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Review paper

Aplastic Anemia in Pregnancy: A Case-Based Comprehensive Review of the Literature

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Abstract

Background and Aim: Aplastic anemia (AA) is a rare and life-threatening hematologic disorder characterized by pancytopenia and bone marrow failure. Paul Ehrlich was the first to describe aplastic anemia in 1888, having observed it during an autopsy of a young pregnant woman who tragically passed away following a sudden, severe illness.Its occurrence during pregnancy is exceedingly rare, posing significant risks and management challenges for both the mother and the fetus. Aplastic anemia during pregnancy is a rare condition, and the incidence of it is not well-established due to its rarity. In general, the incidence of aplastic anemia is estimated to be around 2 to 7 cases per million people per year in Western countries, while higher incidences have been reported in Asia, with up to 15 cases per million people per year and in Albania the incidence resulted in 1.35 per million inhabitants. In pregnancy, the occurrence of AA is even more rare and poses significant risks and management challenges for both the mother and the fetus.

Method: We present here a 23-years old patient diagnosed with Severe Aplastic Anemia during the second trimester of pregnancy and we performed a comprehensive literature review of the past 20 years papers published in English language identified through searches in PubMed, Medline, Embase, and the Cochrane Library, to provide an in-depth analysis of the current understanding of AA in pregnancy, encompassing its etiology, pathophysiology, diagnosis, treatment, and outcomes.

Results: The etiology of AA in pregnancy is often idiopathic, with potential causes including exposure to certain chemicals, radiation, medications, viral infections, and autoimmune or genetic factors. Although the exact mechanism of AA in pregnancy is not fully understood, it is hypothesized that pregnancy-associated immune modulation may play a role in the development or exacerbation of the disease.

Conclusion: Given the rarity and complexity of AA in pregnancy, there is a need for a comprehensive review of the literature to better understand the current state of knowledge and best practices in managing this challenging condition.

Keywords: *Aplastic Anemia, Pregnancy, Hematological disorders in pregnancy, Bone marrow failure, Obstetric complications, Maternal-fetal health*

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Introduction

Aplastic anemia (AA) is a rare and life-threatening hematologic disorder characterized by pancytopenia, which is a reduction in all blood cell lines (red blood cells, white blood cells, and platelets), and bone marrow failure [1], [2]. Documented for the first time by the Nobelist German physician and scientist Paul Ehrlich in 1885, having observed it during an autopsy of a young pregnant woman who tragically passed away following a sudden, severe illness, the term "anemia aplastique" was introduced only in 1904 by Anatole Chauffard [3]. And we still search on the diagnosis and treatment of this same disease since 1885. The incidence of AA is estimated to be around 2-5 per million people per year in Western countries [2], [4], [5], [6] while higher incidences have been reported in Asia with incidence rates 4- to 5-fold higher [7], [8], [9], and in Albania the incidence resulted in 1.35 per million inhabitants [10]. In pregnancy, the occurrence of AA is even more rare and poses significant risks and management challenges for both the mother and the fetus.

The etiology of AA in pregnancy is often idiopathic, with potential causes including exposure to certain chemicals, radiation, medications, viral infections, and autoimmune or genetic factors (1). The pathophysiology of AA involves the failure of hematopoietic stem cells to differentiate into mature blood cells, resulting in pancytopenia and an empty bone marrow [11]. Although the exact mechanism of AA in pregnancy is not fully understood, it is hypothesized that pregnancy-associated immune modulation may play a role in the development or exacerbation of the disease [12], [13].

Diagnosis and management of AA during pregnancy present unique challenges, as the clinical presentation of AA can be similar to that of normal pregnancy-related changes, such as anemia and thrombocytopenia [12], [14], [15]. Furthermore, the optimal treatment strategy for pregnant women with AA remains unclear due to the rarity of the condition and the potential risks associated with the standard treatments for non-pregnant patients [16].

Given the rarity and complexity of AA in pregnancy, there is a need for a comprehensive review of the literature to better understand the current state of knowledge and best practices in managing this challenging condition. This review aims to provide an in-depth analysis of the existing literature on AA in pregnancy, focusing on its etiology, pathophysiology, diagnosis, treatment, and outcomes, and to identify gaps in knowledge that warrant further research.

