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Knowledge gaps in reproductive and sexual health in girls and women with sickle cell disease

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Abstract

There is an immediate need to address long-standing questions about the reproductive health of girls and women with sickle cell disease (SCD). There are many SCD-related reproductive risks and uncertainties across girls' and women's reproductive lifespan, with particularly outstanding concerns about menstruation, contraception, fertility and pregnancy. Extant literature addressing women's reproductive health topics is mostly descriptive; there are few high-quality interventional studies. In 2020, the Centers for Disease Control and Prevention and the Foundation for Women and Girls with Blood Disorders convened an expert panel to assess the knowledge gaps in women's reproductive health in SCD. The panel identified significant limitations to clinical care due to the need for research. The panel also identified prominent barriers to research and care. In this report, we frame these issues, providing a roadmap for investigators, funding agencies, and policy makers to advance care for girls and women with SCD.

Keywords

Sickle Cell Disease; women's health; reproductive health; health disparities

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Background

The survival of children with sickle cell disease (SCD) well into their reproductive years creates the necessary precondition to address long-standing questions about the reproductive health of affected girls and women(1–4). Girls and women with SCD are at risk for having SCD pain with menses and thrombotic complications with oestrogen-containing contraception (5,6). Adolescent and young women with SCD look forward to having biologically related children (7), but anticipatory guidance and preconception counselling is complex for many reasons. In addition, unplanned pregnancy is common, highlighting the need for proactive rather than reactive reproductive health care (8–11). A summary of important publications addressing reproductive health concerns for girls and women with SCD is summarized in Table 1.

Reproductive healthcare for girls and women with SCD is limited by the absence of practice standards, the lack of clearly delineated responsibilities among specialties, and inadequate research to address pressing concerns. Research is hampered by a lack of prioritization of reproductive health research among specialists caring for individuals with SCD and the need to 1) optimize methods for conducting women's health research; 2) establish infrastructure for multi-centre and multi-disciplinary collaboration; and 3) ensure funding to support this research agenda (12,13). The purpose of this paper is to provide a roadmap for investigators and funding agencies to advance reproductive healthcare for girls and women with SCD.

Approach to developing this report

In 2020, the Centers for Disease Control and Prevention (CDC) convened an expert panel to discuss gaps in the care of girls and women with SCD. Working group participants included five manuscript co-authors (LHP, CH, MJP, AJ, KSW). The Foundation for Women and Girls with Blood Disorders (FWGBD) then convened a second public gathering to discuss the working group's findings. This gathering included paediatric and adult haematologists and a physician assistant who collectively represented eleven academic medical centres in the U.S.A. Participants from the CDC included health policy analysts, epidemiologists, research biologists and policy directors. Finally, members of the Sickle Cell Disease Foundation of California, a prominent community-based organization, attended this meeting. Additional leaders of the FWGBD's SCD Learning Action Network (KSW, DS, REW, AN) contributed to this report.

Table 2 and Table 3 summarize our findings, providing reproductive health research priorities and framing reproductive health questions about SCD treatments and curative therapies. In each domain, patient characteristics such as age, genotype, and geographic location need to be considered to define best practices, inform research approaches and interpret data. The issues identified apply to all or most SCD treatment modalities.

Lifespan approach to reproductive care

Most aspects of this care intersect with or are complicated by having SCD in some way. Consequently, girls and women with SCD need developmentally appropriate reproductive health care across their lifespan. The 2014 National Heart, Lung, and Blood Institute Sickle

Cell Disease Guidelines suggest that all individuals with SCD implement a reproductive life plan (14). Even though reproductive life planning is an overlapping concern between paediatric and adult care, and indeed some young women are already mothers when they transition to adult care, reproductive life planning and reproductive healthcare it is not a standard component of existing SCD transition planning documents. The Working Group takes a lifespan approach to considering reproductive healthcare concerns in girls and women with SCD and recognizes that the responsibility for this healthcare, although closely intertwined with SCD care, may not be perceived as the domain of paediatric or adult SCD specialist.

Menstruation

Girls with SCD achieve sexual development milestones later than their unaffected peers; the extent to which SCD therapies modify the onset of menses is not established (Smith-Whitley, 2014; Alleyne *et al*, 1981; Queiroz *et al*, 2020). Studies of menopause are challenging because onset coincides with the median age of death for affected women (1,15).

