REVIEW ARTICLE

Sepsis in pregnancy and early goal-directed therapy

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Summary: Sepsis is a major cause of serious morbidity and mortality in pregnant women and their babies. Conventional management has evolved over many years. Improved understanding of the underlying pathophysiology and randomized clinical trials have led to recommendations for the formalization and standardization of the management of severe sepsis in non-pregnant patients. Most of these recommendations are applicable to pregnancy. The Surviving Sepsis Campaign and Early Goal Directed Therapy have relevance to the care of pregnant women with serious infection and are reviewed here.

Keywords: sepsis, pregnancy, early goal-directed therapy

INTRODUCTION

Pregnant women are more vulnerable to infection and more likely to develop serious complications than non-gravid women. This article will discuss the diagnosis of sepsis in pregnancy, its potential complications, its treatment with attention to recent trials of adjunctive therapy and the applicability of conventional intensive care-based notions of management (for example, early goal-directed therapy [EGDT]) that have not been validated in pregnancy.

BURDEN OF SEPSIS

Even though obstetric haemorrhage and complications of pre-eclampsia are the most common causes of intensive care unit (ICU) admission in pregnancy, 20–30% of admissions result from other causes, mostly sepsis. In a recent global analysis of the causes of maternal death, the contribution of sepsis as a cause of maternal mortality was between 2.7% in developed countries and 11.6% in developing countries.[1] Infectious disease ranks as one of the four most common causes of maternal mortality and severe morbidity wherever records are available.

Any systemic or ascending genitourinary infection during pregnancy may cause preterm labour leading to fetal morbidity and mortality in addition to its effects on the mother. Hence, early diagnosis and treatment of infections such as asymptomatic bacteriuria, bacterial vaginosis in high-risk patients and Group B streptococcal colonization improve pregnancy outcomes and reduce the likelihood of fetal and neonatal sepsis.

Several physiological changes that occur during pregnancy limit the ability of the pregnant woman to compensate for the derangements produced by severe sepsis. In addition, pyelonephritis, chorioamnionitis, mastitis, wound infection and puerperal pelvic sepsis are encountered frequently in pregnant and postpartum women, all of which may progress to a systemic illness of great severity.

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CHANGES IN PHYSIOLOGY AND ANATOMY DURING PREGNANCY

Significant physiological alterations occur within weeks of conception and the difference from the non-pregnant state progressively increases as pregnancy advances. Cardiac output (CO) increases steadily, reaching a peak of 30–40% above non-pregnant levels by 26–30 weeks, with higher levels in multiple pregnancy. This results from an increment in blood volume by 40% and increases in stroke volume and heart rate. A profound reduction in the systemic and pulmonary vascular resistance occurs due to vasodilation of arterial and venous smooth muscle. Echocardiographic measures of function, wall tension and other parameters demonstrate that the heart is under steadily increasing stress during normal pregnancy.[2] Clinical correlates include dyspnoea, palpitations and tiredness. In normal pregnancy there is a decrease in colloid osmotic pressure, mostly due to a decline in serum albumin, which is also exaggerated by sepsis. These changes render the pregnant woman vulnerable to pulmonary oedema under conditions of added stress and endothelial dysfunction, such as sepsis or severe preeclampsia. Older, obese and diabetic women are at increased risk.

Relevant changes in respiratory physiology include an increase in tidal volume but a reduction of residual volume and functional residual capacity. Increased respiratory rate and minute ventilation result in respiratory alkalosis, with compensatory mild metabolic acidosis. In the setting of sepsis, particularly complicated by respiratory failure, these changes lessen the pregnant woman's ability to compensate for the metabolic acidosis that often complicates severe infection.

From early pregnancy, renal plasma flow and glomerular filtration rate increase substantially, resulting in decreased blood urea and creatinine concentrations. The renal collecting system dilates because of smooth muscle relaxation and developing obstruction of the ureters (particularly the right) at the pelvic brim by the expanding uterus. This leads to urinary stasis, an increased incidence of asymptomatic bacteriuria and a greater risk of pyelonephritis.

