Prevalence and incidence of congenital anomalies amongst babies born to women with sickle cell disease and exposed to hydroxyurea during pregnancy: a systematic review protocol

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Review question/objective: What is the prevalence and incidence of congenital anomalies among babies born to women with sickle cell disease (SCD) and who have been exposed to hydroxyurea (HU) therapy at any time in their pregnancy?
The objective of this review is to identify the proportion of babies born with congenital anomalies among babies born to mothers with SCD who have been exposed to HU therapy at any point during pregnancy and to describe the specific types of congenital anomalies encountered.

Keywords sickle cell disease; hydroxyurea; congenital anomalies; pregnancy

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Introduction

Sickle cell disease (SCD) is a recessively inherited hemoglobinopathy characterized by distortion of the red blood cell into a characteristic sickle shape that is easily hemolyzed during periods of low oxygen tension. Its clinical presentation includes painful crises and manifestations of end organ damage as a consequence of chronic anemia, hemolysis and microvascular occlusion.[1]

The global distribution of SCD closely mirrors that of malaria; this is due to inherent protection against malaria and hence evolutionary selection of sickle cell trait (SCT).[2,3] Several mechanisms for this protection have been postulated; these include a reduction in parasite growth in sickled erythrocytes, increased phagocytosis of sickled infected erythrocytes and a reduction in severe malaria due to reduced cytoadherence of the affected red cells.[4] The malaria endemic region coincides with the middle- and low-income countries in Sub Saharan Africa (SSA), South America and India. It is estimated that the prevalence of SCT ranges between 10%–40% in the tropics, and the global number of heterozygous individuals is 50 million.[5,6] The number of neonates born with SCD was approximated at 300,000 in 2010 and is projected to increase to over 400,000 by 2050.[7]

General improvement in infant and child health in countries with high prevalence of SCD, in addition to improved survival of children with SCD due to the adoption of new treatment modalities, has led to a higher global burden of sickle cell anaemia.[5] Migration, initially during the slave trade and currently due to economic reasons, has led to more children being born with SCD in high income countries where healthcare is better, further improving survival into the post-child age.[8,9] In some parts of SSA it is estimated that SCD accounts for approximately 6% of the mortality in children, some undiagnosed.[8]

Universal screening of at risk populations with early onset of treatment in the pediatric population has led to improved survival rates especially in the Western world, where presently all children with SCD have a chance of survival to adulthood.[10] Transition for sickle cell patients from childhood to adulthood is fraught with danger, with data suggesting that mortality for sickle cell patients aged between 20 and 25 years is double that of those aged between 15 and 19 years.[8] The selection of the SCT

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by malaria and its global spread through migration, makes the chance of it being encountered by practitioners likely, even in areas that are traditionally of low endemicity for malaria or SCD prevalence. The improving survival rates in childhood in the face of high mortality in adulthood calls for more research into protocols for treating sickle cell anemia (SCA) in adults and conditions associated with adulthood, such as pregnancy.

Management for SCD has largely been aimed at avoiding the triggers of sickle cell crises and management of pain when crises occur; rehydration, blood transfusion, prophylactic antibiotics and vaccinations are some of the interventions used.[1] Transplantation of hematopoietic stem cells has been shown to be curative for SCD and recipients have been known to have event free survival rates of up to 80%.[10] The best results are obtained when transplants are done in early life before the need for blood transfusion and the onset of end organ damage.[10] Gene therapy using autologous stem cells can potentially cure SCD and obviate the need for matching donors. These advances in the treatment of pediatric patients emphasize the need for a corresponding increase in expertise in treating older patients and in handling SCD in conditions that are associated with adulthood and advanced age.[2,5]

Hydroxyurea (HU), also known as hydroxycarbamide, is an anticancer medication that inhibits ribonucleotide reductase. It is a cheap, orally administered bone marrow suppressant that has been shown to raise the level of fetal hemoglobin (HbF). The polymerization of sickle cell hemoglobin (HbS) in low oxygen tension, which is the basis of pathology in SCD, is reduced by the presence of HbF, the reduction in propensity for the red blood cells (RBC) to sickle being proportionate to the concentration of HbF. Hydroxyurea thereby lends itself as a drug for managing SCD.[1]

