DIAGNOSIS AND MANAGEMENT OF MATERNAL SEPSIS AND SEPTIC SHOCK

ANAESTHESIA TUTORIAL OF THE WEEK 235

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QUESTIONS

Before continuing with this tutorial, try to answer the following questions. The answers and a brief explanation can be found at the end of the article.

1. Regarding the most recent (2006-2008) triennial report of UK maternal deaths from the Centre for Maternal and Child Enquiries (CMACE)
    a. Sepsis was the second most common cause of direct maternal death after thromboembolic disease
    b. Deaths from β-haemolytic streptococcus Group B infection have increased in the UK
    c. The use of early warning scoring charts to monitor obstetric patients in hospital was recommended
    d. Substandard care did not occur in any of the sepsis related deaths

2. Maternal sepsis and infection
    a. Often presents early due to the physiological changes of pregnancy
    b. May present with hypothermia
    c. Is most commonly due to bacterial pathogens
    d. May warrant hysterectomy as part of its management

3. Regarding the management of sepsis and septic shock
    a. Antibiotic therapy should always be delayed until all necessary cultures have been taken
    b. A target haemaglobin over 10g/dl should be maintained
    c. Steroids are not recommended in the management of septic shock
    d. A central venous oxygen saturation ≥ 65% is a goal of resuscitation

INTRODUCTION

Pregnant women are vulnerable to infection and their pregnant state increases their risk of developing serious complications from an infection. Worldwide, infection and the complications of sepsis are among the most common causes of severe maternal morbidity and mortality.

In the UK, sepsis is the leading cause of direct maternal death. The most recent triennial report (2006-2008) of maternal deaths from the Centre for Maternal and Child Enquiries (CMACE) found that deaths from sepsis have risen rather than declined in recent time, in contrast to the other major causes of direct maternal mortality.[1] The increased number of deaths secondary to community-acquired β-haemolytic streptococcus Group A infection has been postulated as the main reason for the rise in sepsis related mortality.

This article will discuss the early identification of maternal sepsis, the physiological changes that make pregnant women more susceptible to the complications of sepsis and current recommendations for the diagnosis and management of sepsis and septic shock in pregnancy.

DEFINITIONS

Bacteraemia - viable bacteria in blood.
Infection - inflammatory response to the presence of a microorganism in normally sterile tissue.
Systemic Inflammatory Response Syndrome (SIRS) - an inflammatory response diagnosed by two or more of the variables shown below:

- Fever or hypothermia (core temperature < 36 C or > 38 C)
- Tachycardia (Heart Rate (HR) > 90 / min)
- Tachypnoea (Respiratory Rate (RR) > 20 / min)
- White cell count (WCC) >12 x 10^9 /l or < 4 x 10^9 /l

    - NB: above criteria relate to non-pregnant patients. [2]
      Average WCC in third trimester is 8.5 x 10^9/l
      WCC range in pregnancy: 5.1 - 12.2 x 10^9/l
      Post delivery WCC: 20 - 30 x 10^9/l

Sepsis - SIRS in the presence of infection.
Severe sepsis - sepsis with associated organ dysfunction, hypotension or hypoperfusion.
Septic shock - sepsis + refractory arterial hypotension despite adequate fluid resuscitation.

FEATURES OF SEVERE SEPSIS

- Hypotension
- Arterial hypoxaemia
- Raised lactate
- Acute oliguria (urinary output < 0.5 ml/kg/h)
- Deranged renal function
- Deranged liver function
- Altered mental status
- Coagulation abnormalities
- Hyperglycaemia in absence of diabetes

Shock is a state of compromised tissue perfusion that causes cellular hypoxia leading to tissue hypoxia and vital organ dysfunction. During shock, perfusion is insufficient to meet the metabolic demands of the tissues and anaerobic metabolism occurs. This is unsustainable and, if not corrected, will progress to cellular dysfunction, cell death and end organ damage.

PHYSIOLOGICAL CHANGES OF PREGNANCY IN RELATION TO SEPSIS AND SEPTIC SHOCK

A number of physiological changes occur in pregnancy and several of these changes will increase susceptibility to infection or the consequences of it.

Cardiovascular System

In early pregnancy, circulation becomes hyperdynamic with a reduced systemic vascular resistance (SVR). Maternal cardiac output increases steadily as a result of increased heart rate and stroke volume, reaching a peak of 30-50% above pre-pregnant values by approximately 30 weeks gestation. A 40% increase in blood volume occurs, reaching a maximum at about 32 weeks gestation.

