

Hemoglobin Cc in Pregnancy; a Case Series of 6-cases Managed Over 7 Years at the University College Hospital, Ibadan

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Abstract

Background: Hemoglobinopathies are the most common genetic defects globally, the majority of them are in sub-Saharan Africa and Southeast Asia. Hemoglobin C is a common hemoglobin variant although the prevalence of homozygous genotype CC (HbCC) is unknown. Approximately 28,000 infants are born annually with HbCC. HbCC is associated with intracellular hemoglobin crystallization with increased viscosity and reduced red blood cell life span. Although HbC is prevalent in much of sub-Saharan Africa, there is little data in the literature to address whether people with HbCC have clinical manifestations and even less is understood about this during pregnancy.

Objective: This study describes the clinical features of pregnant women with HbCC.

Method: This is a case series of all mothers who delivered at the University College Hospital between 2017 – 2023. All parturients had haemoglobin electrophoresis to determine their haemoglobin genotype in pregnancy. Women with hemoglobinopathies were identified and their case notes were retrieved. Data was extracted from their case notes with the aid of proforma.

Results: Among the 11,496 deliveries over the study period, 180 (1.6%) had haemoglobinopathies and N (0.05%) had HbCC. The women with HbCC were aged 31 to 44 with a mean age of 35.7 years. Four (66%) of these women had previous deliveries. Two (33%) had their hemoglobin genotype diagnosed in childhood, others were diagnosed during their first pregnancy. The mean PCV was 27.7($\pm$ 3.0)%, and they all had less than 33% which is the threshold for anemia diagnosis.

Four (two-thirds of them had blood transfusions at least once. Complications reported were bone pain (n=1), hypertensive disorders in pregnancy (n=1), and malaria (n=1). Four had caesarean delivery for obstetric indications or maternal request.

Conclusion: HbCC among parturients is rare. Anemia was prevalent among women with HbCC and, as expected, Although bone pain was reported in one of the six cases, there were no features of sickle cell disease among HbCC women. The majority underwent caesarean section for obstetric indications unrelated to their haemoglobin genotype.

INTRODUCTION

Hemoglobinopathies are the commonest genetic defects globally affecting more than 250 million people with the highest proportion in Sub-Saharan Africa and South-East Asia.¹ Hemoglobin C was first described in 1950 in heterozygous form and the homozygous hemoglobin C was later identified in 1953.² Hemoglobin C is a structural variant of normal adult hemoglobin with the substitution of the amino acid at position 6 of the β globin chain from glutamine to lysine. A similar substitution is seen in hemoglobin S from glutamine to valine causing sickle cell disease, a life-limiting disease.³ Hemoglobin C is a common structural variant of hemoglobin and yet the exact prevalence remains unknown.³ It has been projected that annually, more than 600,000 and over 28,000 newborns in Africa have hemoglobin AC and hemoglobin CC (HbCC) genotypes

respectively.³ About 4% of young adults in Ibadan were reported to be carriers of the hemoglobin C genotype. The prevalence of hemoglobin SC has been reported to be about 0.1 to 1.1% in Nigeria.^{4,5}

Heterozygous inheritance of hemoglobin C is a carrier state and is asymptomatic except when inherited with another abnormal beta globin variant like hemoglobin S or β -thalassemia. Hemoglobin SC is a form of sickle cell disease.⁶ People with HbCC may have microcytic hyperchromic anemia with high mean corpuscular hemoglobin concentration(MCHC).^{7,8} Anemia may result from intracellular hemoglobin crystallization predisposing to increased viscosity and reduced red blood cell life span.⁸ However, HbCC does not cause intracellular polymerization during low oxygen tension.⁹ The extent to which HbCC causes clinical complications is not established.⁷ Mild hemolytic anemia, splenomegaly, scleral jaundice, cholelithiasis and abdominal pain are described in with HbCC.⁸

The course of pregnancy among women with HbCC is not established, and information is needed to define clinical care.¹⁰ This study evaluated the clinical characteristics of pregnant women with HbCC.

MATERIALS AND METHOD

The study was conducted at the University College Hospital (UCH) Ibadan, a tertiary health facility and a teaching hospital in Ibadan, the capital city of Oyo state in the southwestern part of Nigeria. The hospital is a referral center for primary and secondary health facilities across the state. This was a cross-sectional review of 7 years of data (January 2017 to December 2023). All parturients had haemoglobin electrophoresis to determine their haemoglobin genotype; women with haemoglobinopathies were identified and their health records retrieved. Proformas were used to extract data from case notes of women with hemoglobinopathies managed at the University College Hospital, Ibadan, over the period under study. The findings among women with HbCC are summarized here and discussed.

