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Journal of Gynecology & Obstetrics

Research Article | Open Access

Sepsis in Pregnant and Puerperal Women Living in High Income Countries: an Update for Clinicians

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Received: 11 November 2017; **Accepted:** 13 December 2017; **Published:** 20 December 2017

Abstract

Background: Maternal sepsis has been defined by a World Health Organization (WHO) technical working group as a "life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period". This condition is due to a systemic and deregulated host response to infection, which results in damage to organs or tissues that can worsen in severe sepsis and septic shock. Therefore, it has to be considered a syndrome rather than a disease.

Aim of the study: Draw up a paper concerning the overall maternal sepsis clinical management from the causal agents and risk factors, to the diagnosis, treatment and prevention in order to give support to physicians who have to face up this complex syndrome.

Materials and Methods: We reviewed PubMED from March to August 2017 searching "pregnancy", "pregnant", "gestation", "puerperium" "sepsis", "maternal sepsis", "mortality" and "pregnancy outcome." We focused only on pregnant women and after childbearing, so excluding the terms "foetus", "infant", "new-born", "children", "vertical transmission"; in addition, the reference lists of the selected articles had been examined for further relevant resources. The information was extracted only from articles published in English language.

Results: The incidence of maternal sepsis has increased in the last years due to the growing number of pregnant women aged > 35 years or having co-morbidities, being both conditions that increase risk. The most common organisms identified include *Lancefield group A beta-haemolyticus Streptococcus, Escherichia coli, Staphylococcus aureus* and anaerobes; mixed infection with Gram positive and Gram negative are possible. In high income countries the most common risk factors are: obesity, impaired immunity/immunosuppressant medication, anemia, vaginal discharge, history of pelvic infection, history of group B streptococcal infection, amniocentesis and other invasive procedures, cervical cerclage, prolonged spontaneous rupture of membranes, GAS (*Group A Streptococcus pyogenes*) infection in close contact/family members, black or other minority ethnic group origin, failure to recognize severity. Suggestive signs of sepsis include: pyrexia, hypothermia, tachycardia, tachypnea, hypoxia, hypotension, oliguria, impaired consciousness, failure to therapy; nevertheless these signs may be absent and not necessary correlate with the severity of sepsis. Once developed, maternal sepsis may progress more quickly during pregnancy or puerperium than in the not pregnant state. When sepsis is suspected, the priority is to restore perfusion by initiating fluid infusion and treat the underlying infection by giving antibiotics: intravenous broad spectrum antibiotics is recommended within one hour of suspicion of severe sepsis. Definitive therapy has to be prompt on the basis of the bacterial cultural isolation. The best way to reduce the chances of encountering sepsis during pregnancy is to prevent infections.

Conclusion: Despite the under reporting trend, sepsis still remains a leading cause of preventable maternal death worldwide. Early diagnosis represents the key point to save mothers' and newborns' lives also in high income Countries, thus for a correct clinical management of maternal sepsis is essential own an accurate knowledge of its risk factors and causal pathways to be able to prevent and/or recognize immediately this life-threatening disease. Therefore a Maternal Sepsis Task Force, providing clear and simple recommendations -obtained by expert consensus after thorough review of the available literature- assisting healthcare providers in their clinical decision making, is strongly required.

Keywords: Sepsis; Risk factors; Bacterial infections diagnosis; Management; Prevention; Pregnancy; Puerperium

Introduction

Since 1950th, several "physiological" changes in the maternal immune system have been showed to lead to a state of immunosuppression during pregnancy during the pregnancy that, joined to an increased production of sex hormones and immune suppressive cytokines, may affects the response to most infectious agents [1-6]. This condition of immunosuppression during pregnancy does result in an increased immunoglobulin production, a decreased T-cell mediated response (due to a shift in the Th1/Th2 balance toward the Th2 response), and an expansion of regulatory T-cells in pregnant women [2,4,6].

In this context, the production of prostaglandin E2 (PG-E2) and specific interleukins (IL), like IL-4 and IL-10, plays a central role [4-6]. In fact, the maternal immune system enhancesPG-E2, IL-4 and IL-10 production in response to the progressively fetus changes: it dampens the maternal immune responses against fetal tissues through suppression of maternal Th1 immune response, down-regulation of lymphocyte and neutrophil activity, inhibition of production of Th1 cytokines (IL-12 and IFN gamma) and enhancement of production of Th2 cytokines (IL-5 and IL-10) [4-6].

These phenomena contribute to explain the not negligible risk of developing severe infections leading to a sepsis during the pregnancy and mainly during the puerperium, namely the period between childbirth and 42 days (6 weeks) after childbirth.

Since a trend of increased incidence of sepsis-related maternal mortality has been reported in the last years, proper prevention measures and early recognition, diagnosis and treatment are still needed to decrease its incidence.

For this reason, we have focused on the impact of maternal/puerperal sepsis in high income Countries, in order to update the knowledge regarding the diagnostic and therapeutic approaches for clinicians.

What is the Maternal / Puerperal Sepsis?

Differently from infection, defined as inflammatory response to microorganism, or bacteremia, defined as the presence of bacteria in blood, sepsis may be defined as a life-threatening multi-organ dysfunction caused by a systemic, dysregulated host response to infection, which results in damage to organs or tissues [7]. Following the recognition of bacterial cell wall components and its products (exotoxins and endotoxins), the immune system, triggered by bacteria, initiates a cascade of events including the release of pro-inflammatory

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mediators and cytokines, the recruiting of additional inflammatory cells and the activation of complement. This leads to cellular injury with ischemia, mithocondrial dysfunction, apoptosis, immune suppression, Multi Organ Failure (MOF) and death [8].

Therefore, sepsis has to be considered a syndrome rather than a disease, raised from systemic inflammatory response syndrome (SIRS) to several insults, not limited to infectious agents. It can worsen in *severe sepsis* (sepsis associated with MOF) and *septic shock* (sepsis with hypotension despite adequate fluid replacement therapy, along with perfusion abnormalities).