The heart may be considered to be under ever increasing stress as a normal pregnancy progresses. If a pregnant woman develops sepsis, this stress on her heart will be further compounded by sepsis-induced reduction in SVR, vasodilation and myocardial depression, which may result in rapid haemodynamic collapse.

Additionally, in normal pregnancy, there is a reduction in serum albumin which affects colloid osmotic pressure making women more vulnerable to pulmonary oedema should cardiac failure occur.

Respiratory System

As pregnancy progresses, increased minute ventilation occurs and results in a mild respiratory alkalosis despite a reduced tidal volume. There is a compensatory mild metabolic acidosis. These factors will reduce a woman's ability to compensate for any acidosis that develops as part of sepsis and septic shock, particularly if there is any respiratory failure.

Renal System

Ureteric dilatation, caused by smooth muscle relaxation, and compression of the ureters by the gravid uterus as they pass over the pelvic rim increase the risk of pyuria and pyelonephritis.

RECOGNITION OF SEPSIS AND SEPTIC SHOCK

Pregnant women with sepsis can deteriorate and die rapidly after the onset of symptoms. Prompt recognition, stabilisation and treatment of the underlying cause can avoid the rapidly spiralling deterioration that leads to cell death and, ultimately patient death. The recognition of shock is clinical and depends on identification of the cluster of subtle signs that indicate developing tissue hypoxia and organ dysfunction. Tachypnoea and tachycardia are often early signs, followed by hypotension and poor urine output. It is only once shock has progressed some way that the patient will also show the classical picture of pale, clammy skin, cool peripheries and altered level of consciousness. The altered physiology of a pregnant woman may obscure the early signs of developing shock, making recognition and early treatment even more difficult.

In the UK, maternal death enquiries have repeatedly shown that failure to recognise developing sepsis and septic shock and late, inadequate or inappropriate treatment of shock, contributes to maternal death.
The most recent CMACE report into maternal deaths emphasises early recognition of the following signs and symptoms of maternal sepsis: [1]

- Pyrexia - this is common but its absence does not rule out sepsis
- Hypothermia - a significant finding that may indicate severe infection
- Persistent tachycardia >100 beats per minute
- Tachypnoea (RR >20 breaths/min) - may be considered sepsis until proven otherwise
- Leucopaenia (WCC $<4 \times 10^9$/l)
- Diarrhoea and/or vomiting
- Lower abdominal pain
- Abnormal or absent fetal heart beat

A key recommendation of the last two maternal death reports is that in all hospitals, Modified Early Obstetric Warning Scoring (MEOWS) charts should be used to aid timely recognition, treatment and referral of women who have or who are developing a critical condition. [1]

Early warning charts are recommended in the monitoring of all acutely ill patients in hospital in the UK. [3] They are widely used in medical and surgical practice and should be familiar to all anaesthetists. They are based on the monitoring of five simple variables: mental function, heart rate, systolic and diastolic blood pressure, respiratory rate and temperature. Hourly urine output may be included if the patient is catheterised. If the measured physiological variables exceed set parameters, medical attention or intervention is triggered. The parameters set in standard early warning systems are well established but do not take into account the changes that occur in the cardiovascular and respiratory systems during pregnancy and, if used with a pregnant patient, may trigger unnecessary action. Studies are currently being undertaken to establish what parameters should be adopted for use in pregnancy to trigger initial medical review and treatment and, if no improvement, referral to Critical Care or an Outreach team. Until the data is available as to the best parameters to use in early pregnancy, it seems sensible that standard early warning systems should be adopted and, if necessary, modified by individual hospitals.

MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Management of shock is aimed at stabilising the patient while diagnosing and treating the underlying cause.

Patients with sepsis are critically ill and require urgent and aggressive resuscitation by a multidisciplinary team including obstetricians and gynaecologists, anaesthetists, intensivists and microbiologists. The response to treatment in this group of patients is highly unpredictable and mortality is high. Treatment is more likely to be effective, and severe sepsis avoided, if appropriate therapy is started early.

The goals of management are to resuscitate the patient and eliminate the underlying infection using appropriate antibiotics and often surgery. A variety of supportive interventions in critical care may be required.

The Surviving Sepsis Campaign (SSC) developed guidelines for the management of sepsis and septic shock based on review of the current literature by an international panel of experts. [4] It must be noted that few, if any outcome studies on critically ill patients include pregnant women but it seems reasonable to extrapolate the SSC guidelines to this group of patients where possible. The most recent CMACE report has echoed the SSC guidelines which recommend a protocolised approach to the early resuscitation of the patient with treatment directed towards achieving the following goals within the first six hours after diagnosis of sepsis.

