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Research Article

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Aplastic Anemia in Pregnancy

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Abstract

Aplastic anemia [AA] is a rare and life-threatening hematologic disorder characterized by pancytopenia and bone marrow failure. First documented in 1888 by Paul Ehrlich, AA has since been a subject of interest, especially its rare presentation during pregnancy. Pregnancy-associated aplastic anemia (p-AA) remains a scarce and challenging condition, with an incidence higher in Asian regions than in Western countries. The pathophysiology of AA is multifactorial, involving immune-mediated destruction of hematopoietic stem cells, often triggered by drugs, environmental toxins, or infections. Hormonal and immunological changes during pregnancy can worsen symptoms, although the exact mechanisms are not well understood. Diagnosing primary autoimmune aplastic anemia (p-AA) is challenging due to the physiological changes in blood during pregnancy, often requiring a bone marrow biopsy for confirmation. Complications for the mother, such as hemorrhage and infections, along with risks for the fetus, including preterm birth, highlight the seriousness of this condition. Current treatment approaches focus on supportive care, including blood transfusions, while immunosuppressive therapies like cyclosporine can provide additional benefits in some instances. Bone marrow transplantation can be curative, but it is contraindicated during pregnancy due to significant risks to the fetus. Given the rarity and complexity of AA in pregnancy, there is a need for a better understanding of the current state of knowledge and best practices in managing this challenging condition, involving multidisciplinary teams with hematologists, obstetricians, and anesthesiologists to optimize outcomes.

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

Introduction

Aplastic anemia [AA] is defined as a rare and heterogeneous 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 with a hypocellular bone marrow without evidence of an infiltration of abnormal or malignant cells and without fibrosis [1-3].

The history of the very first documented case with AA has always been object of interest and research among the scientists. Aplastic anemia was documented for the first time by the Nobelist German physician and scientist Paul Ehrlich in 1888, describing a pregnant 21 years old women with high fever, severe and fatal pancytopenia, who tragically passed away following a sudden death. Ehrlich having observed during the autopsy of this young pregnant woman a yellow bone marrow, instead of the reddish normal appearance, described the bone marrow as "strikingly hypocellular" [3]. The term "anemia aplastique" was introduced only in 1904 by Anatole Chauffard who performing the histologic evaluation of the bone marrow of his patient presenting with hepatosplenomegaly and who passed away from rapid severe anemia, saw a fatty bonne marrow and described it as "frappee de sterilitè" or sterile [4]. The word "aplastic" takes his origin from the Ancient Greece and is literally translated as "a" – without and "plasis" – form, so "without form", meanwhile "anemia" means without blood [5]. We still use the term of Anatole Chauffard to describe this condition, despite the fact that the patients present with severe pancytopenia and not only anemia, struggling to search on the diagnosis and treatment of this same disease since 1888.

The incidence of AA is estimated to be around 2-5 per million people per year in Western countries [2, 6-9] while higher incidences have been reported in Asia with incidence rates 4- to 5-fold higher [10-12], and in Albania the incidence resulted in 1.35

per million inhabitants [13].

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 [14]. But on the other hand, pregnancy - associated aplastic anemia [p-AA] is a rare and at the same time a serious condition where aplastic anemia [AA] is diagnosed for the first time during pregnancy [15]. The etiology of p-AA is often idiopathic, with potential causes including exposure to certain chemicals, radiation, medications, viral infections, and autoimmune or genetic factors [1]. Although the exact relationship between pregnancy and the onset or exacerbation of AA still remains unclear and the 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 [15-17].

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 [15,18,19]. 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 [20].

Given the rarity and complexity of AA in pregnancy, there is a need for a better understanding of the current state of knowledge and of the best practices in managing this challenging condition, focusing on its definition, etiology, pathophysiology, diagnosis, treatment, and outcomes, and to identify gaps in knowledge that warrant further research [21].

