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Expecting More: The Case for Incorporating Fertility Services into Comprehensive Sickle Cell Disease Care

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Summary

Assisted reproductive technologies (ART) are not yet systematically available to people with sickle cell disease (SCD) or their parents. Fertility care for these groups requires addressing SCD-associated infertility risks, fertility preservation options, pregnancy possibilities and outcomes, and, when needed, infertility treatment. People with the chance of having a child with SCD may use IVF with preimplantation genetic testing to conceive an unaffected child. Also parents of children with SCD may use this technology to identify embryos to become potential future matched sibling donors for stem cell transplants. In the United States, disparities in fertility care for the SCD community is especially stark. Universal newborn screening identifies SCD and sickle cell trait, guidelines direct preconception genetic carrier screening, standard-of-care fertility preserving options exist. However, potentially transformative SCD treatments and cures are not used due to iatrogenic infertility concerns. In diversely resourced care settings, obstacles to providing fertility care to people affected by SCD persist.

In this Viewpoint, we contend that fertility care must be incorporated into the comprehensive SCD care model, supporting alignment of SCD treatment goals with reproductive life plans and delivering on the promise of individualized, high-quality care for people with SCD and their families. We consider the obligation to provide fertility care in light of the medical evidence, with acknowledgement of formidable obstacles to optimizing care, and powerful historical and ethical considerations.

Keywords

Fertility; Reproductive Health; Pregnancy; Sickle Cell Disease; Ethics; Fertility Preservation

Introduction

Survival is improving for children with SCD; a growing population of affected individuals are expected to survive into their reproductive years[1]. Also, innovations in fertility preservation and infertility treatment have emerged. Despite indications for fertility care, assisted reproductive technologies (ART) do not reach most people with SCD. However, people with SCD and their families have diverse indications for ART (Figure 1) including to preserve fertility, treat infertility, for in vitro fertilization with preimplantation genetic testing for monogenic disorders to select embryos without SCD, and/or for prenatal testing for SCD[2]. The absence of systematically provided fertility care for SCD raises concerns at the intersection of SCD-community vulnerabilities attributable to geography, race, sex, age, socioeconomic status, disease, and, for some, research participation.

In this Viewpoint, we address existing evidence identifying infertility risks and indications for ART in SCD, barriers to providing ART care. We also consider the ethical implications of failing to provide ART care, and describe a path to advance fertility care for SCD. This

framework may help propel changes in care delivery and clinical guideline development, as well as inform legal reforms. Around the world, the circumstances contributing to ART care deficiencies for people with SCD vary as national politics, history, culture, and resources contribute to the availability of SCD and fertility care[3] National law varies, examples of laws governing ART use are shown in the appendix (page 2). The state of fertility care in the U.S. is a focus here because the SCD comprehensive care model is evolving and because it is unsettling that in a high resource setting fertility care is inequitably provided to some, but not all Americans. Using the U.S. as a case study clarifies obstacles common to many care contexts[3] Challenges in obtaining fertility care have implications for people with SCD and their families Worldwide[3]

I. Indications for assisted reproductive technologies due to infertility and genetic risks

Sickle cell disease is itself a risk factor for infertility causing direct gonadal injury and, possibly, restricting opportunities to conceive due to disease-related limitations. In this sense, sickle cell disease treatments may be understood as protecting future fertility since physical and social function and overall survival are prerequisites for biological reproduction. However, critical treatments, some sickle cell disease therapies, and cures pose established and theoretical infertility risks (table 1), raising the stakes of addressing fertility concerns in routine clinical care.

Infertility risks & fertility preservation for people with testicles—SCD itself is a well-recognized infertility risk for people with testicles, who we will refer to men and boys in this publicaton.[15] The testes and penis are damaged by haemolysis, hypoxic-ischemic injury, and priapism which can result in low testosterone, semen abnormalities and erectile dysfunction[7,8] The majority (91%) of adult men with SCD have at least one abnormal value on semen analysis[8] Hydroxyurea may further reduce sperm counts, sometimes leading to frank azoospermia (complete absence of sperm).[14] Hydroxyurea's toxic effects on sperm seems to be reversible and limited studies indicate that the spermatogonial pool is untouched by therapy. However larger, systematic studies in men of reproductive age who have received life-long hydroxyurea treatment are needed to draw firm conclusions[11] Chronic red cell transfusion may prevent gonadal damage associated with SCD pathophysiology; a possibility raised by studies in younger male patients, aged 14 to 16 years with SCD.[13] However, transfusional iron overload may cause testicular iron deposition and exposure to reactive oxygen species that can damage sperm and impair spermatogenesis[13] While the effects of iron overload on male fertility is addressed in people without SCD, the effects of chronic iron overload on testicular function and spermatogenesis in men with SCD is inadequately studied. Curative therapies require exposure to gonadotoxic preparative regimens posing significant and potentially irreversible infertility risks as alkylating agents are universally used in SCD protocols and are classified as high-risk for future infertility.[14,16]

