Reproductive issues in sickle cell disease

Kim Smith-Whitley

As medical advances improve survival, reduce disease-related morbidity, and improve quality of life, reproductive issues will take higher priority in the sickle cell disease (SCD) community. A wide variety of topics are addressed in this chapter, including fertility, gonadal failure, erectile dysfunction, and menstrual issues in SCD. Etiologies of impaired male fertility are multifactorial and include hypogonadism, erectile dysfunction, sperm abnormalities, and complications of medical therapies. Much less is known about the prevalence and etiology of infertility in women with SCD. Other reproductive issues in women included in this review are pain and the menstrual cycle, contraception, and preconception counseling. Finally, long-term therapies for SCD and their impact on fertility are presented. Transfusional iron overload and gonadal failure are addressed, followed by options for fertility preservation after stem cell transplantation. Focus is placed on hydroxyurea therapy given its benefits and increasing use in SCD. The impact of this agent on spermatogenesis, azoospermia, and the developing fetus is discussed. (Blood. 2014;124(24):3538-3543)

Introduction

Reproductive issues in women and men with sickle cell disease (SCD) include a wide array of complications that are relatively common; however, data from well-designed, large clinical studies are limited. Many studies are quite old, but remain relevant because they describe clinical complications and problems that persist in the SCD population today despite advances in medical therapy. Not unexpectedly, some of the reproductive issues in SCD arise due to chronic medical therapies that are used increasingly to prevent or manage SCD-related morbidity.

Fertility in men

Infertility in men with SCD has been studied more frequently than infertility in women and appears to have multiple causes, including hypogonadism, sperm abnormalities, and erectile dysfunction (ED) due to priapism. Although a delay in sexual maturation of 1.5-2 years, on average, occurs in adolescents and young adults with SCD, most go on to have normal sexual maturation. However, up to 24% of men with SCD may develop hypogonadism, a clinical syndrome associated with poor testosterone production, infertility, ED, and poor libido. Clinical characteristics include sparse facial, pubic, and axillary hair and small testicular size. Clinical laboratory findings are low testosterone levels with variable follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels.

Possible underlying pathophysiologic mechanisms of hypogonadism include disruptions in the hypothalamic-pituitary-gonadal axis leading to primary testicular failure. However, studies are inconsistent as to whether primary testicular failure or secondary hypothalamic-pituitary dysfunction is the cause. A recent report found low serum testosterone levels in 8 of 34 men with SCD and all 8 had low FSH and LH levels, suggesting a central mechanism. Multiple theories as to why these abnormalities develop in males with SCD include zinc deficiency and vasoocclusion of testicular blood vessels, but the precise cause is unknown. The theory regarding vasoocclusion of testicular vessels is interesting given reports of recurrent testicular infarction in individuals with SCD.

Therapies to alleviate the symptoms of hypogonadism have been limited. Testosterone undecanoate injections and clomiphene have been used with variable results. Many men treated with testosterone reported improved libido and decreased ED; however, normal testosterone levels were not attained or sustained in many men during 12 months of treatment. Although azoospermia has occurred after testosterone injections, this therapy has been well tolerated without increased episodes of priapism. However, other safety end points such as cardiovascular complications and the development of prostate cancer have not been fully investigated.

Sperm abnormalities

Sperm abnormalities are frequent in males with SCD, with rates as high as 91%. Low sperm density, low sperm counts, poor motility, and increased abnormal morphology occur more frequently in males with SCD than in controls. Although some reports suggest that delayed puberty in males contributes to sperm abnormalities in those <25 years of age, these abnormalities improve in older men as testosterone levels increase. These abnormalities may be due to testicular infarction or hypogonadism, although sperm abnormalities are reported even when testosterone, FSH, and LH are normal. Sperm abnormalities are not always related to impaired fertility in men with SCD. Although subjects with sperm abnormalities report fathering children, more sophisticated, prospective studies are needed to determine the clinical importance of abnormal sperm analysis and its impact on male fertility in SCD.
ED

ED occurs frequently in men with SCD, with prevalence rates as high as 21%-35% reported.18-20 The etiology of ED is unclear, but is largely the result of prolonged or recurrent priapism. Management of ED due to priapism depends on the extent of penile tissue fibrosis. Penile implants have been used successfully, but multiple complications can occur.21,22 A general clinical philosophy is that prevention is better than treatment because of the relatively poor outcomes of surgical interventions for severe ED due to priapism. Therapeutic strategies to limit the duration of priapism events and to prevent priapism recurrences should be used aggressively.

