Journal of Mind and Medical Sciences

Volume 10 | Issue 2 Article 15

2023

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Recommended Citation

Gorecki, Gabriel Petre; Balalau, Oana Denisa; Comandasu, Diana Elena; Stanescu, Anca Daniela; and Tomescu, Dana Rodica (2023) "Best therapeutic practices in the management of obstetric sepsis," *Journal of Mind and Medical Sciences*: Vol. 10: Iss. 2, Article 15.
DOI: https://doi.org/10.22543/2392-7674.1436
Available at: https://scholar.valpo.edu/jmms/vol10/iss2/15

Journal of Mind and Medical Sciences

https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/

ISSN: 2392-7674

Best therapeutic practices in the management of obstetric sepsis

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ABSTRACT

Background. Physiological changes that occur during pregnancy make maternal sepsis a difficult condition to diagnose and treat, still having a fairly high mortality rate. Consequently, an early diagnosis and prompt therapeutic management of sepsis can significantly decrease mortality. The purpose of this study is to review literature data that present current practices in the management of obstetric sepsis. *Methods*. To collect the data required for the study, we performed a search of published articles in the PubMed and Google Scholar databases related to obstetric sepsis. Research paper articles from the period 2012-2022 were included in the analysis. In addition, 145 articles from the period 2012-2022 were evaluated, with the aim of finding out in which situations the risk of maternal death is higher. Thus, the analysis included a total number of 151 articles, which were divided into two distinct stages. *Results*. The risk of maternal death is higher among patients with the human immunodeficiency virus (HIV), followed by Escherichia coli, genital tract infection, cancer, drug users and in the case of patients with chronic liver disease. *Conclusions*. After analyzing the data, we found that prompt and focused antibiotic therapy as well as fluid resuscitation are essential to increase the chances of survival of these patients.

Category: Original Research Paper

Received: May 05, 2023
Accepted: June 26, 2023
Published: October 25, 2023

Keywords:

obstetric sepsis, maternal sepsis, septic shock, therapy, best practices

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Introduction

Worldwide, between 20-40% of maternal deaths are caused by sepsis during the peripartum period [1-3]. Due to the physiological changes that occur during pregnancy, maternal sepsis is a condition with a high mortality rate, which becomes quite difficult to diagnose, thus leading to delays in the application of therapeutic protocols aimed at reducing mortality [4-6].

Post-abortion sepsis can occur following a miscarriage, a surgical abortion or even the consequence of an illegal abortion. It is usually caused by an ascending infection that leads to endometritis or parametritis, and which later progresses to sepsis [7-9].

Validated diagnostic criteria for maternal sepsis and septic shock may reduce their impact on maternal health globally. Unfortunately, the overlapping manifestations of the physiological adaptations that occur during pregnancy and the signs and symptoms of infection and sepsis can cause delays in both diagnosis and treatment [10,11].

When signs of sepsis are not recognized and treated promptly, they can progress rapidly in pregnant women or women who have recently given birth, leading to life-threatening pathophysiological imbalances [12].

Infertility, fetal death, chronic pelvic inflammatory disease, organ failure, bilateral tubal blockage, chronic pelvic pain are major morbidities associated with obstetric sepsis. Therefore, early detection and prompt therapeutic action are essential for a successful outcome.

For the identification and prognosis of patients with sepsis, machine learning prediction models outperformed already used sepsis scoring systems, including SOFA, SIRS, qSOFA, and MEWS. Using machine learning algorithms to predict patients with sepsis could help

To cite this article: Gorecki GP, Balalau OD, Comandasu DE, Stanescu AD, Tomescu DR. Best therapeutic practices in the management of obstetric sepsis. *J Mind Med Sci*. 2023;10(2):304-311. doi:10.22543/2392-7674.1436

doctors actively monitor and take preventive measures to improve patients' conditions [13].