In the past the terms of maternal sepsis, genital tract sepsis, puerperal fever, puerperal sepsis and puerperal infection had been often used as synonymous in the literature. In order to overcome all the previous definition, a World Health Organization (WHO) technical working group has adopted only the term of *maternal sepsis* indicating a "life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period" [9,10]. The maternal sepsis has to be distinguished by the puerperal infection, defined as any infection occurring during the puerperium that involves the genital and urinary tract, breasts and respiratory system and infections such as HIV, tuberculosis, and H1N1 influenza virus, without septic evolution [9,10].

What is the Burden of Maternal Sepsis in the High Income Countries?

Sepsis can cause several problems for the maternal health, including death in more severe cases and long- term consequences such as pulmonary edema, acute renal or liver failure, myocardial ischaemia, cerebral ischemia, disseminated intravascular coagulation (DIC), infertility, ectopic pregnancy and chronic pelvic pain; in addition can hamper maternal infant bonding, hindering breastfeeding [9,10]. Lastly, it generates health care costs and increases the likelihood of admission of pregnant women to the intensive care unit (ICU) or readmission to hospital, after the delivery [9,10].

The incidence of maternal severe sepsis has increased in the last years due to the growing number of pregnant women aged > 35 years or having co-morbidities respect to the past. Once developed, the sepsis may progress more quickly during pregnancy or puerperium than in the not pregnant state [11].

Maternal sepsis still represents a major health problem, occurring over 5,000,000 cases per year in the world [12], and one of the main cause of maternal mortality worldwide, with about 75,000 deaths per year [12-14]. In high income Countries, the prevalence of maternal sepsis is lower than in middle or low income Countries: the incidence rate is about 0.1-0.6 cases per 1,000 deliveries and the death rate is up to 10% of all causes of maternal death, but an alarming increase of maternal mortality has recently been recorded in the United States and in the United Kingdom [15].

In the United States the maternal mortality rate due to sepsis is still higher respect to European Countries and accounts for approximately 7.5 cases per 100,000 live births each year [16]. Persistent racial disparities have been observed in pregnancy-related mortality; in fact the mortality rate is 3 to 4 times higher for black women than white ones women [17] and nearly half of the deaths from sepsis had been reported in African - American women and women of other ethnic minorities.

In the United Kingdom, whereas the improvements in healthcare have led to a massive reduction in many causes of direct maternal deaths such as those related to hypertension, thromboembolic disease and hemorrhage, sepsis remains the main cause of direct maternal death. An increase of 25% of numbers of deaths from sepsis has been reported in the last decade, passing from 0.85 deaths per 100,000 maternities in 2003–2005 to 1.13 deaths in 2006–2008 [18].

In nine European Countries, the maternal mortality rates widely range: the mean rate was0.8 per 1,000 deliveries, with incidences varying between 0.0 in Austria (no case in 6,022 deliveries) to 4.0 in Norway (12 cases in 3,010 deliveries) [18].

A recent study from the Netherlands showed a maternal mortality ratio from sepsis of 0.73 per 100,000 live births, while the rate of Serious Acute Maternal Morbidity (SAMM) from sepsis during a 2-year period had been 21 per 100, 000 deliveries [19]. Moreover, 8% of all obstetric ICU admissions in the Netherlands has been due to sepsis [13].

In Italy, where the maternal mortality rates is 0,3 x 1000 deliveries [20], sepsis represents the third cause of *direct maternal death* (6%) defined as death due to obstetrician complications in pregnancy, delivery and puerperium for interventions, negligence or poor treatment, and cause at least 2.5% of *indirect maternal death* defined as death due to pre-existing diseases arisen during pregnancy or worsened by pregnancy or to infection like meningitis or HIV, and cause 3% of *obstetrical near miss* , defined by WHO as cases in which a woman should die but survived to complications raised during pregnancy, delivery or within 42 days from the end of pregnancy thanks to medical assistance and the "good fortune" [21].

As previously indicated, most maternal deaths occurred immediately after childbirth, during the post-partum period.

What are the Causal Agents?

The most common organisms identified include Lancefield group A *beta-haemolyticus Streptococcus*, *Escherichia coli*, *Staphylococcus aureus* and anaerobes (Table 1); mixed infection with Gram positive and Gram negative are possible, especially in women with chorioamnionitis.

Group A Streptococcus pyogenes (GAS) infections are very common in pregnancy because of breaches of mucosal barriers, alterations of vaginal pH and decreased cellular immunity. Since GAS is hypervirulent and may produce pyrogenic exotoxins, the consequence is a toxic shock syndrome. The natural reservoir of GAS is the human rhino-pharynx and it can be transmitted by aerosolized droplet; then GAS metastasizes through bacteremia and can cross intact membranes such as the genital tract ones. On the basis of antigenic differences in the M protein, an important virulence factor that confers anti-phagocytic properties, GAS can be classified in several strains [22]: GAS strain M28 is predominant in women with genital tract sepsis, while the strain M21 is most common in GAS pharyngitis. Whereas there is an association between M28 and maternal sepsis, M21 appears to be more strongly associated with maternal mortality [23]. During puerperium, the burden of GAS infection increases up to 50% and may cause a severe fulminant infection within 24–48 hours of delivery, abortion, or rupture of membranes. This is due to a specific bacterial antigens such as streptococcal pyogenic exotoxin A (SpeA), streptococcal pyrogenic exotoxin C SpeC, responsible of an excessive release of immunomodulators resulting in a severe and rapid onset of sepsis. Pregnancy is associated with a modulated immune state that may alter macrophage response to GAS infections, leading pregnant and postpartum women 20-fold more vulnerable to develop GAS infection

Table 1: Bacterial causes of puerperal sepsis.