Fertility preservation as a care standard exists for postpubescent boys and men by use of sperm cryopreservation. For prepubescent boys, testicular tissue cryopreservation remains experimental. To successfully bank sperm, men may need to discontinue hydroxyurea to improve sperm recovery.[14] Repeating semen analysis approximately three months after

stopping hydroxyurea might allow adequate recovery, but the precise time course of recovery is not established[14] and pre-hydroxyurea treatment semen analysis is not usually available for comparison. Pre-treatment semen analysis might help identify SCD-attributable semen abnormalities, helping to identify when baseline is reached. In France, post-pubertal males are conservatively offered the opportunity to sperm bank before initiating hydroxyurea.[15] This practice is not yet widespread. Outside of the pre- haematopoietic stem-cell transplantation (HSCT) setting, there are no universally accepted approaches to offering fertility preservation for SCD.

Infertility risks & fertility preservation for people with ovaries—When discussing infertility risks and preservation for people with ovaries, we will refer to people in this group as women and girls. Women with SCD have a narrower reproductive window than unaffected women: adults with SCD studied in the USA, UK and Nigeria demonstrate an accelerated age-associated decline in ovarian reserve, suggesting that biological infertility occurs earlier than in unaffected women and leading these investigators to conclude that counselling is indicated for women with SCD[4–6,9,17] Some adolescent and young women, aged 12 to 30 years, with sickle cell anaemia (haemoglobin SS and haemoglobin $S\beta^0$) have diminished ovarian reserve, which is a risk factor for premature ovarian insufficiency, infertility, poor in vitro fertilization outcomes and an indication for offering fertility preservation.[6,9,10] Whether disease severity or SCD treatment is the primary driver of this finding is an area of ongoing research. SCD therapies may help avoid ovarian injury associated with SCD pathophysiology. However, hydroxyurea and chronic transfusion therapy also pose potential infertility risks. In three studies, hydroxyurea use among post-pubertal adolescents and women with sickle cell anaemia was associated with diminished ovarian reserve and the number to harm (cause diminished ovarian reserve) was 1.9 – 4.1.[9] Additional studies are needed to establish whether hydroxyurea is a proxy for disease severity or a cause of diminished ovarian reserve[18] Transfusion may help protect ovarian reserve, which is suggested by one study of 26 young adult women aged 19 to 30 years with sickle cell anaemia in which no subject receiving chronic red cell transfusions (N=8) had diminished ovarian reserve.[9] However, iron overload associated with chronic transfusions poses at least a theoretical infertility risk as ovarian iron deposition and follicular damage is possible and might impair fertility[12] Finally, HSCT is an indication for fertility preservation, as the universal use of alkylating agents threatens female fertility. Also, when total body irradiation is required, female reproductive organs cannot be shielded.[14,16]

Fertility preserving options exist as care standards for prepubescent and postpubescent people using ovarian tissue cryopreservation and oocyte or embryo cryopreservation. Both have been reported in girls and women with SCD with normal ovarian follicle density in ovarian tissue of girls with sickle cell anaemia before HSCT.[18,19] As expanding opportunities for fertility preservation arise, addressing the potential risks associated with these interventions is important. Both ovarian tissue and oocyte harvest require anaesthesia which can cause SCD complications.[18] Furthermore, controlled ovarian hyperstimulation for oocyte harvest can cause ovarian hyperstimulation syndrome, venous thromboembolism and SCD complications[18]. Thus, women with SCD undergoing fertility preservation require close clinical monitoring. Whether and when to discontinue hydroxyurea before fertility

preservation for women is not established[29] and is challenging as SCD complications can occur during therapy hiatus.

Assisted Reproductive Technologies as an Intergenerational Concern— Opportunities to use ART are important not only for people with SCD, but also for their families. The parents of children with SCD and adults with SCD worry about having an affected child. Even in high resource settings, many do not know that IVF with preimplantation genetic testing exists.[20–22,24,25] Interest in this technology may in part be explained by the reality that having a child with SCD may use as much as 34% of a family's income[26] and some parents choose not to have additional children after the birth of a child with SCD. In a single report of 60 couples in the U.K. who used IVF with preimplantation genetic testing to avoid SCD in offspring, the cumulative livebirth rate was 54% per cycle and 63% per couple; this rate might have been higher had couples elected used their maximum allowable IVF cycles.[24] The availability of preimplantation genetic testing may affect additional family building choices as testing may be done select embryos without SCD that are also human leukocyte antigen matched to an affected child. Such an embryo might ultimately become a matched, unaffected sibling donor without SCD for HSCT. The low number of embryos are identified for transfer with this approach and even when successful, other obstacles and ethical considerations may limit uptake.[27]

