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Septic Shock in Obstetrics and Gynecology

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1. Introduction

Septic shock is a life-threatening clinical syndrome caused by decreased tissue perfusion and oxygen delivery, as a result of severe infection and sepsis. The insertion of bacteria or viruses into the blood stream produces a condition called bacteremia or viremia. Sepsis is the systemic inflammatory response due to bacteremia. When sepsis worsen to the point where blood pressure cannot be maintained with intravenous fluid alone, then the condition is called septic shock and may be accompanied with multiple organ dysfunction (liver, kidney, heart, brain). The mortality rate remains high, range between 25 and 50%[1]. Septic shock is the first cause of deaths in intensive care units patients[2].

1.1 Causes of septic shock

Most episodes of septic shock are caused by gram negative and gram positive organisms. Bacteremia is not necessary to develop sepsis, since patients with septic shock have a positive blood culture only in 40% to 70% of the cases[3]. A number of organisms may produce exotoxins or endotoxins that also initiate a systemic response. Gram negative bacteria contain endotoxin, a complex lipopolysaccharide, in the cell membrane. Lysis of them leads to the release of endotoxin. Some gram positive organisms produce also an exotoxin and "toxic shock syndrome" toxin; their release produces a similar response to lipopolysaccharides. Most cases of septic shock (approximately 70%) are caused by endotoxin-producing Gram negative bacteria. However, 5% to 10% have a fungal cause, and 15% to 20% are polymicrobial[4]. In emergency patients and the increased use of arterial and venous catheters, Gram positive cocci are implicated, as well.

Invasion of the microorganism into soft tissue leads in a complex cascade of events involving monocyte, macrophage and neutrophil recognition, activation, and initial release of inflammatory mediators. This constitutes a hyper-inflammatory state5,6. The release of inflammatory cytokines, chemokines, prostanoids, reactive oxygen, and nitrogen species leads to endothelial dysfunction and increased vascular permeability, myocardial suppression, and activation of the coagulation cascade. Patient's survival correlates with the recovery of the inflammatory responses[7].

The response to a microorganism depends on its virulence, size of the inoculum, co-morbid conditions, age, nutritional status and genetic polymorphisms in immune related genes[6].

Early recognition, prompt diagnostic workup and immediate initiation of therapy improve the prognosis of patients with septic shock syndrome.
Shock associated with sepsis can be caused by a variety of pathologic phenomena. It needs to be recalled that other mechanisms can be responsible. Hypovolemic shock can occur under conditions of sepsis due to massive fluid accumulation at the local site of infection. Other non-immunogenic causes of shock during sepsis that require consideration are cardiogenic causes.

1.2 Differential diagnosis of septic shock

Septic shock must be differentiated between systemic inflammatory response syndrome, sepsis, severe sepsis, hypotension, and multiple organ dysfunction syndrome as definitions were set in 1991 by the American College of Chest Physicians and the Society of Critical Care Medicine[8,9].
The phrase "systemic inflammatory response syndrome" describes the inflammatory process that can be generated by infection or by noninfectious causes such as pancreatitis, burns, and trauma. The response is manifested by two or more of the following conditions: 1) temperature greater than 38^{o}C or less than 36^{o}C, 2) heart rate greater than 90 beats per minute, 3) respiratory rate greater than 20 breaths per minute or arterial carbon dioxide pressure less than 32 mmHg, and 4) white blood cell count greater than 12000/mm^{3} or less than 4000/ mm^{3} or greater than 10% band forms. Sepsis as was described above is systemic inflammatory response syndrome due to infection. Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypotension is defined as a systolic blood pressure <90 mmHg or a reduction of greater than or equal to 40 mmHg from baseline. Finally multiple organ dysfunction syndrome is the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

2. Incidence of sepsis and septic shock

An accurate estimation of the incidence of sepsis and septic shock is hampered by the lack of reliable case definition. Inconsistent application of sepsis definition criteria contributes to confusion and variability in the literature[10]. The Centers for Disease Control estimated an incidence of 73.6 per 100,000 population in 1979, rising to 175.9 per 100,000 in 1989[11]. The rates have been probably increased because of more immuno-suppressed patients, new immunomodulating therapy, increased use of invasive devices (e.g., central venous catheters), and an increase in antibiotic resistance[5,6,12]. A review of discharge data on approximately 750 million hospitalizations in U.S.A. over a 22-year period (1979-2000) identified 10,319,418 cases of sepsis[5]. Sepsis was more common among men than among women (mean annual relative risk, 1.28; 95% CI: 1.24-1.32) and among non-white persons (mean annual relative risk 1.90; 95%CI: 1.81-2.00)[5]. However, these data is hampered due to the broad definition of sepsis and may be overestimate the accurate incidence of sepsis and septic shock since include all the ICD-9-CM* codes for definition of sepsis (038 [septicemia], 020.0 [septicemic], 790.7 [bacteremia], 117.9 [disseminated fungal infection], 112.5 [disseminated candida infection], and 112.81 [disseminated fungal endocarditis]. Organ

* ICD-9 CM denotes International Classification of Diseases, Ninth Revision, Clinical Modification

failure was defined by a combination of ICD-9 CM and CPT† codes. In general, there are few population-based prospective cohort studies that allow us to accurately delineate the incidence of sepsis and septic shock.
The mortality rate from sepsis is approximately 40% in adults, and 25% in children. It is significantly greater when sepsis left untreated for more than seven days[13].

