



Pattern of Haemolysis During Pregnancy in Women with Sickle Cell Disease (SCD), and its Effects on Feto-maternal Outcome

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INTRODUCTION

- Chronic haemolysis in SCD has been associated with complications like pulmonary hypertension, chronic leg ulcer, renal impairment, acute vaso-occlusion, VTE and death¹⁻⁵
- Hyperhaemolysis occurs in stressful conditions including pregnancy
- Pregnancy in SCD, can be life-threatening; it is associated with increased rates of adverse fetomaternal outcome⁶

AIM/ HYPOTHESIS

AIM

To determine the association between haemolysis and fetomaternal outcomes in pregnant women with SCD

HYPOTHESIS

Pregnancy is associated with hyperhaemolysis and will result in poor fetomaternal outcome

METHOD

STUDY DESIGN/ SITE

A prospective cohort study of adults conducted at the Obstetrics Department, Korle-Bu Teaching Hospital, and Ghana Institute of Clinical Genetics (an adolescent and adult sickle cell clinic)

DATA COLLECTION

- **Enrollment and follow-up:**
 - 25 pregnant women with SCD (HbSS:16; HbSC:9), and 2 sets of matched controls (23 pregnant women without SCD and 25 SCD non-pregnant women)
 - Pregnant women (SCD/non-SCD) were matched for gestational age (GA; ± 2 weeks); enrolled during the second trimester and followed up prospectively till six weeks postpartum
 - SCD group (pregnant/non-pregnant) were matched for age (± 2 years) and genotype and were in their steady state at enrollment
- **Outcomes:**
 - Maternal outcomes: acute pain episode, acute chest syndrome (ACS) and severe anaemia
 - Fetal outcomes: spontaneous abortion, intrauterine fetal death (IUFD)/stillbirth, preterm birth, and low birthweight
- **Laboratory samples:**
 - Selected haemolytic markers [Hb, absolute reticulocyte count, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), serum bilirubin and urobilinogen] were analyzed for the pregnant women at each study visit. The non-pregnant SCD women had only baseline samples analyzed

DATA ANALYSIS

One-way analysis of variance was used to compare the means of the selected haemolytic markers

STUDY DEFINITIONS

- The diagnostic criteria for hyperhaemolysis by Ballas et al was used⁷

RESULTS

- The participants (n=73) were aged between 21-42 years. There was no significant difference in mean ages of the pregnant women (SCD/non-SCD) at 29.8 ± 5.2 vs 31.7 ± 5.4 years respectively; $p=0.42$. The mean age of the non-pregnant SCD women was 29.6 ± 5.4 years
- Mean GA at enrollment and delivery for all pregnant women were 19.4 and 36.6 weeks respectively.
- Using the diagnostic criteria for hyperhaemolysis, none of the pregnant women with SCD had hyperhaemolysis. One woman with SCD at 28-, 36-weeks' GA and six weeks postpartum each had a drop in Hb $\geq 20\%$ from baseline, with no corresponding 25% increase in reticulocyte count from baseline values.
- There were no significant differences in the concentrations of haemolytic markers during study follow-up.
- Thirteen acute pain episodes occurred in nine pregnant women with SCD (HbSS:8; HbSC:1) with 61.5% occurring in the third trimester. The pain incidence rate was 1.23 events per patient-years.
- There was no admission for ACS during the study period.
- The pregnant women with SCD had more caesarean deliveries [18(72.0%) vrs 4(19.0%); $p=0.01$]; preterm births [10(41.7%) vrs 5(27.8%); $p=0.35$], low birthweight babies [7(29.2%) vrs 3(16.7%); $p=0.74$] and IUFD [2(8.0%) vrs 0(0.0%)] comparatively.

Table 1: Mean baseline laboratory parameters of pregnant women with SCD compared to pregnant women with HbAA

Baseline characteristics (N = 48)	Pregnant women with SCD, n = 25	Pregnant women with HbAA, n = 23	p-value
Mean Hb, (std dev) (g/dL)	8.8 (1.8)	10.4 (1.2)	0.00
Mean absolute reticulocyte count, (std dev) ($\times 10^9/L$)	122.7 (80.7)	115.5 (22.6)	0.88
Mean total bilirubin, (std dev) ($\mu\text{mol/L}$)	26.2 (13.5)	23.7 (11.3)	0.38
Mean direct bilirubin, (std dev) ($\mu\text{mol/L}$)	5.5 (3.4)	1.7 (1.4)	0.00
Mean indirect bilirubin, (std dev) ($\mu\text{mol/L}$)	20.6 (11.2)	19.0 (10.7)	0.56
Mean aspartate aminotransferase (AST), (std dev) (IU/L)	30.5 (15.9)	15.6 (5.9)	0.01
Mean lactate dehydrogenase (LDH), (std dev) (IU/L)	322.1 (73.3)	185.9 (99.3)	0.00
Urobilinogen test, n (%)			
Normal	25 (100.0)	23 (100.0)	
Increased	0 (0.0)	0 (0.0)	
Bilirubin, n (%)			
Negative	25 (100.0)	23 (100.0)	
Positive	0 (0.0)	0 (0.0)	