Significant changes in coagulation and fibrinolysis occur. These systems are activated, increasing vulnerability to disseminated intravascular coagulation as a complication of severe sepsis.

Anatomical changes such as increased body weight, particularly in women already overweight or obese, reduce the cardiorespiratory reserve and make complications such as wound sepsis more likely after caesarean delivery. In late pregnancy and after a caesarean, elevation of the diaphragm and poor inspiration predispose to basal atelectasis and chest infection.

DOMINANT INFECTIONS IN PREGNANCY

The chief sites of infection in pregnancy are the urinary tract (pyelonephritis), the pelvic structures (chorioamnionitis and endomyometritis), surgical wounds (caesarean) and the breasts (mastitis) (Table 1). Pregnant women are prone to infection of sites of vascular cannulation and after urological procedures performed in the presence of an infected urinary tract. Occasionally, epidural puncture site infection occurs, particularly when the catheter remains *in situ* for more than 48 hours.

The most prevalent organisms responsible for severe infection include *Escherichia coli*, group B streptococcus, klebsiella and staphylococcus. Group A beta haemolytic streptococci also cause puerperal fever and rare strains may cause necrotizing fasciitis. Anaerobic organisms are possible causative agents of pelvic infection and wound sepsis, including necrotizing fasciitis, a dramatic illness that threatens both life and limbs. Clostridium species are rare in the developed world but may be seen elsewhere in cases of induced abortion under non-sterile circumstances. *Listeria monocytogenes*, although a serious infection in pregnancy, is rare, although occasionally and for unknown reasons, outbreaks occur.[3] Of the viral causes of severe sepsis in the developed world, the most frequent are influenza and varicella, presenting as a pneumonia that may require intensive care.

Table 1 **Common infections and pathogens leading to septic shock in pregnancy**

Infections that may lead to septic shock and usual organisms (in brackets)	Likely pathogens causing septic shock in pregnancy
Pyelonephritis (1, 4)	1 *Escherichia coli*
Perinephric abscess (1, 4)	2 Bacteroides
Pneumonia (6, 7)	3 Clostridium
Chorioamnionitis (1, 2, 8–12)	4 Klebsiella
Endomyometritis (primarily after caesarean delivery) (1, 2, 5, 9, 12)	5 *Pseudomonas aeruginosa*
Septic abortion (1, 3)	6 Streptococcus species
Necrotizing fasciitis (2, 3, 6, 9)	7 *Staphylococcus aureus*
Caesarean wound infection (1, 2, 6, 7)	8 Group B streptococcus
Severe mastitis (7)	9 Peptostreptococcus
Malaria and other tropical infections	10 Enterococcus
	11 *Listeria monocytogenes*
	12 Enterobacter

DIAGNOSIS OF INFECTION

There are two aspects to the diagnosis of infection. The first confirms the suspicion of sepsis, and the second involves localization of its source. In most cases, the diagnosis of infection is not difficult. Women generally experience chills, sweating, faintness or syncope and there may be vomiting, rash, headache, dyspnoea, or pain related to sites of sepsis as mentioned below. On clinical examination, fever is almost invariably present, although in overwhelming sepsis the temperature may be below 36°. Tachycardia, tachypnoea, hypotension and low urinary output complete a picture of severe illness. It should be noted that the heart rate in normal pregnancy may be up to 100 per minute, but fever and the other features mentioned are never normal and require careful evaluation.

Diagnosis of the site of infection is important because it will often determine whether surgical therapy is required. Local tissue infections are characterized by signs of inflammation at the site. Chorioamnionitis is associated with tenderness of the uterus and preterm labour. Pyelonephritis causes extreme loin pain and tenderness to renal percussion and mastitis gives rise to a reddened sector in the breast as well as systemic symptoms. The signs of pneumonia, cholecystitis and wound infection are well recognized. Postpartum endometritis is suggested by offensive lochia and unusual bleeding. In the rare cases of necrotizing fasciitis, extreme pain in a periphery is the dominant feature, associated with signs of prostration and severe sepsis.