3. Sepsis and septic shock during pregnancy

3.1 Prevalence and mortality rate in pregnancy

Septic shock in obstetric patients is rare because pregnant women are younger and have less co-morbid conditions. The common area of infection is the pelvis and the responsible microorganisms are sensitive in most of the broad spectrum antibiotics. Specific data on serious acute maternal morbidity due to sepsis are scarce, partly because of lack of a uniform definition of sepsis, but reported incidences in western countries vary from 0.1 to 0.6 per 1000 deliveries[14]. Although the incidence of septic shock in obstetric patients is low and has been decreased throughout the years it remains a significant factor of maternal morbidity and mortality related with pregnancy. Sepsis continues to account for approximately 7.6% of maternal deaths in the United States[15].
WHO defines puerperal sepsis as infection of the genital tract occurring at any time between the onset of the rupture of membranes or labour and the 42nd day postpartum in which fever and one or more of the following are present: pelvic pain, abnormal vaginal discharge, abnormal odour of discharge, and delay in the rate of reduction of size of the uterus[16]. It is estimated that puerperal sepsis causes at least 75,000 maternal deaths every year, mostly in low-income countries[17]. Studies from high-income countries report incidence of maternal morbidity due to sepsis of 0.1-0.6 per 1000 deliveries[17].

3.2 Are pregnant women more prone to infections and sepsis?

The concept that pregnancy is associated with immune suppression has created a myth of pregnancy as a state of immunological weakness and therefore, of increased susceptibility to infectious disease. Pregnancy represents the most important period for the conservation of the species, thus, it is fundamental to strengthen all the means to protect the mother and the fetus. The maternal immune system is characterized by a reinforced network of recognition, communication, trafficking and repair, in order to maintain the well-being of the mother and the fetus[18]. The fetus provides a developing active immune system that will modify the way the mother responds to antigens[18]. Therefore, it is appropriate to refer to pregnancy as a unique immune condition that is modulated but not suppressed[19].
Pregnancy has three distinct immunological phases that are characterized by distinct biological processes[20,21]. The first stage of implantation is a pro-inflammatory condition that the blastocyst has to invade the endometrial tissue in order to implant; the endometrium has to be replaced by trophoblast and new vessels in order to secure an adequate placental-fetal blood supply[22]. The placentation phase of pregnancy characterized by an anti-inflammatory state, where, the mother, the placenta, and the fetus are symbiotic[18]. Finally, during the last immunological phase, the mother needs to deliver the baby, and this can only be achieved through renewed inflammation. Parturition is characterized by an influx of immune cells

† CPT Current Procedural Terminology

into the myometrium in order to promote recrudescense of an inflammatory process[23,24]. A recent longitudinal study during uncomplicated pregnancies revealed a general trend toward enhanced counter-regulatory cytokine expression (IL-10), and an overall decrease of pro-inflammatory (Th1; TNFa, IL-1β, and IL-6) cytokines expression[25]. Pregnancy itself does not impair the woman's immunological system and other risk factors have to be implemented to develop infections in pregnant women.

3.3 Risk factors and routes of infection in pregnancy

Sepsis during pregnancy usually is the result of invasion of the uterine cavity with bacterial pathogens. Although transplacental spread of infection can occur in women with bacteremia that doesn't correlate with pregnancy, the most common route is an ascending infection from bacteria colonize the vagina and/or the cervix[15]. Pelvic infections in pregnant women have their microbiologic origin in one of three sources: the endogenous vaginal microflora, the intestinal microflora, and sexual transmission[26]. The infection occurs via migration of the organisms from the vagina through the endocervix into the uterus. Some organisms may traverse the columnar epithelium, as is the case with infection caused by Neisseria gonorrhoeae and Chlamydia trachomatis[26]. Bacteria such as Streptococcus agalactiae may gain entrance to the uterus and fallopian tubes via the lymphatics[26]. A third route of migration is by ascending into the pregnant uterus and colonizing amniotic fluid. Then bacteria are able to reproduce and reach numbers in excess of 10^5 per milliliter of amniotic fluid[27].

Risk factors for the development of maternal sepsis include home birth in unhygienic conditions, low socioeconomic status, poor nutrition, primiparity, anaemia, prolonged rupture of membranes, prolonged labour, multiple vaginal examinations in labour (more than five), caesarean section, multiple pregnancy, artificial reproductive techniques, overweight and obstetrical manoeuvres[14,28].

3.4 Reasons for infection and sepsis during pregnancy

Physiologic changes in the lower genital tract, such as a decreased in pH and increased glycogen in the vaginal epithelium, place the pregnant woman at risk for intra-amniotic infection. Pregnant women, with the enlargement of uterus, especially during the 3rd trimester, may cause stricture or even obstruction of the ureter, predisposing for the development of pyelonephritis. In addition, normal pregnancy is characterized by numerous changes in the hemostatic system, creating the hypercoagulable state which increases the risk of venous thromboembolic event occurrence[29]. An elevated leukocyte count, associated with a slightly increased c-reacting protein, and increased heart rate of 15-20 bpm, may mask early signs and symptoms of infection favouring the dissemination of bacteria into the blood-stream. Conditions that predispose pregnant women to septic shock syndrome can be intra-amniotic infection, septic abortion, septic pelvis thrombophlebitis, postpartum endometritis, pyelonephritis, wound infection, necrotizing fasciitis, appendiceal abscess, cholecystitis and invasive procedures like amniocentesis, chorionic villus sampling, and cervical cerclage placement.

