REVIEW DERLEME

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Overview of the Relationship Between Obstetric Factors and Maternal Deaths: Systematic Review

Obstetrik Faktörler ve Maternal Ölüm Arasındaki İlişkiye Genel Bir Bakış: Sistematik Derleme

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ABSTRACT Throughout pregnancy, various organ systems, such as cardiovascular, respiratory, gastrointestinal, and more, adapt to pregnancy under normal physiological conditions. In addition to being a natural process, pregnancy causes physiological, psychological, and anatomical changes in the pregnant woman's organism. These changes begin immediately after fertilization, and they help meet the mother's and baby's metabolic needs and maintain the health of the mother and baby in the best possible way. All systems are affected to different degrees by the needs of the fetus. Maternal death is defined as maternal deaths resulting from direct factors related to pregnancy or the gestation process or from factors indirectly aggravated by these factors during pregnancy, during birth, or within 42 days after birth, regardless of the duration and place of pregnancy. Maternal deaths are subdivided into 2 groups: direct and indirect obstetric deaths. Direct maternal deaths resulting from obstetric complications of pregnancy. Indirect maternal deaths are caused by a pre-existing disease or diseases that develop during pregnancy and are not directly related to obstetric causes but are aggravated by the physiological effects of pregnancy. Many countries are making efforts on different issues to reduce maternal deaths, and most of these efforts yield successful results. However, in some countries, maternal mortality rates are still relatively high. Maternal deaths are a significant global health problem that must be solved as a priority. In this review, obstetric factors that cause maternal deaths and indirect causes triggered by these factors are mentioned.

Keywords: Maternal death; obstetric complication; pregnancy; maternal-fetal relations; pregnancy outcome

ÖZET Gebelik boyunca, kardiyovasküler, solunum, gastrointestinal, üriner ve diğer organ sistemleri, normal fizyolojik koşullar altında gebeliğe uyum sağlar. Gebelik, doğal bir süreç olmasının yanı sıra, fizyolojik, psikolojik ve anatomik değişikliklere de yol açar. Bu değişiklikler, döllenmeden hemen sonra başlayıp, annenin ve bebeğin metabolik ihtiyaçlarını karşılamaya, anne ve bebeğin sağlığını en iyi şekilde korumaya yardımcı olur. Tüm sistemler, fetüsün ihtiyaçları doğrultusunda farklı derecelerde etkilenir. Maternal ölüm, doğrudan gebelikle veya doğum süreciyle ilgili faktörlerden ya da bu faktörlerin gebelik sırasında, doğum sırasında veya doğumdan sonraki 42 gün içinde dolaylı olarak kötüleşmesinden kaynaklanan anne ölümlerini tanımlar. Doğrudan ve dolaylı olmak üzere maternal ölümler 2 gruba ayrılır. Doğrudan maternal ölümler, gebeliğin obstetrik komplikasyonlarından kaynaklanırken, dolaylı maternal ölümler, gebelik sırasında gelişen ve obstetrik nedenlerle doğrudan ilişkili olmayan, ancak gebelikteki fizyolojik değişikliklerle kötüleşen, önceden var olan hastalıklar nedeniyle meydana gelir. Birçok ülke, maternal ölümleri azaltmaya yönelik çaba sarf etmektedir ve bu çabaların çoğu başarılı sonuçlar vermektedir. Ancak bazı ülkelerde maternal mortalite oranları hala nispeten yüksektir. Maternal ölümler, öncelikli olarak çözülmesi gereken önemli bir küresel sağlık sorunu olarak ön plana çıkmaktadır. Bu derlemede, maternal ölümlere neden olan obstetrik faktörler ve bu faktörlerin tetiklediği dolaylı nedenler ele alınmaktadır.

Anahtar Kelimeler: Maternal ölüm; obstetrik komplikasyon; gebelik; maternal-fetal ilişkiler; gebelik sonucu

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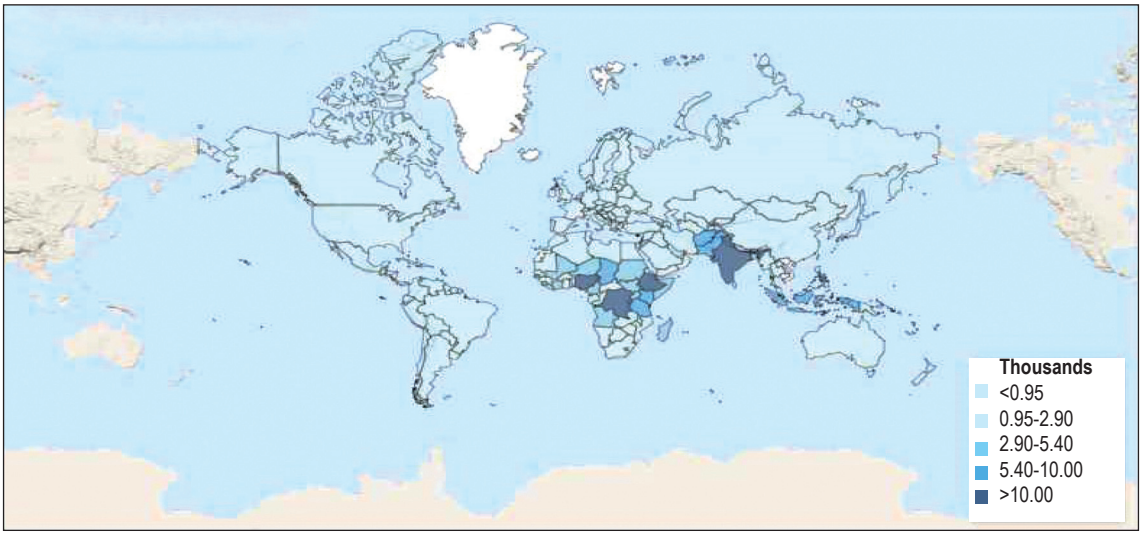