Microrganism	Rate of isolation (%)
Group A streptococcus (Streptococcus pyogenes)	>50
Escherichia coli	20-30
Straphylococcusaureus	10-15
Clostridium spp. and other anaerobes	2-5
Streptococcus pneumoniae	2-5
Pseudomonas spp.	2-10
Klebsiella spp.	2-5
Acinetobacter spp.	2-5

compared to no pregnant women [24]. Since nearly 30%of the general population carried GAS, the transmission may easily occur by contact with others, especially children, through respiratory spread or skin-to-skin contact, including by the health workers, that handle puerperal women without gloves. Some women infect themselves after delivery, presumably through the contamination of the perineum or through bacterial travel in the bloodstream from distal organ sites GAS carried by [25]. Several factors could contribute to the increase in puerperal deaths related to GAS infection, including the natural fluctuations in the year-to-year rates of GAS infections, the predominance of hypervirulent GAS strains, or the increased susceptible at-risk pregnant population [26].

Other pathogens associated with maternal deaths include *Escherichia coli,* typically responsible of urinary sepsis, premature rupture of membranes (PROM) and cerclage, *Staphylococcus aureus* and anaerobes, more common following caesarean section. Placental separation may be the trigger in some cases the bacteraemia, especially when the labor has been prolonged. Herbert et al. evidenced that the incidence of wound infection and puerperal fever occurs more frequently in women who undergo labor before cesarean birth compared to women who undergo cesarean in the absence of labor [27].

Bacteraemia due to other organisms such as *group B streptococcus*, *Mycoplasma hominis*, *Ureaplasma* spp, and *Chlamydia* spp., that cause endometritis, may present as fever without the features of severe sepsis.

What are the Risk Factors?

Several obstetric causes and maternal comorbidity may favour the onset of maternal sepsis, as listed in Table 2. In high income countries the most common ones, as identified by the confidential enquiries into Maternal death, resulted to be: obesity, impaired immunity/immunosuppressant medication, anemia, vaginal discharge, history of pelvic infection, history of group B streptococcal infection, amniocentesis and other invasive procedures, cervical cerclage, prolonged spontaneous rupture of membranes, GAS infection in close contact/family members, black or other minority ethnic group origin, failure to recognize severity [11,22,28,29]. Differently, in low income countries, the risk factors are represented by poverty, unhygienic birth conditions, lack of skilled birth assistants, long distance to healthcare facility, unavailable medical supplies, young age, primiparity, anaemia, HIV, TB, malaria and, as for the high income ones, failure to recognize the severity of sepsis [22].

Obesity is an important and often underestimated risk factor, since itself has been shown to have substantial effects on immune surveillance and violates the well-balanced system of adipocytes and immune cells, with subsequent disturbance to the immune surveillance system. This leads to dysregulated immune response, impaired chemotaxis and altered macrophage differentiation [28,29].

The delivery procedures which have been linked to puerperal sepsis include caesarean section, retained products of conception, prolonged rupture of membranes, multiple gestation, cervical cerclage, amniocentesis or other invasive procedure, vaginal trauma during birth, wound haematoma, primaparity, multiple vaginal examinations and delivery outside health facilities. These factors may vary related to the geographical area [11].

Cesarean section is considered the main risk factor associated of puerperal sepsis, especially when the handling of tissue or instrumental proceeding occurs in absence of aseptical conditions.

Yokoe et al. found that the surgical site infections account for 3.4% of all post-cesarean infections respect to 0.3% of infections in the women who gave birth vaginally. These data were confirmed by Hebert et al. on a cohort of 33,251 pregnant women who gave birth through the Tennessee Medicaid program in 1991: the infection rate was 4-foldincreased in women who had a cesarean birth (7,9%) compared to women who gave birth vaginally (1,8%). In addition, the incidence of wound infection and puerperal fever were more frequent in women who undergo labor before cesarean birth compared to women who undergo cesarean in the absence of labor.

Also episiotomy, perineal laceration, endometritis, chorioamnionitis, and retained products of conception, invasive procedures such as amniocentesis, cervical cerclage, or fetal surgery may enhance the risk for infection. The risk of developing postoperative endometritis and puerperal sepsis is higher in primiparous women because they are likely prone to complications as anemia, to prolonged obstructed labor and more likely undergo to instrumental delivery and multiple vaginal examinations, that especially in not aseptic condition, predispose ascent of the genital tract by both endogenous and exogenous organisms [18]. Because the rupture of the fetal membranes removes a natural barrier to ascending bacterial infection, the risk of maternal sepsis increases with the duration of the latent period in patients with prolonged rupture of fetal membranes.

What Signs Can Make the Diagnosis Suspected?

In no pregnant adult, the clinical criteria correlating with sepsis relies on the presence of at least two signs as systolic blood pressure of ≤100 mmHg, respiratory rate ≥ 22/min and altered mental status, constituting the Sequential Organ Failure Assessment (SOFA) score [7]. Unfortunately, these criteria cannot be translated and applied during the pregnancy because of multiple physiologic changes, listed in Table 3, occur during the ante-partum and post-partum period that may alter some parameters such as body temperature, heart rate, respiratory

Table 2: Common obstetrical and patient's risk factors for puerperal sepsis.

Obstetric factors	Patient factors
Caesarean section	Obesity
Retained products of conception	Impaired immunity/immunosuppressant therapy
Prolonged rupture of membranes	Anaemia
Multiple gestation	Impaired glucose tolerance
Cervical cerclage	Vaginal discharge
Amniocentesis or other invasive procedure	History of pelvic infection
Vaginal trauma during birth	History of group B streptococcal infection
Wound haematoma	Group A streptococcal infection in close contact
Primipara	Age >35 years
multiple vaginal examinations and delivery outside health facilities	Poor socioeconomic background and/or ethnic minority Group
	Congestive heart failure
	Chronic renal failure
	Chronic liver failure

rate, white blood count. In addition, the cardiopulmonary physiologic changes can contribute to an exaggerated septic response and can have deep effects on fetal and maternal viability [8].

In the maternal sepsis the signs and symptoms are usually nonspecific; they include fever of 38°C (100,4°F) or greater, although in advanced stages temperatures of 36.0°C (96,8°F) or less, with or without chills, may occur. Generalized body aches and malaise may be present therefore initial diagnosis could be misconstrued as a viral illness. Tachycardia (beats per minute > 120), tachypnea (respiratory rate>20/minute), hypotension (systolic pressure < 90 mmHg and or 40 mmHg below the baseline) are common findings and indicate life-threatening illness. The most common laboratory finding is a white cell count of greater than 15,000/microL or leucopenia in advanced sepsis (Table 4), however these findings are not always reliable because leukocytosis (even healthy pregnant women often have a white cell count above 12,000/microL and mild tachycardia are due to the physiological changes during pregnancy.

