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Original Article

Adverse Pregnancy Outcomes in Sickle Cell Trait: a Prospective Cohort Study Evaluating Clinical and Haematological Parameters in Postpartum Mothers and Newborns

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Abstract. ***Background*: Sickle cell trait (SCT) is a congenital condition caused by the inheritance of a single allele of the abnormal haemoglobin beta gene, HbS. Carriers of SCT are generally asymptomatic, and they do not manifest the clinical and haematological abnormalities of sickle cell anaemia (SCA). However, there is evidence that they display some symptoms in stressful situations. Pregnancy is a stressful physiological event, and it is not clear if SCT adversely affects pregnancy outcomes, particularly in those from developing countries where people regularly suffer from nutritional insufficiency.**

Objective: **This study aims to investigate pregnancy outcomes in Sudanese women with SCT.**

Subjects and methods: **Pregnant women with (HbAS, n=34) and without (HbAA, n=60) SCT were recruited during their first trimester at El Obeid Hospital, Kordofan, Western Sudan. Following appropriate ethical approval and informed consent from the participants, detailed anthropometric, clinical, haematological, obstetric, and birth outcome data were registered. In addition, blood samples were collected at enrolment and at delivery.**

Results: **At enrolment in the first trimester, the SCT group did not manifest SCA symptoms, and there was no difference in the haematological parameters between the SCT and control groups. However, at delivery, the women with SCT, compared with the control group, had lower levels of hemoglobin (Hb, p=0.000), packed cell volume (PCV, p=0.000), mean corpuscular haemoglobin (MCH, p=0.002) and neutrophil counts (p=0.045) and higher mean corpuscular volume (MCV, p=0.000) and platelet counts (p=0.000). Similarly, at delivery, the babies of SCT women had lower birth weight (p=0.000), lower Hb (p=0.045), PCV (p=0.000), MCH (p=0.000), and higher neutrophil (p=0.004) and platelet counts (p=0.000) than the babies of the healthy control group. Additionally, there were more miscarriages, stillbirths, and admissions to the Special Care Baby Unit (SCBU) in the SCT group.**

Conclusions: **The study revealed that SCT is associated with adverse pregnancy outcomes, including maternal and neonatal anaemia, low birth weight, and increased risk of stillbirth, miscarriage, and admission to SCBU. Therefore, pregnant women with SCT should be given appropriate pre-conceptual advice and multidisciplinary antenatal and postnatal care.**

Keywords: Sickle cell trait; Pregnancy; Pregnancy outcome.

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Introduction. Sickle cell anemia (SCA) is a group of genetic blood disorders characterised by a mutation involving haemoglobin's beta chain. People who inherit one sickle cell gene and one normal gene have sickle cell trait (SCT), whereas those who inherit two abnormal genes have SCA.[1]

Archibald[2] was the first person to report the presence of the HbS gene in Sudan. Subsequently, several studies revealed that the country has a high prevalence of SCA, with an HbS allele frequency ranging between 0.8% in the North and over 30% in the Western part of the country.[3–5] The high HbS allele frequency is due to consanguineous marriages, an influx of tribes affected by the disease from West Africa, and a history of endemic malaria.[6–7]

SCA is associated with severe clinical and haematological manifestations, including recurrent vaso-occlusive crises, anaemia, neurological, renal, hepatic, growth, and ophthalmological complications,[1] and poor pregnancy outcomes.[8] Individuals with SCT generally do not display the haematological and clinical symptoms of SCA. Indeed, some of them are unaware that they carry the faulty gene; however, there is evidence that they may exhibit complications during stressful situations or life events[9–12] or vigorous physical activities.[13]

Pregnancy is a stressful physiological event, often associated with emotional changes, anxiety, and depression.[14–15] Impact of SCT on pregnancy outcome has been equivocal, with some studies have reported adverse outcomes,[16–27] and contraception has been suggested,[28] whereas others have not,[29–30] also in consideration of greater resistance of carriers to malaria in pregnancy[29.] The reasons for the contradictory findings are not clear. However, factors such as nutritional status before and during pregnancy may play a significant role. Although the prevalence of sickle cell genes in Sudan and other low-income countries like Sub-Saharan African countries is high,[4,31] published data are scarce on pregnancy outcomes in women with SCT.

