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Neel S. Iyer

Matthew H. Mossayebi

Tracy J. Gao

Lylach Haizler-Cohen

Daniele Di Mascio

See next page for additional authors

Authors

Neel S. Iyer, Matthew H. Mossayebi, Tracy J. Gao, Lylach Haizler-Cohen, Daniele Di Mascio, Rodney A. McLaren, and Huda B. Al-Kouatly

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REVIEW ARTICLE

Glucose-6-phosphate dehydrogenase deficiency as a cause for nonimmune hydrops fetalis and severe fetal anemia: A systematic review

Neel S. Iyer[1] | **Matthew H. Mossayebi**[2] | **Tracy J. Gao**[3] | **Lylach Haizler-Cohen**[4] | **Daniele Di Mascio**[5] | **Rodney A. McLaren Jr**[1] | **Huda B. Al-Kouatly**[1]

[1]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[2]Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

[4]Department of Obstetrics and Gynecology, MedStar Washington Hospital Center, Washington, DC, USA

[5]Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy

Correspondence
Huda B. Al-Kouatly, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College, Thomas Jefferson University, 833 Chestnut Street, Philadelphia, PA 19107, USA.
Email: huda.al-kouatly@jefferson.edu

Abstract

Background: Glucose-6-phosphate dehydrogenase (*G6PD*) deficiency is an X-linked recessive disorder that predisposes individuals to hemolysis due to an inborn error of metabolism. We performed a systematic literature review to evaluate *G6PD* deficiency as a possible etiology of nonimmune hydrops fetalis (NIHF) and severe fetal anemia.

Methods: PubMed, OVID Medline, Scopus, and clinicaltrials.gov were queried from inception until 31 April 2023 for all published cases of NIHF and severe fetal anemia caused by *G6PD* deficiency. Keywords included "fetal edema," "hydrops fetalis," "glucose 6 phosphate dehydrogenase deficiency," and "fetal anemia." Cases with workup presuming G6PD deficiency as an etiology for NIHF and severe fetal anemia were included. PRISMA guidelines were followed.

Results: Five cases of *G6PD*-related NIHF and one case of severe fetal anemia were identified. Four fetuses (4/6, 66.7%) were male and two fetuses (2/6, 33.3%) were female. Mean gestational age at diagnosis of NIHF/anemia and delivery was 32.2 ± 4.9 and 35.7 ± 2.4 weeks, respectively. Four cases (66.7%) required a cordocentesis for fetal transfusion, and two cases (33.3%) received blood transfusions immediately following delivery. Among the four multigravida cases, two (50%) noted previous pregnancies complicated by neonatal anemia. When reported, the maternal cases included two *G6PD* deficiency carrier patients and two *G6PD*-deficient patients. Exposures to substances known to cause *G6PD* deficiency-related hemolysis occurred in 3/6 (50%) cases.

Conclusion: Six cases of NIHF/severe fetal anemia were associated with *G6PD* deficiency. While *G6PD* deficiency is an X-linked recessive condition, female fetuses can be affected. Fetal *G6PD* deficiency testing can be considered if parental history indicates, particularly if the standard workup for NIHF is negative.

KEYWORDS

fetal anemia, *G6PD* deficiency, hydrops fetalis, prenatal diagnosis

1 | INTRODUCTION

Nonimmune hydrops fetalis (NIHF) is defined by the presence of abnormal fluid collection in two or more fetal compartments in the absence of red cell alloimmunization. (DeBolt et al., 2022) Nonimmune hydrops may occur as a result of a wide spectrum of etiologies including infectious, structural (such as cardiac abnormalities), genetic, metabolic, and hematologic (Society for Maternal-Fetal Medicine (SMFM), Norton, et al., 2015; Quinn et al., 2021). Our previously published systematic review showed that after the standard workup (Society for Maternal-Fetal Medicine (SMFM), Norton, et al., 2015) for NIHF, 40%–81% of cases lack a definitive diagnosis, (Iyer et al., 2021) making it difficult for providers to counsel about potential treatments and implications for future pregnancies. If the cause of NIHF remains unknown after the standard workup, maternal and family history may provide additional information to guide testing.

