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Pregnancy Outcomes with Hydroxyurea Use in Women with Sickle Cell Disease

Barbara L. Kroner, PhD, MPH[1], **Jane S. Hankins, MD, MS**[2], **Norma Pugh, MS**[1], **Abdullah Kutlar, MD**[3], **Allison A. King, MD, PhD**[4], **Nirmish R. Shah, MD**[5], **Julie Kanter, MD**[6], **Jeffrey Glassberg, MD, MA**[7], **Marsha Treadwell, PhD**[8], **Victor R. Gordeuk, MD**[9] **Sickle Cell Disease Implementation Consortium**

[1]Division of Biostatistics and Epidemiology, RTI International, Research Triangle Park, NC

[2]Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN

[3]Sickle Cell Center, Augusta University, Augusta Georgia

[4]Division of Hematology and Oncology, Washington University School of Medicine, St. Louis, MO

[5]Pediatric Hematology/Oncology, Duke University, Durham, NC

[6]University of Alabama, Birmingham, AL

[7]Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

[8]Department of Hematology/Oncology, UCSF Benioff Children's Hospital Oakland

[9]Department of Medicine, University of Illinois at Chicago, Chicago, IL

Abstract

Hydroxyurea reduces pain crises, acute chest syndrome and blood transfusions in sickle cell disease (SCD), but potential detrimental effects on fertility and birth outcomes impede its use. Data on the effects of hydroxyurea taken for SCD during conception and pregnancy are scarce. The Sickle Cell Disease Implementation Consortium collected self-reported pregnancy history, corresponding hydroxyurea use, and pregnancy outcomes in women with SCD in the clinical setting. Among 1285 women 18-45 years of age, 737 (57.4%) reported 1788 pregnancies (1079 live births, 394 miscarriages, 40 stillbirths, 207 abortions, 48 current pregnancies, and 20 missing outcomes) of which 241 (15.9%) live births, miscarriages or stillbirths were conceived while on hydroxyurea. In univariate analyses, pregnancy number more than three, severe sickle genotype, history of stillbirth or miscarriage, and chronic kidney disease at enrollment were covariates

Corresponding Author: Victor R. Gordeuk, MD, University of Illinois at Chicago (MC 712), 820 S. Wood Street, Chicago, IL 60612, Tel: (312) 996-5680, Fax: (312) 996-5984, vgordeuk@uic.edu.

Authorship Contribution

B.L.K., J.W.H., A.K., A.A.K., N.S., J.K., J.G., M.T., and V.R.G. designed the study; J.W.H., A.K., A.A.K., N.S., J.K., J.G., M.T., and V.R.G. participated in the acquisition of data; B.L.K. and N.P. analyzed the data, and created the tables; V.R.G and B.L.K. drafted the paper; and all authors revised and approved the final version of the manuscript.

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significantly associated with a pregnancy ending in miscarriage or stillbirth. After adjustment for covariates and additional SCD severity markers in multivariate analyses, hydroxyurea use during conception and pregnancy, but not during conception only, was associated with an increase in the odds ratio (OR) of miscarriage or stillbirth (OR 2.21, 95% confidence interval [CI] 1.40-3.47). In analyses of live birth outcomes, hydroxyurea use during conception and pregnancy was associated with birth weight <5.5 pounds in full-term infants (OR 2.98, 95% CI 1.09-7.38) but not with prematurity or serious medical problems at birth. These findings suggest that hydroxyurea use may be safe up to the time of conception, but that clinicians should continue to advise caution regarding use during pregnancy.

Keywords

sickle cell disease; hydroxyurea; pregnancy; miscarriage

Introduction

Hydroxyurea is the cornerstone of pharmacological management of sickle cell disease,[1] although in recent years several new agents have been approved by the United States Food and Drug Administration (FDA).[2–4] Hydroxyurea therapy for sickle cell disease increases hemoglobin F, reduces pain crises, acute chest syndrome and blood transfusions, and possibly increases survival.[5] Hydroxyurea is an inhibitor of ribonucleotide reductase that was developed to inhibit the growth of cancer cells and may have teratogenic potential. Whether hydroxyurea is safe to use by women during conception and pregnancy is an important question for the management of sickle cell disease.

Data from animal models and reports of spontaneous abortion and fetal death in humans have raised questions about the safety of hydroxyurea during pregnancy.[6,7] In 2007, an Expert Panel of the the National Toxicology Program and the National Institute of Environmental Health Sciences thoroughly reviewed available animal and human data on the reproductive and developmental toxicity of hydroxyurea.[8] The Panel concluded that there were no human data on the reproductive effects of hydroxyurea, but that animal data raised concern that the agent may increase the risk of congenital anomalies or abnormalities of fetal growth after exposure of pregnant women. Sampson and colleagues assessed the effect of a clinically relevant dose of hydroxyurea used for the treatment of sickle cell disease on ovulation rate and embryo development in adult female mice, and reported that hydroxyurea compromised folliculogenesis and the development of generated embryos.[9]

African American women are already at increased risk for miscarriage compared to Caucasian women,[10] and sickle cell disease itself is associated with intrauterine growth restriction, preterm delivery, increased peirnatal mortality and low birth weight.[11,12] Any additional potential detrimental effects of hydroxyurea on fertility and birth defects are an impediment to its use. A better understanding of conception and pregnancy with respect to hydroxyurea use will aid clinicians in counseling patients about the potential side effects of hydroxyurea therapy. The Sickle Cell Disease Implementation Consortium (SCDIC) Registry[13] was designed to answer questions regarding hydroxyurea use and fertility

outcomes in patients with sickle cell disease. These included the impact of hydroxyurea use by females at conception or during pregnancy on fetal/infant outcomes including conception, miscarriage, stillbirth, birth defects and low birth weight. These findings are the focus of this report.

