Hemoglobin
international journal for hemoglobin research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ihem20

Ethical and Clinical Considerations in the Use of Hydroxyurea in Pregnant Women with Sickle Cell Disease

Gayatri Desai, Kapilkumar Dave, Sumeet Devare & Shrey Desai

To cite this article: Gayatri Desai, Kapilkumar Dave, Sumeet Devare & Shrey Desai (07 Feb 2024): Ethical and Clinical Considerations in the Use of Hydroxyurea in Pregnant Women with Sickle Cell Disease, Hemoglobin, DOI: 10.1080/03630269.2024.2310283

To link to this article: https://doi.org/10.1080/03630269.2024.2310283

Published online: 07 Feb 2024.

HEMOGLOBIN
https://doi.org/10.1080/03630269.2024.2310283

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

OPEN ACCESS Check for updates

Ethical and Clinical Considerations in the Use of Hydroxyurea in Pregnant Women with Sickle Cell Disease

Letter to the editor

Sickle cell disease (SCD) is an inherited blood disorder characterized by the tendency of red blood cells to become sickle-shaped and block capillaries, leading to vaso-occlusion and anemia [1, 2]. Pregnant women with SCD have an increased risk for adverse maternal, fetal and neonatal outcomes [3–6]. The risk of maternal death is ten times higher compared to normal pregnancies [4, 7]. The risk of maternal death was 30 times higher in our cohort of pregnant women with the disease. Additionally, pregnant women with SCD have a multifold higher risk of intrauterine growth restriction, intrauterine fetal death (IUFD), stillbirth, anemia, low birth weight (LBW), and preeclampsia/eclampsia [4].

The standard of antenatal care in pregnancy with SCD is low-dose aspirin, folic acid supplementation, treatment by a multidisciplinary team, frequent antenatal care visits, regular sonographies, education of the patient and family members, and tertiary level care in case of complications [8, 9]. Top-up blood transfusion is recommended for acute anemia. However, prophylactic blood transfusion is not universally recommended and is quite challenging in low- and middle-income countries [9]. Despite providing the standard of care, maternal and fetal outcomes have been unfavorable in a variety of clinical settings, even in high-income countries [6].

Hydroxyurea (HU) is an antimetabolite that is used in nonpregnant patients with SCD to decrease the incidence/risk of complications, including acute chest syndrome (ACS), vaso-occlusive crisis, and stroke [8]. HU is approved for the treatment of SCD among nonpregnant patients by many drug regulatory authorities, including in India. It is included in the national guidelines in India and other countries for the treatment of SCD [10, 11].

Therefore, there is a growing interest in exploring the use of HU during pregnancy in women with SCD [12, 13]. There are a few reasons to justify the role of HU during pregnancy. First, HU reduces the incidence of acute chest syndrome, stroke and vaso-occlusive crisis among non-pregnant patients [14, 15]; these are the major causes of maternal deaths and morbidity in SCD. Placental studies among women with SCD have revealed microthrombi, sickle-shaped cells and infarcts. HU tends to reduce sickling of red blood cells. Thus, it is plausible that HU may reduce the risk of stillbirth, IUFD, LBW and preterm deliveries although there are no human studies.

HU is currently not recommended in pregnancy. Patients are advised to stop the drug before planning a pregnancy [16]; based on it being an antimetabolite. Some animal studies have reported congenital anomalies among fetuses, such as partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, and missing lumbar vertebrae. Although the dose used in these animal studies was much higher than the currently recommended doses used in humans [17–19].

However, there have been more than 300 pregnancies in which hydroxyurea was administered during pregnancy as reported in case series and cohort studies globally. These studies reported no increased risk of fetal malformation more than the baseline risk in the general population [20–24]. The use of HU in pregnancy may be considered in second and third trimester as per one such study [13]. The British Haematological Society has recommended that HU might be considered in those pregnant women where the risk of stopping the drug outweighs the risk of continuing it after explaining the risks and benefits to the patients [13]. However, no trials have looked at the effectiveness of HU on maternal, fetal and neonatal outcomes.

