

Hydroxyurea does not reduce ovarian reserve in patients with sickle cell disease, study shows

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Credit: National Institutes of Health

In female patients living with sickle cell disease (SCD), hydroxyurea had no effect on ovarian reserve, suggesting that fertility preservation measures prior to treatment may be unnecessary, according to a study published in [Blood Advances](#).

SCD is the most common inherited red blood cell disorder in the United States, affecting an estimated 100,000 people. According to the Centers for Disease Control and Prevention (CDC), SCD affects one out of every 365 Black or African American births and one out of every 16,300 Hispanic American births.

SCD's rigid, sickle-shaped cells can become lodged in blood vessels, causing a multitude of serious health issues, including vaso-occlusive crisis (VOC), a leading cause of death among those with SCD whereby the cells create blockages large enough to reduce or cut off blood flow to organs.

Hydroxyurea, a drug introduced in the mid-1990s, is commonly used to reduce the frequency of VOC and other SCD-related effects, including acute chest syndrome and the need for blood transfusions. However, concerns have long persisted about the medication's potential effect on fertility.

"Many female patients with SCD avoid hydroxyurea due to concerns about fertility," said Tamara Diesch-Furlanetto, MD, of the University Children's Hospital Basel in Switzerland, and the lead study author.

"However, they should be more confident in hydroxyurea as a therapy. It reduces VOC and hospitalization rates, increasing their quality of life, and, according to the data from this study, doesn't impact fertility."

For the study, Dr. Diesch-Furlanetto and her colleagues collected ovarian tissue samples before [stem cell transplantation](#) to assess the effect of hydroxyurea on ovarian reserve. Data analysis and histological analysis—the process of examining tissue samples under a microscope—were conducted retrospectively.

The long-held notion that hydroxyurea reduces fertility in female patients with SCD stems from four previous studies that indirectly

evaluated the drug's impact by measuring changes in the levels of serum anti-Müllerian hormone (AMH), which is expressed by granulosa cells of growing [ovarian follicles](#). These studies found that AMH was significantly lower in patients with SCD who had been treated with hydroxyurea.

Of the 76 patients included in the [retrospective study](#) who underwent ovarian tissue cryopreservation (OTC), 35 received hydroxyurea prior to OTC, with 50 having not yet gone through puberty at the time of OTC. The median age at OTC was 10.2 years, and no patients received hydroxyurea during OTC.

To determine ovarian reserve, Dr. Diesch-Furlanetto and her colleagues calculated the density of primordial follicles, which are present at birth and comprise the majority of the ovaries.

The researchers measured the density of these previously dormant follicles now exhibiting transforming, proliferating cells. They found that the median density of primordial follicles was not significantly lower in those who had received hydroxyurea compared with those who had not (5.8 follicles/mm² vs. 4.2 follicles/mm², respectively).

When adjusted for age, the density of growing follicles in their primary stage was marginally lower in those who had received hydroxyurea compared to those who had not (0.2 follicles/mm² vs. 0.5 follicles/mm², respectively).

This observation aligns with previous studies, explaining why AMH was lower in patients with SCD. The study authors hypothesize that while this difference can be attributed to hydroxyurea, which increases cell death and oxidative stress, leading to cell damage, it only alters the developmental process of growing follicles, not their quantity.

"This is the first time we can say, after examining histological tissue, that hydroxyurea doesn't impact [ovarian reserve](#)," said Dr. Diesch-Furlanetto. These results confirm her clinical observations, with many of her [female patients](#) with SCD successfully conceiving despite previous and contradicting literature.

"Individuals living with SCD should still consider preserving ovarian tissue before [[hematopoietic stem cell transplantation](#) (HSCT)], but it's not obligatory if they are just being treated with hydroxyurea," said Dr. Diesch-Furlanetto.

These findings could make hydroxyurea more appealing to those who might benefit from the drug but have not pursued it as a therapy because of concerns about reduced fertility or the costs associated with fertility preservation. As of early last year, [only 11 states](#) mandated private insurance coverage for fertility preservation, with public insurance covering it in just two states.

Due to its retrospective nature, the study had a few limitations, including a lack of data on patients' AMH levels at the time of OTC and an imbalance in the number of patient records between the two treatment groups, which may affect some statistical analyses. Additionally, OTC was performed in patients after not receiving hydroxyurea for an extended period of time, making it difficult to draw conclusions about the drug's impact on growing follicles.

Further, the study did not compare the [follicle](#) densities of patients with SCD to those of a healthy control group.

Looking ahead, Dr. Diesch-Furlanetto hopes for prospective studies regarding [hydroxyurea](#)'s impact on fertility and additional research on ovarian tissue transplantation.

She and her colleagues are currently investigating whether patients with SCD who received a haploidentical stem cell transplant experienced a recovery in their AMH levels.

More information: *Blood Advances* (2024).
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