Oocyte cryopreservation in a patient with sickle cell disease prior to hematopoietic stem cell transplantation: first report

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Abstract

Purpose To report the first occurrence of successful ovarian stimulation, oocyte retrieval and oocyte cryopreservation for fertility preservation in an adolescent with severe sickle cell disease scheduled to undergo a hematopoietic stem cell transplant

Methods Case report

Results A 19 year old female with severe sickle cell disease presented for fertility preservation counseling prior to hematopoietic stem cell transplantation. She ultimately underwent ovarian stimulation using a minimal stimulation GnRH antagonist protocol resulting in the successful banking of oocytes prior to transplant. The unique hazards associated

with ovarian stimulation in patients with sickle cell disease, such as thrombosis and vaso-occlusive events, are discussed and the methods undertaken to minimize these risks are described.

Conclusions Controlled ovarian hyperstimulation and oocyte banking for fertility preservation is feasible in young women with sickle cell disease requiring hematopoietic stem cell transplant and deserves further investigation. Given the elevated risk of thrombosis and predisposition to painful vaso-occlusive events, controlled ovarian hyperstimulation in patients with sickle cell disease is not straightforward and requires a multi-disciplinary team approach to adequately address and minimize the risks in this unique patient population.

Capsule Successful ovarian stimulation, vaginal egg retrieval, and oocyte cryopreservation in a patient with severe sickle cell disease was performed for fertility preservation prior to hematopoietic stem cell transplantation, and the interventions taken to minimize the risks of ovarian stimulation in this patient with significant medical comorbidities are described.

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Introduction

Sickle cell disease (SCD) is the most common hemoglobinopathy in the US and is characterized by hemolysis and vaso-occlusive events stemming from the abnormal hemoglobin molecule, which tends to polymerize under hypoxic conditions [1]. Such polymerization causes “sickling” of red blood cells, leading to recurrent painful events due to microvascular occlusion, multiple organ system dysfunction, and increased mortality. Particularly concerning sequelae of SCD are the associated neurologic and pulmonary complications, such as stroke and acute chest syndrome. Up to 24% of patients with SCD will experience a clinically evident stroke by age 45 [2]. Moreover, acute chest syndrome is seen in up to

half of patients with SCD and remains a leading cause of death and a risk factor for early mortality [3, 4].

Currently, hematopoietic stem cell transplantation (HCT) is the only treatment for SCD that offers the opportunity for a complete cure. Patients demonstrating stable engraftment following HCT from an HLA-matched donor no longer suffer from the hemolytic and vaso-occlusive complications inherent to SCD [5]. Indeed, the event-free survival following matched sibling HCT has been reported to be as high as 85% [5]. However, infertility and premature ovarian insufficiency are common following the conditioning regimens typically used for HCT [6–11]. Walters and colleagues demonstrated that the majority of females had elevated gonadotropin levels consistent with premature ovarian insufficiency following HCT. Similar studies of gonadal function after HCT for other etiologies such as acute lymphoblastic leukemia and beta-thalassemia also demonstrate a significant risk of gonadal failure in long-term follow-up studies [12, 13].

In theory, embryo, oocyte, and ovarian tissue cryopreservation are fertility preservation options that could be offered to patients with SCD planning to pursue HCT. However, to our knowledge, there are currently no reports in the literature describing controlled ovarian stimulation (COS) in patients with SCD, a requirement for either embryo or oocyte cryopreservation. Although still considered experimental, oocyte cryopreservation is, at this time, a significantly more mature technological advance when compared to ovarian tissue cryopreservation, as approximately 1,000 births have been reported from previously frozen oocytes [14]. Thus, it may be desirable for young women with SCD considering HCT to pursue this option for fertility preservation. However, given the prevalence of vaso-occlusive events in SCD, the risks associated with COS in this clinical setting are ambiguous. Given their red blood cells (RBCs) abnormalities, patients with SCD are at increased risk for thromboembolic disease [15, 16]. Whether the supraphysiologic estradiol levels associated with COS increases this risk significantly is unknown. Furthermore, hemoconcentration associated with ovarian stimulation may also amplify the risk of vaso-occlusive events and pain. In this report, we describe a patient with SCD who underwent COS, vaginal oocyte retrieval, and successful cryopreservation of oocytes prior to beginning conditioning therapy for a matched-sibling HCT. The clinical steps taken to minimize the risk of complications from COS in a patient with SCD are described.

Case report

A 19 year old G0 with past medical history significant for SCD was scheduled to undergo a HCT from a matched sibling donor. The patient had originally been diagnosed with sickle

cell disease when she was 6 months of age. She suffered from multiple episodes of acute chest syndrome and numerous hospitalizations to treat vaso-occlusive pain crises. Her surgical history was notable for a prior cholecystectomy and splenectomy secondary to SCD.

Given the severity of her disease and requirement for frequent hospitalizations for pain crises, HCT using a matched sibling donor (the patient's sister) with curative intent was recommended by her hematologist. The patient and her family were interested in pursuing this option given the likelihood of long-term complications resulting from SCD, but were concerned regarding the high risk of ovarian failure following conditioning for HCT, even though a reduced conditioning regimen without total body irradiation (TBI) was planned to help reduce the risk of gonadal failure.