Clearly, standard of care fertility-preserving interventions are relevant to contemporary SCD care. Clinicians, patients, and families may now compare established and theorized infertility risks associated with untreated SCD to disease-specific treatments and cures.[14] People with SCD and their families require counselling about ART opportunities, even as studies defining pregnancy outcomes following fertility preservation for people with SCD are limited in number and confined to the post-HSCT setting.[14] Counselling can incorporate existing evidence and evidence gaps which, even under the best circumstances, is complicated. However, for most people with SCD, significant roadblocks prevent opportunities to receive ideal clinical care.

II. Barriers to ART Education, Counselling, Referral, and Care

The chance to use ART to preserve fertility or build a family is stymied by layered barriers to care including that experts are lacking, wait-times are long and financial systems to address care costs are incomplete or non-existent.

Fertility care is limited by the lack of comprehensive SCD care for affected individuals in many countries. Inadequate or absent SCD care compromises opportunities to provide disease-specific fertility care.[1] However even comprehensive SCD centres with access to fertility experts lack standard approaches to providing fertility care. SCD guidelines identify infertility risks in SCD, but do not contain recommendations for the timing, personnel, or content of fertility counselling.[28,29] The absence of reccomendations might partly reflect evidence gaps at the time guidelines were written.[2] Now emerging evidence can inform practice. For example, investigators in Nigeria, the U.S., and U.K. have concluded that the low ovarian reserve in women with SCD compared to unaffected women presents an indication to provide fertility counselling, consider monitoring of ovarian reserve and to share fertility preservation opportunities.[5,9,10] The conservative approaches that

direct oncofertility care provision may be applied to SCD.[9,30–32] Growing recognition of HSCT-associated infertility risks presents another, indicated opportunity to perform fertility assessments. After HSCT, follow-up clinics are needed to address whether fertility preservation opportunities remain or whether infertility treatments are indicated.[31,33] The prospects for successful fertility preservation in this setting is low, putting the onus for care in the pretransplant setting.[34]

Some clinicians worry that addressing uncertainties about the effects of hydroxyurea on fertility will deter treatment acceptance[35,36] and some limit HSCT referrals due to infertility concerns.[37] Fertility risks are, for some patients and families, a reason for treatment refusal.[6] In the U.S., infertility risks are reportedly addressed during routine hydroxyurea counselling at a centre with high levels of treatment uptake.[13,38] Many clinicians feel challenged to integrate fertility care into standard SCD care. Haematologists are not trained to provide ART counselling and may lack confidence about how to counsel about a topic that is sensitive and private, requires tailored information sharing, acknowledgment of uncertainty, attention to emerging evidence, and awareness of patients' health literacy.[22,39] Individualized fertility counselling attends to patients' values and preferences and includes information about required evaluation procedures (such as masturbation or transvaginal ultrasound). The need to address acute disease complications or difficulties with medication adherence may override fertility discussions.[40–42] However, addressing fertility risks and opportunities for fertility preservation might help align SCD treatment with patient's goals and might even help increase use of SCD treatments and cures. This possibility, which might improve SCD treatment uptake, deserves consideration as life expectancy for people with SCD is stagnant and adult morbidity is considerable.[43]

Even with counselling and referral for care, the costs associated with ART care in much of the world starkly restricts access to care as insurance either does not exist or does not provide sufficient coverage for most people[16], even in countries with a publicly funded health sector.[31] Fertility preservation for girls and women is especially expensive, requiring costly medications, resource-intensive clinical monitoring, and sedated oocyte retrieval or laparoscopic surgery to harvest ovarian tissue for cryopreservation. Even with partial insurance coverage, people may be unable to afford out-of-pocket IVF costs, which average $12,000 (£ 9,745) per cycle.[44] In the U.S., 19 states have some legislation governing fertility coverage: IVF coverage is required in 13 states and fertility preservation coverage in 11 states (some states require both). However, government employees and most publicly insured people are excluded from these mandates which also vary in allowed treatments and qualification for coverage. Unsurprisingly, there are persistent disparities in access to care[45] and even when coverage is mandated, Black and Hispanic women disproportionately report facing barriers to receiving fertility care.[46]

