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REVIEW ARTICLE

Sepsis during pregnancy or the postpartum period

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Sepsis is an important cause of maternal morbidity and mortality worldwide. Early recognition and timely treatment are the key to ensuring a favourable outcome. This article reviews recent literature about definitions, pathophysiology, incidence, diagnosis, management, treatment, prevention and outcome of sepsis during pregnancy and the postpartum period.

Keywords: Infection, pregnancy, sepsis, septic shock, severe sepsis

Introduction

Sepsis may be defined as a generalised inflammatory response in the host, with systemic manifestations, caused by one or more infectious agents. Sepsis is an important cause of morbidity and mortality worldwide (Sands et al. 1997; Angus et al. 2001; Fernandez-Peres et al. 2005). Its management is particularly challenging during pregnancy and the postpartum period (Afessa et al. 2001; Quah et al. 2001; Paruk 2008).

In the last enquiry of maternal deaths in the United Kingdom, sepsis was the leading cause of direct maternal death (Centre for Maternal and Child Enquiries 2011). Therefore, the development of guidelines for the treatment of maternal sepsis and the creation of specific scoring systems constitute urgent priorities, which can predict early clinical deterioration (Royal College of Obstetricians and Gynaecologists (RCOG) 2012a, 2012b; Albright et al. 2014).

Definitions

Historically, definitions of sepsis and related complications were slightly inaccurate (Barton and Sibai 2012). In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine published a consensus to standardise these definitions, which have recently been revised in the 'Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012' (Dellinger et al. 2013).

Systemic inflammatory response syndrome (SIRS)

The SIRS refers to non-specific systemic manifestations that are triggered by any aggression against the host. It is present when there are at least two of the following manifestations: body temperature over 311.15 K (38 °C) or less than 309.15 K (36 °C), heart rate over 90 bpm, respiratory rate over 20 breaths per minute or $PaCO_2$ less than 32 mmHg, white blood cell count over 12×10^9/l or less than 4×10^9/l or greater than 10% immature band forms (Levy et al. 2003; Bamfo 2013). SIRS is still an interesting concept because of its sensibility to early identify a state of systemic response to aggression (RCOG 2012b).

Sepsis

The most recent evidence defines sepsis as the presence (probable or documented) of infection associated with systemic manifestations. Severe sepsis is present when there is sepsis-induced organ dysfunction or tissue hypoperfusion. Septic shock is defined as sepsis-induced hypotension that persists despite adequate fluid resuscitation. Sepsis-induced hypotension is defined as systolic blood pressure (SBP) less than 90 mmHg or mean arterial pressure (MAP) less than 70 mmHg or a decrease of SBP of more than 40 mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension (Dellinger et al. 2013).

Maternal sepsis

Although maternal sepsis is a small fraction of total sepsis cases, it is still a persistent problem (Khan et al. 2006; van Dillen et al. 2010). The signs and symptoms of sepsis in pregnant women may not be present or can be less distinctive than in the non-pregnant population (Fein and DuVivier 1992). Known physiological changes that occur during pregnancy make the diagnosis of sepsis in this population more difficult (Guinn et al. 2007).

Currently, there are no sepsis definitions validated for pregnant women (Bamfo 2013). However, the RCOG has Green-top Guidelines with recommendations on diagnostic criteria for bacterial sepsis during pregnancy (Table I) (RCOG 2012a) and following pregnancy (RCOG 2012b).

Pathophysiology of sepsis during pregnancy

The pathophysiology of sepsis is complex and not fully understood. The severity of the manifestations is determined not only by the virulence of the microorganism, but also by several host factors (Dolea and Stein 2003; Guinn et al. 2007).

Inflammatory response

When there is an infection, the host inflammatory response works to localise and eliminate the invading organisms. The initiation of sepsis occurs by recognising microbial components

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Table I. Diagnostic criteria for sepsis for pregnant women.

Infection, documented or suspected, and some of the following:
General variables:
Fever [>311.45 K (38.3 °C)]
Hypothermia [core temperature <309.15 K (36 °C)]
Heart rate > 100 bpm
Respiratory rate > 20 breaths per minute
Impaired mental state
Significant oedema or positive fluid balance (>20 mL/kg over 24 hr)
Hyperglycaemia (plasma glucose > 7.7 mmol/l) in the absence of diabetes
Inflammatory variables:
Leukocytosis (white blood cell count > 12×10^9/l – note that a transient leukocytosis is common in labour)
Leukopenia (white blood cell count < 4×10^9/l)
Normal white blood cell count with greater than 10% immature forms
Plasma C-reactive protein > 7 mg/l
Hemodynamic variables:
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg)
Organ dysfunction variables:
Arterial hypoxemia (Pao2/Fio2 < 40 kPa). Sepsis is severe if <3.3 kPa in the absence of pneumonia or <26.7 kPa in the presence of pneumonia
Oliguria (urine output < 0.5 mL/kg/hr for at least 2 h despite adequate fluid resuscitation)
Creatinine increase > 44.2 µmol/l. Sepsis is severe if creatinine level >176 µmol/l
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100 x 10^9/l)
Hyperbilirubinemia (plasma total bilirubin> 70 µmol/l)
Tissue perfusion variables:
Hyperlactatemia (>4 mmol/l)
Decreased capillary refill or mottling

