Review on Updates in Diagnosis and Management of Puerperal Sepsis

Abstract:

Puerperal sepsis caused 31% of pregnancy - related deaths in a retrospective study from Mbarara, Uganda, making it the most leading cause of maternal deaths mortality. The majority of postpartum infection research has taken place in high-resource countries, where risk factors such as inadequate cleanliness, poor socioeconomic position, prolonged labor, and these factors could differ in low- resources countries due to changes in the patient environment and healthcare system. The pathogenesis of puerperal sepsis is extremely complicated and poorly understood. as the pregnant woman acquire different adaptations on both scales, immunological and physiological which are intended to help the fetus develop, all these changes can hinder the mother's ability to defend against infection during pregnancy and the puerperium. Management of puerperal sepsis based on three main levels, the first is the prevention of sepsis using empirical antibiotics, the second one is for the management of the septic patient using resuscitation and source control, if the case continues to worse, admission to ICU is necessary where some measurements should be taken such as glycemic control, using oxygen, vasopressors and steroids.

Introduction:

Globally, postpartum infection is the primary cause of maternal death. Every year, over five million cases of pregnancy-related infection occur worldwide, with around 75,000 of these cases resulting in mortality [1]. Infection rates are higher in places where facilities are low, and many infection-related maternal fatalities can be avoided. Between the time of delivery and the 42nd day after delivery, postpartum infections are a subtype of maternal infections [2]. Puerperal sepsis, infection at surgical sites, urinary tract infections, and wound infections are the most prevalent maternal infections [3]. Puerperal sepsis caused 31% of pregnancy - related deaths in a retrospective study from Mbarara, Uganda, making it the most leading cause of maternal deaths mortality [4]. The majority of postpartum infection research has taken place in high-resource countries, where risk factors such as inadequate cleanliness, poor socioeconomic position, prolonged labor, and these factors could differ in low- resources countries due to changes in the patient environment and healthcare system [5, 6].

Puerperal sepsis is the third most common direct cause of maternal death, accounting for 11% of all maternal deaths globally. Sepsis also has a role in other prevalent causes of maternal mortality, including hemorrhage and thromboembolism [7]. Despite increased maternal mortality and morbidity, as well as the unpredictability of emerging causative organisms, maternal sepsis has received less attention and research than other leading causes of maternal death [8]. Early detection of sepsis is a leading source of avoidable morbidity, lead to delayed treatment and increased care, which can save more lives. Our understanding of sepsis pathophysiology has vastly increased, and we now have a better understanding of the interaction between maternal physiology and sepsis, which has significant consequences for sepsis diagnosis in the prenatal, intra-partum, and postpartum periods. [9, 10]

South Asia (14 percent) had the highest proportion of maternal fatalities caused by sepsis. Postpartum sepsis could be easily prevented with easily available and fairly low therapies. Maternal mortality in advanced nations decreased dramatically in the mid-twentieth century, with a significant amount of this decrease related to the management and cure of maternal infections and sepsis. Case fatality rates were as high as 20% before using antibiotics. Case fatality rates could reach 2% when effective antibiotic medication is provided. [11-18] Morbidity rates for sepsis are 20 times greater than death rates, with consequences such as septicemia, shock, peritonitis, and abscess development necessitating surgery. Chronic pelvic inflammatory illness and bilateral tubal blockage, both of which can affect future fertility, are long-term implications, especially if therapy is postponed or insufficient. Infections can also be transmitted to babies within the antepartum period or by contact during birth, presenting a significant risk. [19-21]

Infection, the host's reaction to infection, and organ failure all have a significant rule in sepsis. Because a large range of infections can elicit life-threatening responses in several organs, sepsis presents a wide range of clinical manifestations [22, 23]. Pregnant women are more susceptible

to infections and sepsis than non-pregnant women for a variety of reasons. The incidence for sepsis increases during the postpartum period, due to physiological, physical and immunological changes that occur during pregnancy. Examples for physiological adaptive responses to pregnancy are hyper-dynamic circulation, increased heart rate, decreased oxygen reserve, and high risk to coagulation [24, 25]. other factors such as mother's struggles within the 2nd phase of delivery, procedures during labor, or bleeding may mask signs and symptoms of infection and sepsis. As a result, sepsis detection and management may be delayed. Another issue to consider is that intra-uterine infections and antepartum maternal illnesses account for high percentage of newborn sepsis. [26, 27]