Moreover, septic shock in pregnancy can be due to reasons that don't correlate with pregnancy. Non-obstetric septic shock can be caused by pneumonia and peritonitis with origin in colon, gastro-duodenum, post-duodenal small bowel, biliary tract and appendix. (Table 1)

Obstetrics	Non-obstetrics
Intra-amniotic infections	Pyelonephritis
Chorioamnionitis	Septic pelvic thrombophlebitis
Septic abortion	Abscess of the appendix
Invasive procedures for prenatal diagnosis (amniocentesis, chorionic villous sampling)	Cholecystitis
Cervical cerclage placement	Pneumonia
Post-partum endometritis	Peritonitis (colon, small bowel, gastro-duodenum, biliary tract)
Wound infection	
Necrotizing fasciitis	

Table 1. Conditions that predispose women to sepsis and septic shock syndrome during pregnancy

3.5 Chorioamnionitis and intra-amniotic infection

Intra-amniotic infections before 1970 was a major cause of maternal mortality because of patient delays in seeking treatment, unavailability of intensive care, and the absence of broad spectrum antibiotics[30]. Nowadays, the association of intraamniotic infections with septic shock, coagulopathy, and adult respiratory syndrome (ARDS) is rare, accounting for less than 1% in cases of intraamniotic infections[30,31].

It is important to note that intraamniotic infections in pregnancy usually are polymicrobial in nature. The most common route is an ascending infection from one or more of the endogenous flora of the cervix or vagina. The most frequent causative pathogens are Aerobic Bacteria (group B *β-hemolitic Streptoccocus, Enteroccocus*, other *Streptoccocus* species, *Escherichia coli, Hemophilus Influenzae, Pseudomonas species, Staphylococcus aureus, Klebsiella-Enterobacter* species, *Proteus* species), Anaerobic Bacteria (*Peptococcus* species, *Peptostreptococcus* species, *Clostridium* species, *Bacteroides* species, *Fusobacterium* species) and other (*Gardnerella vaginalis, Mycoplasme Hominis, Ureaplasma Urealyticum, Chlamydia Trachomatis*) (Table 2). It is important to note when group B β-Streptococcus or Escherichia coli are the causative pathogens, the incidence of bacteremia is higher (18% and 15%, respectively)[30].

As a consequence of intraamniotic infection is the spontaneous rupture of membranes by weakening the membranes, either by a direct effect of microorganisms on the membranes or indirectly by activation of the host defense mechanisms. However, there is not an absolute and exclusive correlation between intra-amniotic infection and spontaneous rupture of membranes. Rupture of membranes predispose but not secure the development of intra-amniotic infection. This is especially true, after the administration of broad spectrum antibiotics.

An estimated 5-10% of women with intraamniotic infections have bacteremia[30]. Almost half of the patients with bacteremia will demonstrate signs and symptoms of sepsis[32]. Approximately 40% of patients with sepsis have the condition progress to septic shock[33]. Progression from intraamniotic infections to bacteremia, sepsis, and septic shock can occur in a few days or several hours. Typical clinical manifestations of septic shock appeared additionally to the signs of intraamniotic infections and include altered mental status, peripheral vasodilation, tachypnea, tachycardia, temperature instability, hypotension, increased cardiac output, and decreased peripheral resistance[31,34]. If the condition is not

promptly identified and aggressively treated, progressive symptoms of peripheral vasoconstriction, oliguria, cyanosis, ARDS, disseminated intravascular coagulation, decreased cardiac output, and decreased peripheral resistance may occur[34].

Aerobic bacteria	
	Group B β-hemolytic Streptococcus
	Streptococcus species
	Enterococcus
	Escherichia coli
	Haemophilus influenza
	Staphylococcus aureus
	Pseudomonas species
	Klebsiella species
	Proteus species
	Enterobacter species
Anaerobic bacteria	
	Peptococcus species
	Peptostreptococcus species
	Clostridium species
	Bacteroides species
	Fusobacterium species
Other	
	Gardnerella vaginalis
	Mycoplasma Hominis
	Ureaplasma urealyticum
	Chlamydia trachomatis

Table 2. Common causative pathogens of ascending infection in pregnant women.

Chorioamnionitis is an acute inflammation of the membranes and chorion of the placenta. Typically is the result of ascending polymicrobial bacterial infection in the setting of membrane rupture. It can also occurs with intact membranes after infection with *Ureaplasma* species and *Mycoplasma hominis*, found in the lower genital tract[35]. Only rarely is hematogenous spread implicated in chorioamnionitis, as occurs with *Listeria monocytogenes*[36].Overall, 1-4% of all births in the U.S.A. are complicated by chorioamnionitis[36]; however, the frequency varies markedly by diagnostic criteria, specific risk factors, and gestational age[37,38]. The key clinical findings include fever, uterine fundal tenderness, maternal tachycardia (>100/min), fetal tachycardia (>160/min), and purulent or foul amniotic fluid[36,39]. The most common organisms isolated in up to 47% and 30% respectively, in cases of culture confirmed chorioamnionitis are *Ureaplasma urealyticum* and *Mycoplasma hominis*[40,41].

Chrorioamnionitis leads to a 2 to 3-fold increased risk for caesarean delivery and to 2 to 4-fold increase in endomyometritis, would infection, pelvic abscess, bacteremia, and post-partum hemorrhage[42-44]. Women with chorioamnionitis in 10% have positive blood cultures (bacteremia)[36]. Fortunately, septic shock, disseminated intravascular coagulation, adult respiratory distress syndrome, and maternal death are only rarely encountered[44,45]. In contrast, fetal exposure to infection may lead to fetal death, neonatal sepsis, and septic shock. In one study, neonatal pneumonia, sepsis, and perinatal death occurred respectively,

in 4%, 8%, and 2% of term deliveries associated with chorioamnionitis[46]. The frequency of neonatal sepsis is reduced by 80% with intrapartum antibiotic treatment[47].
Prompt initiation of antibiotic therapy is essential to prevent both maternal and fetal complications in the setting of clinical chorioamnionitis[44]. Time-to-delivery after institution of antibiotic therapy has been shown to not affect morbidities; therefore caesarean section to expedite delivery is not indicated for chorioamnionitis unless there are other obstetric indications[44,48].

