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Haematological Complications of HIV Infection in Pregnant Women

Valerie Esame Njar[1], Frances Ugonne Ogunnaya[2], Ofonmbuk Friday Bronson[1] and Emmanuel Ifeanyi Obeagu[3]*

[1]*Department of Haematology and Blood Transfusion Science, University of Calabar, Nigeria*

[2]*Department of Internal Medicine, Newark Beth Israel Medical Center, 201Lyons Avenue, USA*

[3]*Department of Medical Laboratory Science, Kampala International University, Uganda*

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***Corresponding author:** Emmanuel Ifeanyi Obeagu, Department of Medical Laboratory Science, Kampala International University, Uganda

Introduction

At the end of 2020, there were an estimated 37.7 million (30.2–45.1 million) people living with Human immunodeficiency virus (HIV), over two thirds of whom (25.4 million) are in the WHO African Region [1-4]. HIV infection is a multisystem disease and haematological abnormalities are among the most common complications of HIV. HIV infection in pregnancy has become the most common complication of pregnancy in some developing countries [5-9]. This has major implications for the management of pregnancy and birth, with an estimated 2.3 million HIV positive women getting pregnant each year, about 700,000 children will be born infected, acquiring infection predominantly from their mothers [10]. The majority of these women and children live in underdeveloped countries, with Africa accounting for two-thirds of infected adults and 90% of the world's children with HIV [11-12].

According to data from the Nigeria National HIV/AIDS Indicator and Impact Survey (NAIIS), about 1.9million people in Nigeria are living with HIV with a national prevalence of 1.4% among adults aged 15 - 49years (Joint United Nations Programme on HIV/AIDS [13]. Estimates from the Joint United Nations Programme on HIV/AIDS also show that women aged 15-49 years are more than twice as likely to be living with HIV than men (1.9% versus 0.9%.); this difference in HIV prevalence between women and men greatest among younger adults, with young women aged 20–24 years more than three times as likely to be living with HIV as young men in the same age group [13]. HIV epidemic continues to affect young women within the reproductive age with a prevalence of 4.1% among pregnant women in Nigeria [14].

HIV infection is characterized by progressive weakening of the immune system attributed to the decrease in the number of circulating CD4+T-helper cells. This predisposes HIV patients to a variety of opportunistic infections and neoplastic disorders. The most severe phase of HIV infection leads to acquired immunodeficiency syndrome (AIDS) where the CD4+ cell count drops below 200/mm3 and is marked by multisystem disease and the appearance of particular opportunistic infections as well as prevailing hematological abnormalities [15].

Although normal pregnancy is associated with numerous physiological changes in various organ-systems including the haematological system, these haematological alterations in pregnant women with HIV is complicated not only by HIV infection itself but also by the Antiretroviral (ARV) drugs as well as the medical and psychosocial comorbidities (such as stigma experiences, depression, sleep difficulties, anxiety, alcohol use, etc) associated with HIV [16]. Haematological abnormalities described in gestational women with HIV infection/AIDS include impaired haematopoiesis, immune and non-immune mediated cytopenias, and altered coagulation.

Pregnancy-Induced Haematological Changes

During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to accommodate the demands of the fetoplacental unit [17]. These changes begin after conception affecting almost every organ system, but resolve after pregnancy with minimal residual effects in uncomplicated pregnancies [18]. The most significant of these haematological changes include physiologic anemia, neutrophilia, mild thrombocytopenia, increased procoagulant factors, and diminished fibrinolysis; with these changes often witnessed in the woman's plasma volume, red blood cells, white blood cells, platelets, and coagulation factors [17].

Changes in Plasma Volume

Plasma volume increases progressively throughout normal pregnancy with the total gain of plasma volume at term averaging

1100–1600 mL and resulting in a plasma volume of 4700–5200 mL, 30–50% above that found in nonpregnant women [17]. Most of this increase occurs by 34 weeks' gestation and is proportional to the birthweight of the baby [17]. Since the expansion in plasma volume is often relatively greater than the increase in red cell mass, there is an ensuing fall in haemoglobin concentration, haematocrit and red blood cell count which result in haemodilution [17].

Changes in Red Cell Mass

RBC mass begins to increase at 8-10 weeks of gestation and steadily rises by 20–30% (250-450mL) above nonpregnant levels by the end of pregnancy in women receiving iron supplementation; however, among women not on iron supplementation, this increase is only by 15-20% [17]. As earlier stated, the greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume is responsible for the modest fall in hemoglobin levels (i.e., physiological or dilutional anemia of pregnancy) observed in healthy pregnant women [17].

Changes in Platelet Count

Platelet counts tend to fall progressively during normal pregnancy, although it usually remains within normal limits [18]. Gestational thrombocytopenia is characterized by mild asymptomatic thrombocytopenia occurring in the third trimester in a patient without any history of thrombocytopenia (other than in the previous pregnancy) and usually resolves postpartum [17].