Materials and Methods

The aim of this study is to review the studies that present the practices used in the management of obstetric sepsis. The Google Scholar database was used, and for obstetric sepsis we obtained 224,000 articles. To facilitate the analysis, we decided to investigate the articles from the period 2012-2022, obtaining a number of 17,900 articles. The PubMed database was also queried, thus generating 261 articles for obstetric sepsis (period 2012–2022). In the end, we had to study a total of 18,161 articles.

We proposed to analyze in the first stage 20 articles according to the following criteria: full paper articles, not be duplicated, research paper type, a large number of citations, publication period starting with 2012. From the 20 articles we managed to extract only 6 that corresponded to the topic of analysis. In the second stage, we set out to analyze 250 articles from the period 2012-2022 in which we wanted to find out in which situations the risk of maternal death is higher. The selection of articles was made on the same principle as in the first stage. We were able to retrieve 145 articles from the Google Scholar. In total, we analyzed 151 articles from the PubMed database and from the Google Scholar search engine, by Prisma Model, as presented in Figure 1.

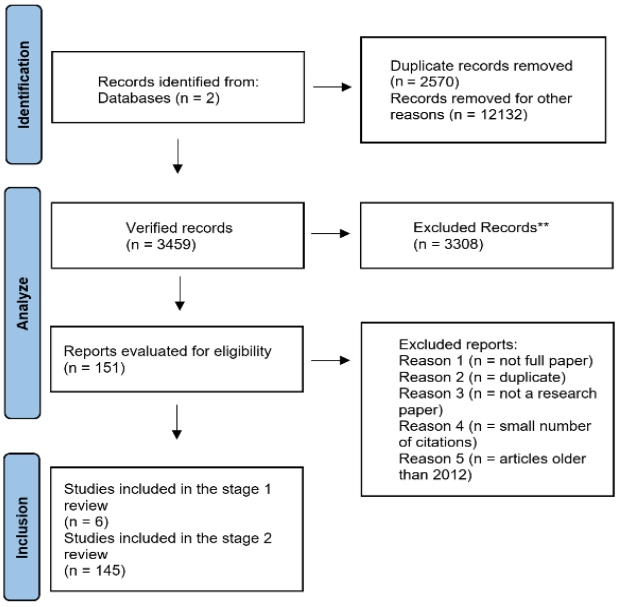

Figure 1. Identification and selection of studies analyzed

Results

We propose to present 6 articles following the analysis process: authors and year of publication, purpose, results, conclusions and limitations. Thus, we obtained the following results from the review process, which are presented in the Tables 1-6.

Table 1. Results obtained by Albright et al. (2014) [14].

Purpose	A retrospective cohort study of pregnant and postpartum patients with suspected SIRS or sepsis was performed.
Number of subjects included	850 women were included.
Inclusion criteria	Women at high risk of sepsis were included. Only those who had blood cultures or a flu swab sent to the clinical laboratory were included. Blood cultures or an influenza swab were used as surrogate markers for a patient presenting with signs or symptoms of sepsis.
Results	Of the 850 hospitalized patients. 9 were admitted to the intensive care unit (1.1%), 32 of the women were in the telemetry unit (3.8%), and none died. The most common diagnosis at presentation was influenza-like illness (ILI) (60.4%), followed by viral non-respiratory syndrome (11.1%), pyelonephritis (5.3%), endometritis (4.5%), pneumonia (2.4%), mastitis (1.2%), chorioamnionitis (0.7%) and septic abortion (0.6%).
Conclusions	A sepsis scoring system of the S.O.S. type (Obstetric Sepsis Score) was used for all pregnancy-specific physiological changes. This system was able to identify pregnant and postpartum patients at risk of admission to the intensive care unit for sepsis within 48 hours of presentation to the emergency department.
Limitations	The study is retrospective and was conducted at only one institution. Patients included were only those with signs of sepsis in the emergency department and not those who became septic after admission.

Table 2. Results obtained by Aarvold et al. (2017) [15].

