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Iron stores in pregnant women with sickle cell disease in Africa. A protocol for systematic review and meta-analysis

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Iron stores in pregnant women with sickle cell disease in Africa. A protocol for systematic review and meta-analysis

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Word counts: abstract: 230, main text: 1320, tables: 5, figures: 1

ABSTRACT

Introduction: Sickle cell disease (SCD) is the most common inherited disease worldwide. The greatest disease burden is seen in sub Saharan Africa. Early diagnosis and improved care of people living with SCD has seen an increase in number of women with SCD reaching reproductive age. Iron deficiency anaemia remains the most common cause of anaemia in pregnancy, affecting 51 to 63% of pregnancies in Africa. However, unavailability of guidelines on supplementation of iron in this pregnant subpopulation often leaves clinicians in a fix. We suggest conducting the first systematic review and possible meta-analysis on iron status of pregnant women with SCD.

Methods and analysis: We will search data sources (PubMed, MEDLINE, EMBASE, Google scholar, Africa Journal Online (AJOL), Africa Index Medicus, Popline and the Cochrane library) for studies on iron status of pregnant women with SCD. After study selection, full text

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procurement, extraction of data and synthesis, we will evaluate individual studies for quality, risk of bias and heterogeneity. Felicitous statistical methods shall be used to pool prevalence estimates for matching studies globally and in subpopulations. This protocol is in line with the 2015 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Ethics and Dissemination: There is no requirement for ethical approval as the proposed study will use published data. The findings of this study will be published in a peer review journal and presented at conferences.

Key words: sickle cell disease, iron status, pregnancy, protocol, systematic review/meta-analysis

Strengths and Limitations

- This review will summarised published data on iron status of pregnant women with sickle cell disease in Africa and thus provide information on prevalence and associated factors of iron deficiency anaemia amongst pregnant women with sickle cell disease in Africa
- The proceeds of this review will provide a trove of guidance to clinicians on whether or not to supplement iron to pregnant women living with sickle cell disease.
- The review will be important to authorities involved in formulation of health policies as it will serve as a basis for writing guidelines on iron supplementation in pregnancy
- This study will be limited to Africa; however, the highest burden of sickle cell disease is seen in this region

INTRODUCTION

Sickle cell disease (SCD) is a disease caused by inheritance of a defective haemoglobin gene resulting in red blood cells changing shape in hypoxic conditions and chronic haemolysis (1). SCD is the most common inherited disease worldwide. The world health organization (WHO) reports that approximately 60% of the world's 229 countries are endemically affected with haemoglobin disorders(2). About 85% of sickle cell disorders and 70% of SCD affected births occur in Africa (2).

Over 7% of pregnant women worldwide carry a significant haemoglobin gene variant(2). Pregnancies in SCD has been shown to be associated with adverse maternal and foetal outcomes

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in both low and high income countries (3). Maternal mortality in a previous report has been shown to be about 29 folds higher in pregnant women with SCD when compared to pregnant women without SCD (4). With better understanding of the disease and improved care being given to patients with sickle cell disease, more women with SCD have been reaching reproductive age. Factors capable of influencing morbidity/mortality associated with this condition does need to be properly reviewed for clinicians to better advise themselves

The averagely low adult female iron body stores plus increased pregnancy iron requirements often put pregnant women at risk of iron deficiency anaemia (5–8). Iron deficiency anaemia in pregnancy is a known significant contributor to maternal mortality. Daily iron supplementation in pregnancy is recommended by WHO as a proactive measure to reduce anaemia and its associated complications in pregnancy(9). However there are no clear guidelines on this supplementation of iron in the sickle cell disease subpopulation. Absence of available data often leaves clinicians in a dilemma.

In the SCD subpopulation, chronic haemolysis leads to recurrent transfusions and thus risk of iron overload(10). This risk of iron overload amongst patients with SCD and risk of iron deficiency in pregnancy makes supplementation of iron to pregnant sicklers a difficult decision. Several studies have thus been done to evaluate iron stores amongst pregnant women with sickle cell disease with varying outcomes (12–16). We previously provided an opinion on iron supplementation in this subpopulation (11). However the subjective nature of opinion papers makes its recommendations feeble. Harmonising published data in a systematic review and meta analysis would provide better and more resilient recommendations for supplementation of iron to Pregnant women with SCD

Objectives

We aim to systematically review and perform meta-analysis of existing data on iron stores amongst pregnant women with SCD.

1) To estimate the prevalence of iron deficiency anaemia amongst pregnant women with SCD
2) To assess factors associated with iron deficiency anaemia amongst pregnant women with SCD

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3) Evaluate the foetal and maternal outcomes among pregnant women with SCD who are supplemented with iron

METHODS

This protocol has been written following guidelines of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (17) available on table 1. It shall be registered on PROSPERO International Prospective Register of Systematic reviews

Eligibility Criteria

We shall include all observational studies and clinical trials conducted worldwide from all prior studies to August 2018 on iron status in pregnant women with sickle cell disease

We shall exclude;

1) All mini-reviews, commentaries and editorials
2) Abstracts whose full data would not be available even upon requesting from the author
3) Unpublished manuscripts and conference abstracts
4) Studies whose diagnostic method of iron assays do not meet international requirements (serum ferritin and transferin receptor in serum)
5) Duplicates; studies published with same or different titles in more than one journal; the most updated version shall be considered.
6) All studies not published in English
7) Studies not done in Africa

Search strategy and sorting of relevant studies

The search for relevant studies will be done online and shall be done in two ways

Search in electronic bibliographic databases

The following data sources shall be searched for eligible studies: PubMed, MEDLINE, EMBASE, Google scholar, Africa Journal Online (AJOL), Africa Index Medicus, Popline and

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the Cochrane library. The search will be done by combining relevant terms related to SCD, iron stores and pregnancy as illustrated in table 2.

Forwards and backwards citation search

Citations in identified studies shall be reviewed for studies with similar objectives. This will be done to identify additional data sources that were missed during the search in bibliographic databases.

Selection procedure for studies to be included in the review

Literature search will be performed independently by two investigators (DA and BMK). Study titles and abstracts will be reviewed and full texts of potentially eligible articles will then be retrieved using EndNote software version X8. Preselected full texts will further be screened for eligibility using a pretested predefined form created on Epi info software version 7.2.2.6. For studies with disagreements between investigators a consensus shall be reached by consulting a 3rd investigator (TN). Publications with ambiguous data shall be resolved by contacting authors by email for clarity. Potentially eligible studies that are excluded will be documented with reasons for exclusion. A detailed Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow chart shall be used to depict the selection process (Figure 1).