Changes in WBC Count

Pregnancy is associated with leukocytosis, primarily due to increased circulation of neutrophils. The neutrophil count begins to increase in the second month of pregnancy and stabilizes in the second or third trimester [17]. However, the white blood cell count falls to the normal nonpregnant range by six days after childbirth [17].

In healthy women with normal pregnancies, there is no change in the absolute lymphocyte count and no significant changes in the relative numbers of T and B lymphocytes; the monocyte count is generally stable while the basophil count may slightly decrease and the eosinophil count may slightly increase . Additionally, normal pregnant women can have a small number of myelocytes or metamyelocytes in the peripheral circulation [17].

Changes in the Coagulation System

Changes in the coagulation system during pregnancy produce a physiological hypercoagulable state (in preparation for haemostasis following delivery) The concentrations of certain clotting factors, particularly VIII, IX and X, are increased, while concentrations of endogenous anticoagulants such as antithrombin and protein S decrease [18]. Fibrinogen levels rise significantly by up to 50%, fibrinolytic activity is decreased while Factor V remains unchanged [17]. All these alterations favour clotting, this predisposing the pregnant and postpartum woman to venous thrombosis. This increased risk is present from the first trimester and for at least 12 weeks following delivery [18]. Normalization of coagulation parameters varies depending on the factor, but all should return to baseline from 8 weeks postpartum [17]. In most cases, in vitro assays of coagulation [activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT)] remain normal in the absence of anticoagulants or a coagulopathy [18].

Haematological Complications in HIV-Infected Pregnant Women

Hematological aberrancies become more severe during the late stages of the disease signifying the importance of active virus replication and high levels of viremia in the causation of disease (Bhardwaj et al., 2020). They include anomalies of coagulation, cytopenias affecting different cell lineages, and faulty haematopoiesis. These abnormalities are brought on by a variety of factors, including immune-mediated cell lysis, direct cytopathic effects of viruses or secondary to infections, drug toxicity and neoplasms [10]. Unlike the normal physiological changes occurring in pregnancy that resolve after pregnancy with minimal residual effect, these aberrancies persist even after parturition [18].

Haematological manifestations of HIV are common and diverse, occurring at all stages of infection. Common haematological emergencies that occur in HIV-infected pregnant women include the high-grade lymphomas, particularly Burkitt lymphoma, and thrombotic thrombocytopenic purpura (TTP). Immune thrombocytopenic purpura (ITP), opportunistic infections and drug side-effects are also frequent causes of cytopenias [16].

Cytopenia

Cytopenias (decrease in the number of blood cells) are one of the most frequent complications of HIV and may be broadly classified as being either as a result of a bone marrow production defect or due to increased peripheral loss or destruction of blood cells. Anaemia is the most common cytopenia occurring in up to 95% of HIV patients during their disease course (Volberding et al., 2003). A wide range of etiologic factors may cause anemia, but for the sake of this review, only those causes specific to HIV infection will be considered. The most frequent cause of anemia in HIV-infected patients is anemia of chronic disease which results basically from a disruption in bone marrow cytokine homeostasis. HIV is cytotoxic to T-helper lymphocytes, which causes B cell dysregulation and altered cytokine release. An explanation to this pathogenesis is that HIV-infected T cells directly suppress growth of bone marrow progenitors, thus suppressing haemopoiesis. CD4, the cell-surface receptor target of HIV, is carried by T-helper lymphocytes, monocytes and microvascular endothelial cells which are abundant in the bonemarrow. Hence, infection of monocytes in the bone marrow alters the release of cytokines, which in turn inhibits the ability of haemopoietic progenitor cells to respond appropriately to anemia and other peripheral

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cytopenias. This explains why pancytopenia is the norm in most people with advanced HIV [16]. It is however important to note that HIV-related cytopenias can also be drug-induced, resulting from intake of antiretrovirals such as

Immune Thrombocytopenic Purpura (ITP)

Zidovudine (AZT) and stavudine (d4T), as well as co-trimoxazole (Bactrim) and the antituberculosis medications isoniazid, rifampicin, and rifabutin. It is therefore recommended that cytopenic HIV patients be placed on highly active antiretroviral therapy (HAART) because it reduces cytokine imbalances. However, if patients develop a new cytopenia while on HAART, drug-induced cytopenia must be considered, and a change in HAART regimen may be necessary [16].

An association between HIV and thrombocytopenia was first described in 1982 [19]. ITP (a syndrome in which platelets become coated with autoantibodies to platelet membrane antigens, resulting in splenic sequestration and phagocytosis by mononuclear macrophages and subsequent reduction in the number of circulating platelets) is the most common cause of thrombocytopenia in HIV patients, affecting up to 30% of those infected. Despite the clinical presentation being comparable to non-HIV-associated ITP, the cause is hypothesized to be owing to an HIV-induced auto-antibody formed against an amino-acid sequence within the platelet surface glycoprotein IIIa [16]. Many patients present with ITP as the first manifestation of HIV, although it can occur in both early and advanced disease. Dominguez and coworkers studied platelet kinetics in 41 HIV-infected thrombocytopenic patients and found that platelet survival was lower in those with CD4 counts above 200 cells/mL than in those with counts below this level, implying that platelet destruction is more important in patients with high CD4 counts, and decreased platelet production is more important in those with lower CD4 counts [20]. Similar kinetic studies performed by Cole et al concluded that HIV-infected patients have ineffective delivery of viable platelets to the peripheral circulation, despite a 6-fold elevation in thrombopoietin levels and a 3-fold expansion of megakaryocyte mass compared to normal controls. This finding suggests the possibility of HIV-induced apoptosis of megakaryocytes and is compatible with the results of kinetic experiments, which found increased platelet turnover but no change in platelet survival following the initiation of zidovudine (AZT) therapy, indicating that platelet production had increased during treatment [21].