Methods

Study Population.

The study population included adult female patients from eight sickle cell disease treatment centers across the United States enrolled in the SCDIC Registry.[13,14] Although we limited this report to females at least 18 years of age, participants were eligible for recruitment in the registry based on the following inclusion criteria: male or female, 15 to 45 years of age, confirmed diagnosis of sickle cell disease (subtypes hemoglobin SS, SC, Sβ-thalassemia, SO, SD, SE or SF diagnosed by hemoglobin electrophoresis or fractionation), literacy in English, and willingness to provide informed consent or assent. Participants were excluded from enrollment if they had sickle cell trait (hemoglobin AS) or had a successful hematopoietic stem cell transplant. Recruitment of participants began in October 2017 at outpatient clinics, hospital inpatient settings, sickle cell disease support group meetings, conferences and other platforms according to the discretion of the centers as their IRB approval permitted.[15] The protocol stated that patients should be enrolled in the Registry while they were in steady state (absence of vaso-occlusive crisis and other reasons for hospitalization for 4 weeks and no transfusion for three months) but this was not a strict requirement.

Ethical Approval.

Ethical approval was received by the institutional review boards at each of the eight SCDIC study sites prior to data collection efforts. Written informed consent was obtained before participant enrollment into the study.

Data Collection and Measures.

Data were collected using participant self-report surveys, medical records and laboratory abstraction forms. The data collection instruments were developed by the SCDIC steering committee, which consisted of at least one sickle cell disease expert from each of the eight sites.[16] The survey consisted of validated instruments that assessed socio-demographic information (age, race, ethnicity, marital status, level of education, employment status, household income and insurance status), measures of well-being, and hydroxyurea use. The frequency and severity of pain were assessed using five items from the pain episode frequency and severity domain of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me).[17] ASCQ-Me is a validated measure for assessing the health-related quality of life among people with sickle cell disease.[17] Hydroxyurea use (currently using versus past use only and never used) and current medications, including opioid use (yes/no) were collected via self-reported surveys.

The medical records and laboratory forms collected data on the participants' sickle cell disease genotype, vital signs, blood transfusion history, current medications, number of

healthcare visits for acute pain in the past year, specialists involved in care, number of emergency department and hospital admissions in the past year, history of sickle cell disease complications and most recent standard laboratory measures. Sickle cell disease complications were classified according to respiratory, cardiovascular, digestive, musculoskeletal, genitourinary, immune, and central nervous systems. The complications were obtained from ICD-9 codes and physician notes. Only the date of the most recent complication in each category was recorded.

Data for the medical and laboratory forms were abstracted from participants' electronic health records by trained research staff. Laboratory measures were obtained during steady state, which was defined as at least two weeks before or after: 1) hospitalization, 2) a blood transfusion, or 3) a major acute event (e.g., stroke or vaso-occlusive event). Survey and abstracted health record data were entered into a REDCap database, assessed for completeness and discrepancies by the data coordinating center, and referred back to each site for resolution.

A pregnancy form was designed specifically to address whether there was an association between adverse pregnancy outcomes and hydroxyurea use. The form asked female participants whether or not they had ever conceived a pregnancy, and if so, the chronological order of conceptions with pregnancy end date. For each pregnancy, participants were also asked whether or not hydroxyurea was taken at the time of conception (including within the month prior to conception) and during the pregnancy. Duration and dose of hydroxyurea use, other medication use, and concurrent co-morbidities in the mother with each pregnancy were not obtained. The outcome of each pregnancy was reported as a live birth, stillbirth, miscarriage, abortion or current pregnancy and the outcomes were not further defined on the survey. Multiples within a pregnancy were also recorded. If there was a live birth, females were also asked whether the baby was premature and the corresponding weeks of gestation, had a birth weight greater or less than 5.5 pounds, and whether or not a doctor stated that the baby had a serious medical condition related to birth, and what that condition was named.

Data Definitions and Coding.

A composite variable for hydroxyurea exposure was created based on the responses from the use at conception and use during pregnancy questions. Unique categories for the composite variable included 1) hydroxyurea use at conception only, 2) hydroxyurea use at conception and during pregnancy, 3) hydroxyurea use during pregnancy only, and 4) no hydroxyurea use during conception or pregnancy. We considered that hydroxyurea use at conception only (category one) would likely indicate patients chronically on hydroxyurea who stopped its utilization once pregnancy was discovered. We also considered that hydroxyurea use during conception and during pregnancy (category two) might indicate sickle cell disease of such clinical severity that it was warranted to continue hydroxyurea therapy despite potential adverse effects on pregnancy. Only 16 women reported starting hydroxyurea during their pregnancy (category three; 12 live births, 3 miscarriages and 1 stillbirth) and this category of hydroxyurea use was excluded from the multivariate analyses due to small numbers. Pregnancy number was categorized as first, second or third (values 1-3) and fourth or more (value greater than 3). Age at each pregnancy was categorized as 18-25 years, 26-30 years,

31-35 years, and greater than 35 years. Healthcare utilization for acute pain included visits to an infusion center, acute care clinic or emergency department or a hospital admission for pain. Chronic kidney disease was defined as physician documentation of chronic kidney disease or serum creatinine concentration >0.8 mg/dL for hemoglobin SS or hemoglobin S-beta0-thalassemia patients or >1.2 mg/dL for hemoglobin SC patients on at least two consecutive tests determined at steady-state.[18] Prematurity was defined as a live birth with less than 37 weeks gestation or a self-report of prematurity. Low birthweight was defined as less than 5.5 pounds in an infant that was not premature. Serious medical conditions in a live birth that were self-reported by the mother were limited in the analysis to genetic disorders other than sickle cell disease, birth defects, early death, and other abnormalities or serious conditions unrelated to prematurity (e.g., enlarged kidney, heart problems, seizures).

