COMMENTARY

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TO THE EDITOR:

Addressing fertility in adolescent boys with sickle cell disease: emerging clinical and ethical dilemmas

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Sickle cell disease (SCD) affects 100 000 Americans, mostly belonging to racially minoritized, underserved populations.[1] Because of the increasing use of disease-modifying therapies, such as hydroxyurea, individuals with SCD are surviving into adulthood with less morbidity.[1,2] Long-term effects of SCD and its treatments are coming into focus, such as potential impacts on fertility and reproductive health.[2,3] Recent recommendations are to incorporate these topics (eg, fertility, contraception, sexual health, genetic counseling, pregnancy-related care) into routine, comprehensive care for SCD.[3] In this commentary, we will review recent evidence regarding fertility concerns and research gaps in boys and men with SCD, specifically focusing on clinical and ethical challenges salient to adolescents.

Men with SCD are at risk for impaired fertility due to the effects of the disease and treatments.[4] Multiple causative factors have been implicated[5]: impaired spermatogenesis from testicular infarction, chronic anemia, hypothalamic-pituitary-gonadal axis disruption (occurring in ~25% of men),[6,7] and priapism (reported in 74%) leading to sexual dysfunction.[8] Research shows adult men with SCD have abnormal semen concentration and quality at baseline, and SCD treatments may also affect these parameters.[4] Stem cell transplantation, a curative treatment, is associated with a high infertility risk.[9] However, findings regarding hydroxyurea have been mixed: one study showed that after only 6 months of hydroxyurea, men may have a dramatic reduction in sperm concentration, whereas another small study showed no significant difference in semen parameters between those on hydroxyurea compared with those who had never received hydroxyurea.[4,10] Impaired spermatogonial pool and quality are prevalent in boys with SCD, both with and without treatment with hydroxyurea, undergoing testicular biopsy for fertility preservation before stem cell transplantation.[11,12] The effects of treatment duration and the potential for recovery if hydroxyurea is temporarily discontinued for planned conception remain unknown.[4] Studies have not systematically examined fertility outcomes in men with SCD. Further, although a recent study showed low instances of fatherhood in men with SCD treated with hydroxyurea,[13] the clinical implications of these semen abnormalities and high rates of erectile dysfunction from priapism[8] on actual fertility are poorly understood.

In the context of these knowledge gaps and conflicting findings, clinicians are left wondering if and how to best counsel adolescent boys with SCD and their families on the potential fertility impacts of SCD and its treatments. Research in other populations where fertility has been better studied, such as childhood cancer survivors, has underscored the importance of timely and comprehensive fertility counseling and resulted in risk stratification tools.[14,15] Notably, a recent study showed that most adolescent boys with SCD and their caregivers had a desire for biological children, were unaware of the potential fertility impacts of their disease and treatments, and wanted more information.[16] Thus, not

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addressing the potential for semen abnormalities with hydroxyurea and how this may or may not equate to impaired fertility is no longer a viable option.[3]

Although no evidence-based clinical practice guidelines have been developed, Meacham et al recently published recommendations stating fertility should be addressed, ideally with handouts and the incorporation of teach-back methods, before gonadotoxic treatment.[17] Experts suggest offering a semen analysis before starting hydroxyurea and during treatment,[18] yet there are many barriers to implementation. First, there are substantial benefits to initiating hydroxyurea early in life.[19] Thus, in many cases, hydroxyurea is started before the onset of puberty and/or spermarche when experimental testicular tissue cryopreservation is the only fertility preservation option.[20] Second, it is unclear if/how results showing oligospermia and other abnormal semen parameters should affect SCD treatment discussions and decisions in adolescence.[4] Given limited other treatment options, clinical trials, and observational studies supporting hydroxyurea as the cornerstone disease-modifying therapy for children and adults with SCD,[19] and the fact that biological parenthood for adolescents is typically a future rather than an imminent desire, the benefit of obtaining a single semen analysis while on hydroxyurea remains unclear. Third, unlike evidence-based guidelines published for youth with cancer, it is unclear if/when fertility preservation should be recommended for youth with SCD.[3] Fourth, there are logistical barriers to obtaining semen testing, as testing is not typically conducted within pediatric health care centers or covered by insurance.[9]

In this context, there are several ethical dilemmas, particularly when providing care to adolescents.[3] In considering beneficence vs nonmaleficence, clinicians may hesitate to share data regarding the potential impacts of SCD and hydroxyurea on semen parameters with patients and families when the actual impact on fertility remains poorly understood.[21,22] Specifically, it may be unclear whether offering semen testing, given the possibility of an abnormal result, outweighs potential harms. For example, if an adolescent being treated with hydroxyurea has severe oligospermia, he may want to discontinue his treatment for an undefined period of time, against the wishes of his caregivers and SCD providers. Although awaiting improvement in his semen parameters, he may have a poor clinical outcome due to discontinuing his treatment.

In contrast, nondisclosure has implications for patient/family autonomy and precludes the capacity for informed, shared decision-making. Research in other populations at risk for infertility suggests youth want to be told about these risks as early as possible, with increasing information over time, and that they want to be included in discussions and decisions.[23] Finally, the lack of insurance coverage for semen testing or sperm banking raises substantial concerns for justice and nonmaleficence.[9] Offering this service/procedure may create distress among youth and families who do not have the financial means to take advantage of the referrals and services.

In summary, emerging research suggests adolescent boys and men with SCD may have abnormal semen parameters and indicates this concern should be discussed with patients and families[3,4,9,18]; however, the specific impacts of the disease and treatments on the ability to have a biological child remain unknown. Preliminary evidence suggests hydroxyurea may have negative impacts on sperm concentration and quality,[4] but this has not been well-studied in adolescents. It is unclear whether semen parameters may improve if hydroxyurea is temporarily discontinued,[4] (which may be considered in adult men unable to conceive and in conjunction with transfusion therapy), and also whether this practice should be considered in adolescents to facilitate sperm banking. Hematology providers should initiate these conversations with patients and families to convey what is and is not known, enable informed treatment decision-making, and preserve patient and provider trust. Ultimately, additional fertility-focused SCD research is needed to inform these discussions, develop clinical practice guidelines, and optimize reproductive and psychosocial outcomes.

This research requires more government, industry, and foundation funding[24] and national registries that include fertility and reproductive health variables.[9] Investigators must collaborate with adolescent boys with SCD and their caregivers to ensure feasibility and acceptability; educational materials should be culturally tailored, health literacy–focused, and widely accessible given the barriers and health disparities affecting this population.[17] Semen sample collection and examination must be streamlined, as most pediatric centers do not have on-site testing. Finally, with the high out-of-pocket costs for fertility testing and preservation, equitable access to this under-resourced population must be assured through public and private insurers.[9] This discussion is timely given current legislative efforts to expand health care access for individuals with SCD.[25] Clinicians should partner with policymakers to ensure reproductive justice and avoid worsening health disparities for a population that is already underserved.[9]

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