HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Birth Defects Res. 2022 May ; 114(8): 295–303. doi:10.1002/bdr2.2000.

Maternal hereditary hemolytic anemia and birth defects in the National Birth Defects Prevention Study

Eleni A. Papadopoulos[1], **Sarah C. Fisher**[1], **Meredith M. Howley**[1], **Marilyn L. Browne**[1,2], **National Birth Defects Prevention Study**

[1]Birth Defects Registry, New York State Department of Health, Albany, New York, USA

[2]Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York, USA

Abstract

Objectives: Hereditary hemolytic anemia (HHA) results from genetic mutations that cause red blood cell abnormalities. Little research exists on the relationship between HHA and birth defects. Using data from the National Birth Defects Prevention Study (NBDPS), we described characteristics of HHA-exposed women and estimated associations between HHA during pregnancy and specific birth defects.

Methods: The NBDPS was a population-based, case–control study of major birth defects and included pregnancies with estimated delivery dates from October 1997 through December 2011. Participants were ascertained from hospital discharge lists or birth defect registries at 10 sites. Trained interviewers collected information about pregnancy exposures via telephone questionnaire. We described characteristics among HHA-exposed women and calculated crude odds ratios and exact 95% confidence intervals for defects with ≥3 exposed cases.

Results: Among 31 HHA-exposed women (28 cases/3 controls), 13 (42%) reported sickle cell anemia, 17 (55%) reported thalassemia, and one (3%) reported hereditary spherocytosis. The average age at delivery for HHA-exposed case women was 27.3 years (range: 17–38). The majority (82%) of HHA-exposed case women reported additional conditions during pregnancy, including hypertension, genitourinary infections, and respiratory illnesses. Additionally, 93% of case women reported using medication during pregnancy. Among the 28 cases, 18 (64%) had isolated birth defects. The defects with ≥3 exposed cases were anencephaly, atrial septal defect, gastroschisis, and cleft palate. Except for anencephaly, the 95% confidence intervals for all estimates were close to or included the null.

Conclusion: This hypothesis-generating study adds to the sparse literature on the association between HHA and birth defects.

Correspondence Eleni A. Papadopoulos, Birth Defects Registry, New York State Department of Health, Albany, New York, USA. eleni.papadopoulos@health.ny.gov.

ETHICS STATEMENT

The Centers for Disease Control and Prevention Institutional Review Board (IRB), along with the IRBs for each participating site, have approved the NBDPS. The Centers for Disease Control and Prevention IRB has approved the BD-STEPS.

Keywords

birth defects; hereditary hemolytic anemia; National Birth Defects Prevention Study; sickle cell disease; thalassemia

1 | INTRODUCTION

Anemia is a common condition in pregnancy that occurs when the body has an abnormally low number of circulating red blood cells (Bencaiova, Burkhardt, & Breymann, 2012; McLean, Cogswell, Egli, Wojdyla, & de Benoist, 2009). There are two main types of anemia. The more common type occurs due to a nutritional deficiency from specific vitamins and minerals, such as iron, vitamin B_{12}, or folic acid, and can be treated with changes in diet and oral supplementation (Sun, McLeod, Gandhi, Malinowski, & Shehata, 2017). The other main type is hemolytic anemia, which is caused by hemolysis: the early destruction of red blood cells (Vieth & Lane, 2014). Hemolytic anemia is much rarer and can be hereditary; certain gene mutations cause red blood cells to have an abnormal shape and shorter lifespan (Lee & Okam, 2011; Vieth & Lane, 2014). Hereditary hemolytic anemia is usually diagnosed at birth and can be a life-long illness with painful complications. Some patients are regularly prescribed opioid analgesics to treat these symptoms (Phillips & Boyd, 2017).

There are various types of hereditary hemolytic anemia (HHA), including sickle cell anemia, thalassemia, and hereditary spherocytosis, and the prevalence varies by characteristics such as race/ethnicity. For example, sickle cell anemia predominately affects infants of non-Hispanic Black race/ethnicity (Wang et al., 2013), whereas thalassemia is more common among infants of East Asian and Middle Eastern descent (Feuchtbaum, Carter, Dowray, Currier, & Lorey, 2012). Sickle cell anemia is dangerous in pregnancy and can lead to significant maternal morbidity and mortality. An increase in painful sickle cell crises, which occur when sickle-shaped red blood cells clump together blocking blood vessels, are more common in the third trimester of pregnancy. Women with sickle cell disease may require prophylactic blood transfusions to decrease the risk of crises (Alayed, Kezouh, Oddy, & Abenhaim, 2014). Thalassemia complications are dependent on subtype; some women may have mild cases during pregnancy while others have more moderate symptoms. In severe cases, women with thalassemia are dependent on transfusions, and cardiac and liver function may be affected (Petrakos, Andriopoulos, & Tsironi, 2016). Hereditary spherocytosis ranges in severity of presentation and common clinical features include jaundice, low hemoglobin levels, and an enlarged spleen. Many cases are mild, but life events, including pregnancy, may lead to diagnoses due to more severe symptoms or routine blood tests (Bolton-Maggs, 2004).