3.6 Does the mode of delivery affect the incidence of sepsis and septic shock?

Nowadays, rates of caesarean section (CS) are progressively increasing in many parts of the world. There has been an increasing tendency for pregnant women without justifiable medical indications for CS to ask for this procedure. Despite the World Health Organization's estimate that CS rates should not be >15%, in the developed world, CS rates are already above 30%[49,50]. Following CS, maternal mortality and morbidity may result from a number of infections including endometritis, urinary tract infection and surgical site infection, which if deep rather than superficial, increase hospital stay and cost per case[51-53]. The most common infection-related complication following CS is endometritis[53]. A major risk factor for post-CS infection is emergency CS (compared with elective).
The rate of infection following CS is 1.1–25% compared with 0.2–5.5% following vaginal birth[54-56]. In antepartum patients the most common infection is asymptomatic bacteriuria with an incidence estimated at 4-7%. However, with the use of prophylactic antibiotic treatment is extremely rare these infections to become sepsis and septic shock, regardless of the mode of delivery. Recent evidence suggests that pre-incision broad spectrum antibiotics are more effective in preventing post-CS infections than post-clamping of the cord narrow-range antibiotics, without prejudice to neonatal infectious morbidity[57]. Prophylactic antibiotics can reduce the incidence of endometritis following CS by two thirds to three quarters[53].
Data from Europe for the years 2003–2004 showed a range of maternal mortality ratio from 2/100,000 live births in Sweden, to 29.6/100,000 in Estonia[58]. Direct maternal mortality associated with CS was about 0.06‰[59]. However, very few women are dying from primary infection and sepsis. Haemorrhage is the main cause of death following by thromboembolism and preeclampsia. Even though the majority of women are dying during puerperium (60%), the infection mostly started during pregnancy or delivery and only in rare cases after delivery and subsequently was not correlated with the mode of delivery. Collectively, we can suggest that CS affects the incidence of infection and hospitalization of women but is not correlated with severe sepsis and septic shock.

3.7 Amniocentesis, chorionic villous sampling (CVS): Routine procedures but invasive?

Although amniocentesis and CVS are routine procedures in prenatal diagnosis and are nowadays performed in most clinics under continuous ultrasonographic vision and aseptic conditions, they are invasive procedures carrying potential risks of serious complications for both the mother and the fetus. Intrauterine infection is a rare event after invasive prenatal diagnostic procedures[60]. According to data from large studies, the incidence of chorioamnionitis is 5 per 1,000 cases after CVS; 3.7 per 1,000 cases after amniocentesis; and 8.8 per 1000 cases after cordocentesis, compared with 3 per 1,000 cases in non-exposed

women[61,62]. Infection is usually mild to moderate. There are, however, sporadic reports in the literature describing cases of post-procedure sepsis with devastating results60. Deterioration to septic shock may develop in 0.03% to 0.19% of intra-amniotic infection cases[63].

Contamination of the uterine cavity after amniocentesis or CVS may occur through ascending infection, direct inoculation of intestinal germs, and rarely, after use of deficiently sterilized equipment and direct spread of the infection from the vagina to the blood stream, by-passing the uterus[64]. Direct inoculation of vaginal or cervical pathogens into the uterine cavity may underlie the development of sepsis after trans-cervical CVS[65-67]. The reported rate of transient post-procedure bacteremia is 4.1% for transcervical CVS and nearly zero for transabdominal procedure[64,68]. Inoculation of intestinal germs has been implicated in cases of sepsis after transabdominal procedures. In such cases, peritoneal signs are expected to predominate[69].

Incubation time is usually short, and the onset of symptoms is usually manifested within 24 hours after the procedure. The onset can be insidious, but the clinical and laboratory indicators deteriorate quickly, and the progress can be fulminant[60]. *Clostridium perfrigens*, together with *Escherihia coli*, are the most common pathogens encountered in cases of sepsis after prenatal diagnosis and they are associated with severe and serious complications. Other pathogens isolated from endometrial remnants or blood cultures after amniocentesis or CVS include *Klebsiella pneumoniae, Enterobacter, Staphylococcus aureus, Serratia rubidaea, Citrobacter, Clostridium welchii, group B β-hemolytic streptococcus,* and *Candida albicans* (Table 3).

Administration of prophylactic antibiosis is not recommended since most retrospective studies failed to prove a direct association between needle insertion and maternal or fetal complications[70-72]. Prospective, double-blind studies in this topic are lacking. In cases of sepsis, evacuation of the uterine cavity and suction curettage can be performed. In severe cases prompt hysterectomy with the dead fetus in situ may be advisable if there is evidence of sepsis with hemolysis, multiple organ failure and rapid progress of infection. However, the decision to perform hysterectomy is difficult, especially in a case of a young nulliparous woman or a woman with an affected child and should be performed only in cases where woman's life is at risk. Although very rare, potentially fatal sepsis can occur after invasive prenatal diagnostic procedures. Sepsis can begin with very subtle clinical signs and symptoms, but quickly develop complications, which can become irreversible if intervention is delayed.