Fertility in women

Little is known about fertility in women with SCD because few studies have addressed this topic prospectively using standard clinical end points, control groups, or appropriate normative data.23-25 Early studies used the number of pregnancies reported during reproductive years as a surrogate for fertility.23,25 When pregnancy rates of patients with SCD and healthy controls have been compared, the lower number of pregnancies in women with SCD has been used to infer that fertility is reduced in women with SCD.23,25 Presently, we understand that many factors other than infertility may have influenced the number of pregnancies per patient. This is supported by studies finding similar conception rates in women with SCD and healthy controls.26 Currently, there is no consensus on whether women with SCD are at increased risk for infertility.25

Menarche onset and menstrual patterns in SCD

Although menses onset is delayed in females with SCD,1,2 menstrual bleeding patterns are normal.25 An unfortunate feature of menstrual bleeding in women with SCD is its association with an increased SCD-related pain rate.23-25 In a subpopulation of women, increased SCD-related pain occurs at different stages of the menstrual cycle and this pattern may be related to fluctuations in the levels of estrogen and progesterone.29 This has led to a theory that regulation of these fluctuations with hormonal therapy may decrease the pain associated with menses. Progesterone used as daily oral or depot preparations decreases SCD-related painful events in a subset of women.30

Sexuality and reproductive choices in women with SCD

Information on sexuality in women with SCD is limited.31-33 Given the well-described data on delayed puberty and adverse outcomes associated with pregnancy, how this knowledge may influence sexuality and reproductive decision making is relevant but unexplored. However, attitudes regarding contraception and unplanned pregnancy suggest that women with SCD are interested in avoiding pregnancy and use contraception, although at lower rates than the general population.26

Unplanned pregnancy and SCD

Unplanned pregnancy remains high globally and contraceptive use varies widely by country, age, and race/ethnicity.34 In women with SCD, unplanned pregnancy rates have been high historically and remain high.35-40 A recent study in the United Kingdom compared unintended pregnancy rates and contraception choice in 2 historical cohorts: 156 women in 1993 and 102 women in 2010.40 Although unintended pregnancy decreased from 64% in 1993 to 53% in 2010, this rate remains high. These high rates may be due to many factors, including barriers to contraception access, failure of contraception practices, and patient preferences. Barriers to access may be at the physician level because physicians may be underprescribing hormonal contraceptives. Studies reporting physicians’ prescribing patterns for contraception and patient preferences for contraception in women with SCD are needed.

Contraception choices for women with SCD

Combined hormonal contraceptive agents. Combined hormonal contraceptive use in patients with SCD has been fraught with concerns regarding thrombotic complications and increased pain. Theoretical concerns are related to the underlying pathophysiology of SCD and its “prothrombotic” state. Abnormal RBC rheology, hyperviscosity, endothelial dysfunction, and adhesion; increased platelet activation; venous sludging; and abnormal coagulation may be associated with increased thrombotic complications in patients with SCD. These factors may lead to increased venous stasis, clotting, and pain in women with SCD receiving estrogen.41 Regardless of these safety concerns, few studies have addressed this issue. Although the studies are small, ~150 individual patients may have received combined hormonal contraceptives. Thrombotic events have been reported to occur in a small number of patients.36,40,42-44 However, a slightly larger number of patients have reported increased pain events.

Progesterone-only contraceptive agents. Progestin-only contraceptives should be a good choice in women with SCD due to a lower rate of thrombotic complications in the general population and early studies suggesting that progesterone may be associated with lower rates of acute painful events.30 Published reports on progesterone-only compound use in women with SCD are small and complicated by the multitude of agents used, such as progestin-only pills, injectables, and implants. One of the biggest barriers to progesterone-only medication is its side effect profile, particularly unpredictable vaginal bleeding. These progesterone-only compounds have changed over the years to narrow the side effects, and this limits the ability to compare data between studies.