Risk of Bias Assessment

Assessment will be done using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute/National Heart, Lung, and Blood Institute (Table 3) for observational studies and the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Tables 4 and 5) for studies which employed a randomized design.

Data Collection Process

A data abstraction sheet will be produced on Epi infos version 7.2.2.6 statistical software and pretested by investigators. Data to be extracted from selected studies shall include; First author, year of publication, country of study population, duration of study, study design and setting, mean or median age, sex distribution, sickle cell genotype, gestation age distribution, transfusion history, laboratory test used to measure body iron stores, iron status, mean cell volume,

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prevalence of iron deficiency anaemia and outcome of foetus and mother. For multinational studies we will separate the results and present them per country.

Statistical Analysis

The data will be analyzed using STATA V.14 statistical software. Random effects meta-analysis models will be reported over fixed-effects models due to the possibility of heterogeneity between the various studies retrieved. The chi-squared test for heterogeneity and the I^2 statistic will be used to assess the degree of heterogeneity among studies. Sensitivity analyses will be conducted to obtain pooled effects from different study designs (randomized controlled trials, cross-sectional, case-control and cohort study designs and the different diagnostic tests used to measure iron deficiency).

For objective one, a pooled prevalence for the proportion of pregnant women with SCD will be obtained if two or more studies provide this measure. Similarly, for objective two, if two or more studies report on a factor associated with SCD in pregnancy and provide a measure of effect for this relationship (odds ratio); a pooled analysis will be carried out. The various maternal and foetal outcomes of SCD in pregnancy will be described qualitatively.

Report and amendment of the review

The systematic review and meta-analysis will be presented according to the PRISMA 2015 guidelines using the PRISMA checklist which will be published with the final report. No amendments are intended for this protocol; however, any amendments shall be clearly documented.

CONCLUSIONS

There is controversial evidence regarding the role of iron supplementation in pregnant women with SCD and the associated pregnancy outcomes. Summarizing existing data on this issue through a comprehensive review is of utmost importance given that the majority of persons with SCD live in sub-Saharan Africa, a region characterized by profligate use of iron supplements as well as an alarming lack of appropriate resources to guide clinicians on how to use iron supplements in pregnant sicklers.

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Ethics and dissemination

Ethical clearance is not required as the current review will be based on published data. We intend to publish the final manuscript as an original article in a peer reviewed journal. Review findings will be presented at conferences, to concerned institutions and submitted to relevant health authorities. Regular updates of this review will be done as needed.

List of abbreviations

SCD: sickle cell disease; WHO: World Health Organization; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

Author Contributions

DA conceived the manuscript. DA, BMK and TN wrote and reviewed the manuscript. All authors approved the final version of the manuscript

Data statement

Not applicable

Competing interest

None declared

Funding

There was no funding for the writing of this protocol

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Tables

Table 1: PRISMA-P 2015 checklist for the study protocol of a systematic review on iron stores in pregnant women with sickle cell disease.

Section and topic	Item No	Checklist item	Page
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1	If the protocol is for an update of a previous systematic review, identify as	N/A

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	b	such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3&4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10&11
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4&5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5

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Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

Table 2:Search strategy for MEDLINE and adaptability to other databases

Search	Items
1	Sickle cell disease OR Sickle cell anaemia OR sickle cell anemia OR sickle cell haemoglobinopathy OR haemoglobinopathy OR hemoglobinoathy OR abnormal haemoglobin OR abnormal haemoglobin OR sickler OR sicle cell OR Drepanocytosis OR HbSS OR HbSC OR
2	Pregnancy OR Gestation OR Pregnant OR Gestational age OR gravidity OR gravid OR Expectant mothers OR trimester
3	Iron status OR iron stores OR iron supplementation OR serum iron OR iron deficiency OR serum ferritin OR bone marrow stainable iron OR Total iron binding

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	capacity OR transferrin OR iron overload OR microcytic anaemia OR microcytic anemia OR anaemia OR anemia OR iron deficiency anaemia OR iron deficiency anemia OR low body iron OR body iron OR low serum iron OR high serum iron OR high body iron OR normal serum iron OR normal body iron OR iron OR blood iron OR iron indices OR body iron indices OR serum iron indices
4	Africa* OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR "Guinea Bissau" OR "Ivory Coast" OR "Cote d'Ivoire" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe OR "Central Africa" OR "Central African" OR "West Africa" OR "West African" OR "Western Africa" OR "Western African" OR "East Africa" OR "East African" OR "Eastern Africa" OR "Eastern African" OR "North Africa" OR "North African" OR "Northern Africa" OR "Northern African" OR "South African" OR "Southern Africa" OR "Southern African" OR "sub Saharan Africa" OR "sub Saharan African" OR "subSaharan Africa" OR "sub Saharan African)"
5	#1 and #2 and #3 and #4

Table 3: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Developed by the National Heart, Lung and Blood Institute (NHLBI)

Criteria	Yes	No	Other (CD,

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			NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and			

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outcome(s)?			
Quality Rating (Good, Fair, or Poor) (see guidance)			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

*CD, cannot determine; NA, not applicable; NR, not reported

Table 4: Cochrane Risk of Bias Tool - *Cochrane Collaboration modified tool for assessing risk of bias for RCT's, PART I*

Using the guidance provided at the end of this form, select either "high", "low" or "unclear" for each judgment. When complete, proceed to **Part II of the Quality Assessment Form REF ID:**					
Domain	**Description**	**High risk of bias**	**Low risk of bias**	**Unclear risk of bias**	**Reviewer Assessment**
Selection bias ***Random sequence generation***	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. **Reviewer Comments:**	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**Judgement Random sequence generation** □ **High** □ **Low** □ **Unclear**
Selection bias ***Allocation concealment***	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	Intervention allocations likely could not have been foreseen in advance of, or during, enrollment	Not described in sufficient detail	**Judgement Allocation concealment** □ **High** □ **Low** □ **Unclear**

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	during, enrollment. **Reviewer Comments:**				
Reporting bias ***Selective reporting***	Stated how the possibility of selective outcome reporting was examined by the authors and what was found. **Reviewer Comments:**	Reporting bias due to selective outcome reporting.	Selective outcome reporting bias not detected	Insufficient information to permit judgement (*It is likely that the majority of studies will fall into this category.)*	**Judgement Selective reporting** □ **High** □ **Low** □ **Unclear**
Other bias ***Other sources of bias***	Any important concerns about bias not addressed above. If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry. **Reviewer Comments:**	Bias due to problems not covered elsewhere in the table.	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.	**Judgement Other sources of bias** □ **High** □ **Low** □ **Unclear**

