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Review Article

Exposure to Hydroxyurea and Pregnancy Outcomes in Women with Sickle Cell Anemia

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Abstract

Sickle cell disease is one of the most common monogenic causes of hemolytic anemia worldwide. The main pathophysiology is based on the single nucleotide polymorphism resulting in hemoglobin polymerization leading to sickle red blood cells. The sickled red blood cell will produce vaso-occlusion affecting multiple organs and this is the clinical hallmark of sickle cell disease. The repeated episodes of vaso-occlusion lead to damages to many organs including the brain, the bones, kidneys lungs, etc. The approval of Hydroxyurea for management of sickle cell disease by FDA in 1998 marked a major pharmacotherapeutic milestone in treatment of Sickle cell disease. Hydroxyurea was found to significantly reduce the incidence of Vaso-occlusive crisis, acute chest syndrome and need for blood transfusion. Hydroxyurea is an anti-neoplastic drug and the side effects and toxicity of hydroxyurea in pregnancy and lactation has been documented in preclinical animal studies. This has generated a lot of concern about the safety of Hydroxyurea in pregnant and lactating women. Many anecdotal and accidental use of Hydroxyurea in pregnant women has not validated the toxicity claims in animal studies.

Hydroxyurea offers a lot of advantages in reducing the mortality and morbidity associated with sickle cell disease. There is hesitancy on the part of most healthcare workers managing pregnant and lactating sickle cell disease patients to accept the use of Hydroxyurea in pregnancy because of the safety concern. More retrospective data need to be collected as it is not ethically acceptable to do randomized control trials to validate the safety of hydroxyurea in pregnancy and lactation.

INTRODUCTION

Sickle Cell Disease (SCD) is the most common genetic disease globally, affecting approximately 100,000 people in the United States and about 3.2 million people worldwide [1,2]. Sickle cell anemia (SCA) or homozygous sickle mutation is the most common and most severe form, accounting for 70% of patients of African ethnicity with SCD [2,3]. Approximately 300,000 babies are born with SCA every year with this number projected to increase to 400,000 in 2050 [4]. SCA is caused by a homozygous inheritance of the sickle gene–single nucleotide polymorphism of beta globulin HBB gene (GTG for GAG) resulting in the substitution of hydrophobic valine residue for hydrophilic glutamic acid residue at position six of the beta globin chain. The changes in the beta globin chain results in formation of sickle Hemoglobin. In addition to SCA, other forms of SCD include compound heterozygous inheritance of HbS/Beta thalassemia zero, HbS/Beta thalassemia plus, or HbSC genes and other rarer forms. HbS polymerizes with deoxygenation leading to rigid, sickle shaped RBC with decreased deformability, leading to ischemia-reperfusion injury, hemolysis, vaso-occlusive disease, endothelial damage and eventually end organ damage.

Therefore mentioned pathologic mechanisms result in the acute and chronic manifestations of sickle cell anemia. Acute manifestations include acute painful vaso- occlusive crisis, which is the classic feature of sickle cell anemia, bacterial infections (especially from encapsulated organisms) as a result of damage to the spleen from intraparenchymal sickling and acute chest syndrome which is potentially life threatening. Other acute presentations are worsening anemia from aplastic, hyperhemolytic and splenic sequestration crises, acute stroke and multiorgan failure. Chronic complications usually become more prominent in the third decade of life and may lead to dysfunction or failure in multiple organs resulting in significantly reduced quality of life, increased health care utilization and reduced life expectancy [5]. The range of chronic complications includes pulmonary hypertension and other cardiopulmonary issues, chronic kidney disease, retinopathy, chronic leg ulcers, avascular necrosis, recurrent priapism and cognitive decline. [5] A large study showed that cardiac and pulmonary issues account for up to 45% of mortality in SCD [6].

Medical management of Sickle Cell Disease

Management of sickle cell anemia has traditionally been palliative, with supportive, symptomatic, preventative and abortive treatment options. Other than palliation, there have been developments in pharmacotherapy and more recently in curative cellular therapies-gene therapy and stem cell transplantation [1,7]. In addition to pain management that could be pharmacologic or non-pharmacologic, disease modifying drugs are important alongside transfusion therapies. There is a scarcity of pharmacologic agents for SCA that received FDA approval.

