Acute pain crisis in a patient with sickle cell disease undergoing ovarian stimulation for fertility preservation prior to curative stem cell transplantation: case report and literature review

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Abstract

Purpose Hematopoietic stem cell transplantation (HSCT) is a cure for sickle cell disease (SCD) but frequently results in permanent sterility. The complications associated with oocyte cryopreservation and risks of future pregnancy are increased in SCD patients. This case report discusses risk reduction strategies and includes a literature review of pregnancy after HSCT.

Case A 23-year-old woman underwent ovarian stimulation for fertility preservation resulting in cancelation due to acute pain crisis. She underwent a successful oocyte retrieval after exchange transfusion to decrease her hemoglobin S to 30%. This is the second report of a pain crisis in a woman with SCD undergoing oocyte banking.

Conclusion(s) Women with SCD undergoing fertility preservation may be at increased risk of complications from ovarian stimulation. Risks in pregnancy after HSCT should also be considered before proceeding with fertility preservation.

Keywords Sickle cell disease · Fertility preservation · Pain crisis · Stem cell transplantation

Background

Sickle cell disease (SCD) is a genetically inherited blood disorder. Patients with SCD have an abnormality in the oxygen-carrying protein of hemoglobin, which results in an abnormal “sickle” cell shape of their red blood cells (RBCs). Patients with SCD have hemoglobin S, which differs from normal adult hemoglobin (hemoglobin A) by a single amino acid substitution (a valine replacing a glutamine in the sixth position of the beta chain of globin). Sickle RBCs have a shorter lifespan of 10 to 12 days compared to 120 days, secondary to hemolysis [1]. Sickle RBCs do not travel through blood vessels properly, resulting in blood vessel occlusion, subsequent lack of oxygen transportation to tissues, and severe pain secondary to tissue hypoxia. Poor tissue perfusion eventually results in end-organ damage including pulmonary complications, kidney disease, and increased susceptibility to infections and stroke [2].

Hematopoietic stem cell transplantation (HSCT) has been shown to improve the symptoms of SCD in over 80% of patients and is the only known “cure.” HSCT involves eradication of the patient’s own abnormal hematopoietic cells by total body irradiation (TBI) and replacement with those of a healthy matched donor, generally a sibling [3]. HSCT treatment protocols also include chemotherapeutic agents to prevent graft-vs-host disease after transplantation. Long-term survival in young patients with SCD after HSCT are 82–86% [4]. Unfortunately, one of the common long-term sequelae of both TBI and chemotherapeutics is permanent sterility [5]. Females undergoing HSCT have a 90% risk of permanent ovarian failure [6, 7]; therefore, women with SCD may consider fertility preservation prior to HSCT.

Female fertility preservation options include mature oocyte or embryo cryopreservation and ovarian cortex cryopreservation. Ovarian cortex cryopreservation is still considered

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experimental. Embryo cryopreservation has been approved for decades, but mature oocyte cryopreservation has only been endorsed by the American Society for Reproductive Medicine (ASRM) since 2013 [8]. The number of women undergoing oocyte cryopreservation for the purpose of banking oocytes for both medical and non-medical reasons is increasing, with 6186 cases reported in the USA in 2014 [9]. Therefore, healthcare providers should be aware of the risks of fertility preservation as well as the risks of future pregnancy in these patients.

ASRM published guidelines in 2013 recommending that patients undergoing treatments that may impact future fertility be counseled regarding risks and reproductive options. The guidelines also state that patients with hematologic malignancies may have an increased risk of complications associated with treatments for fertility preservation [10]. Consideration should be given to the risk of bleeding associated with oocyte retrieval and the risk of thrombosis in patients with SCD. Furthermore, ovarian hyperstimulation syndrome, which is a known risk of gonadotropin administration, may be more complicated in patients with underlying renal and pulmonary disease. We present the second report of a complication in a patient with SCD undergoing oocyte cryopreservation. This report includes a review of the literature and discussion of risk reduction strategies, as well as a review of the risks of future pregnancy.

Case report

The patient is a 23-year-old woman with SCD referred for fertility preservation prior to HSCT. She began to develop complications from her SCD at age 3 years when she was hospitalized with anemia. At 18 years of age, she began to develop more significant complications including multiple pain crises, pneumonia, pulmonary embolism, and avascular necrosis of the left hip. Her hematologist recommended that she undergo HSCT due to recurring complications of SCD that were becoming unresponsive to medical management. She was being managed long term on hydroxyurea for her SCD and anticoagulation with enoxaparin since her pulmonary embolism. She received exchange transfusions and narcotics only during acute flares of her SCD. Her most recent admission and transfusion was 1 year prior to undergoing ovarian stimulation for fertility preservation. Her hemoglobin S was consistently at 93 to 94%. Her most recent hemoglobin S obtained 5 months prior to ovarian stimulation for oocyte banking was 93.4%.