Use this form to assess risk of bias for randomized controlled trials.
Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).
Risk of selection, reporting, and other bias are assessed in the **Quality Assessment Form Part I.**
Risk of performance, detection, and attrition bias are assessed using the **Quality Assessment Form Part II.**

Table 5: Cochrane Collaboration modified tool for assessing risk of bias for RCT's, PART II

Risk of bias for the domains in the Form Part II will be assessed for each main or class of outcomes. Please indicate the specific outcome and complete the assessment for each. **REF ID:**					
Outcomes:					
Domain	**Description**	**High risk**	**Low risk**	**Unclear risk of**	**Reviewer**

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		of bias	**of bias**	**bias**	**Assessment**
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective. **Reviewer Comments:**	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**Judgement Blinding (participants and personnel)** □ **High** □ **Low** □ **Unclear**
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective. **Reviewer Comments:**	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**Judgement Blinding (outcome assessment)** □ **High** □ **Low** □ **Unclear**
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced	Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data	**Judgement Incomplete outcome data** □ **High** □ **Low** □ **Unclear**

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	exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported. **Reviewer Comments:**		bias	provided)	

Use this form to assess risk of bias for randomized controlled trials.
Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains of bias (selection, performance, attrition, reporting, and other).
Using the guidance provided at the end of this form, select either "high", "low" or "unclear" for each judgement.

Figure Legends

Figure 1: PRISMA flow diagram

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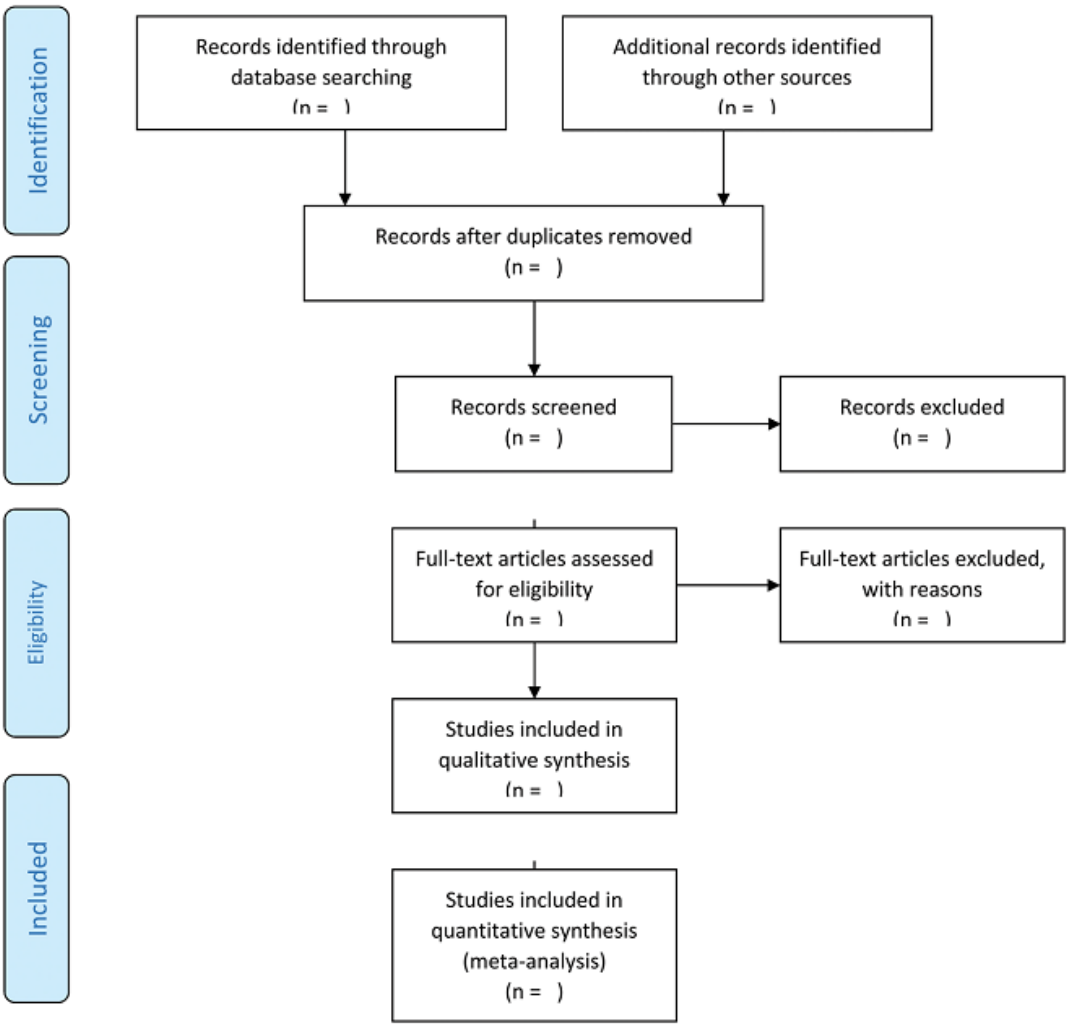

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Section and topic	Item No	Checklist item	Page
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3&4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10&11
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4&5

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nt			
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

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BMJ Open

Iron stores in pregnant women with sickle cell disease. A protocol for systematic review and meta-analysis

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Keywords:	HAEMATOLOGY, Anaemia < HAEMATOLOGY, Prenatal diagnosis < OBSTETRICS, PUBLIC HEALTH

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Iron stores in pregnant women with sickle cell disease. A protocol for systematic review and meta-analysis

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Word counts: abstract: 230, main text: 1320, tables: 5, figures: 1

ABSTRACT

Introduction: Sickle cell disease (SCD) is the most common inherited disease worldwide. The greatest disease burden is seen in sub Saharan Africa. Early diagnosis and improved care of people living with SCD has seen an increase in number of women with SCD reaching reproductive age. Iron deficiency anaemia remains the most common cause of anaemia in pregnancy, affecting 51 to 63% of pregnancies in Africa. However, unavailability of guidelines on supplementation of iron in this pregnant subpopulation often leaves clinicians in a fix. We suggest conducting the first systematic review and possible meta-analysis on iron status of pregnant women with SCD.

