Fertility Concerns and Access to Care for Stem Cell Transplantation Candidates with Sickle Cell Disease

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ABSTRACT
Sickle cell disease (SCD) affects 100,000 Americans and causes significant psychiatric illness and poor quality of life in many domains, including infertility. Hematopoietic cell transplantation (HCT) is the only available cure for SCD, but it can entail chronic toxicities, including psychiatric conditions, such as depression and anxiety, and sterility in both men and women. There is scant literature on fertility or psychiatric outcomes for patients with SCD receiving HCT, and none considering the additive ramifications of the stresses of SCD, transplantation, and infertility. Financial toxicity is a significant concern for all patients undergoing HCT. Treatment for infertility is also very expensive, and access to fertility services is variable in the United States, adding to the medical and quality of life burden for this patient population. Here we review the relevant areas of SCD and infertility, SCD and psychiatric wellness, access to care, and infertility and quality of life. Collectively, these data suggest that the group of patients with SCD who undergo HCT and experience infertility are at particularly high risk for poor quality of life, worsening psychiatric health, and poor access to adequate fertility treatment.

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INTRODUCTION
Sickle cell disease (SCD) is the most common monogenic disorder, affecting approximately 100,000 Americans, primarily those of African and Afro-Caribbean descent [1]. Patients with SCD are faced with decreased life expectancy (42 years for men, 48 years for women [2,3]) and severely impaired quality of life [1]. In addition to the symptoms of anemia and pain crises, patients with SCD struggle with various effects of their illness. Because of the high frequency of prepubertal mortality in the past, fertility had not been an area of focus in this population until fairly recently [4]. However, with at least 95% of patients with SCD living to reproductive age, it has become apparent that SCD confers a high prevalence of subfertility and infertility, which have disease-related and treatment-related etiologies [5,6]. Patients with SCD who undergo hematopoietic cell transplantation (HCT) are at particularly high risk for subfertility and infertility because of the use of alkylating agents and radiation in pretransplantation conditioning regimens, although early data show that fertility-preserving treatments have been effective in this population [6]. Because of under-counseling and poor access to assisted reproductive technology (ART), this is a population that has both an increased need for and a decreased ability to access effective fertility treatments [7-9]. There are significant quality of life and mental health impacts of SCD, HCT, and infertility, and no studies have specifically considered the ramifications of this combination. Although many other effects of HCT are equally important to overall quality of life, fertility has received relatively less attention and uniquely impacts the SCD community.

Subfertility in SCD
Men with SCD have lower baseline fertility than the general population. Zinc deficiency, vaso-occlusion, and hypoxemia of gonadal vasculature are proposed etiologies of hypothalamic-pituitary-adrenal (HPA) axis disruption, which can result in hypogonadism in both men and women with SCD. In men, this can decrease testosterone production, libido, and fertility and cause erectile dysfunction [4,6]. Both primary and secondary hypogonadism lead to sperm abnormalities, including decreased sperm density, decreased sperm count, decreased...
sperm motility, and abnormal morphology in up to 91% of men with SCD [5,6]. Another proposed etiology of infertility in men is erectile dysfunction, with a prevalence of 21% to 35%, secondary mostly to recurrent priapism. Testicular infarction, sometimes requiring orchiectomy, also has been cited as a potential cause of infertility in men with SCD [4]. The overall rate of infertility in men with SCD is not known.

For women, the modern data are minimal, and whether fertility rates are decreased overall remains unclear. Premature ovarian insufficiency in women is generally measured by low ovarian reserve, which can be determined in several ways: by low anti-Müllerian hormone (AMH) or high follicle-stimulating hormone (FSH) blood levels, or low antral follicle count on ultrasound [10]. However, in women with SCD, premature ovarian insufficiency has historically been estimated by observational studies of the total rate of pregnancy, which is lower than that in the general population, but these data are insufficient on which to base causal conclusions [6]. For example, a 2010 United Kingdom survey of 102 women with SCD had a total of 150 lifetime pregnancies, 53% of which were unplanned [11]. This is somewhat lower than the fecundity rate in the general population, which in healthy women up to age 34 years has been reported to be 87% over 12 months of attempting to conceive naturally, declining modestly to 72% for women age 35 to 40 years [12,13]. No study has specifically found premature ovarian insufficiency in women with SCD who had no history of potentially sterilizing treatments.