Abnormal red blood cells characterizing HHA can lead to reduced oxygen levels in the placenta, potentially causing placental hypoxia and affecting fetal development (Chen et al., 2018; Trampont et al., 2004). Increased risk of several adverse pregnancy outcomes has been documented in women with HHA, particularly preterm birth (Fozza et al., 2017; Kuo & Caughey, 2016), small for gestational age (Elenga et al., 2016; Kuo & Caughey, 2016),

pre-eclampsia (Chen et al., 2018; Elenga et al., 2016; Kuo & Caughey, 2016), intrauterine growth restriction (Boafor et al., 2016) perinatal mortality (Boafor et al., 2016), and low birthweight (Boafor et al., 2016). The literature on the relationship between HHA and birth defects, however, is sparse. One study found sickle cell disease was associated with cardiac defects, abdominal wall defects and congenital lung defects (Kuo & Caughey, 2016). Using data from the National Birth Defects Prevention Study (NBDPS), we described women who reported HHA during pregnancy and estimated the risk of specific types of birth defects in their offspring. We sought to use these findings to generate hypotheses for future research.

2 | METHODS

The NBDPS was a population-based, multi-site, case–control study in the United States designed to investigate risk factors associated with more than 30 categories of major structural birth defects (Reefhuis et al., 2015; Yoon et al., 2001). The NBDPS included pregnancies with estimated delivery dates (EDDs) between October 1, 1997 and December 31, 2011. Case women had pregnancies ending in livebirth, stillbirth, or termination ascertained from birth defects surveillance systems at participating sites in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Case women were excluded if the birth defect affecting their pregnancy was attributed to a known chromosomal or single-gene abnormality. Following ascertainment, clinical geneticists reviewed each case to confirm study eligibility and to classify them as isolated (one or more major birth defects in the same organ system), multiple (major birth defects in more than one organ system), or complex (a group of defects believed to be pathogenically related, but the primary defect is not apparent). Congenital heart defects (CHD) were further classified based on cardiac phenotype, complexity, and presence of non-CHDs (Botto, Lin, Riehle-Colarusso, Malik, & Correa, 2007). Control women had liveborn, nonmalformed infants that were randomly selected from hospital discharge lists or birth certificates from the same geographic catchment areas as the cases. Due to changes in birth defect ascertainment, some sites did not collect certain birth defects in all years. We excluded controls for these years and sites with incomplete data when estimating odds ratios. All interviewed study participants provided informed consent.

Trained interviewers conducted computer-assisted telephone interviews in English or Spanish with case and control women. The women were interviewed between 6 weeks and 24 months after the EDD and asked about their demographics, behaviors, medical history, and medication use from 3 months before pregnancy to birth. Women reported HHA in response to interview questions about illness during pregnancy. Before 2006, women were asked if they had “any other disease or illnesses that we have not already talked about, such as chronic disease, infectious disease, or sexually transmitted diseases.” Starting in 2006, women were asked if they had “any other chronic disease or illness that we have not talked about such as asthma, thyroid disease, an autoimmune disease, or other chronic or long-term diseases.” Women reported the name of their disease, diagnosis date, symptoms, and any related medication use (including medication name, timing, and frequency of use). The Slone Epidemiology Center Drug Dictionary was used to code all reported medications. We also reviewed all comment fields in the questionnaire to identify reports of HHA in other parts of the interview. We considered a woman to have HHA if she reported any of

the following disorders during pregnancy: hereditary spherocytosis, hereditary elliptocytosis, thalassemia, sickle cell disease, or other hemoglobinopathies. Women who reported sickle cell trait were not considered to have HHA since symptoms and complications are rare; they were excluded from this analysis (Trampont et al., 2004).

We conducted a descriptive analysis to investigate patterns in the occurrence of birth defects and maternal characteristics among women who reported HHA. We described the specific birth defects that affected their pregnancies, as well as maternal demographics, medical histories, and behaviors during pregnancy. Due to the rarity of control women reporting HHA ($n = 3$), we only described characteristics among case women. We calculated chi-square tests to determine differences in characteristics among case women with and without HHA. Additionally, to determine if there is an association between HHA and the risk of birth defects, we estimated crude odds ratios and exact 95% confidence intervals for birth defects with at least three exposed cases. We excluded 217 women (151 cases, 66 controls) who reported sickle cell trait, anemias that were not considered HHA, and women who did not specify the type of anemia. The unexposed group included case and control women who did not report any type of anemia.

3 | RESULTS

Of the 31,867 case and 11,763 control women in this analysis, 28 case (0.09%) and three control (0.03%) women reported HHA during pregnancy. Of these 31 women, 17 (55%) reported thalassemia, 13 (42%) reported sickle cell anemia, and one (3%) reported hereditary spherocytosis. All three exposed control women reported thalassemia.