People with SCD may be further excluded from using ART by virtue of their insurance and care indication. People with SCD in low-income and middle-income countries mostly rely upon private clinics that are inaccessible to most people. This reliance is also true in the U.S. where 60% of people with SCD are publicly insured and only two states include fertility preservation coverage for publicly insured people[45] and where all government employees are denied coverage for ART care. In some places, restricted ART access for people with

SCD is partly a consequence of policies that only incrementally expand access to fertility care. In the U.K., policies enable ART access, but priority is given to those with a higher chance of treatment success.[47] People with SCD can be denied ART if they have diminished ovarian reserve or may not qualify for fertility preservation before gonadotoxic therapies because they are not yet infertile.[16,31,47] IVF with preimplantation genetic testing use is also restricted in many places (Appendix, page 2). In the U.K., people with the genetic potential to have a child with SCD receive coverage through the National Health Service (NHS) for three cycles of IVF with preimplantation genetic testing.[24] However, in many places where SCD is common, prenatal diagnosis with the possibility for continuing or terminating a pregnancy is used and IVF with prenatal genetic testing is largely inaccessible.[48]

SCD-related barriers to providing fertility care rest on a foundation of global reproductive healthcare inequality. Comprehensive fertility care for people with SCD and their families is needed even as abortion is restricted in the U.S., despite movement toward liberalizing abortion access across the globe.[49] Abortion restrictions jeopardize ART care because IVF involves embryo creation and storage. Also, because beyond outlawing abortion, some state laws give embryos citizenship rights that are equivalent to or supersede the rights of pregnant people.[50] Often therapeutic abortion, not IVF preimplantation genetic testing, is used to end pregnancies affected by SCD, and is the most readily available option for most people. There is some indication that, given the opportunity, couples would prefer IVF with preimplantation genetic testing to therapeutic abortion; when these options are not shared or are unavailable, couples are denied comprehensive reproductive choices.[51]

III. Ethical Considerations

The failure to provide equitable access to ART services for people who are at risk for having a child with SCD requires ethical appraisal since existing evidence and technological advances have thus far not inspired coordinated action to reach affected families in most countries.

Denying reproductive autonomy to people with SCD through inadequate preconception genetic testing and counselling, insurmountable personal costs for care, or inadequate specialists risks recapitulating coercive reproductive injustice. In the U.S., histories of rape, forced pregnancy and state-sanctioned, non-consensual sterilization disproportionately affected Black communities who are more likely to be affected by SCD in the U.S.[52] SCD history is entwined with this history. In the 1970s, Linus Pauling infamously endorsed eugenic approaches to reducing the incidence of SCD, while the poorly named Sickle Cell Control Act[53] heightened fears that sickle cell testing could lead to reproductive coercion, forced sterilization, unequal reproductive care, and inadequate genetic counselling.[54–56] Hemoglobinopathy testing is compulsory in parts of the Middle East and Africa and is used to either discourage or legally prohibit marriage between couples who may have an affected child.[57] Progressive advances in fertility care and genetic testing require the SCD community to reckon with how to ensure that non-coercive, patient-centered fertility care is offered to people with SCD and their families to make SCD and fertility treatment choices in alignment with their preferences and values. Although ART may not be widely available for most people with SCD, counselling that respects autonomy can be offered. Ideally, this

counselling addresses what is known about infertility risks, genetic inheritance, and existing family building options to support reproductive healthcare decisions.

People with SCD and their families should receive equitable access to the benefits, not just the risks, afforded by medical advances in testing. Fertility care is a benefit of hemoglobinopathy testing but testing that might help people make reproductive choices instead leads to harm. There are longstanding fears that sickle cell testing could be weaponized against intended beneficiaries.[54,58] These decade old reports validate concerns. In 2021, *New York Times'* reporters[59] published evidence that medical examiners attributed the deaths of dozens of men in police custody to sickle cell trait carriage, even though this attribution is not medically plausible. Families that might benefit from testing are also not receiving care: Another *New York Times* story[60] identified that in the U.S., preconception counselling is not reaching couples with genetic potential to have a child with SCD, despite a recommendation to universally offer preconception screening from the American College of Obstetricians and Gynecologists. Meanwhile, newborn screening programs identify children in need of life-saving interventions. As these programs are increasingly implemented in high prevalence, low-resource settings, essential resources are urgently needed to implement life-saving care.[61] These testing programs also identify carriers of hemoglobinopathy traits, this information also needs to be available and understood to those who are tested. In these diverse care settings, there is a need to ensure that the people who bear the risks of hemoglobinopathy disease and trait testing also benefit from knowing the results.[57]

