Risks associated with fertility preservation for women with sickle cell anemia

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Objective: To highlight the risk of complications among women with sickle cell anemia (SCA) receiving fertility preservation treatment (FPT) before hematopoietic stem cell transplant (HSCT).
Design: Single-center case series.
Setting: Academic fertility center.
Patient(s): Women aged 15–32 years with SCA undergoing FPT before HSCT.
Intervention(s): Retrospective, systematic review.
Main Outcome Measure(s): FPT modality, SCA complications during FPT.
Result(s): Over an 8-year period (2009–2017), seven women with SCA ages 15–32 years (mean 28.5 years) underwent FPT with embryo cryopreservation (n = 1), oocyte cryopreservation (n = 4), and ovarian tissue cryopreservation (n = 2). The five women subjects who underwent oocyte or embryo cryopreservation were treated with an antagonist controlled ovarian hyperstimulation protocol and individualized gonadotropin dosing. The trigger medications included leuprolide acetate (n = 2), and human chorionic gonadotropin (n = 3). Most patients (n = 5) received a disease-modifying therapy for SCA (hydroxyurea or chronic transfusions) before FPT. Three patients experienced periprocedural SCA complications that included life-threatening respiratory failure, painful crisis requiring interruption of a stimulation cycle, and severe postharvest painful crisis.
Conclusion(s): Women with SCA may choose to undergo diverse FPT strategies before HSCT and are at risk for serious SCA-related complications. Evidence-based strategies to mitigate SCA-related morbidity and to optimize fertility preservation outcomes are needed. (Fertil Steril® 2018;110:720–31. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Bone marrow transplant, female infertility, fertility preservation treatment, sickle cell anemia, sickle cell disease

Sickle cell anemia (SCA, comprising hemoglobin SS and hemoglobin Sβ^0 genotypes) is a life-limiting disease characterized by hemolytic anemia, vascular dysfunction, chronic end-organ injury, and early death. A growing number of patients with SCA are pursuing hematopoietic stem cell transplant (HSCT) to cure their SCA (1). Recipients of HSCT are exposed to gonadotoxic therapies, including alkylating agents such as cyclophosphamide and busulfan and total body irradiation (2). These exposures are associated with up to an 80% risk of premature ovarian failure. Consequently, patients are referred for fertility preservation treatment (FPT) before HSCT (3). In consultation with a reproductive endocrinologist, women with SCA may choose from the three main options for FPT currently available: embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation (OTC). These approaches require controlled ovarian hyperstimulation (COH), deep sedation for oocyte retrieval, or general anesthesia for ovarian tissue harvest.

The risks of COH, oocyte retrieval, and ovarian tissue harvest are not well defined for patients with SCA, so they may be underappreciated. In the general population,

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the routine complications of COH include headache, nausea, abdominal distention, and fluid retention. Patients with SCA have altered pain perception, and they may not tolerate periprocedural discomforts well (4, 5). Less commonly, ovarian hyperstimulation syndrome (OHSS) complicates COH (3,6,7). Moderate to severe OHSS occurs in approximately 1% to 5% of COH cycles, and it is associated with pleural effusion, acute renal insufficiency, and venous thromboembolism (VTE) (8).These complications are concerning for patients with SCA because SCA is a thrombophilic condition at baseline and because chronic vascular, pulmonary, renal, and hepatic injury contribute to intolerance to fluid shifts and vulnerability to hepatic and renal insults (4,5, 9–12). When patients with SCA are hospitalized or receive sedation or general anesthesia, they are at increased risk of developing life-threatening pulmonary complications (5).

Because FPT is highly valued by many patients and families in choosing SCA therapies, patients may choose to pursue FPT before HSCT despite the risks and uncertain benefits (13–15). Clinicians have few SCA-specific data with which to counsel patients for FPT, which leaves these patients with uncertainty when they must make decisions. This retrospective analysis of women with SCA undergoing FPT before HSCT at an academic fertility center examines their FPT choices, periprocedural management, and treatment complications. The women who experienced complications during FPT are described to highlight SCA-specific complications of FPT and to explore fundamental management considerations.