3.8 Septic abortion

Septic abortion, an abortion related with infection and complicated by fever, endometritis, and parametritis, remains one of the most serious threats to the health of women throughout the world[85]. More than 95% of the septic abortion and septic shock cases are synonymous with illegal, criminal or non-medical abortions[86]. The most important effect of the legalization of abortion on public health in the U.S.A. was the almost elimination of deaths due to infection from illegal abortion[87,88]. The mortality rate after septic abortion has been decreased dramatically after the introduction of broad spectrum antibiotics. In the U.S.A., is 0.4 cases per 100,000 legal abortions, whereas, in Europe is 1 case per 100,000 legal abortions[89,90]. Abortion remains a primary cause of maternal death in Third World countries. W.H.O. estimates that 25-50% of the 500,000 maternal deaths that occurs every year result from illegal abortion[91]. Abortion-related deaths result primarily from sepsis[92].

Author	Procedure	Management	Complications	Outcome	Culture
Wurster et al.[63]	Amniocentesis	Hysterectomy	NA	Recovery	*C. welchii*
Fray et al.[73]	Amniocentesis	Hysterectomy	NA	Recovery	*Clostridium+S. rubidaea+Citrobacter*
Muggah et al.[74]	CVS	Hysterectomy	DIC-ARDS	Recovery	*E. coli*
Hovav et al.[75]	Amniocentesis	D&C	ARDS-ARF	Recovery	*C. perfrigens+E.coli*
Ayadi et al.[76]	Amniocentesis	D&C	DIC-ARDS-cardiac arrest	Deceased	*C. perfrigens+E.coli*
Thabet et al.[77]	Amniocentesis	Expulsion	DIC-MOF	Recovery	*Klebsiella+Enterobacter*
Winer et al. (2 cases)[78]	Amniocentesis	Induction of abortion	DIC-cardiorespiratory arrest	Recovery	*E.coli*
Lau Tze Kin et al.[79]	Amniocentesis	Abortion+antibiotic	DIC-hypoxemia	Recovery	*E. coli*
Paz et al.[80]	CVS	Antibiotic	-		*Candida albicans*
Hamanishi et al.[69]	Amniocentesis	Abortion+hysterectomy	DIC-MOF	Recovery	*E.coli*
Li Kim Mui et al.[81]	Cordocentesis	Abortion	-	Recovery	*C. perfrigens+S. aureus*
Plachouras et al.[60]	Amniocentesis+ Cordocentesis	Hysterectomy	DIC-MOF	Recovery	*C. perfrigens*
Oron et al.[64]	CVS	Antibiotic	-	Recovery	*Group B β-hemolytic Streptococcus*
Kye Hun Kim et al.[82]	Amniocentesis	Conservative	DIC-AMI	Recovery	*E.coli*
Thorp et al.[83]	Amniocentesis	Conservative	DIC	Deceased	*E.coli*
Elchalal et al. (2 cases)[84]	Amniocentesis	Antibiotic+D&C	DIC-MOF	Deceased	*E.coli*

NA: not available; CVS: chorionic villous sampling; DIC: disseminated intravascular coagulation; ARDS: adult respiratory distress syndrome; D&C: dilation and curettage; ARF: acute renal failure; MOF: multiple organ failure; AMI: acute myocardial infarction

Table 3. Case report of sepsis after invasive prenatal diagnosis

The risk of sepsis from abortion rises from the first trimester of pregnancy to the second[89]. In the first trimester, abortion is readily performed by vacuum curettage, usually in an outpatient setting. Incomplete abortions produced by incompetent physicians represent another risk factor. Insertion of rigid foreign objects into the uterus or cervix increases the risk of perforation and infection[93]. Intrauterine instillation of soap solution containing cresol and phenol has been abandoned, due to the risk of uterine necrosis, renal failure, toxicity to the central nervous system, cardiac depression, and respiratory arrest[94].

The bacteria associated with septic abortion are usually polymicrobial, derived from the normal flora of the vagina and endocervix, with the important addition of sexually transmitted pathogens[95,96]. Septic shock complicates approximately 0.7% of septic abortions and the offending organisms are Gram-negative bacteria (*Escherichia coli, Aerobacter aerogenes, Proteus mirabilis* or *vulgaris* and *Pseudomonas aeruginosa*) which produce an endotoxin[86]. However, Gram-positive bacteria (*Clostridium welchii or perfrigens, Neisseria gonorrhoae, Staphylococcus epidermisis, Streptococcus agalactiae*), anaerobic bacteria and

Chlamydia trachomatis are all possible pathogens[86, 97]. Because of the variety of bacterial agents that can be associated with septic abortion, no-one antibiotic agent is ideal. The regimens recommended for outpatient management of pelvic inflammatory disease (PID) are appropriate for early post-abortion infection limited to the uterine cavity[95].

The diagnosis of septic abortion must be considered when any woman of reproductive age presents with vaginal bleeding, lower abdominal pain, and fever. If the woman has had symptoms for several days, a generalized, serious illness may be present. Bacteremia, which is more common with septic abortion than with other pelvic infection, may result in septic shock and the adult respiratory distress syndrome[98]. Management of severe sepsis requires eradication of the infection and supportive care for the cardiovascular system and other involved organ systems. Any tissue remaining from the pregnancy must be evacuated without delay as soon as antibiotic therapy and fluid resuscitation have been started. In critically ill women with severe sepsis, a hysterectomy will probably be needed. Other indications of laparotomy are uterine perforation with a suspected bowel injury, a pelvic abscess, and clostridial myometritis[98].

