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).


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. 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.)

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.

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

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Sickle cell anemia (SCA, comprising hemoglobin SS and hemoglobin Sβ0 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,
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.

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 regimen’s benefits. For the women who chose 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 the 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
# Table 1

Sickle cell anemia patients evaluated for fertility preservation or infertility: Johns Hopkins University cohort from 2009–2017 (N = 7).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Preservation type</th>
<th>Age (y)</th>
<th>History</th>
<th>SCA treatment</th>
<th>Hgb before procedure</th>
<th>% HbS before procedure</th>
<th>Anterior follicle count</th>
<th>Days stimulated</th>
<th>Peak estradiol (total units)</th>
<th>Gonadotropin IU/d</th>
<th># Oocytes retrieved (GV, MI, MII)</th>
<th># Oocytes/embryos cryopreserved</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ovarian tissue cryo</td>
<td>27</td>
<td>Painful crisis, ~20-30 RBC transfusions</td>
<td>2U pRBC before stim</td>
<td>10.2</td>
<td>77</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Pain crisis after laparoscopy (Case 1)</td>
</tr>
<tr>
<td>2</td>
<td>Oocyte cryo</td>
<td>26</td>
<td>Many ACS</td>
<td>HU</td>
<td>–</td>
<td>70.4</td>
<td>2</td>
<td>13</td>
<td>3567</td>
<td>450 (5850)</td>
<td>Leuprolide</td>
<td>21</td>
<td>Respiratory failure (Case 2)</td>
</tr>
<tr>
<td>3</td>
<td>Embryo cryo</td>
<td>28</td>
<td>Multiple sickle cell painful crisis, ~10/y</td>
<td>HU</td>
<td>7.4</td>
<td>–</td>
<td>Small follicles</td>
<td>10</td>
<td>244</td>
<td>300 (3000)</td>
<td>HCG</td>
<td>11</td>
<td>Pain crisis during stimulation (Case 3)</td>
</tr>
<tr>
<td>4</td>
<td>Oocyte cryo</td>
<td>32</td>
<td>Sickle cell painful crises</td>
<td>2U pRBCs 1 month prior</td>
<td>10.1</td>
<td>71.2</td>
<td>10</td>
<td>10</td>
<td>983</td>
<td>150-225 (1875)</td>
<td>HCG</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Ovarian tissue cryo/ unilateral oophorectomy</td>
<td>25</td>
<td>Renal vein thrombosis, SLE nephropathy tx with immunosuppressives including cyclophosphamide</td>
<td>1U pRBCs day prior to surgery</td>
<td>7.2</td>
<td>62.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Oocyte cryo</td>
<td>28</td>
<td>Many painful crisis (3-4/y)</td>
<td>HU</td>
<td>9</td>
<td>72.6</td>
<td>Small follicles</td>
<td>12</td>
<td>815</td>
<td>225-300 (3300)</td>
<td>Leuprolide</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Oocyte cryo (transabdominal retrieval)</td>
<td>15</td>
<td>Monthly transfusions &gt;2/y</td>
<td>HU</td>
<td>–</td>
<td>9.4</td>
<td>–</td>
<td>14</td>
<td>457</td>
<td>225 (2925)</td>
<td>HCG</td>
<td>14</td>
<td>2 stim cycles required due to low yield; pRBCs 2 d post retrieval at an outside hospital</td>
</tr>
</tbody>
</table>

Note: In our cohort, the patients had never been pregnant before and were referred to reproductive endocrinology and infertility for counseling for fertility preservation treatment options before HSCT. History, laboratory results, COH protocols, outcomes, and complications are compared. A dash indicates that no data are available for that patient. ACS = acute chest syndrome; COH = controlled ovarian hyperstimulation; cryo = cryopreservation; D3 = day 3; ECMO = extracorporal membrane oxygenation; GV = germinal vesicle; HbS = hemoglobin S; HCG = human chorionic gonadotropin; HSCT = hematopoietic stem cell transplant; HU = hydroxyurea; MI, MII = metaphase I and II; PE = pulmonary embolism; pRBC = packed red blood cells; RBC = red blood cells; SCA = sickle cell anemia; SLE = systemic lupus erythematosus; tx = treatment.
cryopreservation surgery was canceled because she was hospitalized with a painful crisis.