Since several infection of urinary tract or low respiratory tract may occur during pregnancy and puerperium, these infection have to be promptly diagnosed and treated to avoiding the evolution to sepsis. Pyelonephritis is one of the most common urinary infections during pregnancy, due to *Escherichia coli, Klebsiella, Proteus* and *Pseudomonas spp*. It often affects the right kidney because of the compression of the gravid uterus and for unclear reasons, and may lead to acute respiratory distress syndrome (ARDS). During pregnancy pyelonephritis in promoted by hydronephrosis, urinary reflux and high levels of progesterone [8]. A sepsis starting from the genital tract may present with severe abdominal pain and unrelieved tenderness.

Another important although not very common infection in pregnancy is bacterial pneumonia, caused by the same microorganism found in the no pregnant patient (*Klebsiella pneumoniae, Haemophilus influenzae*). It is often misdiagnosed and is a major cause of maternal and fetal mortality.

GAS infection is more devious in this setting of patients, presenting also with confusing symptoms like nausea, vomiting and diarrhea; in some cases it can determine necrotizing fasciitis (because of tissue necrosis), watery vaginal discharge, generalized maculopapular rash or purpura fulminans, conjunctival effusion and maternal death. Despite the use of penicillin and antiseptic practice, these infection re-emerged since 1980. Clinical manifestations of GAS infections are abdominal pain, fever and tachypnea; hypotension leads to fulminant streptococcal toxic shock syndrome. Laboratory findings are leukocytosis with immature white blood cells; abdominal ultrasound, blood and urine cultures may help in making diagnosis.

The development of maternal sepsis is usually associated to the presence of endometritis and perineal or abdominal wound infection. Approximately 1% to 4% of women with endometritis after cesarean delivery may have serious complications such as abscess, hematoma, necrotizing fasciitis, and septic pelvic thrombophlebitis. Puerperal wound infection is usually suspected when the woman complain of additional discomfort and pain at the wound site.

How to Confirm the Suspect?

Some investigators have attempted to define a different set of parameters for pregnant and puerperal women which may be useful in identifying a state of SIRS. A set of adjusted SIRS criteria was firstly described by Waterstone (2001) and Acosta (2014) who identified a maternal heart rate of 100 beats per minute (versus 90 beats/min in non pregnant women) and white blood cell counts greater than 20.000/microL(versus 12000 cells/microL in no pregnant women) [22]. Thereafter, sepsis screening tools based on Modified Early Obstetric Warning System (MEOWS) [23] have been developed (Figure 1) and

Table 3: Physiologic changes occurring during the pregnancy.

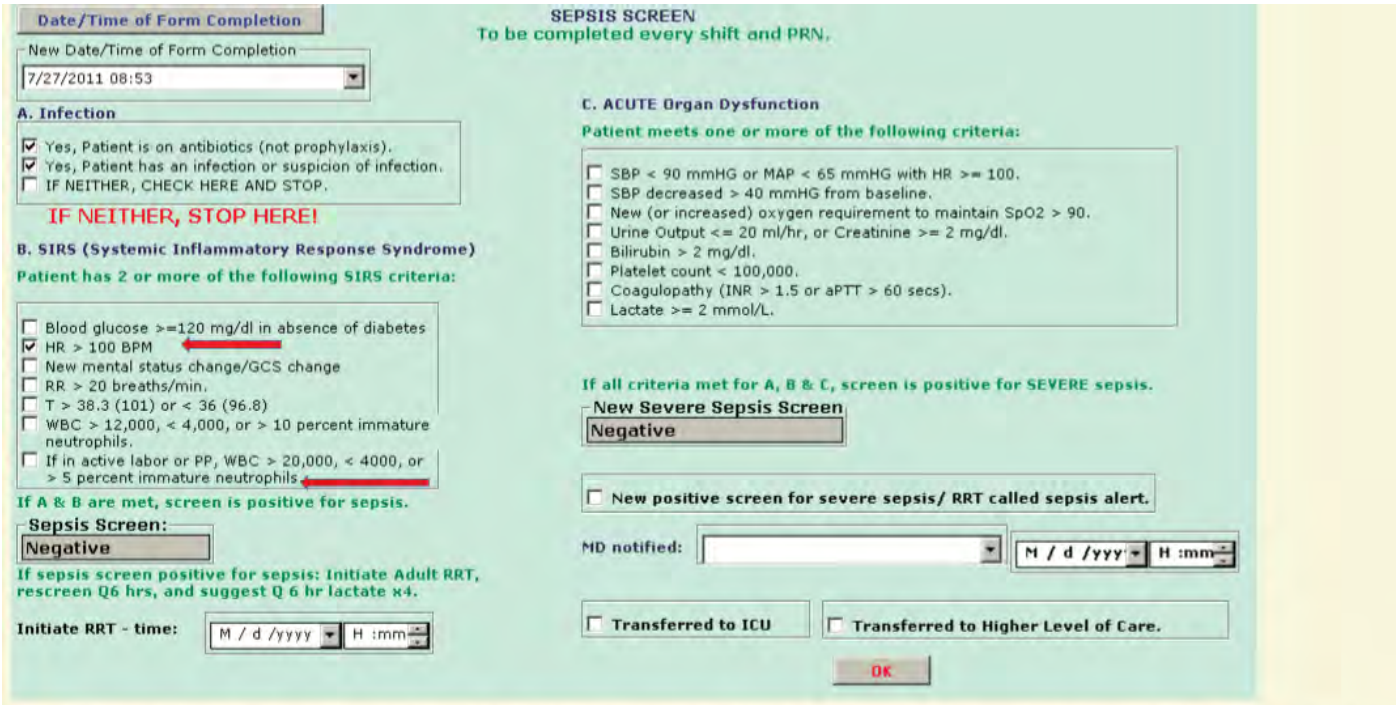
Where	What
Immune system	Downregulation of cell mediated immunity: reduction of CD4/CD8 ratio → decrease T-cell activity → protect the immunologically distinct foetus from maternal inflammatory response
Cardiovascular System	• increase in maternal blood volume → expansion of plasma decrease of hemoglobin ("anemia of pregnancy") • increase of Cardiac output and stroke volume → increase of heart rate→decrease in systemic vascular resistance
Ematologic system	Thrombocytopenia (confused with or accentuated by sepsis)Pregnancy is a procoagulant state, with risk of thromboses.Decreases in fibrinolytic activity maybe further compromised by sepsis.
Positional changes of the mother	modify venous return with obstruction of the vena cava by the gravid uterus → Lateral decubitus or sitting posture improves venous return and hemodynamic parameters
Serum proteins	decline during pregnancy with a modest decrease of colloid osmotic pressure (COP)
Respiratory system	respiratory rate remains unchanged BUT increase in respiratory depth -tidal volume and minute ventilation- by progesterone's stimulation of central respiratory center → modest respiratory alkalosis →compensatory metabolic acidosis (compensation is difficult in presence of sepsis)
Renal system	Renal blood flow is augmented during pregnancy BUT in this stressful period renal perfusion may be preferentially compromised with risk of acute renal injury