Fertility care in SCD systems must account for the reality that girls and women are at particular risk for harm.[2,62] Women are more likely than men to report that infertility is a source of extreme pain or stres[31] and less likely to be referred for fertility preservation[63] even though clinicians believe women care more about reproduction and want to discuss it more than men.[64] In general, women are under-counselled about infertility risks associated with medical treatment and, this is also a racial disparity that may reach people with SCD. In the U.S., people with SCD are mostly Black and Black women especially experience delays in receiving infertility care[46] and have poorer IVF outcomes than white women, an inadequately explained finding that is not attributable to biologically mediated difference, and that needs further investigation.[65] Unfortunately, ART registries are not structured to collect information that could address SCD-specific knowledge gaps.[2] Women provide most of the care for children with SCD and report mental disorders, stigma, relational compromise, and economic jeopardy; some may also have grief associated with the death of another child with SCD.[66] Fertility care for SCD must honour personal choices to use, or not, fertility preservation, therapeutic abortion, or IVF with preimplantation genetic testing for SCD and help spotlight the ways that improving outcomes for people with SCD is intimately tied to women's health and well-being.

The need to address fertility for children with SCD is, to some degree, contingent up treatment choices, and raises additional ethical concerns. People under the age of full legal responsibility should participate in medical decision-making to their maximum ability, which is a challenging dictum in practice given the complexities of SCD care. Fertility preservation allows minors whose future fertility is threatened to retain future reproductive

decision-making rights.[67] When decisions are made for children, the general ethical approach is to support their right to an open future. This right helps ensure that as many decisions as possible are preserved for minors to make once they attain age of majority or maturity.[68] Offering this care also requires accounting for uncertainty as the precise risks for infertility from untreated SCD or its therapies are not established.[14] The implications of future infertility for survivors of childhood SCD are incompletely considered. Infertility confers grave social and economic consequences that are disproportionately experienced by women. In countries where SCD is most prevalent and ART resources are slim, this reality needs focused consideration, especially as childhood survival improves, hydroxyurea use starts in childhood, and curative intervention expands to these low resource settings.[69,70]

Finally, vulnerability arises when people with SCD are also research participants. Fertility preservation is available as part of some SCD curative trials.[14] This option eliminates a barrier to pursuing cure, but also raises the possibility that access to fertility care will motivate trial participation. Also, fertility preservation provided on a research basis may only cover upfront costs, and a finite number of years of gamete storage, but the youngest research participants may require two decades of gamete storage before individuals reach the age of majority. Ongoing storage fees may become an unaccounted for, indefinite expense (US $300–500 or £240–400 per year). If cryopreserved gametes are ultimately discarded due to financial constraints, then this perceived benefit of research participation may become meaningless. The need for fertility care on a research basis may become more pronounced as studies of therapeutics and cures expands to low resource societies.

IV. Advancing Fertility Care in Sickle Cell Disease

Ensuring that all people with SCD have access to comprehensive and expert SCD care is necessary to ensure that infertility risks, opportunities for fertility preservation and the existence of IVF with preimplantation genetic testing are incorporated into SCD care (Panel).[71] We have highlighted structural components of building access to ART care for people with SCD (Figure 2). This multidisciplinary care will include haematologists, and reproductive healthcare experts (i.e., paediatric endocrinology, genetic counsellors, urology, reproductive endocrinology/infertility, and maternal foetal medicine). Addressing fertility care will help create referral pathways, clinical education opportunities, solutions for individual concerns, and opportunities for care system delivery optimization and resource allocation.

Newborn screening programs are essential for identifying and treating children with SCD and create recognized opportunities for counselling to address family building for affected families. Hemoglobinopathy trait carriers around the world might wish to use prenatal diagnosis, IVF with preimplantation genetic testing or therapeutic abortion, or not. They need neutral, patient-centered, primary care clinicians and informed community health workers for information to appraise reproductive risks and review reproductive choices.[56] Healthcare providers involved in pre-conception and post-conception counselling – obstetricians and gynaecologists, general practitioners, nurses, and community health workers – must be involved in hemoglobinopathy testing, counselling, and ensuring that, when indicated, comprehensive reproductive options are addressed.[22] Developing the

personnel and reproductive healthcare infrastructure to provide fertility counselling will allow systems to respond when care access expands or technology advances, for example, as IVF with preimplantation genetic testing becomes more widely available or as non-invasive prenatal diagnostic testing for SCD becomes possible.[72]

While developing counselling infrastructure is a step towards providing fertility care, other considerations are needed in the paediatric and adult SCD care settings (Appendix, page 1).[15] Paediatric oncofertility specialists honour the need for dyadic care and consider patients' developmental needs during the provision of fertility care, incorporating future reproductive concerns into opportunities to optimize SCD treatment and care during childhood. Fertility preservation indications are expanding for SCD, and may be reviewed with attention to risks, benefits, uncertainties, and barriers to available interventions.[14]