A revised definition of sepsis and septic shock was released in 2016. The quick sequential (sepsis-related) organ failure assessment (qSOFA) besides sequential organ failure assessment (SOFA), were used to help in the prediction and identification of sepsis since their release. These, however, have not been tested in pregnant or puerperal women, as application of the previously mentioned criteria is hindered by the physiological variations that occur during pregnancy. 25 This was recognized by the international medical research community [28]. The World Health Organization (WHO) conducted a comprehensive study and specialist counseling in 2017, which led to a specific definition that stated: "Maternal sepsis is a life-threatening condition characterized by organ failure due to infection during different periods such as pregnancy, labor, post-abortion, or postpartum"[29].

Endometritis is defined by the WHO as "a genital tract infection that occurs between the labor and the next 42nd day postpartum after labor and is accompanied by fever and one or all of the following symptoms: pelvic pain, abnormal discharges or odor from vagina, and latency in the rate of uterus shrinkage [30, 31]. “A mixture of broad-spectrum antibiotics administered using intravenous way is the conventional treatment for postpartum Endometritis, Furthermore, in resource-poor places; there are currently no worldwide standards for oral medicines, which have an impact on women who have inadequate access to good healthcare. [32, 33]

Pathophysiology and risk factors of puerperal sepsis:

The pathogenesis of puerperal sepsis is extremely complicated and poorly understood. as the pregnant woman acquire different adaptations on both scales, immunological and physiological which are intended to help the fetus develop, all these changes can hinder the mother's ability to defend against infection during pregnancy and the puerperium. Pregnancy-induced physiological hyperventilation, which is thought to be caused by progesterone, causes a respiratory alkalosis that is balanced by an increase in renal bicarbonate excretion. As a result, pregnant woman may not be able to balance metabolic acidosis caused by sepsis. Furthermore, other changes that occur to support the keep a healthy pregnancy are similar to those seen in early sepsis, making identification difficult. [34-36] the pathophysiology could be linked to:

The cardiovascular system:

The alterations to the cardiovascular system that develop during septic shock are linked to an increased death rate. During sepsis, the percentage of nitric oxide is elevated, which causes relaxation of the smooth muscle, and vasodilation. Estradiol which is increased during pregnancy causes up-regulation of nitric oxide and prostaglandins, which cause physiological adjustments needed to sustain the developing fetus. This, make pregnant women more vulnerable to infection-induced sudden hypotension, resulting in hypo-perfusion of tissues and organ failure. [37, 38]

Immunology:

Having a better knowledge of the complicated immunology at work during pregnancy is emerging. Pregnant women are mostly immunologically tolerant to allow for fetal growth and development. This theory was the main one for long time which was proposed by Medawar, this concept is subjected to some changes now. Multiple researches and investigations into the pathophysiology of pregnancy, the functions of both the innate and adaptive systems are being unraveled as a result of extensive study into the immunology of pregnancy in health and disease. The growth of 'immunosuppressive' regulatory T cells, for example, is linked to immunological tolerance in healthy pregnancy. Failure to do so has been linked to the causes of recurrent miscarriages and preterm labor. [39- 42]

Risk factors:

There are several risk factors for sepsis and development to septic shock, which can be classified as either obstetric-related or patient-related risk factors.

Patient-related risk factors

Pre-existing medical disorders, ethnic status, febrile sickness, or antibiotic use in the two weeks before to presentation is all patient-related major risk factor for puerperal sepsis, according to the UK Obstetric Surveillance System [43]. Chronic liver failure, renal failure, human immunodeficiency infection, congestive heart failure, and diabetes are among conditions that have a relationship with maternal sepsis [44]. The frequency of maternal sepsis is strongly associated with lower socioeconomic position, and there is a strong social gradient related to sepsis. In the United States, Medicaid dependency is linked to the development of maternal sepsis, poverty is also linked to a greater rate of caesarean section (CS) which is an independent risk factor for maternal sepsis. [45]