Cervical dilation with laminaria placement has been also associated rarely, with septic abortion and septic shock[99]. Laminarias are sea plant with hydroscopic properties that enable their expansion up to five times in diameter over 12-24 hours, thereby gradually dilating the cervix. The potential of laminarias to harbor pathogens led some investigators to speculate that colonization of laminaria tents may lead to post-abortion infection. However, with modern sterilization techniques, the associated infection rates are similar to those achieved with standard methods for cervical dilation[99].

Nowadays, medical termination of pregnancy using mifepristone and/or misoprostol doesn't require admission to the hospital or anesthesia and is alternative to surgical termination[100]. The incidence of uterine infection after medical termination of pregnancy is very low. However, severe and fatal infections have been reported in certain cases; most of them were associated with *Clostridium* infections and development of toxic shock syndrome[101-103]. Klebsiella pneumoniae has also been reported as the cause of septic shock after medical termination of pregnancy with misoprostol-only regimen[100]. Although a direct association of these drugs and septic shock has established, it was postulated that mifepristone blocks both progesterone and glucocorticoid receptors and affects the innate immune system[104]. However, most of these severe and occasionally fatal complications are the result from inappropriate usage of drugs without any medical monitoring and consultation.

3.9 Non-obstetric causes of septic shock

Septic shock in the pregnant woman usually results from an infection in the urinary or genital tract. Pyelonephritis is the most frequent cause of bacterial shock associated with pregnancy[105]. Enlargement of the uterus during the 2nd and 3rd trimester of pregnancy may cause stricture and/or obstruction of the ureters, a condition that predisposes to urinary infections and pyelonephritis. Escherichia coli is responsible for most of the cases. *Klebsiella pneumoniae*, *Proteus species*, and *Enterobacter-Citrobacter* are less common pathogens.

All pregnant women should be screened for the presence of bacteriuria at their first prenatal visit. Failure to treat bacteriuria during pregnancy may result in as many as 25% of women experiencing acute pyelonephritis106. Acute pyelonephritis has an incidence of approximately 0.1-1% in pregnancy; most occurs at second trimester107. It is associated with

multiple complications, including fetal growth restriction, preterm labour, cerebral palsy and septicemia, although the underlying mechanisms are poorly understood[108]. One mechanism could be the alteration in the profile of angiogenic and anti-angiogenic factors (increased expression of vascular endothelial growth factor [VEGF], decreased expression of PIGF and sVEGFR-2) observed in cases with acute pyelonephritis that resembles the one observed in sepsis[109]. In most reports of acute pyelonephritis the incidence of bacteremia is not stated. However, 20% of women with severe pyelonephritis will develop complications that include septic shock syndrome or its presumed variants[110]. These latter include renal dysfunction, hemolysis and thrombocytopenia, and pulmonary capillary injury. In another series of 55,621 pregnant women with acute pyelonephritis, the incidence of septic shock in pregnancy was 3.77%[111]. The first fatal case of gestational interstitial tubulonephritis and chronic pyelitis caused by *Escherichia coli* has been recently described [112]. In the great majority of cases, continued fluid and antimicrobial therapy result in a salutary outcome, but there is still an occasional maternal morbidity.

Post-partum endometritis (PE) can also result to septic shock. Patients with PE may show a delayed response to antibiotic treatment because of the development of septic pelvic vein thrombosis26. In these cases heparin should be administered. Patients who do not respond to antibiotics and heparin should be considered to have thrombosis of the vasculature of the uterus or an abscess26. Decreased perfusion of the myometrium does not permit adequate antibiotic levels to be established in the myometrium and uterine necrosis could be observed. In such occasions, hysterectomy should be performed.

Various other conditions have been reported to predispose the pregnant woman to sepsis and septic shock including pelvic abscess, wound infection, necrotizing fasciitis, appendiceal abscess, acute cholecystitis, septic pelvic vein thrombosis, pneumonia, pancreatitis, and lupus.

4. Septic shock in gynecologic patients

In Gynecology, incidence of sepsis have been increased during the last 15 years, presumably due to an aging population, an increase in the number of invasive procedures performed, and possibly due to a resistance to the current antibiotic treatment appeared in the infecting pathogens. Sepsis-related situations in Gynecology can be found, in women using intra uterine devices (IUD), after untreated pelvic inflammatory disease (PID), after toxic shock syndrome provoked mainly by the use of tampons during menstrual period, and in patients with gynecological cancer. The above causes will be discussed explicitly, thereafter.

4.1 Toxic shock syndrome

Toxic shock syndrome (TSS), is a rare, life-threatening, multiorgan illness that is caused by toxins that circulate in the bloodstream. Development of TSS involves three distinct stages: local proliferation of toxin-producing bacteria at the site of infection, production of toxin, and exposure of this toxin to the immune system with resultant immune response[113,114].

Toxic shock syndrome was initially identified as a pediatric infection in 1978[115]. Subsequent reports identified an association with tampon use by menstruating women.[116-118]. Menstrual TSS is more likely in women using highly absorbent tampons, using tampons for more days of their cycle, and keeping a single tampon in place for a longer period of time. Over the past two decades, the number of cases of menstrual TSS (1 case per 100,000) has steadily declined; this is thought to be due to the withdrawal of highly absorbent tampons from the market[116].

In the most typical form of toxic shock syndrome, the bacteria, most commonly, group A *Streptococcus, Staphylococcus aureus* and *Clostridium sordellii* produce an enterotoxin that transfers into the bloodstream, provoking the overstimulation of the immune system. This, in turn, causes the severe symptoms of TSS, such as: fever, rash, myalgias, diarrhea, vomiting, headache, sore throat, vaginal discharge, rigors, desquamation (typically of the palms and soles), hypotension, and multi-organ failure (involving at least 3 or more organ systems[116,119,120]. The mortality rate of toxic shock syndrome is approximately 5-15%, and recurrences have been reported in as many as 30-40% of cases[121,122].