Glucose-6-phosphate dehydrogenase (*G6PD*) deficiency is an X-linked recessive disorder in which a variant in the *G6PD* gene (305900) leads to deficient expression of the corresponding enzyme. The *G6PD* enzyme is involved in protecting erythrocytes from oxidative stress. (Harcke et al., 2019) Deficiency of this enzyme can lead to increased hemolysis in the presence of certain exposures, such as sulfonamide use or fava bean consumption. The condition is most prevalent in Africa, the Middle East, and parts of Mediterranean Europe. However, more than 10% of Black males in the United States are affected (Genetics Home Reference, U.S. National Library of Medicine, 2006).

G6PD deficiency has been well-described in pediatric literature as a potential cause for childhood anemia. Clinical guidance from the Society for Maternal-Fetal Medicine (SMFM) has recommended consideration of *G6PD* testing when NIHF or fetal anemia is diagnosed; however, the typical disease course in pregnancy and fetal and pregnancy outcomes have not been previously described. (Society for Maternal-Fetal Medicine (SMFM), Mari, et al., 2015; Society for Maternal-Fetal Medicine (SMFM), Norton, et al., 2015) Here, we performed a systematic literature review to identify all published cases of NIHF and severe fetal anemia occurring in the setting of *G6PD* deficiency. Our primary objective was to describe the typical clinical presentation, disease course, and fetal outcomes.

2 | METHODS

PubMed, Ovid MEDLINE, Scopus, and clinicaltrials.gov were reviewed from inception until 31 April 2023 for all cases of NIHF and fetal anemia that were attributed to *G6PD* deficiency. Keywords included "fetal edema," "hydrops fetalis," "glucose 6 phosphate dehydrogenase deficiency," and "fetal anemia." Related MESH terms were used in our search (Appendix A). There was no language restriction. The literature search was supplemented by reviewing relevant citations in the initial studies identified. Two investigators (N.S.I. and M.H.M.) performed the literature search with the help of the librarian.

Two reviewers (N.S.I. and M.H.M.) initially screened all manuscripts independently, and then, the results were reviewed together. The criteria for the diagnosis of NIHF or severe fetal anemia in each study, maternal clinical presentation, and maternal and neonatal outcomes were recorded. Additionally, the NIHF workup and *G6PD* workup were documented. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for a systematic review of observational studies. (Page et al., 2021) This study was exempt from institutional review board approval.

3 | RESULTS

Six cases of NIHF and severe fetal anemia attributed to *G6PD* deficiency were published in the literature (Figure 1) (Keller et al., 2015; Masson et al., 1995; Mentzer & Collier, 1975; Molad et al., 2013; Perkins, 1971; Suria et al., 2014). These six cases are summarized in Table 1. Of these six cases, five (83.3%) described NIHF, (Masson et al., 1995; Mentzer & Collier, 1975; Molad et al., 2013; Perkins, 1971; Suria et al., 2014) while one (16.7%) reported severe fetal anemia (Keller et al., 2015). Two of the six (33.3%) fetuses were female (Molad et al., 2013; Suria et al., 2014). The mean gestational age at diagnosis of NIHF/anemia was 32.2 (±4.9) weeks. Out of the five cases with NIHF, four reported the diagnostic criteria of NIHF, and this included fetal abdominal ascites (n=4), pleural effusions (n=3), skin edema (n=2), and pericardial effusions (n=1). One fetal anemia case was suspected by a fetal middle cerebral artery peak systolic velocity of 1.65 MoM. Four cases (66.7%) underwent cordocentesis that confirmed fetal anemia and were subsequently transfused (Keller et al., 2015; Masson et al., 1995; Molad et al., 2013; Suria et al., 2014).

Three cases reported notable maternal medical and family history. One patient had a known family history of *G6PD* deficiency, and subsequently had a postive molecular diagnosis at 22 weeks and weekly fetal ultrasounds starting at 24 weeks. Also, family history of hydrops fetalis in a maternal brother and maternal uncle were also reported for this patient (Keller et al., 2015). Another disclosed neonatal jaundice and adult anemia in multiple