We observed differences in characteristics between case women who reported HHA and case women who did not, including differences by HHA type (Table 1). The average age of unexposed case women was 27.7 years (SD: 6.2), while case women who reported sickle cell anemia had an average age of 23.6 years (SD: 3.9) and case women with thalassemia had an average age of 30.0 years (SD: 7.0). Similarly, we observed differences between case women with and without HHA by race/ethnicity. Only 10% of case women without HHA were non-Hispanic Black, while 39% of case women with HHA were non-Hispanic Black. This was driven by the fact that 62% of case women with sickle cell anemia were non-Hispanic Black, whereas 57% of case women who reported thalassemia were non-Hispanic White. Women with HHA were more likely to have a lower household income or non-livebirth compared with case women without HHA. Other characteristics, including prepregnancy body mass index, maternal hypertension, maternal cigarette smoking, maternal education, and maternal US nativity, were similar among case women with and without HHA. Among those with live born infants, the frequency of preterm birth and low-birth weight was similar between case women with and without HHA. Within HHA subtypes, case women with sickle cell anemia had higher proportions of preterm birth (40%) and lower proportions of low-birth weight (20%) compared with women with thalassemia (preterm birth, 25%; low-birth weight, 33%).

Of the case women with HHA who reported a date for their first prenatal care visit, 54% reported initiating care in the first 2 months of pregnancy. The majority (82%) of case

women with HHA reported one or more additional conditions during pregnancy, including hypertension (19%), genitourinary infections (29%), and respiratory illnesses (54%). None of the women with HHA reported either prepregnancy or gestational diabetes. Additionally, 26 (93%) case women with HHA reported medication use during pregnancy. Of these, the most commonly reported medications were nonopioid analgesics (89%) and antibiotics (29%). Also, 26 (93%) case women reported prenatal multivitamin use. A small number of women with HHA, all with sickle cell anemia, reported treatments specific to HHA, including four (14%) who reported opioid use (two in the first trimester), two (7%) who reported a blood transfusion in the first trimester, and one (4%) who reported hydroxyurea use in the first trimester (data not shown).

Of the 28 case women with HHA, 18 (64%) had a pregnancy with an isolated birth defect while 10 (36%) had a pregnancy with more than one defect (Table 2). Of the pregnancies affected by multiple defects, all had unique combinations of birth defects. Among pregnancies of women with HHA, we observed 20 different birth defects: anencephaly, spina bifida, microtia, Dandy–Walker malformation, cataracts, cleft palate without cleft lip, anorectal atresia, hypospadias, longitudinal limb deficiency, craniosynostosis, biliary atresia, gastroschisis, amniotic band syndrome, tetralogy of Fallot, d-transposition of the great arteries, partial anomalous pulmonary venous return, coarctation of the aorta, secundum atrial septal defect (ASD), perimembranous ventricular septal defect, and heterotaxy. Of the more than 50 specific birth defects included in the NBDPS, we observed three exposed cases each for four birth defects: anencephaly, ASD, cleft palate without cleft lip, and gastroschisis. For each of these defects, there were two women with thalassemia and one woman with sickle cell anemia. While one case woman had a pregnancy affected by both ASD and cleft palate, all others were distinct individuals. The crude ORs for HHA and each birth defect were elevated, ranging from 3.8 for ASD to 17.9 for anencephaly, but confidence intervals were very wide. Additionally, the confidence intervals for all ORs except anencephaly either included or were very close to the null value of 1.0 (Figure 1).

4 | DISCUSSION

This study described 31 women (28 cases and three controls) who reported HHA during pregnancy. Our analysis suggests that HHA is not associated with the majority of birth defects included in the NBDPS. For 36 of the 52 defects examined, we observed 0 exposed cases and an additional 16 defects had either 1 or 2 exposed cases. Among the 28 case women who reported HHA, we observed 20 different birth defects among their offspring. We estimated crude associations between HHA and four specific birth defects and observed an increased risk of all four defects. However, all but one confidence interval either included or was close to the null. All confidence intervals were exact given the small number of exposed cases and extremely wide.

We found differences in demographics among different HHA types and compared with unexposed women. Case women with HHA differed from case women without HHA in terms of race/ethnicity, household income, and livebirth status. Case women with sickle cell anemia were younger, on average, than case women with thalassemia. Also, more case women with sickle cell anemia were non-Hispanic Black compared with case women

with thalassemia. These findings are similar to what has been previously described in the literature, where sickle cell anemia occurs most often in those of sub-Saharan African descent and thalassemia most commonly affects those of Asian and Mediterranean descent (Vichinsky, MacKlin, Waye, Lorey, & Olivieri, 2005; Wang et al., 2013). Similar to our findings, previous studies have also found that women with sickle cell disease tend to have a younger age at delivery (Al Jama et al., 2009; Al Kahtani et al., 2012) than women with thalassemia (Sorrentino et al., 2020; Vafaei, Karimi, Akbarzadeh Jahromi, Asadi, & Kasraeian, 2020).