Resuscitation goals:

- Central venous pressure (CVP): 8 - 12 mmHg
- Mean arterial pressure (MAP) ≥ 65 mmHg
- Urine output ≥ 0.5 ml/kg/h
- Central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70% or ≥ 65% respectively

Fluid therapy

If the patient is hypotensive, fluid resuscitation should begin immediately with warmed fluid challenges of 1000 ml of crystalloids or 300 - 500 ml of colloid given over 30 minutes. Larger volumes may be required in septic shock but this must be done with careful monitoring as the myocardial suppression caused by sepsis and the existing strain of pregnancy may make the patient more susceptible to fluid overload.

It may be useful to insert a central venous catheter (CVC) but this must not delay resuscitation of the patient. Central venous pressure (CVP) monitoring may help guide effective fluid therapy and warn of impending fluid overload as shown by rising cardiac filling pressures without haemodynamic improvement. The CVC can also be used for vasopressor and inotrope infusion and for sampling central venous blood to monitor tissue oxygenation. Other methods of monitoring cardiac output, for example oesophageal doppler monitoring, may be used to guide and optimise fluid resuscitation if they are available.

Antimicrobial therapy

Intravenous antibiotics should be started as early as possible, always within the first hour of recognising severe sepsis. It is recommended that a 'broad spectrum' approach be adopted, using one or more agents active against the likely bacterial or fungal pathogens and with good penetration into the presumed source. The choice of antibiotics may be refined once a microbiological diagnosis has been made and should be reviewed daily to optimise efficacy, prevent resistance, avoid toxicity and minimise costs.

Appropriate cultures should be obtained if this does not cause a significant delay in commencing antibiotic therapy. At least two sets of blood cultures are advised, of which one should be taken though a fresh venous puncture. If any vascular access devices have been in place for more than 48 hours, a blood culture sample should be taken from each of these. Other sites should be cultured as clinically indicated including:

- swabs from throat, vagina, baby (if infection suspected during labour and/or delivery)
- mid-stream urine
- other relevant samples including: sputum, breast milk, stool if indicated

The rate of deaths in the UK due to sepsis in the 2006-2008 triennium was 1.13 per 100,000 maternities (29 women) largely as a result of community-acquired Group A Streptococcal disease (13 women). [1] The rise of this pathogen as a cause of death mirrors the increase of its prevalence in the general

population and is a cause for concern.

Other likely pathogens in pregnant or recently pregnant women include: Escherichia coli, Clostridium, Staphylococcus aureus, Coliforms, Streptococcus species, Enterococcus faecalis, Listeria monocytogenes and Klebsiella. Potential sources of these infections include pyelonephritis, chorioamnionitis, endometritis, septic abortion, necrotizing fasciitis and wound infection.

Table 1. The following antibiotic recommendations are taken from the CMACE report 2006-2008. [1] Reproduced with permission from John Wiley and Sons Publishers.

Where the organism is unknown and the woman is not critically ill	co-amoxiclav 1.2g 8hrly + metronidazole 500mg 8hrly or cefuroxime 1.5g 8hrly + metronidazole 500mg 8hrly or cefotaxime 1-2g 6 to 12hrly + metronidazole 500mg 8hrly
In cases of penicillin and cephalosporin allergy	clarithromycin 500mg 12hrly + gentamicin or clindamycin 600mg to 1.2g 6-8hrly + gentamicin
In severe sepsis or septic shock	piperacillin-tazobactam 4.5g 8hrly + gentamicin 3-5mg/kg daily or ciprofloxacin 600mg 12hrly + gentamicin 3-5mg/kg daily a carbopenem such as meropenem 500mg - 1g 8hrly may be added metronidazole 500mg 8hrly may be considered to provide anaerobic cover
If Group A streptococcal infection is suspected	clindamycin (600mg to 1.2mg 6-8hrly) is more effective than penicillin as it inhibits exotoxin production
If there are risks for MRSA	add teicoplanin 10mg/kg 12hrly for 3 doses then 10mg/kg daily or linezolid 600mg 12hrly

Blood product administration

It is common for patients with severe sepsis to develop a coagulopathy and thrombocytopaenia. If the patient is not actively bleeding and no invasive procedures are planned it may be possible to tolerate the abnormal laboratory clotting results. If the platelet count falls to 5 x 10^9 /l, platelets should be given regardless of bleeding. If there is significant risk of bleeding or if surgery or invasive procedures are planned, platelets will be required to maintain the count above 50 x 10^9 /l.