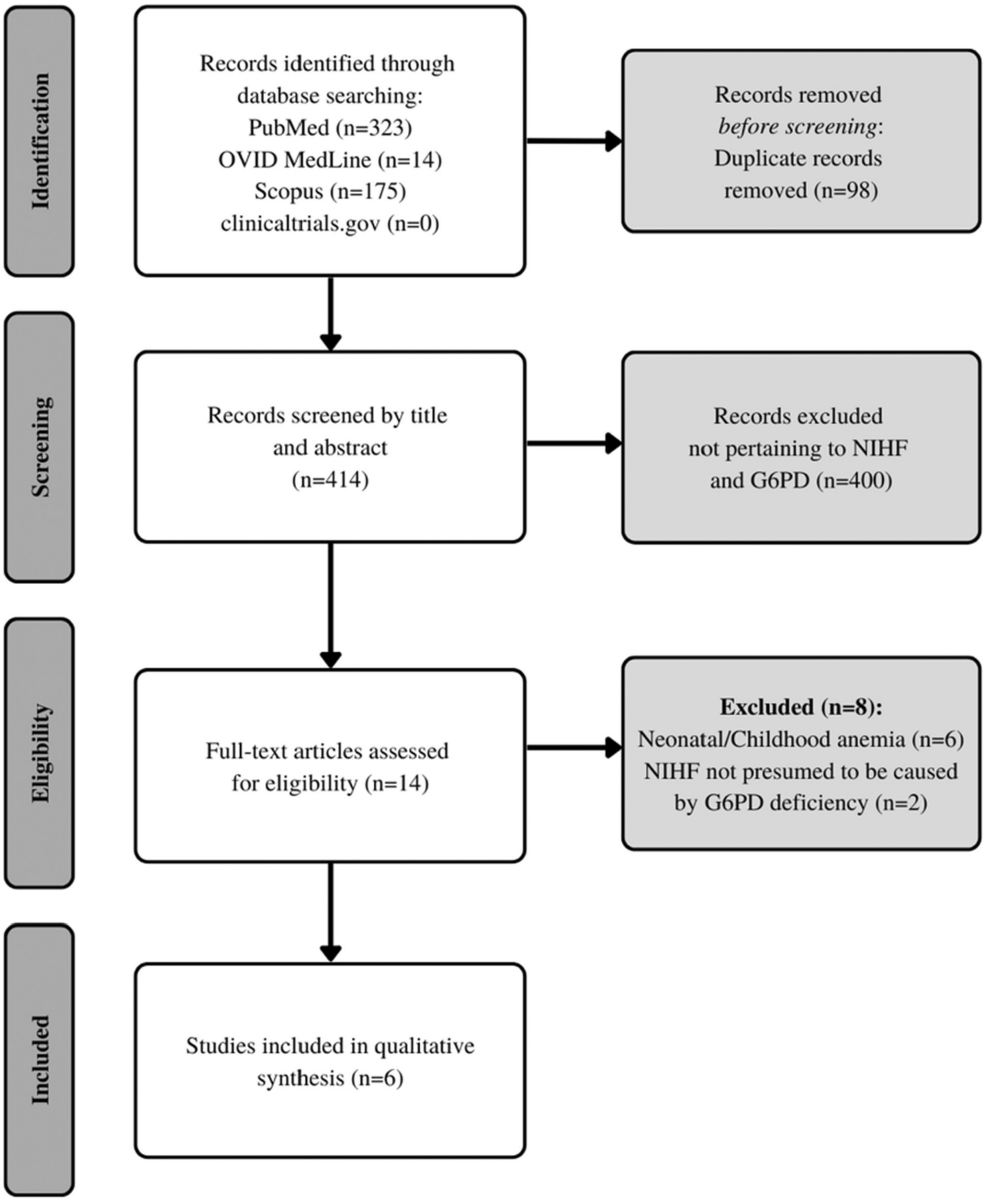

FIGURE 1 PRISMA flow diagram for NIHF/severe fetal anemia caused by G6PD deficiency. This figure depicts the PRISMA flow diagram used for case inclusion. Records were identified through database searching, and duplicate records were removed. Records not pertaining to NIHF and G6PD were excluded. Full-text articles were assessed, and records describing neonatal/childhood anemia and NIHF not presumed to be caused by G6PD deficiency were excluded. A total of six studies were included in qualitative synthesis. G6PD, glucose-6-phosphate dehydrogenase; NIHF, nonimmune hydrops fetalis.

