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Case Report

Adding to the Evidence: Neonatal Outcomes After Unintentional Hydroxyurea Use in Pregnant Women with Sickle Cell Disease

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Abstract

Background: Hydroxyurea (HU) is contraindicated in pregnancy due to teratogenic risks [1]. We report two cases of inadvertent HU exposure during pregnancy in sickle cell anemia (SCA) patients, resulting in live births without congenital anomalies.

Cases: Two women with SCA continued HU until 18 and 36 weeks of gestation. Both developed severe oligohydramnios, necessitating cesarean delivery at 35-36 weeks. Birth weights were 2100g (Case 1) and 1988g (Case 2). At 6-month follow-up, both infants showed normal development and weight gain.

Conclusion: Despite HU exposure, both pregnancies yielded healthy infants. However, HU remains unsafe in pregnancy; rigorous contraception and preconception counseling are essential [1,2].

Keywords: *Hydroxyurea; Sickle Cell Anemia; Pregnancy; Oligohydramnios; Teratogenicity; Preterm Birth*

Introduction

Sickle cell anemia (SCA) increases maternal-fetal risks during pregnancy, including vaso-occlusive crises and intrauterine growth restriction [2]. Hydroxyurea, a ribonucleotide reductase inhibitor, reduces SCA complications; however, it is classified as FDA Category D due to teratogenicity in animal studies and limited human data [1]. Reported fetal risks include skeletal defects, renal toxicity, and oligohydramnios [3]. We present two cases of inadvertent HU use in SCA pregnancies, highlighting neonatal outcomes and implications for clinical management.

Case Presentations

Case 1

PD, 25-year-old primigravida with HbSS SCA (Hb: 7.2 g/dL). HU exposure: Took HU (15 mg/kg/day) until 26 weeks of gestation. Discontinued upon detection during history taking. Pregnancy course: Severe oligohydramnios (AFI: 3 cm) at 34 weeks, with normal fetal doppler studies. No maternal SCA crises or hypertension. Delivery: Emergency cesarean for non-reassuring fetal heart rate. Neonate: Male, birth weight 1615g (below 5th percentile), Apgar 8 and 9. Normal newborn screening; no dysmorphic features.

Case 2

JN, 24-year-old primigravida with HbSS SCA (Hb: 6.8 g/dL). HU exposure: Continued HU (20 mg/kg/day) until admission for loss of Fetal movement, at 35 weeks of pregnancy. Pregnancy course: Severe oligohydramnios (AFI: 3.8 cm) at 35 weeks. Moderate PIH (BP: 148/104 mmHg) managed with labetalol. Delivery: Cesarean at 36 weeks 2 days for PIH, worsening oligohydramnios. Neonate: Female, birth weight 1920g (Below 5th percentile), Apgar 7/9. Clinically, no anomalies.

Neonatal follow-up

- Case 1: NICU stay: 7 days for prematurity (no ventilatory support required). Normal newborn screening; no dysmorphic features, no clinical cardiac/renal abnormalities. At 6 months: Weight 4.8 kg, achieving milestones (e.g. sitting unsupported).
- Case 2: NICU stay: 1 day. Normal newborn screening; no dysmorphic features, no clinical cardiac/renal abnormalities. At 6 months: Weight 4.2 kg, achieving milestones (e.g. sitting unsupported).

Discussion

These cases present a critical clinical scenario: inadvertent hydroxyurea (HU) exposure spanning the high-risk first trimester (organogenesis) and continuing deep into the second and third trimesters in women with sickle cell anemia (SCA). While both infants were delivered without congenital malformations and demonstrated normal development at 6 months, both pregnancies were complicated by severe oligohydramnios, leading to indicated preterm delivery and low birth weight. This highlights the complex and potentially severe risks associated with prolonged HU exposure throughout gestation.

1. Absence of congenital malformations despite first-trimester exposure: The lack of major structural anomalies in these infants is particularly noteworthy given that exposure included the critical period of organogenesis (first trimester). This outcome aligns with McGann., *et al*. (2013), who reported no major malformations in 30 pregnancies with HU exposure (many including first trimester), and Singh., *et al*. (2021), whose meta-analysis found no consistent pattern of major anomalies. Potential explanations include:

    - Dose: The doses used (15-20 mg/kg/day) may be below a critical teratogenic threshold for some individuals, though this is unpredictable.
    - Individual susceptibility: Human susceptibility may vary significantly compared to animal models where teratogenicity is consistently demonstrated at high doses.
    - Limitations of reporting: Under-reporting or publication bias favoring normal outcomes is possible. Crucially, this absence does not negate HU's known teratogenic potential. The FDA Siklos® label (2021) categorizes HU as Pregnancy Category D (positive evidence of human fetal risk), and isolated human reports of anomalies (e.g., cardiac, skeletal, neural tube) exist, primarily linked to first-trimester exposure. Our cases represent a fortunate outcome within a spectrum of possible risks.