Despite the above, it is often difficult to localize the source of a septic illness even after careful clinical evaluation and re-examination. In these cases, imaging modalities such as ultrasound, computed tomography or magnetic resonance imaging help define inflammation or the collection of pus. Echocardiography in women with a clinically normal heart very rarely yields an unexpected diagnosis but is useful in intravenous drug users, particularly those with staphylococcal bacteraemia as there may be right-sided endocarditis.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS

The term systemic inflammatory response syndrome (SIRS) was defined in 1992 after a Consensus Conference[4] and has since been adopted globally. SIRS is triggered by localized or generalized infection and by non-infectious causes such as trauma, thermal injury, anaphylaxis or sterile inflammatory processes. It is considered to be present when patients have more than one of the following clinical findings: body temperature $>38^{\circ}C$ or $<36^{\circ}C$, heart rate >90 per minute, hyperventilation (evidenced by a respiratory rate of >20 per minute, or a Pa CO_2 <32 mmHg) and a white blood cell count of $>12{,}000\ \mu L^{-1}$ or $<3000\ \mu L^{-1}$.

The 2001 International Sepsis Definitions Conference concluded that these diagnostic criteria were too sensitive and non-specific.[5] Definitions for sepsis, severe sepsis and septic shock remained unchanged.[4,5] 'Sepsis' requires the presence of both infection (the invasion of tissue, fluid or a body cavity by pathogenic microorganisms) and a systemic inflammatory response. 'Severe sepsis'

refers to sepsis complicated by organ dysfunction. 'Septic shock' refers to acute circulatory failure in a septic patient with persistent hypotension unexplained by other causes. 'Hypotension' is defined as systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <60 mmHg or a reduction in SBP of >40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes.

Conventional definitions are not directly applicable in pregnancy, during which mild hypotension is physiological and many changes in laboratory values are normal. For example, white cell count and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate (ESR) are almost invariably elevated. Nevertheless, it is reasonable to regard persistent hypotension despite adequate fluid resuscitation in a setting of infection as septic shock, particularly if accompanied by lactic acidosis.

PATHOPHYSIOLOGY AND IMMUNOLOGY OF SEPSIS

The host response to infection depends on multiple host factors such as age, presence of co-morbidities, nutritional status and various genetic polymorphisms that contribute to a predisposition to severe sepsis. The virulence of the organism, size of the inoculum and its susceptibility to antibiotics also play a major role in determining the outcome. Initially, sepsis activates inflammatory mediators, but later there is a shift towards an anti-inflammatory immunosuppressive state. In addition, apoptotic cell death of lymphocytes, possibly induced by stress-induced endogenous steroids, may trigger sepsis-induced anergy, anti-inflammatory cytokines and decreased antibody production. This impairs the response to pathogens. Excessive release of oxidants and proteases by neutrophils is believed to be responsible for tissue injury and the complement cascade is activated, with effects on inflammation and coagulation.

Protein C is depressed in patients with severe sepsis, attributed in part to increased conversion to activated protein C (APC) and subsequent inactivation of APC by serine proteases.[6] Adult patients with severe sepsis vary markedly in their ability to generate APC endogenously.[6] Proinflammatory pathways activate coagulation with thrombin formation, platelet aggregation and formation of microthrombi, while tumour necrosis factor inhibits anticoagulant pathways. These events result in decreased tissue perfusion, hypoxaemia and lactic acidosis.