relatives (Mentzer & Collier, 1975). The third case was significant for a prior delivery of a male infant with presumed G6PD deficiency with subsequent infant death of an undetermined cause at 59 days of life (Perkins, 1971). Two out of the four multiparous patients (50%) reported previous pregnancies complicated by neonatal anemia (Mentzer & Collier, 1975; Perkins, 1971). Moreover, two (2/4, 50%) were *G6PD* deficiency carriers (Keller et al., 2015; Mentzer & Collier, 1975) and two (2/4, 50%) were *G6PD*-deficient (Molad et al., 2013; Perkins, 1971). The remaining two cases did not specify maternal *G6PD* deficiency status (Masson et al., 1995; Suria et al., 2014).

The mean gestational age of delivery was 35.7 ± 2.4 weeks. Among the five cases with diagnosed hydrops fetalis, two (40%) were diagnosed on autopsy following stillbirth or neonatal death (Mentzer & Collier, 1975; Perkins, 1971). One case reported treatment of a UTI with sulfisoxazole 17 days prior to spontaneous delivery of a stillborn infant. Autopsy showed severe anemia and hydrops fetalis (Perkins, 1971). The second case reported neonatal death 2 hours after delivery. Autopsy showed generalized brawny edema, atelectatic lungs, pleural effusions, and hepatosplenomegaly, with evidence of extramedullary hepatic hematopoiesis and erythroid hyperplasia within

TABLE 1 Summary of published cases of NIHF/severe fetal anemia caused by G6PD deficiency.

Case	Perkins (1971)	Mentzer and Collier (1975)	Masson et al. (1995)	Molad et al. (2013)	Suria et al. (2014)	Keller et al. (2015)
Maternal race	Black	Asian	Black	White	Asian	White
Diagnosis	Hydrops fetalis	Hydrops fetalis	Hydrops fetalis	Hydrops fetalis	Hydrops fetalis	Severe anemia
Diagnostic criteria	NR	Abdominal ascites, generalized skin edema, pleural effusions	Abdominal ascites, pleural effusions	Abdominal ascites, pericardial effusions	Abdominal ascites, generalized skin edema, pleural effusions	MCA PSV = 1.65 MoM
Time of diagnosis	Postpartum	Postpartum	Prenatal	Prenatal	Prenatal	Prenatal
GA at diagnosis	36w	38w	24w	33w	31w	31w
GA at delivery	36w	38w	34w	34w	33w	39w
Mode of delivery	Vaginal delivery	Vaginal delivery	Emergency cesarean section	Emergency cesarean section	Emergency cesarean section	Emergency cesarean section
Fetal sex	M	M	M	F	F	M
Hydrops evaluation	Maternal and fetal hemoglobin electrophoresis; Direct and indirect Coombs testing	Maternal, paternal, and fetal hemoglobin electrophoresis; Direct and indirect Coombs testing	Direct and indirect Coombs testing; fetal karyotype; CMV, Rubella, Parvovirus	Direct and indirect Coombs testing; fetal karyotype; CMV, Rubella, Parvovirus, Toxoplasmosis, EBV, HSV, HIV testing	Direct and indirect Coombs testing; CMV, Rubella, Toxoplasmosis, HSV; Thyroid function testing	NR
G6PD diagnosis	G6PD enzyme activity	G6PD enzyme activity	G6PD enzyme activity	G6PD enzyme activity	G6PD enzyme activity	G6PD gene testing
Fetal outcome	Stillbirth	Neonatal Death	Living	Living	Living	Living
Maternal G6PD status	Homozygous	Heterozygous	Not specified	Homozygous	Not specified	Heterozygous: c.1249C>T p.Arg417Cys
*Fetal G6PD enzyme level/activity	0.8 U/gHgb (N: 15.5 U/gHGb)	Abnormal, enzyme level not reported	35 mU/10^3 RBC (N: 95–125 mU/10^3 RBC)	6 IU (N: 10–14.2 IU)	10.65 U/gHgb (N: 10.15–14.71 U/gHgb)	NR

*The manuscript by Suria et al., mentions that the enzyme level was "low normal" at birth, acknowledging that at the time of the test, the baby's reticulocyte count was elevated and the baby had received intra-uterine transfusion about three weeks earlier, which could result in a transient and mildly elevated enzyme level.