On postoperative day (POD) 1, the patient developed severe back and groin pain that required hospitalization. The laboratory values showed hemoglobin 9.3 g/dL, normal white blood cell count (13.7 K/μL) and platelet count (342 K/μL), baseline creatinine 0.6 mg/dL, and hyperferritolemia (601 ng/mL), consistent a mild transfusional iron overload. She received fluid resuscitation and a hydromorphone patient-controlled analgesia pump with improved pain on POD 2. She was transitioned to an oral pain regimen and discharged home, but she was readmitted on POD 6 with severe, prolonged pain and was discharged on POD 17. The patient subsequently underwent successful haploidentical HSCT.

Case 2. A 26-year-old woman, para 0, with HbSS and a history of severe SCA complications was referred for FPT before HSCT. During childhood she had experienced many painful crises and ACS; as an adult, she had avascular necrosis that required hip replacement, VTE, severe ACS that required extracorporeal membrane oxygenation, and red cell alloimmunization. She was treated with chronic red cell exchanges, and she subsequently started hydroxyurea and indefinite anticoagulation with rivaroxaban for recurrent VTE.

Her fertility evaluations included an ultrasound scan revealing a normal uterus and ovaries with an antral follicle count of 2. Her antimüllerian hormone (AMH) level was 0.67 ng/mL. After counseling, she elected to undergo oocyte cryopreservation. On cycle day 2, her estradiol level was <20 pg/mL, follicle-stimulating hormone (FSH) level was 12.6 mIU/mL, and luteinizing hormone (LH) level 11.6 mIU/mL. On menstrual cycle day 2, COH was initiated with 300 IU of recombinant FSH and 150 IU of recombinant hMG. Her cycle day 2 estradiol level was 53 pg/mL, FSH was 9.7 mIU/mL, and LH was 3.5 mIU/mL. On menstrual cycle day 2, COH was initiated with 300 IU of recombinant FSH. She was hospitalized overnight on cycle day 6 for a painful crisis. Laboratory results demonstrated baseline hemoglobin (7.4 g/dL), increased reticulocyte count (22.5%), and baseline white blood cell count (15.9 K/μL) and platelets (317 K/μL).Canceling the cycle was considered, but the painful crisis resolved quickly, and the remainder of her stimulation was uneventful. On cycle day 7, 5 mg of letrozole daily was added to her antagonist stimulation protocol; on day 9, gonadotropins were changed to 225 IU of recombinant FSH and 75 IU of recombinant human menopausal gonadotropin. She was triggered with urinary hCG on cycle day 11 with a peak estradiol of 244 pg/mL. She underwent successful transvaginal oocyte retrieval of 11 oocytes, which were inseminated by in vitro fertilization. Seven oocytes fertilized, and seven cleavage-stage embryos were cryopreserved.

DISCUSSION

Women with SCA who chose to undergo FPT, especially COH and oocyte retrieval, may be at risk for severe, even life-threatening clinical events. Three women in this cohort experienced SCA-related complications, including a severe painful crisis after laparoscopic OTC, a life-threatening episode of ACS that required intensive care, and severe midstimulation pain crisis. Painful crisis and mild OHSS have been previously reported in women with SCA (17–19). Table 2 provides a summary of our data with published reports of complications associated with FPT in patients with SCA, and highlights the kinds of complications, their onset in relation to FPT procedures, and symptoms and management. Ours is the first report of life-threatening ACS in the setting of COH. These cases provide a valuable lens through which to view SCA-specific considerations for patients undergoing FPT. This cohort highlights the diverse risks and uncertainty these medically complex patients assume when electing FPT.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Age (y)</th>
<th>Complication</th>
<th>Onset</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dovey et al., 2012 (18)</td>
<td>1</td>
<td>19</td>
<td>Acute painful crisis</td>
<td>During recovery from anesthesia for oocyte retrieval 4 d after oocyte retrieval</td>
<td>Low back and pelvic pain for &lt;24 h  Abdominal pain, vomiting, ascites resolved on day 7</td>
<td>Overnight admission for pain control  Supportive care</td>
</tr>
<tr>
<td>Lavery et al., 2016 (17)</td>
<td>1 (case 7)</td>
<td>18</td>
<td>Mild OHSS with 200 ml of ascites and ovarian volumes 317–398 mL</td>
<td></td>
<td></td>
<td>Exchange transfusion, then resumed ovarian stimulation with following the cycle Intravenous hydration, PCA for pain control and RCE with resolution on post-operative day 17</td>
</tr>
<tr>
<td>Matthews and Pollack, 2017 (19)</td>
<td>1</td>
<td>23</td>
<td>Acute painful crisis</td>
<td>On day 6 of ovarian stimulation</td>
<td>Severe pain</td>
<td>Exchange transfusion, then resumed ovarian stimulation with following the cycle Intravenous hydration, PCA for pain control and RCE with resolution on post-operative day 17</td>
</tr>
<tr>
<td>Pecker, 2018 (this study)</td>
<td>3 (case 1 - 3)</td>
<td>27</td>
<td>Acute painful crisis</td>
<td>Post-operative day 1 from ovarian cryopreservation surgery</td>
<td>Pain in back and groin</td>
<td>Exchange transfusion, then resumed ovarian stimulation with following the cycle Intravenous hydration, PCA for pain control and RCE with resolution on post-operative day 17</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td></td>
<td>Acute chest syndrome with respiratory failure and bacteremia</td>
<td>Within 12 h of oocyte retrieval</td>
<td>Chest pain and shortness of breath</td>
<td>Rule-out pulmonary emboli, then intensive care with emergent RCE transfusion, intubation, antimicrobials, pain control, supportive care IV hydration, opiate pain control</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td></td>
<td>Acute painful crisis</td>
<td>Pain on cycle day 6 requiring overnight hospitalization</td>
<td>Diffuse pain</td>
<td>Rule-out pulmonary emboli, then intensive care with emergent RCE transfusion, intubation, antimicrobials, pain control, supportive care IV hydration, opiate pain control</td>
</tr>
</tbody>
</table>

