BMJ Open Iron stores in pregnant women with sickle cell disease: a protocol for a systematic review and meta-analysis

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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%–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/fetal outcomes of iron deficiency anaemia among pregnant women with SCD.

Methods and analysis We will search the following electronic databases for studies on the iron status of pregnant women with SCD: PubMed, MEDLINE, EMBASE, Google Scholar, African Journals Online, African Index Medicus, Popline and the Cochrane Library. After the selection of eligible studies from the search output, review of full text, data extraction and data synthesis will be performed. Studies obtained from the review shall be evaluated for quality, risk of bias and heterogeneity. Appropriate 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 guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.

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-reviewed journal and will be presented at conferences.

Trial registration number CRD42018109803.

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 subsequent chronic haemolysis.¹ SCD is the most common inherited disease worldwide. The 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

Strengths and limitations of this study

- 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.

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 fetal 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 have 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

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 number	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, email 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, timeframe) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review.	3 and 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 and 11
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review.	4 and 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 (ie, 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 preplanned data assumptions and simplifications.	5
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation 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

Continued

Table 1 Continued

Section and topic	Item number	Checklist item	Page
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 Grading of Recommendations Assessment, Development and Evaluation (GRADE)).	5

N/A, not applicable; PRISMA-P, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.

subpopulation, chronic haemolysis leads to recurrent transfusions and a risk of iron overload.¹⁰ This risk of iron overload among patients with SCD and risk of iron deficiency in pregnancy make supplementation of iron in pregnant women with SCD a difficult decision. Several studies have been done to evaluate iron stores among 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 among pregnant women with SCD. The following are the specific objectives:

1. To estimate the prevalence of iron deficiency anaemia among pregnant women with SCD.
2. To assess sociodemographic, obstetric and clinical factors associated with iron deficiency anaemia among pregnant women with SCD.
3. To evaluate fetal (birth weight, anaemia, anomalies, stillbirth, neonatal death and infant death) and maternal (maternal anaemia, transfusion, preterm delivery, acute complications of SCD, oligohydramnios,

caesarean delivery and maternal mortality) outcomes 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 2015 checklist,¹⁷ available in [table 1](#). The protocol has been registered on the PROSPERO International Prospective Register of Systematic Reviews (registration ID: CRD42018109803). The study shall be carried out 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 SCD, as illustrated in [table 2](#).¹⁸ There will be no language limitation.

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,

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: intervention/exposure	Iron deficiency among pregnant women with SCD.	
C: comparison	Pregnant women with SCD who are not iron-deficient.	
O: outcome(s)	Fetal (birth weight, anaemia, anomalies, stillbirth, neonatal death and infant death) and maternal (maternal anaemia, transfusion, preterm delivery, acute complications of SCD, oligohydramnios and caesarean delivery) outcomes among pregnant women with SCD who are iron-deficient.	Studies which fail to report fetal and or maternal outcomes.
S: study design	All observational studies and clinical trials.	<ul style="list-style-type: none"> ▶ All mini-reviews, commentaries, editorials, case reports and case series with small sample size. ▶ Abstracts whose full data would not be available even on requesting from the authors. ▶ Unpublished manuscripts and conference abstracts. ▶ Duplicates; studies published with same or different titles in more than one journal; the most updated version shall be considered.

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 "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 "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 "blood iron" OR "iron indices" OR "body iron indices" OR "serum iron indices" OR "ferritin"	
S9	S7 OR S8		
S10	S3 AND S6 AND S9		

African Journals Online, African 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.

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 V.X8 software. Preselected full texts will be screened for eligibility using a pretested predefined form created on Epi Info V.7.2.2.6 software. 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 Reviews and Meta-Analyses (PRISMA) flow chart shall be used to depict the selection process ([figure 1](#)).

Risk of bias assessment

Two reviewers (DA and 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

Figure 1 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols flow diagram.

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

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?			
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 (eg, 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):			
Developed by the National Heart, Lung, and Blood Institute. CD, cannot determine; NA, not applicable; NR, not reported.			

observational studies, and the Cochrane Risk of Bias Tool for Randomized Controlled Trials (tables 5 and 6) for studies which used a randomised design.

Data extraction

A data abstraction sheet produced on Epi Info V.7.2.2.6 statistical software and pretested by investigators will be used to extract 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 fetus and the mother. For multinational studies we will separate the results and present them per country.

Data synthesis and analysis

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 χ^2 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 (randomised controlled trials, cross-sectional, case-control and cohort study designs and the different diagnostic tests used to measure iron deficiency).