Obstetric-related risk factors

Operative intervention is the most significant obstetric risk factor for postpartum maternal sepsis, as caesarean section (CS) is related to a 5 to 20% elevation in infectious death rates in comparison to vaginal birth. Although bacterial prophylaxis and sterility are routine practice in the UK. Caesarean section is reported to have the highest risk, followed by elective CS and the least one is the surgical vaginal birth. long -lasting rupture of the membranes, a previous history of pelvic infection, a previous exposure to group B or group A streptococcal infection, numerous

pregnancies, preterm pre-labor rupture of membranes (PPROM), any invasive procedures such as amniocentesis or similar ones are all considered obstetric risk factors. [43-46]

Diagnosis:

Polymerase chain reaction and mass spectrometry:

The accuracy and speed of analysis are two major advantages mass spectroscopy and PCR-based procedures, they are, however, costly and may identify non-pathogenic species. Using blood cultures and blood samples, multiplex polymerase chain reaction (PCR) can discover the DNA sequence of numerous pathogens and their genes. However, more research into its therapeutic effectiveness is needed before it can be widely used. Similarly, utilizing a time-of-flight (TOF) mass spectrometer, matrix-assisted laser desorption/ionization (MALDI) can detect a wide range of organisms including both fungus and bacteria from clinical isolates and cultures. PCR is now recommended by NICE for the diagnosis of children meningococcal meningitis due to its accuracy and sensitivity. [47 ,48].

Modifying early warning scores for pregnant women:

The modified early warning score (MEWS) is a useful tool for identifying sick patients; it has the disadvantage of being imprecise. Obstetric morbidity had a sensitivity of 89 percent and specificity of 79 percent was found in a study published in 2012. Albright et al. developed a predictive algorithm to identify obstetric sepsis patients who need to be admitted to the intensive care unit (ICU). They integrated data collected from blood testing into the standard early warning score. The results could be either normal, or ≥6 which means the necessity to admission to ICU. A comparable composite assessment, with higher performing biomarkers uncovered in future trials, could potentially yield even better results. [49, 50]

Tools for antimicrobial evaluation:

Traditional culture and sensitivity tests have limited specificity and are time consuming in clinical practice, making it difficult to confirm a systemic microbial infection. Only 30–40% of blood cultures will give positive results in septic patients, and the findings will not be accessible for at least 24 hours, so the traditional methods are no longer suitable. A variety of novel technologies are being developed that have the ability to quickly identify organisms and antibiotic resistance patterns, allowing for prompt and optimal treatment while minimizing the effort for using the suitable antibiotic. [51]

C-reactive protein and procalcitonin biomarker:

U sing biomarkers has many advantages such as recognizing patients in the initial stages of sepsis, distinguishing sepsis from other non-infectious inflammatory diseases, estimating the severity of the case and the suspected outcomes and finally assisting the physician to determine

the suitable treatment procedures [52]. C-reactive protein (CRP), White cell count (WCC), procalcitonin (PCT), and lactate are the most commonly used biomarkers in clinical practice. Procalcitonin is more selective for bacterial infection than white cell count and C-reactive protein, which are general for inflammation infections [53]. Although there are a variety of procalcitonin assays available, a meta-analysis undertaken by NICE found insufficient evidence to recommend routine usage to guide acute management during bacterial infection. The new Surviving Sepsis Campaign (SSC) reported that caution should be given in extrapolating this diagnostic tool to the pregnant woman, especially in the lack of a normal range, as the quality of this technique is known to be low. [54]

Lactate biomarker:

Lactate values are thought to be similar in healthy pregnant to those in the overall population. rise in lactate levels can indicate increased metabolic load that comes with pregnancy; if this is worsened by hemorrhage or sepsis, a pregnant woman's capacity to balance it may be hampered. In maternal sepsis, an increased serum lactate level is linked to a bad prognosis. Serum values of >4 mmol/l, together with clinical indications of septic shock, are linked to mortality rates of up to 46% in non-pregnant women. on one hand, blood lactate is a good tool for detecting tissue hypoxia hypo-perfusion, on the other hand it is not enough for confirmation, so measurement of metabolic acidosis by different tools should be taken into consideration. [43,55]

Prevention and Management:

Prophylaxis and prevention

Using antibiotic for prophylaxis after caesarean section (CS) was found to reduce the risk of morbidity, wound infection, puerperal sepsis, and other significant infection-related complications, according to a Cochrane systematic review. The fundamental goal is to prevent sepsis, nowadays; multiple screening tools are available to detect asymptomatic bacteriuria. Numerous studies have emphasized the increased incidence of infections during the peripartum and postpartum periods, with surgical births identified as a significant risk factor. The ANODE study was conducted in 2018, found that when one dose of intravenous antibiotic was given a median of 3 hours after birth, there was a 56 percent reduction in established maternal infection. It was also linked to a lower risk of infection in the perineum. These findings, indicates that the currently used guidelines should be revised and changed for more beneficial control and prevention.

