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Exposure to Hydroxyurea during Pregnancy: A Case Report of Congenital Malformation, Update on the Current Evidence and Management of Sickle Cell Disease during Pregnancy

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Abstract

Hydroxyurea (hydroxycarbamide) is an approved drug for sickle cell disease treatment. Although teratogenic effects of hydroxyurea were reported in animal studies, there is little evidence of its teratogenic effects on the developing human foetus. This study reports a 26 year-old primigravida, known patient with sickle cell disease, conceive when she was on hydroxyurea. The treatment was stopped at 26 weeks of gestation. The obstetric ultrasound done at 30 weeks of gestation showed multiple congenital malformations. Termination of pregnancy was performed after counselling. This study looks at the current literature review on the use of hydroxyurea during pregnancy and emphasizes the comprehensive management of sickle cell disease during pregnancy.

Keywords: Exposure to hydroxyurea; Congenital malformation; Management of sickle cell disease during pregnancy

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Introduction

Hydroxyurea (HU) is a myelosuppressive drug, on the market since 1968 for the treatment of hematological malignancies, including resistant chronic myeloid leukemia, locally advanced squamous cell carcinomas of the head and neck (excluding the lip) in combination with chemoradiation, and HbSβ+-thalassemia [1-3]. To date, it has a proven efficacy of prevention of recurrent vaso-occlusive crises and acute chest syndrome in adults and children older than 2 years with sickle cell disease (SCD). In pregnant mothers with sickle cell disease, HU has been used as a category D drug in the Australia therapeutic good administration (AU TGA), but not assigned in the United States food and drug administration (FDA) [4,5] safety of drugs in pregnant women. Several case reports found that the drug may have minimal teratogenic effects on the developing foetus. In our context, since women with SCD frequently conceive when under HU, it is necessary to improve our knowledge about the use of HU during pre-conception or organogenesis in SCD patients and eventually emphasizes the management strategies in a particular context of resource-limited settings.

Case Report

A 26 year-old on follow up for sickle cell disease since 2011 at Moi Teaching and Referral Hospital (MTRH), the largest tertiary hospital of western Kenya. Regarding her obstetric and gynecologic history, she is primigravida, her normal last menstrual period was on 15th November, 2019, estimated date of confinement (EDC) on 22nd August, 2020. However, her antenatal care follows up during pregnancy was erratic and not consistent due to financial hardship. For past medical history, she was diagnosed with sickle cell disease in 2011 and has had several episodes of hospital admission for anaemia and painful crisis prior the confirmed diagnosis. Regarding her family history, she is the second born in family of seven. Her parents, brothers

and sisters are alive and healthy. She's a single, living with her parents, and she has tertiary education level.

For laboratory investigations, the haemoglobin electrophoresis was performed in 2011 after a positive sickledex test. The following **Table 1** summarizes her full haemogram evolution since diagnosis.

For imaging investigations, her chest x-ray was severally reported normal during painful crises. The echocardiogram reported mild aortic stenosis, moderate pulmonary hypertension, and normal ejection fraction, while the electrocardiogram was normal. However, her obstetric ultrasound performed at 30 weeks' gestation showed multiple congenital anomalies and moderate polyhydramnios (see ultrasonographic images).

Regarding the management, since the diagnosis of sickle cell disease was confirmed in 2011, the patient started with oral hydroxyurea 1g daily. The dosage was increased to 1.5g daily in 2013 due to increase of vaso-occlusive crisis frequencies. Other drugs included oral palludrine 100 mg daily until 2012, oral folate 5 mg daily. In 2017, the patient was severally admitted for painful crises. For her, that period was characterized by several interruption of treatment due to financial hardship. In addition, she missed her period when she was on hydroxyurea, but she stopped treatment at 26 weeks of gestation at her own initiative.