Definition of Aplastic Anemia

Aplastic anemia [AA] is a rare but highly fatal hematopoietic stem cell – disorder, characterized by the failure of the bone marrow leading to a deficiency in the production of blood cells with peripheral cytopenia [1-3]. Aplastic anemia is marked by several degrees of pancytopenia and a hypocellular bone marrow with a cellularity of <25 % (or 25 to 50 % if <30 % of residual cells are hematopoietic) [22], due to the immune-mediated attack against the blood-forming cells also well known as “the hematopoietic stem cells” [HSCs] resulting in a decrease number of them [23]. Is important to emphasize the fact that the bone marrow of the patients with AA does not show fibrosis [with no increase in reticulin], or abnormal and /or malignant infiltrates, which helps in the differential diagnosis of AA from other bone marrow disorders [24].

In the other hand, pregnancy - associated Aplastic anemia [p-AA] is defined as the first – time diagnosis of AA made during the period of pregnancy, marked by pancytopenia and hypocellular bone marrow, and is associated with severe maternal complications occurring in 79% of pregnancies, such as hemorrhage, pre-eclampsia, and infections, as well as fetal complications like preterm birth and fetal growth restriction [15-19]

Epidemiology of AA in Pregnancy

Aplastic anemia is a rare disease with an incidence and a prevalence significantly varying across different regions around the world. Studies suggest that the incidence of aplastic anemia is influenced by geographic location, with higher rates observed in various Asian countries compared to Europe and North America with a biphasic age distribution and increased risk in the developed countries [27], and variations within countries like Thailand and India potentially due to environmental and socioeconomic factors, but real-world data on its incidence and outcomes remain limited. In the Western countries for example, the incidence of AA is low with around 2.34 to 2.35 cases per million inhabitants per year as in Israel [25], Barcelona [2] and Sweden [26]. Comparing the incidence of AA between Europe, China, Japan and US, AA is more common in Japan and China compared to Europe and the United States, and being higher in Japan compared to other countries [27-29]. The incidence rates in Asia range from 0.39 to 0.74 per 10,000 people annually, which is two to three times higher than the rates in Western countries [30].

The incidence of AA in African countries may be similar to or slightly higher than in Western countries, but in Tanzania, the estimated incidence of acquired AA is approximately 3.8 to 5.9 cases per million per year, which is higher than the incidence in Western countries, and in Zimbabwe, the prevalence of acquired AA among men aged 15 years and above was found to be 27%, indicating a significant occurrence of the condition [31,32]. In Algeria, the incidence of AA resulted of 0.2 per 100,000 inhabitants per year, with a slight male predominance and a median survival of 3,8 years *[33]*.

In India, AA accounts for 20-30% of pancytopenia cases, with reported frequencies significantly higher than those in the West. While European studies suggest an incidence of approximately 2 cases per million annually, the incidence in Asian countries may be 2-3 times higher, reaching 6 to 8 cases per million per year [34]. In a prospective multicenter observational study conducted in 348 patients with aplastic anemia age over 15 years old in Thailand, from 2014 to 2016, the reported annual incidence of AA was 4.6 per million inhabitants, with severe and very severe aplastic anemia (SAA/VSAA) being more common presenting with an annual incidence of 3.8 per million, with a 2-year survival rate of 20.1 % indicating poorer outcomes in these groups. Age distribution showed two peaks: one between 15-25 years and another after 60 years with worsening prognosis in those aged 60-89 years [35].

In a nationwide prospective study conducted from 2014 to 2016 aimed to update the incidence and demographic characteristics of AA across six regions of Thailand, a total of 346 adult patients (≥15 years old) were included, with a median age of 59 years. The overall annual incidence was 4.6 per million, with higher rates observed in males (5.0 per million) and older age groups, particularly those aged 80-89 (14.5 per million) [36].

Also, another nationwide study, this time in Taiwan, using data from the National Health Insurance Research Database (NHIRD) between 2001 and 2010, analyzed 1270 AA patients over the age of 2. The overall incidence was 5.67 per million people annually, with a biphasic age distribution—peaking in individuals aged ≥70 years (19.83 per million) and children aged 2–9 years (5.26 per million) aligning with that in other Asian countries, reinforcing the association between advanced age and poorer prognosis [37].

Also, a study conducted in Pakistan demonstrated that AA is primarily triggered by epidemiological, etiologic and genetic factors with a peak in the onset of the disease between 10 to 29 years of age [38].