FIGURE 1: Trends in maternal mortality 2000-2020[1]

Each year, approximately a quarter of a million women die due to pregnancy-related causes. The reasons for maternal deaths are varied. In developing countries, the reason is primarily difficulties in accessing health services, while in developed countries, maternal deaths are typically linked to multiple risk factors such as chronic disorder, obesity, smoking, etc. It was reported that approximately 287.000 women died during or after pregnancy and childbirth in 2020, and almost 95% of these maternal deaths occurred in low- and lower-middle-income countries (Figure 1). Maternal deaths are classified according to their causes and delay patterns. These models are defined as 3-lag models by the World Health Organization (WHO). The 1st stage of delay usually occurs when parents realize the situation late. Lack of medical knowledge is one of the most important reasons for this. The 2nd stage delay occurs due to poverty or living far from healthcare facilities. Third-phase delay usually occurs due to misdiagnosis or inadequate treatment.

MATERNAL DISEASES

PREECLAMPSIA

Preeclampsia is a hypertensive disorder affecting 6-12% of pregnancies. It causes over 75,000 maternal and more than half a million infant deaths annually worldwide. Rising risk factors like obesity, *in vitro* fertilization, and advanced maternal age have increased its incidence to 5-10% globally.[2] While the exact cause remains unknown, generalized endothelial dysfunction is recognized as a key factor. Preeclampsia typically occurs after the 20th week, linked to a dysfunctional placenta that releases "toxic factors" into maternal circulation. Symptoms include hypertension, proteinuria, headaches, edema, and abdominal pain. If untreated, it can lead to severe complications, including organ failure and fetal death.[2-4] Managing preeclampsia is complex due to its unpredictable nature. Although aspirin can delay onset, there is no cure; delivery of the placenta is the only definitive treatment, often leading to premature birth. Timing of delivery is critical to prevent severe outcomes.[2,4] Research highlights the role of circulating anti-angiogenic factors, particularly the protein sFlt-1, which inhibits placental growth factor (PlGF) and is linked to preeclampsia. Introducing biomarkers like sFlt-1 and PlGF in the USA has shown promise in reducing maternal morbidity and mortality, contributing to shorter hospital stays and improved outcomes.[5]

HYPERTENSION

Hypertensive disorders of pregnancy (HDP) are common complications worldwide, affecting about 10%

of pregnancies and impacting maternal, fetal, and neonatal health. Hypertension may be pre-existing or arise during pregnancy, sometimes only becoming evident during labor or postpartum. Classification of HDP is vital for management and prognosis. It is defined as hypertension occurring in the 2nd half of pregnancy or within 24 hours postpartum, without proteinuria, and typically resolving within 6-12 weeks after delivery. Women with HDP face a higher risk of future hypertension, with 15-25% developing preeclampsia, rising to nearly 50% if HDP is detected before 32 weeks.[4,6,7] Women with pulmonary arterial hypertension (PAH) should generally avoid pregnancy; if pregnant, early termination or delivery may be advised based on PAH severity. In cases of maternal cardiac arrest, fetal heart rate monitoring should continue until the mother stabilizes.[8] Significant hemodynamic changes occur during labor and postpartum, necessitating careful management. Treatment may include antihypertensives and prophylactic anticonvulsants like magnesium sulfate. Labetalol (Cosma, Italy) is the most common beta-blocker used; bisoprolol (AXXO GmbH, Germany) and metoprolol (AXXO GmbH, Germany) are alternatives, while atenolol (S.I.M.S., Italy) should be avoided. Caution is advised for asthmatic patients. Safe antihypertensive medications during pregnancy are also safe for breastfeeding. Methyldopa (LGM Pharma, U.S.) has a 30% risk of postpartum depression and is typically discontinued after birth. Angiotensin-converting enzyme (ACE) inhibitors like enalapril (Arshine Pharmaceutical, China) are safe during breastfeeding, but angiotensin receptor blockers are contraindicated due to teratogenic risks.[9]

INTRAHEPATIC CHOLESTASIS

Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disorder related to pregnancy in women.[10] This condition poses minimal risk to the mother; however, serum bile acids can cross the placental barrier and accumulate in the fetus and amniotic fluid, potentially leading to severe perinatal complications such as intrauterine fetal death, meconium staining of amniotic fluid, and preterm birth.[11] For many years, ursodeoxycholic acid (UDCA) has been recommended as the drug of first choice in the treatment of ICP. UDCA is a naturally occurring hydrophilic bile acid and accounts for only 3-5% of human physiological bile acids. Pathophysiologically, UDCA ameliorates cholestasis by reducing bile acid levels by inhibiting the secretion of endogenous hydrophobic bile acids and increasing bile acid excretion by upregulating hepatic metabolic enzymes and bile acid transport proteins. Obstetricians hope that UDCA may improve maternal symptoms and reduce adverse perinatal outcomes by treating ICP, but there is currently insufficient evidence to support this.[12] S-adenosyl-methionine (SAMe), a glutathione precursor, is also considered a treatment option for ICP. SAMe affects the composition and fluidity of hepatocyte membranes, increasing hormone metabolite methylation and bile excretion.[13] While UDCA is the recommended 1st-line drug in the treatment of ICP, SAMe can be used as a 2nd-line drug or in combination therapy in the treatment of ICP.[11]