Purpose	The study aimed to analyze five mortality prediction scores (one obstetric-based and four general) in the septic obstetric population and compare them with a nonobstetric septic control group.
Number of subjects included	797 women were included.
Inclusion criteria	The women were in the 16-50 age group with a diagnosis or suspicion of sepsis. All pregnant and postpartum patients up to 6 weeks postpartum were included. An age- and sex-matched non-obstetric control population was drawn from a single-center critical care population.

Results	The Obstetrics Sepsis Score, designed specifically for sepsis in obstetric populations, was no better than overall severity of illness scoring systems. Additionally, the Sepsis in Obstetric Performance Score was not different in an obstetric sepsis population compared to a nonobstetric sepsis population.
Conclusions	The obstetric-specific S.O.S. (Septic Obstetric Patients) score has been shown to have poor predictive value for mortality in both septic obstetric and nonobstetric populations. Also, disease severity scores based on organ failure, such as the MODS (Multiple Organ Dysfunction Score), are superior to the obstetric-specific SOS score in an obstetric population. Indeed, the MODS score performs equally well in obstetric and nonobstetric (age- and sex-equivalent) populations.
Limitations	Even though there was a large number of patients in the databases, the final figures of the septic cohort are small and therefore there is a significant geographical variation in the mortality figures.

Table 3. Results obtained by Leisman et al. (2017) [16].

Purpose	Determining mortality and costs associated with adherence to an aggressive 3-hour sepsis bundle versus nonadherence to a greater or equal bundle element for patients with severe sepsis and septic shock.
Number of subjects included	Cohort 1: five tertiary and six community hospitals. Cohort 2: single tertiary, academic medical center. Cohort 3: five tertiary and four community hospitals.
Inclusion criteria	Consecutive sample of all patients with severe sepsis and septic shock (defined as: infection, ≥ 2 systemic inflammatory response syndrome and hypoperfusion organ dysfunction) identified through a quality initiative. The exposure was full 3-hour bundle compliance. Bundle elements are as follows: 1) blood cultures before antibiotics; 2) parenteral antibiotics administered less than or equal to 180 minutes from greater than or equal to two systemic inflammatory response syndrome `and` lactate ordered, or less than or equal to 60 minutes from `time-zero`, whichever occurs earlier; 3) dairy result available less than or equal to 90 minutes postorder; and 4) 30 mL/kg IV crystalloid bolus initiated less than or equal to 30 minutes from `time zero`.
Results	Cohort 1: 5,819 total patients; 1,050 (18.0%) bundle compliant. Mortality: 604 (22.6%) versus 834 (26.5%); CI, 0.9–7.1%; adjusted odds ratio, 0.72; CI, 0.61–0.86; p value is less than 0.001. Cohort 2: 1,697 total patients; 739 (43.5%) bundle compliant. Mortality: 99 (13.4%) versus 171 (17.8%), CI, 1.0–7.9%; adjusted odds ratio, 0.60; CI, 0.44–0.80; p value is equal to 0.001. Mean costs: $14,845 versus $20,056; CI, –$4,798 to –5,624; adjusted β, –$2,851; CI, –$4,880 to –822; p value is equal to 0.006. Cohort 3: 7,239 total patients; 2,115 (29.2%) bundle compliant. Mortality: 383 (18.1%) versus 1,078 (21.0%); CI, 0.9–4.9%; adjusted odds ratio, 0.84; CI, 0.73–0.96; p value is equal to 0.013. Mean costs: $17,885 versus $22,108; CI, –$2,783 to –5,663; adjusted β, –$1,423; CI, –$2,574 to –272; p value is equal to 0.015.
Conclusions	In three independent cohorts, 3-hour bundle compliance was associated with improved survival and cost savings.
Limitations	Compliant groups had lower frequency of some comorbidities and organ dysfunction criteria. Nonexperimental findings cannot show causality.

The study by Albright et al. (2014) showed that until that time, no scoring system had been developed that took into account the normal physiological changes of pregnancy. This is also the reason why morbidity and mortality in a pregnant population has been accurately predicted. So S.O.S. became a modified sepsis scoring system for pregnancy-specific physiologic changes that was able to identify pregnant and postpartum patients at risk for sepsis intensive care unit admission within 48 hours of emergency department presentation [14].