The first agent approved for SCA by the FDA was hydroxyurea in 1998 [1] and it took another 19 years before another approval for L-glutamine in 2017 [8]. With recent advances in the understanding of sickle cell pathophysiology however, there has been an increase in clinical trials and two new FDA approvals in 2019-Crizanlizumab-tmca and Voxelotor[9]. Despite the recent advances, access to care as well as health care expenses remains an issue in treating SCD. Access to Hydroxyurea is still limited especially for the millions of patients with this disease in Africa. As further therapies get approved, the expensive cost of these newer therapies and the associated potential financial burden may limit their availability to patients in the United States, and especially to those in less resource rich countries. Both Crizanlizumab and Voxeletor cost about $100,000/year which is likely to constitute a significant barrier to uptake for the foreseeable future and there is still a dearth of long term data about them [10]. Furthermore, although these agents can be used as monotherapy, they can also be used in combination with Hydroxyurea. For that reason, while pushing further drug development, Hydroxyurea remains the first line therapy for SCD patients and the best studied drug with the greatest potential in the global market.

With the quality of life and survival of patients with SCD improving, more women are reaching reproductive age leading to an increase in pregnancy rate among women with SCD. However, challenges have developed, including issues related to reproduction. Pregnancy continues to be high risk for patients with sickle cell anemia including those with mild disease. Maternal perinatal mortality could be unpredictable due to serious complications of sickle cell disease and is estimated to be around 4% [11]. Among these complications, we mention acute chest syndrome (ACS), pulmonary emboli, infections, preeclampsia, hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. Currently, we really lack data about use of FDA approved medications in pregnant women with Sickle Cell Disease. Prophylactic transfusion has not been shown to reduce complications, but it comes with its own risks of infection, allo-immunization, and iron overload. Women with sickle cell anemia who become pregnant should be followed by Maternal Fetal Medicine and hematology and any complications should be aggressively managed. Folic acid is recommended both in pregnant women and in patients with SCD and thus pregnant sickle cell anemia patients should clearly be continued on folic acid as well as non-iron containing prenatal vitamins. However, the standard medication for sickle cell disease, hydroxyurea, has been contraindicated in pregnancy due to historic concern about potential teratogenic effects. This article will focus on Hydroxyurea use in pregnant Sickle Cell Disease patients.

Hydoxyurea

Hydroxyurea was the first drug approved for SCA and it is the most studied so far. It is Hydroxycarbamide, an anti-neoplastic agent originally synthesized for myeloproliferative disorders treatment in 1869. It was FDA approved for treatment of Sickle Cell Disease in 1998.

One of the strategies for treating sickle cell disease is induction of HbF by pharmacologic means. HbF is known to improve erythrocyte deformability by limiting intracellular HbS polymerization due to its higher oxygen affinity. Additionally, increased HbF is associated with a lower risk of early death [12]. Hydroxyurea is a neoplastic agent that has proven efficacy for inducing HbF with clinically significant effects in SCA [1,5,13-15]. Hydroxyurea exhibits its antineoplastic effects by inhibiting DNA synthesis and repair as a ribonucleotide reductase inhibitor. Although mechanisms by which hydroxyurea induces HbF have not been fully explained, it is known to involve guanylyl cyclase [16] and SAR1 (a GTPase) [17], cell cycle kinetics with stress erythropoiesis may also be contributory [18]. Apart from its effect on HbF induction, other proposed mechanisms of action for hydroxyurea include reduction in the number of adhesive reticulocytes [19]. It also reduces inflammation in SCD by reducing circulatory neutrophils and monocytes and by altering circulating monocyte subsets. [20] In children, hydroxyurea has been shown to cause changes in the plasma proteosome leading to reduced activation of clotting factors and decreased inflammation [20].

A placebo-controlled randomized phase 3 multicenter trial in adults demonstrated a significant reduction in the frequency of painful crises (2.5 crises/year vs 4.5 crises per year in control group), acute chest syndrome episodes, time to painful crises, hospital admissions and number of transfusions [15]. Hydroxyurea has also been shown to be effective at reducing duration of hospital stay and frequency of hospital admissions in children [21]. Long-term treatment in children showed durable benefits without any significant long-term safety issues [22,23]. Similarly, BABY HUG, a phase 3 randomized trial in infants (9-18 months) showed benefit in reducing pain, dactylitis, acute chest syndrome, hospitalizations and transfusions rates, although it did not show benefit for preserving organ function [13].

Hydroxyurea has been investigated for its role in both primary and secondary stroke prevention. The SWiTCH trial a multicenter randomized phase 3 trial, showed that when compared to continuing the standard treatment of transfusions and iron chelation, switching to hydroxyurea was inferior for secondary stroke prevention [24]. A subsequent randomized phase 3 trial, the TWiTCH showed non-inferiority when hydroxyurea is compared to transfusions for primary prevention of strokes in patients with high transcranial doppler (TCD) flow velocities [25] but the methodology of this study has been questioned [26]. While transfusion remains the standard of care for primary prevention of strokes in patients with abnormal TCDs, hydroxyurea may be indicated in cases where a transfusion program is difficult to implement [27].