As mentioned in earlier sections, progesterone was reported to decrease the frequency of acute pain in women with SCD as early as 1972.45 After preliminary studies of progesterone and testosterone demonstrated decreased sickling, investigators performed a crossover study in 28 women treated with progesterone and 16 men treated with testosterone. Although results were preliminary, they reported an 80% reduction in pain in the treated group. De Cuena et al published their crossover study of 23 women with the SS type of SCD 21-41 years of age who received placebo either before or after depot medroxyprogesterone acetate (DMPA).46 Acute pain episodes decreased in women during the DMPA phase. In addition, hemoglobin, fetal hemoglobin, and RBC survival increased, whereas reticulocytes, bilirubin levels, and irreversibly sickled RBCs decreased. This led to the conclusion that improved RBC survival may be due to the increased survival of RBCs containing higher concentrations of fetal hemoglobin. Finally, de Abood et al reported 43 women with SCD who had pain in the last year and were nonrandomly assigned to progesterone, combined hormonal contraceptives, or surgical sterilization.44 All groups had decreased pain at 1 year and the largest proportion of women who became pain free was in the progesterone-only group.

Use of implantable progesterone-only containing compounds has been reported in small prospective studies in women with SCD.46,47
Although these studies report a decrease in pain without adverse events, details on the adverse events are insufficient. However, increased or abnormal uterine bleeding, a frequent complaint in women using progesterone-only compounds, does occur. It may be that some of the newer preparations will have less of this side effect and may allow greater adherence to long-term use.

**Guidelines on contraception use in SCD.** In 2004, the World Health Organization released recommendations on the use of contraceptives in women with SCD, and, in 2006, the American College of Obstetricians and Gynecologists adopted similar recommendations. They stated that the benefit of combined injectable contraceptives, low-dose combined hormonal contraceptives, and IUDs outweighed the risks associated with the increased morbidity and mortality associated with pregnancy. Currently, the US Medical Eligibility Criteria for Contraceptive Use 2010 continues to support these recommendations. Combined hormonal contraceptives are classified as level 2, meaning that “the advantages of using the method generally outweigh the theoretical or proven risks.” Progesterone-only containing pills are classified as level 1, meaning that these agents can be used without restrictions. However, it is concerning that these recommendations are based primarily on the increased risks associated with pregnancy in this patient population rather than on reliable, accurate safety information specific to hormonal contraception and SCD.

**Long-term therapies for SCD and reproductive issues**

Long-term therapies such as chronic transfusion, hydroxyurea (HU), and hematopoietic stem cell transplantation (HSCT) have reduced SCD-related morbidity. However, as utilization of these therapies increases, more attention is drawn to their associated adverse effects and toxicities. Issues have been raised regarding HU use, abnormal sperm production, and teratogenic effects. In addition, fertility preservation after HSCT and the endocrine abnormalities associated with transfusional iron overload remain concerns. Because women with SCD are at risk for pregnancy-related complications as well as the potential teratogenic effects of HU, contraception counseling is paramount to decreasing unplanned pregnancies. Hormonal contraceptive use is controversial in SCD primarily due to the theoretical increased risk for venous thromboembolism and risk for acute pain events. When counseling pediatric and adult patients with SCD who are considering these long-term therapies, hematologists should be prepared to address these issues.

**HSCT and fertility preservation**

The risk of impaired fertility after HSCT depends on many factors, including exposure to pelvic radiation, gonadotoxic chemotherapeutic agents, and stage of pubertal development at the time of transplantation. HSCT remains the sole cure for SCD, with event-free survival rates averaging 85%–90% for allogeneic transplantations. Graft rejection, GVHD, and transplantation-related mortality remain primary concerns, but other transplantation-related outcomes such as endocrine dysfunction and impaired fertility are important issues as well. If the toxicity of conditioning regimens could be decreased while maintaining low rates of graft rejection, HSCT may be considered more often in patients with SCD before severe acute complications and major end-organ damage occur. Myeloablative conditioning regimens before HSCT for SCD cause infertility, particularly in females. In one study, 8 of 14 adolescent females had evidence of primary ovarian failure after HSCT, although 2 women had successful pregnancies, 1 after preimplantation genetic diagnostic testing. Other reports of successful pregnancies after gonadal failure after HSCT have involved ovarian tissue transplantations from siblings. Nonmyeloablative HSCT has been successful in adults with SCD using HLA-matched sibling donors. Even when gonadal failure develops after these less toxic conditioning regimens, fertility may be improved after hormonal therapy. Many speculate that these types of conditioning regimens may limit toxicity and preserve fertility. However, due to the unpredictable risk of infertility, patients may opt for procedures to preserve fertility before HSCT regardless of conditioning regimens.

