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Hemophagocytic syndrome occurring during pregnancy

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Abstract
Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a rare but life-threatening condition characterized by excessive immune activation and subsequent tissue damage. The occurrence of HPS during pregnancy presents unique diagnostic and therapeutic challenges due to overlapping symptoms with other pregnancy-related conditions and the need to balance maternal and fetal health. This review aims to provide an overview of the pathophysiology, clinical presentation, diagnostic criteria, and management strategies for HPS in the context of pregnancy.

Keywords: Hemophagocytic syndrome, fetal health, HPS, pregnancy

Introduction
Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a rare but severe hyperinflammatory disorder characterized by excessive and uncontrolled activation of the immune system. This leads to widespread inflammation, tissue damage, and multi-organ failure. The syndrome can manifest in two main forms: primary (familial) HPS, which is often linked to genetic mutations affecting immune cell function, and secondary (acquired) HPS, which can be triggered by infections, malignancies, autoimmune diseases, and other external factors.

The occurrence of HPS during pregnancy presents unique and complex challenges for both diagnosis and management. Pregnancy itself induces significant physiological changes, including alterations in the immune system, which are necessary to maintain maternal tolerance to the fetus. These changes can obscure the clinical presentation of HPS, delay diagnosis, and complicate treatment. The overlapping symptoms of HPS with other pregnancy-related conditions, such as preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), and acute fatty liver of pregnancy, further complicate the clinical picture.

HPS during pregnancy can pose significant risks to both the mother and the fetus. For the mother, the hyperinflammatory state can lead to severe complications such as multi-organ dysfunction, coagulopathy, and profound cytopenias, necessitating aggressive and timely intervention. For the fetus, maternal HPS can result in adverse outcomes including intrauterine growth restriction, preterm birth, and, in severe cases, fetal demise.

The pathophysiology of HPS in pregnancy involves the dysregulated activation of macrophages and cytotoxic T lymphocytes (CTLs), which leads to the excessive release of pro-inflammatory cytokines such as interferon-gamma, tumor necrosis factor-alpha, interleukin-6, and interleukin-1. This cytokine storm drives the clinical manifestations of the disease, including persistent high fever, hepatosplenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, and elevated liver enzymes. The hemophagocytosis observed in bone marrow, liver, spleen, and lymph nodes is a hallmark of the disease, where activated macrophages engulf blood cells, further contributing to cytopenias.

Given the rarity and complexity of HPS during pregnancy, a high index of suspicion is required for timely diagnosis. Diagnostic criteria for HPS include clinical features and laboratory findings such as fever, splenomegaly, cytopenias affecting at least two blood cell lines, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, low or absent NK cell activity, hyperferritinemia, and elevated soluble CD25 levels.

The management of HPS in pregnancy necessitates a multidisciplinary approach involving hematologists, obstetricians, infectious disease specialists, and other healthcare providers. Treatment focuses on controlling the hyperinflammatory response and addressing any underlying triggers, with options including corticosteroids, etoposide, cyclosporine, intravenous immunoglobulin (IVIG), and supportive care. Balancing maternal health needs with fetal safety is critical, and decisions regarding the timing and mode of delivery must be individualized based on the clinical situation.

Main Objective

The main objective is to understand and effectively manage hemophagocytic syndrome (HPS) during pregnancy to improve maternal and fetal outcomes through early diagnosis, appropriate treatment, and a multidisciplinary approach.

Hemophagocytic syndrome (HPS)

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a severe and potentially fatal hyperinflammatory disorder characterized by excessive activation of the immune system. The condition results from the uncontrolled activation and proliferation of macrophages and cytotoxic T lymphocytes (CTLs), which leads to widespread inflammation and tissue damage. This immune dysregulation causes the macrophages to engulf hematopoietic cells, including red blood cells, white blood cells, and platelets, a process known as hemophagocytosis. There are two main forms of HPS: primary (familial) and secondary (acquired). Primary HPS is often caused by genetic mutations that affect the cytotoxic function of CTLs and natural killer (NK) cells. Mutations in genes such as PRF1, UNC13D, and STX11 impair the ability of these immune cells to kill infected or abnormal cells effectively. This genetic predisposition leads to continuous activation of immune cells and a persistent inflammatory state. Secondary HPS can be triggered by various conditions, including infections (most commonly viral infections like Epstein-Barr virus and cytomegalovirus), malignancies (such as lymphomas), autoimmune diseases (such as systemic lupus erythematosus), and certain medications. These triggers can cause a similar dysregulation of the immune system, even in individuals without a genetic predisposition.