Adapted from Royal College of Obstetricians and Gynaecologists (2012a).

as aggressors, which will activate transcription of genes for the inflammatory and immune response (Vincent and Abraham 2006). Macrophages and neutrophils are activated, release inflammatory mediators and activate CD4 T cells. These cells then release proinflammatory cytokines, which will perpetuate the inflammatory process, and release anti-inflammatory cytokines in order to keep a balanced system (Guinn et al. 2007). However, the compensatory anti-inflammatory response further complicates sepsis by preventing recovery from the initial insult (Schrier and Wang 2004; Fernandez-Peres et al. 2005; Hotchkiss and Karl 2006). TNF-α and IL-1 act as proinflammatory cytokines and as pro-coagulants (van der Poll et al. 1990; Boehme et al. 1996; Vervloet et al. 1998; Larosa 2002; Fernandez-Peres et al. 2005).

Haemodynamic response

The host haemodynamic response occurs early in the course of sepsis. Nitric oxide production induces vasodilatation, creating a 'relative' hypovolemia that activates the sympathetic nervous system, resulting in tachycardia (Guinn et al. 2007). The pregnant patient undergoes complex physiologic changes that need to be considered (Guinn et al. 2007).

Cardiovascular system

The normal cardiovascular changes of pregnancy are similar to those that occur in sepsis and may therefore mask its initial presentation and aggravate decreased organ perfusion (Bridges et al. 2003). As septic shock progresses, signs of hypoperfusion develop and reduced oxygen supply to the tissues causes anaerobic metabolism, lactate accumulation, decreased uterine perfusion, foetal acidosis and end-organ failure (Fernandez-Peres et al. 2005).

Haematologic system

Leukocyte count increase and platelet count decrease is typical during pregnancy, as well as increased clotting factors and decreased fibrinolysis (Guinn et al. 2007). These changes can favour the formation of intravascular fibrin during advanced sepsis (Fernandez-Peres et al. 2005).

Plasma volume and red cell mass increase during pregnancy, but the former increases more. Proteins decrease, resulting in lower colloid osmotic pressure. So, during sepsis, pregnant patients are more susceptible to pulmonary oedema (Cole et al. 2005; Guinn et al. 2007).

Renal system

Renal plasma flow and glomerular filtration rate increase during pregnancy, resulting in lower levels of creatinine. So, even normal non-pregnant serum levels of this metabolite can signify mild renal compromise (Guinn et al. 2007).

Gastrointestinal system

The smooth muscle tone of the gastrointestinal tract is reduced during pregnancy, which heightens the risk of aspiration pneumonia (Guinn et al. 2007). The hypoperfusion of the gastric mucosa that occurs during sepsis originates mucosal atrophy, which leads to bacterial translocation and exacerbation of the disease (Pastor et al. 1995; Tadros et al. 2003).

Respiratory system

During pregnancy, there is mucosal oedema, hyperaemia and capillary congestion in the upper airways (Pereira and Krieger 2004). Concerning pulmonary function, there is an increase in tidal volume and a decrease in residual volume and functional reserve capacity; the total lung capacity is slightly decreased but the vital capacity is not affected (Guinn et al. 2007). There is a significant increase in minute ventilation (Elkus and Popovich 1992; Pereira and Krieger 2004), causing a decline in $PaCO_2$, which leads to a compensated respiratory alkalosis. This is beneficial in a normal pregnancy, but it is detrimental in the case of sepsis, because it predisposes to rapid decline in oxygenation and decreased ability to compensate a metabolic acidosis (Guinn et al. 2007).

Immune system

One of the gaps in our understanding of infectious diseases during pregnancy is the old concept that pregnancy represents an immunocompromised state created in order not to reject the growing foetus, which predisposes the mother to infectious diseases (Lucas et al. 2012). Nowadays, this old concept has been replaced and pregnancy is considered a state of immunomodulation, where a competent immune response is crucial to protect the mother and the foetus (Mor and Cardenas, 2010; Mor et al. 2011; Lucas et al. 2012).