The patient was referred for consultation with a Reproductive Endocrinologist and fertility preservation options, including embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation were discussed with the patient and her family. She was not interested in cryopreserving embryos using donor sperm. The option of pursuing pregnancy using a donated oocyte in the future was also discussed, but the family had religious objections to this approach. Although the experimental nature of both ovarian tissue and oocyte cryopreservation were reviewed, the patient was mainly interested in pursuing oocyte cryopreservation given the longer track record of this technology. The risks of thromboembolism and vaso-occlusive pain crises in the setting of elevated estradiol levels and possible hemoconcentration related to ovarian stimulation were a particular concern. The patient and her family were counseled regarding the possibility of such risks, and the lack of prior experience in the published literature was highlighted. The patient was enrolled in an IRB-approved study of oocyte banking at the University of Pennsylvania Medical Center and informed consent was obtained.

After significant discussion and coordination with the patient's primary hematologist and HCT physician, the decision was made to proceed with COS utilizing a low-dose antagonist protocol with a GnRH agonist trigger in conjunction with continuous IV hydration and thromboprophylaxis to minimize the risks of hemoconcentration and thromboembolism, respectively. Ovarian reserve testing the month prior to stimulation demonstrated a day 3 FSH value of 10.7 IU/L, estradiol 45 pg/mL, and antral follicle count of 20. With the patient's next menstrual cycle, she was started on IV fluids at twice the maintenance rate as a continuous ambulatory infusion through a previously placed portacath. She also started thromboprophylaxis with Enoxaparin 30 mg administered subcutaneously every 12 h with target factor anti-Xa levels of 0.1–0.3. On cycle day 3, the patient was started on recombinant FSH at 112.5 units daily. On stimulation day 6, both a GnRH antagonist and recombinant

LH were initiated at doses of 0.25 mg and 75 units, respectively. Estradiol and LH levels were monitored every 24–48 h starting on stimulation day 5, with follicle monitoring via transvaginal ultrasound (TVUS) every 48 h. Final oocyte maturation was triggered with 1 mg leuprolide acetate on stimulation day 8 when TVUS revealed two follicles >18 mm in size. The patient's peak estradiol level on the day of maturation trigger was 859 pg/mL. Enoxaparin was withheld for 24 h prior to the oocyte retrieval.

The patient underwent vaginal oocyte retrieval 37 h after leuprolide trigger. The procedure was performed under IV sedation in the ambulatory IVF facility where a total of 9 oocytes were collected and 8 mature oocytes were vitrified using a previously published approach [17]. The procedure was uncomplicated, but the patient experienced pelvic and lower back pain that was difficult to control post-operatively in the ambulatory setting. She was admitted to the hospital overnight. A pelvic ultrasound did not demonstrate any evidence of intra-abdominal bleeding. She recovered promptly and was discharged the following day, and had no further complications from ovarian stimulation or the egg retrieval. She went on to undergo a successful HCT the following month.

Discussion

To our knowledge, this is the first report of ovarian stimulation and oocyte banking in a patient with sickle cell disease planning to undergo HCT for the treatment of her disease. While HCT is the only definitive cure for SCD, this therapy carries a high risk of infertility and ovarian failure. Overall, ovarian failure after HCT has been observed in 65–84% of pediatric transplant recipients and in over 90% of adult recipients [6–11]. While data are limited on fertility post transplant, retrospective reports suggest that only 0.6–5% of HCT survivors achieve pregnancy. The risk of infertility and gonadal failure appears to be dependent on the type of therapy and the doses administered. In particular, exposure to cyclophosphamide, busulfan and TBI is associated with high risk for gonadal failure. In addition, younger age at transplant is associated with preservation of reproductive function [18, 19]. While there is no available data on the reproductive risks of newer, low intensity HCT regimens, these regimens presumably have less of a negative impact on future reproductive function.

While many patients receiving gonadotoxic agents have a cancer diagnosis, cancer therapies, including HCT, are being increasingly used for the treatment of medical conditions. As recommended by the American Society of Clinical Oncology, the reproductive risks of cancer therapies and fertility preservation options should be routinely discussed with patients prior to treatment [20]. The risks and success of available fertility preservation techniques including embryo,

oocyte and ovarian tissue cryopreservation should be discussed with patients facing fertility threatening therapies. While embryo banking is currently considered the only standard (non-experimental) procedure, improved success with oocyte banking and ovarian tissue banking offer single females the possibility of having biological children with a future partner. Live birth rates after oocyte banking have been reported to range between 2% and 5% per oocyte banked, and over 1,000 births have been reported to date [14, 21–23]. Autologous transplantation of previously frozen and thawed ovarian cortical tissue has resulted in 13 live births to date [24], including a live birth in a patient with sickle cell disease treated with HCT [25]. Nonetheless, counseling can be particularly difficult in patients like the one described since limited data exist on the risks associated with fertility preservation strategies in women with co-existing medical conditions.

