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Recurring pregnancy loss and sickle cell disease: A case of missed opportunities for interventions at a tertiary institution in Zimbabwe, 2024

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Introduction

- Sickle cell disease (SCD) is caused by a mutation in the β-globin chain of the Hb molecule
- Sickle Hb, has high tendency of polymerizing when deoxygenated

- How normal tissue perfusion is interrupted by abnormal sickle cells is complex and poorly understood
  - Resultant is vaso-occlusion and its complications
- Some physiological changes of pregnancy are exacerbated in SCD
  - Increased risk of morbidity and mortality

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Presenting complaint

- Mrs NK, 26 –year old P1+1 G3, EGA-32+5
- Presenting on 21 July 2024
  - Sudden onset pleuritic chest pain x4/7
  - Productive cough with white sputum x4/7
  - General body malaise
- Booked pregnancy at 22/40 and received routine management
- Two similar episodes managed on antibiotics at local hospital
- Multiple episodes of painful crises in current pregnancy

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Background history

Housewife, Married to one partner for 4 years. Stays in Shamva. Partner comes from Shamva

Grew up in Guruve with Mozambiquan maternal and Zambian paternal origins

No history of recreational drug use/alcohol consumption

Pica since adolescents

Dropped out of school due to recurrent leg aches, joint swelling and resp tract infections

Stillbirth at 32/40 in 2022 and T1 miscarriage in 2023

History suggests multiple episodes of crises and jaundice

Managed at all levels of health care

Father had another family and her half-siblings are alive and well

Mother of recurrent undiagnosed illnesses

Sibling died of illnesses suggestive of SCD crises

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Assessment and management

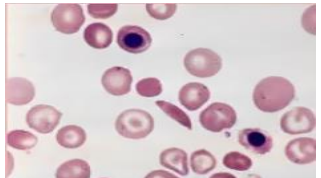
Examination

- Small stature
- Mucosal pallor, jaundice, angular cheilitis
- Bronchial breath sounds
- HOF 32cm, FHHR, Cephalic
- EFW 2292g and normal dopplers

- **Impression- community acquired pneumonia**

Management

- Ceftriaxone and azithromycin
- Clexane
- CXR- hilar fullness and patchy infiltrates in the lower zones
- Dexamethasone course
- Malaria and hepatitis screen negative
- Normocytic anaemia with Hb 8.8g/dl and transfused 2 units PCs
- Sickle cell screen positive



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Progress post admission

- Developed pain crisis with right sided chest and upper quadrant pain 3 weeks post-admission
- Transfused 2 units PCs
- MDT Meeting recommendations
  - Delivery by IOL under epidural anaesthesia
  - Maintain Hb between 9.5-10g/dl
- Elective LSCS was conducted at 36 weeks
- A live girl newborn with APGAR 8 and 9, and birth weight 2300g was delivered
- Stable upon discharge after a week

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Targeted screening for hemoglobinopathies

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Review > J Obstet Gynaecol Can. 2008 Oct;30(10):950-959. doi: 10.1016/S1701-2163(16)32975-9.

Carrier screening for thalassemia and hemoglobinopathies in Canada

[Article in English, French]

Sylvie Langlois [1], Jason C Ford [1], David Chitayat [2]; CCMG PRENATAL DIAGNOSIS COMMITTEE; SOGC GENETICS COMMITTEE

Collaborators, Affiliations + expand

PMID: 19038079 DOI: 10.1016/S1701-2163(16)32975-9

Recommendations: 1. Carrier screening for thalassemia and hemoglobinopathies should be offered to a woman if she and/or her partner are identified as belonging to an ethnic population whose members are at higher risk of being carriers. Ideally, this screening should be done pre-conceptionally or as early as possible in the pregnancy. (II-2A) 2. Screening should consist of a complete blood count, as well as hemoglobin electrophoresis or hemoglobin high performance liquid chromatography. This

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Targeted screening for hemoglobinopathies

- Race and ethnicity- based strategy screening for haemoglobinopathies (ACOG, 2021)
- Universal screening of people planning to conceive or at 1st ANC visit (ACOG, 2023, RCOG)
  - Race and self identification ethnicity are poor proxies for genetics
  - Haemoglobinopathy risk is US is 1/66 people
- At risk individuals receive genetic counselling on risks and reproductive options
- *Is screening through electrophoresis/sickle cell prep/molecular/non-invasive cell-free DNA testing feasible locally?*

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Screening ECHO can be performed in those with chest symptoms