There is growing consensus that individuals at risk for gonadal failure after exposure to gonadotoxic drugs should be offered fertility preservation. Although experience is limited, patients with SCD have success with procedures and therapies that preserve fertility. Cryopreservation options have expanded and depend on stage of pubertal development. Cryopreservation of sperm in pubertal males is standard and improvement of sperm banking techniques and increased use of intracytoplasmic sperm injection may increase successful outcomes. Cryopreservation of testicular tissue, considered experimental, is an option in prepubertal boys, but is waiting for the development of technology and procedures for restoring human fertility.

Preservation of embryos, mature oocytes, and ovarian tissue is an option for females before HSCT. Cryopreservation of mature oocytes has advanced to the point that this procedure is no longer considered experimental. The procedure requires that the women undergo treatment with hormonal therapy to stimulate increased production of mature oocytes. It should be noted, however, that women with SCD are at risk for thrombosis and increased acute pain while being exposed to increased estrogen levels during ovarian stimulation. Successful oocyte preservation after controlled ovarian stimulation in a 19-year-old woman with SCD has been described using a protocol to avoid hyperstimulation and incorporating anticoagulation for thrombosis prevention. Although oocyte collection was successful, the patient required hospitalization for pain management postoperatively. In addition, successful pregnancies in women with SCD after ovarian tissue preservation have been reported. For girls who are <18 years of age, particularly those <12 years, ovarian tissue preservation is an option, although outcomes in SCD are not clear.

**Transfusional iron overload and infertility**

Patterns of transfusional iron overload in patients with SCD seem to be different from those in patients with thalassemia. Endocrinopathy from transfusional iron overload is manifested as hypothyroidism, diabetes mellitus, growth failure, and gonadal dysfunction, and all appear to be more common in thalassemia than in SCD. Transfusional iron overload, if untreated, may lead to infertility caused by hypothalamic-pituitary dysfunction and altered circulating levels of FSH and LH. Gonadal failure in patients with SCD on chelation therapy occurs at similar rates in those with SCD without iron overload. Menarche onset appears to be appears to be less delayed in patients with SCD receiving chronic transfusion therapy compared with patients with thalassemia major. Generally, focus is placed on chelation therapy to reduce organ damage. In women with thalassemia major, biomarkers have been used to assess reproductive capacity, but similar studies have not been performed in women with SCD.
HU therapy and abnormal spermatogenesis

HU therapy has been shown to decrease episodes of acute pain and acute chest syndrome without major toxicity in children and adults with SCD. However, given HU’s impact on rapidly dividing cells, concerns around toxicity remain. Young children who receive HU appear to have normal growth, but information on pubertal development is less clear. However, 2 reproductive issues loom with the use of HU in both the pediatric and adult populations: abnormal spermatogenesis and teratogenic effects. Published literature on these topics is limited. Much information is in case reports and case series, with few prospective studies or case-control studies. This makes evidence-based counseling on the risk of developing sperm abnormalities or infertility on HU challenging.

There is a theoretical risk of HU affecting sperm development given that it is an antimetabolite. HU is a ribonucleotide reductase inhibitor primarily acting as an S-phase-specific cytotoxic agent that impairs DNA synthesis. These effects are relatively short lived once the drug is removed. Therefore once-daily administration of HU has brief, intermittent cytotoxic effects on dividing cells. Early studies on HU use in patients with SCD showed that this chemotherapeutic agent was well tolerated with a low toxicity profile. Side effects investigated in clinical studies have primarily included BM suppression, alopecia, and skin changes. However, data are limited on human fetal development with in utero exposure to HU or neonatal development when exposed to HU through breast milk. No epidemiologic or prospective studies have investigated HU’s impact on human spermatogenesis or fertility. However, systematic reviews of human and animal data have been published.

Animal studies have been used to study the impact of progressively increasing doses of HU on testicular growth and spermatogenesis. Doses of HU in mice at 50 mg/kg orally or 100 mg/kg intraperitoneally correlate with 25 mg/kg oral doses in humans. These doses of HU in mice increase testicular germ cell apoptosis, induce testicular atrophy, decrease sperm count, decrease sperm motility, and increase abnormal sperm morphology. A study using sickle-cell-transgenic mice demonstrated that these mice have hypogonadism at baseline. After treatment with HU at 25 mg/kg/d, these mice exhibited decreased testicular size and increased sperm abnormalities compared with controls.

