternal death in both developed and developing countries. Early recognition of the severity of an infection and effective maternal resuscitation by a multidisciplinary team of intensivists, anesthetists, neonatologists, obstetrician, midwives and pharmacists according to the standards set for delivering maternal critical care is the cornerstone for maternal and foetal wellbeing.

KEY POINTS:

- Avoid aortocaval compression after 20 weeks of gestation by maintaining a lateral maternal tilt
- Monitor modified early obstetric warning score (MEOWS) for early recognition of critical illness in the obstetric population. early signs
- Implement resuscitation bundle within 3 hours of suspicion of maternal sepsis.
- Consider thromboprophylaxis early
- Consider antenatal steroids if preterm delivery anticipated
- Do not neglect perineal and breast care while managing the critically ill mother in the intensive care unit
- Involve the pharmacist to prescribe drugs that pose less risk to the fetus during pregnancy, are safe if breast feeding and ensure appropriate dosing.

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