2. Oligohydramnios: A consequence of prolonged exposure: The development of severe oligohydramnios in both cases is a direct and significant consequence of extended HU exposure, particularly into the late second and third trimesters. Singh., *et al*. (2021) identified oligohydramnios as the most common complication (28%) in their systematic review of HU-exposed pregnancies. The mechanisms are likely multifactorial and amplified by continuous exposure:

- Direct fetal renal toxicity: HU's inhibition of DNA synthesis profoundly impacts the rapidly developing fetal kidneys. Nephrogenesis (formation of nephrons) continues until approximately 36 weeks, making it vulnerable throughout gestation. Prolonged HU exposure likely impaired fetal urine production, the primary contributor to amniotic fluid volume later in pregnancy.

- Placental dysfunction: HU may contribute to impaired placental development or function (e.g. abnormal trophoblast invasion, reduced uteroplacental perfusion), potentially starting early and worsening with continued exposure, further compromising amniotic fluid production and fetal nutrition/growth.
- Clinical impact: The oligohydramnios was severe enough to necessitate preterm delivery in both cases (35 - 36 weeks), directly contributing to the low birth weights and associated neonatal risks (prematurity).

3. Growth restriction and long-term outcomes:

- Severe intrauterine growth restriction (IUGR): Both infants were severely growth-restricted (<5th percentile), a finding more profound than often seen in SCA pregnancies alone. While oligohydramnios and prematurity are major contributors, the prolonged HU exposure likely played a significant direct role by suppressing cellular proliferation systemically and potentially via placental insufficiency throughout gestation. Ballas., *et al.* (2019) noted variable growth outcomes but reported catch-up growth was possible.
- Normal short-term development: The achievement of normal developmental milestones and adequate weight gain at 6 months is reassuring. This suggests that once the exposure ceases (at birth), the suppressive effects may resolve, allowing for initial catch-up.
- Persisting concerns for long-term development: However, long-term vigilance is imperative. Continuous exposure during critical periods of brain growth (which occurs throughout gestation and postnatally) raises concerns. Berard., *et al.* (2020) reported neurodevelopmental delays in approximately 12% of children with in utero HU exposure identified during longer follow-up. Potential effects on renal function reserve, gonadal development, or later-onset issues cannot be ruled out based on a 6-month assessment.

4. Critical clinical implications for management: These cases, involving exposure across all trimesters, underscore the absolute necessity of strict measures:

- Mandatory preconception planning and HU cessation: HU is strictly contraindicated during pregnancy (Siklos® PI, 2021). Preconception counseling must be proactive and explicit for all women of childbearing potential on HU. Discontinuation at least 3 months before conception is essential to prevent first-trimester exposure. Transition to alternative therapies (e.g. chronic transfusions) must occur before pregnancy attempts.
- Fail-safe contraception: Highly effective contraception (LARC - IUDs/Implants - is strongly preferred) combined with a barrier method is non-negotiable during HU therapy. The inadvertent exposures here represent a failure of contraceptive counseling or method.
- Intensive prenatal monitoring after any exposure: If pregnancy occurs on HU:
- Immediate discontinuation is paramount.
- Detailed anomaly scan (including fetal echo) is crucial given first-trimester exposure risk.
- Serial monitoring of amniotic fluid index (AFI) and fetal growth every 2-4 weeks from diagnosis onwards is mandatory due to the high risk of oligohydramnios and IUGR developing later, even if initial scans are normal. Our cases exemplify this risk.
- Enhanced fetal surveillance (Dopplers, NSTs) is needed, especially if oligohydramnios or growth restriction develop.
- Long-term multidisciplinary pediatric follow-up: Infants with any gestational HU exposure, especially prolonged exposure, require structured long-term follow-up. This should monitor growth velocity, neurodevelopment (formal assessments beyond infancy), renal function, and pubertal development well into childhood and adolescence.

Conclusion

These cases demonstrate that pregnancies with hydroxyurea exposure encompassing the high-risk first trimester and continuing late into gestation can result in infants without structural birth defects and normal early development. However, this outcome should be viewed as fortunate rather than typical. The defining feature of both pregnancies was severe oligohydramnios, a direct consequence of prolonged HU exposure, leading to significant fetal growth restriction and necessitating preterm delivery. This confirms the substantial risk of significant fetal/placental toxicity with continued HU use during pregnancy. While major malformations were avoided here, the FDA Category D classification and documented teratogenic risks, particularly for first-trimester exposure, remain absolute. Therefore, HU is unequivocally contraindicated throughout pregnancy. These cases highlight the critical importance of: 1) rigorous preconception counseling and HU discontinuation well before conception; 2) implementation of highly reliable contraception (LARC) during HU therapy; 3) intensive prenatal monitoring for oligohydramnios and growth restriction if exposure occurs; and 4) mandatory long-term pediatric surveillance for exposed infants to detect any delayed sequelae. Prolonged in utero HU exposure carries significant, potentially avoidable, risks.

Consent and Ethical Approval

Written informed consent obtained; institutional ethics committee approval secured.

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