The study by Aarvold et al. (2017) contradicts the study by Albright et al. (2014) who say that the best predictor of mortality in the obstetric population is the MODS score. This score was significantly better than the physiology-based SAPS II (Simplified Acute Physiology Score) and APACHE II (Acute Physiology and Chronic Health Evaluation) scores and the obstetric-specific SOS score. On the other hand, MODS and SOFA scores performed better in the obstetric population, suggesting that perhaps an organ-based system is more accurate. This is because of poorer outcomes in patients with multiple organ dysfunction than those in whom organ function is preserved [15].

The study by Leisman et al. (2017) showed that adherence to the 3-hour bundle is sufficient to improve clinical outcomes for patients without relying on invasive monitoring or complex physiological endpoints. We intend to carry out further analysis for the following studies [16].

Table 4. Results obtained by Ferrer et al. (2014) [17].	
Purpose	The aim of the study was to analyze the relationship between the timing of antibiotic administration and mortality.
Number of subjects included	One hundred sixty-five ICUs in Europe, the United States, and South America.
Inclusion criteria	28,150 patients with severe sepsis and septic shock were entered.
Results	After diagnosis of sepsis, a total of 17,990 people were given antibiotics and then included in the analysis. The cohort as a whole had an in-hospital death rate of 29.7%. There was a statically significant increase in the probability of death associated with the number of hours of delay in first antibiotic administration. In-hospital mortality adjusted for severity (sepsis severity score), source of ICU admission (emergency department, ward, versus ICU), and geographic region increased steadily after 1 hour of time to antibiotic administration. Results were similar in patients with severe sepsis and septic shock, regardless of the number of organ failure.
Conclusions	Delay in first antibiotic administration was associated with increased in-hospital mortality.
Limitations	The appropriateness of antibiotic therapy in this patient population has not been analyzed. The study did not look at the reasons for the delay or the cause of the delay in antibiotic administration.

Table 5. Results obtained by Holanda et al. (2020) [18].	
Purpose	The study aimed to analyze the risk factors for death in patients with sepsis admitted to the obstetric intensive care unit of a hospital.
Number of subjects included	155 patients
Inclusion criteria	155 patients with sepsis
Results	14.2% (n=22) died. Risk factors for death were septic shock at the time of hospitalization (relative risk [RR]=3.45; 95% confidence interval [CI]: 1.64–7.25), need for vasopressors during hospitalization (RR= 17.32; 95% CI: 4.20 –71.36), lactate levels >2mmol/L at diagnosis (RR=4.60; 95% CI: 1.05–20.07) and Sequential Organ Failure Assessment score >2 at diagnosis (RR=5.97; 95% CI: 1.82–19.94). Following multiple logistic regression analysis, only the need for vasopressors during hospitalization remained as a risk factor associated with death (odds ratio [OR]=26.38; 95% CI: 5.87–118.51).
Conclusions	The need for vasopressors during hospitalization is associated with death in obstetric patients with sepsis.
Limitations	The analysis was performed only on one center. The study was based on the review of medical records, the fact that some data were missing may raise doubts about the chronology of certain events.

Table 6. Results obtained by Al-Ostad et al. (2015) [19].	
Purpose	Estimation of the incidence rate and mortality rate of sepsis, as well as the associated risk factors for their development during pregnancy, labor, delivery and the postpartum period.
Number of subjects included	5 million births
Inclusion criteria	The 1998–2008 database from the Healthcare Utilization and Cost Project, death from sepsis during admission for delivery, was used.
Results	The overall incidence of maternal sepsis was 29.4 per 100,000 births (95% CI: 28.0–30.9) with a sepsis case fatality rate of 4.4 per 100 births (95% CI: 3.5-5.6). Both the incidence of maternal sepsis and the sepsis-related mortality rate have increased over the past decade.
Conclusions	Mortality from maternal sepsis during labor and delivery is a growing and important problem in Westernized countries.
Limitations	The study was limited to a single geographic area.