The aim of the study is to investigate pregnancy outcomes in Sudanese women with SCT.

Subjects and Methods.

Subjects. Three hundred sixty-seven (n=367) pregnant women attending their first antenatal appointment during their first trimester at El Obeid Hospital, Kordofan, Western Sudan, were screened for sickle cell gene. Of the 367 women who signed the consent & screened, 34 (n=34) had SCT (HbAS), and the remaining had normal haemoglobin (HbAA). The 34 women with SCT and the 60 (n=60) HbAA, aged 18-40, who fulfilled the inclusion /exclusion criteria and were willing to participate in the study, were selected. The exclusion criteria included those with SCA, thalassemia, other chronic diseases, a physical disability, restricted access to food, and malnourished. In addition, those who were living far from the hospitals were also excluded.

Detailed demographic, obstetric, medical history, dietary habits, and birth outcome data were meticulously documented. A blood sample, 5 ml, was collected at enrolment and delivery (maternal and cord blood). The study was approved by the Ministry of Health of Sudan, the University of Khartoum Medical School, and the London Metropolitan University ethical committees.

Methods. *Demography.* In this prospective observational study, a questionnaire was specifically developed to extract participants' obstetric, medical and haematological history data from hospital records.

Anthropometry. Weight and height were assessed using standard measurement methods.

Haematological variables including haemoglobin concentration (Hb), PCV, MCV, mean MCH, and white cell (WBC) and platelet (PLTS) counts were collected. HbS was quantified using a capillary electrophoreses machine (Minicab Sebia flex piercing, Lisses, France).

Statistical analysis. The data are expressed as mean ± standard deviation (sd) or percentages, and the level of statistical significance is set at $p<0.05$. Quantitative data were tested for normality and homogeneity of variance and subsequently analysed with an independent t-test (parametric data) or Mann–Whitney U test (non-parametric data). Socio-demographic, clinical, and laboratory characteristics data with cells' frequency of five or more were assessed with a chi-square test on the contingency platform. Chi-square, Yate's Correction of Continuity, and Fisher's exact test were used when the observed cell count was less than five (n=5), under the assumption of independence of rows and columns and conditional on the marginal totals. SPSS Statistics for Windows, version 26 (IBM SPSS Ltd., Woking, Surrey,

UK) was used to analyse the data.

Results.

Demographic and clinical characteristics. **Table 1** presents the demographic and clinical characteristics of the women with SCT (HbAS) and normal haemoglobin (HbAA). There was no difference in age, weight, height, or body mass index at baseline between the two groups (p>0.05).

Although SCT women compared with the healthy control group, had lower levels of educational achievements – illiterate and primary (44.1 vs 25.0%; P=0.108), middle and high school (47.1 vs 55.0%; p>0.05) and university (8.8 vs 20.0%; p=0.000) (**Table 1**); however, the two groups had comparable employment and household income (p=.989), **table 2**. Although it did not reach a level of statistical significance, women with SCT were less likely to own their own house (41.2 vs 60.0%; p=.210) and more likely to live with their relatives (38.2 vs 25.0%; p>0.05) or in rented accommodation (20.6 vs 15.0%; p>0.05).

The study reveals that consanguineous marriage is still common in Western Sudan, particularly for those with a genetic disorder who are economically disadvantaged. Compared with the control group, there was a higher level of marriage to first and second-degree relatives in the women with SCT (64.7 vs 43.3 %; p=.046) and their respective parents (61.8 vs 56.7 %;

Table 1. Mean (± sd) demographic and clinical characteristics of the women with (HbAS, n=34) and without (HbAA, n=60), at baseline (first trimester).