Based on the ultrasonographic findings, counselling was conducted regarding termination of pregnancy. The induction of labour (IOL) with sublingual synthetic prostaglandin E1, PGE1 50 mcg and an intracervical catheter inserted as per hospital protocol regarding IOL and/ or termination of pregnancy. A life female infant with multiples congenital malformations was born (see photos), and passed on few hours later. The patient was discharged through haematologic and cardiac clinic for follow up.

Discussion

Sickle cell disease is an inherited haemoglobinopathy associated with increased risk of complications and premature death among affected people [6]. It includes a series of pathological genotypes resulting from the inheritance of HbS. The variants of SCDs include sickle cell anaemia (SS), sickle cell haemoglobin-C disease (SC), sickle beta-Plus Thalassemia and sickle beta-zero thalassemia, sickle cell haemoglobin-D disease (Punjab), and Sickle haemoglobin-O Disease [6]. The abnormality is due to the substitution of a glutamic acid by a valine at the sixth position on the β-globin chain, resulting in pathologic hemoglobin called hemoglobin S, from an autosomal recessive mutation on chromosome 11 [6-9]. The disease is present mostly in blacks with the prevalence of sickle cell trait (heterozygosity) as high as 30% [6,7]; however, the most common form is caused by homozygosity for the β-globin S gene mutation. In sub-Saharan Africa, evidence has shown that the disease has a high prevalence (10% to 40%) in malaria-endemic tropics [9,10]. Therefore, evidence has shown that sickle-cell trait (SCT) offers protective advantage against malaria. This protection is not applied to homozygous individuals with sickle cell anemia; instead it makes them more susceptible to not only malaria but to also other infections [10].

Reproductive health and SCD

Reproductive challenges for men and women with SCD are numerous. Although individuals with SCD have physical and sexual development delay [6], fertility challenges are mostly consequences of various factors including poor nutrition, repetitive infections, blood transfusions, painful crisis, and frequent hospital admissions [6]. These factors negatively affect the socioeconomic life of individuals with SCD and in most of developing areas of sub-Saharan Africa, the disease is considered as burden for the family and the community. The inability of those women to conceive is also related to chronic inflammation, oxidative stress, transfusion-related haemochromatosis, and ovarian sickling, causing ischemia and reperfusion injury to the ovary [11]. In high income countries, those patients received haematopoietic stem cell transplantation (the only curative therapy), sometimes involves conditioning regimens containing alkylating agents and total body irradiation that contribute to infertility and premature ovarian failure [11]. Another important reason for infertility is hypogonadotrophic hypogonadism due to deposition of iron in the hypothalamo-pituitary axis because of multiple blood transfusions and iron overload [6]. Furthermore, impairment of infertility is also related to some drugs used to control vaso-occlusive crisis. For example, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit ovulation and decrease progesterone levels in women of reproductive age [12]. In the EULAR 2015 study, diclofenac was found to significantly impair ovulation ten days after treatment and the dominant follicle remained unruptured in 75% of patients who received diclofenac compare to those who received other NSAIDs [12]. Therefore, the prolonged use of NSAIDs in women of reproductive age at need of childbearing should be discouraged.

Pregnancy and SCD

Pregnancy in sickle cell disease can be complicated. In sub-Saharan Africa, the disease affects up to 3% of births [9]. Vaso-

Table 1 Trends of complete blood count for the patient since time of diagnosis.

Variables	Units	Normal	14/11/2011	19/12/2012	11/09/2013	10/12/2014	18/05/2016	28/02/2018	09/01/2019	25/06/2020
RBC	10^6/uL	4.0-5.5	2.15	2.39	2.19	2.66	2.57	2.24	2.71	1.97
HB	g/dL	12.0-17.4	8.5	10.7	10.2	10.5	10.1	8.5	9.7	7.2
HCT	%	36-52	24.94	30.79	30.39	31.95	29.63	24.1	26.2	20.4
MCV	fL	76-96	115.90	128.80	138.98	119.90	115.10	107.5	96.6	103.8
PLT	10^3/uL	150-400	352	426	483	360	595	494	566	618
Reticulocytes Count	%	0.2-2								11.8