Red blood cells should be given when the haemoglobin is less than 7.0 g/dl with the aim of achieving a target haemoglobin of 7 - 9 g/dl. If the woman has any significant cardiac or respiratory comorbidities it may be necessary to have a higher transfusion trigger to maintain tissue oxygenation while avoiding an excessive increase in the cardiac workload.

Vasopressors

It is a stated resuscitation goal to achieve and maintain mean arterial pressure greater than or equal to 65 mmHg within the first six hours following diagnosis of severe sepsis. Cardiac function may be compromised as a result of the septic shock and patients can easily become fluid overloaded if given excessive volumes of fluid during resuscitation. In these circumstances an infusion of norepinephrine

(noradrenaline) or dopamine, via a CVC, is recommended to achieve and maintain the desired mean arterial pressure and excessive fluid should be avoided. Use of low-dose dopamine for renal protection is no longer recommended.

Corticosteroids

High-dose corticosteroid therapy is no longer recommended in the management of sepsis. Low-dose (e.g. < 300mg hydrocortisone / day) may be used in adult septic shock when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors.

Glucose control

Intravenous insulin infusions are used to control hyperglycaemia in patients with severe sepsis. An infusion regimen which aims to keep the blood glucose less than 10 mmol/l is recommended. If tighter glycaemic control is aimed for, for example 4-6 mmol/l, then there is more risk of severe hypoglycaemia and the overall Critical Care mortality is higher.

Other treatments in Critical Care

Patients in Critical Care are at risk of developing stress ulcers and deep vein thrombosis. Prophylactic treatment for these conditions is advised.

It may be necessary for the patient to receive treatments such as mechanical ventilation and renal replacement therapy, to support organ systems that have failed as a result of the septic shock while recovery has a chance to occur. A discussion of these treatments is beyond the scope of this article.

Removing the source of sepsis

- The focus of infection should be identified as a priority and if surgery is necessary to remove the source of sepsis, it should be considered early.

- If the uterus is the primary focus of infection, retained products should be excluded by ultrasound examination and exploration of the uterine cavity considered.

- Hysterectomy should be considered if the woman is critically ill and may be life saving.

SUMMARY

Septic shock arising in pregnancy or after delivery may be difficult to diagnose and women may deteriorate rapidly. Early warning scoring systems may aid prompt diagnosis so treatment can begin rapidly and a crisis may be averted. If shock develops, it will affect multiple organ systems and may do so rapidly and catastrophically. Management must be multi-disciplinary including early liaison with the Critical Care team. It is vital for the staff first encountering the patient to act quickly to provide adequate and appropriate resuscitation, broad-spectrum antibiotics and definitive treatment of the underlying problem to minimise the duration and severity of tissue hypoperfusion and improve the chance of a good outcome. The majority of sepsis occurring in the obstetric population is bacterial and sensitive to widely available antibiotics.

It is helpful to remember the advice from CMACE 2006 - 2008; ***"Be aware of sepsis – beware of sepsis."*** [1]

Key Points

- Sepsis can lead to rapid deterioration and death in pregnant women
- Always suspect sepsis in all sick pregnant women until proven otherwise
- Use of a Modified Early Warning Scoring chart is recommended for all pregnant women in hospital
- Start broad spectrum antibiotics as early as possible
- Involve Obstetric, Gynaecology, Microbiological and Critical Care teams early

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1.
   a. **F** - sepsis was the leading cause of direct maternal death in the 2006-2008 UK maternal death enquiry
   b. **F** - deaths from β-haemolytic streptococcus Group A infection have increased in the UK
   c. **T**
   d. **F**

2.
   a. **F** - the physiological changes of pregnancy may mask the early signs and symptoms of maternal sepsis
   b. **T** - may present with hypothermia or hyperthermia
   c. **T** - so is amenable to antibiotic treatment
   d. **T**

3.
   a. **F** - ideally cultures should be taken before antibiotics but this must not delay treatment
   b. **F** - a target haemaglobin of 7 - 9g/dl has been recommended
   c. **F** - steroids may be indicated when hypotension remains poorly responsive to fluid resuscitation or vasopressor therapy
   d. **F** - a central venous oxygen saturation ≥ 70% is a goal of resuscitation

REFERENCES AND FURTHER READING

1. Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118** (Suppl. 1): 1–203

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