In adult SCD care, infertility risks are included in family planning discussions.[73] This approach helps individualize counselling and helps determine assessments and referrals.[14] Where semen analysis and ovarian reserve testing is available, opportunities for testing can be shared. Patient preference helps dictate assessments since outside of the pre-transplant setting, there is not yet a clear approach to universal screening. Thus, semen analysis and ovarian reserve testing (or referral for testing) may be offered through a shared decision-making process that clarifies the potential benefits and limitations of testing. Testing can help affected individuals decide whether to pursue fertility preservation or timing of pregnancies. In acknowledgement of infertility risks, adults with SCD can be monitored during attempts to conceive and conservative referrals for infertility care made for couples who have been trying to conceive for longer than six months. Global efforts to expand IVF access are relevant for the SCD community and even when not yet available, supportive care can be offered to families experiencing infertility-related stressors. Poor access to ART should not deter counselling. For some young adults with SCD, simply knowing that IVF with preimplantation genetic testing exists alleviates anxiety.[22] Even when ART care is not a publicly available, these discussions might shape employment choices (towards those who provide better fertility benefits), financial priorities and family building plans.

An invigorated care model alone will not fill evidence gaps or surmount cost-related barriers to care. International, federal, state, and non-governmental organizations will need to devote resources to optimize care. We have adressed actions needed to advance fertility care in the U.S., a high-resource country with draconian reproductive healthcare laws, where action to address inequality and affirm the value of the lives and families of people with SCD is urgently needed (Table 2). Ultimately, these overarching needs must be widely addressed to advance fertility care for SCD:

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Guidelines that standardize fertility care indications will galvanize equitable care delivery by use of medical criteria to dictate care. Care standards will inform content, timing, and approach to fertility care and form a foundation for measuring quality and developing research. Like most SCD care standards, regional or national recommendations are necessary as all guidelines are informed by the best available scientific evidence and

with sensitivity to available resources. Focused research funding will address outstanding questions about fertility in SCD (panel 2). Definitive studies about hydroxyurea's effects on ovarian follicles and the spermatogonial pool is especially critical as a growing population of young children with SCD empirically take chronic hydroxyurea.[14] Patient centered optimizing fertility care delivery in SCD are also necessary in low-resource, high prevalence countries as well as in high resource settings.

Policies are needed that minimize out of pocket expenses and enable fertility preserving care for patients with current or anticipated iatrogenic infertility and those interested in IVF with preimplantation genetic testing.[46] In the U.S., advocacy organizations help bridge fertility care gaps in cancer by negotiating lower costs for fertility preservation with fertility centres and pharmaceutical companies and through direct grants to individuals.[31] These approaches can also support people with SCD.[31] For publicly insured people in the U.S. to access fertility care, the Centers for Medicaid and Medicare must act. The NHS funds fertility treatment up to age 40 years and fertility preservation on medical grounds and needs to make SCD an indication for care *in anticipation* of infertility risks. In low-resource settings, expanding the SCD and fertility care workforces will be essential to gain access to ART care.

The ability to have biological children, if one desires, is an essential aspect of freedom and pursuing happiness. Integrating ART into care for people with SCD with recognized fertility risks is no extravagance; the action upholds a fundamental human right. SCD care limitations are rooted in hundreds of years of racial healthcare transgressions and inequalities, and over a half-century of failures to fund SCD research, registries, and care. We should expect more. Investments in SCD treatment and care along with robust healthcare policies are needed to ensure that people with SCD and their families receive equitable, indicated fertility care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ART	Assisted reproductive technologies
HSCT	Hematopoietic Stem Cell Transplant
HLA	Human leukocyte antigen
IVF	In Vitro Fertilization
SCA	Sickle cell anaemia