CARDIOVASCULAR DISEASES

Maternal cardiovascular diseases (CVD) occur in 1-4% of pregnancies and account for 10-15% of maternal deaths in developed countries. Cardiac surgery is rarely needed. Physiological changes during pregnancy can destabilize stable patients.[4,6,7] Blood volume increases by about 50%, raising cardiac output, which peaks in the 2nd trimester due to higher stroke volume and heart rate (10-20 beats/min). Systemic vascular resistance decreases, causing blood pressure to drop in the 1st 2 trimesters. A reduction in blood colloidal osmotic pressure can lead to pulmonary edema, while late pregnancy pressure on the inferior vena cava reduces venous return.[14] Up to 68% of pregnancy-related CVD deaths are preventable through awareness and effective treatment. Recognizing CVD risks during pregnancy is essential. Indirect complications include arrhythmias, heart failure, peripartum cardiomyopathy, thromboembolism, and acute coronary syndrome. Cardiac changes may lead to new or recurrent arrhythmias.[15,16] Peripartum cardiomyopathy, marked by left ventricular dysfunction, occurs late in pregnancy or postpartum. Pregnant women face a thromboembolism risk that is 4-5 times higher, with 80% of cases being venous. Deep vein thrombosis constitutes 75% of

cases, while pulmonary embolism occurs in 20-25%. Half of thromboembolic events happen during pregnancy, half postpartum, resulting in 1.1 deaths per 100,000 births and 9% of U.S. maternal deaths. In developed countries, thromboembolic diseases rank among the top maternal mortality causes. Given their prevalence, effective prevention and treatment are crucial in antenatal care. Acute coronary syndrome accounts for over 20% of maternal deaths. Addressing preventable cardiovascular events requires a multidisciplinary cardio-obstetric approach.[16]

ACUTE KIDNEY INJURY

Pregnancy-related acute kidney injury (PR-AKI) significantly impacts maternal and fetal morbidity and mortality. Sepsis is the most common cause of PR-AKI, often linked to inadequate prenatal and postnatal care. Other contributing factors include preeclampsia, cesarean sections, and bleeding.[17] The incidence and causes of PR-AKI differ between developed and developing countries due to socioeconomic factors. With improved obstetric care and liberalized abortion laws, PR-AKI has become less common in developed regions. It is often associated with hypertensive disorders and chronic kidney disease, increasing the risk of CVD later in life.[18] A 2016 study noted a 10% annual increase in PR-AKI, attributed to factors such as advanced maternal age, obesity, diabetes, hypertension, multiple pregnancies, and cesarean deliveries. The high incidence is largely due to a lack of prenatal care, with sepsis being the leading cause.[19,20] Preeclampsia's exact causes are unclear but may involve genetic, vascular, immune, and placental factors. Conditions like eclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome are life-threatening, with HELLP syndrome occurring in 0.5-0.9% of pregnancies and a mortality rate of about 1.1%.[21] Management of PR-AKI includes identifying the underlying cause, fluid resuscitation, timely dialysis, and, if necessary, immediate delivery of the fetus. Fluid therapy should be tailored to the patient's needs, and diuretics may be used cautiously to manage fluid overload. High-dose loop diuretics should be given judiciously to avoid ototoxicity.[22] Medications requiring high fluid volumes should be administered with caution. If conservative measures fail, ultrafiltration or dialysis may be needed. Mycophenolate (LGM Pharma, U.S.) is a teratogen that increases the risks of miscarriage and congenital malformations, while corticosteroids and calcineurin inhibitors are safer alternatives during pregnancy.[23] Immediate delivery is required for severe preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy. Glucocorticoids are administered if delivery occurs before 34 weeks to reduce respiratory distress risk in newborns. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome are acute syndromes characterized by microangiopathic hemolytic anemia and thrombocytopenia. Plasma exchange is the primary treatment for TTP, with doses of 1-1.5 times the plasma volume recommended. Rituximab (AXXO GmbH, Germany) may be used in refractory cases but should be applied cautiously during pregnancy due to potential fetal toxicity.[24]