Many studies have reported increased risk of preterm birth, intrauterine growth restriction, pregnancy-related hypertension (including pre-eclampsia), and genitourinary infections among women with HHA (Al Jama et al., 2009; Al Kahtani et al., 2012; Alayed et al., 2014). Our results mirrored these findings, with 16% and 29% of case women reporting hypertension and genitourinary infections, respectively. These percentages are higher than those reported among pregnant women in the U.S, where approximately 7–15% of pregnant women report hypertension (Bornstein, Eliner, Chervenak, & Grünebaum, 2020; Fisher et al., 2018; Monseur, Morris, Hipp, & Berghella, 2019) and 9–17% of pregnant women report genitourinary infections (Howley et al., 2018; Whitehead, Callaghan, Johnson, & Williams, 2009). However, we were only able to calculate these percentages among case women, who may have a higher baseline risk of hypertension and genitourinary infections even without HHA.

The literature on the association between HHA and birth defects is sparse. The Birth Defects Monitoring Program, operated by the Centers for Disease Control and Prevention to monitor trends in birth defects from hospital discharge lists across the United States, found that women with HHA had offspring with an excess of CHDs when compared with women without HHA (Khoury, Waters, Martin, & Edmonds, 1991). The authors identified cases of ASD, ventricular septal defect, patent ductus arteriosus, and other unspecified heart defects among offspring of women with HHA but did not find an excess of any specific CHDs, nor did they find an excess of other specific non-CHDs. In our analysis, the only CHD for which we were able to calculate a crude OR was ASD, for which there were three exposed case infants. While the OR was elevated, the wide confidence interval included the null value of 1.0 (OR: 3.8, 95% CI: 0.5, 28.1).

Besides ASD, we calculated crude estimates for three other specific birth defects. While all the ORs were elevated, those for cleft palate and gastroschisis had lower CI bounds close to 1.0 and were very wide. The OR for anencephaly was elevated and excluded the null value of 1.0 but was still very imprecise. Two previous studies assessed the risk of neural tube defects (NTD) among women with thalassemia (Ibba et al., 2003; Lam & Tang, 1999). In one study of 309 women with thalassemia and 1506 women without thalassemia, there were nine NTD-affected pregnancies: five with spina bifida and four with anencephaly (Lam & Tang, 1999). All of the anencephaly-affected pregnancies were among women with thalassemia, while the spina bifida-affected pregnancies were among women without thalassemia. Another study of 75 NTD-affected pregnancies found that women with beta-thalassemia had a higher percentage of anencephaly-affected pregnancies compared with women without thalassemia (Ibba et al., 2003). However, women with alpha-thalassemia

had a lower percentage of anencephaly-affected pregnancies compared with women without thalassemia. Although these studies were small, both found an increased risk of NTDs overall among women with thalassemia compared with women without thalassemia. The mechanism by which HHA can lead to NTDs is unclear, but studies have shown that women with HHA may suffer from depleted folate reserves due to the decrease in healthy red blood cells (Castaldi et al., 1983; Dixit et al., 2016). These low folate reserves may explain our finding of increased risk of anencephaly among women with HHA, since low folic acid has been found to be associated with NTDs in numerous studies (Ibba et al., 2003; Williams et al., 2015). Two of the three women with an anencephaly-affected pregnancy in our study reported taking a folic acid-containing multivitamin or prenatal vitamin, however standard supplements may be inadequate to overcome particularly low folate reserves due to HHA. Additionally, while one woman reported initiating use 2 months before pregnancy, the other began during the first month of pregnancy, which may not have allowed her to build up adequate nutrient stores. Guidelines suggest women with certain risk factors, such as those with a previous NTD-affected pregnancy, take higher folic acid doses during a subsequent pregnancy ("ACOG Committee Opinion No. 762: Pre-pregnancy Counseling," 2019). HHA is not currently considered a risk factor for NTDs according to these guidelines, so women in our study reporting supplement use would likely have been taking the daily recommended value. With the exception of anencephaly, we did not observe enough exposed cases of other NTDs to estimate risk associated with HHA. Among case women with HHA, there was one case of spina bifida and no cases of encephalocele.

Our study had a few limitations. The ORs we calculated were based on very small numbers in both case and control groups, which resulted in low statistical power and wide, imprecise confidence intervals. For this reason, we were unable to adjust for any confounders, which may introduce bias. We found differences in maternal race/ethnicity and household income between case women with and without HHA, and not controlling for these factors may mask the true OR. However, the rest of the covariates that we evaluated in Table 1 were similarly distributed between case women with and without HHA. Given our highly imprecise confidence intervals, we cannot rule out that the elevated ORs we observed are different from the true estimates. Another limitation of our study is that we had a low number of control women with HHA in our sample, which prevented us from evaluating differences between control women with and without HHA. Additionally, women with HHA self-reported their diagnoses which could potentially lead to recall errors and exposure misclassification. Since women were not specifically asked about HHA in the interview, it is possible that HHA was under-ascertained. However, the prevalence of HHA subtypes in our study is comparable to that of other analyses. Others estimated the prevalence of sickle cell anemia based on newborn bloodspots in the United States to be 0.05%, similar to the 0.03% in our study (Sontag et al., 2020). Finally, for most specific birth defects examined, we observed less than three exposed cases; we did not evaluate null or potentially protective effects associated with birth defects that occurred less frequently than expected.