Treatment-Related Subfertility

Many of the primary treatments for SCD impact fertility in both men and women. Chronic transfusion causes iron overload, leading to deleterious buildup of iron in the hypothalamus, pituitary, and ovaries [14]. Disruption of the hypothalamic-pituitary-gonadal axis can cause hormonal changes leading to gonadal failure in both men and women, and also can lead to hypothryroidism and diabetes, which in turn exacerbate infertility [14].

Hydroxyurea, a mainstay treatment for SCD, is a ribonucleotide reductase inhibitor, which impairs DNA synthesis, thereby damaging actively dividing cells, including gametes [6]. In men, this produces abnormal sperm, lower sperm count, and decreased fertility [4,5]. This effect has been found to be partially reversible after cessation of hydroxyurea use [4]. In female mammalian models, hydroxyurea has teratogenic effects on the central nervous system, vertebral bodies, limbs, skull, and craniofacial structure [6]. A small study in humans found no effect of hydroxyurea use on fetal development, but dose was not tracked [15]. Another study found that among young women with SCD receiving hydroxyurea, there was a 24% incidence of significantly decreased AMH, reflecting poor ovarian reserve and decreased fertility [14].

Chronic use of pain medications also can contribute to infertility. opioids decrease the overall fertility rate in women, decrease estradiol level by 48% to 57%, and decrease luteinizing hormone and FSH levels by 30%–all thought to be secondary to suppression of the HPA axis and subsequent downregulation of gonadotropin-releasing hormone [14]. NSAIDs also decrease ovulation, as COX-2 inhibition reduces prostaglandin synthesis and impairs ovulation, fertilization, and implantation [14]. One study found that meloxicam ingestion independently caused a 55% to 78% rate of dysfunctional ovulation in healthy surgically sterilized women [16].

HCT Transplant and Gene Therapy-Related Infertility

Allogeneic HCT is currently the only known cure for SCD [17], with sustained engraftment and resolution of vaso-occlusive crises exceeding 90% in healthy young recipients of HLA-matched stem cells [18]. Between 2013 and 2017, a total of 737 HCTs were performed for SCD in the United States [19]. The number of HCTs performed in this population is expected to increase along with the growing population of patients with SCD surviving to adulthood [1], as well as with increased demands owing to improved outcomes of HCT [20,21], an enlarging donor pool, and increasing access to transplantation programs. Another major advancement that may lead to a significant increase in the number of HCTs is the use of genetically modified autologous hematopoietic cells, which potentially can overcome many of the challenges with allogeneic HCT [18,22,23].

Because chemotherapy targets actively dividing cells, maturing ovarian follicles are likely to be damaged during treatment by inducing apoptosis in the surrounding granulosa cells. The mechanism of damage and degree of effect of chemotherapeutic agents on dormant primordial follicles are variable. Of the 6 relevant classes of chemotherapeutic agents—alkylating agents, platinum derivatives, antibiotics, antimetabolites, plant alkaloids, and taxanes—alkylating agents pose the highest risk to future fertility, being associated with the highest age-adjusted rate of premature ovarian insufficiency [24]. HCT often involves higher doses of chemotherapy than are used elsewhere and can require post-transplantation cyclophosphamide, an alkylating agent associated with a 60% rate of ovarian failure [24,25]. The risk of infertility is significantly increased when the irradiation site includes the pelvic region [6], which can result in ovarian injury and diminished follicle reserve. Total body irradiation has been associated with a 90% rate of ovarian failure, with half of the nongrowing follicles lost at a dose of 2 Gy [24]. For women accessing cryopreservation, radiation-induced damage to the uterus can still interfere with future embryo implantation and subsequent uterine growth [6,24,26]. HCT can require combining total body irradiation at 4 Gy with chemotherapy, which may have additive gonadotoxic effects [24]. Recent gene therapy options have continued to include melphalan, busulfan, and radiation for conditioning, all of which significantly contribute to post-transplantation infertility [14,10].