Pain and dysmenorrhea

Menstruation-related morbidity is underappreciated, undertreated, and associated with poor quality of life (16). No evidence-based recommendations guide management. In the historic Cooperative Study of Sickle Cell Disease, women had higher rates of SCD-related pain than men; this difference was most notable during women's reproductive years which raises the possibility that menses-triggered pain contributed to this finding (17). Women differentiate SCD-related menstrual pain from dysmenorrhea. One-third report SCD-related pain in the week before or during their menstrual cycles (5). Women with SCD indicated that male providers are dismissive of concerns about menstruation associated SCD pain (18). Studies are needed to understand the biological mechanisms that drive SCD-related pain during menstruation and to define evidence-based interventions for management and prevention of this common complication.

Fertility preservation

Fertility preservation for girls and women with SCD needs is increasingly important because of improved survival, the increased use of treatments that may compromise fertility and existence of approaches to preserve fertility in pre- and post-menarchal girls and women. At present, ovarian reserve testing is not universally offered to women with SCD. Exposure to gonadotoxic preparative regimens before HSCT or gene therapy is the only indication for fertility preservation in affected girls or women (19,20).

Recent evidence suggests women with SCD have a reduced reproductive lifespan as indicated by accelerated decline in ovarian reserve starting in 25 – 30-year-olds (15,21,22). Direct end-organ injury to the ovaries from SCD, possibly from ovarian sickling (23), may drive the premature decline in ovarian reserve. Secondary hypopituitarism is described in girls with thalassemia, but girls with SCD usually have intact endocrine function, even in the presence of iron overload (24). There is limited data about whether transfusional iron

overload affects oocyte quality and/or quantity (24,25) and none about SCD treatments approved over the last few years (crizanlizumab, l-glutamine and voxelotor). Several studies raise the possibility that hydroxyurea accelerates the decline of ovarian reserve in some girls and women (15,22,26,27). With limited data, clinicians are confronted by how and if to address open questions about hydroxyurea and future fertility during shared decision-making conversations about treatment. This concern must be understood in the context of strong evidence that hydroxyurea has profound clinical benefit for children around the globe (28–30). Whether addressing uncertainty about effects on fertility will dissuade parents from accepting treatment for their affected children is not established (31). Comparing the long-term fertility effects of existing and emerging treatment options may help guide counselling. The Sickle Cell Transplant Evaluation of Long-Term and Late Effects Registry will compare the fertility effects of hydroxyurea and HSCT (OTA HL152762).

Both ovarian tissue and oocyte or embryo cryopreservation are standards of care to preserve fertility in at-risk populations (32) and their use is reported in girls and women with SCD, usually before HSCT (25,33,34). However, SCD fertility research lags significantly behind oncofertility research as indicated by the presence of oncofertility guidelines and communication standards for individuals with cancer, but their absence for individuals with SCD (35,36). As with oncofertility research, early studies in SCD fertility focused on boys and men. The effects of hydroxyurea on sperm is more substantively addressed than is the effect of hydroxyurea on oocytes (22,26,37–44). Systematic studies are needed to define indications for fertility preservation, peri-procedural risks and risk mitigation strategies during fertility preservation, and outcomes relating to immediate fertility preservation and pregnancy when cryopreserved oocytes or ovarian tissue are used (33).

How existing fertility preserving approaches should influence clinical practice is unresolved due to insufficient research *and* because of inequitable access to fertility preservation for girls and women with SCD. This is a meaningful barrier to optimizing SCD care (45,46). In the United States, no federal law ensures that individuals with SCD, will have access to fertility preserving care or artificial reproductive technologies. Access to fertility preservation in European countries varies. Funding for longitudinal, cooperative studies will inform optimal approaches and indications for fertility preservation, but this work will be inadequate in the absence of policies to address this financial toxicity of SCD and ensure access to care (47).

Preconception Care

Preconception counselling is sub-optimal for women with SCD and unintended pregnancies are common (9,48,49). Preconception counselling is resource intensive as it includes:

- Need for partner testing and genetic counselling to provide accurate information about the chance of having a child with SCD (50);
- Discontinuing and discussing commonly used medications with established or potential teratogenicity in individuals with SCD (3,51);
- Pre-conception end-organ assessments (retinopathy, echocardiogram, pulmonary function tests, renal function);

- Risk and benefit of SCD treatment in pregnancy hampered by a lack of definitive interventions to alter the trajectory of high-risk pregnancy (52–54);
- Outstanding questions about whether SCD and its treatments compromise fertility (22,26);
- Inequitable access to fertility preservation (45).

