Pregnancy-Related Thromboembolism in Sickle Cell Disease

EDITOR'S PICK

Sickle cell disease is a blood disorder that shortens life expectancy and research is currently lacking on pregnant females with the condition. This review considers some of the most important aspects of pregnancy-associated sickle cell disease and thromboembolism, the present understanding of the disease, pathology, clinical issues, recent therapies, and clinical management of both mothers and fetuses. Pregnancy in sickle cell disease is an emerging issue requiring attention and education activity in Europe. Therefore, it is very important that this review article is widely distributed.

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Abstract

Haematological disorders are predominant in the tropical and subtropical countries where major problems of sickle-cell disease (SCD) and thalassaemias are often recorded. However, reports of these conditions have increased in the Western hemisphere more recently. Genetic counselling, early detection of the disease condition, and determining an appropriate treatment regimen remains the solution. Most molecular types of SCD have been determined and the pathological impact of individual types along with the degree of severity is known to clinical investigators and physicians. There is, however, a significant need for a proper counselling system for the clinical diagnosis in most countries. Lack of funding, trained personnel, relevant physicians, instruments, and laboratories are the challenges to overcome. Pregnancy-associated SCD and thromboembolism require special mention due to their mortality rate, complexity of treatment, and care necessities. This review considers some of the most important aspects of pregnancy-associated SCD and thromboembolism, shedding light on the present understanding of the disease condition, pathology, clinical issues, the association with venous thromboembolism, recent treatment measures, and clinical and social management of pregnant women and fetuses for patients with SCD. Integrated social and clinical care along with extensive timely medical and clinical counselling for patients can improve the present situation which is growing in different countries. To save future generations and pregnant mothers from the haematological disorders that could be either prevented or treated, essential genetic screening or counselling should be made a priority by governments. In addition, social education and campaigns related to the disease condition can help to improve the situation.

INTRODUCTION

The growth of the human population could be attributed to better healthcare facilities and medical management. Management of regular health concerns including pregnancy and neonatal management has become more efficient with time. Yet, maternal morbidity, especially because of a specific condition such as sickle cell disease (SCD), is considerable. The impact is tremendous in developing countries including the Sub-Saharan region, Middle-Eastern countries, Asia, and Latin American countries. The estimated global burden of sickle cell anaemia in children under 5 years of age could become 500,000 cases by the year 2050.[1] Unfortunately, the burden of SCD is high in Nigeria, the Democratic Republic of Congo, and India. Specific countries have high risk of child or maternal death caused by SCD; for example, in French Guiana, one in every 235 children is affected by such a genetic disorder.[2]

Sickle Cell Disease

In SCD, red blood cells (RBC) are crescent-shaped, restricting blood flow in the narrow blood vessel and causing tissue damage and pain. SCD is an autosomal recessive genetic disorder. Haematological and genetic analyses suggest that there are many forms of SCD due to various homozygous genotypes, haemoglobin S (*HbS*), and the different heterozygous states of haemoglobin C. There are several subtypes, including haemoglobin SS, haemoglobin SC, haemoglobin SB+ (beta) thalassaemia, haemoglobin SB 0 (beta-zero) thalassaemia, haemoglobin SD, haemoglobin SE, and haemoglobin SO. Those who inherit the mutated HbS gene from one parent may not have many health issues and are considered as having sickle cell trait (SCT). Thus, patients with the SCT serve as a carrier of SCD with a single copy of the mutated gene. Patients mostly remain asymptomatic and lead a normal life; however, patients with SCD have both the mutated genes, are symptomatic, and display some or all clinical signs associated with the disease. Presentation of these symptoms varies from patient to patient depending on their demographic, clinical, and other factors.

SICKLE CELL TRAIT AND PATHOLOGY

The predominance of sickle cell anaemia in different regions of Africa is due to the abundance of SCT in the population that naturally aids in surviving malaria.[3] SCD occurs as a result of a point mutation in the gene for beta-globin where *Glu-6* is altered to *Val-6* promoting the production of HbS. Such abnormal haematological conditions reduce the natural lifespan of the population due to one or the more severe complications.[4] Patients with these conditions also tend to have a higher epidemiology of venous thromboembolism (VTE);[4,5] therefore, an increased trend should be observed in pregnant women in these populations. Interestingly, a recent study on pregnant women and the increased trend of VTE in pregnancy and postpartum suggested no difference in the occurrence of pulmonary emboli or other VTE in pregnant women with SCT compared to women who did not have the condition.[6] However, special attention should be given to pregnant women with SCT. Although SCT is an apparently benign state, it requires proper diagnosis for future generations and possible differentiation with beta-thalassaemia. A detailed analysis to differentiate between the thalassaemic and SCT condition should be opted for before confirming SCT.[7] SCT is not always harmless: certain conditions of SCT can invoke thrombosis.[8] Moreover, adequate facilities and training for medical practitioners are required to tackle any general or emergency situations to manage complications that may arise.[9] Advanced monitoring and detection technology such as optofluidic resonator-based methods may help in the timely detection of SCD conditions.[10] Although there is population-specific evidence for increased risk of SCD or SCT, global estimation of the disease reports otherwise where higher prevalence of the disease condition was noted for the African–American population, Saudi Arabian population, among others. Consequently, SCD and SCT have become a global challenge for researchers and medical practitioners.[11,12]