SCD	Sickle cell disease

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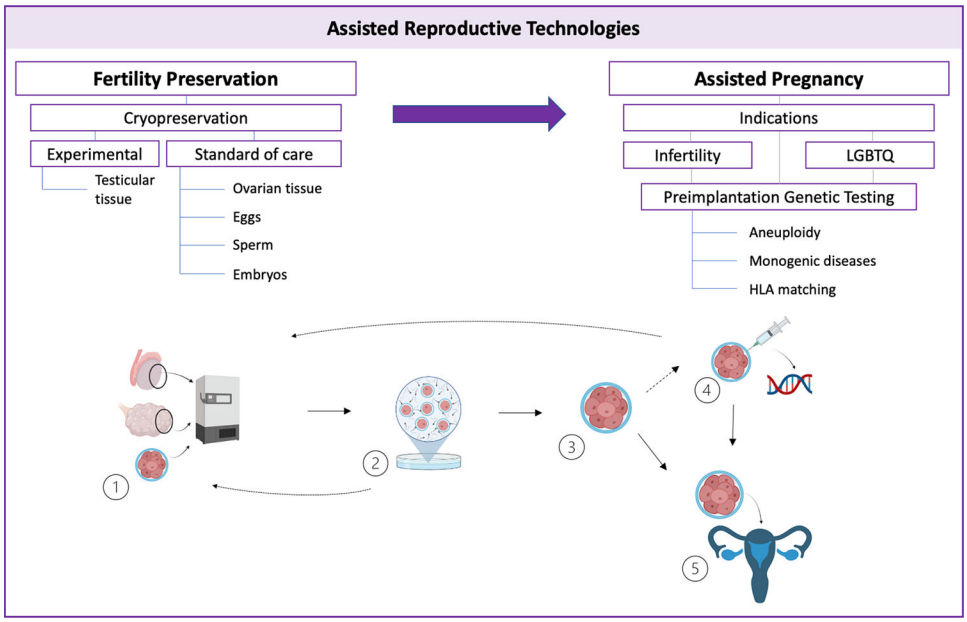

Figure 1.

Assisted reproductive technologies (ART) use for people with sickle cell disease and their families

ART might be used for fertility preservation, infertility treatment, by LGBTQ couples, and for preimplantation genetic testing. (1) Sperm, eggs, ovarian tissue, and embryos can be cryopreserved as care standards whereas testicular tissue cryopreservation is experimental. (2) Embryos are made by in-vitro fertilization (IVF) at the time of fertility preservation or gametes can be used to generate embryos via IVF once pregnancy is desired. (3) Embryos can be stored, or (4) sampled for testing to assess aneuploidy, for monogenetic diseases such as sickle cell disease, or for haploidentical matching with sibling before (5) introduction to the uterus.

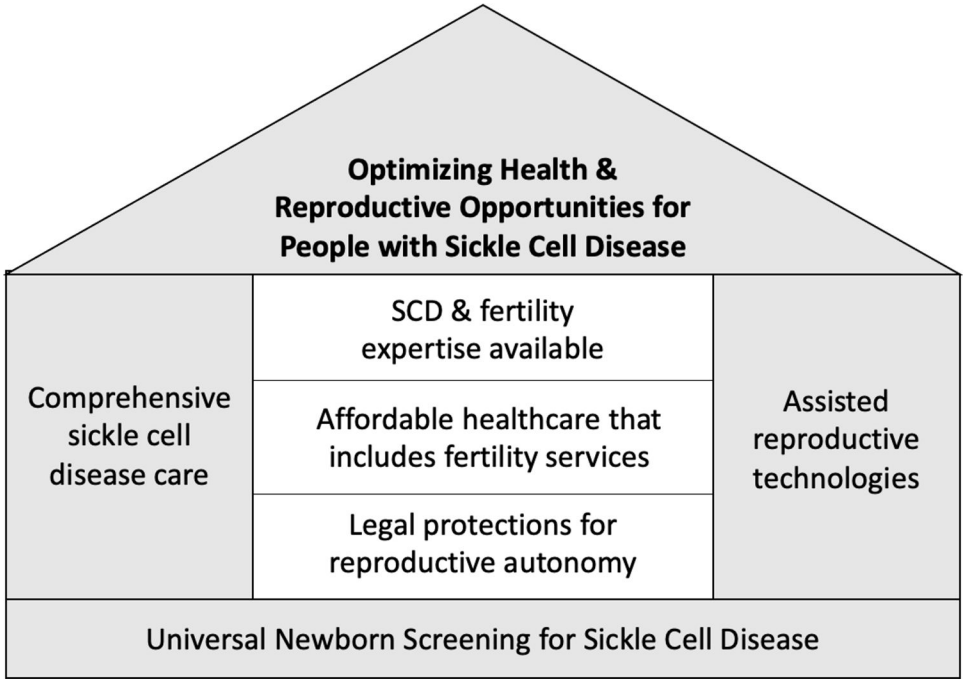

Figure 2.
Optimizing health and reproductive opportunities for people with sickle cell disease

Table 1

Putative infertility risks associated with sickle cell disease and its treatments and cures.

Few infertility risks are universal features of SCD, underscoring the need for individualized care that considers age, sex, genotype, disease complications and measures of treatment dose, duration and adherence. Uncertainties related to infertility risks can be incorporated into information sharing about disease complications and treatment benefits.