Haemodynamic changes accompany the systemic inflammatory response early. In septic shock there is a complex interaction between pathological vasodilation, relative and absolute hypovolaemia, direct myocardial depression and altered blood flow distribution.[7] Myocardial depression during sepsis is multifactorial, the precise cause remaining unclear but relating to depressants such as cytokines and nitric oxide, and disturbed flow or oxygen utilization in the myocardium, rather than global ischaemia.[8,9]

Vasodilation and a decrease in systemic vascular resistance (SVR) occur, the mechanisms implicated including activation of adenosine triphosphate-sensitive potassium channels, increased nitric oxide synthesis and vasopressin deficiency.[10] A baroreceptor-mediated increase in heart rate due to the relative hypovolaemia is exacerbated by cardiac under filling, adrenergic stimulation and fever.[9,11] Tachycardia in the presence of decreased SVR increases CO. Vasoconstrictive hormones, such as vasopressin and endothelin, are released and the renin–angiotensin–aldosterone system is activated in an attempt to maintain vascular tone and intravascular volume.[11] Increased capillary permeability and venodilation decrease venous return, which combined with myocardial depression reduces stroke volume and ejection fraction in the early stages of sepsis.[12] Subsequently, and after fluid therapy, high normal or elevated CO is common.[12] If preload has been restored adequately, persisting hypotension reflects reduced SVR and impaired cardiac contractility.[12]

Even after correction of these derangements, tissue hypoperfusion may persist due to regional redistribution of blood flow, microvascular abnormalities and cellular inability to use oxygen.[7,12]

Table 2 summarizes the physiological changes of severe sepsis and pregnancy.[11,13,14]

MANAGEMENT OF THE PREGNANT WOMAN WITH SEVERE SEPSIS

The management of the critically ill septic patient has evolved as evidence for or against benefit from various interventions has accumulated. The following section summarizes key trials. Recommendations or suggestions from the 'Surviving Sepsis Campaign' (SSC) guidelines are described.[15] Grading of these recommendations is based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system in which quality of evidence is rated as high (A), moderate (B), low (C) or very low (D) (Table 3) and recommendations are graded as strong (grade 1) or weak (grade 2).[15] The terms 'recommend' and 'suggest' indicate a strong or weak recommendation, respectively.[15] The guidelines are based on non-pregnant data, which should be considered when extrapolating their application to pregnant women. The risks and benefits to the woman and her baby should be considered.

It is important to note that applying the usual diagnostic criteria for sepsis and the systemic inflammatory syndrome to the pregnant population is problematic.[16] This also applies to prognostic scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) system,[14] which have not been validated in the pregnant population.

Early recognition and prompt therapy are vital. Initial management (within the first 6 hours) should involve immediate resuscitation (grade 1C), diagnosis ideally with blood cultures sent before antibiotic therapy is commenced (grade 1C), antibiotic therapy within one hour of diagnosis of septic shock (grade 1B) and identification and control (grade 1C).[15]

EARLY GOAL-DIRECTED THERAPY

A randomized, controlled study demonstrated that EGDT improved survival in emergency department patients presenting with severe sepsis and septic shock.[17] This approach in the initial six-hour resuscitation period significantly reduced in-hospital, 28-day and 90-day mortality[17] and has been supported by several other studies.[18] The protocol employs fluid resuscitation and vasopressor therapy in the initial six hours to achieve measurable goals and is supported by the SSC. Goals are central venous pressure (CVP) of 8–12 mmHg, MAP ≥65 mmHg, urine output ≥0.5 mL/kg/h and central venous (superior vena cava) ($Scv0_2$) or mixed venous oxygen saturation ($SV0_2$) ≥70% or ≥65%, respectively (grade 1C). Transfusion of packed red cells to achieve a haematocrit ≥30 and/or administration of dobutamine to achieve $Scvo_2$ ≥70%

