ISFP – Newsletter

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Diminished ovarian reserve in young women with sickle cell anemia

Pecker LH, Hussain S, Mahesh J, Vadadhan R, Christianson MS, Lanzkron S. *Blood,* 2022;139:1111-1115.

Impact of hydroxyurea on follicle density in patients with sickle cell disease

Diesch-Furlanetto T, Sanchez C, Atkinson A, et al. *Blood Adv,* 2024;Jul 18:Bloodadvances.2023011536.

Background:

Severe sickle-cell disease (SCD) (SS or S/β^0-thalassemia) is one of the most common monogenic blood disorders worldwide.

Approximately 300,000 babies are born with the disease annually, mostly in low- and middle- income countries. Over the last four decades, advances in treatment and supportive care have extended the life expectancy of patients with SCD. Hematopoietic stem-cell transplantation (HSCT) is the only established curative therapy for patients with severe SCD, resulting in a disease-free survival of 98% at five years (1). Another major advance in SCD care was the introduction of hydroxyurea (HU) in the mid-1990s; this treatment decreases the frequency of vaso-occlusive crisis (VOC), acute chest syndrome episodes and the need for transfusions (2).

Fertility preservation (FP) is complex for patients with sickle-cell disease (SCD), because of the disease itself and the treatments involved. The stimulation of ovulation may be associated with a risk of VOC and hospitalization in patients with SCD, even if these patients are well prepared (3). The cryopreservation of ovarian tissue before HSCT is recommended and safe if the patients have undergone blood transfusion or exchange to achieve a hemoglobin S level < 30% (4), to prevent complications.

Hydroxyurea (HU), a once daily oral medication, has emerged as the primary disease-modifying therapy for SCD. The accumulated body of evidence demonstrates that hydroxyurea is a safe and effective therapy for SCD. However, it remains unclear whether HU affects ovarian reserve or not, and whether FP should be offered before HU use.

Summary of the articles:

- **Diminished ovarian reserve in young women with sickle cell anemia**

One of the aims of this study was to determine whether HU use was associated with a diminished ovarian reserve (DOR).

A cohort of 26 women aged 19 to 30 years was studied. AMH and antral follicular count were determined on menstrual cycle days 3 to 5. The authors also compared the results for DOR and HU exposure in their cohort with those for other cohorts of patients of the same age.

Fifteen patients were on HU at the time of study, and three were on HU treatment and a chronic transfusion program.

All subjects with DOR (*n*=5) were taking HU. A comparison of the results obtained with those for previously published cohorts led to the conclusion that only subjects “currently taking” HU or who had “taken HU at some time in their lives” had DOR.

This study, based on indirect markers of ovarian reserves, highlights the potential role of HU in diminishing ovarian reserve in patients with SCD and raises the question of FP before HU treatment.

Impact of hydroxyurea on follicle density in patients with sickle cell disease

The aim of this study was to investigate the impact of HU on the density of primordial and growing follicles through a histological analysis of ovarian tissue sections in girls/women with SCD who underwent ovarian tissue cryopreservation (OTC) before HSCT to preserve fertility.

The study included 76 women with a median age at OTC of 10.2 years [range: 4.0-28.3 years]. Fifty patients (65.8%) were prepubertal at OTC. Thirty-five (46.0%) patients were exposed to HU before OTC.

After adjustment for age, the follicle density of the primordial follicles did not differ significantly between the two groups (exposed and not exposed to HU) (p=0.39) and the density of the growing follicles was marginally lower in the HU group than in the HU-naïve group (p=0.09).

The authors concluded that HU does not affect the reserve of primordial follicles in patients with SCD. They concluded further, that fertility preservation is, therefore, not necessarily required before HU treatment. In patients who have already been exposed to HU, FP is indicated before HSCT, as the ovarian reserve will not have been altered by HU treatment.

Conclusions:

- In direct evaluations of ovarian reserve on histological sections, HU treatment has no impact on primordial follicle density, but may affect growing follicles, potentially accounting for the diminished AMH levels observed in other studies.
- FP is not necessary before the introduction of HU, especially before puberty, when the only feasible technique for FP is ovarian tissue cryopreservation.
- It can be difficult to interpret falls in AMH levels. AMH, which is secreted by small growing follicles, is an indirect marker of ovarian reserve. A decrease in AMH levels may be linked solely to damage to the growing follicles, rather than a decrease in ovarian reserve.

References:

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2- Strouse JJ, Lanzkron S, Beach MC et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. Pediatrics 2008;122:1332-1342.
3- Pecker LH, Maher JY, Law JY, Beach MC, Lanzkron S, Christianson MS. Risks associated with fertility preservation for women with sickle cell anemia. Fertil Steril 2018;110:720-31.
4- Missontsa MM, Bernaudin F, Fortin A et al. Ovarian tissue cryopreservation for fertility preservation before hematopoietic stem cell transplantation in patients with sickle cell disease: safety, ovarian function follow-up, and results of ovarian tissue transplantation. J Assist Reprod Genet 2024;41:1027-1034.

*Please note: The newsletter reflects the opinion of the author and not of the ISFP.