Management

Management of puerperal sepsis requires physician to take into considerations the physiological variables caused by pregnancy. The need of having a low index of suspicion to help early detection, doing necessary investigations and monitoring (cultures, blood lactate, and hourly

urine output), and initiating necessary therapy (oxygen, intravenous fluids, and antibiotics) are all important considerations in the management. Management is based on two key approaches: resuscitation and source control

- **Resuscitation:** Initial I.V fluid resuscitation at a frequency of 30 ml/kg is recommended by the SSC. this rate has been reduced to 20 ml/kg aiming to alleviate the risk of casing pulmonary edema due to lower colloid oncotic pressure. When there is a blood lactate of >4 mmol/l and/or a mean arterial pressure of >65 mmHg, this should be started right away for the treatment of septic shock. Using crystalloid or colloid fluids for treatment is another issue, but some confirmatory data was given about the advantage of crystalloids as it lacks the renal toxicity associated with synthetic colloids, so Crystalloids are the primary choice of intravenous fluids. [52,56]
- **Source control:** Antibiotics must be started to control the source. Only for the treatment of septic shock combining two types of antibiotics is necessary. However, while Escherichia coli and group B streptococcus are among the most prevalent bacterial pathogens in maternal sepsis, E. coli and group A streptococcus are associated with the most serious complications. As a result, clinical evaluation and the suspected infection site influence antibiotic selection. Physicians mostly start with empirical antibiotic that can eradicate gram positive, gram negative and anaerobic organisms the outcomes of the culture are then used to determine the suitable antibiotic. Antibiotics alone are insufficient in some situations, necessitating abscess draining or the removal of disease - causing organisms [52, 57]

Management at intensive care unit ICU:

Admission to ICU due to puerperal sepsis is rare, but some guidelines are designed to manage this condition [58]. Glycemic control: The implications of strict glycemic control during acute maternal sickness are unknown, given the awareness of elevated glucose resistance during pregnancy. There has been no consensus on the influence of glycemic control versus conventional treatment on ICU sepsis morbidity and death rates due to conflicting data. Physicians are currently aiming for values of fewer than 180 mg/dl (10 mmol/l). 50 This is unlikely to harm the infant; uncontrolled hyperglycemia, on the other hand, poses a bigger risk.[52]

Oxygen: Oxygen must be supplied to attain a saturation of 94 percent, and when patients are severely ill, a mixed venous oxygen saturation (SvO2) of 65 percent or 70 percent, is the goal. The SvO2 in healthy pregnant in her last trimester is around 80%, currently, the information to suggest the optimum SvO2 in a severely ill pregnant patient are limited.[59]

Steroids: A systematic evaluation of 42 clinical trials published in 2018 found that steroids reduced 28-day fatality of patients in ICU by 2%. However, the research supporting this finding is of poor quality, and that the recommendations are not relevant to the obstetric population. In

the case of maternal sepsis, physicians generally favor withholding intravenous hydrocortisone. The recent guidelines do not support steroid treatment for sepsis; however, caution is advised while boosting fetal lung maturity. Steroid treatment is generally recommended for other benefit outside of sepsis, including in respiratory disease and connective tissue disease, but continuous steroid use may have a deleterious influence on the developing fetus, with concerns about birth weight and head circumference.[60]

Vasopressors: If a pregnant woman is admitted to the ICU with septic shock, vasopressors can be utilized. Because of its efficacy, noradrenaline is the primary choice for treatment. Catecholamine, particularly dopamine, can trigger arrhythmias, therefore adding vasopressin can help lower catecholamine levels. Sepsis has been linked to myocardial depression that can be reversed, and inotropes should be evaluated when cardiac output is low. Levosimendan is an inotropic agent having vasodilator effects that is still relatively new. It also contains anti-inflammatory and anti-oxidative properties, which could protect against sepsis-related tissue damage. [61,62]