Our study also had strengths. Very few studies have assessed the risk of birth defects for women with HHA. Although we were unable to calculate adjusted risk estimates, our findings are hypothesis-generating for future analyses. The NBDPS data set is population-based, and the control population is demographically diverse and representative of the

catchment areas. Additionally, the ascertained birth defect cases were subject to strict eligibility criteria and examined by clinical geneticists, limiting outcome misclassification.

This descriptive analysis studied the relationship between HHA and the risk of birth defects. The literature on this topic is sparse and more studies are needed to address research gaps. It is important that future studies evaluate any differences in birth defect risk among HHA types. Specifically, future studies should account for the rarity of HHA in their study design to ensure sufficient prevalence of the exposure with the ability to adjust for confounders and calculate precise estimates. Previous studies have established that women with HHA experience significant morbidity during pregnancy and it is important to further study whether birth defects pose an additional risk. Despite its limitations, this hypothesis-generating analysis may serve as a catalyst for future research.

ACKNOWLEDGMENTS

This project was supported through Centers for Disease Control and Prevention (CDC) cooperative agreements under PA #96043, PA #02081, FOA #DD09–001, FOA #DD13–003, and NOFO #DD18–001 to the Centers for Birth Defects Research and Prevention participating in the National Birth Defects Prevention Study (NBDPS) and/or the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). Coding of drug information in the National Birth Defects Prevention Study used the Slone Drug Dictionary under license from the Slone Epidemiology Center of Boston University. We thank Upasana Chalise for replicating the analysis.

DATA AVAILABILITY STATEMENT

The study questionnaires and process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book and analytic code may be made available upon request.

REFERENCES

Al Jama FE, Gasem T, Burshaid S, Rahman J, Al Suleiman SA, & Rahman MS (2009). Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, eastern Saudi Arabia. Archives of Gynecology and Obstetrics, 280(5), 793–797. 10.1007/s00404-009-1002-7 [PubMed: 19271230]

Al Kahtani MA, AlQahtani M, Alshebaily MM, Abd Elzaher M, Moawad A, & Aljohani N (2012). Morbidity and pregnancy outcomes associated with sickle cell anemia among Saudi women. International Journal of Gynaecology and Obstetrics, 119(3), 224–226. 10.1016/j.ijgo.2012.07.008 [PubMed: 22986097]

Alayed N, Kezouh A, Oddy L, & Abenhaim HA (2014). Sickle cell disease and pregnancy outcomes: Population-based study on 8.8 million births. Journal of Perinatal Medicine, 42(4), 487–492. 10.1515/jpm-2013-0275 [PubMed: 24344096]

Bencaiova G, Burkhardt T, & Breymann C (2012). Anemia: prevalence and risk factors in pregnancy. European Journal of Internal Medicine, 23(6), 529–533. 10.1016/j.ejim.2012.04.008 [PubMed: 22863430]

Boafor TK, Olayemi E, Galadanci N, Hayfron-Benjamin C, Dei-Adomakoh Y, Segbefia C, … Oppong SA (2016). Pregnancy outcomes in women with sickle-cell disease in low and high income countries: A systematic review and meta-analysis. BJOG, 123(5), 691–698. 10.1111/1471-0528.13786 [PubMed: 26667608]

Bolton-Maggs PH (2004). Hereditary spherocytosis; new guidelines. Archives of Disease in Childhood, 89(9), 809–812. 10.1136/adc.2003.034587 [PubMed: 15321852]

Bornstein E, Eliner Y, Chervenak FA, & Grünebaum A (2020). Concerning trends in maternal risk factors in the United States: 1989–2018. EClinicalMedicine, 29–30, 100657. 10.1016/j.eclinm.2020.100657

Botto LD, Lin AE, Riehle-Colarusso T, Malik S, & Correa A (2007). Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Research. Part A, Clinical and Molecular Teratology, 79(10), 714–727. 10.1002/bdra.20403 [PubMed: 17729292]

Castaldi G, Bagni B, Trotta F, Menegale G, Cavallini AR, & Piffanelli A (1983). Folic acid deficiency in beta-thalassaemia heterozygotes. Scandinavian Journal of Haematology, 30(2), 125–129. 10.1111/j.1600-0609.1983.tb01456.x [PubMed: 6836226]

Chen C, Grewal J, Betran AP, Vogel JP, Souza JP, & Zhang J (2018). Severe anemia, sickle cell disease, and thalassemia as risk factors for hypertensive disorders in pregnancy in developing countries. Pregnancy Hypertens, 13, 141–147. 10.1016/j.preghy.2018.06.001 [PubMed: 30177043]

Dixit R, Nettem S, Madan SS, Soe HH, Abas AB, Vance LD, & Stover PJ (2016). Folate supplementation in people with sickle cell disease. Cochrane Database of Systematic Reviews, 2, Cd011130. 10.1002/14651858.CD011130.pub2 [PubMed: 26880182]

Elenga N, Adeline A, Balcaen J, Vaz T, Calvez M, Terraz A, … Carles G (2016). Pregnancy in sickle cell disease is a very high-risk situation: An observational study. Obstetrics and Gynecology International, 2016, 9069054. 10.1155/2016/9069054 [PubMed: 27403164]