Abbreviations: CMV, cytomegalovirus; GA, gestational age; G6PD, glucose-6-phosphate dehydrogenase; Hgb, hemoglobin; MCA, middle cerebral artery; MoM, multiples of median; NR, not reported; PPROM, preterm premature rupture of membranes; PSV, peak systolic velocity; RBC, red blood cells.

the bone marrow (Mentzer & Collier, 1975). These two cases were delivered vaginally (Mentzer & Collier, 1975; Perkins, 1971), while the remaining four underwent emergent cesarean delivery at the time of delivery (Keller et al., 2015; Masson et al., 1995; Molad et al., 2013; Suria et al., 2014). Indications for emergent cesarean delivery included recurrence of hydrops fetalis (Masson et al., 1995), fetal anemia (Molad et al., 2013), prolonged rupture of membranes (Suria et al., 2014), and failure to progress in labor (Keller et al., 2015).

In terms of fetal and neonatal outcomes, there was one stillbirth (16.7%) and one neonatal death (16.7%). Of the four living infants, two (50%) received blood transfusions immediately following delivery (Masson et al., 1995; Molad et al., 2013), while one (25%) was re-admitted at 8 months for blood transfusion (Keller et al., 2015). The two cases that received blood transfusions following delivery reported readmission during the first year of life for additional blood transfusions at 30 days (Masson et al., 1995) and 6 weeks (Molad et al., 2013), respectively. The fourth infant was lost to follow-up after initial discharge from the hospital (Suria et al., 2014).

One case (16.7%) reported molecular testing for *G6PD* deficiency in utero, via cordocentesis (Keller et al., 2015), while neonatal *G6PD* deficiency testing was reported in the 5/6 (83.3%) remaining cases by G6PD enzyme levels (Perkins et al., 1971; Mentzer & Collier, 1975; Masson et al., 1995; Molad et al., 2013; Suria, et al., 2014).

Of the five cases with hydrops fetalis, three (60%) reported maternal exposures to substances that are known to cause *G6PD* deficiency-related hemolysis. Of these three cases, one (33%) reported usage of sulfa-containing medication (Perkins, 1971), one (33%) reported fava beans consumption (Molad et al., 2013), and one (33%) reported consumption of both fava beans and ascorbic acid (Mentzer & Collier, 1975). All three of these exposures occurred within 1 month preceding hydrops diagnosis and delivery (Mentzer & Collier, 1975; Molad et al., 2013; Perkins, 1971).

4 | DISCUSSION

G6PD deficiency appears to be a rare cause of NIHF and severe fetal anemia. While *G6PD* deficiency has been well-described in the pediatric literature, particularly in the evaluation of neonatal hyperbilirubinemia and anemia (Liu et al., 2015; Watchko et al., 2013), our systematic review is the first to summarize the association between suspected G6PD deficiency as an etiology for NIHF and severe fetal anemia.

Further workup for NIHF is essential to effectively counsel patients about potential treatment options, possible neonatal outcomes, and implications for future pregnancies. Thus, with a known family history, patients should be evaluated for *G6PD* deficiency as a potential cause of NIHF or severe fetal anemia following standard workup (Society for Maternal-Fetal Medicine (SMFM), Mari, et al., 2015; Society for Maternal-Fetal Medicine (SMFM), Norton, et al., 2015). When fetal anemia is suspected prenatally, evaluation for fetomaternal hemorrhage is recommended (Troia et al., 2019).