Statistical Analyses.

The primary outcome in the analysis was self-reported loss of non-terminated pregnancies, which was further stratified by miscarriage and stillbirth in secondary analyses. Primary analysis was overall loss of non-terminated pregnancies because we did not precisely define the fetal age range of miscarriage and stillbirth in the survey. Other secondary outcomes were premature live birth, low birthweight in an infant that was not premature, and any serious medical problem in the infant. We examined the relationship of hydroxyurea use at conception and during pregnancy to the primary and secondary outcomes with demographic characteristics, pregnancy number, age at pregnancy, history of miscarriage or stillbirth in a previous pregnancy, and sickle cell genotype. As having been prescribed hydroxyurea can be regarded as a surrogate for having more severe sickle cell disease, we also included current hydroxyurea use and four measures of clinical severity of the mother at enrollment (hemoglobin level, history of chronic kidney disease, history of pulmonary hypertension, and number of healthcare encounters for acute pain in the previous year) as covariates. Characteristics of the female SCDIC study population and the subsets that did and did not report at least one pregnancy were summarized by frequency and percentage or mean, median and standard deviation. Differences in characteristics were determined by Chi-square, Wilcoxon rank sum, or T-tests, as appropriate for variable type and distribution. Univariate models were used to examine the relationships between each outcome and the hydroxyurea predictors and covariates. All statistically significant covariates were then included in the initial multivariate logistic regression models. In addition, pregnancy number, prior history of stillbirth or miscarriage, mother's age at pregnancy, and the four measures of clinical severity at enrollment were also included in all models, regardless of significance, to adjust for multiple pregnancies, known risk factors, and known correlated outcomes. Backward elimination was applied to reduce the model to the subset of statistically significant variables while continuing to retain the inclusion of the above predetermined covariates. After backward elimination identified the best fitting models, the composite variable for hydroxyurea use (at conception only or at conception and during pregnancy) was added to the models. In addition to summary statistics, results included the model-based odds ratio estimates with 95% confidence intervals (CI). Reference groups for odds ratios were age 18-25 at pregnancy and those without the characteristic or condition. Analyses were conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics.

A total of 1285 adult female subjects with sickle cell disease were enrolled into the Registry and 737 (57.4%) reported they had conceived at least one pregnancy on the pregnancy form; the total number of pregnancies reported was 1788. The characteristics of the 1285 females and those with (n=737) and without (n=548) at least one pregnancy are shown in Supplemental Table 1. Pregnancy history was reported by more women not taking hydroxyurea at enrollment (435/699; 62.2%) versus those taking hydroxurea at enrollment (283/548; 51.6%), a finding that may be confounded by genotype. In the group with at least one pregnancy, the majority of subjects were 25 years of age or older, never married, high school graduates, and unemployed with an annual household income of $25,000 or less. At least 70 percent had a severe sickle genotype and over 82 percent had no history of chronic kidney disease or pulmonary hypertension at entry into the Registry. There were significant demographic differences between those with and without conception of a pregnancy in age, marital status, education, employment and household income. In addition, those that reported conceiving at least one pregnancy were significantly more likely to have a higher number of healthcare visits for pain in the year prior to enrollment and less likely to currently be taking hydroxyurea at enrollment than those without conception of a pregnancy (Supplemental Table 1).

Hydroxyurea use and pregnancy outcome.

Of the 1788 reported pregnancies, 1079 (60.3%) were live births, 394 (22.0%) were miscarriages, 40 (2.2%) were stillbirths, 207 (11.6%) were elective abortions, 48 (2.7%) were current pregnancies, and 20 (1.1%) were missing the outcome. Miscarriages (range per person 1-8) had occurred among 242 females and stillbirths (range per person 1-4) had occurred among 36 females. Among the 680 women that reported a live birth, miscarriage or stillbirth, 167 (24.6%) reported at least one pregnancy conceived while taking hydroxyurea.

Table 1 presents a summary of 1513 non-terminated pregnancies by analytic outcome (miscarriage, stillbirth and live birth), order of pregnancy, age of mother at pregnancy, history of stillbirth or miscarriage in a prior pregnancy, and measures of sickle cell disease severity in the mother at the time of enrollment. Pregnancies are further broken down by hydroxyurea use at conception and during pregnancy. Although differences can be seen in the distribution of outcomes in those pregnancies that were exposed to hydroxyurea at both conception and during pregnancy, formal statistical analyses of these data by pregnancy outcome are presented in other tables in this paper.

Univariate analysis of subject-level predictors of miscarriage and stillbirth combined are shown in Supplementary Table 2; these include demographics, sickle cell type, pregnancy number, age at pregnancy, history of stillbirth or miscarriage at time of pregnancy, measures of sickle cell disease severity, hydroxyurea use at enrollment, hydroxyurea use at conception only, and hydroxyurea use at conception and during pregnancy. Pregnancy number greater than three, severe sickle cell type, history of stillbirth or miscarriage, history

of chronic kidney disease and hydroxyurea use at conception and during pregnancy were all significantly associated with a higher rate of miscarriage and stillbirth combined.