Feuchtbaum L, Carter J, Dowray S, Currier RJ, & Lorey F (2012). Birth prevalence of disorders detectable through newborn screening by race/ethnicity. Genetics in Medicine, 14(11), 937–945. 10.1038/gim.2012.76 [PubMed: 22766612]

Fisher SC, Van Zutphen AR, Werler MM, Romitti PA, Cunniff C, & Browne ML (2018). Maternal antihypertensive medication use and selected birth defects in the National Birth Defects Prevention Study. Birth Defects Research, 110(19), 1433–1442. 10.1002/bdr2.1372 [PubMed: 30260586]

Fozza C, Asara MA, Vacca N, Caggiari S, Monti A, Zaccheddu F, … Antonucci R (2017). Pregnancy outcome among women with Beta-thalassemia major in North Sardinia. Acta Haematologica, 138(3), 166–167. 10.1159/000480450 [PubMed: 28992618]

Howley MM, Feldkamp ML, Papadopoulos EA, Fisher SC, Arnold KE, & Browne ML (2018). Maternal genitourinary infections and risk of birth defects in the National Birth Defects Prevention Study. Birth Defects Research, 110(19), 1443–1454. 10.1002/bdr2.1409 [PubMed: 30402975]

Ibba RM, Zoppi MA, Floris M, Manca F, Axiana C, Cao A, & Monni G (2003). Neural tube defects in the offspring of thalassemia carriers. Fetal Diagnosis and Therapy, 18(1), 5–7. 10.1159/000066375 [PubMed: 12566767]

Khoury MJ, Waters GD, Martin ML, & Edmonds LD (1991). Are offspring of women with hereditary hematologic disorders at increased risk of congenital cardiovascular malformations? Genetic Epidemiology, 8(6), 417–423. 10.1002/gepi.1370080608 [PubMed: 1806411]

Kuo K, & Caughey AB (2016). Contemporary outcomes of sickle cell disease in pregnancy. American Journal of Obstetrics and Gynecology, 215(4), 505.e501. 10.1016/j.ajog.2016.05.032

Lam YH, & Tang MH (1999). Risk of neural tube defects in the offspring of thalassaemia carriers in Hong Kong Chinese. Prenatal Diagnosis, 19(12), 1135–1137. [PubMed: 10590431]

Lee AI, & Okam MM (2011). Anemia in pregnancy. Hematology/Oncology Clinics of North America, 25(2), 241–259. 10.1016/j.hoc.2011.02.001 [PubMed: 21444028]

McLean E, Cogswell M, Egli I, Wojdyla D, & de Benoist B (2009). Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005. Public Health Nutrition, 12(4), 444–454. 10.1017/s1368980008002401 [PubMed: 18498676]

Monseur BC, Morris JR, Hipp HS, & Berghella V (2019). Hypertensive disorders of pregnancy and infertility treatment: A population-based survey among United States women. Journal of Assisted Reproduction and Genetics, 36(7), 1449–1456. 10.1007/s10815-019-01490-1 [PubMed: 31134412]

No Author. (2019). ACOG Committee Opinion No. 762: Prepregnancy Counseling. Obstetrics and Gynecology, 133(1), e78–e89. 10.1097/aog.0000000000003013 [PubMed: 30575679]

Petrakos G, Andriopoulos P, & Tsironi M (2016). Pregnancy in women with thalassemia: Challenges and solutions. International Journal of Women's Health, 8, 441–451. 10.2147/ijwh.s89308

Phillips C, & Boyd MP (2017). Perinatal and neonatal implications of sickle cell disease. Nursing for Women's Health, 21(6), 474–487. 10.1016/j.nwh.2017.10.007

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, … Honein MA (2015). The National Birth Defects Prevention Study: A review of the methods. Birth Defects Research. Part A, Clinical and Molecular Teratology, 103(8), 656–669. 10.1002/bdra.23384 [PubMed: 26033852]

Sontag MK, Yusuf C, Grosse SD, Edelman S, Miller JI, McKasson S, … Shapira SK (2020). Infants with congenital disorders identified through newborn screening - United States, 2015–2017. MMWR. Morbidity and Mortality Weekly Report, 69(36), 1265–1268. 10.15585/mmwr.mm6936a6 [PubMed: 32915168]

Sorrentino F, Maffei L, Caprari P, Cassetta R, Dell'Anna D, Materazzi S, & Risoluti R (2020). Pregnancy in thalassemia and sickle cell disease: The experience of an Italian thalassemia center. Frontiers in Molecular Biosciences, 7, 16. 10.3389/fmolb.2020.00016 [PubMed: 32118041]

Sun D, McLeod A, Gandhi S, Malinowski AK, & Shehata N (2017). Anemia in pregnancy: A pragmatic approach. Obstetrical & Gynecological Survey, 72(12), 730–737. 10.1097/ogx.0000000000000510 [PubMed: 29280474]