		HbAS (Mean ± sd)	**HbAA (Mean ± sd)**	**p-value**
Age (years)		26.5 ± 6.0	27.2 ± 6.5	0.639
Weight (kg)		63.4 ± 15.1	61.4 ± 13.1	0.500
Height (cm)		160.8 ± 6.1	157.6 ± 9.7	0.081
BMI (kg/m^2)		24.3 ± 4.8	24.9 ± 6.0	0.645
Blood glucose (mmol)		5.1 ± 0.6	5.6 ± 1.5	0.117
Education	Illiterate & primary	15 (44.1)	15 (25.0)	0.108
	Middle & high school	16 (47.1)	33 (55.0)	-
	University	3 (8.8)	12 (20.0)	-
Occupation	Employed	4 (11.8)	7 (11.7)	0.989
	Unemployed	30 (88.2)	53 (88.3)	-
Parental relationship	1st & 2nd degree	21 (61.8)	34 (56.7)	0.630
	Unrelated	13 (38.2)	26 (43.3)	-
Spouse relationship	1st & 2nd degree	22 (64.7)	26 (43.3)	0.046
	Unrelated	12 (35.3)	34 (56.7)	-
Siblings with SCA	Yes	22 (64.7)	8 (13.3)	0.000

Table 2. Meal frequency, house ownership, and income in Sudanese pounds of the pregnant women with (HbAS, n=34) and without (HbAA, n=60), at enrolment.

Meals	**Response**	**HbAS, N (%)**	**HbAA N (%)**	**P-value**
Have regular breakfast	Yes	33 (97.1)	58 (96.7)	0.917
	No	1 (2.9)	2 (3.3)	-
Have regular lunch	Yes	33 (97.1)	59 (98.3)	0.681
	No	1 (2.9)	1 (1.7)	-
Have regular dinner	Yes	23 (67.6)	49 (81.7)	0.123
	No	11 (32.4)	11 (18.3)	-
Household income	Low <1,000	21 (61.8)	36 (60.0)	0.297
	Average 1,000–2,000	13 (34.2)	20 (30)	-
	High >2,000	0 (0%)	4 (6.7)	=
House ownership	Own house	14 (41.2)	36 (60.0)	0.210
	Rent	7 (20.6)	9 (15.0)	-
	Live with relatives	13 (38.2)	15 (25.0)	-

p= .000).

Haematological parameters. At enrolment in the first trimester, the SCT group did not manifest SCA symptoms, and there was no difference in the haematological parameters between the SCT and control groups (**Table 3**). At delivery (**Table 4**), women with SCT compared with the control group had lower levels of Hb (p=0.000), PCV (p=0.000), MCH (p=0.002), and neutrophil counts (p=0.045), and higher MCV (p=0.000) and platelet counts (p=0.000). Similarly, at delivery, the babies of SCT women had lower Hb (p= 0.045), PCV (p=0.000), MCH (p=0.000), and higher neutrophil (p=0.004) and platelet (p=0.000) counts (**Table 5**).

Table 3. Mean (± sd) haematological parameters of the women with (HbAS) and without (HbAA) SCT at baseline (first trimester).

	HbAS	HbAA	p-value
Hb (g/dL)	11.8 ± 1.4	12.2 ± 1.2	0.108
PCV (%)	34.4 ± 3.7	36.2 ± 3.3	0.020
MCV (FL)	80.2 ± 7.0	83.6 ± 5.7	0.011
MCH (pg)	27.1 ± 2.8	28.4 ± 2.6	0.015
White cell count (X 10^3)	7.2 ± 1.9	7.1 ± 2.7	0.875
Neutrophils (%)	67.1 ± 10.8	66.5 ± 9.3	0.772
Lymphocytes (%)	26.9 ± 7.9	27.6 ± 8.2	0.691
Platelets (X 10^3)	266.9 ± 67.0	273.4 ± 78.6	0.830

Table 4. Mean (± sd) haematological parameters of the women with (HbAS) and without (HbAA) SCT at delivery.

