Reproductive Issues in Sickle Cell Disease

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ABSTRACT

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 community. A wide variety of topics are captured in this discussion including fertility, gonadal failure, erectile dysfunction and menstrual issues in sickle cell disease. 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 sickle cell disease. Reproductive issues in women included in this review are pain and the menstrual cycle, contraception and pre-conception counseling. Finally, long-term therapies for sickle cell disease and their impact on fertility will be 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.
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 sickle cell 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 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, erectile dysfunction 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 is
the cause or secondary hypothalamic-pituitary dysfunction. A recent report found low serum testosterone levels in eight of thirty-four men with SCD and all eight 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 vaso-occlusion of testicular blood vessels, but the precise cause is unknown. The theory regarding vaso-occlusion 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 erectile dysfunction; however normal testosterone levels were not attained or sustained in many men during twelve months of treatment. Although azoospermia has occurred following testosterone injections, this therapy has been well tolerated without increased episodes of priapism. However, other safety endpoints 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 as compared to controls. While some reports suggest that delayed puberty in males contributes to sperm
abnormalities in those less than 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 significance of abnormal sperm analysis and its impact on male fertility in SCD.

**Erectile Dysfunction**

Erectile dysfunction (ED) occurs frequently in men with SCD with prevalence rates as high as 21-35% reported. The etiology of ED is unclear, but is largely the result of prolonged or recurrent priapism. Management of ED in men with SCD due to priapism varies and often depends on the extent of penile tissue fibrosis. Penile implants have been used successfully, but multiple complications can occur. A general clinical philosophy is that prevention is better than treatment because of the relatively poor outcomes of surgical interventions for severe erectile dysfunction 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, as few studies have addressed this topic prospectively using standard clinical endpoints, control groups or...
appropriate normative data\textsuperscript{23-25}. Early studies have used the number of pregnancies reported during reproductive years as a surrogate for fertility\textsuperscript{23,25}. When pregnancy rates between patients with SCD and normal 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\textsuperscript{23}. Presently we understand that many factors other than infertility may influence the number of pregnancies per patient. This is supported by studies finding similar conception rates in women with SCD and normal controls\textsuperscript{26}. Currently there is no consensus on whether women with SCD are at increased risk for infertility\textsuperscript{25}.

**Menarche Onset and Menstrual Patterns in SCD**

Although menses onset is delayed in females with SCD,\textsuperscript{5,6} menstrual bleeding patterns are normal\textsuperscript{1}. An unfortunate feature of menstrual bleeding in women with SCD is its association with an increased SCD-related pain rate\textsuperscript{1,27-29}. 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\textsuperscript{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\textsuperscript{30}.

**Sexuality and Reproductive Choices in Women with SCD**
Information on sexuality in women with SCD is limited. 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.

Unplanned Pregnancy and Sickle Cell Disease

Unplanned pregnancy remains high globally and contraceptive use varies widely by country, age and race/ethnicity. In women with SCD, unplanned pregnancy rates have been high historically and remain high. A recent study in the UK compared unintended pregnancy rates and contraception choice in two historical cohorts: 156 women in 1993 and 102 women in 2010. 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 as physicians may be under-prescribing 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 red cell rheology, hyperviscosity, endothelial dysfunction and red cell adhesion, increased platelet activation, venous sludging and abnormal coagulation may bring about increased thrombotic complications in patients with SCD. These factors most likely contribute to increased venous stasis, increased clotting and increased pain in women with SCD receiving estrogen. Regardless of these safety concerns, few studies have addressed this issue. Although the studies are small, approximately 150 individual patients may have received combined hormonal contraception. Thrombotic events and pain events have been reported in a less than 1% of these patients.

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. 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. 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. 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 Ceulaer and colleagues published their crossover study of 23 women with the SS type of SCD aged 21-41 years who received placebo either before or after depo-medroxyprogesterone acetate (DMPA). Acute pain episodes decreased in women during the DMPA phase. In addition, hemoglobin, fetal hemoglobin and red cell survival increased while reticulocytes, bilirubin levels and irreversibly sickled red blood cells decreased. This led to the conclusion that improved red cell survival may be due to increased survival of red cells containing higher concentrations of fetal hemoglobin.

Finally deAbood reported 43 women with SCD who had pain in the last year and were non-randomly assigned to progesterone, a combined hormonal contraceptive agent and surgical sterilization. All groups had decreased pain at one 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\textsuperscript{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 does occur, a frequent complaint with progesterone-only compounds. 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 Sickle Cell Disease. In 2004, the World Health Organization released recommendations on the use of contraceptives in women with SCD and in 2006 The American College of Obstetrics and Gynecology adopted similar recommendations\textsuperscript{48}. They stated that the benefit of combined injectable contraceptives, low-dose combined oral 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\textsuperscript{49}. Combined hormonal contraceptives are classified as level 2 where “the advantages of using the method generally outweigh the theoretical or proven risks.” Progesterone-only containing pills are classified as level 1 where 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. Since women with SCD are at risk for pregnancy-related complications as well as the potential teratogenic effects of HU, contraception counseling is paramount to decrease unplanned pregnancies. When counseling pediatric and adult patients with SCD who are considering these long-term therapies, hematologists should be prepared to address these issues.