The incidence significantly varies across different geographic regions, suggests the potential influences from environmental, genetic, and socioeconomic factors in the development of this disease. Geographically, the regional patterns in the incidence of AA in Thailand, demonstrated the highest incidence recorded in the eastern region (6.3 per million), likely due to industrial exposure, followed by the northeastern region (5.5 per million), particularly in industrial and agricultural areas [36,10]. Differences in AA incidence within regions of Thailand suggest that environmental and occupational exposures, such as pesticides and industrial pollutants, may play a role in the etiology of the disease.

In India, the incidence of AA is higher in northern districts of West Bengal and is associated with lower socioeconomic status [35,39]. In Malaysia, a hospital-based case-control study of the genetic predispositions combined with environmental factors have suggested the contribution of this combination to the higher incidence of AA in certain aboriginal populations in this area [18].

Facing this rarity of AA, his occurrence in pregnancy (p-AA) is a even more rare life-threatening condition with 54 cases reported during the interval of time from 1975 to 2020 [16]. A single-center study in North America reported 19 pregnancies in 9 women with AA, over 30 years, highlighting the rarity of the condition [40].

In a retrospective case-control study conducted in Peking from January 2003 to January 2016, analyzing the maternal-fetal outcomes of pregnancies complicated by aplastic anemia (AA) compared to the healthy controls, only 85 patients were diagnosed with p-AA [17]. A systematic review conducted in 2018, identified 17 observational studies on aplastic anemia in pregnancy with 70 women reported [41]. Studies conclude that p-AA is rare and often difficult to diagnose due to the physiological hematological changes during pregnancy that can mask the disease [16, 42-43].

Etiology and pathophysiology of AA in Pregnancy*:*

Aplastic anemia (AA) is a rare and potentially fatal disorder characterized by bone marrow failure and peripheral cytopenias with a multifactorial etiology. Studies suggest that aplastic anemia, existing in two forms, inherited AA and acquired AA with the latter one often triggered by external factors like drugs, chemicals and/or infections, is primarily driven by an immune-mediated destruction of hematopoietic stem cells [HSPCs] as a central feature, often involving cytotoxic T cells and cytokines like interferon – γ [INF-γ] and tumor necrosis factor α [TNFα] combination of autoimmune mechanisms [11,22,42,43].

The exact cause of aplastic anemia in pregnancy is not well understood and the etiology remains uncertain. Potential contributing factors including chemicals, drugs, infections, irradiation, leukemia, inherited disorders and their specific link to pregnancy remains however controversial. Until now still remains unclear whether pregnancy triggers bone marrow failure or if the condition is unrelated to pregnancy [16,44,45], but there is a possibility that pregnancy itself may trigger AA, as some cases have shown remission of AA after abortion or delivery, suggesting a potential etiologic or conditioning role of pregnancy [46-48].

Aplastic anemia is caused by immunological changes, as the center point of the pathophysiology of the disease, and is regarded as a autoimmune disease. Studies shows that the immunological changes are even more significant during the period of the pregnancy. The maternal immune system's adaptations during pregnancy are essential for balancing tolerance toward the allogeneic fetus and for reducing maternal pathogen defense and maternal fatalities [49]. Disruptions in this balance can lead to autoimmune conditions generating adverse pregnancy outcomes such as preeclampsia, HELLP syndrome, and recurrent spontaneous abortion [50].

During pregnancy, the maternal immune system undergoes modifications to allow tolerance of the growing fetus while maintaining defense against pathogens leading to natural improvement in autoimmune diseases such as rheumatoid arthritis (RA). Several immune mechanisms, including HLA disparity between mother and fetus, glycosylation of IgG, and alterations in both innate and adaptive immune cells, contribute to the pregnancy-related improvement of RA. Regulatory T cells expand, and effector T cell activity is reduced, supporting this amelioration. After delivery, these immunomodulatory effects subside, often leading to postpartum disease flares as immune activity returns to pre-pregnancy levels [51].

Does drug exposure cause AA, or even more… be the cause of p-AA? Responding to this question, some studies suggest drug exposure increases the risk of aplastic anemia, while other studies indicate it is an uncommon cause.