Case Report

A 23-year-old woman, who was at the 6-month mark of her pregnancy, sought medical attention at the University Obstetrics and Gynecology Hospital “Queen Geraldine” in Tirana, Albania. Her primary complaints included fatigue that had begun three weeks prior and had been growing progressively worse, as well as a noticeable increase in paleness. On clinical examination, she appeared pallid, feverish, and presented with ecchymoses on her forearms and body. There was no evidence of splenomegaly or lymphadenopathy. A complete blood count revealed a marked pancytopenia, characterized by hemoglobin at 6.8 g/dl, white blood cell count at 1200/mm^3 (with an absolute neutrophil count of 350/mm^3), and platelet count at 15,000/mm^3. Despite this, her biochemical analyses fell within normal limits.

The results of a gynecological ultrasound showed no abnormal findings. Her medical history did not include any previously diagnosed diseases, and there were no known familial diseases. The complete blood count performed earlier in her pregnancy was within normal ranges. Furthermore, her serum levels of ferritin, vitamin B12, and folic acid were all within the normal range. Liver function tests and viral studies did not show any abnormal results.

Given her presentation, the hematologist was consulted. The patient underwent a bone marrow aspiration followed by flow cytometry, which demonstrated significantly reduced bone marrow cellularity, without evidence of clonality or dysplastic features. The subsequent bone marrow biopsy showed cellularity at 15%, with no presence of fibrosis or clonality. Thus, the constellation of clinical features and investigations pointed towards the diagnosis of Severe Aplastic Anemia.
The patient was transferred in the Service of Hematology for further assistance. Based in the specific context of the pregnancy the choice of therapy needed to balance the urgency of treatment for the mother with the potential for harm to the fetus. We decided to start treatment with supportive care with frequent transfusions of packed red cells and platelets and also prophylactic antibiotics and antifungals. The patient was closely monitored for the fetal development and successfully naturally delivered a healthy male child with all clinical indicators falling within the normal range. Even after delivery and an additional three weeks of postpartum hospital observation, there was no noted improvement in the patient's hematological parameters.
The decision was made to initiate treatment with cyclosporine, to which the patient consented. However, upon returning home, she chose not to adhere to the medication regimen. Tragically, she passed away at home, refusing further medical intervention or hospital care.

Comprehensive Review of the Evidence

The intricate relationship between aplastic anemia (AA) and pregnancy presents both medical and obstetric challenges. This review aims to provide an in-depth exploration of current literature focusing on the etiology, pathophysiology, diagnosis, treatment, and outcomes of AA in pregnancy.

Etiology of AA in Preganacy:

Aplastic anemia (AA) during pregnancy presents a unique interplay of factors contributing to its onset. This in-depth examination focuses on immune-mediated reactions, drug exposure, and viral infections as key etiological agents, further exploring the link between pregnancy-induced immunological changes and the onset of AA.

Several factors could contribute to the onset of AA in pregnancy, including immune-mediated reactions, drug exposure, and certain viral infections [17]. A crucial link has been suggested between pregnancy-induced immunological changes and the onset of AA [18].

a. Immune-mediated reactions: Immunological changes are central to the pathophysiology of AA, which is regarded as an autoimmune disease [18]. These changes are even more significant during pregnancy, a period marked by distinct immunomodulation designed to protect the fetus while still allowing maternal defense against pathogens. It has been hypothesized that this delicate balance could be disturbed in some women, leading to autoimmunity and resulting in diseases such as AA [18], [19].
b. Drug Exposure: Medications taken during pregnancy can contribute to the development of AA. Drugs such as nonsteroidal anti-inflammatory drugs, certain antibiotics, antithyroid drugs, and antiepileptics have been implicated in causing bone marrow suppression [17]. Careful review and management of a pregnant woman's medication profile is necessary to mitigate this risk.
c. Viral infections: Viral infections are another recognized etiological factor for AA. Epstein-Barr virus (EBV), hepatitis viruses, human immunodeficiency virus (HIV), and parvovirus B19 have been implicated in the pathogenesis of AA by causing direct damage to hematopoietic stem cells or triggering an aberrant immune response [17]. Therefore, proper infection control and treatment during pregnancy become crucial in preventing the onset

of AA.

A crucial link has been suggested between the above factors and pregnancy-induced immunological changes in the onset of AA. During pregnancy, the maternal immune system undergoes adaptation to tolerate the semi-allogenic fetus, inducing a temporary state of altered immunity. It has been hypothesized that these changes could trigger or exacerbate the pathological mechanisms underlying AA in susceptible individuals [17], [19].