In multivariate analysis of the association of hydroxyurea use with the 434 pregnancies that ended in miscarriage or stillbirth (Table 2), there was no significant association of the combined outcome of miscarriage or stillbirth with hydroxyurea use at conception only (OR [95% CI] 0.71 [0.37-1.29]) when compared to no hydroxyurea use. However, in the same model, the odds of a pregnancy ending in either a miscarriage or stillbirth were over two times higher when hydroxyurea was used at conception and during pregnancy (OR [95% CI] 2.21 [1.40-3.47]) compared with no hydroxyurea use after adjusting for covariates. Covariates in the model that were significantly associated with miscarriage or stillbirth were severe sickle genotype (OR [95% CI] 1.62 [1.09-2.41]), history of stillbirth or miscarriage (OR [95% CI] 1.77 [1.25-2.48]), and chronic kidney disease at time of enrollment (OR [95% CI] 1.47 [1.01-2.14]). Interestingly, a higher number of visits for acute pain in the year prior to enrollment (OR [95% CI] 0.98 [0.96-1.00]) was associated with a lower risk of miscarriage or stillbirth.

When we limited the multivariate analyses to only the women with a severe sickling genotype, the results were similar to when all genotypes were included. In women with a severe genotype, there was no association with the odds of having a miscarriage or stillbirth when hydroxyurea was taken at conception only, but the odds of miscarriage or still birth when hydroxyurea was taken at conception and during pregnancy were 2.24 (95% CI 1.37-3.65) compared to women with a severe genotype that did not use hydroxyurea at conception or during pregnancy. The only covariate in the model that was significant for miscarriage or stillbirth in women with a severe genotype was a history of miscarriage or stillbirth in a previous pregnancy (OR [95% CI] 1.65 [1.09-2.48]).

In multivariate analysis of the association of hydroxyurea use with the 394 pregnancies that ended in miscarriage (Supplemental Table 3), the odds were very similar to those found when the pregnancy outcomes of miscarriage and stillbirth were combined. There was no association between miscarriage and hydroxyurea use at conception only (OR [95% CI] 0.57 [0.27-1.11]) when compared to no hydroxyurea use. In contrast, tThe odds of a pregnancy ending in a miscarriage were 2.21 times higher when hydroxyurea was used at conception and during pregnancy (95% CI 1.38-3.50) compared with no hydroxyurea use after adjusting for covariates. As in the combined outcome, covariates in the model that were significantly associated with miscarriage were severe sickle genotype (OR [95% CI]. 1.62 [1.08-2.46]), history of stillbirth or miscarriage (OR [95% CI] 1.94 [1.36-2.75]), and chronic kidney disease at time of enrollment (OR [95% CI] 1.50 [1.01-2.20]), but a higher number of visits for acute pain in the year prior to enrollment (OR [95% CI] 0.98 [0.96-1.00]) was significantly associated with a lower risk of miscarriage.

In multivariate analysis of hydroxyurea use with the 40 pregnancies that ended in stillbirth (Supplemental Table 4), there was no significant association between hydroxyurea use at either conception alone or also during pregnancy with stillbirth after adjusting for the other covariates and known risk factors (OR [95% CI] 2.58 [0.70-7.56] and 1.86 [0.41-6.08],

respectively). In the same model, there was no significant association between stillbirth and any of the covariates included in the model.

In multivariate subanalyses of the association of hydroxyurea use with miscarriage and with stillbirth in just the first pregnancy from the 737 women in the study, the results were similar to those when all pregnancies were included. Hydroxyurea use at conception and during pregnancy was significantly associated with miscarriage (OR [95% CI] 2.51 (1.12-5.51) while hydroxyurea use at conception alone or also during pregnancy was not significantly associated with stillbirth. None of the covariates were significantly associated with either miscarriage or stillbirth.

Hydroxyurea use and live birth outcomes.

Specific outcomes among the 1079 live births included prematurity (n=384, 35.6%), birth weight under 5.5 pounds in an infant not premature (n=69, 6.4%), and serious medical problems in the infant related to birth (n=53, 4.9%) (Table 1). In univariate analyses, pregnancy number greater than three, unemployment, history of stillbirth or miscarriage, severe sickle genotype, lower hemoglobin, and pulmonary hypertension were significantly associated with prematurity, while pregnancy number greater than three and history of stillbirth or miscarriage were significantly associated with serious medical problems in the infant. No covariates were associated with low birth weight in univariate analysis. Hydroxyurea use at conception alone or at conception and during pregnancy was not significantly associated with any of the live birth outcomes in univariate analyses. In the best fitting multivariate models (Table 3), hydroxyurea use at conception only was not associated with any of the live birth outcomes and hydroxyurea use at conception and during pregnancy was associated with low birth weight (OR [95% CI] 2.98 [1.09-7.38]) but not the other live birth outcomes, including birth defects.

Discussion

We conducted a study to determine the the relationship of self-reported pregnancy outcomes to self-reported hydroxyurea usage in patients with sickle cell disease who were enrolled in a multicenter registry. Data was collected on a form specifically designed to ask this question before enrollment in the registry was started. The overall rate of pregnancy loss due to miscarriage and stillbirth of 28.7% in the sickle cell disease cohort we report is higher than the self-reported loss of non-terminated pregnancies in the US from 1990-2011 of 19.7%.[19] Similarly, the stillbirth rate in this cohort of women with sickle cell disease (2.6%) is higher than the overall stillbirth rate for the US in 2014 (0.6%), defined as fetal deaths in pregnancies that last to at least 20 weeks of gestation.[20] These findings underscore the increased risk of pregnancy loss in women with sickle cell disease, and provide an important context for assessing the effect of hydroxyurea therapy on pregnancy outcomes. After attempting to account for the severity of the underlying sickle cell disease, we found that self-reported use of hydroxyurea during conception only was not associated with a composite oucome of miscarriage and stillbirth, but use of hydroxyurea at conception and during pregnancy was associated with a two-fold increased risk of this outcome.