occlusive crisis, acute chest syndrome, osteonecrosis, hepatic necrosis, leg ulcers, anaemia, infections, and thromboembolic events are significantly increased in pregnant mother due to physiological changes of pregnancy, which include increased metabolic demand, increased blood viscosity and hyper-coagulability [13]. These complications are life-threatening for both the mother and foetus. For example, vaso-occlusion crisis leads to villous fibrosis, necrosis, and infarction on the placenta, causing uteroplacental insufficiency and chronic foetal hypoxia, intrauterine growth restriction, and foetal demise [6]. The incidence of adverse maternal and perinatal outcomes is higher in sub-Saran Africa and Asia where the prevalence of SCD is estimated up to 40%, the highest worldwide [7,8]. Factors contribute to increased incidence of adverse outcomes in sub-Saharan Africa include lack of universal access to state-of-the-art care by multidisciplinary teams with expertise in the management of high-risk pregnancies, lack of preconception care in most of facilities, lack of resources, and poor compliance to antenatal care due to poor socioeconomic status.

Management

Recent studies have been focused to improvement in medical care in patients with SCD. To date, there is increased number of women who survive into adulthood and get pregnant; however, the outcome of pregnancy is an important field of concern in modern's practice of the art of obstetrics and gynaecology. The obstetric care starts with preconception counseling for all women of childbearing age. Preconception counseling, perceives as the gold standard of optimizing the obstetric care in high-risk patients plays multiple roles. First, most interventions to reduce adverse maternal and perinatal adverse outcomes need to be in place prior to embark pregnancy; second, preconception counseling allows identification, assessment, and possible modification of risk factors that may influence maternal and perinatal outcomes; third, education of woman desiring pregnancy about specific risk factors which may affect her decision to become pregnant at that particular time [14,15]. Evidence has shown that for some women, their risk of complications during that particular time may be too high to attempt pregnancy; therefore, their conditions should be under optimal control before attempting pregnancy [14]. In low and middle-income countries, studies are in congruent with the current report that adverse perinatal outcomes are due to lack of preconception counselling and limited universal access to state-of-the-art care [16,17]. Indeed, this gap should be addressed and women of reproductive age should be sensitized on the importance of preconception counselling.

During pregnancy, the management is divided into three components, mainly antenatal care, intrapartum care, and postpartum care. Today, having a healthy infant is the highest desire of the affected couple is the wish of clinicians. With advanced medicine, prenatal diagnosis has contributed to identify unborn infants at risk of having SCD. The advantages of prenatal diagnosis are multiples: 1) it gives the opportunity for expectant couples to have an accurate, rapid result about the genotype of their foetus; 2) it offers an option for the parents to terminate the pregnancy at an early period in case of positive result; and 3) the result prepares the couple psychologically and medically for the arrival of the new child when abortion is not an option [18]. The prenatal diagnosis includes, 1) chorionic villus sampling performs in the first trimester at 10 to 12 weeks of gestation and DNA analysis is the method of choice; 2) amniocentesis offers in second trimester at 16-20 weeks of gestation and DNA analysis or foetal blood sampling by cordocentesis at 18 to 19 weeks of gestation; and 3) caelocentesis for aspiration of caelomic fluid performs at 7-9 weeks of gestation allows earlier prenatal diagnosis for monogenic disorders like beta-thalassemia and sickle cell anemia [19]. These prenatal diagnosis tools are out of reach of majority of affected couples in resource-limited settings. This narrows the therapeutic intervention scenarios to improve perinatal outcome. Another option particularly for couples who would like to have a healthy infant, is preimplantation genetic diagnosis, involving the selective transfer of unaffected embryos following *in-vitro* fertilization (IVF) [20]. This is an option currently available in sub-Saharan Africa; but expensive.