The pathophysiology of HPS involves the excessive release of pro-inflammatory cytokines, such as interferon-gamma, tumor necrosis factor-alpha, interleukin-6, and interleukin-1. These cytokines further activate immune cells, creating a vicious cycle of inflammation. The resulting "cytokine storm" leads to the clinical manifestations of HPS, which include persistent high fever, hepatosplenomegaly (enlargement of the liver and spleen), and cytopenias (reduced levels of red blood cells, white blood cells, and platelets). Other common laboratory findings include hyperferritinemia (elevated ferritin levels), hypertriglyceridemia (elevated triglyceride levels), and elevated liver enzymes.

The diagnosis of HPS is based on clinical criteria established by the Histiocyte Society. These criteria include fever, splenomegaly, cytopenias affecting at least two cell lines, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in bone marrow or other tissues, low or absent NK cell activity, hyperferritinemia, and elevated soluble CD25 levels (a marker of T-cell activation).

The management of HPS involves controlling the hyperinflammatory state and addressing any underlying triggers. Treatment typically includes immunosuppressive therapy with corticosteroids, etoposide, and cyclosporine, as well as targeted treatments for any identified infections or malignancies. Intravenous immunoglobulin (IVIG) may also be used to modulate the immune response.

Pathophysiology

The pathophysiology of hemophagocytic syndrome (HPS), or hemophagocytic lymphohistiocytosis (HLH), involves a profound and uncontrolled activation of the immune system, leading to widespread inflammation and tissue damage. This hyperinflammatory state is primarily driven by the overactivation of macrophages and cytotoxic T lymphocytes (CTLs), which release large quantities of pro-inflammatory cytokines, including interferon-gamma, tumor necrosis factor-alpha, interleukin-6, and interleukin-1. These cytokines further activate other immune cells, perpetuating the cycle of inflammation. In patients with genetic predispositions, mutations in genes critical for the cytotoxic function of CTLs and natural killer (NK) cells, such as PRF1, UNC13D, and STX11, impair the ability of these cells to kill target cells effectively. This dysfunction leads to the accumulation and persistent activation of immune cells. Without the proper regulatory mechanisms to shut down the immune response, macrophages begin phagocytosing (engulfing and digesting) blood cells and their precursors, leading to cytopenias, particularly anemia, thrombocytopenia, and leukopenia. Secondary HLH, which can occur in response to infections (especially viral infections like Epstein-Barr virus), malignancies, or autoimmune diseases, involves similar pathways of immune activation. The triggering event leads to the excessive activation of the immune system in genetically predisposed individuals or those with already compromised immune regulation. The massive release of cytokines, known as a "cytokine storm," causes severe systemic inflammation, affecting multiple organ systems. This results in clinical manifestations such as persistent high fever, hepatosplenomegaly, elevated liver enzymes, coagulopathy, hypertriglyceridemia, and hyperferritinemia. The intricate balance between the immune response's activation and regulation is critically disrupted in HPS, leading to the clinical syndrome's severe and often life-threatening nature. The excessive immune activity damages tissues directly and indirectly by causing widespread inflammation and subsequent organ dysfunction, which can rapidly progress if not promptly and effectively managed.

Clinical Presentation

The clinical presentation of hemophagocytic syndrome (HPS) occurring during pregnancy is often complex and can mimic other pregnancy-related conditions, making diagnosis challenging. Pregnant women with HPS typically present with persistent high fever that does not respond to standard antipyretic treatments. This fever is often accompanied by hepatosplenomegaly, where the liver and spleen become enlarged, which can be detected through physical examination or imaging studies. Patients frequently exhibit cytopenias, which involve reductions in one or more blood cell lines, such as anemia (low red blood cells),