Trampont P, Roudier M, Andrea AM, Nomal N, Mignot TM, Leborgne-Samuel Y, … Decastel M (2004). The placental-umbilical unit in sickle cell disease pregnancy: A model for studying in vivo functional adjustments to hypoxia in humans. Human Pathology, 35(11), 1353–1359. 10.1016/j.humpath.2004.07.003 [PubMed: 15668892]

Vafaei H, Karimi S, Akbarzadeh Jahromi M, Asadi N, & Kasraeian M (2020). The effect of mother's β-thalassemia minor on placental histology and neonatal outcomes. The Journal of Maternal-Fetal & Neonatal Medicine, 1–8. [PubMed: 29804488]

Vichinsky EP, MacKlin EA, Waye JS, Lorey F, & Olivieri NF (2005). Changes in the epidemiology of thalassemia in North America: A new minority disease. Pediatrics, 116(6), e818–e825. 10.1542/peds.2005-0843 [PubMed: 16291734]

Vieth JT, & Lane DR (2014). Anemia. Emergency Medicine Clinics of North America, 32(3), 613–628. 10.1016/j.emc.2014.04.007 [PubMed: 25060253]

Wang Y, Kennedy J, Caggana M, Zimmerman R, Thomas S, Berninger J, … Grosse SD (2013). Sickle cell disease incidence among newborns in New York state by maternal race/ethnicity and nativity. Genetics in Medicine, 15(3), 222–228. 10.1038/gim.2012.128 [PubMed: 23018751]

Whitehead NS, Callaghan W, Johnson C, & Williams L (2009). Racial, ethnic, and economic disparities in the prevalence of pregnancy complications. Maternal and Child Health Journal, 13(2), 198–205. 10.1007/s10995-008-0344-2 [PubMed: 18484175]

Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M, … Kirby RS (2015). Updated estimates of neural tube defects prevented by mandatory folic acid fortification: United States, 1995–2011. MMWR. Morbidity and Mortality Weekly Report, 64(1), 1–5. [PubMed: 25590678]

Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, … Edmonds LD (2001). The National Birth Defects Prevention Study. Public Health Reports, 116(Suppl 1), 32–40. 10.1093/phr/116.S1.32

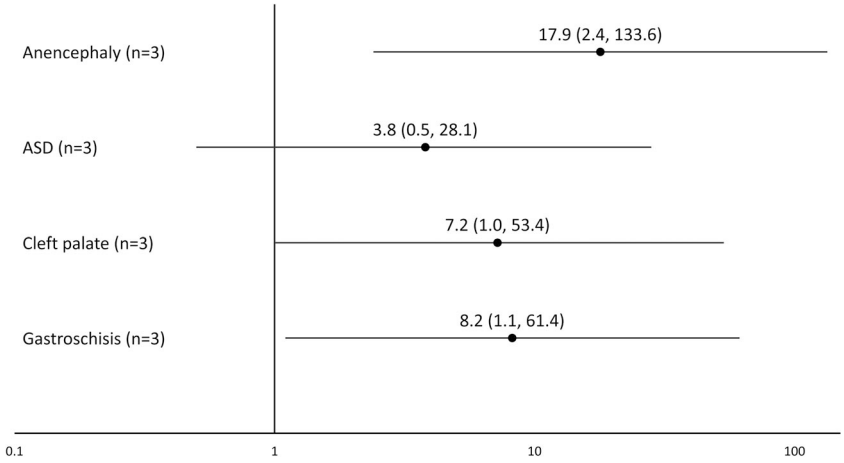

FIGURE 1.

Crude odds ratios and exact 95% confidence intervals for the associations between hereditary hemolytic anemia and birth defects with at least three exposed cases in the National Birth Defects Prevention Study. There are three control women with HHA, 11,760 unexposed controls for anencephaly, ASD, and gastroschisis, and 11,623 unexposed controls for cleft palate. ASD, atrial septal defect; HHA, hereditary hemolytic anemia

TABLE 1

Characteristics of case women in the National Birth Defects Prevention Study, by type of hereditary hemolytic anemia[a]