Table 2 **Physiological changes in pregnancy and in sepsis**

System	Pregnancy physiological changes	Sepsis-induced changes	Combined effect
Cardiovascular	Low systemic vascular resistance with vasodilation. Increase in blood volume by 40%. Increased heart rate. Increased cardiac output. Fall in blood pressure. Aorto-caval compression	Vasodilation and reduced systemic vascular resistance. Tachycardia. Myocardial depression. Hypotension.	Rapid haemodynamic collapse.
Respiratory	Low pulmonary vascular resistance and plasma colloid osmotic pressure. Increased tidal volume, decreased residual volume and functional residual capacity. Increased minute ventilation with compensated respiratory alkalosis.	Enhanced pulmonary microvascular pressure and permeability. Sepsis-induced acute lung injury.	Increased susceptibility to pulmonary oedema. Rapid decline in oxygenation. Adult respiratory distress syndrome. Decreased ability to compensate for metabolic acidosis.
Coagulation	Elevated factors I, II, VII, VIII, IX and XII. Plasminogen activator inhibitors I and II increase 5-fold. Reduced protein S. Antithrombin and protein C not significantly affected.	Procoagulant effects. Increased thrombin production and reduced activated protein C associated with platelet aggregation. Decreased fibrinolysis via increase in plasminogen activator inhibitor 1	Increased microvascular fibrin thrombi. Tissue hypoperfusion and end organ dysfunction.
Renal	Renal plasma flow and glomerular filtration rate increase. The renal collecting system dilates. Predisposition to urinary tract infection.	Ischaemia– reperfusion injury. Vasoconstriction. Angiotensin activity and cytokine-mediated renal cell injury.	Acute tubular necrosis. Renal failure.

or $Scv0_2$ $\geq$65% is recommended if not achieved with fluid resuscitation to the CVP target within six hours (grade 2C).[15]

These studies excluded pregnant women and no evidence-based goal-directed recommendations exist for this group.[11,14,16] Normal pregnancy-induced physiological changes confound the application of EGDT during pregnancy because the CVP may be increased to 10 mmHg, the MAP is decreased and the $Scv0_2$ may be as high as 80%.[11,16] CO monitoring may be useful to guide fluid resuscitation but has not been studied formally in this setting.

FLUID THERAPY

Fluid resuscitation involves crystalloids, colloids or both. Currently, no evidence supports that one type of intravenous fluid is superior in the septic patient.[15,19] A recent review found that colloids were equivalent to crystalloids in terms of outcome for critically ill patients but few of the studies evaluated included patients with sepsis.[20]

The Saline versus Albumin Fluid Evaluation (SAFE) study concluded that 4% albumin is as safe and effective as normal saline in ICU patients.[21] There was no difference in 28-day mortality between the two groups.[21] The ratio of albumin to saline volume was approximately 1:1.4, suggesting that much larger volumes of crystalloid than colloid may be unnecessary, as was previously surmised.[20]

Table 3 **Determination of the quality of evidence as part of the GRADE system (ref[15])**

Classification of quality of evidence
A Randomized controlled trial
B Downgraded RCT or upgraded observational studies
C Well-done observational studies
D Case series or expert opinion

The renal toxicity of certain hydroxyethyl starch (HES) preparations has been demonstrated in septic patients. A randomized trial comparing 6% HES (200/0.6–0.66) with 3% fluid-modified gelatin in severe sepsis or septic shock found HES to be an independent risk factor for acute renal failure.[22] The VISEP trial compared 10% pentastarch (HES 200/0.5) with Ringer's lactate and found significantly higher rates of acute renal failure in the HES group, with a trend toward higher 90-day mortality.[23] However, a study in non-pregnant patients without sepsis showed that 6% HES accompanied by approximately twice its volume of crystalloid improved renal function compared with gelatin.[24]

The incidence of allergic reactions is greatest with gelatins and dextran, followed by HES, and least with albumin.[25]

While the optimal fluid therapy for septic patients is undecided, crystalloid overload is known to be harmful.[26,27] Albumin is a scarce resource, very expensive, has the potential to transmit viral disease and may not be as physiologically beneficial as low molecular weight starch.[28] Gelatin colloids have a short duration of effect and a higher risk of allergic reaction. Starches have a long duration of effect and intermediate molecular weight–low substitution starch persists in the intravascular compartment in septic patients.[29] High molecular weight–high substitution starches should be avoided.

The 'SSC' recommends fluid resuscitation with either natural/artificial colloids or crystalloids (grade 1B) and supports the role of fluid challenge, as opposed to fluid administration at replacement rates.[15] Overall, a balanced approach that employs maintenance crystalloid therapy and goal-directed colloid administration currently represents best practice.