There are three distinct immunological phases during pregnancy, roughly corresponding to the first, second and third trimesters (Mor 2007; Mor and Koga 2008; Lucas et al. 2012). The first phase occurs with implantation and placentation being a phase of strong inflammatory response, which affects the mother's well-being (Dekel et al. 2010; Mor and Cardenas 2010). The second phase is a state of anti-inflammatory response, ideal for rapid foetal growth and development. The last phase is characterised by renewed inflammation, in order to prepare parturition and delivery of the baby. So, pregnancy is a pro-inflammatory and anti-inflammatory condition (Romero 2005; Mor 2008; Mor and Cardenas 2010).

Another important concept is that there is a complex and multifactorial interaction between sex hormones and the immune system (Szekeres-Bartho and Wegmann 1996; Straub 2007; Robinson and Klein 2012). A shift from Th1 to Th2 immunity during pregnancy is proposed as a possible cause for the altered response to viral infections, making them more severe (Wegmann et al. 1993; Jamieson et al. 2006; Pazos et al. 2012; Kourtis et al. 2014). Besides that, the placenta and the foetus represent an additional immunological organ, because they also respond to microbial infections (Mor and Cardenas 2010).

The foetus

The majority of data related to maternal sepsis has put the emphasis on maternal outcomes, with brief reports of foetal outcome (Hazelgrove et al. 2001; Selo-Ojeme et al. 2005; Cartin-Ceba et al. 2008). The maternal–foetal barrier can be disrupted by the inflammatory process during sepsis, leading to foetal compromise or loss. However, it is believed that the foetus is more resistant than its mother to the inflammatory process, possibly because its immune system is not fully developed in utero (Paruk 2008). Nevertheless, when the mother develops shock, blood flow to vital organs is prioritised, limiting the flow to the uterus (Cartin-Ceba et al. 2008).

Epidemiology

Sepsis is a common cause of morbidity and mortality overall. It is the leading cause of death in critically ill patients in the US (Fernandez-Peres et al. 2005; Guinn et al. 2007; van Dillen et al. 2010).

Maternal sepsis is an infrequent but persistent condition (van Dillen et al. 2010). As the definition of sepsis and its related conditions are not being uniformly used, particularly in obstetrics, the incidence and prevalence of sepsis that come from various studies around the world are likely to be inaccurate (Bamfo 2013). An old study reported a prevalence of bacteraemia of 7.5 per 1000 obstetric admissions, with sepsis affecting 8–10% of that population (Blanco et al. 1981).

It appears that the outcome of sepsis during pregnancy may be better than in the non-pregnant population, because of the younger age, fewer comorbidities and usually localised source of infection (Paruk 2008). Nowadays, it is estimated that sepsis accounts for 15% of maternal deaths worldwide (Maharaj 2007a, 2007b; Lucas et al. 2012; Bamfo 2013). In the United Kingdom, deaths due to sepsis have nearly doubled over the past decade. In fact, sepsis was the most common cause of direct maternal death, particularly genital tract sepsis related to community acquired Group A streptococcal disease (Centre for Maternal and Child Enquiries 2011).

Septic shock is rare in pregnancy, occurring in 0.002–0.01% of all deliveries (Barton and Sibai 2012). Sepsis has been reported as the cause of 6–22% of maternal intensive care unit admissions (Sheffield 2004; Zwartt et al. 2010; Timezguid et al. 2012). Recent epidemiological data from obstetric intensive care admissions in Maryland, USA, show that sepsis causes 7.1% of those admissions with substantial increase in admissions for sepsis and trauma throughout the study period (1999–2008) (Wanderer et al. 2013).

Globally, the maternal mortality rate in 2013 was 210 maternal deaths per 100,000 live births, which is lower than in previous years. However, there are important differences between low and high-income countries, with 62% of the deaths occurring in the sub Saharan Africa (World Health Organization 2014). In a retrospective review of maternal bacteraemia cases in Ireland, the women born outside the country were more likely to develop bacteraemia (O'Higgins et al. 2014). The HIV/AIDS pandemic is an important contributor to maternal deaths in Africa and Asia, particularly with the burden of the opportunistic infections (van Dillen et al. 2006; Black et al. 2009; van Dillen et al. 2010).

Puerperal sepsis causes at least 75,000 maternal deaths per year, particularly in low-income countries (van Dillen et al. 2010).

Risk factors

Existing evidence identifies a number of risk factors for maternal sepsis (Table II). In a recent case–control study that analyses risk factors for sepsis, mainly in the postpartum period, obesity, younger maternal age, operative vaginal delivery, multiparty, anaemia, labour induction, caesarean section and preterm birth were considered to be significant risk factors for maternal sepsis. Given the limited power of the sample, further research is necessary, in order to validate this knowledge (Acosta et al. 2012).