Table 4: Clinical and laboratory signs of puerperal sepsis.

Clinical signs of severe peripartum sepsis	Laboratory panel of severe sepsis
Pyrexia or hypothermia	Leucopenia or leukocytosis
Tachycardia	Raised C-reactive protein
Tachypnoea	Raised lactate/low pH
Diarrhoea	Thrombocytopenia
Pain (variable degree, opiate required)	Coagulopathy
Vaginal discharge/abnormal lochia	
Blanching erythema (toxic shock)	
delay in the rate of reduction of the size of the uterus (<2 cm/day during the first 8 days).	

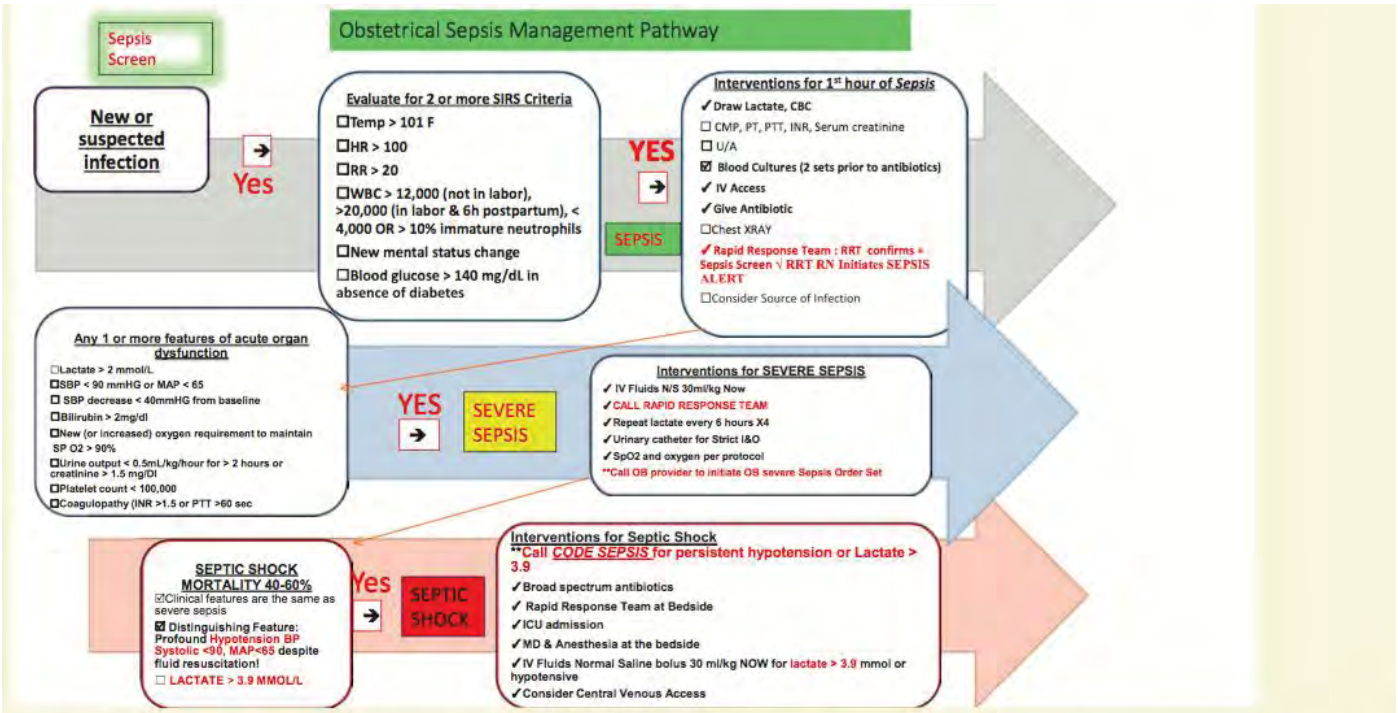
are now available for obstetricians along with quick reference guides (Figure 2) [23].

Also the Royal College of Obstetricians and Gynecologists has identified the clinical features suggestive of sepsis in pregnant or puerperal women in order to create a specific guidelines for diagnosis of sepsis in obstetric patients (Table 5).



aPTT = activated partial thromboplastin time; GCS = Glascow Coma Scale; HR = heart rate; ICU = intensive care unit; INR = international normalized ratio; MAP = mean arterial pressure; PP = postpartum; RR = respiratory rate; RRT = rapid response team (nurse); SBP = systolic blood pressure; SpO2 = oxygen saturation; T = temperature; WBC = white blood cell count.

Figure 1: Sepsis Screening Tool [23].