Without preemptive cryopreservation of embryos, eggs, or sperm, the exposure to alkylating agents and radiation in HCT is a clear cause of infertility: conception is 36-fold less likely for male and female survivors of HCT compared with their own siblings [27,28]. The data on fertility outcomes specifically in patients with SCD undergoing HCT are limited in quantity and quality, but what evidence does exist indicates significantly decreased total fecundity rates. In an observational study of HCT recipients with SCD age ≥25 years, among 31 females, only 5 had children, and among 19 men, only 3 had children. Although these numbers are dramatically lower than the general fecundity rate of almost 90%, these subjects were not asked whether they were attempting conception, and those who did have successful pregnancies had a mix of medical supports in achieving pregnancy, precluding interpretation of these findings [29].

A 2015 study of 56 female patients with SCD age 10 to 21 years assessed decreased ovarian reserve, defined as AMH <5th percentile or FSH >40 U/L (consistent with menopause), in patients grouped by exposure: no lifetime chemotherapy exposure, current hydroxyurea, or history of HCT. The 14 chemotherapy-naïve patients had no evidence of decreased ovarian reserve. Eight of 33 patients (24%) on hydroxyurea had low AMH, and none had elevated FSH. Nine of 9 patients who had undergone HCT had low AMH, and 8 of these 9 (89%) also had menopausal levels of FSH; therefore, 100% of HCT recipients had evidence of diminished ovarian reserve [30]. These are pilot data combining prepubertal and postmenarchal women, and prospective longitudinal studies are needed to establish clinical significance.
ART

ART includes all forms of medical support to achieve pregnancy, including insemination, in vitro fertilization (IVF), and related technologies. When iatrogenic sterilization is anticipated, the indicated treatment is preemptive cryopreservation of mature oocytes, sperm, embryos, or ovarian tissues [6]. A series of cases provides evidence in both men and women that IVF combined with other ART techniques can be effective for patients with SCD undergoing transplantation [6,31-34]. Even outside of HCT, ART has important indications in SCD. Because SCD is a genetic illness with a known single mutation, IVF together with preimplantation embryonic selection (PGS) can be used to prevent transmission of the genes causing SCD. Hemoglobinopathies are among the most common indications for the use of PGS, and experts anticipate that PGS may be recommended for all patients with SCD or sickle cell trait in the future [35]. Families with cultural or religious reasons for not considering amniocentesis for diagnosis (and selective termination) may be particularly interested in availing themselves of this technology. In addition, couples with an affected child may use PGS to ensure that their additional children do not have SCD, or in some cases to ensure via HLA selection that the next child could potentially later become a stem cell donor for their sibling [34,36]. Therefore, IVF serves to preserve fertility, decrease morbidity in future offspring, and facilitate treatment for family members in this population. The use of ART is also more feasible in patients with SCD than in patients with many cancer diagnoses, because the timing of the transplantation is less urgent, and for some male patients, it may be possible to withhold hydroxyurea temporarily to improve sperm count and function. Oncologists may recommend that cancer patients avoid any delay in chemotherapy and also avoid exposure to higher estrogen levels owing to concerns about hepatic function and the risk of thrombosis, or to surgical retrieval procedures owing to the risk of infection and bleeding [10]. These issues are mostly obviated in SCD. In SCD, there is also concern for increased risk of thrombosis and increased pain during ovarian stimulation, but there is evidence that prophylactic anticoagulation and lower-intensity ovarian stimulation can decrease these risks [6]. In addition, the average age at transplantation for patients with SCD is younger compared with cancer patients, meaning that those who are able to access ART for cryopreservation have a greater opportunity to ultimately conceive.

Open access to ART is significantly limited by practical barriers. The median out-of-pocket cost of a single cycle of IVF and the cost of a successful pregnancy via IVF in the United States have been estimated at $24,000 and $61,000, respectively [37]. The cost of cryopreservation for patients already burdened with significant medical costs—from chronic SCD and the costs associated with transplantation—can become an insurmountable barrier to future fertility. HCT costs include significant physician and medication copays, a long period of lost income for the patient during convalescence, for many patients a decreased ability to work and temporary loss of income for their caregiver, as well as incidental costs, such as transportation and in some cases the cost of temporary housing near the transplantation center [38]. Adding these costs to that of cryopreservation is not viable for many patients. In a recent study of insurance claims data, of 411 male and female patients age 18 to 40 years who had undergone HCT, only 29 (7%) had any type of fertility-related service—even a consultation—billed over a 30-month period. Only 15 of those patients ultimately had an ART procedure of any kind, with female sex, decreased age, allogeneic HCT, and residency in the northeastern United States predictive of increased utilization [7]. Whether some of those patients were able to reproduce without support, paid entirely in cash for their treatment, or had no interest in reproduction is not known.