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease

Authors: Florence Parent, M.D., Dora Bachir, M.D., Jocelyn Inamo, M.D., François Lionnet, M.D., Françoise Driss, M.D., Gylna Loko, M.D., Anoosha Habibi, M.D., +10, and Gerald Simonneau, M.D. Author Info & Affiliations

Published July 7, 2011 | **N Engl J Med 2011;365:44-53** | **DOI: 10.1056/NEJMoa1005565** | **VOL. 365 NO. 1**

RESULTS

The prevalence of a tricuspid regurgitant jet velocity of at least 2.5 m per second was 27%. In contrast, the prevalence of pulmonary hypertension as confirmed on catheterization was 6%. The positive predictive value of echocardiography for the detection of pulmonary hypertension was 25%. Among the 24 patients with confirmed pulmonary hypertension, the

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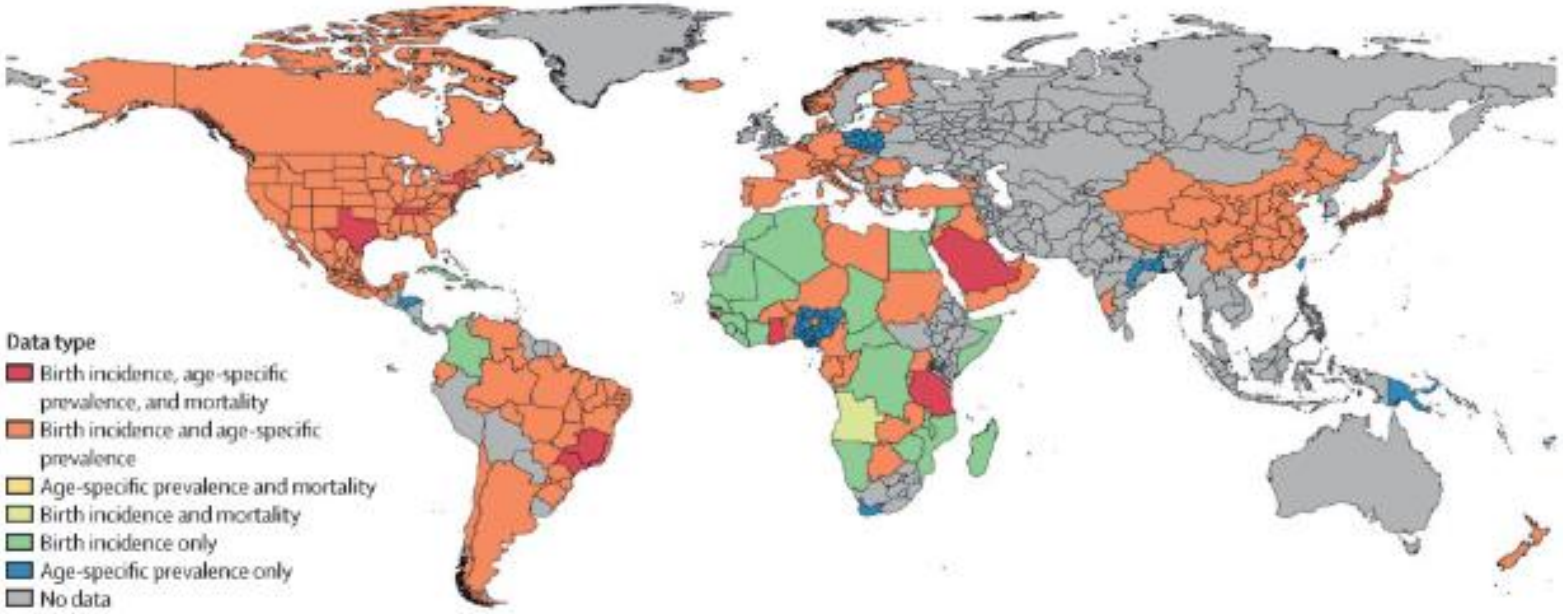
Availability of hemoglobinopathy data by country