Methods and analysis: We will search data sources (PubMed, MEDLINE, EMBASE, Google scholar, Africa Journal Online (AJOL), Africa Index Medicus, Popline and the Cochrane library)

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for studies on iron status of pregnant women with SCD. After study selection, full text procurement, extraction of data and synthesis, we will evaluate individual studies for quality, risk of bias and heterogeneity. Felicitous statistical methods shall be used to pool prevalence estimates for matching studies globally and in subpopulations. This protocol is in line with the 2015 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Ethics and Dissemination: There is no requirement for ethical approval as the proposed study will use published data. The findings of this study will be published in a peer review journal and presented at conferences.

Review registration number: CRD42018109803

Key words: sickle cell disease, iron status, pregnancy, protocol, systematic review/meta-analysis

Strengths and Limitations

- This review will be the first to summarise published data on iron status of pregnant women with sickle cell disease.
- This systematic review will reduce the risk of bias by using an independent review process.
- The meta-analysis to be performed will improve the precision of the prevalence of iron deficiency anaemia in women with sickle cell disease.
- Most studies on iron deficiency is sickle cell disease are likely to be done in resource-limited settings, so the pooled prevalence may not reflect reality in other settings.
- Considering that this review will include various study designs, there is a potential risk of heterogeneity in the results.

INTRODUCTION

Sickle cell disease (SCD) is a disease caused by inheritance of a defective haemoglobin gene resulting in red blood cells changing shape in hypoxic conditions and chronic haemolysis (1). SCD is the most common inherited disease worldwide. The world health organization (WHO) reports that approximately 60% of the world's 229 countries are endemically affected with

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haemoglobin disorders(2). About 85% of sickle cell disorders and 70% of SCD affected births occur in Africa (2).

Over 7% of pregnant women worldwide carry a significant haemoglobin gene variant(2). Pregnancies in SCD has been shown to be associated with adverse maternal and foetal outcomes in both low and high income countries (3). Maternal mortality in a previous report has been shown to be about 29 folds higher in pregnant women with SCD when compared to pregnant women without SCD (4). With better understanding of the disease and improved care being given to patients with sickle cell disease, more women with SCD have been reaching reproductive age. Factors capable of influencing morbidity/mortality associated with this condition, thus need to be properly reviewed for clinicians to better advise themselves

The averagely low adult female iron body stores plus increased pregnancy iron requirements often put pregnant women at risk of iron deficiency anaemia (5–8). Iron deficiency anaemia in pregnancy is a known significant contributor to maternal mortality. Daily iron supplementation in pregnancy is recommended by WHO as a proactive measure to reduce anaemia and its associated complications in pregnancy(9). However there are no clear guidelines on this supplementation of iron in the sickle cell disease subpopulation. Absence of available data often leaves clinicians in a dilemma.

In the SCD subpopulation, chronic haemolysis leads to recurrent transfusions and thus risk of iron overload(10). This risk of iron overload amongst patients with SCD and risk of iron deficiency in pregnancy makes supplementation of iron to pregnant sicklers a difficult decision. Several studies have thus been done to evaluate iron stores amongst pregnant women with sickle cell disease with varying outcomes (12–16). We previously provided an opinion on iron supplementation in this subpopulation (11). However the subjective nature of opinion papers makes its recommendations feeble. Harmonising published data in a systematic review and meta-analysis would provide better and more resilient recommendations for supplementation of iron to pregnant women with SCD

Objectives

We aim to systematically review and perform meta-analysis of existing data on iron stores amongst pregnant women with SCD.

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1) To estimate the prevalence of iron deficiency anaemia amongst pregnant women with SCD
2) To assess factors associated with iron deficiency anaemia amongst pregnant women with SCD
3) Evaluate the foetal (birth weight, anaemia, anomalies, stillbirth, neonatal death, and infant death) and maternal outcomes (maternal anaemia, transfusion, preterm delivery, acute complications of SCD, oligohydramnios, and cesarean delivery) among pregnant women with SCD who are supplemented with iron

METHODS

This protocol has been written following guidelines of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (17) available on table 1. It shall be registered on PROSPERO International Prospective Register of Systematic reviews. The study shall be carried for a 6months period (June 20th, 2019 to December 20th 2019).

Eligibility Criteria

We shall include all observational studies and clinical trials from all prior studies till "date of data search end" on iron status in pregnant women with sickle cell disease

We shall exclude;

1) All mini-reviews, commentaries, editorials, case reports and case series with small sample size (<30 participants).
2) Abstracts whose full data would not be available even upon requesting from the author
3) Unpublished manuscripts and conference abstracts
4) Duplicates; studies published with same or different titles in more than one journal; the most updated version shall be considered.

Search strategy and sorting of relevant studies

The search for relevant studies will be done online and shall be done in two ways

Search in electronic bibliographic databases

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The following data sources shall be searched for eligible studies: PubMed, MEDLINE, EMBASE, Google scholar, Africa Journal Online (AJOL), Africa Index Medicus, Popline and the Cochrane library. The search will be done by combining relevant terms related to SCD, iron stores and pregnancy as illustrated in table 2.

Forwards and backwards citation search

Citations in identified studies shall be reviewed for studies with similar objectives. This will be done to identify additional data sources that were missed during the search in bibliographic databases.

Selection procedure for studies to be included in the review

Literature search will be performed independently by two investigators (DA and BMK). Study titles and abstracts will be reviewed and full texts of potentially eligible articles will then be retrieved using EndNote software version X8. Preselected full texts will further be screened for eligibility using a pretested predefined form created on Epi info software version 7.2.2.6. For studies with disagreements between investigators a consensus shall be reached by consulting a 3rd investigator (TN). Publications with ambiguous data shall be resolved by contacting authors by email for clarity. Potentially eligible studies that are excluded will be documented with reasons for exclusion. A detailed Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow chart shall be used to depict the selection process (Figure 1).

Risk of Bias Assessment

Assessment will be done using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute/National Heart, Lung, and Blood Institute (Table 3) for observational studies and the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Tables 4 and 5) for studies which employed a randomized design.

Data Collection Process

A data abstraction sheet will be produced on Epi infos version 7.2.2.6 statistical software and pretested by investigators. Data to be extracted from selected studies shall include; First author, year of publication, country of study population, duration of study, study design and setting,

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mean or median age, sex distribution, sickle cell genotype, gestation age distribution, transfusion history, laboratory test used to measure body iron stores, iron status, mean cell volume, prevalence of iron deficiency anaemia and outcome of foetus and mother. For multinational studies we will separate the results and present them per country.