The hospital-based case-control study conducted in Pakistan in 2021, studying 887 patients for the association of drugs with aplastic anemia has shown that carbamazepine, thiazides, and mebendazole were associated with increased risk of aplastic anemia [52]. The same conclusion has been shown from the population-based case-control study conducted in Thailand in 1427 patients diagnosed with AA from the year 1989 to 1994, demonstrating thiazide diuretics, sulfonamides, and mebendazole use significantly associated with increased risk of aplastic anemia [53]. In the face of these facts is really important to emphasize that taking medications during pregnancy can contribute to the development of AA. In the other hand a hospital -based control-study conducted in Latin American countries concluded in 2009, resulted in an 50% unclear association between drug exposure [chloramphenicol and azythromycine] and AA [54].

Studying the exposure to antimicrobials [beta-lactam antibiotics, chloramphenicol, macrolides, trimethoprim/sulfamethoxazole, and tetracycline] and the association with AA, antimicrobial drug use was notably higher among aplastic anemia patients (49.74%) compared to controls (29.31%), indicating a possible link between these medications and the onset of AA [55].

Some cardiovascular drugs, such as furosemide, have been demonstrated to be associated with an increased risk of aplastic anemia, while propranolol, dipyridamole, digoxin, and acetyldigoxin are significantly associated with agranulocytosis [56]. There is evidence suggesting that also anticonvulsants like phenytoin and carbamazepine can lead to aplastic anemia due to toxic drug metabolites linked to an inherited abnormality in metabolite detoxification [57].

So we can summarise that pregnancy leads to significant alterations in the pharmacokinetic properties of medications, impacting their distribution, absorption, metabolism, and excretion, affecting maternal and fetal health [58], suggesting that specific drug exposure during pregnancy can cause p-AA.

Research has consistently demonstrated a strong link between exposure to pesticides, industrial chemicals, and an increased risk of developing aplastic anemia [59]. Occupational and environmental contact with various chemical agents, including heavy metals such as lead, arsenic, and cadmium, is associated with toxic effects on the hematopoietic system [60,61]. AA is significantly associated with certain environmental exposures, such as rural living and exposure to pesticides. People in rural areas or lower socioeconomic settings, where contact with environmental toxins is more prevalent, are at increased risk, with rural living and pesticide exposure being significant risk factors and increasing the likelihood of AA by 3.58 times [62].

Furthermore, exposure to solvents like benzene has been frequently linked to a significantly elevated risk of aplastic anemia 3.5 times [10].

Acquired aplastic anemia (AA) is a rare, life-threatening condition caused by autoimmune destruction of hematopoietic stem cells, and gene polymorphisms, particularly in metabolic pathways, are believed to contribute to its development. Genetic factors, such as deletions in the GSTM1 and GSTT1 genes, which are involved in detoxifying environmental toxins, have been linked to an increased susceptibility to aplastic anemia. The GSTT1 null genotype, which involves the homozygous deletion of the glutathione S-transferase theta 1 gene, has been significantly associated with GSTT1 null genotype is significantly associated with a 1.74 times higher risk of AA, and also with increased risk for acquired aplastic anemia in children, because it can modulate the metabolism of exogenous pollutants or toxic intermediates, contributing to disease susceptibility [63,64].

Other genetic factors associated with AA are the somatic mutations, HLA gene mutations and germline genetic variants. Somatic mutations in myeloid cancer candidate genes and clonal hematopoiesis are prevalent in AA patients, with certain mutations correlating with clinical outcomes and response to therapy [65,66].

A genome-wide association study (GWAS) identified significant SNPs in the major histocompatibility complex (MHC) on chromosome 6p21. The top SNP, rs1042151A>G, encodes a p. Met 76Val change in the HLA-DPB1 gene and is linked to increased SAA risk. Additional risk alleles include DPB103:01, DPB110:01, and DPB1*01:01. These findings suggest that specific HLA-DPB1 and possibly HLA-B alleles may influence SAA risk through altered immune function, particularly via potentially affecting DP peptide binding specificity, expression, and other factors [67].