Finally, partner testing to determine hemoglobinopathy carrier status is indicated. This testing may be used to provide counselling on the foetal risk for SCD and opportunity for in vitro fertilisation with preimplantation genetic testing. In some countries partner testing is systematically available (50). In the U.S.A. several barriers to partner testing persist. First, despite universal newborn screening for SCD, which also identifies individuals with SCT, this information is not systematically shared with families or retained in medical records. Second, unintended pregnancy is common and limits preconception counselling. Third, access to testing may be compromised based on insurance coverage (50,55). Finally, providers may not follow testing guidelines and even order the wrong screening test(56,57).

Evidence-based communication tools are needed to standardize comprehensive and complex counselling about fertility risks, contraception choices, and family planning in the context of pregnancy and postpartum risks for individuals with SCD. Incentives for research collaboration across subspecialties should be encouraged to improve partnerships among haematologists, high-risk obstetricians, reproductive endocrinologists, psychologists, and genetic counsellors.

Pregnancy

Women with SCD are at risk for significant pregnancy related morbidity and mortality (52,53). Studies are needed to identify risk factors for adverse outcomes for mother and foetus, evaluate SCD treatments for safety and efficacy when used in pregnancy, and to optimize pregnancy management and outcomes (58,59). The extent to which established risk factors for poor pregnancy outcomes in the general population affect women with SCD is incompletely addressed by the existing literature. Pressing research needs include: defining the necessary preconception evaluations of end-organ function, treatment optimization, timing or need for treatment modification (both pre- and post-conception) and whether findings and interventions modify pregnancy risks, rigorously studying interventions for pregnant women that reduce maternal and foetal morbidity and mortality, clarifying breastfeeding contraindications, and counselling and implementation of postpartum contraception (52,53,58,60).

Existing technologies can determine whether a foetus is affected by SCD. However novel, non-invasive foetal genetic testing methods that isolate foetal DNA from maternal blood (61) or the cervix(62), need further evaluation in the SCD population. In addition, research that furthers our understanding of how women with SCD make reproductive decisions and experience parenthood is needed (63–65).

Artificial reproductive technologies – in vitro fertilization

In high income countries, the use of artificial reproductive technologies for family building is increasing. Women with SCD may pursue artificial reproductive technologies due to infertility, with cryopreserved ovarian tissue, oocytes or embryos, or in conjunction with pre-implantation genetic testing. In vitro fertilization with preimplantation genetic testing (IVF+PGT) is relevant for some women with sickle cell disease *and* sickle cell trait because it provides opportunities to conceive children unaffected by SCD(66,67), and to select embryos for implantation that may be a match for HSCT in an affected child. In the United Kingdom, the National Health System makes IVF + PGT-M available to all couples at risk for having a child with SCD. A contemporary case series of 60 treated couples in London identified use by couples with diverse economic backgrounds and successful outcomes, including in three women with SCD (67). Significant barriers to uptake of this reproductive technology include that couples may be unaware of its existence (68,69) and may lack insurance coverage. Data about outcomes, regardless of indication, are needed. In the U.S.A., systematic data reporting on artificial reproductive technologies is federally mandated, but sickle-cell related variables are not collected. A recent report identified 16.5% of embryos created for the purpose of having an HLA-matched sibling were suitable for transfer(70). Patient education and counselling that address complex risks and benefits of treatment. Existing patient education materials about IVF+PGT-M exceed the reading levels of most Americans (71), highlighting the value of genetic counsellors and others trained to provide accessible education on complex genetic and reproductive concepts. The cost of IVF + PGT-M to prevent SCD or to implant HLA-matched embryo to produce a matched sibling donor need further study and might inform compassionate policy solutions for care (70,72).