Aetiology

The causes of sepsis in obstetric patients may be divided into obstetric and non-obstetric (Table III). In developed countries,

Table II. Risk factors for sepsis in obstetrics.

Obstetric
Vaginal discharge
History of pelvic infection
History of group B streptococcal infection
Multiple pregnancy
Assisted reproduction
Amniocentesis and other invasive procedures
Cervical cerclage
Prolonged spontaneous rupture of membranes
Caesarean section
Vaginal trauma
Wound haematoma
Retained products of conception
Non-obstetric
Obesity
Impaired glucose tolerance and diabetes
Impaired immunity and immunosuppressant medication
Maternal age over 35 years
Of black or other minority ethnic group origin
Low socioeconomic status
Group A Streptococcus infection in close contacts and family members
Medical conditions: Malaria, Hepatitis, HIV/AIDS, Sickle cell disease

Adapted from Bamfo (2013) and Royal College of Obstetricians and Gynaecologists (2012a, 2012b).

Table III. Aetiology of sepsis in obstetrics.

Obstetric causes
Genital tract causes
Septic abortion
Chorioamnionitis
Endometritis
Wound infection following caesarean section or episiotomy or vaginal and perineal lacerations
Infection following invasive procedures (infected cerclage, necrotising fasciitis)
Non-genital tract causes
Pyelonephritis
Lower urinary tract infection
Breast infection
Septic pelvic thrombophlebitis
Non-obstetric causes
Appendicitis
Cholecystitis
Pancreatitis
Gastroenteritis
Pharyngitis
Tuberculosis
Malaria
Pneumonia
HIV
Influenza A and B (secondary infection)
Toxic shock syndrome

the most common causes of maternal sepsis are puerperal sepsis and urinary tract infections (Maupin 2002; Morgan and Roberts 2013). In developing countries, HIV, malaria and community-acquired pneumonia are common non-obstetric causes of maternal sepsis (Guinn et al. 2007). The most important causes of septic shock are pyelonephritis, chorioamnionitis and endometritis (van Dillen et al. 2010).

Early in pregnancy, septic abortion or termination of pregnancy are the most common causes of sepsis (Lucas et al. 2012). Nowadays, the occurrence of septic abortion is rare in high-income countries, much at the expense of the use of prophylactic antibiotics with surgical abortion (Sawaya et al. 1996). The occurrence of infection as a result of invasive procedures of prenatal diagnosis is a rare event (Plachouras et al. 2004).

Asymptomatic bacteriuria, lower urinary tract infections and pyelonephritis are common during pregnancy (Guinn et al. 2007). It is estimated that asymptomatic bacteriuria has an incidence of 4–6% during pregnancy and, if left untreated, in almost 20–40% of cases can arise pyelonephritis (Gilstrap and Ramin 2001; Macjeko and Schaeffer 2007; Lucas et al. 2012). Acute pyelonephritis is the most common cause of septic shock in the pregnant patient (Morgan and Roberts 2013).

Chorioamnionitis refers to the inflammation of the chorion, amnion and placenta, often with upward polymicrobial infection in membrane rupture scenario. Serious complications such as septic shock and maternal death are rare although expeditious management is recommended in order to protect the foetus (Morgan and Roberts 2013). Endometritis is a fairly common puerperal complication. It also occurs by ascending polymicrobial infection originating from the lower genital tract (Faro 2005). Mode of delivery is the most important risk factor, with higher rates associated with caesarean section (Morgan and Roberts 2013).

Infections of wounds and surgical-site infections may occur in areas of abdominal or perineal incision (Bamfo 2013). The widespread use of prophylactic antibiotics before caesarean section has reduced the rate of post-operative infections (Morgan and Roberts 2013). Necrotising fasciitis is a soft tissue infection with the presence of extensive necrosis involving tissues up to and including the deep fascia (Khan et al. 2006). It is a rare but life-threatening condition that demands urgent surgical exploration (Morgan and Roberts 2013). Mastitis affects up to 20% of postpartum women but is a rare cause of sepsis (Lucas et al. 2012).

Community-acquired pneumonia occurs in 0.5–1.5 per 1000 pregnancies in the US (Bamfo 2013; Morgan and Roberts 2013). The majority of the cases are of bacterial origin (Chen et al. 2012) and there is an increased morbidity of pneumonia in pregnancy (Morgan and Roberts 2013).

Influenza infection in pregnant women has been associated with higher rates of morbidity and mortality than in general population. When complications take place, there is a rapid lung inflammatory response that can cause maternal death (Morgan and Roberts 2013). In the 2009 H1N1 influenza A pandemic, pregnant women were at increased risk of severe disease, particularly in the third trimester of pregnancy (Mosby et al. 2011). Pregnant women are also more severely affected by infections with hepatitis E virus, herpes simplex virus and malaria parasites (Kourtis et al. 2014).