Acquired aplastic anemia (aAA) is characterized by a deficiency in early hematopoietic cells, leading to insufficient blood production and an increased risk of myelodysplastic syndrome (MDS) and leukemia. While the exact cause remains unclear, aAA is thought to be driven by HLA-restricted T cell immunity, with past studies focusing on HLA class II pathways. Recent research suggest a potential link between HLA class I mutations and autoimmunity in aAA. This may have been overlooked due to the complexity of analyzing the MHC region with WES [64, 69].

Patients with severe aplastic anemia (SAA) may have unrecognized inherited bone marrow failure syndromes (IBMFS) due to phenotypic variability [70]. Based on this, re-evaluating the case of the pathologist Paul Ehrlich, often recognized as the first

well-defined case of aplastic anemia in 1888, has been suggested that an inherited bone marrow failure syndrome may have been an underlying factor in the diagnosis [71, 72].

Viral infections are another recognized etiological factor for AA. Typically, aplastic anemia develops after a viral infection, such as parvovirus B19, or idiopathically, with immune-mediated mechanisms speculated as the cause of both liver damage and bone marrow failure. Human parvovirus B19 is significantly associated with aplastic anemia and with erythroid aplasia and halting red blood cell production [73]. Studies have shown a higher prevalence of parvovirus B19 infection in AA patients compared to healthy controls, indicating its role in the disease's pathogenesis [74].

Over the years, studies have described the increasing occurrence of hepatitis-associated aplastic anemia with males more likely to develop bone marrow failure following hepatitis, while females having lower survival rates. These findings suggest subclinical hepatitis may contribute to a significant number of so-called idiopathic aplastic anemia cases[75].

*Aplastic anemia (AA) is a rare, life-threatening condition c*haracterized by pancytopenia and a hypocellular bone marrow, while pure red cell aplasia (PRCA) involves a selective reduction in red blood cell production. Viral infections, such as parvovirus B19, cytomegalovirus, and Epstein-Barr virus, have been linked to immune-mediated bone marrow failure in both AA and PRCA. Six recent cases of AA or PRCA were associated with previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, suggesting a potential viral trigger [76].

Parvovirus B19, in particular, has been linked to red-cell aplasia, leukopenia, and thrombocytopenia. A study involving 27 aplastic anemia patients and 20 healthy controls revealed a significantly higher presence of parvovirus B19-specific IgM and viral DNA in the aplastic anemia group compared to the controls (40.7% vs. 5% for IgM, and 37% vs. 0% for viral DNA). These findings indicate active or recent parvovirus B19 infections in aplastic anemia patients, although further research is necessary to fully understand the mechanisms by which this virus causes bone marrow failure [77].

Herpesviridae family infections, such as herpes simplex virus type 1 (HSV-1), have been associated with the onset of aplastic anemia (AA). Case studies have demonstrated that antiviral treatment can lead to significant improvement in patients with AA, suggesting a direct link between viral infections and the condition. In one case, a 56-year-old woman presented with fever, painful swallowing, and necrotic oropharyngeal ulcers. She was found to have severe pancytopenia, and a bone marrow biopsy confirmed AA. PCR testing revealed an active HSV-1 infection. Following antiviral therapy, both her mucosal lesions and blood counts improved rapidly. This case underscores the potential role of viral infections, particularly HSV-1, in triggering AA and highlights the need to consider viral causes when diagnosing and treating the disease [78,79].

The development of aplastic anemia (AA) often involves the immune-mediated destruction of hematopoietic stem cells (HSCs), with interferons playing a pivotal role. Type I and II interferons, elevated during viral infections, can induce bone marrow aplasia and contribute to AA. IFN-γ, in particular, activates HSCs during infections, impairing their self-renewal capacity and leading to HSC depletion. Type I interferons (IFN-α/β) further exacerbate this by promoting HSC proliferation during inflammation, causing bone marrow failure. Patients treated with IFN-α often show bone marrow suppression and cytopenias. Persistent viral infections, such as those seen in lymphocytic choriomeningitis virus (LCMV)-infected mice lacking perforin (P0/0), also lead to progressive pancytopenia due to excessive secretion of TNF and IFN-γ by CD8+ T cells. Depleting these cells protects hematopoiesis, highlighting the critical role of IFN-γ and TNF in bone marrow failure during viral infections. Limiting these factors could potentially safeguard hematopoietic function [80,81].