Statistical Analysis

The data will be analyzed using STATA V.14 statistical software. Random effects meta-analysis models will be reported over fixed-effects models due to the possibility of heterogeneity between the various studies retrieved. The chi-squared test for heterogeneity and the I^2 statistic will be used to assess the degree of heterogeneity among studies. Sensitivity analyses will be conducted to obtain pooled effects from different study designs (randomized controlled trials, cross-sectional, case-control and cohort study designs and the different diagnostic tests used to measure iron deficiency).

For objective one, a pooled prevalence for the proportion of pregnant women with SCD will be obtained if two or more studies provide this measure. Prevalence of iron deficiency anaemia among pregnant women with SCD will further be categorised as per diagnostic method of iron stores. Subgroup analysis to determine the prevalence of iron deficiency anaemia in the various regions (Africa, Europe, North America, South America, the Middle East and Asia) will also be performed.

Similarly, for objective two, if two or more studies report on a factor associated with SCD in pregnancy and provide a measure of effect for this relationship (odds ratio); a subgroup analysis will be carried out. The various maternal and foetal outcomes of SCD in pregnancy will be described qualitatively.

Report and amendment of the review

The systematic review and meta-analysis will be presented according to the PRISMA 2015 guidelines using the PRISMA checklist which will be published with the final report. No amendments are intended for this protocol; however, any amendments shall be clearly documented.

Patient and Public Involvement

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There will be no involvement of patients or the public in this review

CONCLUSIONS

There is controversial evidence regarding the role of iron supplementation in pregnant women with SCD and the associated pregnancy outcomes. Summarizing existing data on this issue through a comprehensive review is of utmost importance given that the majority of persons with SCD live in low income areas, regions characterized by profligate use of iron supplements as well as an alarming lack of appropriate resources to guide clinicians on how to use iron supplements in pregnant sicklers.

Ethics and dissemination

Ethical clearance is not required as the current review will be based on published data. We intend to publish the final manuscript as an original article in a peer reviewed journal. Review findings will be presented at conferences, to concerned institutions and submitted to relevant health authorities. Regular updates of this review will be done as needed.

List of abbreviations

SCD: sickle cell disease; WHO: World Health Organization; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

Author Contributions

DA conceived the manuscript. DA, BMK and TN wrote and reviewed the manuscript. All authors approved the final version of the manuscript

Data statement

Not applicable

Competing interest

None declared

Funding

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There was no funding for the writing of this protocol

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deficiency anemia. Geneva Ina WHO, UNICEF; 1998;

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Tables

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Table 1: PRISMA-P 2015 checklist for the study protocol of a systematic review on iron stores in pregnant women with sickle cell disease.

Section and topic	Item No	Checklist item	Page
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3&4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10&11

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Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4&5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
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Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

Table 2:Search strategy for MEDLINE and adaptability to other databases

Search	Items
1	Sickle cell disease OR Sickle cell anaemia OR sickle cell anemia OR sickle cell

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	haemoglobinopathy OR haemoglobinopathy OR hemoglobinoathy OR abnormal haemoglobin OR abnormal haemoglobin OR sickler OR sicle cell OR Drepanocytosis OR HbSS OR HbSC OR SCD OR SS OR SC
2	Pregnancy OR Gestation OR Pregnant OR Gestational age OR gravidity OR gravid OR Expectant mothers OR trimester
3	Iron status OR iron stores OR iron supplementation OR serum iron OR iron deficiency OR serum ferritin OR bone marrow stainable iron OR Total iron binding capacity OR transferrin OR iron overload OR microcytic anaemia OR microcytic anemia OR anaemia OR anemia OR iron deficiency anaemia OR iron deficiency anemia OR low body iron OR body iron OR low serum iron OR high serum iron OR high body iron OR normal serum iron OR normal body iron OR iron OR blood iron OR iron indices OR body iron indices OR serum iron indices OR Iron OR ferritin
4	#1 and #2 and #3

Table 3: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Developed by the National Heart, Lung and Blood Institute (NHLBI)

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			

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6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			
Quality Rating (Good, Fair, or Poor) (see guidance)			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

*CD, cannot determine; NA, not applicable; NR, not reported

Table 4: Cochrane Risk of Bias Tool - *Cochrane Collaboration modified tool for assessing risk of bias for RCT's, PART I*

Using the guidance provided at the end of this form, select either "high", "low" or "unclear" for each judgment. When complete, proceed to **Part II of the Quality Assessment Form REF ID:**

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Domain	Description	High risk of bias	Low risk of bias	Unclear risk of bias	Reviewer Assessment
Selection bias ***Random sequence generation***	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. **Reviewer Comments:**	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**Judgement Random sequence generation** □ **High** □ **Low** □ **Unclear**
Selection bias ***Allocation concealment***	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment. **Reviewer Comments:**	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	Intervention allocations likely could not have been foreseen in advance of, or during, enrollment	Not described in sufficient detail	**Judgement Allocation concealment** □ **High** □ **Low** □ **Unclear**
Reporting bias ***Selective reporting***	Stated how the possibility of selective outcome reporting was examined by the authors and what was found. **Reviewer Comments:**	Reporting bias due to selective outcome reporting.	Selective outcome reporting bias not detected	Insufficient information to permit judgement (*It is likely that the majority of studies will fall into this category.)*	**Judgement Selective reporting** □ **High** □ **Low** □ **Unclear**

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Other bias ***Other sources of bias***	Any important concerns about bias not addressed above. If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry. **Reviewer Comments:**	Bias due to problems not covered elsewhere in the table.	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.	**Judgement Other sources of bias** □ **High** □ **Low** □ **Unclear**

Use this form to assess risk of bias for randomized controlled trials.
Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).
Risk of selection, reporting, and other bias are assessed in the **Quality Assessment Form Part I.**
Risk of performance, detection, and attrition bias are assessed using the **Quality Assessment Form Part II.**

Table 5: Cochrane Collaboration modified tool for assessing risk of bias for RCT's, PART II

Risk of bias for the domains in the Form Part II will be assessed for each main or class of outcomes. Please indicate the specific outcome and complete the assessment for each. **REF ID:**					
Outcomes:					
Domain	**Description**	**High risk of bias**	**Low risk of bias**	**Unclear risk of bias**	**Reviewer Assessment**
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**Judgement Blinding (participants and personnel)** □ **High** □ **Low** □ **Unclear**

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	whether the intended blinding was effective. **Reviewer Comments:**				
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective. **Reviewer Comments:**	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**Judgement Blinding (outcome assessment)** □ **High** □ **Low** □ **Unclear**
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported. **Reviewer Comments:**	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided)	**Judgement Incomplete outcome data** □ **High** □ **Low** □ **Unclear**

Use this form to assess risk of bias for randomized controlled trials.