Characteristic	Any HHA[b] *n* = 28	Sickle cell anemia *n* = 13	Thalassemia *n* = 14	No hereditary hemolytic anemia *n* = 31,839
Maternal age (years)	Average (SD) 27.3 (6.6)	Average (SD) 23.6 (3.9)	Average (SD) 30.0 (7.0)	Average (SD) 27.7 (6.2)
Maternal race/ethnicity	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Non-Hispanic White	9 (32.1)	0 (0)	8 (57.1)	18,702 (58.7)
Non-Hispanic Black	11 (39.3)	8 (61.5)	3 (21.4)	3194 (10.0)
Hispanic	2 (7.1)	2 (15.4)	0 (0)	7805 (24.5)
Asian/Pacific Islander	2 (7.1)	0 (0)	2 (14.3)	880 (2.8)
Other	4 (14.3)	3 (23.1)	1 (7.1)	1248 (3.90
Pre-pregnancy body mass index (kg/m^2)				
Underweight (<18.5)	4 (14.3)	2 (15.4)	2 (14.3)	1648 (5.4)
Normal (18.5 to <25)	17 (60.7)	9 (69.2)	8 (57.1)	15,433 (50.9)
Overweight (25 to <30)	4 (14.3)	1 (7.7)	2 (14.3)	6992 (23.1)
Obese (30+)	3 (10.7)	1 (7.7)	2 (14.3)	6250 (20.6)
Maternal hypertension[c]	5 (17.9)	4 (36.4)	1 (7.1)	3691 (11.8)
Early pregnancy cigarette smoking[d]	8 (28.6)	4 (33.3)	4 (28.6)	6270 (20.2)
Maternal education				
High school diploma or less	12 (44.4)	7 (58.3)	5 (35.7)	13,378 (42.0)
More than high school	15 (55.6)	5 (41.7)	9 (64.3)	17,581 (55.2)
Household income				
<$10,000	12 (44.4)	9 (75.0)	3 (21.4)	5738 (19.8)
$10,000–$50,000	7 (25.9)	3 (25.0)	4 (28.6)	13,469 (46.4)
>$50,000	8 (29.6)	0 (0)	7 (50.0)	9850 (33.9)
Maternal US nativity	22 (81.5)	9 (75.0)	12 (85.7)	24,788 (80.0)
Live birth	23 (82.1)	10 (76.9)	12 (85.7)	30,588 (96.1)
Preterm birth[e]	8 (34.8)	4 (40.0)	3 (25.0)	7586 (24.8)
Low birthweight[e]	7 (30.4)	2 (20.0)	4 (33.3)	6742 (22.3)

[a] Totals vary due to missing values.

[b] HHA, hereditary hemolytic anemia, includes sickle cell anemia, thalassemia, and hereditary spherocytosis. Only one case woman reported hereditary spherocytosis, and therefore this information is only included in the HHA totals.

[c] Maternal hypertension was defined as women who reported either chronic or gestational hypertension.

[d] Early pregnancy refers to the time period from the month before through the third month of pregnancy.

[e] Preterm birth and low birthweight counts and percentages are among livebirths. Preterm birth was defined as <37 weeks gestation and low birthweight was defined as <2500 g at delivery.

TABLE 2

Clinical classification of hereditary hemolytic anemia-exposed offspring

	Any HHA[a]		**Sickle cell anemia**		**Thalassemia**	
	***n* = 28 cases**		***n* = 13 cases**		***n* = 14 cases**	
Birth defect[b]	All cases	Isolated cases[c]	All cases	Isolated cases[c]	All cases	Isolated cases[c]
Non-heart defect						
Anencephaly	3	2	1	1	2	1
Spina bifida	1	1	0	0	1	1
Microtia	1	0	0	0	1	0
Dandy-Walker malformation	1	0	0	0	1	0
Cataract	1	1	1	1	0	0
Cleft palate without cleft lip	3	2	1	1	2	1
Anorectal atresia	1	1	0	0	1	1
Hypospadias	2	1	0	0	2	1
Longitudinal limb deficiency	1	1	1	1	0	0
Craniosynostosis	1	1	1	1	0	0
Biliary atresia	1	0	0	0	1	0
Gastroschisis	3	3	1	1	2	2
Amniotic band syndrome	2	2	1	1	0	0
Congenital heart defect						
Tetralogy of Fallot	1	1	1	1	0	0
d-Transposition of the great arteries	1	0	0	0	1	0
Partial anomalous pulmonary venous return	1	1	1	1	0	0
Coarctation of the aorta	2	1	1	0	1	1
Secundum atrial septal defect	3	0	1	0	2	0
Perimembranous ventricular septal defect	1	0	0	0	1	0
Heterotaxy	2	0	2	0	0	0

Abbreviation: HHA, hereditary hemolytic anemia.

[a]HHA includes sickle cell anemia, thalassemia, and hereditary spherocytosis. Since there was only one case woman who reported hereditary spherocytosis, this information is only included in the HHA totals.

[b] There were 36 birth defects for which there were 0 exposed cases, including: encephalocele, hydrocephaly, cerebellar hypoplasia, holoprosencephaly, anophthalmia/microphthalmia, glaucoma, anotia/microtia, choanal atresia, cleft lip without cleft palate, cleft lip with palate, esophageal atresia/stenosis, small intestinal atresia/stenosis, duodenal atresia/stenosis, colonic atresia, cloacal exstrophy, bladder exstrophy, bilateral renal agenesis/hypoplasia, transverse limb deficiency, diaphragmatic hernia, omphalocele, sacral agenesis, truncus arteriosus, interrupted aortic arch, double outlet right ventricle with transposition of the great arteries, double outlet right ventricle-other, conoventricular septal defect, atrioventricular septal defect, total anomalous pulmonary venous return, hypoplastic left heart syndrome, aortic stenosis, pulmonary atresia, pulmonary valve stenosis, Ebstein anomaly, tricuspid atresia, muscular ventricular septal defect, and single ventricle.

[c] Isolated cases are those with one or more major birth defects occur in the same organ system. Among congenital heart defects, these cases are simple, isolated, which means they have been diagnosed with only 1 congenital heart defect and 0 nonheart defects.