Our philosophical approach in this study is to believe woman to accurately report hydroxyurea use during a pregnancy and to remember important events such as miscarriage and stillbirth. However, this approach is not perfect.[21,22] A study from Norway found that among mothers with a previous pregnancy loss documented in the record, 73.5% had a recall of this loss.[23] Our finding that severe sickling genotype in this study is a significant predictor of miscarriage, still birth and prematurity is consistent with a number of studies of pregnancy outcomes in sickle cell disease by other investigators,[12] and this helps address concerns that our findings are overly biased by a reliance on patient recall for the outcomes. Also consistent with other studies, not necessarily in patients with sickle cell disease,[24] we found that history of pregnancy loss was a predictor of miscarriage or still birth in this study. Increasing age is a strong predictor of miscarriage in other studies,[24] but we did not identify age as a predictor of miscarriage in this data set, perhaps because there were only 40 preganancies in women over 34 years. In univariate analysis, the odds ratio was 1.65 for this age group but there was not enough power to show statistical significance. Nevertheless, we have controlled for age, history of pregnancy loss and severe sickling genotype before drawing conclusions about the independent effect of hydroxyurea on pregnancy outcomes in this study.

We found that a substantial number of pregnancies reported by women with sickle cell disease were conceived while on hydroxyurea. Using hydroxyurea at conception but not during the pregnancy was not associated with miscarriage or stillbirth. Furthermore, there was no evidence of an increase in congenital anomalies if hydroxyurea was used by the mother either at conception or during the pregnancy. This is consistent with a 17 year follow up of patients in the Multicenter Study of Hydroxyurea, which concluded that exposure to hydroxyurea during pregnancy did not result in congenital anomalies of children born live to mothers with sickle cell disease.[25] However, we did find that hydroxyurea use at both conception and during pregnancy was independently associated with miscarriage and, in the infants that had a live delivery, with birth weight less than 5.5 pounds. There was a trend toward an association between hydroxyurea use at conception and during pregnancy with stillbirth (OR 2.6) that did not reach significance, perhaps due to the small number of events. A statistical association does not prove causality and use of hydroxyurea may represent a marker of more severe disease. To attempt to account for this, we adjusted for markers of severity to the extent the data allowed, including hemoglobin concentration and histories of chronic kidney disease, pulmonary hypertension and frequent pain episodes at the point of entry into the registry. We also used hydroxyurea use at the time of enrollment in the registry as one of several registry baseline variables to profile underlying disease severity in the research participants. This variable of hydroxyurea use at registry baseline was not associated with stillbirth or miscarriage.

Physicians and caregivers routinely counsel male and female patients to discontinue hydroxyurea if a pregnancy is planned.[26] Therefore, the use of hydroxyurea at conception can be viewed as an inadvertent occurrence with the hydroxyurea being discontinued in females once the pregnancy is discovered. In keeping with this, of 222 pregnancies in our study that did not end in elective abortion and that were conceived while on hydroxyurea, only 40 (18.0%) continued on hydroxyurea past the first trimester.

There are important limitations to our study. First of all, this study is based on self-reported pregnancy history from a survey designed to specifically address pregnancy outcome, but the exposure to hydroxyurea and pregnancy outcomes may have been affected by recall bias. There are other limitations as well, for example whether hydroxyurea use impairs conception is an open and important question, but this dataset cannot answer that question. Furthermore, age does not seem to be associated with miscarriage in this cohort, and this lack of an association may be a limitation of this dataset that is biased toward younger subjects. Another limitation is that the dates of pregnancies ending in miscarriage were more often missing than other pregnancy outcomes. We did our best to resolve these missing data, but pregnancies with missing dates were excluded from multivariate analyses because the order and age of the mother could not be determined. Furthermore, the availability and use of hydroxyurea has increased over time. Additional limitations are that we do not have information regarding the dose and duration of hydroxyurea use, the type and dose of opioids and other medications used during each pregnancy, or concurrent co-morbidities in the mother which could affect fetal outcomes. We do not know whether or not the male parteners of the patients studied were on hydroxyurea, but this would be rather unusual. We also did not include questions that could help us assess the effect of hydroxyurea on lactation.

Nevertheless, our results suggest that the use of hydroxyurea at up to conception may be safe, but its use at conception and during pregnancy may be associated with adverse pregnancy outcomes, but not with birth defects. Our findings support advising women who become pregnant while on hydroxyurea to discontinue the medication during the pregnancy, if possible, and to use alternative approaches to prevent sickle cell disease complications during this time. If confirmed by further studies, such as an ongoing study about the safety of hydroxyurea in the second trimester of pregnancy and the safety of lactation if done 10 hours after the mother takes a dose of hydroxyurea (ClinicalTrials.gov Identifier: NCT04093986), our findings may have implications for fertility preservation in girls or women with sickle cell disease. For example, if, after controlling for age, hydroxyurea remains associated with miscarriage and the mechanism is unclear, then we need to consider the possibility that oocyte or blastocyst exposure to hydroxyurea may be an issue.