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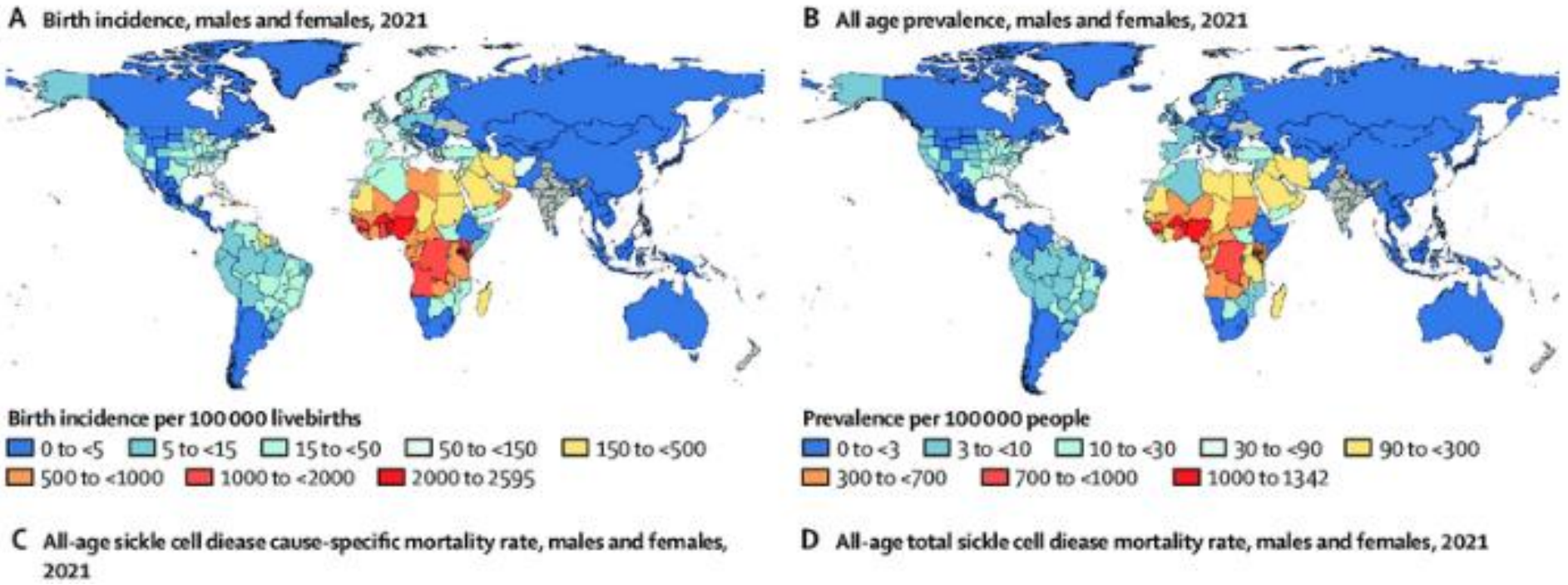
Global incidence and prevalence of SCD



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No data on incidence and prevalence of SCD/trait in Zim

Grant

Sickle Hemoglobinopathy reseArch in Zimbabwe (SHAZ)

Funder: National Heart Lung and Blood Institute (NHLBI)

Grant number: U01HL156943 - Original description ↗

Investigators

PATIENCE KUONA - University of Zimbabwe

PI

Research organization

University of Zimbabwe, Zimbabwe

Abstract

Abstract/Summary The goal of the Sickle Hemoglobinopathy reseArch in Zimbabwe (SHAZ) application is to establish a sustainable infrastructure and operation aimed at addressing the limited data and gaps in Sickle cell disease (SCD) management that currently exists in Zimbabwe and Zambia by contributing to the SCD in Sub-Saharan Africa (SSA) network consortium registry and biorepository. SHAZ aims to create accomplished SCD clinicians and research personnel who will focus on introduction and implementation of the SCD in SSA network registry efforts, enrolling at least 4,000 individuals with SCD from Zambia and Zimbabwe over a five-year period. The SHAZ team will aim to integrate regional SCD evidence-based management guidelines and will

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Aspirin is beneficial to prevent pre-eclampsia

- Risk of pre-eclampsia is increased, 12% vs 8% in controls (Prophet et.al, 2018)
- No specific evidence that aspirin reduces risk of pre-eclampsia in SCD
- United States Preventive Services Taskforce recommends aspirin when absolute risk is >8%
- Low dose aspirin is commenced between 12-28 weeks
- *Updated local guidance on aspirin prophylaxis maybe necessary*

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Management protocols and MDT care improve outcomes

- All pregnancies in individuals with SCD are considered high risk
  - Warrant higher level of expertise of a FMU physician and MDT care (James etal, 2024)
- Implementation of active management protocols for pregnancy in SCD have demonstrated survival benefits
  - Decrease in the mortality rate (27 % to 1.8 %) in Benin (Rahimy etal, 2000)
  - Nearly 90 % reduction in the risk of maternal death in Ghana (Asare etal, 2017)
- A 2022 meta-analysis of studies from low- and middle-income countries showed similar results (Asare etal, 2022)
- *MDT meeting conducted and recommendations were implemented*

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Hydroxyurea prophylaxis reduces mortality

Medline ® Abstracts for References 47,48 of 'Hydroxyurea use in sickle cell disease'

47 PubMed

TI Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment.