Note: A review of previously reported adverse outcomes associated with FPT in adolescent and adult women with sickle cell anemia (SCA) plus the cases reported herein suggests that patients with SCA are at risk for SCA-associated complications during FPT. FPT = fertility preservation treatment; OHSS = ovarian hyperstimulation syndrome; PCA = patient-controlled anesthesia; RCE = red blood cell exchange.

Minimizing the potential procedural risks for patients with SCA is important. Stimulation protocols balance optimal oocyte retrieval against the risk of OHSS. The patients described here were triggered with either hCG or a gonadotropin-releasing hormone agonist to reduce the risk of OHSS. The patients who were triggered with both drugs experienced SCA complications. General anesthesia is also associated with ACS, which can progress to multiorgan failure and death, but these risks are reduced with premedication red cell transfusion and postprocedure pain control and incentive spirometry.

Before general anesthesia, patients with SCA are usually transfused to reduce adverse outcomes. In this setting, the goal is usually to raise the hemoglobin to 9–10 g/dL. Treatment with dexamethasone (used as an antiemetic for case 2) can provoke painful crises associated with increased mortality. Hematologists avoid the use of glucocorticoids when possible. Both COH and OHSS increase VTE risk, and SCA is a thrombophilic condition. Assessing patients for VTE history can guide thromboprophylaxis decisions. Pain associated with COH may be more severe or difficult to control than expected because women with SCA can have higher opioid tolerance, chronic pain, and lower pain thresholds. If a pain crisis or other complication occurs during a COH cycle, cancelation is a risk. For instance, had the painful crisis in patient 3 continued, her cycle would have been canceled.

Procedural risks may differ based on patient age. The women in our cohort were older than those in previous reports, and we anticipate that a growing number of adults with SCA will be referred for FPT before HSCT as regimen-related mortality and morbidity are reduced. Older patients with SCA, whose life expectancy remains in the 5th decade, have had more time to accumulate significant morbidities as their relentless vascular, pulmonary, renal, and hepatic injury has persisted. The patients in this study had a panoply of common preexisting SCA morbidities including stroke, avascular necrosis, frequent pain, alloimmunization, ACS, and VTE. Significant disease-related morbidity is a precondition for undergoing HSCT, so these morbidities may be especially increased among patients pursuing FPT before HSCT.

The choice of FPT modality depends on multiple factors including the patient’s age, pubertal status, partner status, and time available for treatment. Cryopreservation of embryos is currently more efficient than freezing oocytes, but patients with SCA pursuing FPT are often young, may not have a partner, and may not want to use anonymous sperm donors to bank embryos. In this cohort, four women cryopreserved oocytes, two preserved ovarian tissue, and one banked embryos. As of June 2017, approximately 130 live births worldwide have resulted from OTC, but this approach remains an experimental. Oocyte cryopreservation is no longer experimental and is preferred over OTC, but for some patients, OTC is the only option because of time constraints.