Sex hormone therapies

Studies of sex hormone therapies for individuals with SCD are limited. Whether sex-steroid deficiency or supplementation affects polymerization of sickle haemoglobin is not established(73–75). Sex hormone therapies may be used to prevent dysmenorrhea and SCD-pain associated with menstruation, as contraception, for symptomatic menopausal women and for transgender individuals. Two significant concerns raised by treatment with sex hormones are the risk of 1) exacerbating existing hypercoagulability with the administration of exogenous oestrogens(6) and 2) further compromising bone health(76,77). Studies are warranted to generate sufficient data to guide the risk-benefit ratio of long-term sex hormone therapies in women with SCD.

Contraception

The increased pregnancy and menstruation-related morbidities of SCD and the potential teratogenicity of disease-modifying therapies make counselling about contraception therapy essential. Combined hormonal contraception and high-dose progestin contraception is associated with increased cardiovascular and thrombotic risk in the general population. Individuals with SCD are at increased risk of thrombotic events, a complication that is associated with poor clinical outcomes(78). Girls and women with SCD in many countries report varied hormonal and non-hormonal contraception use, with infrequent use of long-acting reversible contraception (9,10,48,79,80). Interest in and use of tubal ligation are not

established. Further studies are warranted to establish risks and benefits of contraceptive methods and to determine the factors that influence contraception choice, the short- and long-term sequelae of these decisions with respect to their overall health, SCD-related complications, desire for fertility, and quality of life.

Hormone therapy for menopause

Data regarding menopausal symptoms in women with SCD are limited (15). Whether the principles of hormone therapy for unaffected women are generalizable to women with SCD needs study, particularly because SCD is a hypercoagulable condition and the thrombogenicity of oestrogen preparations varies(81,82). Research is needed to best characterize the components needed to optimize shared decision-making around hormonal therapy in perimenopausal women with SCD.

Cross sex hormone therapy for transgender individuals with SCD

Transgender individuals with SCD requesting cross sex hormone therapy face theoretical risks with exogenous testosterone (hyperviscosity) or oestrogen (thrombosis). Withholding treatment may have grave consequences, and disease-specific evidence identifying optimal hormone preparations and concurrent SCD treatments is needed(83). Future studies will help define whether these hormonal therapies affect acute and chronic pain or other SCD complications.

Other gynaecologic concerns and sexual health

Whether and how SCD modifies women's risk for breast cancer or fibrocystic breast disease, and for common gynaecological problems such as polycystic ovarian syndrome, endometriosis, and heavy menstrual bleeding is not established. Sexual health concerns, like dyspareunia, might be anticipated in a population with high rates of complex chronic pain, psychiatric co-morbidities, and disproportionately low socioeconomic status, but this topic is largely unexplored (84).

Quality of care indicators

SCD affects all aspects of reproductive health for girls and women, but few quality-of-care indicators are established. Studies focused on implementing existing recommendations for reproductive life planning, preconception counselling and pregnancy care are needed. Studies on the organization of optimal comprehensive, multidisciplinary clinical care for individuals living with SCD should include attention to sex- and gender-specific healthcare needs and address how genetic counselling, and obstetrics and gynaecology care can be included in proposed care systems (85). A successful model within haematology is established: multidisciplinary clinics that include haematologists and obstetrician-gynaecologists who provide high quality care for women and girls with bleeding disorders. Benchmarks related to reproductive health knowledge and decisions need to be integrated into transition assessments, planning and integration into adult care(86). Interventions to optimize communication and persistence of genetic information about SCD and sickle trait status in the medical record are overdue. Appropriate use of this information to generate

testing protocols and recommendations to inform couples of their risk of having a child with SCD require further study. Finally, ordering the correct kind of screening testing for pregnant women with SCD and their partners is an ongoing health inequity that needs attention.

Societal Perspectives

Limitations in current reproductive healthcare for girls and women with SCD are bound to intersectional disparities in reproductive health care for Black women. Structural racism and racist mythologies both contribute to disparities in Black women's reproductive outcomes(87,88). Differences in the broad distribution of health care resources, the availability of SCD experts and insurance coverage contribute to profound limitations to SCD-related reproductive healthcare. In the USA, adults with SCD lack specialists to provide care(85), unintended pregnancy is more common than in Europe(89), and access to comprehensive reproductive healthcare is limited by geography and health insurance status(90–93). European nations differ in approaches to newborn screening for SCD, the availability of SCD expertise and access to comprehensive reproductive health care that includes fertility preservation (94,95). Of course, most girls and women with SCD live in sub-Saharan Africa and India where access to fundamental SCD diagnostics and treatments are profound public and personal health problems(96). In this setting too, the reproductive consequences of SCD and its treatments are needed(97–99). Healthcare policies that build access to reproductive healthcare are required to fully optimize outcomes for girls and women with SCD.