Additional HU mechanisms of action include modifying the interaction between endothelium and RBCs and the rheological properties of HbS containing RBCs.[11] The beneficial effects of HU precede the rise in HbF, implying other mechanisms of action beyond induction of precursor hemoglobin.[11] These may include myelosuppression, and local vasodilation caused by nitric oxide released when HU is metabolized. It is the only drug approved in the United States (US) and Europe for the management of SCD.[2,6]

Studies have shown that HU leads to reduction in painful crises, acute chest syndrome, elevation in Hb and a reduced need for transfusion.[11-13] These beneficial effects are demonstrable without having to attain the maximum tolerable dose, and therefore there is a reduced risk of adverse effects. Nonetheless, reduction in stroke, leg ulcers, priapism, osteonecrosis and splenic sequestration has not been well demonstrated.[11]

Pregnant women with SCD have increased fetal and maternal morbidity, painful crisis being a severe complication. Hypertransfusion, rehydration, steroid therapy, analgesia and oxygen have been used to control the disease in pregnancy, however there are no standardized treatment protocols or dosing recommendations for the management of SCD and crises in pregnancy. Neither are there clinical trials that can guide recommendations.[14]

Hydroxyurea has been shown to be mutagenic, teratogenic and carcinogenic in animals, precluding its use in pregnancy and individuals desiring conception.[13,15] Murine studies have shown that the fetuses of pregnant mice given hydroxyurea develop central nervous system (CNS) anomalies, most frequently exencephaly and encephalocoeles. Cleft lip, cleft palate and skeletal defects of the limbs and tail have also been observed.[16] The rats have tolerated doses of up to 2000 milligrams (mg) per kilogram (kg) of body weight, fetal resorption has occurred at 500 mg and malformations have been seen at doses in excess of 250 mg/kg body weight.[16] However, dosages used in these animal studies are 10 to 100 times the maximum recommended therapeutic doses in humans and therefore the effects on humans should be interpreted with caution.[13,15] Some severe forms of anomalies such as necrosis of the spinal cord, in murine specimens, have been shown to be preventable by the concurrent administration of colchicine or deoxycytidine monophosphate.[17] In this review we seek to document evidence on the anomalies, if any, observed in fetuses or newborns of mothers exposed to HU while pregnant.

Although exclusion of pregnancy and use of contraception by participants are mandatory in the studies that use HU as an intervention, and in patients on chronic HU therapy, there are documented pregnancies in women on the drug, and outcomes of these pregnancies suggest that the expected adverse effects of HU in humans may be exaggerated.[13,15,18,19]

The multicenter study of HU in SCA (MSH) was a randomized, double blind, placebo controlled study on the efficacy of the drug in reducing painful crises in adults.[18] Despite adequate precautions to prevent conception, several study participants conceived and were followed up for up to 17 years post-randomization. The findings suggest that fetal exposure to HU does not lead to congenital anomalies.[18] A case series of 15 women who had exposure to HU in pregnancy revealed no congenital anomalies in the nine resultant deliveries.[13] Another case series of 31 women who had exposure of HU mainly in the first trimester, with doses varying between 0.5 gram and 6 grams per day, resulted in 24 live births, three of which had minor anomalies (hip dysplasia, unilateral renal dilation and pilonidal sinus).[15] This case series however found an increased rate of fetal growth restriction in utero fetal demise and preterm deliveries. The design however did not enable distinguishing if these effects were due to the HU or the underlying illness for which it was prescribed.[15] These studies indicate a need for a robust evaluation on the effect of HU in pregnancy and fetal outcomes. As such, this review aims to estimate the incidence and prevalence of congenital anomalies in babies born to mothers with SCD who have had exposure to HU during their pregnancy.

A preliminary search on MEDLINE, PROSPERO, Google Scholar, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* did not identify any current or ongoing systematic review on the proposed topic.

Inclusion criteria

Participants

This review will consider studies that included pregnant women with SCD who have been exposed to HU therapy, irrespective of dose, frequency and duration, at any point during their pregnancy.