Diagnostic workup

Sepsis diagnosis is clinical. The onset of sepsis may be insidious, particularly in pregnancy and the postpartum period, which makes the diagnosis more difficult (Lucas et al. 2012). Conversely, in some cases, obstetric sepsis can be fulminant and rapidly fatal (Harrison et al. 2006; Dombrovskiy et al. 2007).

A complete history and physical examination are the first step when evaluating a patient with possible sepsis (Guinn et al. 2007). Initially, the clinical signs vary according to the site of infection (Lucas et al. 2012). Clinical signs such as pyrexia, hypothermia, tachypnoea, tachycardia, hypotension, oliguria and impaired consciousness are suggestive of sepsis in obstetric population (RCOG 2012a). One of the earliest clinical signs of sepsis is tachypnoea, which arises from pyrexia, lactic acidosis or cytokine mediated effects on the respiratory centre (Lucas et al. 2012).

Concerning laboratory analysis, we cannot rely on a high white blood cell count as indicative of sepsis, because pregnant women tend to have higher levels of these cells (Lucas et al. 2012). Obtaining blood cultures is crucial to the diagnostic workup and they should ideally be obtained before the antibiotic administration. If there is clinical suspicion of the focus of infection, cultures of additional sites should be obtained (Guinn et al. 2007). Similarly, any relevant imaging studies should be readily conducted in order to identify the source of the infection (RCOG 2012a, 2012b).

Management

The management of sepsis during pregnancy includes two patients, the mother and the foetus (Paruk 2008).

The uteroplacental circulation does not have auto regulation, so maternal infection can easily affect the foetus (Lucas et al. 2012). Effective and prompt maternal resuscitation is the most important factor for restoring foetal well-being (Paruk 2008). Thus, the focus should be on the mother (van Dillen et al. 2010).

The management of sepsis in obstetrics follows the same principles as the management in the general population: resuscitation, identification and control of the source of infection, management of complications and utilisation of organ

protection strategies (Lucas et al. 2012). The concept of early goal-directed therapy (EGDT) is widely used in sepsis and involves its early recognition and the use of resuscitative measures in order to balance systemic oxygen delivery according to oxygen demand (Paruk 2008).

As general measures, intravenous access should be obtained. All patients should have initial laboratory evaluation, with a complete blood count, serum lactate, comprehensive biochemical analysis, coagulation studies, urinalysis and arterial blood gas. Supplemental oxygen should be guided by continuous pulse oximetry, performing arterial blood gas analysis as indicated by the state of the patient (Barton and Sibai 2012). In the pregnant patient, displacement of the uterus to the left minimises aortocaval compression, improving venous return to the heart (Guinn et al. 2007).

According to the RCOG, the management of sepsis in obstetrics should be guided in accordance with the Surviving Sepsis Campaign guidelines. Those guidelines make recommendations based on the quality of the evidence, ranging from high (A) to very low (D). Furthermore, the recommendations are ultimately classified as strong (grade 1) or weak (grade 2).

Initial resuscitation

The first step in the management of sepsis in obstetrics is the use of the so called 'resuscitation bundle' (RCOG 2012a). This step should be accomplished as soon as possible and within the first 6 h (van Dillen et al. 2010):

- Measure lactate level.
- Obtain blood cultures prior to the institution of antibiotic therapy [however, this procedure should not delay more than 45 min the initiation of the antibiotic treatment (Dellinger et al. 2013)]. At least two sets of blood cultures (aerobic and anaerobic) should be obtained (Dellinger et al. 2013) (grade 1C).
- Administer broad-spectrum antibiotics within the first hour of recognition of severe sepsis (1C) or septic shock (grade 1B).
- Treatment should be directed at the normalization of lactate in patients with elevated lactate (Dellinger et al. 2013) (grade 2C).
- In the event of hypotension or lactate >4 mmol/L (hypo-perfusion induced by sepsis), adequate fluid replacement should be started. The recommendations state that the fluid volume replacement should start with crystalloids (grade 1B) (Dellinger et al. 2013).
- The goals of treatment during the first 6 h of resuscitation for patients with hypo-perfusion induced by sepsis are (grade 1C):
    (a) Central venous pressure between 8 and 12 mmHg
    (b) Mean arterial pressure (MAP) ≥65 mmHg
    (c) Urine output ≥0.5 mL/kg/h
    (d) Central venous (superior vena cava) or mixed venous oxygen saturation 70 or 65%, respectively.
- For hypotension that does not respond to initial fluid resuscitation, use vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg (Dellinger et al. 2013).