In this report, we describe a patient with SCD who underwent ovarian stimulation and oocyte banking with no major complications. Given the severity of her SCD, some of the major concerns with pursuing COS in this clinical scenario were the risks of thromboembolism and vaso-occlusive pain crises secondary to elevated estradiol levels and potential hemoconcentration associated with ovarian hyperstimulation.

The risk of thrombosis at baseline is not insignificant in patients with SCD. The most common cause of stroke in SCD patients is large vessel narrowing with superimposed thrombosis, as demonstrated by histopathology studies [15, 16]. Additionally, postmortem evaluations of patients with SCD often reveal old and new thrombi in the pulmonary vasculature [26], and thrombosis in sickle cell patients is also associated with avascular necrosis of large joints, leg ulcers, and certain pregnancy complications [15, 16]. The hypercoagulable state associated with SCD is thought to be due to abnormalities in the cell membrane of RBCs. Repeated cycles of sickling and unsickling can lead to exposure of phosphatidylserine, an anionic phospholipid generally restricted to the inner cell membrane of RBCs [15, 16, 27]. Studies have suggested that this abnormal phosphatidylserine exposure in a subset of RBCs can lead to in vivo activation of coagulation.

Currently, there is no information addressing whether COS and the associated supraphysiologic estradiol levels increase the risk of thromboembolism in patients with SCD. It has been reported that women with SCD experience a significantly higher risk of thromboembolic events in pregnancy, a hyperestrogenic state, compared to women without SCD [28]. However, SCD is not currently considered to be a medical contraindication to treatment with combined oral contraceptives, based on small observational studies [29]. The baseline risk of venous thromboembolic events (VTE) associated with artificial reproductive technologies (ART) is low and estimated to occur in about 0.08–

0.11% of treatment cycles [30]. However, although the magnitude of risk is low, it is worthwhile to note that it is 10-fold higher than the baseline risk of VTE in women of reproductive age. Furthermore, ovarian hyperstimulation syndrome (OHSS) is a significant risk factor for thromboembolism [31]. Moderate OHSS can complicate 3–6% of ART cycles, and severe OHSS is reported in 0.1–2% [32]. A recent review concluded that 70% of ART cycles complicated by VTE are associated with OHSS, and, in the more rare cases of arterial thromboembolism, over 90% of cases are associated with OHSS [30, 32]. The hemoconcentration characteristic of OHSS leads to increased blood viscosity and vascular stasis. Additionally, changes in both the coagulation and fibrinolytic systems have been demonstrated [30, 32].

Based on the above information, we deemed it prudent to administer Enoxaparin for thromboprophylaxis throughout ovarian stimulation, ending on the day prior to scheduled oocyte retrieval. Additionally, we felt that it was critical to minimize the risk of OHSS. To this end, a low-dose stimulation protocol with a GnRH antagonist was utilized, both to maintain relatively low estradiol levels as well as to minimize the risk of OHSS. Additionally, final oocyte maturation was induced using a GnRH agonist, which has been demonstrated to virtually eliminate the risk of OHSS in multiple studies by avoiding the administration of hCG [33, 34]. Finally, to protect against hemoconcentration, the patient was placed on continuous IV hydration, beginning 2 days prior to the initiation of stimulation and continuing throughout vaginal egg retrieval.

Lastly, pain control following egg retrieval can also be a significant challenge in patients with SCD. Intraoperative hypoxemia and acidosis can precipitate vaso-occlusive events and pain [35, 36]. Additionally, patients with SCD are often managed with chronic narcotics to control frequent pain crises and therefore develop a high tolerance to these medications. Postoperative pain management was particularly challenging in this case since the clinical staff was not comfortable with administering large doses of narcotics in the ambulatory setting. Postoperative pain can also be difficult to distinguish from an acute pain crisis. To help avoid pain-related complications post-operatively, specific attention should be paid to the avoidance of hypoxia intraoperatively, as well as ensuring adequate hydration, early ambulation, and optimal pain control [35, 36]. Most patients with SCD have an individualized plan to appropriately manage varying levels of pain. A post-operative pain management algorithm should be adapted from the patient's usual pain management plan, taking into account the individual's baseline narcotic requirements [36–38]. Indeed, incorporation of specific guidelines to aid physicians in the appropriate treatment of pain related to SCD have been shown to significantly improve the delivery of effective pain management in a timely fashion and decrease the need for

hospitalization [39]. Since IVF clinics in free-standing ambulatory settings are not used to caring for such patients, it is important that the clinical team be prepared with an appropriate pain management algorithm prior to beginning the cycle. Ultimately, transfer and admission to the hospital for observation and pain management may be necessary.

Using a multi-disciplinary team approach and thoughtful evaluation of how to avoid potential complications, COS leading to successful oocyte banking was carried out in a patient with severe SCD, allowing her the chance of having a biological child following HCT. Ovarian stimulation for the purpose of fertility preservation in patients with hemolytic anemias considering HCT is worthy of further study to more accurately evaluate the risks and determine the best approach.

Conflict of interest None to disclose

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