Even if FPT results are excellent, a pregnancy in the future is not guaranteed. In this cohort, the mean number of oocytes retrieved was 12.8, but it ranged from 4 to 21 oocytes. In 2013, a pregnancy rate of ~6% per vitrified oocyte was reported, and harvesting at least 15 oocytes is ideal to optimize the chance of achieving a pregnancy in one cycle. Few women in this cohort had oocyte yields exceeding 15 oocytes. Repeating COH cycles to increase oocyte yields may help address this concern for some patients, but in these cases the time and financial constraints were prohibitive.

In addition, HSCT itself reduces the chances of pregnancy. The rates of ovarian failure in patients after HSCT range from 50% to 80%; these numbers likely reflect the variable regimen-related toxicities. Consistent with this range, a long-term follow-up of 14 women cured of SCA by HSCT found that 57% had premature ovarian failure. However, successful pregnancies after FPT and HSCT in patients with SCA have been reported. Whether age at HSCT, a diagnosis of SCA, previous SCA treatments, or disease-specific complications alter oocyte or embryo quality and the subsequent pregnancy rate is unknown. No patient in our cohort has pursued pregnancy to date.

Currently no standardized approach or guidelines for FPT exist for women with SCA. An interdisciplinary approach incorporating the expertise of reproductive endocrinology, hematology, and anesthesia is required for women with SCA who choose FPT for any reason. Figure 1 outlines an approach to evaluate and periprocedurally manage women with all sickle cell genotypes before FPT. We recommend preoperative red cell transfusions and postanesthesia incentive spirometry to prevent ACS, but extensive alloimmunization may make chronic red cell exchange transfusion difficult if not impossible for some patients.

In previous studies, patients have continued indefinite anticoagulation during COH, and another received thromboprophylaxis during COH. In this cohort, none of the women received thromboprophylaxis, but several continued baseline anticoagulation. At our center, patients are thoroughly evaluated before FPT treatment. The fertility specialist works closely with the surgical oncologist, medical oncologist, radiation oncologist, bone marrow transplant, and hematologist to verify candidacy for FPT and coordinate the timing of procedures. Patient safety is prioritized over FPT, so the treatment does not proceed in patients with potentially compromising acute illness.

Patients presenting for FPT before HSCT have usually been treated chronically or episodically with hydroxyurea or chronic transfusions, the primary disease-modifying therapies for SCA. Most of the patients described here (5 out of 7) received one or both of these treatments before FPT. Hydroxyurea is a ribonucleotide reductase inhibitor that reduces the major clinical complications of SCA. Its use is associated with improved survival and enhanced engraftment of transplanted bone marrow. Hydroxyurea induces fetal hemoglobin production, reduces platelet and reticulocyte counts, and improves vascular endothelial signaling. The treatment may be initiated as early as 9 months of age; barring toxicity, it may be continued indefinitely. For some patients pursing FPT, hydroxyurea is a long-standing medication; others may only take it in anticipation of HSCT.
Proposed algorithm for reproductive endocrinologists managing ovarian stimulation and retrieval in girls and women with sickle cell disease (SCD). Involving the primary hematologist to determine the risks based on the individual patient’s disease history is important. Coordinate red blood cell transfusions (simple or exchange) with blood bank specialists who are familiar with the patient’s transfusion history and have knowledge of any red blood cell autoimmunization or alloimmunization. Finally, whether patient plans to continue hydroxyurea before oocyte harvest is a decision that requires input from the patient’s hematologist and hematopoietic stem cell transplant physicians. *Discuss the risks and benefits of continuing hydroxyurea with the hematologist and patient, given the limited data about use in this setting. **Patients on chronic exchange transfusions may already have a hemoglobin S less than 30%.