The study by Ferrer et al. (2014) showed that for the increased risk associated with delay there was a linear increase in the risk of mortality for each hour of delay in antibiotic administration from the first to the sixth hour after patient identification. In other words, sepsis is a time-dependent condition and must be recognized as an urgent situation that requires an immediate response [17].

In the study conducted by Holanda et al. (2020) provided a better understanding of the factors associated with death resulting from sepsis in obstetric patients with the aim of identifying prognostic factors and optimizing management [18].

The study by Al-Ostad et al. (2015) showed that black women, older than 35 years, and smokers were more likely to experience maternal sepsis. An association has also been found between maternal sepsis and diabetes mellitus,

cardiovascular disease, eclampsia, hysterectomy, puerperal infection, preterm birth, postpartum hemorrhage, transfusion, and chorioamnionitis [19].

Discussions

The analysis of this study included a sample of 29,952 patients, 3 cohorts, and a database of 5 million births from 6 specialty studies.

The analyzed studies recommended the following therapeutic practices for the management of obstetric sepsis. The S.O.S. sepsis scoring system (Obstetric Sepsis Score) was able to identify pregnant and postpartum patients at risk of admission to the intensive care unit for sepsis within 48 hours of presentation to the emergency department.

Disease severity scores based on organ failure, such as the MODS (Multiple Organ Dysfunction Score), have been shown to be equally effective in obstetric and nonobstetric (age- and sex-equivalent) populations.

Adherence to the 3-hour protocol was associated with improved survival and significant cost savings.

The administration of antibiotics must be done as soon as possible to avoid the death of the patient.

The selection of articles was made according to the following criteria: complete articles, not to be duplicated, the type of research paper, a large number of citations, and the publication period starting from 2012.

For patients with suspected sepsis, prompt and focused antibiotic therapy and fluid resuscitation are essential for the survival of these cases [20,21].

The study by Bowyer et al. (2017) presents a series of diagnostic and therapeutic indications related to general anesthesia. Thus, the study claims that the septic obstetric patient frequently exhibits hemodynamic instability and has a higher-than-normal pregnancy-related metabolic oxygen requirement. For the administration of general anesthesia, practical considerations include for the airways avoiding delayed gastric emptying, and thus avoiding an increased risk of gastric reflux followed by aspiration. It is recommended that women be premedicated with combined prophylaxis with antacid antihistamines (effervescent ranitidine, 150 mg). A rapid induction sequence is also recommended. For the pulmonary ventilation process, it would be advisable to provide patients with adequate pre-oxygenation before induction of anesthesia. In these patients there is a reduced residual functional capacity, which implies a limitation of the interrelationship between ventilation and perfusion. Consequently, the use of therapeutic ventilation strategies is recommended to maintain adequate oxygenation to minimize possible subsequent lung injury [22].

Regarding the circulatory system, consideration should be given to avoiding aortocaval compression by lateral tilting of the uterus, ensuring adequate fluid resuscitation, including appropriate use of blood products and, if necessary, inotropic support. Alpha adrenergic agonists (especially noradrenaline) are the agents of choice for maintaining uteroplacental flow.

Rapid and effective fluid resuscitation is essential to stabilize septic shock or sepsis-induced tissue hypoperfusion. Given the critical status of this medical emergency, early fluid resuscitation should begin as soon as the patient is diagnosed with sepsis, hypotension, or elevated lactate, and be completed within three hours of diagnosis. The minimum recommended amount of intravenous crystalloid for such therapy is 30 ml/kg according to current guidelines [23].

Effective treatment of sepsis was found to require aggressive resuscitation protocols involving adequate control of the source of sepsis, appropriate antibiotic drugs, and adequate support for failing organs. Therefore, delay in starting appropriate antibiotic treatment increases the risk of death in obstetric patients with sepsis [24,25].

We also aimed to analyze which studies are at risk of bias. Thus, 145 articles from 2012-2022 were analyzed, in which we intended to identify in which situations the risk of maternal death is higher.