The patient was counseled regarding fertility preservation options including ovarian cortex cryopreservation (under our IRB protocol) or mature oocyte cryopreservation. She elected to proceed with mature oocyte cryopreservation and was cleared to proceed by her hematologist. Her menstrual cycle

started 2 days after initial consultation. She was continued on anticoagulation with enoxaparin due to her prior history of thrombosis. Her day 3 laboratory values included an antimüllerian hormone (AMH) of 6.5 ng/mL, day 3 FSH 7.6 mIU/mL, and estradiol (E_2) 25 pg/mL. An ultrasound revealed normal uterus and ovaries and an antral follicle count of 28. She initiated treatment with 225 IU SC FSH (Gonal-F; Merck Serono) and after 3 days of stimulation had an E_2 of 193 pg/mL. Her dose of FSH was decreased to 150 IU and 75 IU SC of hMG (Menopur; Ferring) was initiated daily. On day 5 of stimulation, the E_2 had increased to 336 pg/mL with a lead follicle of 14 mm. A GnRH antagonist (Ganirelix; Merck Serono) was initiated. The following day, the patient was admitted to the hospital with an acute pain crisis and the gonadotropins were discontinued. Her hemoglobin on admission was 7.5 g/dL and her hemoglobin S was 93.5%. The patient spent 5 days in the hospital for pain management for acute pain crisis. Exchange transfusions were initiated by her hematologist with a plan to keep her hemoglobin S under 30% during her next attempt at oocyte cryopreservation and until the start of her HSCT.

The patient reinitiated ovarian stimulation medications on day 3 of her next menstrual cycle (24 days after prior admission). Her last exchange transfusion was 23 days prior to oocyte retrieval and hemoglobin S was 24.7% after transfusion. Her hemoglobin S was checked during the week of ovarian stimulation and was at 30.6% with a hemoglobin of 11 g/dL. She followed the same medication and monitoring plan as her prior stimulation attempt. Her peak E_2 level on day 9 of stimulation was 1669 pg/mL. She received a leuprolide trigger with administration of 80 units (Lupron; Sandoz) 36 and 24 h prior to oocyte retrieval. This was our standard leuprolide trigger protocol at the time of this patient's treatment and was utilized to theoretically extend the duration of the LH surge to optimize oocyte maturation. Our current protocol utilizes a single 1 mg leuprolide trigger. Her anticoagulation was held the day of her procedure and restarted the following day. She underwent an uncomplicated oocyte retrieval with 29 oocytes retrieved. The hemoglobin S was rechecked again 2 days after her oocyte retrieval and had increased to 41.9%. She received another partial exchange transfusion with a decrease to 28.1%. This was her last exchange transfusion as she underwent HSCT from her haplotype identical brother the following week. She had no episodes of painful crises during her stimulation.

Discussion

It is estimated that between 70,000 and 100,000 Americans have SCD and more than 90% of children with SCD in the USA survive into adulthood [11]. While the treatments involved in HSCT may cure SCD, the process results in

permanent sterility in approximately 90% of females [6, 7]. As HSCT survivorship increases, the focus of care has shifted to the identification and treatment of long-term complications of HSCT including fertility and pregnancy concerns [12].

The likelihood of spontaneous pregnancy after HSCT appears low due to the high risk of permanent ovarian failure. A study of 532 women with HSCT reported that 10% had return of ovarian function and only 1.3% established a pregnancy [13]. The largest series of pregnancies after HSCT reported 312 pregnancies, which occurred in only 0.6% of patients or partners of patients in 7 years of follow-up by questionnaire [14]. Therefore, women may elect to undergo fertility preservation prior to HSCT due to the high risk of ovarian failure.

Fertility preservation prior to HSCT

The first report of oocyte cryopreservation prior to HSCT for a female with SCD was reported in 2012. The patient was a 19-year-old scheduled for HSCT using a matched sibling donor. She received ovarian stimulation for fertility preservation. The patient had been placed on thromboprophylaxis with enoxaparin 30 mg administered subcutaneously every 12 h with initiation of gonadotropin administration for ovarian stimulation. She was also placed on IV fluids at twice the maintenance rate as a continuous ambulatory infusion. The oocyte retrieval procedure was uncomplicated, but the patient experienced pelvic and lower back pain that was difficult to control post-operatively and required hospitalization. It was the authors' conclusion that she may have experienced a pain crisis as a result of the ovarian stimulation process [15]. We now report a second similar case.