Conclusion:

Puerperal sepsis is a serious condition that causes high percentage of mortality worldwide, especially in low-status countries. E-coli and streptococcus are the main pathogens leading to sepsis, where the diagnosis could be done by traditional ways which are less sensitive and less specific, so nowadays, more selective tools are used such as detecting biomarkers and PCR. Management of puerperal sepsis based on three main levels, the first is the prevention of sepsis using empirical antibiotics, the second one is for the management of the septic patient using resuscitation and source control, if the case continues to worse, admission to ICU is necessary where some measurements should be taken such as glycemic control, using oxygen, vasopressors and steroids. The management guidelines still need more evaluation and development to ensure better treatment and cure level.

References:

1. Miller AE, Morgan C, Vyankandondera J. Causes of puerperal and neonatal sepsis in resource-constrained settings and advocacy for an integrated community-based postnatal approach. Int J Gynaecol Obstet. 2013;123(1):10–5.
2. Janni W, Schiessl B, Peschers U, Huber S, Strobl B, Hantschmann P, Uhlmann N, Dimpfl T, Rammel G, Kainer F. The prognostic impact of a prolonged second stage of labor on maternal and fetal outcome. Acta Obstet Gynecol Scand. 2002;81(3):214–21.
3. van Dillen J, Zwart J, Schutte J, van Roosmalen J. Maternal sepsis: epidemiology, etiology and outcome. Curr Opin Infect Dis. 2010;23(3):249–54.
4. Lapinsky SE. Obstetric infections. Crit Care Clin. 2013;29(3):509–20.
5. Ngonzi J, Tornes YF, Mukasa PK, Salongo W, Kabakyenga J, Sezalio M, Wouters K, Jacqueym Y, Van Geertruyden J-P. Puerperal sepsis, the leading cause of maternal deaths at a Tertiary University Teaching Hospital in Uganda. BMC Pregnancy Childbirth. 2016;16(1):207.
6. Maharaj D. Puerperal pyrexia: a review. Part I. Obstet Gynecol Surv. 2007;62(6):393–9.
7. Say L, Chou D, Gemmill A, et al.: Global causes of maternal death: A WHO systematic analysis. Lancet Glob Health. 2014; 2(6): e323–e333. PubMed Abstract | Publisher Full Text
8. World Health Organisation: Statement on Maternal Sepsis. (accessed 4 December 2018). Reference Source
9. Lawton B, MacDonald EJ, Brown SA, et al.: Preventability of severe acute maternal morbidity. Am J Obstet Gynecol. 2014; 210(6): 557.e1–6. PubMed Abstract | Publisher Full Text
10. Mor G, Cardenas I: The immune system in pregnancy: A unique complexity. Am J Reprod Immunol. 2010; 63(6): 425–33. PubMed Abstract | Publisher Full Text | Free Full Text
11. Who. Trends In Maternal Mortality: 1990 To 2013. Estimates By Who, Unicef, Unfpa, The World Bank And The United Nations Population Division. Geneva: World Health Organization; 2014.
12. Kassebaum Nj, Bertozzi-Villa A, Coggeshall Ms, Shackelford Ka, Steiner C, Heuton Kr, et al. Global, Regional, And National Levels And Causes Of Maternal Mortality During 1990-2013: A Systematic Analysis For The Global Burden Of Disease Study 2013. Lancet. 2014. doi:10.1016/S0140-6736(14)60696-6.
13. Say L, Chou D, Gemmill A, Tunáalp O, Moller A-B, Daniels J, et al. T1 – Global Causes Of Maternal Death: A Who Systematic Analysis. The Lancet Global Health. 2014;2(6):e323–33.
14. Maharaj D. Puerperal Pyrexia: A Review. Part II. Obstet Gynecol Surv. 2007; 62(6):400–6. doi:10.1097/01.Ogx.0000266063.84571.Fb.