Thus, the largest proportion of this maternal risk (24%) is found in patients with the human immunodeficiency virus (HIV), 29% in patients with Escherichia coli, 17% in patients with genital tract infection, 14% in patients with cancer, 14 % in the case of drug users, and 12% in the case of patients with chronic liver disease (Figure 2).

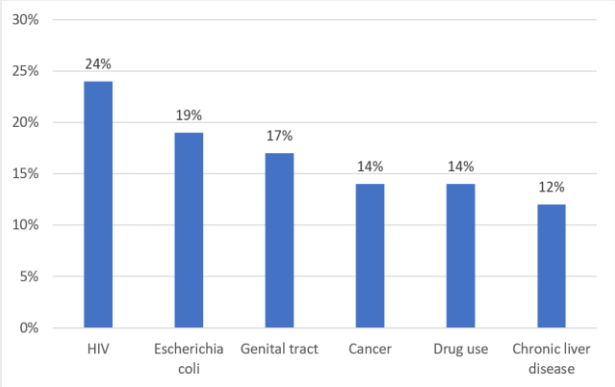

Figure 2. The risk of maternal death

HIV infection may contribute to an increased risk of postpartum infection and infection-related mortality [26].

About 13% of cases require admission to intensive care, so there is a 2.9-fold risk of preterm birth and a 5.8-fold risk of perinatal mortality. In the case of infection of the genital tract for the first and second trimester, fetal loss occurs. The most prevalent organisms are E. coli and group B streptococcus, although the most virulent organisms are E. coli associated with preterm sepsis and group A streptococcus associated with postpartum sepsis [27-29].

Women who give birth by caesarean section are more prone to severe sepsis, while women who give birth vaginally are more prone to infection with group A

streptococcus. On the other hand, women already infected with group A streptococcus have a higher risk of progression to septic shock, in contrast to women infected with another infectious agent [30-32].

The study by Balki et al. (2022) also included among the risks: stillbirths, artificial rupture of membranes, retained products of conception, as well as surgical procedures (hysterectomy, cervical cerclage, dilatation and curettage) and obstetric conditions (postpartum hemorrhage, preeclampsia/eclampsia, and placental abruption) [33].

The study by Shields et al. (2023) presents a series of recommendations on how to manage sepsis during pregnancy and in the postpartum period. Thus, if sepsis and septic shock are medical emergencies, treatment and resuscitation should begin as soon as possible. In the case of severe organ damage in pregnant patients due to an infectious process, the diagnosis of sepsis must be made as quickly as possible, while broad-spectrum antibiotics must be administered (to any pregnant woman suspected of having sepsis) within a maximum of 1 hour. Also, requirements include obtaining cultures (blood, urine, respiratory, etc.) and serum lactate levels in pregnant or postpartum women with suspected or identified sepsis, and early control of the source of sepsis should be completed as soon as possible. Early administration of 1-2 L of crystalloid solutions is also recommended in sepsis complicated by arterial hypotension or suspected organ hypoperfusion [34-39]. Another recommendation concerns the use of norepinephrine as a first-line vasopressor during pregnancy and the postpartum period in sepsis with persistent hypotension and/or hypoperfusion, in addition to fluid resuscitation [36-40]. Therefore, protocols to improve early diagnosis and effective therapeutic management may help reduce the incidence and consequences of maternal sepsis during labor and delivery.

Conclusions

Maternal deaths due to severe sepsis are generally caused by late presentation to the doctor, which further leads to delay in diagnosis and treatment.

The obstetric-specific S.O.S. score has been shown to have a poor predictive value for the assessment of mortality in obstetric septic shock.

Establishing an early diagnosis and rapid multidisciplinary therapeutic management (obstetrician, neonatologist and intensive care physician and anesthetist) are essential for the patient's prognosis.

Transfer to intensive care is necessary if the patient is hemodynamically unstable and requires vasopressor support, requires mechanical ventilation or presents an altered level of consciousness, hemodialysis, multiple organ failure, or hypothermia.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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