Compared with cancer patients undergoing HCT, patients with SCD undergoing HCT are in some ways at a greater disadvantage in terms of the need for and access to ART. The SCD population is on average at a greater baseline financial disadvantage on average: the unemployment rate is as high as 60% [39], and SCD affects a racial cohort with a significantly increased risk of poverty (20.8% of African Americans versus 10.1% of white Americans made no more than $12,784 in 2018 [40]) and a long history of disenfranchisement. In addition, because of the important work done by cancer support organizations, such as the Livestrong Foundation, Team Maggie, The Heartbeat program, and Chick Mission, cancer patients often receive discounts and assistance in accessing fertility care [41]. For example, the clinics partnering with Livestrong provide a minimum of 25% discounted rates on clinical services, and patients can also access free medications. At the Columbia University Fertility Center, which works with Livestrong, the cost of cryopreservation is reduced from $9700 to $5000 [8]. These discounts are not available for patients with SCD at most clinics, greatly increasing the disparity in access to care.

Disparities in access to ART have been studied in cancer survivors, but not in SCD. One study found that female cancer patients without a college degree were significantly less likely to receive or even be counseled about fertility preservation. Age >35 years, annual income <$30,000, homosexuality, and nonwhite race all correlated with decreased ART access [9].

One of the systemic issues behind poor access is the payment structure for ART in the United States. Commercial insurers in most of the United States are not required by law to cover ART [9]. Many other industrialized nations, including most of Europe, have national health plans that provide coverage for fertility treatments, including IVF [42]. Cryopreservation of gametes costs much more for women than for men; in our region, $10,000 versus $1000 in upfront costs, with additional yearly storage fees of approximately $500. For women, there are additional costs associated with medications to stimulate ovulation (typically $4000 per cycle) and procedures needed for oocyte collection [8]. In addition, studies focusing on disparities in ART access have found that even when controlling for costs, having a college degree doubles the chance of successfully accessing ART and having a live birth [43]. In Massachusetts, for example, where insurance coverage for ART is mandatory, there remains unequal access to these treatments for patients of lower socioeconomic status and nonwhite race. Reasons for this may include lack of information, lack of appropriate referrals from primary care physicians, and cultural bias against fertility treatment among socioeconomically disadvantaged groups [43-45]. Seventeen states currently have laws governing infertility coverage, with even fewer requiring employers to offer insurance packages that cover IVF (Figure 1) [46].

Access to Care in Patients with SCD

Although specific research regarding SCD patients’ ability to access ART before HCT has not yet been conducted, there is abundant evidence of these patients’ overall inadequate access to care, including difficulty accessing providers with sufficient knowledge of SCD treatment [3,47-50]. The episodic and urgent nature of vaso-occlusive crises lead patients to receive much of their care in emergency room settings, which is not ideal [50]. In a study of 556 adult patients with SCD, the vast majority reported feeling that their regular outpatient hematologist was knowledgeable and respectful, and 83% viewed making an emergency room visit as worse than tolerating their pain at home [47].
Research on SCD is relatively sparse compared with that on other chronic genetic conditions, and the poor degree of evidence guiding sickle cell management has in itself been cited as a potential disparity in care for this population [51]. There are also inequities in both public and private fiscal support for SCD research, with research funding trailing behind less common genetic diseases, such as cystic fibrosis and muscular dystrophy [52]. Studies have shown poor adherence of physicians to published quality indicator guidelines for SCD and low self-reported rates of physician knowledge of SCD treatment [48,49,52]. This general landscape of poor research base, poor provider knowledge, poor adherence both of physicians and patients to evidence-based recommendations, and patient experience of stigmatization and devaluation strongly suggests that poor access to fertility care is yet another example of the disparity of care for SCD patients.