BP = blood pressure; CBC = complete blood count; CMP = comprehensive metabolic panel; h = hours; HR = heart rate; I&O = intake and output; ICU = intensive care unit; INR =international normalized ratio; IV = intravenous; MAP = mean arterial pressure; MD = physician; OB = obstetric; PT = prothrombin time; PTT = partial prothrombin time; RN = registered nurse; RR = respiratory rate; RRT = rapid response team (nurse); SP or SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; temp = temperature; U/A = urinalysis; WBC = white blood cell count.

Figure 2: Quick reference guide for sepsis screening tool [23].

Suggestive signs of sepsis include one or more of the following: pyrexia, hypothermia, tachycardia, tachypnea, hypoxia, hypotension, oliguria, impaired consciousness, failure to therapy. Nevertheless, these signs may be absent and not necessary correlate with the severity of sepsis.

The presence of fever and at least 2 of the following signs and symptoms as pelvic pain, unusual or foul smelling vaginal discharge or lochia, and uterine sub-involution associated with a laboratory panel are clinical feature suggestive for infection. Since the common causes of postpartum fever include endometritis and wound infections, differential diagnosis should include other infective conditions, such as urinary tract infection, pneumonia, mastitis, viral syndrome, TBC reactivation or not infectious diseases as septic pelvic thrombophlebitis or dehydratation. Less frequently appendicitis or diverticulitis can be involved in the genesis of postpartum fever.

When sepsis is suspected, is necessary to check its origin; any samples (i.e., blood, throat and high vaginal swabs, mild-stream urine) must be collected guided by clinical suspicion of the focus of infection as long as fast screening on the basis of patients' anamnesis [11].

The samples should be collected prior of antibiotic administration, because the antimicrobial therapy may mask the etiology of sepsis; but at the same time, all the diagnostic procedures must never delay the treatment, that should be started without waiting for microbiology results.

Lactate level is the most widely used biomarker used indicating organ dysfunction but it can be falsely elevated in laboring women (increased work of the skeletal muscles in labor). In most cases, the diagnosis of puerperal sepsis mainly based on clinical features compatible with the presence of infection and the growth of bacteria from the genital tract.

Table 5: Royal College of Obstetricians and Gynaecologists guidelines on diagnosis of sepsis in obstetric patients [11].

Diagnosis of sepsis in obstetric patients
Fever or rigours
Diarrhoea or vomiting
Rash
Abdominal/pelvic pain and tenderness
Offensive vaginal discharge
Productive cough
Urinary symptoms
Breast engorgement/redness
Wound infection
Delay in uterine involution, heavy lochia
General, non-specific signs such as lethargy, reduced appetite

How to Manage the Sepsis?

There are no specific guidelines for the management of sepsis in the pregnant/puerperal women: at the same time, since the early recognition of sepsis is associated with improved mortality and outcome, any delay may occur and determine maternal/fetal morbidity and mortality.

Thus, assessing factors associated with severe morbidity (SAMM or "near miss pregnant women") has become a valuable method for developing intervention strategies "upstream" of a sentinel event.

Early goal directed therapy (EGDT) is aimed to restore perfusion and tissue oxygenation. EGDT has become a widely accepted standard of care in the treatment of sepsis in pregnancy but is necessary to remind that some of the target values are different in pregnancy. Sepsis resuscitation bundle [13], summarized in Table 6, are interventions derived from Evidence Based Medicine guidelines introduced by Surviving Sepsis Campaign, an international initiative to reduce mortality by sepsis [22].

Once sepsis is suspected, the priority is to restore perfusion by initiating fluid infusion and treat the underlying infection by giving antibiotics. As regards fluid infusion, it is mandatory to use physiologic salt solutions or lactated Ringer solution in bolus of approximately 30 mL/kg and albumin apart from synthetic colloidal solutions not recommended: if perfusion is not restored, vasoactive agents (such as norepinephrine, epinephrine and vasopressin) and blood products (such as plasma) can be used; dopamine should be considered in case of bradycardia, dobutamine for an increase of cardiac output and corticosteroids for refractory septic shock [8].

Intravenous broad spectrum antibiotics is recommended within one hour of suspicion of severe sepsis: this is lifesaving, according to Surviving Sepsis Campaign. As for the antimicrobial choices, it should be stressed that co-amoxi/clavulanate does not cover *MRSA* or *Pseudomonas spp* and probably increase the risk of necrotizing enterocolitis in newborns exposed to in utero; metronidazole does not cover aerobes, cefurotaxime is associated with *Clostridium difficile* infection; clindamycin covers most streptococci and staphylococci (including *MRSA*) and switches off exotossin production, decreasing mortality; piperacillin-tazobactam covers all microbes apart from *MRSA* and is renal sparing in contrast to amynoglicosides (for example gentamicin) [9].

Empirical and Aetiologic Therapy: flowchart

1) Prompt cultures;
2) Do not delay therapy while awaiting cultures (survival differences seen in delay of antibiotic therapy of only 1 h);

Table 6: Sepsis resuscitation boundle (adapted from Van Dillen et al. [13]).

Accomplished as soon as possible and scored over first **6 hours**	Measure serum lactate
	Obtain blood colture prior to antibiotic administration
	Administer broad spectrum antibiotics a) within 3 h for emergency dpt admissions; b) within 1 h for non emergency admissions
	In case of hypotension or lactate > 4 mmol/l (36mg/dl): a) deliver an initial minimum of 20 ml/kf of crystalloid b) apply vasopressor to mantain MAP > 64 mmHg
	In case of septic shock: a) achieve CVP of > 8 mmHg b) achieve $ScvO_2$ >70%
Accomplished as soon as possible and scored over first **24 hours**	Low dose steroid for septic shock
	Drotrecoginalfa (activated)
	Mantain glucose control higher than lower (but ≤ 150 mg/dl)
	Mantain inspiratory plateau pressure at less than 30 cmH_2O for mechanically ventilated patients.

MAP: mean arterial pressure; CVP: central venous pressure; $ScvO_2$ central venous oxygen saturation

3) Prompt empiric antibiotic therapy using those commonly used broad-spectrum antibiotic regimes (it is also advisable to consider local hospital antibiograms for antibiotic therapy in response to local resistance patterns) (Table 7)

The use of tetracycline, sulfonamide, aminoglycoside (except in life threatening infection), chloramphenicol must be absolutely avoided during the pregnancy.