Conclusion

Women with SCD are surviving into and beyond their reproductive years. Even in the absence of high-quality evidence that is specific to adolescent and adult women living with SCD, we can do more with what we know now to advance reproductive healthcare for this population. There are opportunities to improve their medical care through healthcare policy reform, advocacy, and implementation of preventative care models. These initiatives are important and underutilized, but they are no substitute for long-neglected, hypothesis-driven, patient-oriented studies. Rigorous research studies will bolster the limited evidence available to care for girls and women with SCD. The SCD community – patients, families, and providers – deserves more. The SCD research community and funding agencies must rise to meet this challenge.

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Abbreviations

HSCT	Haematopoietic stem cell transplant
IVF	In vitro fertilization
PGT	Preimplantation genetic testing for monogenetic disorders
SCD	Sickle cell disease
SCT	Sickle cell trait

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Table 1.

Summary of existing research in girls and women with sickle cell disease with attention to date, topic, conclusions, and opportunities for additional study

Category	In-text reference	Summary of published findings	Opportunities for future investigation
Menstruation: dysmenorrhea and acute vaso-occlusive pain	Citation 5	• Acute vaso-occlusive pain is temporally associated with menstruation in a subset of women with SCD • Dysmenorrhea is associated with having acute vaso-occlusive pain associated with menstruation	• Pathophysiology of acute vaso-occlusive pain that occurs in association with menstruation • Optimal hormonal contraception for menses-associated pain
Contraception	Citation 9, 10, 11, 79, 80	• Use of low reliability barrier methods of contraception is common in women with SCD • Unintended pregnancy is common in women with SCD	• Safety of contraception use in women with SCD • Barriers to treatment acceptance • Care structures to prevent unplanned pregnancies
Cross-sex hormone therapies	Citation 83	• Some individuals with SCD are transgender and will request hormone therapy	• Safety of exogenous oestrogen and testosterone
Pregnancy	Citation 52, 53, 59,	• Maternal mortality is increased in women with SCD • Pregnant women with SCD are at risk for hypertensive disorders of pregnancy, adverse fetal outcomes (intrauterine growth restriction, fetal demise, & malformations), miscarriage and pre-term delivery • Transfusion reduces acute pain and acute chest episodes during pregnancy	• Optimal treatment for SCD during pregnancy • Optimal supportive care during pregnancy • Determine teratogenicity of SCD-specific therapies • Implementation & cost-effectiveness of comprehensive care systems
Breastfeeding	Citation 60	• Women without SCD have low levels hydroxyurea in breast milk after a single dose	• Preferences and practices relating to breastfeeding in women with SCD • Feasibility of pump and dump with hydroxyurea therapy during lactation
Ovarian reserve	Citation 19, 21, 22	• Adult women with SCD have accelerated decline in ovarian reserve • Diminished ovarian reserve occurs in a subset of girls and women with SCD	• Extent to which SCD and its treatments affect ovarian reserve • Correlation of ovarian reserve testing with pregnancy outcomes
Fertility preservation	Citation 25, 33	• Girls and women with SCD have used ovarian tissue cryopreservation and oocyte and embryo preservation as fertility preservation strategies	• Optimal timing of fertility preservation interventions • Indications for fertility preservation • Optimal health policies to guarantee access to care
In Vitro Fertilisation with	Citation 67, 68	• Parents of children with SCD are interested in IVF + PGT	• Outcomes from large contemporary data sets

Category	In-text reference	Summary of published findings	Opportunities for future investigation
Preimplantation Genetic Testing		• IVF + PGT has been used successfully in couples affected by sickle cell trait and SCD	• Cost benefit analysis and education, particularly for IVG + PGT to prevent SCD and produce HLA-matched siblings
Menopause	Citation 15	• Brazilian women with SCD enter menopause in their late 40's, and sooner with hydroxyurea	• Epidemiology and risk factors for early menopause • Interaction of menopausal and SCD-related symptoms

Table 2.