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Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains of bias (selection, performance, attrition, reporting, and other).
Using the guidance provided at the end of this form, select either “high”, “low” or “unclear” for each judgement.

Figure Legends

Figure 1: PRISMA P flow diagram

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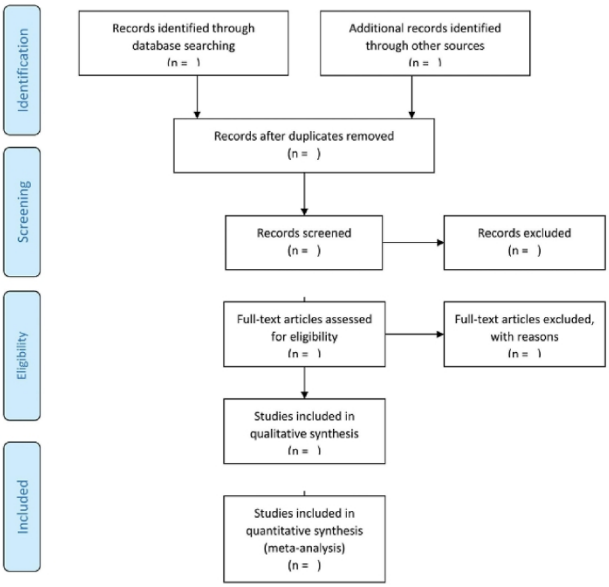

Figure 1: PRISMA P flow diagram

215x279mm (300 x 300 DPI)

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Section and topic	Item No	Checklist item	Page
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3&4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10&11
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4&5

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nt			
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

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Iron stores in pregnant women with sickle cell disease. A protocol for a systematic review and meta-analysis

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Keywords:	HAEMATOLOGY, Anaemia < HAEMATOLOGY, Prenatal diagnosis < OBSTETRICS, PUBLIC HEALTH

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Iron stores in pregnant women with sickle cell disease. A protocol for a systematic review and meta-analysis

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Word counts: abstract: 266, main text: 1567, tables: 6, figures: 1

ABSTRACT

Introduction: Sickle cell disease (SCD) is the most common inherited disease worldwide. The greatest disease burden is seen in sub Saharan Africa. Early diagnosis and improved care of people living with SCD have led to an increase in the number of women with SCD reaching the reproductive age. Iron deficiency anaemia remains the most common cause of anaemia in pregnancy, affecting 51 to 63% of pregnancies in Africa. However, the unavailability of guidelines on supplementation of iron in this pregnant subpopulation often leaves clinicians in a fix. We propose to conduct the first systematic review and possibly a meta-analysis on the prevalence, associated factors and maternal/foetal outcomes of iron deficiency anaemia among pregnant women with SCD.

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Methods and analysis: We will search the following electronic databases; PubMed, MEDLINE, EMBASE, Google scholar, Africa Journal Online (AJOL), Africa Index Medicus, Popline and the Cochrane library: for studies on the iron status of pregnant women with SCD. After the selection of eligible studies from the search output, review of full text, extraction of data and data synthesis will be performed. Studies obtained from the review shall be evaluated for quality, risk of bias and heterogeneity. Felicitous statistical methods shall be used to pool prevalence estimates for matching studies globally and in subpopulations. This protocol has been reported as per the 2015 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.

Ethics and Dissemination: There is no requirement for ethical approval as the proposed study will use published data. The findings of this study will be published in a peer review journal and will be presented at conferences.

Review registration number: CRD42018109803

Key words: sickle cell disease, iron status, pregnancy, protocol, systematic review/meta-analysis

Strengths and Limitations

- This review will be the first to summarise published data on the iron status of pregnant women with sickle cell disease.
- This systematic review will reduce the risk of bias by using an independent review process.
- The meta-analysis to be performed will improve the precision of the prevalence of iron deficiency anaemia in women with sickle cell disease.
- Most studies on iron deficiency in people with sickle cell disease are likely to be done in resource-limited settings, so the pooled prevalence may not reflect reality in other settings.
- Considering that this review will include various study designs, there is a potential risk of heterogeneity in the results.

INTRODUCTION

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Sickle cell disease (SCD) is a disease caused by inheritance of a defective haemoglobin gene resulting in red blood cells changing shape in hypoxic conditions and subsequent chronic haemolysis (1). SCD is the most common inherited disease worldwide. The World Health Organization (WHO) reports that approximately 60% of the world's 229 countries are endemic for haemoglobin disorders(2). About 85% of sickle cell disorders and 70% of SCD affected births occur in Africa (2).

Over 7% of pregnant women worldwide carry a significant haemoglobin gene variant(2). Pregnancies in women with SCD have been shown to be associated with adverse maternal and foetal outcomes (3). Maternal mortality in a previous report was shown to be about 29 times higher in pregnant women with SCD when compared with pregnant women without SCD (4).

Better understanding of the disease pathology and improved patient care has led to more women with SCD reaching reproductive age. Factors capable of influencing the morbidity of this condition need to be properly reviewed to guide clinical case management.

The low adult female iron body stores in tandem with increased pregnancy iron requirements often put pregnant women at risk of iron deficiency anaemia (5–8). Iron deficiency anaemia in pregnancy is a known significant contributor to maternal mortality. Daily iron supplementation in pregnancy is recommended by WHO as a proactive measure to reduce anaemia and its associated complications in pregnancy(9). However, there are no clear guidelines on iron supplementation in the SCD subpopulation. In the SCD subpopulation, chronic haemolysis leads to recurrent transfusions and a risk of iron overload(10). This risk of iron overload amongst patients with SCD and risk of iron deficiency in pregnancy makes supplementation of iron in pregnant women with SCD a difficult decision. Several studies have been done to evaluate iron stores amongst pregnant women with SCD with varying outcomes (11–15). We previously provided recommendations on iron supplementation in this subpopulation (16). Harmonising published data in a systematic review and meta-analysis would provide better and more resilient recommendations on this issue

Objectives

We aim to systematically review existing data on iron stores amongst pregnant women with SCD. The specific objectives are:

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1) To estimate the prevalence of iron deficiency anaemia among pregnant women with SCD;
2) To assess socio-demographic, obstetric and clinical factors associated with iron deficiency anaemia amongst pregnant women with SCD;
3) To evaluate the foetal (birth weight, anaemia, anomalies, stillbirth, neonatal death, and infant death) and maternal outcomes (maternal anaemia, transfusion, preterm delivery, acute complications of SCD, oligohydramnios, cesarean delivery and maternal mortality) among pregnant women with SCD who are iron deficient

METHODS

This protocol has been written following the guidelines of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (17) available in table 1. The protocol has been e registered on the PROSPERO International Prospective Register of Systematic reviews. The study shall be carried for a period of 6 months from the date of publication of this protocol.