MATERIALS AND METHODS

The Johns Hopkins University institutional review board (IRB) approved this study of women with SCA (hemoglobin SS or hemoglobin Sβ^0) who were considering FPT before HSCT and were enrolled in a gonadotoxic therapies and fertility preservation database between 2009 and 2016. Eight women were included. A chart review of women with SCA was performed to obtain SCA-related variables, including prior SCA-related complications and historical disease-modifying treatments (hydroxyurea or red blood cell transfusions); and FPT-related variables including type of fertility preservation, measures of fertility, stimulation protocol, procedural outcomes, and complications. The fertility preservation interventions included embryo cryopreservation, oocyte cryopreservation, and OTC.

Our center has offered OTC as a clinical service since 2006, with 40 ovarian tissue harvests performed to date. We have research protocols with IRB approval for certain patient populations, but the patient described in this study who underwent OTC was not a candidate for any research protocols and she proceeded with OTC on an elective basis. We also have had an IRB for oocyte cryopreservation since the early stages of this technology, but when the patients in this study underwent oocyte cryopreservation it was a clinical service offered outside IRB approval.

RESULTS

Cohort Results

Among eight patients with SCA who considered FPT, one woman chose no FPT after counseling. The details of the seven women who chose to undergo FPT are provided in Table 1. The patients' mean age was 25.8 ± 5.3 years, and diverse FPT strategies were used: embryo cryopreservation (n = 1), oocyte cryopreservation (n = 4), and OTC (n = 2). The COH protocol was individualized to the patient's age, ovarian reserve markers, and baseline antral follicle count. The patients who chose oocyte or embryo cryopreservation (n = 5) were stimulated with an antagonist protocol. The mean duration of gonadotropin treatment was 11.6 days (±4.93 standard deviation [SD]), and the mean total gonadotropin dose was 3,390 IU (±1,913 SD). The trigger medications included leuprolide acetate (n = 2), urinary human chorionic gonadotropin (hCG) (n = 2), and recombinant hCG (n = 1). The oocyte yield was heterogeneous: the mean of the oocytes retrieved was 12.8 (range: 4–21 ± 7.58 SD). The mean number of cryopreserved oocytes for the women who chose this option (n = 4) was 10 (range: 3–21 ± 8.64 SD). Seven embryos were cryopreserved for one woman who chose this FPT. Another woman required two cycles of stimulation due to poor response during the first cycle.

Treatment for SCA varied among the patients, likely reflecting the treatment regimens required before HSCT and baseline disease states. Most (n = 5) received an SCA therapy (hydroxyurea or chronic transfusions) before FPT. Two patients underwent a preoperative red cell exchange transfusion before oocyte retrieval or laparoscopic ovarian tissue harvest. Baseline hemoglobin in individuals with SCA can range from 6–8 g/dL but may increase when they receive hydroxyurea or chronic transfusions. The mean hemoglobin before harvest in our study was 8.9 g/dL (range: 7.2–10.2 g/dL), and four patients' hemoglobin was under 10 g/dL at time of oocyte collection. One patient who had a history of pulmonary embolism continued rivaroxaban anticoagulation during FPT. None of the women in this cohort have yet chosen to pursue a pregnancy with fertilization of cryopreserved oocytes or frozen embryo transfer. No patients developed OHSS, but three experienced SCA-related complications.

Interpreting the laboratory values for people with SCA is not always straightforward. In these cases, interpretation of laboratory values was relative to each patient's baseline. West et al. (16) provide a reference for interpreting laboratory results in untreated patients with SCA.

Case 1. A 27-year-old woman, para 0, with hemoglobin SS (HbSS) and oligomenorrhea was referred to the reproductive endocrinology department before HSCT. Her SCA history was remarkable for multiple painful crises, including 10 episodes in the 6 months before her consultation. She also had a history of acute chest syndrome (ACS), a severe pulmonary complication of SCA. She considered FPT with embryo cryopreservation, oocyte cryopreservation, and OTC, and she chose OTC. As part of the routine preoperative care for a patient with SCA, 2 days before laparoscopic unilateral OTC she received 2 units of packed red blood cells (pRBC) to raise her hemoglobin to 10 g/dL, but her initial ovarian