Further research into these etiological factors is necessary to better understand and manage AA in pregnancy. A deeper grasp of these mechanisms could potentially allow for targeted interventions and better prognostic capabilities, thereby improving the management and outcomes of AA during pregnancy.

Pathophysiology of AA in Pregnancy:

Aplastic anemia (AA) is a syndrome characterized by failure of the bone marrow, leading to a reduced production of blood cells, a condition known as pancytopenia, and a decrease in cellular activity within the bone marrow, referred to as hypocellularity [17]. AA can be described as a medical condition that is acquired rather than inherited, with its root causes generally being associated with various immune-mediated reactions, exposure to certain drugs, and specific viral infections [18].

The association between pregnancy and AA has been a subject of interest since the disease was first documented by Paul Ehrlich in 1888.

Ehrlich documented the inaugural case of aplastic anemia (AA) back in 1888, with his patient incidentally being pregnant at the time. Tragically, she lost her life due to postpartum hemorrhage a month following childbirth [20]. Despite this, the precise causal relationship between pregnancy and AA continues to elude us [21].

Despite this long history, the precise connection between pregnancy and the onset of AA remains ambiguous. Early studies did not establish a clear correlation between pregnancy and AA. For instance, a retrospective analysis comparing the incidence of pregnancy in a group of 35 newly diagnosed AA patients with the expected frequency in the general population did not reveal any significant difference [22].

Contradictorily, other studies have suggested a direct association between pregnancy and the development of AA, advocating that hormonal and immunological changes during pregnancy may potentially exacerbate the condition [18]. Some reviews have even included pregnancy as a possible trigger for AA [21], [23].

During pregnancy, the body undergoes numerous hormonal and immunological transformations. It has been proposed that these changes might potentially worsen the symptoms of AA, although the underlying mechanisms still need to be fully elucidated [21], [24].

While the exact interplay between pregnancy and AA is still not entirely clear, the diversity of the reports emphasizes the complexity of the relationship and the need for further research in this area to fully understand the pathophysiology of AA in pregnant patients.

Diagnosis of AA in Pregnancy:

The process of diagnosing aplastic anemia (AA) in pregnant patients can be a complex one. The usual diagnostic approach primarily revolves around laboratory findings indicating pancytopenia, a condition in which there is a reduction of red and white blood cells as well as platelets, which is commonly observed in AA cases [17], [25]. Confirmation of the diagnosis typically requires a bone marrow biopsy showing a decrease in the production of these cells [22].

However, a key concern when dealing with pregnant patients is the safety and welfare of the unborn child. A bone marrow biopsy, although highly informative, is an invasive procedure. The

potential, even rare, for complications such as infection, bleeding, and discomfort raise concerns, particularly given the possible indirect impacts on the fetus through maternal stress and the risk of infection [18], [19].

This potential hazard poses a real challenge in the medical field when it comes to managing AA in pregnant patients. The desire and need to accurately diagnose to ensure appropriate treatment is balanced against the safety considerations for the fetus. This has led to a general consensus in medical practice that bone marrow biopsies are typically not carried out during pregnancy unless absolutely necessary [22].

The need for a more viable diagnostic approach during pregnancy is evident. Therefore, it is imperative that further research is conducted to develop safer, less invasive diagnostic methods that can be used in such cases [17]. The goal should be to ensure that the accurate diagnosis of AA is not compromised, while at the same time, the safety of the mother and unborn child remains a priority. This is a gap in medical understanding that requires continued investigation and attention.

Treatment of AA in Pregnancy:

Managing aplastic anemia (AA) in expectant mothers is particularly complex, due to potential harmful effects certain treatments may have on the unborn child. Teratogenic risks are posed by immunosuppressive therapies, often used in AA treatment, which may negatively affect fetal development [26]. Furthermore, bone marrow transplantation - another common intervention for AA - carries its own set of hazards, adding to the complexity of the treatment process [27].

Given these risks, an alternative management approach may involve supportive care. This includes measures like blood transfusions and the use of growth factors. While this approach doesn't address the underlying cause of the disease, it manages its symptoms and seeks to sustain the overall health of the patient. It is typically viewed as safer for both mother and child. However, the efficacy of this supportive strategy can fluctuate, depending on factors like the disease's severity and the patient's overall health condition.