CANCERS

ORAL CANCER

Oral cancer in pregnancy (OCiP) is rare but complicates cancer treatment and pregnancy outcomes. Regular tongue examinations for pregnant women are recommended to identify early signs of inflammation or malignancy, with biopsies advised for diagnosis.[25] Cancer is the 2nd leading cause of death among reproductive-age women, affecting about 1 in 118 during pregnancy. Diagnosing cancer during pregnancy raises significant concerns about potential harm to the fetus and the impact of delayed treatment on maternal survival. Currently, there are no standardized treatment protocols, and most information comes from case reports or small series.[26] Common gynecological cancers include uterine, ovarian, and cervical cancers. While the exact causes of OCiP are unclear, the role of human papillomavirus (HPV) is recognized. Pregnancy can induce physiological changes that promote neoplastic growth, including increased metabolic activity and circulating growth factors.[27] Treatment for oral cancer typically involves surgery, chemotherapy, and radiotherapy, but approaches during pregnancy depend on tumor type, location, stage, and patient preference. The posterior oropharyngeal

region, the most common site for OCiP, does not favor HPV receptor activity. Pregnancy also suppresses the immune system, complicating OCiP treatment due to potential fetal harm from medications, radiation, and surgery. Surgical duration is crucial for both mother and fetus, and chemotherapy can adversely affect fetal development. Radiation doses over 0.1 Gray significantly impact both mother and fetus, making treatment challenging without risking adverse outcomes.[28,29] Delaying treatment until after birth can worsen cancer progression and increase the risk of metastasis. The recurrence rate in OCiP (25%) is higher than in non-pregnant patients (19%). A biopsy should be performed on any inflamed oral mucosa to rule out dysplasia. If the tumor is large or metastatic early in pregnancy, termination may be considered.[30] A multidisciplinary approach involving gynecologists, anesthesiologists, and oral oncologists is recommended when discussing treatment options with patients.[25]

BREAST CANCER

Breast cancer is the most common malignancy during pregnancy, with an incidence of 1,030 cases per 100,000 pregnancies. It accounts for 13% of all breast cancers and typically presents in women aged 33-38. These cases often show more advanced stages and a worse prognosis, primarily due to delayed diagnosis, which occurs in 78% of cases, typically between 2-15 months.[31] Histologically, tumors are often invasive ductal, high-grade, and hormone-independent (estrogen receptor negative), similar to those in non-pregnant women. High levels of estrogen and progesterone during pregnancy can lead to false-negative results, necessitating immunocytochemical assessments. Inflammatory breast cancer occurs at the same rate in pregnant and non-pregnant women (3%) but can be mistaken for mastitis, so a biopsy is recommended when abscesses are present. Treatment strategies during pregnancy depend on the cancer's size and stage. Hormone therapy, radiotherapy, and chemotherapy are generally not applied, except for inflammatory breast cancer, which requires chemotherapy and may necessitate pregnancy termination. Surgical removal of the tumor is safe, while radiotherapy is typically postponed until after delivery to avoid harm to the fetus.[32]

HUMAN IMMUNODEFICIENCY VIRUS

Approximately 1.3 million pregnancies occur in people with human immunodeficiency virus (HIV) each year worldwide. A better understanding of the prevention of perinatal HIV transmission has improved significantly in the management of pregnant women with HIV in light of advances in drug development over the past 25 years. In the United States and Europe, the risk of mother-to-child HIV transmission has fallen to historically low levels with the use of antiretroviral drugs. Contributions to this successful prevention effort include screening tests for HIV infection in pregnant women, delivery by cesarean section (when appropriate), and avoidance of breastfeeding. Early diagnosis is essential to reduce the transmission of HIV from mother to baby, and for this, HIV testing is recommended during or before pregnancy. It has been reported that with increased access to antiretroviral treatment (ART), HIV transmission from mother to baby decreased by 18%, and this rate was 9% in 2010. When appropriate precautions are taken in HIV-infected women and babies, HIV transmission from mother to baby can be reduced to less than 1%.[33] However, HIV-related maternal deaths in African countries are still estimated at 25%, even higher than the rate of HDP (18%), the leading cause of maternal deaths.[34] While ART keeps more mothers with HIV alive in utero, ART exposure appears to have an impact on stillbirth, fetal growth restriction, and preterm birth that varies depending on the ART regimen and potentially the timing of ART initiation.[35]

GENITAL TUBERCULOSIS

Female genital tuberculosis (FGTB) is a chronic infectious disease characterized by the spread of *Mycobacterium tuberculosis* from primary to secondary foci in the lungs, usually hematogenous or lymphatic. The prevalence of FGTB varies between countries.[36] In the treatment of drug-sensitive active pulmonary and extrapulmonary tuberculosis, isoniazid, rifampicin (CKD Bio, South Korea), pyrazinamide (Minakem, France), and ethambutol (Sekisui Medical, Japan) should be administered for 2 months, followed by isoniazid and rifampicin-based antituberculosis therapy for 4 months. However, the

effect of this treatment on pregnancy outcomes in women with genital tuberculosis who do not have active tuberculosis disease is controversial. These drugs may have an immunomodulatory effect by reducing the structural damage of granulomas. However, they also cause adverse events such as hepatitis, cutaneous reactions, gastrointestinal intolerance, hematological reactions, and renal failure.[37]