### TABLE 3

Previously reported approaches to ovarian stimulation.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Patients (n)</th>
<th>Age (y)</th>
<th>Antral follicle count</th>
<th>Stimulation/total gonadotropin (IU)</th>
<th>Treatment duration (d)</th>
<th>Peak estradiol (pg/mL)</th>
<th>Trigger</th>
<th>Oocytes retrieved</th>
<th>Pre-stimulation management</th>
<th>Thromboprophylaxis</th>
<th>Hydroxyurea or transfusions prior to stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dovey et al., 2012 (18)</td>
<td>1</td>
<td>19</td>
<td>20</td>
<td>900</td>
<td>6</td>
<td>859</td>
<td>Leuprolide 20IU BID</td>
<td>9</td>
<td>Admission x2 days for IV hydration</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Lavery et al., 2016 (17)</td>
<td>8</td>
<td>16 (median)</td>
<td>16 (median)</td>
<td>2,134</td>
<td>11</td>
<td>–</td>
<td>Leuprolide (n=2), rHCG (n=6)</td>
<td>12</td>
<td>–</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Matthews and Pollack, 2017 (19)</td>
<td>1</td>
<td>23</td>
<td>28</td>
<td>1,125</td>
<td>5</td>
<td>1,669</td>
<td>Leuprolide 80IU 2 doses at 36 and 24h</td>
<td>NR</td>
<td>–</td>
<td>Yes</td>
<td>First stimulation aborted on day 6 due to painful crisis and red cell exchange performed on transfusions</td>
</tr>
<tr>
<td>Pecker, 2018 (this study)</td>
<td>5</td>
<td>25.8±5.3</td>
<td>–</td>
<td>3,390 (SD 1,913)</td>
<td>11.6 (SD 4.93)</td>
<td>1,213 (SD 1,303)</td>
<td>Leuprolide, HCG or rHCG</td>
<td>12.8 (SD 7.58)</td>
<td>No standard approach applied</td>
<td>Confirmed in 1 of 7 patients</td>
<td>3 on hydroxyurea</td>
</tr>
</tbody>
</table>

Note: Patients in this cohort were older than previously reported cases, diverse FPT strategies were used, and most received disease-modifying therapy for sickle cell anemia before hematopoietic stem cell transplant. A dash indicates that no data are available for that patient. BID = twice a day; FPT = fertility preservation treatment; HCG = human chorionic gonadotropin; NR = not reported; rHCG = recombinant human chorionic gonadotropin; SD = standard deviation.

1. Lavery et al. (22) reported on eight cases of 14- to 18-year-old women with HbSS and reported a mean (with 95% confidence intervals) for the following values: gonadotropin dose 2,134 IU (95% CI, 1,593–2,675), duration of treatment 11 days (95% CI, 10.02–11.98), median oocytes retrieved 12 (95% CI, 4.72–19.543). The fewest oocytes retrieved from a patient was 4.

2. Thromboprophylaxis was not necessarily initiated for ovarian stimulation. Our patient received anticoagulation because of a history of venous thromboembolism. Dovey et al. (18) initiated 30 mg low-molecular-weight heparin, twice a day, for prophylaxis.

The other disease-modifying therapy for SCA is red cell transfusion (47), used chronically or episodically. The decision to provide simple or exchange transfusions is made based on hemoglobin level and transfusion indication (56). The women with SCA complications during FPT received disease-modifying therapy for SCA. The extent to which hydroxyurea or blood transfusions for SCA help prevent complications during FPT merits further investigation.

Hydroxyurea exposure has become routine in many protocols in the weeks preceding HSCT, even in patients who are not on chronic therapy (58). How hydroxyurea affects oocyte quantity and quality is unknown. In men, both SCA and hydroxyurea therapy reduce sperm counts (48, 49). Outstanding questions for men treated with hydroxyurea are the degree to which oligo- or azoospermia is reversible, especially when hydroxyurea is started in infancy, and whether reduced sperm counts compromise fertility (49). For women, hydroxyurea may damage oocytes, but the effects on female fertility are poorly defined (50, 51). At least three women in this cohort took hydroxyurea for an unspecified duration before FPT (cases 2, 3, and 6). Their oocyte yields ranged from 4 to 21. One had a 63% fertilization rate and cryopreserved all embryos (n = 7) at the cleavage stage. Another patient (case 2) had low ovarian reserve markers that did not correlate with a robust response to COH. In the third case, four oocytes were harvested, and three were cryopreserved.

While our findings are reassuring, outstanding concerns about hydroxyurea’s effect on oocytes remain. Hydroxyurea is contraindicated in pregnancy due to concerns for teratogenicity (24), and the treatment is discontinued 3 months before conception in women with SCA. Fertilized oocytes from wild-type mice treated with hydroxyurea inconsistently developed into blastocysts and had compromised folliculogenesis (57). In a cohort of adolescents with SCA, longer duration of hydroxyurea use was associated with diminished ovarian reserve (51). Whether hydroxyurea should be routinely discontinued before oocyte harvest has not been established.