The 'sepsis six'

Another interesting concept in the management of sepsis is 'sepsis six', a simple set of measures intended to be performed during the first hour of the diagnosis of sepsis (Daniels et al. 2011). It consists of the following steps:

(1) Administer high flow oxygen
(2) Take blood cultures
(3) Give broad spectrum antibiotics
(4) Give intravenous fluid challenges
(5) Measure serum lactate and haemoglobin
(6) Commence accurate urine output measurement

This strategy does not replace the resuscitation bundle mentioned above, but it is a simple strategy that can be used by any healthcare professional in the first contact with sepsis, providing the patient with life-saving interventions.

Admission to the intensive care unit

These initial steps should be undertaken before trying to transfer the patient to an intensive care unit (RCOG 2012a). The reasons to transfer the patient are related to the need for organ support, such as:

- Dialysis for kidney failure
- Neurological support for impaired mental status
- Cardiac output monitoring for hypotension or raised serum lactate persisting despite fluid replacement
- Ventilatory support requiring intubation
- Hypothermia
- Uncorrected acidosis
- Multi-organ failure (RCOG 2012a).

Antibiotics and source control

The identification and control of the source of the infection, together with early initiation of antibiotic therapy are crucial (Fernandez-Peres et al. 2005). Broad-spectrum antibiotics should be used initially. There is evidence that delaying antibiotic administration increases mortality (Kumar et al. 2006).

The selection of the antimicrobial regimen should be guided by local micro-organisms pattern and must be adjusted according to the cultural results (Fernandez-Peres et al. 2005; RCOG 2012a). Choosing an appropriate antibiotic regimen in pregnancy is challenging, because the physiological adaptations of normal pregnancy can modify drug availability and concentration. Moreover, all antibiotics have some degree of transplacental passage, so the ideal regimen is the one of maximal effectiveness with minimal foetal harm, which is not always possible (Guinn et al. 2007). Tetracyclines and chloramphenicol should be avoided in pregnant women (Fernandez-Peres et al. 2005).

The most commonly used combination in obstetric sepsis is ampicillin plus gentamicin plus clindamycin or metronidazole (Hopkins and Smaill 2002). In Table IV, there are some suggested initial intravenous antibiotic regimens for obstetric sepsis, taken from a British article (Bamfo 2013).

Antibiotic treatment should last at least 7–10 days (Lucas et al. 2012). The antimicrobial regimen should be reassessed daily, in order to try to deescalate the antibiotics spectrum (grade 1B). However, it is common to have negative blood cultures during pregnancy and the majority of obstetrical infections are polymicrobial, making de-escalation a difficult task (Guinn et al. 2007).

Source control is essential and some obstetric infections are susceptible to source control measures. In the presence of

Table IV. Intravenous antibiotic regimen options for obstetric sepsis.

When the microorganism is unknown and the patient is not critically ill:
Amoxicillin/clavulanic acid 1.2 g 8/8 h or cefotaxime 1–2 g 8/8 h or 6/6 h plus metronidazole 500 mg 8/8 h
If the patient is allergic to penicillin and cephalosporins:
Clarithromycin 500 mg 12/12 h or clindamycin 600 mg to 1.2 g 8/8 h or 6/6 h plus gentamicin
In severe sepsis or septic shock (seek urgent microbiological advice):
Piperacillin–tazobactam 4.5 g 8/8 h or ciprofloxacin 600 mg 12/12 h plus gentamicin 3–5 mg/kg/day in divided doses every 8 h.
Or meropenem 500 mg to 1 g 8/8 h ± gentamicin.
Metronidazole 500 mg 8/8 h may be considered to provide anaerobic cover.
If group A Streptococcus infection is suspected:
Clindamycin 600 mg to 1.2 g, 3 or 4 times per day
If there are risk factors for methicillin-resistant Staphylococcus aureus:
Add teicoplanin 10 mg/kg 12/12 h for 3 doses, then 10 mg/kg 24/24 h or linezolid 600 mg 12/12 h

Adapted from Bamfo (2013). using also the recommendations from RCOG (2012a).

chorioamnionitis, delivery should be accomplished as a source control measure, independently of the gestational age (Guinn et al. 2007).

Fluid management and haemodynamic support

Early haemodynamic resuscitation is crucial and the primary objective is to restore adequate oxygen supply for peripheral organs and tissues (Lucas et al. 2012). Large amounts of fluid may be required for initial resuscitation (Guinn et al. 2007). Fluid management is difficult in sepsis, particularly in the critically ill obstetric patient that is more vulnerable to fluid overload (Lucas et al. 2012).