AU Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringer E, Bellevue R, Olivieri N, Eckman J, Varma M, Ramirez G, Adler B, Smith W, Carlos T, Ataga K, DeCastro L, Bigelow C, Saunthararajah Y, Telfer M, Vichinsky E, Claster S, Shurin S, Bridges K, Waclawiw M, Bonds D, Terrin M

SO JAMA. 2003;289(13):1645.

CONTEXT: Hydroxyurea increases levels of fetal hemoglobin (HbF) and decreases morbidity from vaso-occlusive complications in patients with sickle cell anemia (SCA). High HbF levels reduce morbidity and mortality.

OBJECTIVE: To determine whether hydroxyurea attenuates mortality in patients with SCA.

DESIGN: Long-term observational follow-up study of mortality in patients with SCA who originally participated in the randomized, double-blind, placebo-controlled Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), conducted in 1992-1995, to determine if hydroxyurea reduces vaso-occlusive events. In the MSH Patients' Follow-up, conducted in 1996-2001, patients could continue, stop, or start hydroxyurea. Data were collected during the trial and in the follow-up period.

RESULTS: Seventy-five of the original 299 patients died, 28% from pulmonary disease. Patients with reticulocyte counts less than 250 000/mm3 and hemoglobin levels lower than 9 g/dL had increased mortality (P =.002). Cumulative mortality at 9 years was 28% when HbF levels were lower than 0.5 g/dL after the trial was completed compared with 15% when HbF levels were 0.5 g/dL or higher (P =.03). Individuals who had acute chest syndrome during the trial had 32% mortality compared with 18% of individuals without acute chest syndrome (P =.02). Patients with 3 or more painful episodes per year during the trial had 27% mortality compared with 17% of patients with less frequent episodes (P =.06). Taking hydroxyurea was associated with a 40% reduction in mortality (P =.04) in this observational follow-up with self-selected treatment. There were 3 cases of cancer, 1 fatal.

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Hydroxyurea can improve outcomes during pregnancy

- A 2022 review of 1788 pregnancies, use of hydroxyurea had 2-3x the risk of miscarriage or stillbirth, or LBW
  - There were no differences in preterm birth, serious medical problems, or congenital anomalies
  - Balance of risks of vaso-occlusive complications, which could in turn harm the fetus
- Hydroxyurea is generally given in pregnancy (ACOG, 2023)
- Individualized management is advised
- *Local guidance?*

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Thromboprophylaxis and supplementary vaccination reduce occurrence of crises SCD

- LMW heparin must be administered to in-patients except labor and delivery (ACOG, RCOG, Canadian Guidelines)
- Administer to ambulatory/outpatients with history/increased risk of VTE
- Mechanical thromboprophylaxis (pneumatic compression) is recommended for all individuals undergoing cesarean birth
  - Suggested in addition to anticoagulation for those at highest risk
- Polyvalent pneumococcal, Haemophilus influenza type B, and meningococcal vaccines are recommended for pregnant patients with SCD (WHO)

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Prophylactic blood transfusion confers no benefit during pregnancy

Medline ® Abstract for Reference 76 of 'Sickle cell disease: Obstetric considerations'

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76 PubMed

TI Prophylactic versus selective blood transfusion for sickle cell disease in pregnancy.

AU Okusanya BO, Oladapo OT

SO Cochrane Database Syst Rev. 2013;

BACKGROUND: Pregnant women with sickle cell disease (HbSS, HbSC and HbSβThal) may require blood transfusion to prevent severe anaemia or to manage potential medical complications. Preventive blood transfusion in the absence of complications starting from the early weeks of pregnancy or blood transfusion only for medical or obstetric indications have been used as management policies. There is currently no consensus on the blood transfusion policy that guarantees optimal clinical benefits with minimal risks for such women and their babies. The present review replaces and updates a Cochrane review that was withdrawn in 2006.

OBJECTIVES: To assess the benefits and harms of a policy of prophylactic versus selective blood transfusion in pregnant women with sickle cell disease.