SICKLE CELL DISEASE

Sickle cell disease (SCD) is a hereditary autosomal recessive disorder caused by homozygosity for hemoglobin S, where valine replaces glutamic acid in the beta-globulin chain. This results in insoluble hemoglobin tetramers in the deoxygenated state. Although many pregnancies in women with SCD result in live births, they carry heightened risks for maternal and fetal complications due to increased metabolic demand, hypercoagulability, and vascular stasis.[38] Preconception evaluation, including genetic counseling, is essential for SCD patients wishing to become pregnant. Studies show mixed results: while some indicate good fetal outcomes, maternal complications are often increased, including risks of maternal death, sepsis, pneumonia, urinary infections, and deep vein thrombosis. Pregnant women with SCD also face risks of intrauterine growth retardation, preeclampsia, preterm labor, and placental abruption. SCD is prevalent in eastern Africa, the Mediterranean, and the Middle East. Treatment plans should be adjusted before pregnancy; ACE inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs are contraindicated, and hydroxyurea (Sinoway Industrial, China) should be discontinued upon suspected or confirmed pregnancy due to its teratogenic effects. Hydroxyurea can lead to embryo-fetal death, malformations, growth delays, and functional defects. Women on hydroxyurea should be advised to avoid pregnancy. Postnatal follow-up is crucial due to thromboembolism risks. A French study reported 15 maternal deaths among 3,300 live births in women with SCD, resulting in a maternal mortality rate of 454 per 100,000 compared to 9.4 per 100,000 in the general population, highlighting SCD's role as a significant cause of maternal mortality.[39]As shown in the various pregnancy-related diseases, such as preeclampsia, hypertensive disorders, and HIV, significantly affect maternal health, with varying prevalence and mortality rates across different conditions Figure 2.

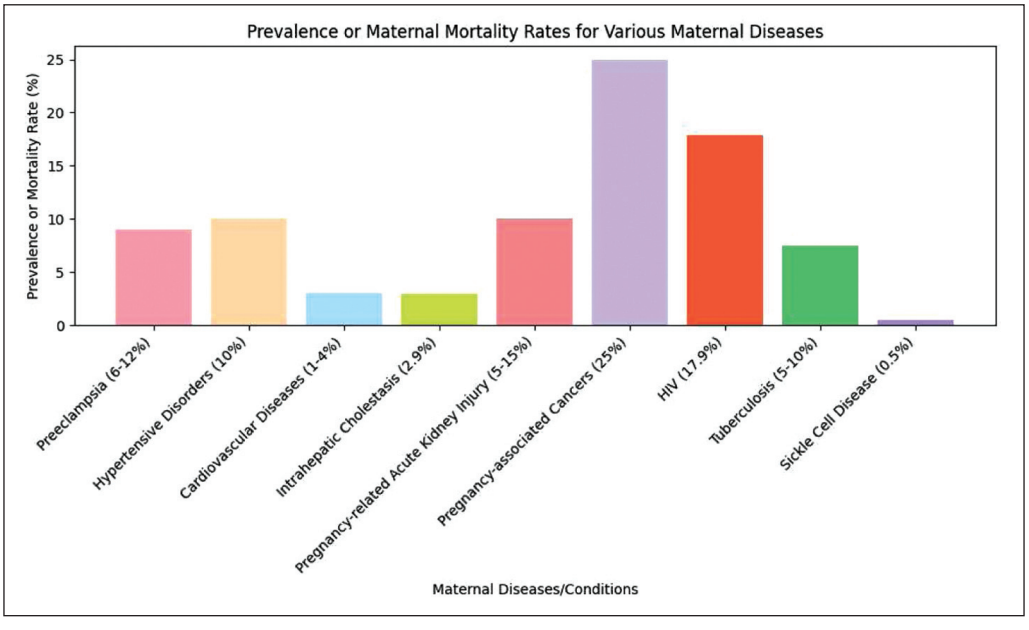

FIGURE 2: Prevalence and maternal mortality rates for various pregnancy-related diseases and conditions, highlighting their impact on maternal health and outcomes
HIV: Human immunodeficiency virus

MATERNAL COMPLICATIONS

CARDIAC ARREST

Maternal cardiac arrest is rare, with previous beliefs attributing most cases to anesthesia management. However, from 2011 to 2014, obstetric anesthesia was linked to only 16 of 66 cardiac arrest cases. Anesthesiologists play a vital role in reducing these incidents, particularly since the risk is higher with general anesthesia than with regional anesthesia. Obesity in pregnant women complicates this, as general anesthesia is best avoided in this population.[40] Despite improvements like aspiration of the epidural catheter, cases of undetected spinal catheter placement still occur. If an epidural bolus is mistakenly administered into the subdural space, it can lead to significant complications, including unexpected bleeding. A practical approach is to administer boluses in smaller portions of 3-5 ml. Delayed recognition of obstetric hemorrhage can lead to hypovolemic shock and maternal cardiac arrest. While it's important to monitor blood loss quantitatively for transfusion decisions, this is often assessed only at the end of a cesarean section rather than during ongoing bleeding. This can result in underrecognition and undertreatment of obstetric hemorrhage.[41,42]