There is a paucity of information about the use of central venous pressure catheters during pregnancy, but when the patient is critically ill, this procedure is undertaken in order to guide the treatment (Guinn et al. 2007). A retrospective case series evaluating the complications of central venous catheters used during pregnancy and postpartum showed that the overall complication rate was similar to the general population, but the infection rate is higher among pregnant patients (Nuthalapaty et al. 2009).

Fluid volume replacement should start with crystalloids (grade 1B). Vasopressor therapy is required to sustain life when life-threatening hypotension occurs. Norepinephrine is the first-choice vasopressor (grade 1B). In the face of low cardiac output in the presence of adequate fluid resuscitation and adequate MAP, an inotropic drug should be used and dobutamine is the agent of choice (Dellinger et al. 2013).

Ventilatory support

In obstetric patients with severe sepsis, Acute Respiratory Distress Syndrome (ARDS) is a common complication and requires mechanical ventilation using a lung-protective strategy (Fernandez-Peres et al. 2005).

Protocols of intermittent sedation should be used and daily interruption should be attempted in order to try to awake the patient and to reduce the number of days on mechanical ventilation (Kress et al. 2000).

Adjunctive measures

The other bundle of the Surviving Sepsis Campaign is the 'sepsis management bundle', a set of adjunctive measures to be accomplished as soon as possible and ideally within the first 24 h (van Dillen et al. 2010).

The use of corticosteroids during sepsis is controversial (Guinn et al. 2007). In the latest guidelines, that use is considered only in patients with septic shock when adequate fluid resuscitation and vasopressor therapy are not able to restore haemodynamic stability (Dellinger et al. 2013). The use of corticosteroids during pregnancy may lead to undesired effects in the mother, such as higher infectious risk, poor glycemic control and delayed wound healing (Fernandez-Peres et al. 2005). The use of antenatal corticosteroids, for foetal lung maturation when preterm delivery of a viable foetus is anticipated in a woman with sepsis, should be considered (RCOG 2012a).

The recombinant form of human activated protein C is no longer indicated in severe sepsis (Barton and Sibai 2012). Intravenous immunoglobulin (IVIG) is no longer recommended in the treatment of adults with severe sepsis or septic shock (Dellinger et al. 2013).

A transfusion of red blood cells is recommended only when haemoglobin concentration decreases to less than 4.34 mmol/l (7.0 g/dl). The use of erythropoietin is discouraged (Dellinger et al. 2013). However, in the pregnant patient, the decision to transfuse should be individualised, according to the foetal and maternal status (Guinn et al. 2007).

In the face of severe sepsis, the prophylactic use of platelets is recommended only when counts are $<10 \times 10^9$/l in the absence of bleeding. Prophylactic platelet transfusion should be made when counts are $<20 \times 10^9$/l and the patient has a significant risk of bleeding. Higher platelet counts ($\geq 50 \times 10^9$/l) are recommended for active bleeding, surgery or invasive procedures (grade 2D) (Dellinger et al. 2013). Correction of coagulopathy in severe sepsis should only be considered if there is continued bleeding or need for operative intervention (Barton and Sibai 2012).

The patients must undergo blood glucose testing every 1–2 h initially, but the tests can be spaced, once the patient is stabilised (Barton and Sibai 2012). Insulin therapy should be started when two consecutive blood glucose levels are higher than 9.99 mmol/l (180 mg/dl); the objective is to maintain blood glucose less than 9.99 mmol/l (180 mg/dl) (Dellinger et al. 2013).

Septic patients have increased risk of thrombosis and this risk is particularly high in obstetric patients. So, all obstetric patients should use intermittent compression devices or external compression stockings (Guinn et al. 2007). If they have no contraindication, prophylaxis of deep venous thrombosis with low molecular weight heparin or low-dose unfractionated heparin are also recommended (Fernandez-Peres et al. 2005). Stress-ulcer prophylaxis with proton pump inhibitor or H2 blocker should also be considered in patients with severe sepsis or septic shock (Fernandez-Peres et al. 2005).

Sepsis is a state of accelerated metabolism (Frankenfield et al. 1995). Thus, patients with sepsis have greater nutritional requirements, especially during pregnancy (Barton and Sibai 2012). Nutritional support should start in the first 48 h after a diagnosis of severe sepsis or septic shock (grade 2C) (Dellinger et al. 2013). Whenever possible, nutritional support should be given enterally (Barton and Sibai 2012).

Foetal evaluation

The foetal health depends on the maternal health (Morgan and Roberts 2013). Foetal and tocodynamic monitoring are indicated

at gestational ages in which extra uterine neonatal survival is possible (van Dillen et al. 2010; Barton and Sibai 2012).