SCD presents with a homozygous gene mutation: a mutation in both alleles. Microscopic, physiological, and biochemical analyses suggest that the RBC shape alters to a sickle or crescent shape due to the mutation and the possibility of clump formation increases manifold, forming

blood vessel blockage, consequently impeding normal blood flow. These physiological events present pain and affect blood pressure. Moreover, the life span of sickle cells is only 10–20 days compared to the normal lifespan of a RBC which is 120 days. Production of RBC by the bone marrow is impacted and there is an acute reduction in RBC number.

Patients with SCT generally do not show any symptoms; however, the condition can be worsened by certain factors such as severe dehydration, physical exertion, and high altitude where the oxygen level demands increase. The established and prominent diagnostic symptoms of SCD are manifestations of bone marrow infarction, this may include mild to severe bone pain, avascular bone necrosis, painful crisis, hypersplenism, cerebrovascular accident, splenic sequestration, meningitis, septicaemia, aplastic crisis, and others.

The blood coagulation system alters in patients with SCD. A variety of biochemical markers associated with thrombin and fibrin generations such as fibrinopeptide A, thrombin–antithrombin complexes, plasmin–antiplasmin complexes, prothrombin fragment 1.2, and D-dimer levels augment in the blood plasma and activate the coagulation process. Assessment of these markers with thrombin generation assays and thromboelastography also confirms alterations that promote the prothrombotic state.

ASSOCIATED HEALTH ISSUES

Common health problems associated with SCD are severe anaemia caused by extensive haemolysis and the short life span of sickle cells, hand–foot syndrome caused by swollen limbs from poor blood flow, splenic sequestration caused by restricted blood flow and an enlarged spleen, hampered growth and maturation, seizures and similar neurological conditions caused by lack of blood flow in brain, heart and lung conditions including pulmonary hypertension, pulmonary fibrosis, and severe heart problems.

PREGNANCY AND SICKLE CELL DISEASE

The physiological changes during pregnancy induce several complications for the mother and the child due to the presence of SCD. Both antepartum and postpartum complications are reported frequently where SCD is associated with pregnancy. Altered metabolism and vasculature in the mother and child further increases the risk of thromboembolism.

Increased metabolic demand, blood supply, blood viscosity, and coagulability can induce complications of SCD in the mother with predominant clinical issues such as thromboembolism, ulcers, and heart and lung issues including pulmonary embolism and infarctions. Necrosis and vaso-occlusive crisis remain the primary manifestations in these cases. All of these clinical conditions may restrict the uteroplacental circulation which is vital for fetal survival. Fetal hypoxia and further complications are the subsequent issues that may arise for pregnant women with SCD.[13] During the gestational period, frequent and repetitive episodes of pre-eclampsia and eclampsia are common due to SCD and impaired circulation.

Excessive risk of maternal morbidity is reported in Jamaica and Saudi Arabia because of unmanageable complications of SCD. The estimated risk factors are relatively high and unexpected due to the association of a number of complications that elevate the morbidity rate.[14-16] Estimated association analysis of maternal outcomes and SCD suggested that there is a higher relative risk for the mothers having SCD compared to the general population and almost twice the risk of pre-eclampsia. Additionally, association analysis of neonatal outcomes and SCD suggested the increased risk of neonatal death along with increased complications for the mother.[17]

VENOUS THROMBOEMBOLISM AND PREGNANCY

VTE is directly associated with SCD, especially in pregnancy. Unfortunately, VTE is triggered during pregnancy and the impact remains severe due to the onset of deep vein thrombosis or pulmonary embolism. Lim et al.[18] reported

that VTE can affect one in 100,000 women at childbearing age in the general population, whereas approximately 500 per 100,000 individuals are affected in an older age group.[18,19] Although VTE is associated with older age, a considerable number of cases of VTE are associated with pregnancy.[20] This condition is probably induced by eclampsia, pre-eclampsia, and other associated complications. Antepartum and postpartum pregnancy-associated VTE was reported to occur in 59 out of every 10,000 pregnancies by Coon et al.,[20] however, the risk of VTE is quite low (2 in every 10,000 per year) in women who are not pregnant.[21,22] Previous assessment through CT pulmonary angiography suggested no difference between patients with SCD and the general population in the case of acute pulmonary.[23]