SEPSIS

The WHO has recently defined maternal sepsis as a life-threatening condition marked by organ dysfunction due to infection during pregnancy, birth, postpartum, or after miscarriage. This expands definitions to include pregnancy-related sepsis, puerperal sepsis, and post-abortive sepsis. Sepsis accounts for 10.7% of maternal mortality globally, ranking 3rd after bleeding and preeclampsia; in developed countries, this figure drops to about 5%.[42] Risk factors for sepsis during pregnancy include obesity, anemia, diabetes, previous pelvic infections, invasive procedures, labor induction, instrumented delivery, cesarean sections, preeclampsia, postpartum bleeding, and mastitis. These factors cumulatively heighten sepsis risk. In developing countries, social factors like inadequate healthcare and lack of antenatal follow-up contribute to increased risks, alongside medical factors such as delayed treatment and a lack of awareness regarding infection severity.[43] Sepsis often manifests as systemic inflammatory response syndrome, an exaggerated response to infection. Due to the highly vascular placental bed, bacteremia can develop rapidly. Diagnosing and treating sepsis in pregnant women differs from non-pregnant cases, as physiological changes like hyperdynamic circulation and hypotension can mask symptoms. Hypercoagulability and limited antibiotic options further complicate treatment. Immediate treatment is crucial to counteract the effects of sepsis, which include hypotension, tissue perfusion issues, hypoxemia, and organ dysfunction. Fluid resuscitation is vital for restoring circulatory volume, aiming for systolic blood pressure above 90 mmHg. Initial treatment involves administering isotonic crystalloid (30 ml/kg/hour), and blood replacement if necessary.[44] Oxygen support should maintain venous oxygen saturation above 70% to protect the fetus. Antimicrobial treatment is critical, as maternal mortality rises by 8% for every hour antibiotics are delayed. Initial antibiotics should be broad-spectrum and intravenous (iv), tailored to local resistance patterns, particularly against Group A *Streptococcus* and *E. coli*.[45] If an infection source is identified, it should be promptly addressed, such as drainage for abscesses or delivery in cases of chorioamnionitis. Thromboembolism prophylaxis should be implemented, using mechanical methods if bleeding diathesis is present. In cases of septic shock, if blood pressure remains low despite 1-2 liters of fluid resuscitation, vasopressor treatment and intensive care are required. Noradrenaline is the preferred vasopressor, as it maintains placental perfusion, intending to keep mean arterial pressure around 65 mmHg.[46]

HEMORRHAGE

Postpartum hemorrhage (PPH) is defined as blood loss exceeding 500 ml after vaginal delivery and 1,000 ml after cesarean section. It is a significant complication characterized by insufficient uterine contraction, leading to a hemoglobin drop below 10% and often requiring transfusion. According to the WHO, PPH is a leading cause of maternal death, particularly in low-income countries, and is responsible for about 1-quarter of maternal deaths globally. Most deaths occur within the first 24 hours, making timely prophylactic use of uterotonics during the 3rd stage of labor critical for prevention.[47] PPH can result from

complications such as uterine atony, lacerations, retained placental products, or congenital coagulation disorders. Factors like consumption and dilutional coagulopathy can also exacerbate bleeding. Early detection and intervention by healthcare professionals are vital to avoid serious complications or mortality. Delays in intervention may arise from late detection of abnormal findings, a rapid decrease in compensatory mechanisms, or delayed communication among medical staff. Tachycardia and blood pressure changes may not manifest until over 1,000 ml of blood is lost, risking hemorrhagic shock. Quick and appropriate treatment is essential for estimating prognosis and managing bleeding. A multidisciplinary team is crucial for reducing maternal mortality from PPH and supporting women from antepartum to postpartum care. Approximately 90% of the estimated 80,000 annual PPH deaths occur in low and medium sociodemographic index countries, with significant numbers in the Democratic Republic of Congo, India, Nigeria, Pakistan, and Ethiopia, which account for 37% of global maternal deaths. This disparity is reflected within countries where maternal deaths predominantly affect the poorest segments of society.[48]

EXTERNAL FACTORS

INTRAPARTUM ANTIBIOTIC EXPOSURE

Obstetric and gynecological surgical interventions are now much safer, thanks to advances in anesthesia, sterilization, surgical training, imaging methods, and laparoscopic and robotic techniques. A key factor in this improvement is the prevention of surgical site infections (SSIs) through prophylactic antibiotic use. SSIs are the most common nosocomial infections, affecting 2-3% of the over 30 million surgeries performed annually in the U.S. They lead to increased mortality, morbidity, longer hospital stays, patient dissatisfaction, and higher costs.[49] Antimicrobial prophylaxis and proper surgical practices are crucial for preventing SSIs. However, the use of broad-spectrum antibiotics can lead to antibiotic resistance; for example, vancomycin (Arshine Pharmaceutical, China) is not recommended for routine prophylaxis unless the patient is known or suspected to be colonized with methicillin (Pfizer, U.S.)-resistant *Staphylococcus aureus*. In cases of multidrug-resistant microorganisms, prophylaxis should be expanded based on antibiotic sensitivity, host factors, and the surgical procedure. If the current antibiotic is effective for treating an infection, an additional dose should be given one hour before surgery. iv administration is preferred for its safety and predictability in achieving effective serum and tissue concentrations. Cefazolin (Arshine Pharmaceutical, China) is commonly used for its narrow spectrum, low side effects, and cost-effectiveness, effective against streptococci and methicillin-sensitive staphylococci. If anaerobic microorganisms are a concern, they should be combined with an anti-anaerobic agent like metronidazole (LGM Pharma, U.S.), or alternatives like cefotetan (ACS Dobfar, Italy) or cefoxitin (ACS Dobfar, Italy) may be used. For gram-negative coverage, second-generation cephalosporins such as cefuroxime (Arshine Pharmaceutical, China) are recommended.[50]