Table 2: Steady state laboratory parameters of SCD women (pregnant/non-pregnant)

Laboratory parameters (baseline)	Non-pregnant women with SCD (N= 25)	Pregnant women with SCD (N= 25)	p-value
Mean Hb, (std. dev.) (g/dL)	8.7 (1.8)	8.8 (1.8)	0.89
Mean absolute reticulocyte count, (std. dev.) ($\times 10^9/L$)	103.0 (32.4)	122.7 (80.7)	0.27
Mean total bilirubin, (std. dev.) ($\mu\text{mol/L}$)	43.0 (36.3)	26.2 (13.5)	0.04
Mean direct bilirubin, (std. dev.) ($\mu\text{mol/L}$)	8.9 (7.9)	5.5 (3.4)	0.05
Mean indirect bilirubin, (std. dev.) ($\mu\text{mol/L}$)	34.1 (31.8)	20.6 (11.3)	0.05
Mean LDH, (std. dev.) (IU/L)	373.2 (152.3)	322.1 (73.3)	0.14
Mean AST, (std. dev.) (IU/L)	42.7 (25.2)	30.5 (15.9)	0.05
Mean ALT, (std. dev.) (IU/L)	35.1 (20.7)	27.9 (22.1)	0.24

Table 3: Trends in concentration of haemolytic markers in pregnant women with SCD during the study period

Laboratory parameters	Enrollment (n=25)	28 weeks gestation (n=23)	36 weeks gestation (n=18)	6 weeks postpartum (n=25)	p-value
Mean Hb, (std dev) (g/dL)	8.8 (1.8)	8.7 (1.2)	9.1 (1.3)	9.2 (1.8)	0.88
Mean absolute reticulocyte count, (std dev) ($\times 10^9/L$)	122.7 (80.7)	117.0 (68.0)	119.9 (43.5)	139.3 (58.6)	0.87
Mean total bilirubin, (std dev) ($\mu\text{mol/L}$)	26.2 (13.5)	28.1 (14.7)	42.7 (28.1)	29.4 (20.4)	0.53
Mean direct bilirubin, (std dev) ($\mu\text{mol/L}$)	5.5 (3.4)	8.2 (9.1)	10.9 (7.5)	6.0 (4.7)	0.46
Mean indirect bilirubin, (std dev) ($\mu\text{mol/L}$)	20.6 (11.3)	19.9 (9.0)	30.7 (26.1)	23.3 (19.0)	0.63
Mean AST, (std dev) (IU/30.5 (15.9)	37.2 (52.6)	34.6 (26.1)	35.2 (23.4)	0.97	
Mean LDH, (std dev) (IU/L)	322.1 (73.3)	328.3 (141.8)	296.3 (143.8)	351.6 (139.6)	0.82

CONCLUSIONS

- Though we did not demonstrate hyperhaemolysis, women with SCD had poorer fetomaternal outcomes as previously described
- Future studies should consider using more sensitive markers of haemolysis such as haptoglobin, haemopexin and erythrocyte adenylate kinase

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REFERENCES

- ¹ Rother RP et al. The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma Hemoglobin: A Novel Mechanism of Human Disease. *JAMA*. 2005;293(13):1653–62.
- ² Reiter CD et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med*. 2002;8(12):1383–9.
- ³ Kato GJ. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood*. 2006;107(6):2279–85.
- ⁴ Kato GJ et al. Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev*. 2007;21(1):37.
- ⁵ Gladwin MT, Kato GJ. Hemolysis-associated hypercoagulability in sickle cell disease: the plot (and blood) thickens! *Haematologica*. 2008;93(1):1–3.
- ⁶ Boافر TK et al. Pregnancy outcomes in women with sickle-cell disease in low and high income countries: a systematic review and meta-analysis. *BJOG Int J Obstet Gynaecol*. 2016;5(123):691–8.
- ⁷ Ballas SK et al, Kesen MR, Goldberg MF, Luty GA, Dampier C, Osunkwo I, et al. Beyond the Definitions of the Phenotypic Complications of Sickle Cell Disease: An Update on Management. *The Scientific World Journal*. 2012. [Accessed 02/19/2018]. Available from: <https://www.hindawi.com/journals/tswj/2012/949535/>

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