15. Td N, Borresen J, Hew-Butler T, Mi L, Jordaan E. Semmelweis And The Aetiology Of Puerperal Sepsis 160 Years On: An Historical Review. Epidemiol Infect. 2008; 136(1):1–9. doi:10.1017/S0950268807008746. S0950268807008746 [Pii].
16. Adriaanse AH, Pel M, Bleker OP. Semmelweis: The Combat Against Puerperal Fever. Eur J Obstet Gynecol Reprod Biol. 2000;90(2):153–8.
17. Pagel C, Lewycka S, Colbourn T, Mwansambo C, Meguid T, Chiudzu G, et al. Estimation Of Potential Effects Of Improved Community-Based Drug Provision, To Augment Health-Facility Strengthening, On Maternal Mortality Due To Postpartum Haemorrhage And Sepsis In Sub-Saharan Africa: An Equity-Effectiveness Model. Lancet. 2009;374(9699):1441–8. doi:10.1016/ S0140-6736(09)61566-X.
18. Hm K, Jm S, Jj Z, Nw S, Ea S, Van Roosmalen J. Maternal Mortality And Severe Morbidity From Sepsis In The Netherlands. Acta Obstet Gynecol Scand. 2009;88(6):647–53. doi:10.1080/00016340902926734. 910899819 [Pii].
19. Rl G, Jc H, Ww A. Intrauterine Infection And Preterm Delivery. The New England Journal Of Medicine. 2000;342(20):1500–7.
20. Ayengar V, Madhulika, Vani S. Neonatal Sepsis Due To Vertical Transmission From Maternal Genital Tract. Indian Journal Of Pediatrics. 1991;58(5):661–4.
21. Dolea C, Stein C. Global Burden Of Maternal Sepsis In The Year 2000. Geneva: World Health Organization; 2003.
22. Acosta CD, Knight M. Sepsis and maternal mortality. Curr Opin Obstet Gynecol. 2013;25(2):109–16.
23. Bauer ME, Bauer ST, Rajala B, MacEachern MP, Polley LS, Childers D, Aronoff DM. Maternal physiologic parameters in relationship to systemic inflammatory response syndrome criteria: a systematic review and metaanalysis. Obstet Gynecol. 2014;124(3):535–41.
24. Buddeberg BS, Aveling W. Puerperal sepsis in the 21st century: progress, new challenges and the situation worldwide. Postgrad Med J. 2015; 91(1080):572–8.
25. Morgan J, Roberts S. Maternal sepsis. Obstet Gynecol Clin North Am. 2013; 40(1):69–87.
26. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. PLoS Med. 2013;10(8):e1001502.
27. Bellizzi S, Bassat Q, Ali MM, Sobel HL, Temmerman M. Effect of puerperal infections on early neonatal mortality: a secondary analysis of Six demographic and health surveys. PLoS One. 2017;12(1):e0170856.
28. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10.

29. Bonet M, Nogueira Pileggi V, Rijken MJ, Coomarasamy A, Lissauer D, Souza JP, et al. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reprod Health 2017;14:67.
30. Who. Mother-Baby Package: Implementing Safe Motherhood In Countries. Geneva: World Health Organization, Maternal Health And Safe Motherhood Program, Division Of Family Health; 1994.
31. Tharpe N. Postpregnancy Genital Tract And Wound Infections. J Midwifery Womens Health. 2008;53(3):236–46. doi:10.1016/J.Jmwh.2008.01.007.
32. World Health Organization. Maternal Health And Safe Motherhood Programme. Education Material For Teachers Of Midwifery : Midwifery Education Modules. 2nd ed. Geneva: World Health Organization; 2008.
33. French L, Smaill F. Antibiotic Regimens For Endometritis After Delivery. Cochrane Database Syst Rev. 2004;4:Cd001067. 10.1002/14651858.Cd001067.Pub2.
34. Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. Lactic acid measurement to identify risk of morbidity from sepsis in pregnancy. Am J Perinatol 2015;32:481–6.
35. Padilla C, Palanisamy A. Managing maternal sepsis: early warning criteria to ECMO. Clin Obstet Gynecol 2017;60:418–24.
36. Joseph J, Sinha A, Paech M, Walters BNJ. Sepsis in pregnancy and early goaldirected therapy. Obstet Med 2009;2:93–9.
37. Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scoletta S. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. J Crit Care 2014;29:500–11.
38. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr 2016;27:89–94.
39. Medawar PB. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symp Soc Exp Biol 1953;7:320–38.
40. La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: regulatory T cells control maternal immune tolerance toward the fetus. Immunol Lett 2014;162:41–8.
41. Guerin LR, Prins JR, Robertson SA. Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? Hum Reprod Update 2009;15:517–35.
42. Ruocco MG, Chaouat G, Florez L, Bensussan A, Klatzmann D. Regulatory T cells in pregnancy: historical perspective, state of the art, and burning questions. Front Immunol 2014;5:389.
43. Bauer ME, Bateman BT, Bauer ST, et al.: Maternal sepsis mortality and morbidity during hospitalization for delivery: temporal trends and independent associations for severe sepsis. Anesth Analg. 2013; 117(4): 944–50. PubMed Abstract | Publisher Full Text | F1000 Recommendation