Eligibility Criteria

We shall include all observational studies and clinical trials with evidence on the iron status in pregnant women with sickle cell disease as illustrated on table 2 (18).

Search strategy

The search for relevant studies will be done online;

Electronic sources; The following databases shall be searched for eligible studies: PubMed, MEDLINE, EMBASE, Google scholar, Africa Journal Online (AJOL), Africa Index Medicus, Popline and the Cochrane library. We will search for all studies from inception to the present. The search will be done by combining relevant terms related to SCD, iron stores and pregnancy as illustrated in table 3.

References in the identified studies shall be reviewed for articles with similar objectives. This will be done to identify additional data sources that were missed during the search in bibliographic databases.

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Study screening

The literature search will be performed independently by two investigators (DA and BMK). The titles and abstracts will be reviewed and the full texts of potentially eligible articles will be retrieved using EndNote software version X8. Preselected full texts will be screened for eligibility using a pretested predefined form created on Epi info software version 7.2.2.6. For studies with disagreements between the investigators, arbitration will be done by a third investigator (TN). Publications with ambiguous data shall be resolved by contacting authors by email for clarity.

Potentially eligible studies that are excluded will be documented with the various reasons for exclusion. A detailed Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow chart shall be used to depict the selection process (Figure 1).

Risk of Bias Assessment

Two reviewers (DA & BMK) will independently assess the methodological quality and the risk of bias for each included study. Assessment will be done using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute/National Heart, Lung, and Blood Institute (Table 4) for observational studies and the Cochrane Risk of Bias Tool for Randomized Controlled Trials (Tables 5 and 6) for studies which used a randomized design.

Data extraction

A data abstraction sheet produced on Epi info version 7.2.2.6 statistical software and pretested by investigators will be used to extract the data from selected studies. Data to be extracted will include; the name of the first author, year of publication, country of study population, duration of study, study design and setting, mean or median age, sex distribution, sickle cell genotype, gestational age distribution, transfusion history, laboratory test used to measure body iron stores, iron status, mean cell volume, prevalence of iron deficiency anaemia and the outcome of the foetus and mother. For multinational studies we will separate the results and present them per country.

Data synthesis and analysis

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The data will be analysed using STATA V.14 statistical software. Random effects meta-analysis models will be reported over fixed-effects models due to the possibility of heterogeneity between the various studies retrieved. The chi-squared test for heterogeneity and the I^2 statistic will be used to assess the degree of heterogeneity among studies. Sensitivity analyses will be conducted to obtain pooled effects from different study designs (randomized controlled trials, cross-sectional, case-control and cohort study designs and the different diagnostic tests used to measure iron deficiency).

For objective one, a pooled prevalence for the proportion of pregnant women with SCD will be obtained if two or more studies provide this measure. Prevalence of iron deficiency anaemia among pregnant women with SCD will further be categorised as per diagnostic method of iron stores. Subgroup analysis to determine the prevalence of iron deficiency anaemia in the various regions (Africa, Europe, North America, South America, the Middle East and Asia) will also be performed.

Similarly, for objective two, if two or more studies report on a factor associated with SCD in pregnancy and provide a measure of effect for this relationship (odds ratio); a subgroup analysis will be carried out. The various maternal and foetal outcomes of SCD in pregnancy will be described qualitatively.

Presentation and reporting of results

The systematic review and meta-analysis will be presented according to the PRISMA 2015 guidelines using the PRISMA checklist which will be published with the final report. No amendments are intended for this protocol; however, any amendments shall be clearly documented.

Patient and Public Involvement

There will be no involvement of patients or the public in this review

CONCLUSIONS

There is controversial evidence regarding the role of iron supplementation in pregnant women with SCD and the associated pregnancy outcomes. Summarizing existing data on this issue

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through a comprehensive review is of utmost importance as a majority of persons with SCD live in low income areas, regions characterized by profligate use of iron supplements as well as an alarming lack of appropriate resources to guide clinicians on how to use these supplements in pregnant women with SCD.

Ethics and dissemination

Ethical clearance is not required as the current review will be based on published data. We intend to publish the final manuscript as an original article in a peer reviewed journal. Review findings will be presented at conferences, to concerned institutions and submitted to relevant health authorities. Regular updates of this review will be done as needed.

List of abbreviations

SCD: sickle cell disease; WHO: World Health Organization; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

Author Contributions

DA conceived the manuscript. DA, BMK and TN wrote and reviewed the manuscript. All authors approved the final version of the manuscript

Data statement

Not applicable

Competing interest

None declared

Funding

There was no funding for the writing of this protocol

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Tables

Table 1: PRISMA-P 2015 checklist for the study protocol of a systematic review on iron stores in pregnant women with sickle cell disease.

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Section and topic	Item No	Checklist item	Page
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3&4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10&11
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4&5

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nt			
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
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Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

Table 2; Inclusion and Exclusion criteria

PICOS strategy(18)	**Inclusion criteria**	**Exclusion criteria**
P-population	Pregnant women with sickle cell disease (SCD)	Pregnant women who do not have SCD
I-	Iron deficiency among pregnant	

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intervention/exposure	women with SCD	
C-comparison	Pregnant women with SCD who are not iron deficient	
O-outcome(s)	foetal (birth weight, anaemia, anomalies, stillbirth, neonatal death, and infant death) and maternal outcomes (maternal anaemia, transfusion, preterm delivery, acute complications of SCD, oligohydramnios, and cesarean delivery) among pregnant women with SCD who are iron deficient	Studies which fail to report foetal and or maternal outcomes
S-study design	All observational studies and clinical trials	1) All mini-reviews, commentaries, editorials, case reports and case series with small sample size. 2) Abstracts whose full data would not be available even upon requesting from the authors 3) Unpublished manuscripts and conference abstracts 4) Duplicates; studies published with same or different titles in more than one journal; the most updated version shall be considered.