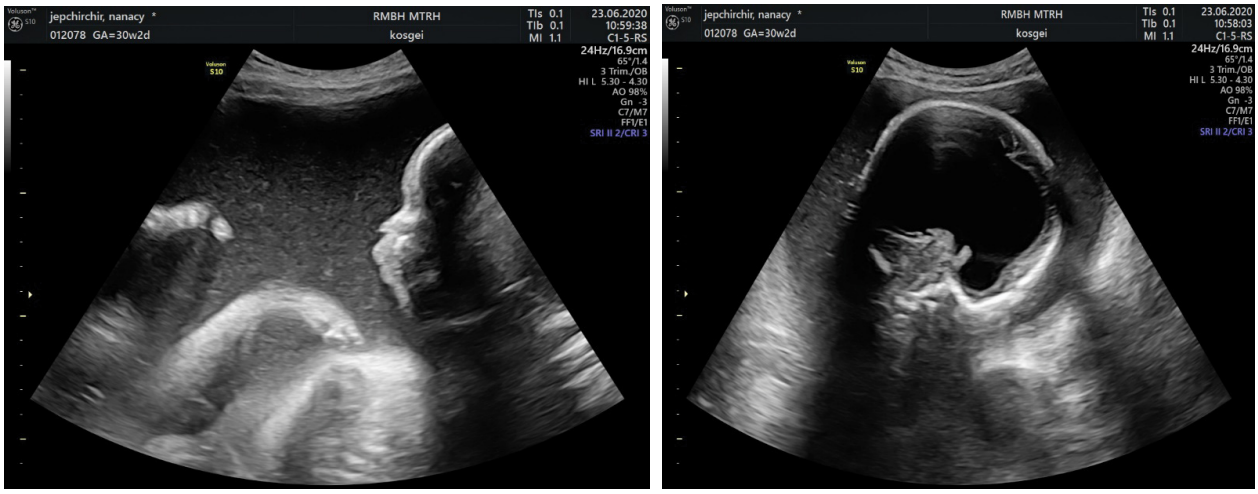
A comprehensive antenatal care (ANC) is an essential component of follow up of those high-risk pregnant women with SCD. During the first visit, the patient should be explained the importance of compliance to the plan of follow up by an obstetrician and haematologist from the first trimester; and she should avoid precipitating factors of sickle cell crises such as exposure to extreme temperatures, infections, dehydration, and overexertion or stress [6]. Anaemia is the most common complication of pregnancy among patients with SCD. However, in contrast to previous studies, the recent evidence does not support the prophylactic transfusion during pregnancy, although it has advantage of reducing incidence of maternal painful crises [21]. Transfusion is indicated in case of severe anaemia, and exchange transfusion is recommended in case of stroke and acute chest syndrome [22]. The risks associated with polytransfusion in patients with SCD include alloimmunization, iron overload, transfusion reactions and infections [23]. Routine ANC blood investigations like complete blood count, HIV, HBsAg, HCV should be done along with urinalysis. The ultrasound is an important tool to assess foetal well-being and rule out anatomical anomalies. If the mother cannot get opportunity for multiple ultrasound scans, the target ultrasound at 18 to 20 weeks of gestation should be offered to rule out congenital malformations [24], and guide further management options such termination of pregnancy if congenital malformation not compatible with life is diagnosed **(Figures 1A and 1B).**

In addition, all pregnant women with SCD should be screened for complications like pulmonary hypertension by 2D echocardiography. Evidence has shown that pulmonary arterial hypertension (PAH) is one of the main complications of sickle cell disease, associated with high mortality and morbidity [25]. Furthermore, retinal screening for proliferative retinopathy, urinary tract infection, iron overload, renal and liver function studies to rule out sickle nephropathy and hepatic involvement should be offered during ANC visits [6].