There are other drugs belonging to category D and category X like valproic acid, warfarin, carbamazepine, propylthiouracil, etc. with an established risk of fetal malformations [25–27]. However, it is standard of care to use these category D/X drugs during pregnancy when maternal benefits outweigh fetal risks. For example, it is standard of care to use warfarin in pregnant patients with mechanical heart valves and propylthiouracil to treat hyperthyroidism during pregnancy [28].

Therefore, a risk-benefit analysis would greatly enhance the ethical and clinical debate about using HU in pregnancy. If there are good quality studies to document the risk and benefits of using HU during pregnancy, then regulators, clinicians and patients may be able to make an informed decision. Considering the very high risk of maternal and fetal outcomes during pregnancy in women with SCD, there is a strong ethical argument to generate good quality evidence about the risks and benefits of using HU during pregnancy with SCD. A well-designed randomized control trial among consenting women might offer such good quality evidence. Unfortunately, no such randomized control trials or even quasi-experimental studies have been conducted so far.

Therefore, we urge researchers to conduct rigorous studies documenting the effectiveness and risks of using HU among pregnant women with SCD. We also propose to the ethics committees to approve the experimental use of HU among pregnant women in a trial setting [29]. However, it would be important for the trialists to follow universal ethical standards. Additionally, the patients should be informed about the risks and benefits of HU, and the patients should be enrolled for the study only after informed consent is received. The investigators should closely follow fetal outcomes through serial sonography for the early detection of any fetal abnormalities. It is preferable to start HU after the completion of the first trimester and once organogenesis is completed; thus, it may further reduce the risk of fetal anomalies with HU. Standard care should be provided to both arms equally to study the effect of HU. A data safety and monitoring board should closely follow the benefits and harms. The ethics committees may allow such trials if the team of investigators takes aforementioned precautions.

In conclusion, we believe that there is a strong ethical and clinical case for conducting a randomized control trial to evaluate the effectiveness of HU toward improving maternal and fetal outcomes of pregnancies in patients with SCD and assess any associated risk.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

[1] Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. Annu Rev Pathol. 2019;14(1):263–292. doi: 10.1146/annurev-pathmechdis-012418-012838.

[2] Steinberg MH. Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. Scientific World J. 2008; 8:1295–1324. doi: 10.1100/tsw.2008.157.

[3] O Ntim E, Daveena M,TS, Louise W, *et al.* Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis. Blood. 2015;125(21):3316–3326.

[4] 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. Obstet Anesth Dig. 2017;37(1):9–10. doi: 10.1097/01.aoa.0000511999.06517.f5.

[5] Desai G, Anand A, Shah P, *et al.* Sickle cell disease and pregnancy outcomes: a study of the community-based hospital in a tribal block of Gujarat, India. J Health Popul Nutr. 2017;36(1):3–3. doi: 10.1186/s41043-017-0079-z.

[6] Lesage N, Deneux Tharaux C, Saucedo M, *et al.* Maternal mortality among women with sickle-cell disease in France, 1996-2009. Eur J Obstet Gynecol Reprod Biol. 2015;194:183–188. doi: 10.1016/j.ejogrb.2015.09.016.

[7] Asnani MR, McCaw-Binns AM, Reid ME. Excess risk of maternal death from sickle cell disease in Jamaica: 1998-2007. PLoS One. 2011;6(10):e26281. doi: 10.1371/journal.pone.0026281.

[8] National Heart Lung and Blood Institute. The management of sickle cell diseasees [Internet]. 2004. p. 1–188. Available from: https://www.nhlbi.nih.gov/files/docs/guidelines/sc_mngt.pdf.

[9] Sickle Cell Disease in Pregnancy. Management of (Green-top Guideline No. 61) [Internet]. RCOG. Available from: https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/sickle-cell-disease-in-pregnancy-management-of-green-top-guideline-no-61/.

[10] Research C for DE and FDA approves hydroxyurea for treatment of pediatric patients with sickle cell anemia. FDA [Internet]. 2019. Feb 9; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-hydroxyurea-treatment-pediatric-patients-sickle-cell-anemia

[11] Central Drugs Standard Control Organisation Directorate General of Health Services Ministry of Health &Family Welfare, Government of India.

[12] Management of sickle cell disease in pregnancy. A British Society for Haematology Guideline - Oteng-Ntim - 2021. British Journal of Haematology - Wiley Online Library [Internet]. Available from: doi: 10.1111/bjh.17671.