Aplastic anemia (AA) has been linked to Epstein-Barr virus (EBV) infections, particularly in immunosuppressed patients [82]. One case involved a 13-year-old girl who developed severe AA after an EBV-induced episode of infectious mononucleosis, suggesting a connection between the virus and AA [83]. Chronic active EBV infection (CAEBV) can also lead to severe symptoms for example, a 73-year-old woman with CAEBV developed AA and progressive liver damage. This case highlights the potential for EBV to induce AA in chronic infections [84].

EBV has been implicated in AA, with evidence suggesting that EBV infection activates cytotoxic T lymphocytes (CTLs) which, in turn, damage hematopoietic stem cells. Studies have shown that EBV copies are higher in the CD8+ T cells of untreated AA patients, correlating with increased levels of interferon-gamma and cytotoxic proteins like granzyme B and perforin. Knockdown of the EBV-encoded nuclear antigen 1 (EBNA-1) gene reduced these effects, indicating a role for EBV in promoting CTL-mediated bone marrow damage [85].

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 [48,86].

Viral infections during pregnancy can lead to complications such as preterm labor, birth defects, pregnancy loss, and increased maternal morbidity. Changes in the maternal immune system during pregnancy can prolong inflammatory responses, delay recovery, and worsen infection outcomes. The interaction between the maternal immune system and the placenta may contribute to higher morbidity and mortality, affecting both fetal development and maternal health [87,88].

Viral infections during pregnancy pose significant risks to both maternal and fetal health, leading to increased morbidity, adverse pregnancy outcomes, and long-term developmental issues in the offspring. These infections can disrupt the delicate immunological balance required for a successful pregnancy, triggering inflammatory responses and directly affecting fetal development. Understanding these mechanisms is essential for developing strategies to eliminate these risks and to improve maternal and fetal health.

Diagnosis of AA in Pregnancy

Diagnosing pregnancy-associated aplastic anemia (p-AA) requires a multidisciplinary approach, including clinical evaluation, complete blood count (CBC), and bone marrow biopsy. Aplastic anemia in pregnancy is rare, with 24 pregnancies in 12 women over 24 years in a single, tertiary hospital [40]. Its diagnosis can be difficult due to the normal hematological changes in pregnancy that may obscure symptoms. Accurate diagnosis and timely management are essential for improving both maternal and fetal outcomes. Common presenting symptoms of pAA during pregnancy include fatigue, chest pain due to severe anemia, petechiae, and hematemesis. Low platelet counts (2.0 x 10^9/L), bone marrow hypocellularity (25%), and late diagnosis during pregnancy are predictors of poor maternal outcomes in pregnancy-associated severe aplastic anemia [89]. Definite evidence of decreased marrow production of all formed elements of the blood is necessary to support the diagnosis of pregnancy-associated aplastic anaemia [48]. Some cases are identified incidentally during routine prenatal care. Routine third trimester CBC screening can identify potential complications and decrease maternal and fetal morbidity and mortality [16].

However, a key concern when dealing with pregnant patients is the safety and welfare of the unborn child. A bone marrow biopsy, is a highly informative invasive procedure and is relatively safe to perform in pregnant women [90]. However, the safety of performing a bone marrow biopsy during pregnancy is a critical concern due to potential risks to both the mother and the fetus. 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 [90,91].

The primary objective in managing pregnancy-associated aplastic anemia (p-AA) is to ensure an accurate diagnosis while prioritizing the safety of both mother and child. This remains an area of limited medical knowledge that requires ongoing research and clinical attention to improve outcomes.

Treatment of AA in pregnancy

Aplastic anemia during pregnancy is a rare but serious condition that poses significant risks to both the mother and the fetus. The management of this condition requires a careful balance between treating the anemia and ensuring the safety of the pregnancy. Supportive care, including erythrocyte and platelet transfusions, is the primary treatment for managing AA during pregnancy the primary treatment option during pregnancy is transfusion, with target hemoglobin levels above 8.0 g/dl and platelet counts exceeding 20,000/cm. Intensive haematological support during pregnancy with aplastic anaemia leads to a healthy baby delivery [15].