Regarding medications during pregnancy, folic acid and low-dose aspirin should be given [24]. However, drugs like hydroxyurea,

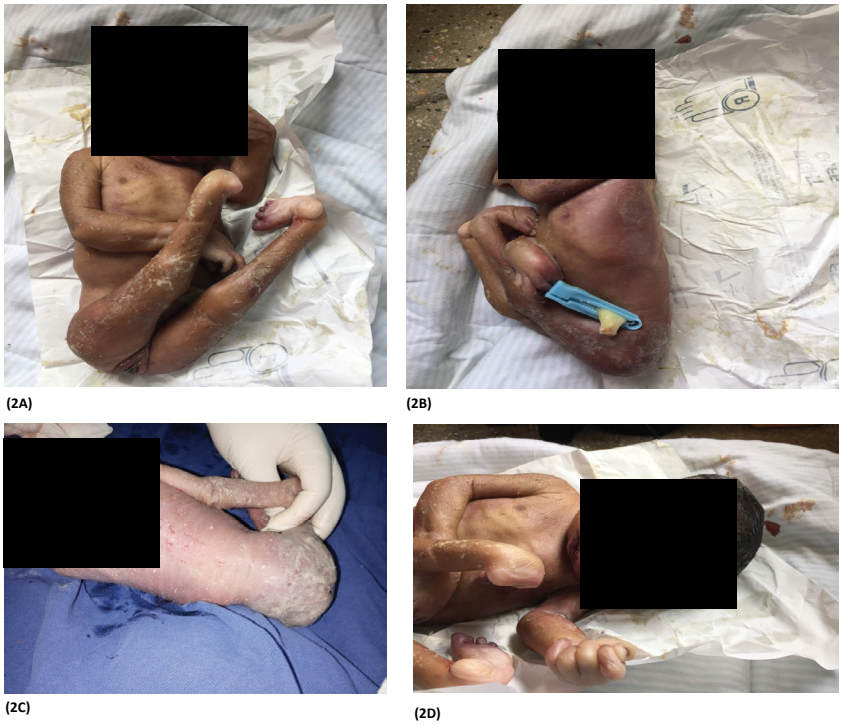
angiotensin-converting Enzyme (ACE) inhibitors, and iron chelators should be discontinued at least 3 months before conception due to the risk of teratogenic side effects [24]. Although teratogenic effects of hydroxyurea were reported in animal studies, there is little evidence of its teratogenic effects on the developing human foetus. However, case reports have shown the possible teratogenic effects among the users in developing foetus [1-7], without further description. In animals, these include decreased foetal viability, reduced live litter sizes, and developmental delays [1]. Further, foetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) have been described among animals, and in one study, the severity was dose-dependent [4]. In this report, figures **(Figures 2A - 2D)** bellow showed congenital anomalies in the current report.

Congenital malformations are multifactorial in origin for which genetic predisposition and environmental factors (including



(1A) **(1B)**

Figure 1 Ultrasonographic images from the maternal-foetal-medicine unit of Moi Teaching and Referral Hospital, June 2020. **(1A)** Hyperflexed limbs with normal hands. **(1B)** Isolated ventriculomegaly.



(2A) **(2B)**

(2C) **(2D)**

Figure 2 Images from Riley Mother Baby Hospital, Moi Teaching and Referral Hospital, June 2020. **(2A)** Bilateral hip flexion contracture. **(2B)** Prominent forehead and thorax. **(2C)** Normal vertebral column. **(2D)** Left forefoot dorsiflexed and abducted, right forefoot is adducted and inverted.