[13] Montironi R, Cupaiolo R, Kadji C, *et al.* Management of sickle cell disease during pregnancy: experience in a third-level hospital and future recommendations. J Matern Fetal Neonatal Med. 2022;35(12):2345–2354. doi: 10.1080/14767058.2020.1786054.

[14] Lanzkron S, Strouse JJ, Wilson R, *et al.* Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med. 2008; 148(12):939–955. doi: 10.7326/0003-4819-148-12-200806170-00221.

[15] Rankine-Mullings AE, Nevitt SJ. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database Syst Rev. 2022;9(9):CD002202.

[16] Yawn BP, Buchanan GR, Afenyi-Annan AN, *et al.* Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033–1048. doi: 10.1001/jama.2014.10517.

[17] Khera KS. A teratogenicity study on hydroxyurea and diphenylhydantoin in cats. Teratology. 1979;20(3):447–452. doi: 10.1002/tera.1420200314.

[18] Chahoud I, Paumgartten FJR. Dose-response relationships of rat fetal skeleton variations: relevance for risk assessment. Environ Res. 2009;109(7):922–929. doi: 10.1016/j.envres.2009.07.013.

[19] Amortegui AJ, Klionsky B, Surti U, *et al.* Experimental intrauterine fetal growth retardation in the rat: effect of a single dose of hydroxyurea or cycloheximide on the fetus at term. Prog Clin Biol Res. 1983;140:13–26.

[20] Kroner BL, Hankins JS, Pugh N, *et al.* Pregnancy outcomes with hydroxyurea use in women with sickle cell disease. Am J Hematol. 2022;97(5):603–612. doi: 10.1002/ajh.26495.

[21] Ballas SK, McCarthy WF, Guo N, *et al.* Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. J Natl Med Assoc. 2009;101(10):1046–1051. doi: 10.1016/s0027-9684(15)31072-5.

[22] Gellen-Dautremer J, Le Jeune S, Receveur MC, *et al.* Hydroxyurea exposure throughout pregnancy in patients with sickle-cell disease: 4 case reports from European Non-Interventional, Multicentric, Prospective Escort-HU study. Blood. 2019;134(Supplement_1):1027–1027. doi: 10.1182/blood-2019-126529.

[23] Jackson N, Shukri A, Ali K. Hydroxyurea treatment for chronic myeloid leukaemia during pregnancy. Br J Haematol. 1993; 85(1):203–204. doi: 10.1111/j.1365-2141.1993.tb08672.x.

[24] Silva FAC, Ferreira ALCG, Pimentel LM, *et al.* The use of hydroxyurea during pregnancy in sickle cell anemia women: a case series and literature review. J Hematol Res. 2021; 8:6–10. doi: 10.12974/2312-5411.2021.08.2.

[25] Hou JW. Fetal warfarin syndrome. Chang Gung Med J. 2004; 27(9):691–695.

[26] Middeldorp S, Vandvik PO, Bates SM, *et al.* VTE, thrombophilia, antithrombotic therapy, and pregnancy. Chest. 2012;141(2 Suppl):e691S–e736S. doi: 10.1378/chest.11-2300.

[27] Soma-Pillay P, Nene Z, Mathivha TM, *et al.* The effect of warfarin dosage on maternal and fetal outcomes in pregnant women with prosthetic heart valves. Obstet Med. 2011; 4(1):24–27. doi: 10.1258/om.2010.100067.

[28] Nelson-Piercy C. Management of antithrombotic therapy for a prosthetic heart valve during pregnancy. UptoDate [Internet]. 2019. Available from: https://www.uptodate.com/contents/management-of-antithrombotic-therapy-for-a-prosthetic-heart-valve-during-pregnancy#H1497381286.

[29] Frequently Asked Questions (FAQs) on New Drugs and Clinical Trials. Central Drugs Standard Control Organization Directorate General of Health Services Ministry of Health and Family Welfare Government of India. [Internet]. Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadPublic_NoticesFiles/faqnd.pdf.

Gayatri Desai, Kapilkumar Dave, Sumeet Devare, and Shrey Desai
SEWA Rural, Jhagadia, India
kapil.dave88@gmail.com