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Table 3: Search strategy for MEDLINE and adaptability to other databases

Searches	Search combinations	Search terms	Number of hits
S1		(MH "Anemia, Sickle Cell+") OR (MH "Sickle Cell Trait")	
S2		"Sickle cell anaemia" OR "sickle cell anemia" OR "sickle cell trait" OR "Sickle cell disease" OR "sickle cell haemoglobinopathy" OR "haemoglobinopathy" OR "hemoglobinoathy" OR "abnormal haemoglobin" OR "abnormal haemoglobin" OR "sickler" OR "sicle cell" OR "Drepanocytosis" OR "HbSS" OR "HbSC" OR "SCD" OR "SS" OR "SC"	
S3	S1 OR S2		
S4		(MH "Pregnancy+") OR (MH "Pregnancy Outcome+") OR (MH "Pregnancy Trimesters+") OR (MH "Pregnancy Complications+")	
S5		"Pregnan*" OR "pregnancy outcome" OR "pregnancy trimesters" OR "pregnancy complications" OR "Gestation*" OR Pregnant OR "Gestation age" OR "gravid*" OR "Expect* mother" OR "trimester" OR "parity"	
S6	S4 OR S5		
S7		(MH "Iron+") OR (MH "Iron, Dietary") OR (MH "Iron Overload+") OR (MH "Dietary Supplements+") OR (MH "Anemia, Iron-Deficiency")	
S8		Iron OR "diet* iron" OR "Iron overload" OR "dietary supplement*" OR "iron deficiency anaemia" OR "iron deficiency anemia" OR "iron status" OR "iron stores" OR "iron supplementation" OR "serum iron" OR	

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	"iron deficiency" OR "serum ferritin" OR "bone marrow stainable iron" OR "total iron binding capacity" OR "transferrin" OR "iron overload" OR "microcytic anaemia" OR "microcytic anemia" OR "anaemia" OR "anemia" OR OR "low body iron" OR "body iron" OR "low serum iron" OR "high serum iron" OR "high body iron" OR "normal serum iron" OR "normal body iron" OR OR "blood iron" OR "iron indices" OR "body iron indices" OR "serum iron indices" OR OR "ferritin"
S9	S7 OR S8
S10	S3 AND S6 AND S9

Table 4: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Developed by the National Heart, Lung and Blood Institute (NHLBI)

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			

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6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			
Quality Rating (Good, Fair, or Poor) (see guidance)			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

*CD, cannot determine; NA, not applicable; NR, not reported

Table 5: Cochrane Risk of Bias Tool - *Cochrane Collaboration modified tool for assessing risk of bias for RCT's, PART I*

Using the guidance provided at the end of this form, select either "high", "low" or "unclear" for each judgment. When complete, proceed to **Part II of the Quality Assessment Form REF ID:**

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Domain	Description	High risk of bias	Low risk of bias	Unclear risk of bias	Reviewer Assessment
Selection bias ***Random sequence generation***	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. **Reviewer Comments:**	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**Judgement Random sequence generation** □ **High** □ **Low** □ **Unclear**
Selection bias ***Allocation concealment***	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment. **Reviewer Comments:**	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	Intervention allocations likely could not have been foreseen in advance of, or during, enrollment	Not described in sufficient detail	**Judgement Allocation concealment** □ **High** □ **Low** □ **Unclear**
Reporting bias ***Selective reporting***	Stated how the possibility of selective outcome reporting was examined by the authors and what was found. **Reviewer Comments:**	Reporting bias due to selective outcome reporting.	Selective outcome reporting bias not detected	Insufficient information to permit judgement (*It is likely that the majority of studies will fall into this category.)*	**Judgement Selective reporting** □ **High** □ **Low** □ **Unclear**

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Other bias ***Other sources of bias***	Any important concerns about bias not addressed above. If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry. **Reviewer Comments:**	Bias due to problems not covered elsewhere in the table.	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.	**Judgement Other sources of bias** □ **High** □ **Low** □ **Unclear**

Use this form to assess risk of bias for randomized controlled trials.
Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).
Risk of selection, reporting, and other bias are assessed in the **Quality Assessment Form Part I.**
Risk of performance, detection, and attrition bias are assessed using the **Quality Assessment Form Part II.**

Table 6: Cochrane Collaboration modified tool for assessing risk of bias for RCT's, PART II

Risk of bias for the domains in the Form Part II will be assessed for each main or class of outcomes. Please indicate the specific outcome and complete the assessment for each. **REF ID:**					
Outcomes:					
Domain	**Description**	**High risk of bias**	**Low risk of bias**	**Unclear risk of bias**	**Reviewer Assessment**
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**Judgement Blinding (participants and personnel)** □ **High** □ **Low** □ **Unclear**

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	whether the intended blinding was effective. **Reviewer Comments:**				
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective. **Reviewer Comments:**	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**Judgement Blinding (outcome assessment)** □ **High** □ **Low** □ **Unclear**
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported. **Reviewer Comments:**	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided)	**Judgement Incomplete outcome data** □ **High** □ **Low** □ **Unclear**

Use this form to assess risk of bias for randomized controlled trials.

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Bias is assessed as a judgement (high, low, or unclear) for individual elements from five domains of bias (selection, performance, attrition, reporting, and other).
Using the guidance provided at the end of this form, select either “high”, “low” or “unclear” for each judgement.

Figure Legends

Figure 1: PRISMA P flow diagram

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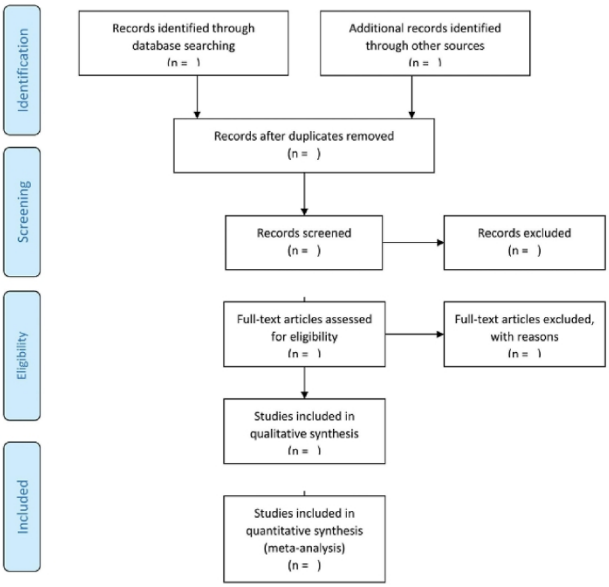

Figure 1: PRISMA P flow diagram

215x279mm (300 x 300 DPI)

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Section and topic	Item No	Checklist item	Page
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
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