blood advances

Hydroxyurea and follicle density in sickle cell

Susan Creary,[1] Chelsea Kebodeaux,[2] and Leena Nahata[1]

[1]The Abigail Wexner Research Institute, Nationwide Children's Hospital, The Ohio State University, Columbus, OH; and [2]Department of Pediatric and Adolescent Gynecology, Nationwide Children's Hospital and Department of Obstetrics and Gynecology, The Ohio State University, College of Medicine, Columbus, OH

Comment on Deisch-Furlanetto et al, page 5227

In this issue of *Blood Advances,* Deisch-Furlanetto et al[1] report data on follicle density from girls and young women with sickle cell disease (SCD) who underwent ovarian tissue cryopreservation (OTC) before hematopoietic stem cell transplant (HSCT). They found that primordial follicle density was comparable between the hydroxyurea (HU)-treated and HU-untreated groups, even after considering pubertal status and age. Primordial follicle density also was not associated with the frequency of vaso-occlusive episodes. Given that HU's impact on reproductive health remains poorly understood, and that prior literature has mainly focused on indirect markers of ovarian reserve,[2,3] these data are the most direct evidence to date that HU may have no impact on the follicle density of young women with SCD. Although pregnancy and live birth outcomes are the best indicator of fertility status, follicle density in pathologic specimens may be one of the most accurate proxy measures available.

These findings are novel and may have significant impacts on management because of the following: (1) many patients with SCD and their families strongly consider the potential effect of the treatment on fertility when making treatment decisions[4]; (2) guidelines recommend offering HU at a very young age, and established fertility preservation options are limited for prepubertal youth; and (3) fertility preservation procedures can include significant SCD-related risks for females.[5] Given all these considerations, findings reported by Deisch-Furlanetto et al suggest that early initiation of HU would still allow for OTC for those who ultimately pursue HSCT.

Strengths of this study include using direct observation of follicles, whereas past studies have only compared indirect measures, such as anti-Müllerian hormone or antral follicle count, which have limitations, particularly in pediatric populations.[2,3] The study also included a larger sample size than prior studies, allowing for better accounting of age and pubertal status in the analysis, which are important factors in follicle analysis.

There are also important study limitations. As noted by the authors, it remains unclear whether follicle density in girls and young women with SCD is normal, given there was no healthy control group. It remains possible that SCD and HU may have an impact on fertility, albeit via different mechanisms other than by decreasing primordial follicle density. Furthermore, this cohort included primarily girls and young women with SCD with a median age of 10.2 years (65.8% of whom were prepubertal at the time of OTC). Studies suggest that diminished ovarian reserve in SCD may occur early but in women who are older than most of those who were included in this study.[6] Thus, the overall risk of premature ovarian insufficiency must still be considered for this population.

In conclusion, these data are the most direct evidence to date about the impact of HU on follicular density, but multiple questions about the impact of SCD and its treatments on reproductive health outcomes still remain. First, the impact of SCD and HU on not just follicle density but on actual fertility is critical to understand. Although follicle density is a marker of fertility, fertility outcomes ultimately depend on many factors, including the overall health of the female who is attempting pregnancy, age at pregnancy attempt, medical and surgical history, and history of other treatments that may affect ovarian function. To date, only 1 study has reported infertility rates in individuals with SCD,[7] but this study was methodologically flawed because it did not assess how many participants had attempted biological parenthood. We are hopeful that as the patients included in this study age and attempt pregnancy by undergoing ovarian tissue transplantation, a future study will also compare their pregnancy outcomes. Lastly, we are now in the era of increasing disease-modifying and curative treatment options for SCD, and the importance of future biological parenthood to all

people with SCD is well documented.[8] Thus, it is critical to also understand the impact of HU on male fertility, given the expanding body of literature showing impaired semen parameters in adolescent and young adult males with SCD receiving HU[9,10] and the most appropriate timing of fertility preservation.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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