In conclusion, our data suggest that a history of prior poor fetal outcome and severe sickle cell disease are significant risk factors for miscarriage or stillbirth in women with sickle cell disease. After accounting for these factors, use of hydroxyurea up to the time of conception does not seem to have an adverse effect on the fetus and may be considered safe. On the other hand, women that continue taking hydroxyurea during pregnancy may have an inceased risk of a low fetal viability or low infant birth weight. For live births, there does not appear to be an increase in birth defects when hydroxyurea is used during pregnancy. Hydroxyurea remains a vital disease-modifying therapy for individuals with SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement.

Data will be publicly available from the NHLBI Data Repository at https://biolincc.nhlbi.nih.gov/home/ by April 2022.

References

1. Platt OS. Hydroxyurea for the treatment of sickle cell anemia. N Engl J Med 2008;358:1362–9. [PubMed: 18367739]
2. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med 2018;379:226–35. [PubMed: 30021096]
3. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med 2017;376:429–39. [PubMed: 27959701]
4. Vichinsky E, Hoppe CC, Ataga KI, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med 2019;381:509–19. [PubMed: 31199090]
5. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995;332:1317–22. [PubMed: 7715639]
6. Wilson JG, Scott WJ, Ritter EJ, Fradkin R. Comparative distribution and embryotoxicity of hydroxyurea in pregnant rats and rhesus monkeys. Teratology 1975;11:169–78. [PubMed: 1154282]
7. Thauvin-Robinet C, Maingueneau C, Robert E, et al. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 2001;15:1309–11. [PubMed: 11480579]
8. Liebelt EL, Balk SJ, Faber W, et al. NTP-CERHR expert panel report on the reproductive and developmental toxicity of hydroxyurea. Birth Defects Res B Dev Reprod Toxicol 2007;80:259–366. [PubMed: 17712860]
9. Sampson M, Archibong AE, Powell A, et al. Perturbation of the developmental potential of preimplantation mouse embryos by hydroxyurea. International journal of environmental research and public health 2010;7:2033–44. [PubMed: 20623009]
10. Mukherjee S, Velez Edwards DR, Baird DD, Savitz DA, Hartmann KE. Risk of miscarriage among black women and white women in a U.S. Prospective Cohort Study. Am J Epidemiol 2013;177:1271–8. [PubMed: 23558353]
11. Boafor 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 2016;123:691–8. [PubMed: 26667608]
12. Oteng-Ntim E, Meeks D, Seed PT, et al. Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis. Blood 2015;125:3316–25. [PubMed: 25800049]
13. DiMartino LD, Baumann AA, Hsu LL, et al. The sickle cell disease implementation consortium: Translating evidence-based guidelines into practice for sickle cell disease. Am J Hematol 2018;93:E391–E5. [PubMed: 30203558]

14. Knisely MR, Pugh N, Kroner B, et al. Patient-reported Outcomes in Sickle Cell Disease and Association with Clinical and Psychosocial Factors: Report from the Sickle Cell Disease Implementation Consortium. Am J Hematol 2020.
15. Masese RV, DeMartino T, Bonnabeau E, et al. Effective Recruitment Strategies for a Sickle Cell Patient Registry Across Sites from the Sickle Cell Disease Implementation Consortium (SCDIC). J Immigr Minor Health 2021;23:725–32. [PubMed: 33034793]
16. Glassberg JA, Linton EA, Burson K, et al. Publication of data collection forms from NHLBI funded sickle cell disease implementation consortium (SCDIC) registry. Orphanet journal of rare diseases 2020;15:178. [PubMed: 32635939]
17. Treadwell MJ, Hassell K, Levine R, Keller S. Adult sickle cell quality-of-life measurement information system (ASCQ-Me): conceptual model based on review of the literature and formative research. The Clinical journal of pain 2014;30:902–14. [PubMed: 24300219]
18. Thompson J, Reid M, Hambleton I, Serjeant GR. Albuminuria and renal function in homozygous sickle cell disease: observations from a cohort study. Arch Intern Med 2007;167:701–8. [PubMed: 17420429]
19. Rossen LM, Ahrens KA, Branum AM. Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. Paediatr Perinat Epidemiol 2018;32:19–29. [PubMed: 29053188]
20. Hoyert DL, Gregory EC. Cause of Fetal Death: Data From the Fetal Death Report, 2014. Natl Vital Stat Rep 2016;65:1–25.
21. Feldman Y, Koren G, Mattice K, Shear H, Pellegrini E, MacLeod SM. Determinants of recall and recall bias in studying drug and chemical exposure in pregnancy. Teratology 1989;40:37–45. [PubMed: 2763209]
22. Newport DJ, Brennan PA, Green P, et al. Maternal depression and medication exposure during pregnancy: comparison of maternal retrospective recall to prospective documentation. BJOG 2008;115:681–8. [PubMed: 18410650]
23. Kristensen P, Irgens LM. Maternal reproductive history: a registry based comparison of previous pregnancy data derived from maternal recall and data obtained during the actual pregnancy. Acta Obstet Gynecol Scand 2000;79:471–7. [PubMed: 10857871]
24. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Haberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. Bmj 2019;364:l869. [PubMed: 30894356]
25. Ballas SK, McCarthy WF, Guo N, et al. Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. Journal of the National Medical Association 2009;101:1046–51. [PubMed: 19860305]
26. Evidence-Based Management of Sickle Cell Disease. NHLBI, NIH, 2014. (Accessed October 25, 2015, 2015, at https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf.)

Table 1.