Routine newborn screening in the United States does not include testing for *G6PD* deficiency, except in the District of Columbia. In most states, *G6PD* deficiency testing is only recommended in newborns with hyperbilirubinemia refractory to phototherapy or newborns who have a family history, ethnicity, or geographic origin that is suggestive of the condition (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004). Furthermore, SMFM recommends consideration of *G6PD* testing when NIHF or fetal anemia is diagnosed (Society for Maternal-Fetal Medicine (SMFM), Mari, et al., 2015; Society for Maternal-Fetal Medicine (SMFM), Norton, et al., 2015). In most places in the world, screening for *G6PD* deficiency in newborns is done by the fluorescent spot test prior to confirmatory testing using either a quantitative enzyme activity assay or molecular DNA testing (Cappellini & Fiorelli, 2008). In the United States, rapid fluorescent spot test or *G6PD* enzyme testing is commonly utilized for initial screening (Hsia et al., 1993; Lin et al., 2005). If screening demonstrates deficiency of *G6PD*, follow-up molecular genetic testing can be considered with *G6PD* full gene sequencing. Deletion/duplication testing may be performed if sequencing is not informative (Hsia et al., 1993). While there are currently 400 known *G6PD* variants with functional interpretations (Algur et al., 2012), the five most common variants accounting for up to 89% of all *G6PD* deficiency cases include c.376A>G, c.202G>A, c.563C>T, c.1376G>T, and c.1388G>A. These variants have ethnic and racial associations, including with African-American (c.376A>G, c.202G>A), Mediterranean (c.563C>T), and Chinese (c.1376G>T, c.1388G>A) populations (Wang et al., 2014). During pregnancy, testing for *G6PD* deficiency will typically be done via sequencing of the *G6PD* gene from an amniotic fluid sample (Wang et al., 2014). In our review, only one out of the six cases had genetic testing (by cordocentesis) and did not result in one of the most common variants listed.

Notably, two of the six (33.3%) cases in our review occurred in female fetuses. Because *G6PD* deficiency follows X-linked recessive inheritance, males who inherit the *G6PD* variant are hemizygous and will usually present with hemolytic symptoms. Whether heterozygous females develop *G6PD* symptoms depends on X chromosome

inactivation and the degree of silencing of the normal and abnormal X chromosomes. Typically, the inactivation occurs randomly, and therefore, the normal and abnormal chromosomes will be deactivated in 50% of the cells. This allows adequate *G6PD* enzyme activity and absence of symptoms in heterozygous females. In cases of unfavorable or skewed X chromosome inactivation, the unaffected X chromosome is silenced in most cells, leading to inadequate *G6PD* enzyme activity and hemolysis symptoms. The prevalence of females who are homozygous for the *G6PD* deficiency variant is reported to be about 1%, even in high risk populations, like racial or ethnic groups with higher disease prevalence (Garcia et al., 2021; Richardson & O'Malley, 2023). These homozygous females present with a more severe phenotype. Recent literature has described DNA methylation as an additional potential reason for why heterozygous females may have various phenotypes, with some developing severe enzyme deficiency (Geck et al., 2023).

Historically, treatment of *G6PD* deficiency has involved elimination and avoidance of drugs, foods, or infections, which can trigger hemolysis in these individuals. Three (50%) cases in our review involved exposure to substances known to cause *G6PD* deficiency-related hemolysis. This reinforces the need for strict counseling for patients with *G6PD* deficiency or carrier status about the potential effects on their pregnancy. In neonates, once hemolysis is diagnosed, treatment usually consists of phototherapy, and in severe cases, exchange transfusion may be warranted (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004). In utero, the only treatment presently available is transfusion via cordocentesis, which four (66.7%) of the fetuses identified in our search received. No gene therapy is currently available to treat *G6PD* deficiency, likely due to the large number of variants that can cause the disease; however, newer studies are exploring the use of molecular activators to correct the most common variants, stabilize the *G6PD* gene, and protect cells from oxidative stress (Lee et al., 2022).

There are no previously published reviews evaluating *G6PD* deficiency as a cause for hydrops fetalis or severe fetal anemia, and as such, our review summarizes the risk factors and clinical outcomes related to this diagnosis. Another strength of our review is the inclusion of only peer-reviewed publications.

A limitation of our study is the fact that a review can only be as reliable as the published cases. This ascertainment bias was mitigated by having minimal exclusion criteria and no language restriction. Given the paucity of published cases, we are unable to determine the true prevalence of *G6PD* deficiency as a cause for NIHF or severe fetal anemia. As our study relied on searching through published cases, it is important to acknowledge the potential impact of publication bias, as cases with non-significant findings often go unreported. As stated previously, our goal in publishing the review was to describe the clinical presentation and pregnancy outcomes related to this diagnosis. Future research should focus on understanding the prevalence of *G6PD* deficiency as a cause for NIHF/severe fetal anemia and potential treatments, given the options presently available for in utero treatment of NIHF/severe fetal anemia due to *G6PD* deficiency.