Research priorities to advance the care of girls and women with sickle cell disease

Growth & development
• Growth and sexual maturation of girls with SCD in the era of disease-modifying therapies
• Osteoporosis risks, preventive measures, and progression over time
Menstruation, menopause, sex hormone therapies and gynaecologic concerns
• Interventions for the prevention and treatment of SCD-pain that is temporally associated with menstruation
• Severe iron deficiency associated with heavy menstrual bleeding
• Determine menopause onset, associated symptoms and optimal management
• Safety of oestrogen-containing contraception and hormone therapies in menopausal and transgender individuals
• Safety of oestrogen-containing contraception and other hormone therapies for SCD-related complications, such as acute pain
• Unintended pregnancy and long-acting reversible contraception use
• Breast disease and gynaecologic pathologies occurrence
• Breast, uterine and ovarian cancer occurrence
Fertility and reproductive life planning
• Reproductive lifespan with attention to genotype, disease complications and treatments
• Risks of infertility and when to initiate infertility evaluations
• Indications for and outcomes of fertility preservation interventions with attention to issues of oocyte quantity (ovarian reserve) and quality
• Success/effectiveness of and risks of fertility preservation interventions
• Standards for the provision of high-quality reproductive health care including studies of care models, sexual and reproductive health education across the transition from paediatric to adult care, and preconception counselling
• Health care utilization studies and cost-effectiveness analyses to identify strategies to leverage existing resources for fertility preservation and artificial reproductive technologies
Pregnancy and antepartum issues
• Risks for maternal mortality, pregnancy-related hypertensive disorders, venous thromboembolism, premature labour and SCD-related pregnancy complications (pain and acute chest syndrome)
• Interventional studies and randomized clinical trials to modify risks to mother and foetus during pregnancy and postpartum (depression, thrombosis, pain, neonatal abstinence syndrome, haemolytic disease of the new-born)
• Preferences about breastfeeding; impact of disease-specific factors and therapies on the feasibility of lactation and safety of breastfeeding
• Establish normal blood pressure values in pregnancy to inform the diagnosis of pre-eclampsia and eclampsia
• Standardization of appropriate testing to determine a couple’s risk for having a child with SCD
Sex-differences in SCD complications across the lifespan
• Sex-specific differences in SCD pathophysiology, symptoms, complications, and clinical outcomes, including response to disease-modifying therapies and success of curative therapies
• Comparison of access to disease-modifying and curative therapies for women versus men
• Incorporation of women’s health outcomes, including menses, bone health, pregnancy and lactation into clinical trials

Table 3.

Key questions regarding disease-modifying therapies and reproductive health in girls and women with sickle cell disease.

All SCD Therapies *

- How does treatment or combined treatment affect growth, bone health, sexual development, onset of menopause or SCD-pain associated with menses?
- Is treatment or combined treatment protective against menstruation associated SCD pain?
- Does treatment or combined treatment protect against known thrombotic complications of oestrogen-containing contraception?
- What are the long-term effects of treatment or combined treatment on ovarian reserve and reproductive potential?
- What are the safety and efficacy of treatment or combined treatment prior to conception, during pregnancy, and while breastfeeding?
- Does treatment or combined treatment affect the quality of oocytes harvested or embryo maturation for cryopreservation?
- Given the complexities related to reproductive risks and treatment during pregnancy, how should shared and informed decision making proceed in children, adolescents and adults? What information should be shared as standard of care?
- Medicaid and other federal insurances do not cover fertility preservation. Does changing access to fertility preservation for girls and women with SCD change participation rates in clinical trials involving potentially gonadotoxic therapies?

Hydroxycarbamide

- Does treatment alter onset of menses or menopause?
- What are fertility outcomes in women treated with long-term hydroxycarbamide therapy? How do they compare to outcomes with women with untreated SCD or those exposed to HSCT preparative regimens?
- What are the miscarriage and teratogenic risks of hydroxyurea in each trimester of pregnancy and compare with potential treatment benefit in pregnancy?

Preparative regimens for HSCT and gene therapy

- How do reproductive outcomes in girls or women treated with non-myeloablative versus myeloablative preparative regimens differ?

* **All SCD Therapies:** hydroxycarbamide, voxelotor, crizanlizumab, L-glutamine, chronic red cell transfusion, non-myeloablative preparative regimen, and myeloablative preparative regimens, gene therapies