The principles of ethics were maintained. Identifiable data from the patients were not included to maintain confidentiality. Ethical approval was obtained from the University of Ibadan/University College Hospital Ibadan Ethical Review with the IRB number UI/EC/25/01224

RESULT

Among the 11,496 parturients over the study period, 180 (1.6% of all parturients) had a form of hemoglobinopathy in pregnancy (Table 1), 119 (66.1% of women with hemoglobinoathy) had hemoglobin SS, 54 (30% of women with hemoglobinoathy) had hemoglobin SC, others had S-thalasemia and only 6 (0.05% of parturients) had hemoglobin CC (Figure 1). Three per cent of women with hemoglobinopathies in pregnancy had homozygous hemoglobin C.

Socio-demographic characteristics

The sociodemographic details of the cases of HbCC in pregnancy are described in Table 2. The age of the women ranged from 31 to 44 years, with a mean age of 35.7($\pm$ 4.3)years and a median age of 35 years. Four of the six subjects had had previous deliveries with at least two children alive.

Hemoglobinopathy diagnoses and management before pregnancy

In four of six cases, diagnoses of HbCC were made in adulthood during their first pregnancy. One of the women with HbCC reported receiving hematology care on account of her hemoglobin genotype before pregnancy. There were no admissions for crises or haemoglobinopathy-related complications before the index pregnancy in any of the cases. Details of care regarding supportive care received on account of their hemoglobin genotype outside pregnancy are summarized in Table 2.0. Malaria prophylaxis was used in one of the cases as recommended for women with sickle cell disease.

Anemia and blood transfusion.

The steady-state packed cell volume (PCV) among the cases before pregnancy ranged from 23% to 31% with a mean of 27.7(±3.0)%. All subjects had steady-state PCV below 33% which is the recommended cut-off for anemia. The mean PCV during pregnancy was similar; 27.7±4.7%. Four subjects had received at least one blood transfusion; transfusion was attributed to anemia before the index pregnancy in two cases and during the index pregnancy in two cases.

Pregnancy-related complications.

As shown in Table 3.0, the complications reported in these women were bone pain(N=1), anemia requiring transfusion (N=2), hypertensive disorders in pregnancy (N=1), and malaria (N=1). None had hemolytic crises, sepsis, acute chest syndrome, hepatomegaly, splenomegaly, disseminated intravascular coagulopathy, or intrauterine growth restriction.

Route of delivery and pregnancy outcomes.

One subject had a preterm delivery at a gestational age of 28 weeks. A high proportion (4 out of 6 cases) of the subjects underwent cesarean section due to obstetric indication (N=3) or maternal request (N=1). The choice of route of delivery was thought to not be directly related to their hemoglobin genotype. All subjects had live births with good outcomes: birth weights were average for their gestational age, and all babies were alive by the seventh day of life.

Table 1. Prevalence of hemoglobinopathies among parturients at the University College Hospital, Ibadan

YEAR	TOTAL DELIVERIES	HEMOGLOBINOPATHIES Incidence (%)	HEMOGLOBIN CC Incidence (%)
2017	1,999	8 (0.4%)	0
2018	1,535	25 (1.6%)	0
2019	2,192	38 (1.7%)	1
2020	1,767	30 (1.7%)	1
2021	963	18 (1.9%)	0
2022	1,633	26 (1.6%)	1
2023	1,407	35 (2.5%)	3
TOTAL	11,496	180 (1.6%)	6 (0.05%)

Table 2. Selected socio-demographic, obstetric, and hemoglobinopathy-related characteristics of the women with hemoglobin CC

Serial number	1	2	3	4	5	6
Year	2019	2020	2021	2023	2023	2023
Age	44	35	32	31	35	37
Occupation	Business	Civil servant	Teaching	Trading	Banking	Business
Level of education	Secondary	Tertiary	Secondary	Tertiary	Tertiary	Tertiary
Previous deliveries	4	2	4	3	0	0
Previous miscarriages	0	2	1	0	1	0
Children alive	3	2	4	3	0	0
Age at diagnoses of HbCC	30	30	31	8	6	37
Care for HbCC	None	None	(Specialist)	None	None	None
Routine drug use and hematinics	None	None	Paludrine and multivitamins	None	None	Iron, folate & fansidar
Previous crises	None	None	None	None	None	None
Previous hospital admissions	None	Two times	Three times	None	None	Twice
Reason for admission	Not applicable	Pregnancy-related	Pregnancy-related	Not applicable	Not applicable	Surgery (myomectomy)
Steady-state PCV	30%	30%	25%	30%	23%	28%
Latest PCV	30%	30%	22%	28%	23%	33%
Blood transfusion before the index pregnancy	1	1	0	0	0	0
Blood transfusion during the index pregnancy	0	0	0	0	1, 2 units pRBCs	1, 2 units pRBCs