Outcomes and hydroxyurea use for all pregnancies[a]

	Pregnancies reported by 737 females (N=1513)[b]	Hydroxyurea at conception only (N=97)	Hydroxyurea at conception and during pregnancy (n=125)	Hydroxyurea during pregnancy only (N=16)[c]	No hydroxyurea exposure (N=1154)
Pregnancy outcome					
Live birth	1,079 (71.3%)	74 (76.3%)	67 (53.6%)	12 (75.0%)	848 (73.5%)
No problem	576 (53.4%)	40 (54.1%)	26 (38.8%)	7 (58.3%)	467 (55.1%)
Prematurity	384 (35.6%)	29 (39.2%)	30 (44.8%))	2 (16.7%)	295 (34.8%)
Birth weight <5.5 lbs	69 (6.4%)	4 (5.4%)	7 (10.4%)	3 (25.0%)	48 (5.7%)
Other serious medical problem in the infant	53 (4.9%)	2 (2.7%)	5 (7.5%)	0 (0.0%)	>41 (4.8%)
Miscarriage	394 (26.0%)	17 (17.5%)	54 (43.2%)	3 (18.8%)	279 (24.2%)
Stillbirth	40 (2.6%)	6 (6.2%)	4 (3.2%)	1 (6.3%)	27 (2.3%)
Pregnancy number >3 [a]	240 (15.9%)	9 (9.3%)	23 (18.4%)	3 (18.8%)	181 (15.7%)
Age of mother at pregnancy, median (IQR)	23 (20-27)	23 (20.5-25.5)	25 (22-30)	22 (21-26)	23 (20-27)
Mother with severe sickling genotype	1,010 (67.4%)	79 (81.4%)	105 (84.7%)	10 (62.5%)	725 (63.6%)
History of stillbirth or miscarriage in mother at time of pregnancy	430 (28.4%)	18 (18.6%)	44 (35.2%)	2 (12.5%)	327 (28.3%)
Markers of SCD severity in mother at enrollment					
Hydroxyurea use	558 (36.8%)	61 (62.9%)	89 (71.2%)	5 (31.3%)	343 (29.7%)
Hemoglobin (g/dL), median (IQR)	9.1 (8.0-10.5)	8.2 (7.7-9.6)	8.7 (7.7-9.8)	10.2 (9.0-11.9)	9.2 (8.0-10.6)
Acute pain visits past year (no.), median (IQR)	3 (1-6)	3 (1-9)	3 (1-9)	2 (0-6)	2 (1-6)
Chronic kidney disease	256 (16.9%)	19 (19.6%)	28 (22.4%)	4 (25.0%)	178 (15.4%)
Pulmonary hypertension	281 (18.6%)	24 (24.7%)	19 (15.2%)	2 (12.5%)	208 (18.0%)

[a]Excludes pregnancies that were current, missing an outcome, or ended in elective abortion

[b]Includes 121 pregnancies with unknown hydroxyurea use at conception or during pregnancy

[c]These 16 pregancies were reported by 13 women, 10 of whom (77%) had severe sickling genotype.

Table 2.

Hydroxyurea use as an independent predictor of miscarriage or stillbirth[a]

Covariate	N	Miscarriage or Stillbirth	N	Live birth	Odds ratio (95% CI)
Pregnancy number greater than three, no. (%)	434	89 (20.5%)	1079	151 (13.9%)	0.96 (0.60-1.50)
Age at pregnancy, no. (%)					
- 26-30	397	84 (21.2%)	1073	229 (21.3%)	0.90 (0.61-1.30)
- 31-35		34 (8.6%)		87 (8.1%)	1.13 (0.66-1.91)
- 35+		15 (3.8%)		26 (2.4%)	0.87 (0.35-2.01)
History of stillbirth or miscarriage, no. (%)	434	170 (39.2%)	1079	260 (24.1%)	**1.77 (1.25-2.48)**
Severe sickle genotype (Hb SS/Hb SBeta0/Hb SD/Hb SO/Hb SE), no. (%)	432	321 (74.3%)	1066	689 (64.6%)	**1.62 (1.09-2.41)**
Markers of Severity [b]					
Number total visits in past year for acute pain, median (IQR), mean (std)	362	3 (1-6), 6.8 (15.22)	910	3 (1-7), 7.2 (13.84)	**0.98 (0.96-1.00)**
Hemoglobin (g/dL), median (IQR), mean (std)	364	9.0 (7.8-10.1) 9.1 (1.68)	920	9.2 (8.0-10.5) 9.3 (1.79)	1.06 (0.95-1.17)
Chronic kidney disease, no. (%)	434	92 (21.2%)	1079	164 (15.2%)	**1.47 (1.01-2.14)**
Pulmonary hypertension, no. (%)	434	81 (18.7%)	1079	200 (18.5%)	0.89 (0.60-1.31)
Predictor					
Hydroxyurea use, no. (%)					
- at conception only	387	23 (5.9%)	989	74 (7.5%))	0.71 (0.37-1.29)
- at conception and during pregnancy		58 (15.0%)		67 (6.8%)	**2.21 (1.40-3.47)**

[a] Excludes pregnancies that were current, missing an outcome, ended in elective abortion, or ended in stillbirth

[b] Status of mother at enrollment

Odds ratios with p<.05 are bolded

Table 3.