VACCINATION

GROUP B STREPTOCOCCUS

Group B *Streptococcus* (GBS) is a bacterial infection that can be found in the vagina and rectum of pregnant women. This bacterium is found in 25% of the vagina and rectum of healthy adult women. Many of these adults may have no clinical findings. GBS is not a sexually transmitted infection. Women who test positive for GBS are colonized with the bacteria. GBS can be passed from mother to baby at birth. Not every baby of a GBS-positive pregnant woman will have an infection. In approximately one in 2,000 vaginal births, the baby will have a GBS infection. Although GBS infection is rare, it can cause severe problems in the baby. The current approach to preventing GBS involves identifying high-risk women (maternal temperature ≥38˚C at delivery, inevitable preterm labor, preterm labor). These include premature rupture of membranes during pregnancy and intrapartum antibiotic prophylaxis (IAP) during labor. Since GBS screening and IAP cannot cover all pregnant women, the mother must be vaccinated against GBS. The 6-valent GBS vaccine under development, certified as a breakthrough therapy by the Food and Drug Administration and listed as a priority medicine by the European Medicines Agency (EMA), is expected to reduce drug resistance and protect new-

borns against both early-onset GBS and late-onset GBS.[51]

CORONAVIRUS DISEASE-2019

The coronavirus disease-2019 (COVID-19) pandemic has sparked debate about the safety of vaccines during pregnancy. However, pregnant women were not included in the phase 3 trials of the BioNTech (Pfizer, Germany) vaccine. As it has been 2 years since the first COVID-19 vaccine and more studies are being conducted, scientific literature must be evaluated to determine the risks of getting vaccinated during pregnancy. Current evidence supports the safety of administering severe acute respiratory syndrome-coronavirus-2 vaccines to pregnant women, but further systematic reviews and meta-analyses are required. Maternal immune activation caused by vaccination may affect the child's neurological development.[52] The first vaccine to combat the COVID-19 disease reached the market in December 2020-Pfizer-BioNTech.[53] Typically, vaccine development takes about 5-10 years. However, there are steps to accelerate this process: Clinical trial phases can be combined, phase III trials can be shortened due to the high number of new cases, and production can be started before phase III trials. No step is left out in the accelerated process, and vaccine safety is ensured by taking all mandatory safety measures. Certain groups, such as pregnant women, were excluded from COVID-19 vaccine trials.[54]

TETANUS

Tetanus vaccine is a vaccine that protects against tetanus, the disease caused by the bacteria *Clostridium tetani*. Tetanus is a severe infectious disease caused by toxins produced by bacteria, which can affect the nervous system and cause muscle spasms. Its fatal consequences are also known. The vaccine is used to provide immunity against tetanus toxin. Usually, the tetanus vaccine is combined with other vaccines and is given regularly during childhood and adulthood. The tetanus vaccine is generally administered through an intramuscular injection. In this way, the immune system aims to produce antibodies against tetanus toxin. The tetanus vaccine protects against tetanus infections that may occur as a result of injuries and is a vaccine that must be renewed regularly.[55] Doctors usually recommend a tetanus shot after the first 3 months. However, if the mother has had a tetanus vaccine within the last 10 years, there is no need for vaccination. Tetanus vaccination administered during pregnancy protects the mother and baby from infection and reduces the risk of disease in the newborn.[56] Tetanus vaccination is essential for many vital factors during pregnancy, significantly decreasing the baby's risk of premature birth and preventing some diseases that occur during pregnancy. It is necessary to reduce infections that may occur in the newborn and to ensure the transmission of antibodies from the mother to the baby through vaccination. At the same time, the tetanus vaccine ensures the baby is resistant in the first 6 months after birth.[57]

SUBSTANCE ABUSE

OPIOIDS

Pregnant individuals with opioid use disorder (OUD) face increased risks of premature birth, fetal growth restriction, and stillbirth. They are 4 times more likely to die during hospitalization.[58] A 2013 study revealed that 42% of pregnancy deaths due to OUD occurred in the immediate postpartum period (1 to 42 days after birth), followed by 22% during labor, 21% antepartum, and 15% late postpartum (42 days to 1 year after birth). Most opioid-related deaths are linked to polysubstance use, with benzodiazepines being a significant risk factor for overdose.[59] Women with substance use disorders (SUD) require specialized, multidisciplinary treatment to address their complex mental and physical health needs during the perinatal period. However, they often encounter barriers to care, including domestic violence and lack of social support, which can lead to increased maternal morbidity and mortality. Understanding how women with SUD perceive maternal mortality and their associated risks is crucial for improving outcomes.[60]

BENZODIAZEPINES

Many pregnant women with anxiety or sleep issues are prescribed benzodiazepines, with about 1.7% using them in the 1st trimester. There is limited knowledge about the combined use of benzodiazepines and opioids among expectant mothers. While opioid use has declined, benzodiazepine use

has risen, and the combination increases the risk of adverse birth outcomes, maternal overdose, and neonatal abstinence syndrome, prolonging newborn hospital stays. One study indicated that pregnant women on benzodiazepines had an 85% higher miscarriage risk.[61] Research on drug and alcohol use's contribution to maternal and neonatal mortality is scarce. Hulse et al. found that women using heroin late in pregnancy had a sixfold increased risk of neonatal death after starting methadone treatment.[61] Among drug-addicted mothers, the neonatal mortality rate was 27.9 per 1,000 births, compared to 6.7 per 1,000 for non-addicted mothers. Similarly, the post-neonatal mortality rate was higher for drug-addicted mothers (61.5/1,000) than for non-addicted births (12.0/1,000). However, 1 study found no increased risk of neonatal mortality or sudden infant death syndrome in infants exposed to cocaine, opiates, or cannabinoids in their first 2 years.[62]