For objective 1, 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

Table 5 Cochrane Risk of Bias Tool: Cochrane Collaboration modified tool for assessing risk of bias for randomised controlled trials, part I

Using the guidance provided at the end of this form, select either 'high', 'low' or 'unclear' for each judgement. 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
<i>Selection bias</i> 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 randomised sequence.	Random sequence generation method should produce comparable groups.	Not described in sufficient detail.	Judgement Random sequence generation ► High. ► Low. ► Unclear.
<i>Selection bias</i> 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, enrolment. 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, enrolment.	Not described in sufficient detail.	Judgement Allocation concealment ► High. ► Low. ► Unclear.
<i>Reporting bias</i> 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 (<i>It is likely that the majority of studies will fall into this category.</i>).	Judgement Selective reporting ► High. ► Low. ► Unclear.
<i>Other bias</i> Other sources of bias	Any important concerns about bias not addressed above. If particular questions/entries were prespecified 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 randomised 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*.

of iron deficiency anaemia in various regions (Africa, Europe, North America, South America, the Middle East and Asia) will also be performed.

Similarly, for objective 2, if two or more studies report on a factor associated with SCD in pregnancy and provide a measure of effect for this relationship (OR), a subgroup analysis will be carried out. The various maternal and fetal 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.

ETHICS AND DISSEMINATION

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.

Table 6 Cochrane Collaboration modified tool for assessing risk of bias for randomised controlled trials, part II

Using the guidance provided at the end of this form, select either 'high', 'low' or 'unclear' for each judgement. Risk of bias for the domains in the Quality Assessment 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
<i>Performance bias</i> 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.
<i>Detection bias</i> 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.
<i>Attrition bias</i> 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 randomised 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 judgement of 'Low risk' or 'High risk' (eg, number randomised not stated, no reasons for missing data provided).	Judgement Incomplete outcome data ► High. ► Low. ► Unclear.

Use this form to assess risk of bias for randomised 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).

CONCLUSIONS

There is controversial evidence regarding the role of iron supplementation in pregnant women with SCD and the associated pregnancy outcomes. Summarising existing data on this issue through a comprehensive review is of utmost importance as a majority of persons with SCD live in low-income areas, regions characterised 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.

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

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical clearance is not required as the current review will be based on published data.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. Boga C, Ozdogu H. Pregnancy and sickle cell disease: a review of the current literature. *Crit Rev Oncol Hematol* 2014;2016:364–74.

2. Modell B. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ* 2008;2008:480–7.
3. Boافر TK, Olayemi E, Galadanci N, *et al.* Pregnancy outcomes in women with sickle-cell disease in low and high income countries: a systematic review and meta-analysis. *BJOG: Int J Obstet Gy* 2016;123:691–8.
4. Muganyizi PS, Kidanto H. Sickle cell disease in pregnancy: trend and pregnancy outcomes at a tertiary hospital in Tanzania. *PLoS One* 2013;8:e56541.
5. Boturão-Neto E, Marcopito LF, Zago MA. An Overview, Iron Metabolism. In: Arora S, ed. *Iron metabolism in humans*. InTech, 2012: 3–23.
6. Milman N, Taylor CL, Merkel J, *et al.* Iron status in pregnant women and women of reproductive age in Europe. *Am J Clin Nutr* 2017;106(Suppl 6):1655S–62.
7. Fisher AL, Nemeth E. Iron homeostasis during pregnancy. *Am J Clin Nutr* 2017;106(Suppl 6):1567S–74.
8. Cunningham FG, Pritchard JA, Mason R, *et al.* Prophylactic transfusions of normal red blood cells during pregnancies complicated by sickle cell hemoglobinopathies. *Am J Obstet Gynecol* 1979;135:994–1003.
9. Stoltzfus RDM. *Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia*. Geneva Ina WHO, UNICEF, 1998.
10. Serjeant G. Management of sickle cell disease: challenges and risks of transfusion. *Int J Clin Transfus Med* 2016;4:109–19.
11. Koduri PR. Iron in sickle cell disease: a review why less is better. *Am J Hematol* 2003;73:59–63.
12. Akinyanju OO, Nnatu SN, Ogedengbe OK. Antenatal iron supplementation in sickle cell disease. *Int J Gynaecol Obstet* 1987;25:433–6.
13. Oluboyede OA. Iron studies in pregnant and non-pregnant women with haemoglobin SS or SC disease. *Br J Obs Gynaecol* 1980;87:989–96.
14. Mohanty D, Mukherjee MB, Colah RB, *et al.* Iron deficiency anaemia in sickle cell disorders in India. *Indian J Med Res* 2008;127:366–9.
15. Vichinsky E, Kleman K. Steven Embury and BL. the diagnosis of iron deficiency anemia in sickle cell disease. *Blood* 1981;58:963–8.
16. Aroke D, Tchouakam DN, Kadia BM, *et al.* Iron supplementation in pregnant sicklers: an opinion. *BMC Pregnancy Childbirth* 2018;18:256.
17. Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
18. O'Connor D, Higgins JP, Green S. Chapter 5; defining the review question and developing criteria for including studies. in: cochrane Handbook for systematic reviews of interventions. *The Cochrane Collaboration* ® 2008:84–94.