infectious, drugs or teratogenic substances) have been implicated. The understanding of the specific risk factors for congenital anomalies is very essential to provide health education that aims at creating awareness and establishing preventive strategic plan [26]. Regarding the teratogenic effects of HU, there is clear description of specific congenital malformations related to HU in developing animal; however, such description is still lacking in human. If HU is not recommended for use during pregnancy, primarily because animal studies have suggested potential teratogenic effects on the foetus. Therefore, in absence of strong data, experts suggest that women of childbearing age and sexually active receiving HU should be advised to use contraception and avoid becoming pregnant. In case there is a desire for pregnancy, crises should be controlled and HU must be stopped 3 months before conception. Pregnancy should not be terminated without evidence of congenital malformation if the patient did not stop HU before conception. The alternative way of reducing crises during the conception period remain chronic blood transfusion until delivery or end of breast feeding with a significant risk of alloimmunization [27]. This is feasible in facilities where access to the blood transfusion is not a major issue. However, education of the patient on triggering factors of painful crises and how to avoid them should be emphasized during antenatal care visits.

Regarding intrapartum care, SCD should not in itself be considered as contraindication to attempting vaginal delivery or vaginal birth after caesarean section. The time of delivery for pregnant women with SCD is 38+0 weeks of gestation [24], or prior, if preeclampsia/eclampsia. This can be achieved through induction of labour (IOL), or by elective caesarean section if indicated. Although there is no consensus about the time of delivery, several studies in developed and developing countries have highlighted increased perinatal mortality, particularly during the later trimester of pregnancy and labour as well [6,9,24]. The perinatal adverse outcomes are related to the risks of abruption, pre-eclampsia, peripartum cardiomyopathy, acute sickle cell crisis, and stillbirths, which increase unpredictably in late third trimester and during labour [2,6,24]. Therefore, experts suggest that, like most 'high-risk' conditions, delivery at 38+0 weeks of gestation will prevent late pregnancy complications and associated adverse perinatal events [24]. Since decades, some studies have questioned vaginal delivery as the optimal mode of delivery for women with SCD. Although, numbers of evidence support vaginal delivery though to be associated with good maternal and perinatal outcomes. In previous studies, most cases of adverse outcomes during labour were attributed to poor surveillance or monitoring of labour, or administration of drugs such as pethidine to control maternal labour pain. Thus, pethidine should not be used during labour and delivery, because it is associated with perinatal adverse effects, including hypoxia, low Apgar score, or admission to nursery [28,29]. Epidural anaesthesia, fentanyl or morphine are efficacious in relieving labour pain or painful crisis in greater satisfaction [29]. The mother should be continuously rehydrated during labour and delivery process [6]. In addition, caesarean delivery should be performed for obstetric indications, defined as inability for the mother to achieve vaginal delivery at specific-time. If caesarean section delivery is decided, evidence supports that the procedure should be performed under regional anaesthesia [24]. General anaesthesia is associated with 25% increased risk of painful crisis after the procedure and it should be avoided [24].

In the postpartum period, it is crucial to assess the degree of anaemia aggravated by blood loss during labor and delivery [2], and transfuse if anaemia or large blood loss was noted. Hydration and oxygenation should be maintained as well and encourage early initiation of breastfeeding and mobilization. Thromboprophylaxis is recommended for seven days following a vaginal delivery or a period of 6 weeks following cesarean section [2,6,24]. Long acting contraception should be advised and/ or provided as an important component of postnatal care. Other effective contraceptive methods include progestin only pills, medroxyprogesterone acetate, and barrier methods [2]. The permanent methods should be advised only if the patient has completed her family size. Regarding the risks and benefits of hydroxyurea during lactation, mother who are breastfeeding are discouraged from taking hydroxyurea, due to mostly theoretical concerns about transfer of the drug into breast milk [25-30].

Conclusion

Sickle cell disease is associated with life-threatening complications both for the mother and the foetus. Hydroxyurea is a potent and safe disease-modifying therapy in patients with sickle cell anemia, including women of reproductive age. However, the use of hydroxyurea during pregnancy and lactation is discouraged due to mostly theoretical concerns about teratogenic effects and transfer of the drug into breast milk. Women of reproductive age with sickle cell disease should receive appropriate preconception counselling before embarking pregnancy and should comply with the management plan to optimize pregnancy outcome.

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