Sperm abnormalities such as oligozoospermia, azoospermia, decreased motility, and increased morphologic abnormalities occur in males with SCD receiving HU. Whether these abnormalities are directly related to HU is unclear. Some investigators suggest that the length of HU therapy may correlate with the degree of sperm abnormalities. In one study, of the patients who started HU in childhood, those who had received HU for 12 years or more had azoospermia. However, most of these studies provide limited data because they involved small, retrospective populations. There are inconsistencies in the age at initiation of HU therapy, length of HU therapy, and timing of follow-up studies once HU is discontinued. Only one small study compared serial sperm counts and morphology before, during, and after HU treatment. Although none of the 5 patients developed azoospermia, all had decreased sperm counts after starting HU. However, it was difficult to determine whether fertility was impaired in this cohort. Data are inconsistent as to whether this reduction in sperm counts is partially or fully reversible. In addition, the timing of recovery after discontinuation of HU is unclear.

Given that sperm abnormalities exist at baseline in the SCD population and the unclear impact of HU on male fertility, clinicians have little information regarding potential azoospermia or oligospermia when counseling patients or families of young children starting HU. The multitude of clinical studies demonstrating decreased morbidity in children and adults with SCD receiving HU is impressive. Its impact on reducing acute complications and improving survival suggests that HU may have a positive effect at limiting SCD-related organ dysfunction long term. Furthermore, some clinicians suggest that HU’s positive impact on vasoocclusive events may limit testicular infarction and improve spermatogenesis.

Nevertheless, more information is needed on the impact of HU on male fertility and sperm production. Counseling patients before HU initiation is challenging given this lack of information. Consensus reports on HU use in SCD suggest that sperm banking or cryopreservation of testicular tissue be offered before starting HU. Close monitoring for sperm abnormalities during HU therapy with serial sperm analyses every 6-12 months has been suggested. However, little guidance is given as to how this information should alter clinical management with respect to temporarily halting or permanently discontinuing HU.

Teratogenic effects of HU therapy

HU is not recommended for use during pregnancy, primarily because of animal data suggesting potential teratogenic effects on the fetus. In animal studies, HU exposure in utero leads to abnormalities in the CNS, vertebral bodies, craniofacial tissue, skull, and limbs of mammals. However, there are limited reports of adverse outcomes in humans after exposure to HU in utero, including early fetal loss and limb anomalies, but these case reports are difficult to interpret. There are multiple reports of normal births after in utero exposure to HU, primarily in women taking HU for leukemia. In addition, no teratogenic effects have been reported when women with SCD became pregnant while taking HU.

The National Toxicology Program (NTP) Center for the Evaluation of Risk to Human Reproduction (CERHR) published an expert panel report on the evaluation of HU’s potential to cause an adverse impact on human development and reproduction. The NTP expressed concern that exposure of pregnant women to HU may cause abnormal fetal growth and development. In addition, they expressed concerns regarding HU use while breastfeeding. The investigators acknowledged that most of the data used to support their reservations came from animal studies because few studies on HU levels in human breast milk and HU teratogenic effects in humans exist. This has been the basis for the current recommendations that sexually active couples use contraception if one person is receiving HU and that those women who are trying to conceive or wish to conceive stop taking HU.

Conclusion

Increased attention to reproductive issues in SCD has implications for clinical practice and future research. This review raises multiple unanswered questions regarding fertility in men and women with SCD and the contributions of HU therapy, HSCT, and severe iron overload. Longitudinal, prospective studies in prepubertal and postpubertal males and females using various end points to detect cellular and functional impairment in fertility should be conducted. These studies should investigate potential biomarkers of fertility so that noninvasive routine monitoring is facilitated. Research studies to better understand the relationship among hypogonadism, sperm abnormalities, ED, and male fertility are necessary to better inform management, treatment, and monitoring across the lifespan and during HU therapy. More information on patterns of contraception...
choices and contraception use, contraception complications, and unplanned pregnancy in women with SCD is needed to better inform preconception counseling. Guidelines for fertility preservation in children and adults with SCD are required, particularly as the use of long-term therapies increases. Finally, research on the human teratogenic effects of HU is essential before its use is permanently abandoned throughout pregnancy and in breastfeeding women. Limiting the use of a potentially beneficial therapy for long periods may not be necessary.

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Correspondence: Kim Smith-Whitley, Division of Hematology, The Children’s Hospital of Philadelphia, 11th Floor Colket Building, 34th St and Civic Center Blvd, Philadelphia, PA 19104; e-mail: whitleyk@email.chop.edu.

References


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Kim Smith-Whitley