Since most infections in obstetric patients tend to be polymicrobial, any antimicrobial therapy chosen should provide a broad-spectrum coverage for Gram-positive, Gram-negative, and anaerobic bacteria.

Current antibiotic recommendation for coverage of *methicillin-resistant S. aureus* (MRSA) would include vancomycin (25mg/kg loading dose up to max 2g, then 15mg/kg q12h iv)

For patients with GAS infections that are not responding to antibiotic therapy, intravenous immunoglobulin has been advocated to improve bacterial clearance and neutralize circulating bacterial toxins

Antibiotic agents used in surgical prophylaxis (often cephalosporin) should be avoided when choosing an antimicrobial regimen for treatment of severe sepsis and septic shock because resistant organisms already may have been selected. In fact, cephalosporin will not provide adequate treatment for *Enterococcus spp* and *Listeria* infections.

4) Prompt definitive therapy on the basis of the bacterial cultural isolation

Women with diagnosis of sepsis should receive treatment with broad-spectrum antimicrobials which cover Gram-positive, Gram-negative, and anaerobic bacteria (Table 8). The origin of infection should be eradicated and may include surgical removal of necrotic tissue.

Apart from antibiotics, even intravenous immunoglobulin (IVIG) can also be used. IVIG has an immune modulatory role and neutralizes the exotoxin's superantigen effect and inhibits production of TNF and ILs in sepsis due to Gram positive. There is also little evidence of benefit in sepsis by Gram negative, endotoxin related. IVIG must not been prescribed in pregnant women affected by congenital deficiency of IgA [11].

Regarding the recommended fetus monitoring, is important to remind that changes in cardiotocography or decelerations must place reassessment of maternal MAP (mean arterial pressure), hypoxia and acidaemia. Preterm delivery must be anticipated only if it would be beneficial to the mother and/or the baby, recommending continuous electronic fetal monitoring in the presence of maternal pyrexia [11]. Finally, appropriate antibiotics prophylaxis must be considered for neonates whose mothers have been found to be affected with GAS infection in the peripartum [11].

Recovery should begin within 48 hours to 72 hours. If, despite an antimicrobial treatment, a clinical improvement does not occur, it is necessary to verify more carefully the presence of bacterial infection and its possible complications such as an abscess. The psoas muscle is the most common site of ascending infection because of its rich vascular supply and direct lymphatic drainage from the genital tract. Psoas abscess may present as pelvic pain, edema, and sepsis [30]. Sonography is the main imaging modality to diagnose pelvic collections, but CT or magnetic resonance imaging (MRI) may be helpful in equivocal cases because of their superior soft-tissue contrast. In this case, a surgical drainage is mandatory.

In the absence of a documented bacterial infection, diagnosis must be revaluated. Some alternatives options are represented by viral endometritis, secondary to herpes simplex virus or cytomegalovirus that should be treated with antiviral therapy, or septic pelvic thrombophlebitis supported by hypercoagulable state during puerperium. Signs and symptoms include unresolved fever despite antimicrobial treatment, continual flank and low pelvic pain that often radiates to the groin area, most commonly in the ovarian vein. On pelvic examination can be noted a rope-like structure present. Diagnosis is made by CT scan or MRI and is needed to add in therapy oral anticoagulants.

How to Prevent Maternal Sepsis?

The best way to reduce the chances of encountering sepsis during pregnancy is to prevent infections [13]. The first recommendation is to wash the hands after touching raw meat, raw eggs, or unwashed vegetables and preparing food or eating, gardening or touching dirt or soil, handling pets avoiding to touch or change dirty cat litter because dirty cat litter might contain a harmful parasite (*Toxoplasma gondii*). The same recommendation are useful after contact with sick people, caring for and playing with children and changing diapers [13] (Table 9).

It is important to avoid unpasteurized (raw) milk and foods made from it, such as soft cheeses (i.e, feta, brie, and queso fresco), unless their labels indicate the use of pasteurized milk, because unpasteurized products can contain bacteria (for example *Listeria*). Moreover, it is necessary to protect from sexually transmitted diseases.

In case of infection during pregnancy, is important to ask physician for *timely treatment to* prevent infection spreading to blood cells. People with *diabetes, cancer, and women in their early 30s* need to be *extra cautious about hygiene and infections* [13].

As regards peripartum, preoperative preparation and interventions with operative delivery can *reduce the likelihood of wound complications* and, therefore, *septic complications*. These include treating infections remote to the surgical site before elective surgery, showering with an antiseptic agent the night before surgery, abstaining from smoking (30

Table 7: Empirical Antibiotic therapy suitable in suspected maternal/puerperal sepsis [32,33].

Drug	Route of administration	Dosage
Community associated		
Co-amixiclav	intravenously	1.2 g tds (NB associated with NEC in certain groups, local decision to avoid where possible – discuss with microbiology if no alternative)
OR		
Cefuroxime	intravenously	1.5 g tds
PLUS		
Metronidazole	Intravenously	500 mg tds(NB probably safe in 2nd and third trimester, avoid high dose)
OR		
Gentamicin	intravenously	1.5 mg/kg, then 1 mg/kg every 8 h: consider once daily in severe sepsis (at dose of 5 mg/kg/die), where poor renal function precludes its use, step up to piperacillin/tzbmonotherapy
OR		
Clindamycin	intravenously	900 mg every 8 h
PLUS		
Gentamicin	intravenously	5 mg/kg/die

Table 8: Definitive antibiotic therapy suitable in maternal/puerperal sepsis [32,33].