We summarized five cases of NIHF and one case of severe fetal anemia associated with *G6PD*. Our review demonstrated that *G6PD* deficiency is a rare cause of NIHF/severe fetal anemia. While *G6PD* deficiency is an X-linked recessive condition, female fetuses can be affected. Fetal *G6PD* deficiency testing can be considered if parental history indicates, particularly if standard workup for NIHF is negative.

AUTHOR CONTRIBUTIONS

NSI and HBA were involved in the conceptualization and development of the study methodology. NSI and MHM performed the literature search and data abstraction with supervision from HBA. NSI, MHM, TJG, LHC, and DDM were involved in the data analysis and manuscript preparation. LHC, DDM, RAM, and HBA were responsible for manuscript revision and review. TJG was responsible for visualization of the figures and tables in the study. RAM and HBA supervised the entire project.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

An ethics statement is not applicable because this study is based exclusively on published literature.

ORCID

Matthew H. Mossayebi https://orcid.org/0000-0003-1717-5934
Tracy J. Gao https://orcid.org/0000-0001-9342-7326

Rodney A. McLaren Jr https://orcid.org/0000-0002-5013-3456
Huda B. Al-Kouatly https://orcid.org/0000-0003-2922-0333

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APPENDIX A

Search strategy

A.1 | OVID-MEDLINE SEARCH STRATEGY

(((exp Edema/ and exp Fetal Diseases/) or exp Hydrops Fetalis/) OR ((fetal edema or fetal hydrops or hydrops fetalis or fetal anemia or fetal anaemia or foetal hydrops or foetal anaemia or foetal anemia or foetal oedema or fetal oedema or foetal edema or hydrops or hydrops fetali).mp)) AND ((exp Glucosephosphate Dehydrogenase Deficiency/) OR ((glucose-6-phosphate dehydrogenase or glucose 6 phosphate dehydrogenase or G6PD or glucosephosphate dehydrogenase or gpd).mp).

A.2 | SCOPUS SEARCH STRATEGY

((INDEXTERMS (("Edema" AND "Fetal Diseases") OR "Hydrops Fetalis")) OR (TITLE-ABS-KEY ((fetal AND edema) OR (fetal AND hydrops) OR (hydrops AND fetalis) OR (fetal AND anemia) OR (fetal AND anaemia) OR (foetal AND hydrops) OR (foetal AND anaemia) OR (foetal AND anemia) OR (foetal AND oedema) OR (fetal AND oedema) OR (foetal AND edema) OR (hydrops AND fetali) OR (hydrops) OR (non-immune AND hydrops AND fetalis)))) AND ((INDEXTERMS ("Glucosephosphate Dehydrogenase Deficiency")) OR (TITLE-ABS-KEY ((glucose-6-phosphate AND dehydrogenase) OR (glucose 6 phosphate AND dehydrogenase) OR (g6pd) OR (glucosephosphate AND dehydrogenase) OR (gpd) OR (g6pd AND deficiency) OR (glucose-6-phosphate AND dehydrogenase AND deficiency)))).

A.3 | PUBMED SEARCH STRATEGY

((("Edema"[MeSH] AND "Fetal Diseases"[Mesh]) OR "Hydrops Fetalis"[MeSH]) OR ((fetal edema OR fetal hydrops OR hydrops fetalis OR fetal anemia OR fetal anaemia OR foetal hydrops OR foetal anaemia OR foetal anemia OR foetal oedema OR fetal oedema OR foetal edema OR hydrops fetali OR hydrops OR non-immune hydrops fetalis))) AND (("Glucosephosphate Dehydrogenase Deficiency"[Mesh]) OR ((glucose-6-phosphate dehydrogenase OR glucose 6 phosphate dehydrogenase OR G6PD OR glucosephosphate dehydrogenase OR gpd OR G6PD deficiency OR glucose-6-phosphate dehydrogenase deficiency))).

A.4 | DATA SOURCES

Ovid MEDLINE, SCOPUS, and Pubmed were searched using terms related to: "fetal edema," "fetal diseases," "fetal anemia," "hydrops fetalis," and "Glucosephosphate Dehydrogenase Deficiency." There was no limitation placed on the language, year, or location of the studies included in the initial search strategy.