Bone marrow transplantation (BMT) is a potentially curative treatment for aplastic anemia (AA). It involves replacing the diseased bone marrow with healthy marrow from a compatible donor. However, its application in cases of pregnancy-acquired AA brings about a unique set of challenges due to the potential risks it poses to both the mother and the fetus.

Pregnancy adds a complex layer of consideration to the decision of BMT. The procedure requires intensive conditioning regimens, including high doses of chemotherapy and/or radiation, which could pose significant risks to the developing fetus [28]. These risks include potential for miscarriage, congenital malformations, intrauterine growth restriction, preterm birth, and long-term developmental issues [29].

From the perspective of the pregnant patient, the intensive preparatory treatments for BMT, as well as the procedure itself, can also present considerable risks, including infertility, infection, graft-versus-host disease, and treatment-related mortality [30]. These risks necessitate a carefully weighed decision-making process, taking into account the mother's health, disease severity, available treatment options, and gestational age.

There is limited data in the literature regarding the use of BMT in pregnancy-acquired AA. Therefore, the need for further research is apparent, both to generate more definitive evidence on its safety and efficacy, and to help guide the development of guidelines for its use in this unique patient population.

When it comes to outcomes for mother and child in cases of AA during pregnancy, they hinge on multiple factors. These include the severity of AA and the promptness of diagnosis. Timely identification of the disease and appropriate subsequent management significantly enhance these

outcomes [31]. Therefore, the need for vigilant monitoring and swift medical intervention is underscored in pregnant women suspected to have AA.

In summary, while existing research provides us with crucial insights into the phenomenon of AA during pregnancy, it concurrently reveals knowledge gaps. These gaps are spread across different facets of AA, including its cause, progression, diagnosis, treatment, and impact in the context of pregnancy. Hence, additional research in this field is paramount. Such exploration will not only bridge these knowledge gaps but also foster improvements in clinical practice, ultimately leading to better outcomes for pregnant women diagnosed with AA.

The clinical approach to a pregnant woman with AA should involve a multidisciplinary team of hematologists, obstetricians, and neonatologists, with the primary goal of optimizing outcomes for both the mother and her child.

Conclusion

Aplastic anemia (AA) is a rare and life-threatening hematologic disorder characterized by pancytopenia and bone marrow failure. Aplastic anemia (AA) during pregnancy presents a myriad of medical and obstetric challenges due to its intricate interplay with the physiological changes induced by pregnancy. AA in pregnancy is primarily linked to immune-mediated reactions, drug exposure, and certain viral infections. The hormonal and immunological transformations during pregnancy might potentially worsen the symptoms of AA, although the underlying mechanisms still need to be fully elucidated. The process of diagnosing aplastic anemia (AA) in pregnant patients can be a complex one. The usual diagnostic approach primarily revolves around laboratory findings indicating pancytopenia, a condition in which there is a reduction of red and white blood cells as well as platelets, which is commonly observed in AA cases. Confirmation of the diagnosis typically requires a bone marrow biopsy showing a decrease in the cellularity of the bone marrow. Managing AA in pregnant patients is challenging due to the potential teratogenic risks of immunosuppressive therapies and the hazards associated with bone marrow transplantation. The current management approach often involves supportive care, including transfusions and growth factors, although the efficacy of this approach depends on several factors such as disease severity and the patient's overall health condition.

Maternal and fetal outcomes in AA during pregnancy largely depend on the severity of the disease and the timing of diagnosis. A timely diagnosis and appropriate management can significantly enhance these outcomes, emphasizing the need for vigilant monitoring and swift medical intervention in pregnant women suspected to have AA.

In conclusion, while the existing literature provides valuable insights into AA during pregnancy, it also reveals several knowledge gaps. Further research in this field is paramount to bridge these gaps and improve clinical practice, ultimately leading to better outcomes for pregnant women diagnosed with AA. A multi-disciplinary approach, involving hematologists, obstetricians, and neonatologists, is recommended for optimal management and outcomes in this unique patient population.

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Conflict of interests

The author declares that she has no pertinent affiliations or monetary associations with any organizations or entities that have a financial stake in or conflict with the subject matter or materials covered in this manuscript. This discludes any current or previous instances of employment, consultancy work, receipt of honorariums, stock ownership or options, expert testimonies, grants or pending or received patents, or any royalties.

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