44. Acosta CD, Kurinczuk JJ, Lucas DN, et al.: Severe Maternal Sepsis in the UK 2011-2012: A National Case-Control Study. PLoS Med. 2014; 11(7): e1001672. PubMed Abstract | Publisher Full Text | Free Full Text.
45. Royal College of Obstetricians and Gynaecologists: Bacterial Sepsis in Pregnancy, Green-top Guideline No.64a. 2012. Reference Source.
46. Conroy K, Koenig AF, Yu YH, et al.: Infectious morbidity after cesarean delivery: 10 strategies to reduce risk. Rev Obstet Gynecol. 2012; 5(2): 69–77. PubMed Abstract | Free Full Text
47. Poole S, Kidd SP, Saeed K. A review of novel technologies and techniques associated with identification of bloodstream infection etiologies and rapid antimicrobial genotypic and quantitative phenotypic determination. Expert Rev Mol Diagn 2018;18:543–55.
48. National Institute for Health and Care Excellence. Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. Clinical guideline 102. London: NICE; 2015 [https://www. nice.org.uk/guidance/cg102/resources/meningitis-bacterial-and-meningoc occal-septicaemia-in-under-16s-recognition-diagnosis-and-managementpdf-35109325611205].
49. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia 2012;67:12 8.
50. Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. The Sepsis in Obstetrics Score: a model to identify risk of morbidity from sepsis in pregnancy. Am J Obstet Gynecol 2014;211:39.e1–8.
51. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis 2015;15:581–614.
52. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43:304.
53. Tujula B, Kokki H, R€as€anen J, Kokki M. Procalcitonin; a feasible biomarker for severe bacterial infections in obstetrics and gynecology? Acta Obstet Gynecol Scand 2018;97:505–6.
54. National Institute for Health and Care Excellence. Procalcitonin testing for diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay). Diagnostic guidance 18. London: NICE; 2015 [https://www.nice.org.uk/guidance/ dg18].
55. Lee SM, An WS. New clinical criteria for septic shock: serum lactate as new emerging vital sign. J Thorac Dis 2016;8:1388–90.
56. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392:75–87.

57. Knowles SJ, O'Sullivan NP, Meenan AM, Hanniffy R, Robson M. Maternal sepsis incidence, aetiology and outcome for mother and fetus: a prospective study. BJOG 2015;122:663–71.
58. Jardine J, NMPA Project Team. Maternity Admissions to Intensive Care in England, Wales and Scotland in 2015/16: A Report from the National Maternity and Perinatal Audit. London: RCOG; 2019 [https://maternityaudit org.uk/FilesUploaded/NMPA%20Intensive%20Care%20sprint%20report. pdf].
59. Trikha A, Singh P. The critically ill obstetric patient - Recent concepts. Indian J Anaesth 2010;54:421–7.
60. Trikha A, Singh P. The critically ill obstetric patient - Recent concepts. Indian J Anaesth 2010;54:421–7.
61. Gustafsson F, Guarracino F, Schwinger RHG. The inodilator levosimendan as a treatment for acute heart failure in various settings. Eur Heart J Suppl 2017;19(Suppl C):C2–7.
62. Harjola VP, Giannakoulas G, von Lewinski D, Matskeplishvili S, Mebazaa A, Papp Z, et al. Use of levosimendan in acute heart failure. Eur Heart J Suppl 2018;20:I2–10.