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is a disorder that causes blood clots (thrombi) to form in small blood vessels throughout the body, leading to reduction in platelet number. Precipitants of TTP include pregnancy, autoimmune disorders, malignancies and drugs, e.g., clopidogrel and statins; however, HIV is the most common virus precipitating TTP. TTP is characterised by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), fluctuating neurological signs, fever and renal impairment. HIV-associated TTP typically occurs in young African females not on HAART and with high viral loads [20]. TTP is a potentially fatal condition which occurs when ultra-large Von Willebrand factor (VWF) multimers cause platelet microthrombi in arterioles and capillaries. These platelet microthrombi lead to intravascular haemolysis and organ ischaemia. The red cells are mechanically sheared as they pass through the platelet thrombi in the microcirculation, leading to the characteristic red-cell fragments or 'schistocytes' on the blood smear [16].

Lymphoma

HIV infection is associated with a markedly increased risk of malignancies, particularly high-grade B-cell lymphoma. HIV infection increases the risk of non-Hodgkins's lymphoma (NHL) by 60 to 200 times [16]. Lymphoma is a late manifestation of HIV infection, more likely to occur in the setting of significant immune suppression, with CD4 cells below 200/mm3, and prior history of an AIDS-defining illness [20]. Chronic antigen stimulation, cytokine dysregulation, and Epstein-Barr virus (EBV) and human herpes virus 8 (HHV8) co-infection are among the proposed mechanisms. EBV has been identified in up to 40% of HIV-associated lymphomas [16].

Similarly, HIV is also known to be associated with a 5 - 10-fold increased incidence of Hodgkin lymphoma (HL), and in these patients there is a higher incidence of bone marrow involvement compared with HIV-negative patients [16]. HIV-positive patients also have an increased incidence of primary bone marrow HL where there is no lymphadenopathy or organ involvement to suggest lymphoma, and generally present with cytopenias and 'B symptoms' (such as weight loss and night sweats) often aggressive clinical course [16].

Although highly active antiretroviral therapy (HAART) has resulted in a highly significant decline in mortality and development of new opportunistic infections, Kaposi's sarcoma, and primary central nervous system lymphoma, as well as significant decreases in systemic AIDS-related lymphoma among patients with AIDS, the decline in lymphoma cases is not as profound as that seen in other AIDS-defining conditions, and lymphoma has now become one of the more common of the initial AIDS-defining illnesses [20].

Neutropenia

HIV is associated with a markedly increased risk of neutropenia (abnormally low neutrophil counts). Common mechanisms of HIV-induced neutropenia include inhibition of granulopoiesis by the virus itself, marrow infiltration by infectious organisms or neoplasia, adverse drug effects, autoimmune neutropenia, and hypersplenism [20].

Thrombosis

HIV is a prothrombotic condition that increases the risk of venous thromboembolism (VTE) by 2 to 10 times when compared

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to HIV-negative individuals of the same age. The risk is highest with advanced disease and co-existing infections and malignancies [16]. The postulated mechanism is that of disruption of the normal balance of coagulation factors with an increase in prothrombotic proteins such as von Willebrand factor (VWF) and decrease in levels of natural anticoagulant proteins such as antithrombin, protein S and protein C. Other predisposing factors include coexistence of malignant, inflammatory, or autoimmune disorders; or vascular damage due to injection drug use, placement of intravenous catheters, or Cytomegalovirus (CMV) infection [16]. Thrombosis resulting from antithrombin deficiency occurs in association with HIV nephropathy as a result of losses of the anticoagulant in the urine. This nephropathy may also result in compensatory hepatic synthesis of factors V, VIII, and X induced by hypoalbuminemia, and increased platelet adhesion and aggregation [22]. Similarly, cytomegalovirus-induced thrombosis in HIV patients is thought to result from the virus promoting adhesion of neutrophils and platelets to the vascular endothelium, and enhancing the synthesis, secretion and survival of factor V and von Willebrand factor [20].

Conclusion

HIV infection remains a global health burden decades after it was first discovered. Pregnancy, HIV and ARV have been shown to affect the haematological parameters of pregnant women; however, their combined effects on these parameters are still not yet fully elucidated. Several remarkable differences exist between HIV-infected pregnant mothers and their HIV-negative counterparts, most of which have been clearly highlighted in this paper.

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