The role of tampons in the pathogenesis of TSS is incompletely understood. Although tampons are not a source for toxigenic *S.aureus* and do not appear to increase the *S. aureus* cell density vaginally, studies have shown that tampons used during menstruation often colonized with this pathogen[123,124]. Vaginal conditions during menses and tampon use, contribute to the proliferation of toxin-producing *S.aureus*. An elevated vaginal temperature and neutral pH, both of which occur during menses are enhanced by tampon use, allowing bacterial proliferation[125]. Endometrial blood can serve as a medium for bacterial growth; persistence of this blood in the cervical and vaginal canal with tampon use has been also shown to increase the proliferation of *S.aureus*[126]. In addition, synthetic fibers are thought to alter the availability of certain substrates to lactobacilli, a normal vaginal colonist that limits the proliferation of *S.aureus*. The same conditions also aid in the production of TSS Toxin-1. Menses and tampon use increase the partial pressure of both oxygen and carbon dioxide, which also stimulate toxin production[127]. In addition, tampons obstruct the flow of endometrial blood and may even cause the reflux of blood and bacteria into the uterus.

Toxic shock syndrome is the typical example of a systemic inflammatory response syndrome, with virtually all of the effects derived from immune mediators rather than as a direct result of infection. The diagnosis of TSS should be considered in a patient who presents with septic shock but without any obvious source of infection. The case fatality rates for menstrual-related STSS have declined from 5.5% in 1980 to 1.8% in 1996[121,122]. Organ supportive therapy remains the standard of care with antibiotics used to prevent recurrence, although newer immune-based therapies are being developed that may help in the treatment of TSS and other inflammatory syndromes in the future.

4.2 Pelvic inflammatory disease (PID)

Pelvic inflammatory disease (PID) refers to acute infection of the upper genital tract structures in women, involving any or all of the cervix, uterus, fallopian tubes, ovaries and surrounding structures. By definition, PID is a community-acquired infection, initiated by a sexually transmitted agent, distinguishing it from pelvic infections due to medical procedures, pregnancy and other primary abdominal processes. Pelvic inflammatory disease in the United States annually accounts for about 2,5 million outpatient visits, 200,000 hospitalizations and 100,000 surgical procedures[128]. It is the most frequent gynecologic cause for emergency department visits (350,000/year)[128,129].

PID is most frequently caused by bacteria that are transmitted through sexual contact and other bodily secretions. Bacteria that cause gonorrhea and additionally the *Chlamydia trachomatis* cause more than half of cases. Many studies suggest that a number of patients with PID and other sexually transmitted diseases are often infected with two or more infectious agents and commonly these are *Chlamydia trachomatis, Neisseria gonorrhoeae* and *Mycoplasma genitalium*[130]. Sexually active adolescent females and women younger than 25

years are at greatest risk, although PID can occur at any age. Abdominal pain (usually lower) or tenderness, fever, nausea, vomiting, back pain, unusual or heavy vaginal discharge, abdominal uterine bleeding, painful urination, painful sexual intercourse are some of the symptoms of PID[131].

The vaginal flora of most normal, healthy women includes a variety of potentially pathogenic bacteria[132]. Among these are species of streptococci, staphylococci, Enterobacteriaceae (most commonly, *Klebsiella* spp, *Escherichia coli*, and *Proteus* spp), and a variety of anaerobes. Compared with the dominant hydrogen peroxide-producing Lactobacillus, these organisms are present in low numbers, and ebb and flow under the influence of hormonal changes, contraceptive method, sexual activity, and other as yet unknown forces. Complete disruption of the vaginal ecosystem can occur, in which anaerobic bacteria assume predominance over the desirable strains of lactobacilli[133]. Then an ascending infection occurs causing: cervicitis, endometritis, salpingitis or hydro-, pyo-salpinx. In tubes and ovaries, salpingo-oophoritis (acute, subacute and chronic) or a tubo-ovarian abscess may also occur. In the peritoneal cavity spreading of the infection causes pelvic and/or generalized peritonitis or a pelvic abscess. Infection may be also spread through the uterine wall into broad ligaments to cause pelvic cellulitis (parametritis), a broad ligament abscess or septic thrombophlebitis of the ovarian or uterine veins, leading to septicemia with few local signs[134].

Bacteremia is an unusual condition and is not correlated with PID. Blood cultures for women hospitalized with acute PID showed negative results in 97% of the cases[135]. The results of blood culture are not affect the clinical management of PID and routine specimens may not be needed from patients hospitalized for acute PID[135]. However, if diagnosis and treatment are not performed in a timely manner, PID may cause sepsis, septic shock and even death. Even if they survive, as many as 15% to 20% of these women experience long-term sequelae of PID, such as ectopic pregnancy, tubo-ovarian abscess, infertility, dyspareunia and chronic pelvic pain. The best treatments for PID are interventions that lead to prevention and early detection[136].