Research outcomes have revealed that in pregnancy, plasma fibrin and D-dimer increases with the progressive gestational age for mothers who are sickle cell carriers, mostly having African and South Asian ancestry. Therefore, fibrin-associated markers, fibrin monomers, or D-dimer could be useful indicators for VTE in women with SCD-associated pregnancies.[24]

MANAGEMENT OF SICKLE CELL DISEASE IN PREGNANCY

SCD-associated pregnancy can result in multiple complications including premature labour, severe pain, restricted fetal growth, and mortality. Spontaneous miscarriage is another unfortunate outcome that occurs frequently.[25,26] Therefore, the pregnancy of patients with SCD should be handled delicately by medical care providers. Information on dehydration, cold, hypoxia, and their relation to SCD should be explained properly to the women who are planning to conceive. Detailed information on the plausible adverse outcomes should also be explained and embolism-related issues should be discussed. Vaccination status should be decided carefully by the medical practitioners, with special consideration given to concerns regarding thromboembolism. Antenatal haemoglobinopathyscreening is mandatory to track conditions. Routine prophylactic blood transfusion should be avoided for patients with SCD; moreover, matching blood type should be completed for extended phenotypes as well as Kell typing to aid in an emergency. Special care should be taken for acute chest syndrome, pulmonary embolism, painful crisis, and other complications.

TREATMENT AND THERAPY

Pregnant women with SCD and VTE should be treated with specific care. Modern diagnostics tools such as compression ultrasonography can be used for assessment of the legs and CT pulmonary angiography can be used for assessment of the lungs. Depending on the outcomes, anticoagulant therapy or other further diagnoses can be made. A novel treatment approach for SCD is highly necessary. Growing research efforts in this direction may yield the expected outcomes. Sphingosine-1-phosphate hampers the oxygen-binding affinity of HbS through structural conformation change as reported by Sun et al.[27] Metabolic re-engineering may lead to novel therapeutics based on the function of sphingosine-1-phosphate.

Assessment of pregnant patients and proper prophylaxis remain the key to proper and safe outcomes. Varying recommendations based on the specific conditions are available depending on the facility and experts available. The regular screening of pulmonary hypertension, blood pressure, urine, retinal function, and iron overload is important. Additional care for possible urinary tract infection, sepsis, and pneumonia should be also considered during regular monitoring. Depending on the condition, penicillin prophylaxis or erythromycin are prescribed. When caring for these patients who are pregnant other factors such as premature labour, perinatal mortality, fetal growth, pain crisis, and delivery via caesarean section should be considered with cautious assessment of the consequences. As previously mentioned, prophylactic blood transfusions are generally avoided. A detailed analysis with a comparison between prophylactic and selective blood transfusion is reported by Okusanya and Oladapo.[28] They have recommended the comparison as inconclusive and suggested that the transfusion process is largely dependent on factors such as blood typing and grouping, cross-matching, and organisational capacities. A report by van Zuuren and Fedorowicz[29] gave the comparative use and relevant outcomes of using

low molecular weight heparin during the vaso-occlusive crisis in pregnant women with SCD. Tinzaparin and dalteparin were found to have a good effect on pain reduction and diminishing the hospital stay. Week-long thromboprophylaxis using low molecular weight heparin for normal delivery and 6 weeks for caesarean delivery was recommended.[13] Even after extensive care and situation handling, the pregnancy with SCD is high-risk and related outcomes for the patients having SCD are comparatively poorer than in the general population.[2,30] The evidence is available on low gestational age associated with VTE.[31] VTE was also associated with the delivery time and postpartum conditions in women.[32] Hence, all these additional complexities further warrant special care for pregnant women with SCD.

CONCLUSION AND FUTURE PERSPECTIVES

The growing number of cases of pregnancy with SCD and its mortality rate requires attention from medical practitioners. Better and improved treatment regimes have provided some improved outcomes in this aspect. The number of possible complications is substantial and requires multidimensional strategy and management. Further development of novel therapeutics and diagnostics can help in managing the complications and yield better outcomes by reducing the mortality rates of pregnant women and neonates.

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