Risk reduction strategies

The hematologic pathology in patients with SCD predispose patients to thrombosis and pain crisis. Pain crises result from trapped RBCs in the microcirculation resulting in tissue ischemia and pain. The mechanisms of hypercoagulability in SCD are vast, including enhanced platelet function, activation of the coagulation cascade, and impaired fibrinolysis. Although SCD itself is associated with underlying hypercoagulability, several factors modify the risk of VTE in this population. Traditional risk factors such as high use of central venous catheters, frequent hospitalization, surgeries, and pregnancy also significantly influence VTE risk in SCD patients.

Exchange transfusions allow for replacement of the patient's blood with that of donor blood, thereby decreasing the percent of circulating sickle cells. This reduces blood viscosity thereby potentially decreasing the risk of thrombotic events and pain crises. Transfusion therapy is strongly recommended prior to major operative procedures to increase hemoglobin levels to 10 g/dL and maintain sickle hemoglobin levels to less than 30%, based on recommendations published

in 2014 [16]. There are less clearly defined guidelines regarding exchange transfusion for patients with SCD prior to minor surgeries, however, there may be some benefit. A randomized study was performed of patients with SCD with planned low-to medium-risk surgeries randomly assigned to "no transfusion" or "transfusion" no more than 10 days before surgery. Thirteen (39%) of 33 patients in the no-preoperative-transfusion group had clinically important complications, compared to five (15%) in the preoperative transfusion group. The most frequent events related to SCD were acute chest syndrome and pain crisis. The unadjusted odds ratio of clinically important complications was 3.8 (95% CI 1.2–12.2) [17]. This study did not evaluate patients undergoing oocyte retrieval; however, it may be prudent to extrapolate their guidelines for minor procedures to SCD patients completing oocyte retrieval.

Anticoagulation is warranted in patients with a prior history of thrombotic events. Approximately 25% of adult SCD patients have a history of VTE with a median age of 30 years. It is unclear if anticoagulation will decrease the risk of a pain crisis in patients with SCD as there have been no randomized trials in patients with SCD. Established guidelines for anticoagulation are for venous thromboembolism management only. Current recommendations rely on individual assessment of thrombotic and bleeding risk factors [18]. However, it is the authors' opinion that patients with SCD without a history of prior VTE may benefit from prophylactic anticoagulation during ovarian stimulation due to the increased risk of thrombosis, but this should be considered in consultation with a hematologist.

Maternal and fetal risks in future pregnancy

Patients with SCD are known to have an increased incidence of pregnancy-related adverse events such as placental hemorrhage, thromboembolism, infection, cardiomyopathy, and maternal and fetal death [19, 20]. HSCT is curative for most patients, therefore, pregnancy-associated risks may be decreased. However, it is not clear what level of residual multi-organ damage may persist after HSCT, or how significantly it may impact risks in pregnancy. Unfortunately, there is limited data on pregnancy outcomes after HSCT.

Most pregnancy outcome data after HSCT is pooled from patients receiving HSCT for many different hematologic diseases and cancers. Therefore, this data may not be directly comparable to SCD patients who may have more evidence of end-organ damage. There is very limited data on the risk of early pregnancy loss after HSCT. Some studies imply an increased risk while others show no increased risk of spontaneous abortion [21]. A review of 83 pregnancies in recipients of HSCT reported an 85% live birth rate [22]. In addition to potential concerns over spontaneous abortion, there have been individual case reports of pregnancy complications after TBI

including intrauterine growth restriction, abnormal placentation, and uterine rupture [23, 24]. This is presumably secondary to the effect of radiation on uterine blood flow.

It is our opinion that patients with SCD deserve special consideration prior to fertility preservation. The risks associated with fertility preservation and the risks of future pregnancy are not clearly defined in SCD women. We present the second case of pain crisis during ovarian stimulation for fertility preservation. It is unclear if the ovarian stimulation directly resulted in the pain crises and this requires further investigation.

Based on limited data, patients may also be at increased risk of pregnancy-related complications secondary to the impact of uterine radiation, as well as residual end-organ damage of the underlying SCD. Healthcare providers are likely to see an increasing number of women with SCD electing to proceed with pregnancy after HSCT. These patients may be considered at higher risk than the general population and should be counseled accordingly. According to 2016 ASRM guidelines, clinicians should thoroughly counsel women at increased risk of complications and this should occur in advance of a decision to initiate fertility preservation treatment [25].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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