Research from other orphan diseases has shown several specific models that can improve access to competent care. Creating a national surveillance system that generates long-term data can help identify both research and clinical gaps that can then be addressed. Improving access to care requires improved public insurance coverage of specialist treatment, which can be achieved by demonstrating the cost-effectiveness of early intervention in the appropriate setting. Finally, increasing the number of well-trained physicians can be achieved in 2 ways: via concerted efforts by fellowships to ensure that all hematology graduates are SCD experts and via community outreach. The Sickle Cell Disease Association of America now provides an SCD certification program for primary care providers [3].

Quality of Life and Psychiatric Effects

Although there are no published data on quality of life or psychiatric illness specific to patients with SCD undergoing HCT and facing infertility, there is literature addressing the psychiatric burden in SCD, in HCT, and in subfertility. Therefore, it can be reasonably surmised that in a population facing the chronic difficulties of SCD, the potential trauma of a HCT, and consequent infertility, the effect may be additive.

The suboptimal quality of life in SCD is multifactorial. Pain and medical needs disrupt and undermine academic achievement and opportunities for employment, leading to greater unemployment and financial stress. The stigma associated with the illness and with the potential for drug addiction causes shame, anger with the healthcare system, social discrimination, loneliness, and isolation [48]. Poor quality of life has been correlated with depression, anxiety, despair, insomnia, loneliness, helplessness, and greater dependence on pain medication in patients with SCD [51]. Estimates of the lifetime prevalence of depression in patients with SCD range from 40% to 50% [53,54], compared with 13.2% in the general US population [55]. The Pain in Sickle Cell Epidemiology Study (PiSCES) found a 27.6% point prevalence of depression in patients with SCD [56,57]. One survey that used the standardized 21-question Beck Depression
In addition to the high rates of psychiatric illness burden, poor quality of life, and demoralizing symptoms from SCD and HCT, patients experiencing infertility as a result of their treatment have further burdens on quality of life. Infertility independently has significant psychosocial implications, including sense of identity, sexual health, and marital relationships for both men and women [66]. Women who have experienced miscarriage have been found to have high rates of depression (5%), anxiety (20%), and post-traumatic stress disorder (38%) [67, 68]. Women with premature ovarian insufficiency have high rates of depression (38% to 41%) and anxiety (47%) [69, 70]. In a survey of infertile couples, 50% of the women and 15% of the men described infertility as the most upsetting experience of their lives, and many expressed a loss of identity and feelings of defectiveness [71]. Patients who experience infertility after HCT often have depression and regret [10]. This concern clearly extends to the SCD community; one of the most consistently noted reasons that patients refuse hydroxyurea to treat SCD is the risk of infertility [4]. A survey of 30 adults with SCD found that one-half considered an outcome of sterility an unacceptable risk of HSTC, with a trend toward male sex predicting rejection of HCT for this reason [72]. In our clinical experience, some patients ultimately do not choose HCT because of concerns about fertility, delay HCT until after their fertile years, or undergo HCT and report infertility as one of their main regrets. Of our heterosexual female patients of reproductive age, all cited infertility as a major barrier to accepting HCT.

CONCLUSIONS

Patients with an original diagnosis of SCD who have undergone HCT and have infertility are at a high risk for depression, anxiety, post-traumatic stress, and poor quality of life. ART has proven effective in SCD patients who undergo HCT and would provide a significant benefit for those using PGS, yet accessing fertility care is financially impossible for many patients. Given the longstanding inequities in clinical care and biomedical research for people of African and Afro-Caribbean descent in general and patients with SCD in particular, barriers to accessing fertility for this high-risk group represent an unacceptable disparity in care.

Future research in this area should assess long-term fertility outcomes in SCD patients undergoing HCT. Physicians and researchers working with this patient population should consider advocating via their national organizations, such as the American Society for Hematology, American Society for Reproductive Medicine, and American Society for Transplantation and Cellular Therapy, for position statements and programs that will help improve care for patients with SCD, especially on behalf of those patients facing the additional burdens associated with HCT and infertility. It would be valuable to encourage a national surveillance system for SCD, improved access to care, and an increased population of competent providers. Academic hematology programs can to some extent control this via their training curricula, and might also consider providing their own educational courses to local primary care physicians in communities with high rates of SCD. Providers across disciplines should be advocating with their state governments to consider mandating that employers provide comprehensive fertility coverage, and at a minimum to adopt policies similar to those in Rhode Island and Illinois, which protect fertility coverage for patients whose infertility is iatrogenic.

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