	HbAS	HbAA	p-value
Hb (g/dL)	10.8 ± 0.6	11.6 ± 1.7	0.018
PCV (%)	31.2 ± 3.0	35.0 ± 5.1	0.000
MCV (FL)	93.6 ± 8.7	84.8 ± 7.1	0.000
MCH (pg)	26.0 ± 2.0	28.5 ± 2.9	0.000
White cell count (X 10^3)	8.2 ± 2.0	9.1 ± 3.2	0.226
Neutrophils (%)	62.9 ± 8.3	68.0 ±11.5	0.045
Lymphocytes (%)	27.2 ± 6.4	25.3 ± 9.9	0.423
Platelets (X 10^3)	265.6 ± 42.7	192.6 ± 53.4	0.000

Table 5. Mean (± sd) haematological parameters of the babies of women with (HbAS) and without (HbAA) SCT at delivery.

	HbAS babies	HbAA babies	p-value
Hb (g/dL)	13.0 ± 4.4	14.9 ± 2.3	0.049
PCV (%)	36.1 ± 4.6	44.1 ± 6.8	0.000
MCV (FL)	100.0 ± 7.4	103.4 ± 7.7	0.161
MCH (pg)	27.9 ± 1.9	34.8 ± 2.0	0.000
White cell (X 10^3)	9.8 ± 1.6	10.5 ± 4.6	0.552
Neutrophils (%)	62.4 ± 5.2	50.9 ±13.7	0.004
Lymphocytes (%)	29.6 ± 5.5	41.8 ± 13.2	0.002
Platelets (X 10^3)	298 ± 37.1	225 ± 56.7	0.000

Table 6. Mean (± sd) birth weight, head circumference, percent SCBU admission and miscarriage of the sickle cell trait (HbAS, n=23) and healthy (HbAA,n= 40) control groups.

	HbAS	HbAA	p-value
Birth weight (kg)	2.9 ± 0.2	3.2 ± 0.3	0.000
Head circumference (cm)	34.5 ± 0.7	34.1 ± 0.7	0.105
Gestation (weeks)	38.04 ± 0.86	38.22 ± 0.59	0.179
	n (%)	n (%)	
SCBU* admission	3(13)	1(2.5)	0.155
Miscarriage and stillbirth	3 (13)	1(2.5)	0.836

SCBU* = Special Care Baby Unit.

Outcome of pregnancy. Birth outcome data are shown in **Table 6**. The mean birth weight of the babies born to the HbAS mothers was lower than that of the HbAA women's babies (p=0.000). However, there was no difference in head circumference between the babies of the two groups (p>0.05).

Three babies needed admission to the Special Care Baby Unit in the SCT group Vs one in control (13 vs 2.5%, p>0.05). The reason for admissions included neonatal jaundice, low APGAR score, and hypoglycemia at birth. Similarly, the levels of miscarriage or stillbirth were higher in the SCT group (13 vs 2.5%; p>0.05) than in the control group pregnancies.

Discussion. This study investigated maternal and foetal outcomes in pregnancies complicated by SCT in Western Sudan. This region of the country is unique in that it has a high prevalence of SCA that overlaps equally with widespread poverty, malnutrition, illiteracy, and consanguineous marriages.

Similarly consistent with the previous studies,[4,31] the majority of the women with and without SCTs are married to their first or second cousins. However, the number is considerably higher (64.7 vs 43.3%) in the SCT group. In addition, a significant number of the women in the current study had low educational backgrounds (illiterate and primary school level).

Our cohort's HbAS and HbAA pregnant women had equal employment opportunities and comparable earnings, however women were not college educated or/and did not own their homes. Indeed, families affected by SCA may not be able to send their children to a university because of the financial burden associated with higher education. Although the numbers of women with SCT in our cohort were small, the findings were consistent with other observations, indicating that women with HbAS suffer from unemployment, lack of health insurance, and marriage discrimination.[4] Other studies which compared SCTs and healthy controls did not find a difference in socioeconomic status.[28]

The current study revealed that siblings of the HbAS group were more likely to be affected by SCA than their

HbAA counterparts (65 vs 13%). A similar observation has been reported in the same region by Munsoor and Alabid.[31] In this region of Sudan, it appears that the tribal habit of marriage among relatives propagates the sickle cell gene. Consanguineous marriage is a factor that supports the spread of the disease.