Immunosuppressive therapy, particularly with agents like cyclosporine, can be beneficial and is often used in combination with supportive care, and also antilymphocyte globulin has been used safely during pregnancy in some cases. Animal studies indicate that high doses of cyclosporine can be teratogenic, but lower doses may not have the same effect. In the other hand cyclosporine does not appear to be a major human teratogen, with studies showing no significant increase in congenital malformations compared to the general population [92,94]. Pregnancy-related aplastic anemia can be effectively managed with cyclosporine and granulocyte-colony stimulating factor, reducing maternal and fetal morbidity and mortality [94,95]. Cyclosporine use during pregnancy is associated with an increased risk of premature delivery and low birth weight infants. The prevalence of prematurity and low birth weight is higher in cyclosporine-exposed pregnancies compared to the general population [92]. Women with aplastic anemia can have uncomplicated pregnancies after immunosuppressive therapy, but complications are common, particularly in those with thrombocytopenia or paroxysmal nocturnal hemoglobinuria [96]. Cyclosporine exposure during pregnancy is similar to that in the mother, and breastfeeding should be avoided due to its presence in maternal breast milk. No specific harmful effects attributable to cyclosporine were observed in newborns, although long-term effects need further investigation [97]

Bone Marrow Transplantation (BMT) is generally contraindicated during pregnancy due to significant risks to the fetus. While BMT is a potentially curative treatment for aplastic anemia, its use in pregnant patients poses challenges due to limited data in the literature regarding it use. The conditioning regimens required, involving high doses of chemotherapy or radiation, carry risks such as miscarriage, congenital abnormalities, preterm birth, and

long-term developmental issues, making it a complex decision in pregnancy-associated cases.

Eltrombopag, a thrombopoietin receptor agonist, use during pregnancy may be acceptable and result in favorable maternal and fetal outcomes in refractory cases with adequate maternal and fetal monitoring, although its routine use is not recommended due to limited data on safety and efficacy [98].

A multidisciplinary team approach is crucial for managing aplastic anemia in pregnancy, involving hematologists, obstetricians, and anesthesiologists to optimize maternal and fetal outcomes. Vaginal delivery is preferred unless there are specific indications for a cesarean section, in which case platelet transfusion is necessary to prevent hemorrhage [15].

In conclusion, aplastic anemia during pregnancy is a rare but serious condition that requires a delicate balance between managing the disease and ensuring the safety of both mother and fetus. Supportive care, such as erythrocyte and platelet transfusions, plays a crucial role in maintaining maternal health during pregnancy. Immunosuppressive therapies like cyclosporine, often used alongside supportive treatments, have shown success in reducing maternal and fetal complications. While bone marrow transplantation is a potentially curative option, it is generally contraindicated during pregnancy due to the risks it poses to the fetus. Emerging treatments, such as eltrombopag, may offer hope in refractory cases, though their use requires close monitoring and further research on safety. Overall, with appropriate management, many women with pregnancy-associated aplastic anemia can have successful pregnancies, though complications remain a significant concern.

Conclusions

Aplastic anemia (AA) is a rare, life-threatening condition characterized by pancytopenia and bone marrow failure, and its occurrence during pregnancy presents significant medical and obstetric challenges. The immune-mediated nature of AA, along with drug exposure and certain viral infections, are key factors in its development. Hormonal and immunological changes in pregnancy can exacerbate symptoms, though the precise mechanisms remain unclear. Diagnosing AA in pregnant women is complicated by overlapping symptoms with normal pregnancy, and typically requires laboratory findings and bone marrow biopsy to confirm.

Treatment is difficult due to the teratogenic risks of immunosuppressive therapies and the dangers associated with bone marrow transplantation. Current management relies on supportive care, such as transfusions and growth factors, with success depending on the severity of the disease and patient health. Outcomes for both mother and fetus are largely determined by early diagnosis and appropriate treatment, highlighting the importance of careful monitoring and timely intervention.

In conclusion, while current knowledge has advanced understanding of AA during pregnancy, critical gaps remain. Further research is necessary to improve clinical management and outcomes. A multidisciplinary approach involving hematologists, obstetricians, and neonatologists is essential for optimizing care for this complex patient population.

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Conflict of Interest

"The authors declare no conflict of interest."

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