Table 3.0 Complications in pregnancy delivery outcomes among women with HbCC

Serial number	1	2	3	4	5	6
Complications						
Bone pain	Yes	No	No	No	No	No
Anemia in pregnancy	No	No	No	No	Yes	Yes
Malaria	No	No	No	No	No	Yes
Chronic hypertension	No	No	No	Yes	No	No
Number of fetus(es)	2	1	1	1	1	1
Preeclampsia	No	No	No	Yes	No	No
Gestational age delivery	28weeks	38weeks + 3days	39weeks	37weeks +days	37weeks	38weeks + 3days
Route of delivery	Vaginal	Elective CS	Vaginal	Emergency CS	Elective CS	Emergency CS
Indication (if CS)	Not applicable	Two previous CS	Not applicable	Severe pre-eclampsia	Maternal request	Previous myomectomy
Birthweight (kg)	1.05/1.20	3.8k	3.3	3.2	2.55	3.0
APGAR score @1min	3/6	9	9	9	9	9
APGAR score @5min	5/8	9	9	9	10	9
SCBU admission	Yes/Yes	No	No	No	No	No
Final fetal outcome (at 7 days)	Alive/Alive	Alive and well	Alive and well	Alive and well	Alive and well	Alive and well

Discussion

This study describes the profile of parturients with hemoglobin CC at the University College Hospital Ibadan. The prevalence of hemoglobinopathies among parturients at the University College Hospital over the study period is 1.6%. This is consistent with the previously reported prevalence of sickle cell disease in Nigeria.¹¹ Only 3% of the women considered to have hemoglobinopathies were HbCC genotype; the prevalence of

hemoglobin CC in pregnancy at the facility at 0.05%. Although Hemoglon CC in pregnancy is known to be rare, the exact prevalence has not been reported.²

In this small cohort, HbCC was usually diagnosed in adulthood, especially during routine screening in pregnancy. Routine nationwide hemoglobin genotyping in childhood is not performed in Nigeria, as is the case in most of sub-Saharan Africa.^{12, 13} The absence of clinical complications of living with hemoglobin CC may make diagnosis unlikely in childhood. However, the diagnosis of hemoglobin CC has reproductive implications beyond the parturient - in a country where rate of HbS trait and HbSS disease very high - the risk of having a HbSC baby is increased since CC will 100% pass C trait to baby. Piel et al estimated that globally, 28,000 newborns each year are born with hemoglobin CC.³

HbCC in pregnancy was not associated with any complication in these cases except for anaemia. This is consistent with the findings of Maberry et al that hemoglobin CC in pregnancy may be associated with mild to moderate anemia but crises and other complications are infrequent.¹⁴ The World Health Organization (WHO) has set a hemoglobin concentration of 12g/dL (hematocrit – 36%) as the lower limit of normal among adult women and 11g/dL (hematocrit – 33%) among pregnant women.¹⁵ The average hematocrit levels among the general population of pregnant women in their first trimester reported at the same facility is 35% (32–38%), which may reduce to 29.4% (28.7–29.9%) in the third trimester.¹⁶ All the women in this study had a steady-state hematocrit of less than or equal to 30%, suggesting anemia that worsened in pregnancy, consistent with the published literature.^{8,14}

Multiple perinatal complications may follow sickle cell disease.^{17,18} However, for those with hemoglobin CC, such complications may be mercifully absent; a larger cohort is needed to draw definitive conclusions for nuanced counseling for women with this genotype. Only one of the women in this study had a preterm delivery. She had twin gestation which is a risk factor for prematurity; this may be unrelated to her hemoglobin genotype. Women with sickle cell disease and other hemoglobinopathies may be more likely to have preterm birth compared to the general population of pregnant women without hemoglobinopathy.^{19,20} Regarding the mode of delivery, two-thirds of the subjects in this study had cesarean section due to obstetric indications and maternal request, not from factors related to their haemoglobin genotype. Hemoglobinopathy is not an indication for a cesarean section, but may be associated with a higher rate of cesarean section compared to the general population.²¹

This study is limited by its case-series design, reporting only six cases over seven years. Conducting a well-structured multicenter prospective study to generate robust data needed to establish the extent to which women with HbCC require additional monitoring or intervention before and during pregnancy. It is also necessary to compare women with HbCC with appropriately matched women with HbAA or HbAS, or HbAC, to identify deviations from the normal (if any) among women with HbCC before labelling HbCC as a form of hemoglobinopathy

Conclusion

HbCC among parturients is rare; it is usually asymptomatic, and diagnosis may not be made until adulthood, during pregnancy. Anemia was prevalent among women with HbCC, and, as expected, bone pain was reported in one of the six cases; there were no features of sickle cell disease among HbCC women before or during pregnancy. The majority had a cesarean section for obstetric indications unrelated to their haemoglobin genotype.