**Hematopoietic Stem Cell Transplantation and Fertility Preservation**

The risk of impaired fertility after hematopoietic stem cell transplant (HSCT) depends on many factors including exposure to pelvic radiation, gonadotoxic chemotherapeutic agents, and stage of pubertal development at time of transplant. Hematopoietic stem cell transplantation remains the sole cure for SCD with event-free survival rates averaging 85 - 90% for allogeneic transplants\(^{50-52}\). Graft rejection, graft-versus-host disease, and transplant-related mortality remain primary concerns but other transplant 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 occurs.

Myeloablative conditioning regimens prior to HSCT for SCD cause infertility particularly in females. In one study eight of 14 adolescent females had evidence of primary ovarian failure post HSCT although two women had successful pregnancies, one after preimplantation genetic diagnostic testing. Other reports of successful pregnancies after gonadal failure following HSCT have involved ovarian tissue transplants from siblings. Non-myeloablative 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 improve using hormonal therapy alone. Many speculate that these types of conditioning regimens should limit toxicity and preserve fertility. However, due the unpredictable risk of infertility, patients may opt for procedures to preserve fertility prior to 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 (ICSI) may increase successful outcomes.
Cryopreservation of testicular tissue, considered experimental, is an option in pre-pubertal boys but is waiting for the development of technology and procedures for restoring human fertility. Preservation of embryos, mature oocytes and ovarian tissue are options for females prior to 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 thromboses and increased acute pain while exposed to increased estrogen levels during ovarian stimulation. Successful oocyte preservation after controlled ovarian stimulation in a 19 year-old 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 post-operatively. In addition, successful pregnancies in woman with SCD after ovarian tissue preservation have been reported. For girls who are less than 18 years of age, particularly those twelve years and under, 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 than in patients with thalassemia. Endocrinopathy from transfusional iron
overload is manifested as hypothyroidism, diabetes mellitus, growth failure, and gonadal dysfunction; all appear to be more common in patients with thalassemia \(^{70}\). Transfusion iron overload, if untreated, may lead to infertility caused by hypothalamic-pituitary dysfunction and altered circulating levels of FSH and LH. Menarche onset appears to be less delayed in patients with SCD receiving chronic transfusion therapy compared to patients with thalassemia major. Gonadal failure in patients with SCD on chelation therapy occurs at similar rates in those with SCD without iron overload \(^{70}\). 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 \(^{71}\).

**Hydroxyurea Therapy and Abnormal Spermatogenesis**

Hydroxyurea (HU) therapy has been shown to decrease episodes of acute pain and acute chest syndrome in children and adults with SCD without major toxicity \(^{72-74}\). However, given hydroxyurea’s impact on rapidly dividing cells, concerns around toxicity remain. Young children who receive HU appear to have normal growth \(^{75}\) but information on pubertal development is less clear. However, two 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 while taking HU challenging.

There is a theoretical risk of HU impacting sperm development given that it is an antimetabolite. Hydroxyurea is a ribonucleotide reductase inhibitor primarily acting as an S-phase specific cytotoxic agent and impairing 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 the HU use in patients with SCD showed that this chemotherapeutic agent was well tolerated with a low toxicity profile. Potential side effects discussed frequently in clinical studies include, primarily, bone marrow suppression, malignancy, 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 hydroxyurea’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
demonstrates that these mice have hypogonadism at baseline\textsuperscript{80}. After treatment with HU at 25 mg/kg/day these mice exhibit decreased testicular size and increased sperm abnormalities when compared to controls.

Sperm abnormalities, such as oligozoospermia, azoospermia, decreased motility, and increased morphologic abnormalities, occur in males with SCD receiving HU\textsuperscript{18,81-84}. Whether these abnormalities are directly related to HU is unclear. Some authors suggest that the length of HU therapy may correlate with the degree of sperm abnormalities\textsuperscript{82,83}. Of the patients who start HU in childhood, those who had received HU for 12 years or more had azoospermia\textsuperscript{83}. However most of these studies provide limited data as they have small, retrospective study populations. There are inconsistencies in the age at initiation of HU therapy, length of HU therapy, and timing of follow-up once HU is discontinued. Only one small study compares serial sperm counts and morphology before, during and after HU treatment. Although none of five patients develop azoospermia, all had decreased sperm counts after starting HU. However it is difficult to determine if fertility was impaired in this cohort. Data is inconsistent as to whether this reduction in sperm counts is partially or fully reversible\textsuperscript{81,82}. Also, the timing of sperm count recovery after discontinuation of HU is unclear.

Given that sperm abnormalities exist at baseline in this 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 hydroxyurea’s positive impact on vaso-occlusive 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 prior to 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 six to twelve 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 Hydroxyurea Therapy

Hydroxyurea 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 central nervous system, 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, possibly early fetal loss or 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 hydroxyurea’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 authors acknowledged that most of the data used to support their reservations stemmed from animal studies as 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 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 contribution from HU therapy, HSCT and severe iron overload. Longitudinal, prospective studies in pre-pubertal and post-pubertal males and females using various endpoints to detect
cellular and functional impairment in fertility should be conducted. These studies should investigate potential biomarkers of fertility so that non-invasive routine monitoring is facilitated. Research studies to better understand the relationship between hypogonadism, sperm abnormalities, erectile dysfunction, 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 use of long-term therapies increases. Finally, research on the human teratogenic effects of HU is essential before permanently abandoning the use of HU throughout pregnancy and in breastfeeding women. Limiting the use of a potentially beneficial therapy for long periods of time may be unnecessary.

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