At baseline, first trimester, the women with and without SCT had comparable weight, height, body mass index, and blood glucose levels. Perhaps this was to be expected, as the two groups had similar meal frequencies (most ate breakfast, lunch, and dinner regularly) and consumed similar types and amounts of foods.

Although the two groups of women had comparable levels of Hb at baseline (first trimester), the SCT group had significantly lower percentages of PCV, MCV, and MCH, probably indicating iron deficiency. A Hb value of less than 11 g/dl during the first and third trimesters is frequently seen, especially in this area of Sudan, with a high prevalence of hunger, malnutrition, and iron deficiency.[32–35]

Consistent with previous reports,[11,18–19] at delivery, this study found significantly lower Hb, PCV percentages, and MCH concentrations in women with SCT compared to their healthy counterparts (HbAA).

Following the recommendation of the WHO,[36] iron and iron-folate tablets are made available free of charge to pregnant women in Sudan.[37] Compliance with iron, folic acid supplementation is related to maternal education level, appropriate antenatal education and care, knowledge about anaemia and iron-folic acid supplements, and regular antenatal care visits.[38–41]

The values of haematological parameters of the babies born to women with SCT and healthy controls closely mirror those of their mothers at delivery, with the Hb, PCV, and MCH levels of the former being significantly lower than those of the latter group, in agreement with earlier studies.[42–43] Therefore, it is evident that maternal SCT had adverse effects on the haematological parameters of their babies. The Hb, PCV, MCV, and MCH values of the babies were significantly lower than those of the neonates of the healthy control group, and the normal cord blood reference ranges reported from Sudan.[44]

Furthermore, babies born to SCT mothers had lower birth weight and a higher chance of admission to the special care baby unit; mothers had more miscarriages and a higher chance of stillbirth than the HbAA group.[25] The reason for admissions to SCABU included neonatal jaundice, low APGAR score, and hypoglycemia at birth. These findings are consistent with other studies, which reported anaemia and neonatal/foetal mortality,[18,20] low birth weight,[20–21] prematurity and pre-eclampsia,[23] intrauterine foetal hypoxia[19] and placental infarction and calcification[20] in pregnancies complicated by SCT.

It is not evident why SCT pregnancy is associated with adverse birth outcomes. Nevertheless, several studies have underscored that iron deficiency and anaemia are risk factors for adverse pregnancy outcomes viz preterm delivery, prematurity, low birth weight;[34,45–46] placental pathologic changes – infarction and calcification – may also play a role, including its association with increased stillbirth.[20,47]

This study has several limitations, including the relatively small size of SCT patients. Also, due to logistic and financial reasons, reticulocyte count and iron studies could not be determined. In addition, the placentae were not evaluated for pathologic changes (placental infarction or calcification) and postpartum follow-up was not conducted. All of these make affirmative conclusions about causes of stillbirth and other adverse outcomes difficult.

Conclusions. The study revealed that SCT is associated with adverse pregnancy outcomes, including maternal and neonatal anaemia, low birth weight, and increased risk of stillbirth. Therefore, women with SCT who embark on pregnancy should be given appropriate pre-conceptual advice and multidisciplinary antenatal and postnatal care

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Authors' contributions. GK conceived the idea, designed and initiated the study and edited the manuscript, AEH. conducted the fieldwork (recruitment, collection of blood samples, data analysis and manuscript drafting), AG helped with the recruitment and collection of demographic data, AS, and MAO, provided valuable advice on SCA and haematology and helped with data evaluation and critical editions of the manuscript, MM, helped with statistical data analysis, AO, and IAK helped with laboratory analysis and AKE facilitated the follow-up with the participants and attended the deliveries.

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