Declarations

Human Ethics

This study on human data is in compliance with the Declaration of Helsinki.

Consent to Participate Declarations:

Retrospective record of managed patient at the University College Hospital, Ibadan were used. The need for individual consent by participants was waived by the University of Ibadan/University College Hospital Ibadan Ethical Review Committee

Ethical approval.

Ethical approval was obtained from the University of Ibadan/University College Hospital Ibadan Ethical Review Committee with the IRB number UI/EC/25/01224

Funding Declaration

No funding was received for this study

Authors contribution:

IOC and OAA conceptualized the study, data was extracted by IOC, OOL and OAA. The manuscript was drafted by IOC under the supervision of OAA. All authors reviewed the manuscript and made contributions.

Declaration of interest:

The authors have no conflicts of interest to declare

Data Availability declaration

Data available on request

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Figures

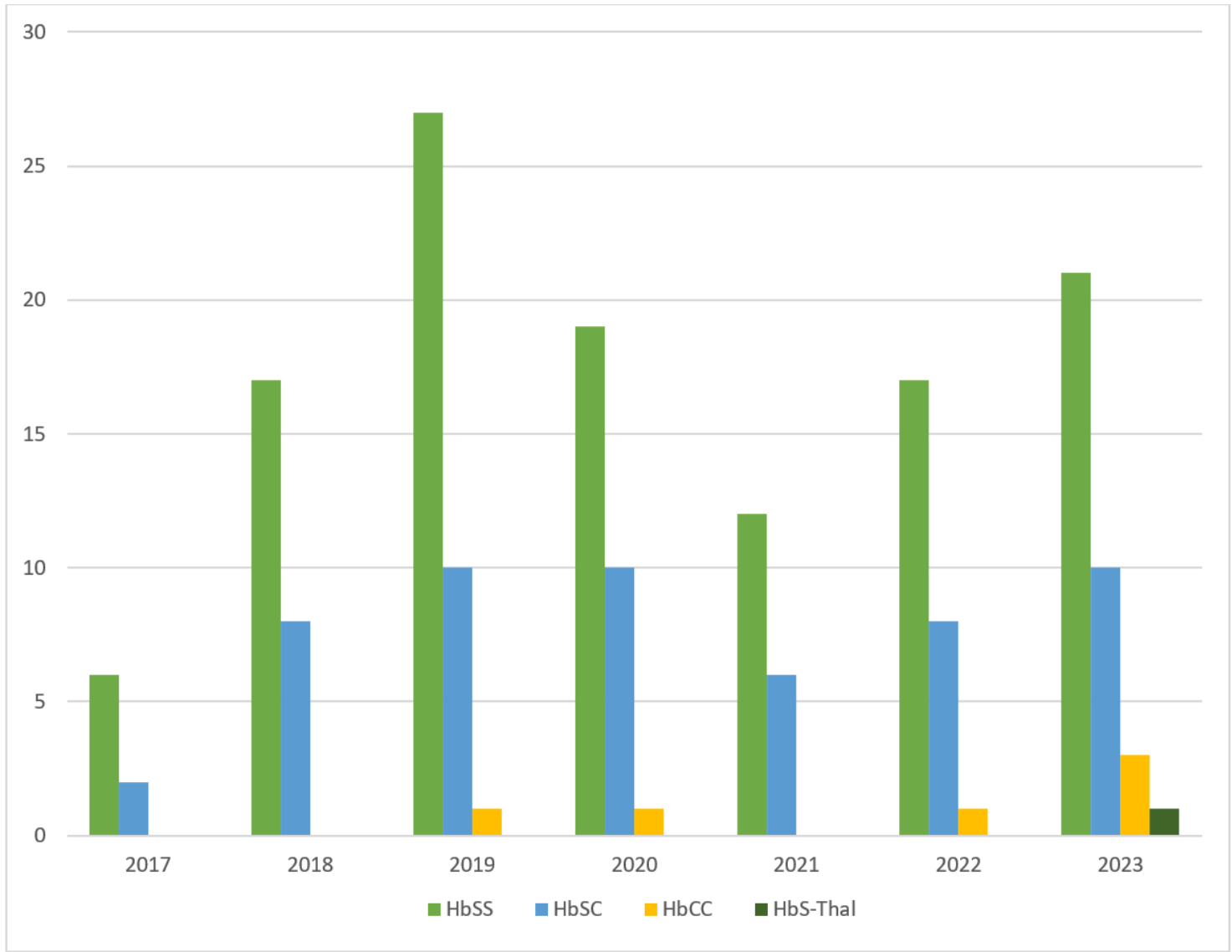


Figure 1

showing the distribution of hemoglobinopathies over 7 years