Hydroxyurea in pregnancy and lactation

Pregnancy in Sickle Cell Disease presents a great risk to the woman and unborn infant [28]. Withholding important medication such as hydroxyurea in pregnancy due to the concern for teratogenicity has been reported to increase maternal and perinatal morbidity especially among the severely affected patients [29]. Hydroxyurea (HU) is a ribonucleoside reduction inhibitor with documented teratogenicity and mutagenicity in animals [30,31]. It was primarily used in many clinical situations as antineoplastic drugs although the precise mechanism of its cytotoxic effect is not fully known [32]. The Food and Drugs Administration (FDA) based on risk to the fetus categorized Hydroxyurea as a class D drug, meaning the use of Hydroxyurea

in pregnancy carries fetal risk and justification is based on circumstances [1]. Based on this FDA categorization the labels packages insert for Hydroxyurea listed pregnancy and lactation as contraindications to use the drug [33]. Most national guidelines currently recommend discontinuation of Hydroxyurea during pregnancy and breastfeeding like American family physician group in their 2014 expert panel report and Royal College of Obstetricians and Gynecologists Green-top Guideline [34,35].

In many clinical interventions where Hydroxyurea has been used, pregnancy has been an exclusion criteria and contraception has been mandatory among the participants. Despite these precautionary measures, there have been reported cases of pregnancies among patients on chronic Hydroxyurea. The outcomes of these pregnancies have shown that the much-feared adverse effect of Hydroxyurea on pregnancy outcome may be exaggerated as most of the infants were born without any evidence of teratogenicity [30,32,36,37]. There have been reported inadvertent use of Hydroxyurea in pregnancy at different gestations age without major malformation in the infants [31,38]. In a review of 31 patients inadvertently exposed to Hydroxyurea during pregnancy, Thauvin-Robinet et al did not find any major malformations among the 24 newborns and among the four that died in utero [30].

Ware et al [33] in HELPS study (Hydroxyurea Exposure in Lactation and Pharmacokinetics) looked at infants exposure to Hydroxyurea through breastfeeding. They reported that the amount of Hydroxyurea transferred through breastmilk is far less than the recommended safety level. This study concluded it is safe for lactating mothers on Hydroxyurea to breastfeed. The current recommendations suggest to avoid breastfeeding at least in the first three hours after hydroxyurea intake [1].

Other studies have also reported better pregnancy outcomes in women who used Hydroxyurea prior to conception and during pregnancies [36,39].

Many studies have reported teratogenicity on animal studies but the doses of Hydroxyurea that were associated with teratogenicity in animals are much higher than the therapeutics doses [30]. In an incident of a patient who became pregnant while on high dose of Hydroxyurea (3 g per day) for treatment of chronic myeloid leukemia, the patient delivered a baby at 37 weeks gestations without any congenital malformation [40].

The concern for safety of Hydroxyurea in pregnancy and lactations is a great barrier to its use in management of Sickle Cell Disease [41]. In a study to determine barriers to use Hydroxyurea in Sickle Cell Disease patients, Titilope et al [41] reported that 48% of their physicians are not prescribing Hydroxyurea because of their concerns about safety in pregnancy and during lactation.

Finally, some recent data suggest that hydroxyurea may be associated with earlier menopause in women with Sickle Cell Disease [42].

CONCLUSION

Pregnant women with SCA have increased risk of perinatal complications and mortality. There is a paucity of approved medications for pregnant women with sickle cell disease. Hydroxyurea is a mainstay in the management of sickle cell patients, but current guidelines preclude its use in pregnancy due to concern about potential teratogenic effects. Although animal studies had reported teratogenicity, there have been reports from multiple human studies showing no malformations when pregnant women at different periods of gestation were inadvertently exposed to hydroxyurea. Furthermore, some studies have suggested better outcomes for women on hydroxyurea prior to and during pregnancy [36]. It is possible that the teratogenicity reported in animal studies may have been associated with the higher doses administered when compared with the doses used in SCA in humans. The evidence from the literature so far should provide re-assurance for physicians who are reticent to prescribe hydroxyurea to young non-pregnant women due to concerns about teratogenicity. Hydroxyurea may be safely discontinued after pregnancy is diagnosed. More data would be needed to determine the safety of hydroxyurea in pregnancy.

CONFLICT OF INTEREST

Abdullateef Abdulkareem and Rasaq Olaosebikan have no financial interest or any conflict of interest.

Sanaa Rizk is a speaker and advisory board member for Global Blood Therapeutics.

Samir Ballas is a consultant for Novartis.

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