VASOPRESSIN

Vasopressin (antidiuretic hormone) has been used in septic shock as an adjunct to noradrenaline.[30,31] Vasopressin is elevated early in septic shock but falls with progression of shock.[32,33] However, a large randomized trial (Vasopressin

and Septic Shock Trial) demonstrated no benefit.[31] Patients with septic shock were randomized to receive vasopressin (0.01–0.03 U/minute) in addition to noradrenaline (at 5 μg/minute) or to continuation of noradrenaline at an increased dose (5–15 μg/minute). No significant differences in mortality, organ dysfunction or serious adverse events were found. This trial did not evaluate vasopressin in 'catecholamine-refractory' septic shock but rather investigated its role as a 'catecholamine-sparing drug'.[30,31] Pregnant patients were excluded.

The SSC recommends either noradrenaline or dopamine to correct hypotension in septic shock (grade 1C) and suggests that vasopressin may be added to noradrenaline. Adrenaline is recommended as the first alternative agent in septic shock poorly responsive to noradrenaline or dopamine (grade 2B).[15] Fetal monitoring is important when vasopressors are administered as there is a valid concern that uteroplacental blood flow may be reduced with these agents (although there are no studies in critically ill women). Even so, it is much more likely that restoring maternal haemodynamic stability will benefit not only the mother but also the fetus.

CORTICOSTEROIDS

The use of corticosteroids in sepsis is controversial. Short courses of high-dose steroids are neither beneficial nor harmful.[15,34,35] In contrast the administration of low, physiological doses (equivalent to 200–300 mg of hydrocortisone daily) for ≥5 days has been advocated in patients with septic shock,[34,35] based mainly on the results of a single study.[36] This randomized trial was conducted in vasopressor-unresponsive septic shock. It demonstrated a significant reduction in mortality, without increased adverse events in patients with relative adrenal insufficiency given low-dose hydrocortisone and fludrocortisone for seven days.[36]

In contrast, the more recent CORTICUS trial did not demonstrate a mortality benefit from steroid therapy in septic shock.[37] Hydrocortisone by an intravenous bolus for five days, and then tapered over six days, did not improve survival or reverse shock. It did hasten the rate of reversal of shock in some patients, but adverse events (e.g. superinfections and hyperglycaemia) were more frequent. Thus, hydrocortisone cannot be recommended for vasopressor-responsive septic shock. It may have a role in the early treatment of patients unresponsive to vasopressors. The SSC recommendations for corticosteroids were changed in 2008,[15] suggesting that intravenous hydrocortisone be reserved for adult patients with septic shock in whom the blood pressure responded poorly to fluid resuscitation and vasopressors (grade 2C). Up to 300 mg of hydrocortisone daily is recommended (grade 1A) but, again, pregnancy was an exclusion criterion in both relevant trials.[36,37]

GLUCOSE REGULATION

The optimal blood glucose target in critically ill patients remains unclear. Trials of intensive insulin therapy have reported inconsistent effects on mortality and increased rates of severe hypoglycaemia.[38,39] One randomized trial involving predominantly cardiac surgical patients in ICU demonstrated reduced mortality and morbidity with tight glucose control.[40] These findings led to recommendations that intensive glucose control be incorporated into guidelines. However, this is now controversial, because further large randomized trials in medical and ICU settings failed to replicate a mortality benefit.[23,38,39,41,42] Indeed, the large NICE-SUGAR study reported that intensive glucose control increased mortality among adults in ICU.[43] Even so, it is possible that intensive glucose control may benefit some patients.[39,43]

The current SSC guidelines, published prior to the NICE-SUGAR trial, recommend that patients with severe sepsis and hyperglycaemia, admitted to ICU, receive intravenous insulin therapy to maintain blood glucose below 8.3 mmol/L (grade 1B).[15] The impact of intensive glucose control in critically ill pregnant patients has not been determined.[16] Based on evidence in non-pregnant ICU patients, it appears reasonable to use insulin therapy, if needed, to maintain blood glucose below 8.0 mmol/L in septic pregnant patients. Close monitoring is essential in order to detect and treat hypoglycaemia.