thrombocytopenia (low platelets), and leukopenia (low white blood cells). These blood abnormalities can lead to symptoms like fatigue, increased susceptibility to infections, and a tendency to bleed or bruise easily. Hyperferritinemia, a significant increase in ferritin levels in the blood, is a hallmark of HPS and reflects the severe inflammatory response. Elevated liver enzymes are common and can signal liver involvement or damage, which may also manifest as jaundice. Hypertriglyceridemia, or elevated triglyceride levels, is another laboratory finding indicative of HPS. Pregnant women with HPS may also present with neurological symptoms, such as altered mental status, seizures, or headaches, if the central nervous system is involved. The symptoms of HPS can overlap with other pregnancy complications, such as preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), or acute fatty liver of pregnancy, making clinical differentiation difficult. Due to this overlap, it is crucial for healthcare providers to consider HPS in the differential diagnosis when a pregnant woman presents with these nonspecific but severe symptoms, and to conduct appropriate diagnostic tests to confirm the diagnosis and initiate timely treatment.

Hemophagocytic syndrome occurring during pregnancy

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), occurring during pregnancy is a rare but serious condition characterized by excessive and dysregulated activation of the immune system, leading to widespread inflammation and tissue damage. This hyperinflammatory state results from the overactivation of macrophages and cytotoxic T lymphocytes (CTLs), which release large amounts of pro-inflammatory cytokines, including interferon-gamma, tumor necrosis factor-alpha, interleukin-6, and interleukin-1. These cytokines further amplify the immune response, creating a vicious cycle of inflammation. The condition can manifest as either primary (genetic) or secondary (acquired) HPS. In primary HPS, genetic mutations affecting the cytotoxic function of CTLs and natural killer (NK) cells, such as mutations in the PRF1, UNC13D, and STX11 genes, impair the ability of these cells to effectively kill target cells. This leads to the continuous activation and proliferation of immune cells, causing severe inflammation. Secondary HPS, more common in pregnancy, can be triggered by infections (such as Epstein-Barr virus or cytomegalovirus), autoimmune diseases, or malignancies, with the physiological changes of pregnancy potentially acting as additional triggers. Clinically, HPS during pregnancy presents with a constellation of symptoms that can overlap with other pregnancy-related conditions, making diagnosis challenging. Persistent high fever, hepatosplenomegaly (enlarged liver and spleen), and cytopenias (reductions in blood cell lines, including anemia, thrombocytopenia, and leukopenia) are common. These blood abnormalities lead to fatigue, increased infection risk, and bleeding tendencies. Hyperferritinemia, reflecting the severe inflammatory state, and elevated liver enzymes, indicating liver involvement or damage, are critical laboratory findings. Hypertriglyceridemia is also frequently observed. Neurological symptoms such as altered mental status, seizures, or headaches may occur if the central nervous system is involved. The overlap of these symptoms with conditions like preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), or acute fatty liver of pregnancy necessitates a high index of suspicion for HPS. Diagnosis involves fulfilling specific criteria, including fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in bone marrow or other tissues, low or absent NK cell activity, hyperferritinemia, and elevated soluble CD25 levels. Management requires a multidisciplinary approach, combining immunosuppressive therapy (corticosteroids, etoposide, and cyclosporine), antiviral or antimicrobial treatment if infections are identified, intravenous immunoglobulin (IVIG), and supportive care to address complications and maintain maternal and fetal health. Early recognition and treatment are crucial to improving outcomes, as delayed diagnosis can lead to severe maternal and fetal morbidity and mortality. A coordinated effort involving hematologists, obstetricians, and other specialists is essential to optimize care for pregnant women with HPS. Further research is needed to develop evidence-based guidelines and improve the understanding of HPS in pregnancy, ultimately enhancing diagnostic and therapeutic strategies.

Conclusion

In conclusion, hemophagocytic syndrome (HPS) during pregnancy is a rare but life-threatening condition that poses significant diagnostic and therapeutic challenges due to its overlapping symptoms with other pregnancy-related disorders. Prompt recognition and a high index of suspicion are critical, as early diagnosis and treatment can significantly improve maternal and fetal outcomes. A multidisciplinary approach involving hematologists, obstetricians, and other specialists is essential for effective management. Understanding the unique aspects of HPS in pregnancy, including its pathophysiology, clinical presentation, and appropriate treatment strategies, is crucial for optimizing care and improving prognosis. Ongoing research and the development of evidence-based guidelines are needed to further enhance the diagnosis and management of this complex condition in pregnant patients.

Conflict of Interest

Not available

Financial Support

Not available

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