Outcomes

This review will consider studies that report on congenital anomalies, especially CNS malformations, skeletal defects, cleft lip and cleft palate, among babies delivered to pregnant women with SCD and exposed to HU therapy, irrespective of the onset, duration and dosage, at any point in their pregnancy.

Context

This review will consider population and hospital based studies from all over the world that have assessed and reported on the incidence and/or prevalence of congenital anomalies among babies born to pregnant women with sickle cell disease.

Types of studies

This review will consider both epidemiological and experimental study designs including prospective and retrospective cohort studies, case control studies, cross sectional studies, case series, individual case reports, randomized controlled trials, non-randomized controlled trials, quasi-experimental and before and after studies.

Methods

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Only studies published in English will be considered for inclusion in this review. It is possible that there are relevant studies published in a different language and will therefore be excluded; we however report that it is unlikely that the incidence and prevalence of congenital anomalies attributable to the use of HU for SCA in pregnancy would show regional variation. Studies published from database inception to the present date will be considered for inclusion in this review, so as to include as many studies as the search strategy would allow.

Information sources

The databases to be searched include: MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), the Cochrane library, Central registry of controlled trials and Web of Science and NHS research register.

The search for unpublished studies will include: Google Scholar, OpenSIGLE, OAlster, PsycExtra,

WorldWideScience.org, Mednar and the WHO library.

Initial keywords to be used will be: sickle cell; pregnancy; malformations; congenital anomalies; hydroxycarbamide and hydroxyurea. The search strategy for MEDLINE is shown in Appendix I.

Study selection

Following the search, all identified citations will be collated and uploaded into the Mendeley (Mendeley Ltd., Elsevier, Netherlands) desktop citation management system and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that meet and could potentially meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). The full text of selected studies will be assessed in detail against the inclusion criteria. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram.[20] Disagreements between reviewers will be resolved through discussion, or with a third reviewer.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review. Standardized critical appraisal instruments from the Joanna Briggs Institute will be used to assess methodological quality.[21] Disagreements between reviewers will be resolved through discussion, or with a third reviewer.

Data extraction

Data will be extracted from included papers using a standardized data extraction tool, for reviews on prevalence and incidence, from the Joanna Briggs Institute Reviewers' Manual.[21] Two independent reviewers will be involved in data extraction and disagreements resolved by consensus. The data extracted will include specific details about the populations, study methods and measures of significance to the review objectives, i.e. prevalence and incidence estimates expressed as proportions. Disagreements that arise between reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request for missing or additional data where required.

Data synthesis

Effect sizes expressed as proportions and their 95% confidence intervals will be calculated for each included study. Where possible, prevalence/incidence data will be pooled in statistical meta-analysis using a random effects model after logit transformation. Heterogeneity will be assessed statistically using the standard Chi-square test and explored using subgroup analyses based on the different study designs included in this review. To determine the impact of study level co-variates on heterogeneity, meta-regression will be carried out. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

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Appendix I: Search strategy for MEDLINE

Search	Query
#13	((((((hydroxycarbamide[MeSH Terms]) OR hydroxycarbamide[Title/Abstract]) OR hydroxyurea[MeSH Terms]) OR hydroxyurea[Title/Abstract])) AND (((sickle cell disease) OR sickle cell disease[Title/Abstract]) OR sickle cell disease[MeSH Terms])) AND ((pregnancy[Title/Abstract]) OR pregnancy[MeSH Terms])
#12	(pregnancy[Title/Abstract]) OR pregnancy[MeSH Terms]
#11	((sickle cell disease) OR sickle cell disease[Title/Abstract]) OR sickle cell disease[MeSH Terms]
#10	(((hydroxycarbamide[MeSH Terms]) OR hydroxycarbamide[Title/Abstract]) OR hydroxyurea[MeSH Terms]) OR hydroxyurea[Title/Abstract]
#9	hydroxycarbamide[MeSH Terms]
#8	hydroxycarbamide[Title/Abstract]
#7	hydroxyurea[MeSH Terms]
#6	hydroxyurea[Title/Abstract]
#5	pregnancy[MeSH Terms]
#4	pregnancy[Title/Abstract]
#3	sickle cell disease[MeSH Terms]
#2	sickle cell disease[Title/Abstract]
#1	sickle cell disease