At present, the clinician providing essential counseling to patients with SCA who are considering FPT before HSCT is confronted by limited available data. To date, there are four reports of 17 women with SCA who have undergone FPT before HSCT. The outcomes are summarized in Table 3. Both HSCT and FPT are elective procedures for patients with SCA, and they are associated with significant uncertainty. The ethics considerations in offering both therapies to patients with SCA have been discussed (29, 59–61).

As is the practice for patients with SCA who are deciding whether to pursue HSCT, our approach is to provide information and counseling about fertility preservation rather than to withhold therapy. Informed consent for these patients incorporates procedural concerns specific to SCA and general FPT risks and uncertainties. For example, in this cohort the patients who cryopreserved oocytes were counseled that clinic-specific success rates were not available because few patients had thawed-frozen oocytes to attempt pregnancy. Counseling and collaboration between the reproductive endocrinology, hematology, and bone marrow transplant teams are essential. Preserved embryos or oocytes may be retrieved for patients pursuing pregnancy even if their HSCT fails. For patients with SCA, this means pursuing a pregnancy that is associated with well-described increases in morbidity and mortality (62).

This study is limited in that it is a small, retrospective case series. Women with SCA undergoing FPT without planned exposure to a HSCT-conditioning regimen were excluded as were patients with other sickle cell genotypes. There is likely a publication bias among the few reports to date, and the adverse events identified here may not accurately define the risks of COH for all women with SCA. An additional limitation is that this is a case series involving a subset of women who have yet to attempt conception, so the pregnancy outcomes are unknown. We plan to follow the reproductive course of these patients in the future.

As HSCT and even gene therapy become more available for patients with SCA (59, 63), referrals for FPT before exposure to gonadotoxic therapy will likely increase. Fertility preservation is important to patients with sickle cell disease, and these patients report strong consideration for or against hydroxyurea and HSCT based on their risk for causing infertility (13–15, 64). The risks associated with FPT for women with SCA are potentially serious and certainly complex. Despite this, women may choose to assume these risks, so clinicians must provide unbiased information to their patients so that they can make decisions consistent with their own values and priorities. Systematic studies of FPT approaches, disease-modifying therapies, and long-term outcomes, perhaps through a national registry, are needed to aggregate data on women with sickle cell disease (of all genotypes) who receive FPT. Increased data in these areas is needed to help meet the needs for this medically fragile population.

REFERENCES


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Riesgos asociados a la preservación de fertilidad en mujeres con anemia de células falciformes.

**Objetivo:** Subrayar el riesgo de complicaciones entre las mujeres con anemia de células falciformes (SCA) que realizan preservación de fertilidad (FPT) antes de someterse a un transplante de células madre hematopoyéticas (HSCT).

**Diseño:** Serie de casos de un centro único.

**Marco/Entorno:** Centro de fertilidad universitario.

**Paciente(s):** Mujeres de edades comprendidas entre 15 y 32 años con SCA sometidas a FPT antes de HSCT.

**Intervención:** Revisión sistemática retrospectiva.

**Resultado(s) principal(es):** Modalidad de FPT, complicaciones de la SCA durante la FPT.

**Resultado(s):** En un periodo de 8 años (2009-2017), siete mujeres con SCA de edades comprendidas entre 15 y 32 años (media 28,5 años) realizaron FPT con criopreservación de embriones (n=1), criopreservación de ovocitos (n=4) y criopreservación de tejido ovarico (n=2). Las cinco mujeres que realizaron criopreservación de ovocitos o embriones siguieron un protocolo de hiperestimulación ovárica controlada con antagonistas y dosis individualizadas de gonadotropinas. La maduración ovárica se indujo con acetato de leuprolide (n=2) y gonadotrofina coriónica humana (n=3). La mayoría de pacientes (n=5) recibieron un tratamiento moderador de la enfermedad para SCA (hidroxiurea o transfusiones crónicas) antes de la FPT. Tres pacientes sufrieron complicaciones de la SCA durante el procedimiento de FPT, incluyendo fallo respiratorio muy grave, crisis de dolor que requirió interrupción del ciclo de estimulación ovárica y crisis de dolor severa postpunción ovárica.

**Conclusión(es):** Las mujeres con SCA pueden elegir entre varias estrategias para realizar FPT antes de someterse a HSCT y corren riesgo de serias complicaciones relacionadas con la SCA. Se necesitan estrategias basadas en la evidencia para optimizar los resultados de la preservación de fertilidad y reducir la morbilidad relacionada con ella en pacientes con SCA.