AUTHORS' CONCLUSIONS: Evidence from two small trials of low quality suggests that prophylactic blood transfusion to pregnant women with sickle cell anaemia (HbSS) confers no clear clinical benefits when compared with selective transfusion. Currently, there is no evidence from randomised or quasi-randomised trials to provide reliable advice on the optimal blood transfusion policy for women with other variants of sickle cell disease (i.e. HbSC and HbSβThal). The available data and quality of evidence on this subject are insufficient to advocate for a change in existing clinical practice and policy.

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Prophylactic blood transfusion confers no benefit during pregnancy

- Transfusions are often used to treat acute complications, in preparation for surgery, and in selected preventive transfusion programs (RCOG, ACOG)
- Raising the Hb too high (>10 mg/dL) may be detrimental to most individuals
- Baseline Hb in many individuals with SCD is approximately 8 g/dL
- Increased Hb can cause hyperviscosity syndrome
- Blood transfusions were associated with reduced maternal morbidity and mortality but not fetal outcomes (Maliknowsky etal, 2015)
- Benefits must be weighed against the harms and burdens of transfusion
  - Transfusion reactions, risk of alloimmunization, hospitalization rate, and cost

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Vaginal delivery at term is preferred

- No medical contraindications to a trial of labor and vaginal birth
- Caesarean birth is reserved for standard obstetric indications (ACOG, RCOG, 2022)
- Need for CTG due to high risk of complications
- Risk of stillbirth and preeclampsia increases with increasing GA
- No high-quality studies have determined the optimal GA for delivery in individuals with SCD
- General recommendation is 37-39 weeks, exact timing decided on an individual basis

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Vaginal delivery at term is preferred

- Evidence is from the 2018 ARRIVE trial
  - Induction at 39 weeks resulted in a reduction in cs, hypertensive disorders of pregnancy, the composite of perinatal death/severe neonatal complications
- Delivery closer to 37 weeks may be appropriate for individuals with high-risk complications/comorbidities
  - High risk of placentally-mediated complications (growth restriction, oligohydramnios) (Fashakin etal, 2022)
- *Earlier delivery by cs was informed by BOH*

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Hydroxyurea is beneficial during breastfeeding

- Breastfeeding should be encouraged for its maternal and infant health benefits
- There is little transfer of hydroxyurea into breastmilk (Ware etal, 2020)
- A mean of 2.2 mg of the drug was present in breastmilk, corresponding to infant dose of 3.4%
  - Lower than 5-10% safety threshold (Ware etal, 2020)
- Approx 1.2 mg are excreted during the first 3 hours and beyond hour 3, very littele/none
  - Can be taken immediately after a feeding (ACOG,2023)

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Progestins are preferred for contraception

- All individuals should be offered individualised contraception
- Progestin-only contraceptives (except for DMPA) are preferred (Tepper etal, 2016)
- The Lev IUD decreases menstrual bleeding and is prefered

- Haemoglobinopathy tesing for the newborn

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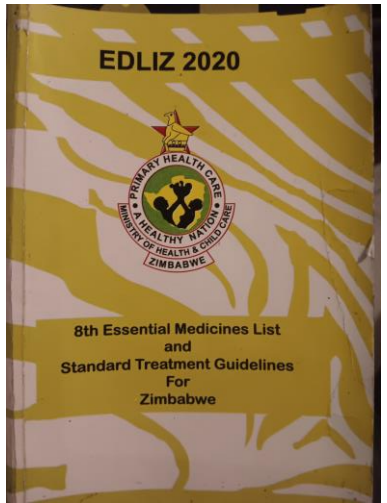
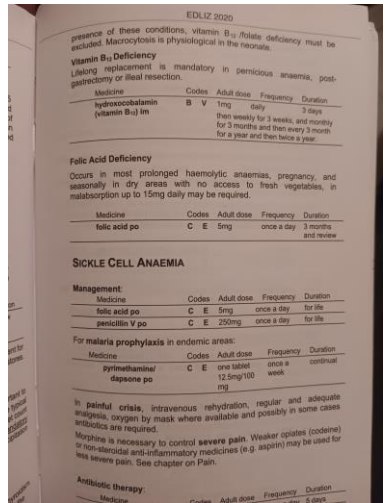
Recommendations

- A multi-disciplinary team care approach is of paramount importance to optimize maternal and perinatal outcomes among women with SCD
- Although women with SCD benefit from individualised care plans, local guidelines on screening and care for women with SCD in the pre-conception, antenatal, delivery and postpartum period are needed to inform timely diagnosis and standard of care to this sub-population





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THANK YOU

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