	People with ovaries	People with testicles
Untreated sickle cell disease	Ovarian reserve decline is accelerated in adulthood[4,5,6]; some adolescents and young adults have diminished ovarian reserve[6,9,10]	Hypogonadism[7,8]
		Sperm abnormalities[7,8]
	Pregnancy is high-risk for maternal and fetal morbidity & mortality[2]	Priapism, & erectile dysfunction[7,8]
Disease modifying therapies	Hydroxyurea: associated with diminished ovarian reserve[6,9,10]; concern for early embryonal developmental changes, teratogenesis[2]	Hydroxyurea: toxic to sperm (reversibility suggested), outstanding questions about long-term effects to spermatogonial pool[11]
	Red cell transfusions: ovarian follicle iron deposition possible[12], pituitary iron overload uncommon, chelators are teratogenic	Transfusions: testicular and pituitary iron deposition possible[13]
	L-glutamine, crizanlizumab, voxelotor: no data	L-glutamine, crizanlizumab, voxelotor: no data
Curative/HSCT preparative regimens	Alkylating Agents: gonadal toxicity and infertility[14]	Alkylating Agents: gonadal toxicity and infertility[14]
	Total Body Irradiation: Reduced ovarian reserve, infertility, uterine damage reducing future blastocyst implantation[14]	Total Body Irradiation: shielding spares the testicles[14]

Table 2

Approaches to address fertility care for haemoglobinopathy trait carriers and people with sickle cell disease in the USA require coordinated actions by institutions and organisations

	Actions to address, clinical care, research and access gaps	
Screening for hemoglobinopathy traits	CDC, USPTF, ACOG, ASH, AAP	Universal pre-conception genetic counseling
		Opportunity for hemoglobinopathy testing
Clinical Care	NHLBI/NIH, ASH, ACOG, ASRM, AAP, ASPHO, SMFM, NASCC	Comprehensive reproductive care guidelines
		Systematic approach to fertility and preconception counseling, evaluations, referrals
Research	CDC ART Surveillance & Research Team, SART	Create ART Surveillance Systems to identify SCD-related use & define outcomes for IVF+PGT in couples without infertility diagnosis
	NIH (NHLBI, NICHD, ORWH), ASH, ASRM, AUA	Create RFAs for high-quality clinical fertility research in SCD
Policy Changes	CMS, HRSA, State and Federal Lawmakers	Fund comprehensive SCD care
		Fund or mandate coverage for patients anticipating iatrogenic infertility
		Comprehensive, non-coercive genetic counseling and ART coverage for people with SCD and hemoglobin carrier couples

ACOG: American College of Obstetrics and Gynecology, ASH: American Society of Hematology, ASPHO: American Society of Pediatric Hematology & Oncology, ASRM: American Society of Reproductive Medicine, ART: Artificial Reproductive Technology, AUA: American Urological Association, CDC: Centers for Disease Control and Prevention, CMS: Centers for Medicaid and Medicare, HRSA: Health Resources and Services Administration, IVF++PGT: In Vitro Fertilization + Preimplantation Genetic Testing, NICHD: National Institute of Child Health and Human Development, NIH: National Institutes of Health, NHLBI: National Heart, Lung and Blood Institute, ORWH: Office for Research in Women's Health, NASCC=National Alliance for Sickle Cell Centers, RFA: Research Funding Announcement; SART: Society for Assisted Reproductive Technologies, SMFM, Society for Maternal and Fetal Medicine, USPTF: United States Preventive Task Force

Panel.

Opportunities to address fertility during routine sickle cell disease care

• During new evaluations unless post-menopause
• At puberty onset or at delayed puberty diagnosis
• Initiation or change in SCD treatment approach including pursuit of curative therapy
• Initiation of hormonal contraception
• Screening for and treating priapism
• Transition from pediatric care; integration into adult care
• Annual preconception counseling and with family planning discussions
• Parents of children with SCD who can be offered referral to genetic counseling and discussion of comprehensive reproductive options (including, but not limited to IVF +PGT-M)

Panel 2:

Research questions regarding fertility, infertility risk and Assisted Reproductive Technology in sickle cell disease

- Define effects of sickle cell disease pathophysiology and treatments on oocyte quality, blastocyst development and miscarriage
- Establish infertility rates and risks in people with sickle cell disease; include all genotypes
- Define gonadoprotection or gonadotoxicity of hydroxyurea, chronic transfusion, and other sickle cell disease therapies in chronically exposed people with attention to dose and duration of treatment
- Establish ideal timing of fertility preserving interventions and study protocols to optimize outcomes and minimize complications
- Identify which sickle cell disease treatments need to be discontinued, and for what time period, before gamete cryopreservation
- Define pregnancy outcomes when cryopreserved gametes are used
- Measure barriers to fertility preservation