Multivariate predictors of live birth outcomes

Prematurity					
Covariate	**N**	**Premature**	**N**	**Full term**	**Odds ratio (95% CI)**
Pregnancy number >3, no. (%)	384	65 (16.9%)	669	79 (11.8%)	0.96 (0.57-1.60)
Age at pregnancy, no. (%)					
- 26-30	379	88 (23.2%)	668	133 (19.9%)	1.21 (0.82-1.79)
- 31-35		38 (10.0%)		48 (7.2%)	1.30 (0.71-2.36)
- 35+		9 (2.4%)		14 (2.1%)	1.17 (0.39-3.33)
History of stillbirth or miscarriage, no. (%)	384	105 (27.3%)	669	147 (22.0%)	**1.64 (1.10-2.44)**
Severe sickle genotype (Hb SS/Hb SBeta0/Hb SD/Hb SO/Hb SE), no. (%)	384	279 (72.7%)	656	390 (59.5%)	1.50 (0.99-2.29)
Markers of Severity [a]					
Number total visits in past year for acute pain, median (IQR), mean (std)	332	3 (1-10) 7.7 (10.37)	555	2 (1-6), 7.0 (15.55)	1.00 (0.99-1.02)
Hemoglobin (g/dL), median (IQR), mean (std)	328	9.1 (7.9-10.3) 9.1 (1.71)	570	9.4 (8.0-10.6) 9.4 (1.84)	0.98 (0.87-1.09)
Chronic kidney disease, no. (%)	384	58 (15.1%)	669	95 (14.2%)	0.91 (0.58-1.40)
Pulmonary hypertension, no. (%)	384	87 (22.7%)	669	104 (15.5)	**1.77 (1.20-2.62)**
Predictor					
Hydroxyurea use, no. (%)					
- at conception only	354	29 (8.2%)	>613	45 (7.3%)	0.94 (0.52, 1.65)
- at conception and during pregnancy		30 (8.5%)		37 (6.0%)	1.11 (0.61, 2.00)
Birth weight < 5.5 pounds, among babies who are not premature					
Covariate	**N**	**Low birth weight**	**N**	**Normal birth weight**	**Odds ratio (95% CI)**
Pregnancy number greater than 3, no. (%)	69	9 (13.0%)	600	70 (11.7%)	1.65 (0.60-4.27)
Age at pregnancy, no. (%)					
- 26-30	69	12 (17.4%)	599	121 (20.2%)	0.85 (0.35-1.88)
- 31-35		3 (4.3%)		45 (7.5%)	0.69 (0.15-2.29)
- 35+		2 (2.9%)		12 (2.0%)	0.63 (0.03-4.36)
History of stillbirth or miscarriage, no. (%)	69	17 (24.6%)	600	130 (21.7%)	1.60 (0.70-3.45)
Severe sickle genotype (Hb SS/Hb SBeta0/Hb SD/Hb SO/Hb SE), no. (%)	69	46 (66.7%)	599	344 (57.4%)	1.09 (0.48-2.48)
Markers of Severity [a]					

Prematurity					
Covariate	**N**	**Premature**	**N**	**Full term**	**Odds ratio (95% CI)**
Number of total visits in past year for acute pain, median (IQR), mean (std)	59	3 (1-8), 9.1 (18.7)	496	2 (1-6), 6.7 (15.1)	1.00 (0.97-1.02)
Hemoglobin (g/dL), median (IQR), mean (std)	61	8.8 (7.2-10.5), 9.1 (1.85)	509	9.5 (8.0-10.7), 9.5 (1.84)	0.93 (0.75-1.14)
Chronic kidney disease, no. (%)	69	11 (15.9%)	600	84 (14.0%)	1.11 (0.44-2.52)
Pulmonary hypertension, no. (%)	69	14 (20.3%)	598	90 (15.0%)	1.90 (0.84-4.02)
Predictor					
Hydroxyurea use no. (%)					
- at conception only	59	4 (6.8%)	554	41 (7.4%))	0.94 (0.22-2.87)
- at conception and during pregnancy		7 (11.9%)		30 (5.4%)	**2.98 (1.09-7.38)**
Other serious medical problem in infant					
Covariate	**N**	**Medical problem**	**N**	**No problem**	**Odds ratio (95% CI)**
Pregnancy number greater than 3, no. (%)	53	14 (26.4%)	995	128 (12.9%)	1.50 (0.56-3.74)
Age at pregnancy, no. (%)					
- 26-30	52	12 (23.1%)	990	207 (20.9%)	0.65 (0.23-1.62)
- 31-35		5 (9.6%)		81 (8.2%)	0.53 (0.08-2.03)
- 35+		2 (3.8%)		21 (2.1%)	2.18 (0.30-9.94)
History of stillbirth or miscarriage, no. (%)	53	22 (41.5%)	995	227 (22.8%)	1.90 (0.80-4.27)
Severe sickle genotype (Hb SS/Hb SBeta0/Hb SD/Hb SO/Hb SE), no. (%)	53	34 (64.2%)	982	634 (64.6%)	1.05 (0.41-2.73)
Markers of Severity [a]					
Number total visits in past year for acute pain, median (IQR), mean (std)	43	3 (1-8), 7.9 (10.92)	839	3 (1-7), 7.2 (13.83)	1.01 (0.98-1.03)
Hemoglobin (g/dL), median (IQR), mean (std)	41	8.9 (8.0-11.1), 9.5 (2.04)	852	9.2 (8.0-10.5), 9.3 (1.79)	1.06 (0.87-1.28)
Chronic kidney disease, no. (%)	53	9 (17.0%)	995	146 (14.7%)	0.93 (0.30-2.37)
Pulmonary hypertension, no. (%)	53	10 (18.9%)	995	181 (18.2%)	0.94 (0.33-2.27)
Predictor					
Hydroxyurea use no. (%)					
- at conception only	48	2 (4.2%)	916	71 (7.8%)	0.84 (0.13-2.95)
- at conception and during pregnancy		5 (10.4%)		61 (6.7%)	1.33 (0.31-4.01)

[a] Status of mother at enrollment

Odds ratios with p<.05 are bolded