4.3 Intrauterine devices (IUD)

Intrauterine contraceptive devices (IUDs) are highly effective, long-term methods of contraception. It is also one of the most cost-effective method available, providing long-term protection[137]. Most modern IUDs are medicated; they contain either copper or a progestin to enhance the contraceptive action of the device. The total number of current IUD users is estimated at over 150 million women worldwide[138]. Infection risk is a relative contraindication to fitting any woman with an IUD, it is only present for a few weeks after insertion and probably arises from an undiagnosed cervical infection at the time of insertion. Although evidence of a direct association between IUD use and PID is scarce, concerns about PID related to IUDs use has limited their use throughout the world. On the other hand, bacteriologic cultures of removed IUDs have shown that the bacterial flora of the removed IUDs consisted of common aerobic and anaerobic microorganisms that do not account for PID[139]. In a study with 200 subjects, the most common bacteria identified from removed IUDs were *Staphylococcus* coagulase negative, *Esherichia coli*, and *Enterococcus faecalis*[139]. The authors concluded that culture of the removed IUDs and therapeutic management of women with positive cultures are not recommended when women are asymptomatic for PID[139]. A systematic review reported the risks of PID with insertion of an

IUD in the presence of existing infection. With IUD insertion in the presence of Chlamydia infection or gonorrhoea, subsequent PID rates were 0-5%, compared to insertion in the absence of infection (0-2%)[140]. Although trial results do not indicate the need to screen for and treat sexually transmitted diseases before inserting and IUD[141], it is rationale to suggest that the insertion of an IUD is indicated only in women with negative vaginal cultures (Table 4)[142].

NOT contraindicated	**Contraindicated**
Increased risk of STI or HIV	Current PID
Continuation after STI diagnosed	Current purulent cervicitis
Past PID	Chlamydial infection
Past ectopic pregnancy	Gonorrheal infection
HIV or AIDS	Pelvic tuberculosis
Diabetes	Puerperal sepsis
Menorrhagia	Septic abortion
Fibroids	
Age<20	

STI: sexually transmitted infection; PID: pelvic inflammatory disease

Table 4. Conditions in which intrauterine contraception is and is NOT contraindicated (WHO, 2004)

In cases of vaginal infection, it is possible that the insertion of an IUD carries bacteria into the uterus and traumatizing the endometrium causes several infections. Cases of vaginitis[143], transfer of actinomyces into the uterine cavity[144], PID[145], and even toxic shock syndrome[146], and sepsis[147], have occasionally been reported. Three cases of streptococcal toxic shock syndrome following insertion of an IUD have been reported, recently[146,148,149]. This pathogen is not normally found in the vaginal flora or after an intrauterine device is inserted[150]. However, an association between the use of IUD and the risk for infection and sepsis does not exist. Conditions which represent an unacceptable health risk if an IUD is inserted are: current PID, current purulent cervicitis, chlamydial or gonorrheal infection, as well as, pelvic tuberculosis, puerperal sepsis, and septic abortion (Table 4)[151].

4.4 Gynecologic cancer

Sepsis and septic shock are not directly associated with gynecologic cancer. The female cancer patient is a vulnerable patient. Usually after having undergone a difficult operation, followed up by several chemotherapy cycles, has reduced defenses against infection due to: a) reduced antibody formation; b) deficient cell immunity; c) reduced or abnormal granulocytes; d) damaged mucocutaneous barriers, such as, ulceration of the oropharynx due to methotrexate toxicity; e) obstruction of biliary and urinary tracts. Thus, myelosuppression may also give rise to an acute septic problem associated with neutropenia, granulocytopenia. In these patients, any infection may have an acute form leading to rapid septicemia and severe shock developing rapidly.

The frequency of patients with gynecologic cancer and septic shock is not seen very often. In a recent study, the mortality rate was 33% (of 6 reported cases, 2 died)[152]. Sepsis can occur independently of the optimal management of cancer. Among 74 women with gynecologic cancer, there was one death due to the development of septic shock in a patient with

optimal cytoreductive operation[153]. Toxic shock syndrome has been developed in a patient with a metastatic cervical cancer[154]. In advanced operations (pelvic exenterosis) where a colostomy has been performed, there is also a possibility of sepsis due to spillage of stool upon maturing the colostomy[155]. When operations for gynecologic cancer involve the intestine there is increased possibility for sepsis. In a series of 113 patients three died due to sepsis post-operatively[156]. Early diagnosis, careful monitoring, prompt removal of septic foci, and appropriate antibiotic and supportive treatment are the most important factors influencing prognosis in these patients.

5. Conclusion

Sepsis and septic shock are not specifically correlated with obstetrics or gynecologic conditions. Risk factors that may predispose an Ob/Gyn patient to infectious agents are essentially the same risk factors that place any patient in harm's way. In Obstetrics, a prior history of peripatum infection, prolonged rupture of membranes, or genitourinary instrumentation associated with cardiovascular instability and fever should raise the possibility of septic shock.

Patients with obstetrics or gynecologic problems are not different in the management of septic shock with other patients that sepsis results from other organs. Management of a patient with septic shock requires simultaneous administration of agents to reverse the pathophysiologic processes set in motion. It is important to treat patients with sepsis early and vigorously. Volume expansion and correction of hypovolemia are critical. Understanding the pathways, mediators, feedback loops and interactions involved in the pathogenesis of sepsis and organ failure has advanced profoundly, giving us the opportunity to treat sepsis-related multiple organ failure, and therefore, improve both survival rates and quality of life of women patients.

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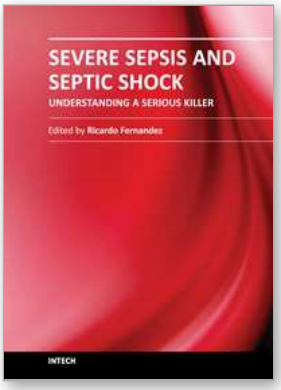

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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease . We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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