Infection	Most likely organisms	Treatment	Comments
Urinary Tract Sepsis	Coliforms Enterococcus sp.	Parenteral Ceftriaxone: 1g 24 h iv or Piperacillin-tazobactam 4.5g q6-8h iv plus Gentamicin 5mg/kg iv (max 480mg q24h), depending on severity. In presence of risk factors for MDR. Piperacillin-tazobactam plus Gentamicin (doses above) Only if documented Hx of ESBL: Meropenem 1g tds iv.	Send urine sample in addition to blood culture. Previous culture results may help guide therapy. Seek advice on oral options and duration of therapy Seek daily review of Gentamicin. Gentamicin is rarely required for more than 7 days.
Intra-abdominal Sepsis	Coliforms	Piperacillin-tazobactam 4.5g q6-8h iv plus Gentamicin 5mg/kg iv (max 480mg q24h), depending on severity. In presence of risk factors for MDR: Piperacillin-tazobactam plus Gentamicin (doses above). Only if documented Hx of ESBL: Meropenem 1g tds iv. MUH / SIVUH*: Piperacillin-tazobactam 4.5g q8h iv plus Gentamicin 5mg/kg iv stat (max 500mg q24h), depending on severity.	If patient requires surgery, send specimen from theatre. See Vancomycin and Gentamicin dosing guidelines. Consider oral therapy when on clinical improvement, seek advice for options.Gentamicin dosing. Seek review of Gentamicin.
Bacterial Pneumonia	*Klebsiellapneumoniae, Haemophilusinfluenzae*	macrolide: erythromycin 250 mg PO every 6 hours for 10 days. plus B lactam es IV ampicillin 2 grams every 6 hours for complicated or severe pneumonia	
GAS infections	Group A Streptococcus	penicillin G 5 million units IV initial dose, then 2,5 – 3 million units every 4 hours until delivery (should be started > 4 hours before delivery) plus clindamycin 900 mg intravenously every 8 h or vancomycin 15 mg/kg intravenously and then dosing by pharmacyfor at least 14 days	

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Table 9: Situations at infectious risk for which a careful washing of hands is recommended to pregnant and puerperal women [13].

After:	*Notes*
Touching **raw meat, raw eggs or unwashed vegetables**	To stay away from **wild or pet rodents (**like a hamster or guinea pig**)** and their **droppings.** In particular *do not touch or change dirty cat litter*becausedirty cat litter might contain a harmful parasite (toxoplasma gondii). Some rodents might carry a harmful virus (lymphocytic choriomeningitis virus LCMV).
Gardening or touching dirt or soil	
Handling **pet**.	
Being around sick people	
Getting saliva (spit) on their own hands	
Caring for and playing with children	Their saliva and urine mightcontain cytomegalovirus (CMV)
Changing diapers	
Before *and* after preparing **food and eating**	

days) before surgery, glycemic control in diabetics, hair removal around the incision by electric clippers (not by razor), wide antiseptic skin prep before the operative procedure, and antimicrobial prophylaxis (Table 10).

A Cochrane systematic review on antibiotic prophylaxis for caesarean section showed that it reduces the incidence of endometritis by 66% to 75% of cases [31]. A single-dose with Gram-positive and Gram- negative bacterial coverage is indicated prescribing cefazolin or cefotetan intravenously (1–2 g), excepting if the patient is already receiving antibiotics for a separate infection. Antibiotic prophylaxis should be administered up to 60 minutes before skin incision and not at cord clamping as was previously commonly made. This antimicrobial timing has been associated with lower rates of surgical site infection and overall maternal infectious morbidities without an increase in adverse neonatal outcomes. Prophylactic antibiotics should be repeated after 4 hours in prolonged surgical cases or those associated with excessive blood loss.

Obese patients, who are at increased risk for surgical site infections also because of the decreased tissue antibiotic levels, should receive a higher dose of preoperative antibiotics; nevertheless the weight cutoff (80 kg, 100 kg, or body mass index [calculated as weight (kg)/[height (m)]^2] greater than 30) for the higher dose is still debated.

Table 10: Preoperative preparation and interventions aimed to reduce peripartum sepsis [13].

Treating infections remote to the surgical site before elective surgery
Showering with an antiseptic agent the night before surgery
Abstaining from smoking (30 days) before surgery
Glycemic control in diabetics
Hair removal around the incision by electric clippers (not by razor)
Wide antiseptic skin prep before the operative procedure, and antimicrobial prophylaxis
Surgical technique should eliminate dead space and minimize tissue trauma and electrocautery use.

Another important factor is to reduce number of cesarean delivery; in addition, minimize use of invasive procedures and decrease the number of vaginal examinations during labor management are simple practices that can effectively reduce the postpartum uterine infection. Therefore judicious hand washing by women and health care workers is mandatory to shrink the transmission of infections.

Lastly an important measure of prevention is to achieve a closer postpartum follow-up, adding a two-week postpartum visit besides 6–8 postpartum visit; this may decrease severity of complications. Finally the incidence of puerperal sepsis can be reduced by educating women about the need for antenatal care and supervised hospital delivery [13].

Conclusion

Despite the under reporting trend, sepsis still remains a leading cause of preventable maternal death worldwide. Understanding risk factors and causal pathways is necessary to avoid late diagnosis and to promote a correct management of this life-threatening disease, which represents the right key to saving mothers' and newborns' lives also in high income Countries.

Since maternal sepsis represents a complicated, infection based, multi organ condition, a collaborative approach involving gynecologist, obstetrician and infectious disease specialist is required; therefore a Maternal Sepsis Task Force has to be underlined and is strongly suggested in this paper. The main objective of this Task Force could be to provide clear and simple recommendations, assisting healthcare providers in their clinical decision making. The recommendations could be obtained by expert consensus after thorough review of the available literature. An evidence-based scoring system could be used, based on a classification of the strength of recommendations and the levels of evidence.

The Maternal Sepsis Task Force should:

1. Have meetings on a regular basis in order to discuss cases, take surgical decisions, and define the type of follow-up.
2. Choose the type, duration, and mode of follow up of antibiotic therapy, according to a standardized protocol, following the current guidelines.
3. Participate in national or international registries, publicly report the mortality and morbidity of their Centre, and be involved in a quality improvement program, as well as in a patient education program.
4. Organize the follow-up on an outpatient visit basis at a frequency depending on the patient's clinical status.

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Citation: Spera AM, Bianco V, Simeone D, et al. Sepsis in Pregnant and Puerperal Women Living in High Income Countries: an Update for Clinicians. J Gynec Obstet 2017; 1:023.

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