RECOMBINANT HUMAN APC

APC is an endogenous serine protease with antithrombotic, profibrinolytic and anti-inflammatory properties and modulates coagulation and inflammation in sepsis.[44] Individuals vary markedly in their ability to convert endogenous inactive protein C to APC.[6] Treatment with recombinant human APC (rhAPC)/drotrecogin alfa (activated) reduces mortality in adult patients with severe sepsis.[45]

Evidence supporting rhAPC comes from two multicentre, randomized controlled trials. The PROWESS study demonstrated a significant reduction in 28-day mortality in adults with severe sepsis (30.8% after placebo versus 24.7% after rhAPC, a 19% relative risk reduction).[45] Subgroup analyses led to approval of the use of rhAPC for patients at a high risk of death (APACHE II score ≥25 or multi-organ failure).[46] The ADDRESS trial evaluated rhAPC in adults with severe sepsis and a low risk of death (APACHE II score <25 or single-organ failure). It demonstrated no significant difference in 28-day mortality.[46] The ENHANCE trial, a single-arm, open-label trial of rhAPC in severe sepsis, supported the favourable benefit/risk ratio observed in PROWESS and suggested that early initiation of therapy was associated with better outcomes.[47]

The SSC suggests that, provided there are no contraindications, rhAPC is indicated for adult patients with sepsis-induced organ dysfunction and a clinical assessment of a high risk of death (grade 2B), but not for those with a low risk of death (grade 1A).[15]

No trials have investigated the efficacy and safety of rhAPC in pregnancy. Pregnant patients were excluded in both the PROWESS and ENHANCE trials. Limited data suggest that pregnancy is a state of acquired resistance to APC,[48] which may reduce the efficacy of rhAPC administered to the pregnant septic patient. Serious bleeding is a major adverse effect of rhAPC.[45,46] This is of concern during pregnancy and the early puerperium because of the risks of obstetric haemorrhage, making rhAPC relatively contraindicated near delivery.[11] The risk of teratogenicity has been raised but placental transfer of APC appears unlikely given its molecular weight of 56 kDa, which is too large for passive diffusion.[48]

There are few case reports but successful outcomes for both mother and baby after rhAPC have been reported in at least two cases of severe sepsis with a high risk of death. One case occurred at 18 weeks and a healthy baby was delivered at 39 weeks gestation; in the other, treatment was given at three weeks gestation and pregnancy was confirmed at five weeks gestation. Successful use of rhAPC has also been reported in the puerperium.[49–51]

FETAL CONSIDERATIONS IN THE MANAGEMENT OF SEPSIS IN PREGNANCY

The welfare of the fetus looms large in the consideration of management of sepsis in pregnancy. Of course fetal outcome is intimately dependent on maternal outcome, and in general whatever is beneficial for the mother is almost certain to benefit the baby. All the therapeutic modalities detailed above are regarded as potentially applicable in pregnancy.

In the general ICU, many staff members are unfamiliar with the management and special requirements of pregnancy. It is advisable that obstetricians, midwives, obstetric anaesthetists and obstetric physicians attend frequently and assist with decisions, particularly in regard to the assessment of fetal welfare and appropriate methods of fetal monitoring. Routine care in the delivery suite, such as using a wedge to avoid supine hypotension (by aortocaval compression) and fetal bradycardia, may be overlooked in a general ICU.

The family of the patient should be kept aware of the status of the fetus at all times. In antenatal patients, endpoints for delivery should be predetermined in order to deal with deterioration expeditiously.

The SSC provides practice guidelines for the management of patients with severe infections. While the various components of EGDT have not been adequately studied in pregnancy, at the time of writing there is no reason to withhold the elements of this rational approach when managing pregnant women with severe sepsis.

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