ANTIDEPRESSANTS

Using antidepressants during pregnancy can pose risks to the baby, but stopping the medication may endanger the mother's health. Antidepressants are crucial for managing depression, which affects 10% of pregnant women. While some believe pregnancy hormones protect against depression, this is not the case. Few antidepressants are considered safe during pregnancy, with no links to congenital disabilities or developmental delays. However, babies may experience withdrawal symptoms like tremors and gastrointestinal issues after birth. If a mother discontinues her antidepressant upon learning she is pregnant, her risk of depression increases fivefold compared to those who continue treatment. Sudden cessation can lead to withdrawal symptoms, including headaches and nausea. Mild cases may improve with supportive therapies, but severe cases typically require medication. Antidepressants can cross the placenta and affect breastfeeding. When considering treatment during pregnancy, the benefits to the mother must be weighed against potential risks to the fetus. Non-drug methods like psychotherapy and relaxation techniques are recommended for mild to moderate depression. For severe cases or when psychotic features are present, medication may be necessary, with careful consideration of teratogenic risks. Electroconvulsive therapy may be an option for moderate to severe depression that is unresponsive to medications. During treatment, the lowest effective dose and ideally a single drug should be used, with close monitoring of the fetus or baby.[63] As outlined in Table 1, the external factors in-

TABLE 1: Comparative summary of the incidence and associated risk factors of external factors in pregnancy

External factor	Risk/incidence	Associated factors	Notes/considerations
Intrapartum antibiotic exposure	SSIs: 2-3% of surgeries.	Prophylactic antibiotics (e.g., cefazolin) to prevent SSI.	Overuse of broad-spectrum antibiotics leads to resistance; iv administration is preferred for efficacy and safety.
GBS	GBS-positive colonization: 25% of pregnant women.	IAP, potential vaccine (6-valent GBS).	Vaccination may reduce drug resistance and protect newborns against early and late-onset GBS infections.
COVID-19 vaccination	No specific incidence, but vaccination safety for pregnant women studies.	Vaccination with SARS-CoV-2 vaccines.	Vaccination is considered safe for pregnant women, but studies are ongoing regarding long-term effects on fetal health.
Tetanus vaccination	Tetanus incidence is rare due to vaccination.	Regular immunization during pregnancy, especially after injury.	Protects mother and newborn from tetanus; boosts immunity via passive transfer of antibodies to the baby.
OUD	Increased risk of premature birth, fetal growth restriction, stillbirth.	Need for multidisciplinary treatment and opioid substitution therapy (e.g., methadone).	High mortality risk during the postpartum period, often related to polysubstance use.
Benzodiazepine	1.7% of pregnant women use benzodiazepines in the first trimester.	Increased risk of adverse birth outcomes, overdose, and neonatal abstinence syndrome.	Combining benzodiazepines with opioids increases risks. Higher miscarriage rates were observed in benzodiazepine users.
Antidepressants	10% of pregnant women affected by depression.	Medication use (e.g., SSRIs) and/or psychotherapy.	Risks include withdrawal symptoms in neonates. Antidepressants cross the placenta; decisions should balance risks.

SSI: surgical site infections; iv: Intravenous; GBS: Group B *Streptococcus*; IAP: Intrapartum antibiotic prophylaxis; COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2; OUD: Opioid use disorder

fluencing pregnancy, such as intrapartum antibiotic exposure, Group B *Streptococcus*, vaccination (e.g., COVID-19, tetanus), and substance use (e.g., opioids, benzodiazepines, antidepressants), significantly impact maternal and neonatal health outcomes. The table provides a comparative summary of the associated risks and interventions, highlighting key incidence rates and considerations for clinical practice.

CONCLUSION

Maternal deaths primarily occur during childbirth and the early postpartum period. Despite progress in reducing maternal mortality globally, efforts remain insufficient. Recent initiatives to decrease these deaths include liberalizing abortion laws, controlling infectious diseases, improving access to hospital services, and enhancing midwifery care. For instance, maternal deaths from bleeding often result from inadequate access to timely intervention. The Millennium Development Goals (MDGs), adopted in 2000 by 189 countries, aimed to reduce maternal deaths by 75% from 1990 to 2015, specifically targeting maternal health. While global maternal mortality rates decreased by 44% during this period, the MDG target was unmet. Consequently, maternal mortality has been prioritized again under the Sustainable Development Goals, which aim to reduce the global maternal mortality rate to below 70 per 100,000 live births by 2030. Key strategies to lower maternal mortality include increasing education, preventing anemia and malaria, improving access to healthcare, ensuring skilled attendance at births, and expanding emergency obstetric care services.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Süleyman Sandal;* ***Design:*** *Süleyman Sandal;* ***Control/Supervision:*** *Süleyman Sandal;* ***Literature Review:*** *Songül Ünüvar;* ***Writing the Article:*** *Süleyman Sandal, Songül Ünüvar;* ***Critical Review:*** *Songül Ünüvar.*

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