In the presence of severe sepsis, foetal tachycardia, minimal or absent foetal heart rate variability, absent accelerations and occasional decelerations can occur. Supportive measures can usually resolve these anomalies (Barton and Sibai 2012).

Uterine contractions which end up in regular continuous contractility may be unusual; however, if it occurs, the problem of tocolysis during sepsis is arisen, because it can increase the risk of pulmonary oedema, particularly when β-agonists are being used. Therefore, before 34 weeks of gestation, magnesium sulphate can be considered (Barton and Sibai 2012).

The decision to deliver the baby should be postponed until the mother is stabilised. Attempting delivery during maternal instability increases the maternal and foetal mortality rates, unless there is an intrauterine infection (RCOG 2012a). In the face of severe sepsis or septic shock and intrauterine infection, disseminated intravascular coagulation, hepatic or renal failure, compromised cardiopulmonary function, confirmed foetal death or gestational age near term, delivery may be indicated. A multidisciplinary team including at least an anaesthesiologist, a paediatrician and an obstetrician should be available in such cases, since the foetal and maternal state can rapidly deteriorate (Barton and Sibai 2012).

Epidural or spinal anaesthesia should be avoided in patients with sepsis (RCOG 2012a). In the event of maternal cardiac arrest, perimortem caesarean section should be considered depending on gestational age, the time lag after maternal cardiac arrest and the medical resources available (Dijkman et al. 2010).

Prognosis

Pregnancies complicated by severe sepsis or septic shock are associated with higher rates of preterm labour and delivery, foetal infection and operative delivery, which result in higher perinatal morbidity and mortality. In spite of being rare during pregnancy, septic shock may also cause important maternal morbidities and even mortality. The maternal mortality rate among women with septic shock varies between 20 and 28% (Barton and Sibai 2012). Some predictors of poor prognosis in septic shock include delay in initial diagnosis, poor response to intravenous fluid replacement therapy, depressed cardiac output, high serum lactate, multiple organ dysfunction and pre-existing debilitating comorbidities (Barton and Sibai 2012).

Different prognostic scoring systems exist to assess the severity of multi-organ dysfunction in critically ill patients. However, these scores are not validated in the obstetric population (Fernandez-Peres et al. 2005). Acute Physiology and Chronic Health Evaluation (APACHE) system is widely used in critical care units. However, its use in obstetric patients revealed conflicting results (Fernandez-Peres et al. 2005).

Early warning systems are also used in acute care. These systems use the evolution of a set of predetermined physiological criteria as indicators of the need to escalate monitoring. There is an early warning system modified for use in obstetric population, the modified early obstetric warning system (MEOWS), but not enough evidence linking the implementation of this system and the improvement in obstetric morbidity (Mackintosh et al. 2014). A study that examined the use of this system in pregnant women with intrauterine infection showed that the risk of contracting sepsis, being transferred to an intensive care unit or dying cannot be predicted (Lappen et al. 2010). The Sepsis in Obstetrics Score (S.O.S.) is a very recent scoring system created to identify risk of intensive care unit admission in pregnant and postpartum women. This score uses parameters like temperature, heart rate, respiratory rate, oxygen saturation, leukocyte count, and lactic acid to create a final value. In the population studied, S.O.S. was able to identify patients at risk of being transferred to the intensive care unit within 48 h after being admitted to the emergency service. However, this is a retrospective study performed in a single institution, so its results may not be generalisable (Albright et al. 2014).

Prevention

Healthcare professionals and patients themselves are very important for the prevention of sepsis in obstetrics. Preoperative preparation can reduce the likelihood of septic complications. Measures like treating infections remote from the surgical site before elective surgery, preoperative surgical hand washing, use of surgical mask, hair removal around the incision site by electric clippers and antimicrobial prophylaxis are crucial in preventing sepsis (Barton and Sibai 2012; Bamfo 2013).

Another important preventive measure is vaccination. Pregnant women are more predisposed to serious influenza disease and so should receive the inactivated vaccine if they will be pregnant during the influenza season, irrespective of the point of gestation in which they are (Barton and Sibai 2012). All healthcare workers and close contacts with women with group A streptococcal infection should be considered for antibiotic prophylaxis (RCOG 2012a).

Conclusion

Maternal sepsis is an infrequent but important complication, causing significant maternal and foetal morbidity and mortality worldwide (van Dillen et al. 2010). Early recognition and treatment of sepsis may improve maternal and foetal outcome.

It is absolutely necessary to validate the definitions of sepsis and its related conditions in obstetrics. Future research should focus on the foetal outcome of the critically ill pregnant women and on the creation of a scoring system that can predict clinical deterioration in this population.

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