Journal of Assisted Reproduction and Genetics (2019) 36:2087–2094
https://doi.org/10.1007/s10815-019-01556-0

ASSISTED REPRODUCTION TECHNOLOGIES

Ovarian stimulation and egg retrieval in the acutely ill patient: special considerations

Kaitlyn Wald[1] · Joseph Letourneau[1,2] · Rachel Eshima-McKay[3] · John Monks[3] · Evelyn Mok-Lin[1] · Marcelle Cedars[1] · Mitchell Rosen[1]

Received: 24 May 2019 / Accepted: 2 August 2019 / Published online: 9 August 2019

Introduction

Over the past decades, assisted reproductive care has become increasingly safe and more widely applied. Egg retrieval has become an outpatient procedure, with ultrasound guidance, and stimulations have increasingly become less aggressive and safer with more individualization and safer trigger options. With this improvement in care, these treatments are considered low risk and applied more widely, including fertility preservation for elective reasons (so-called social egg freezing). However, it is incumbent upon providers to realize the application of even "simple" treatments, in a high-risk population, may have serious consequences.

As long-term survival rates have improved among patients diagnosed with cancer and life-threatening disease, and with these improved survival rates, post-treatment quality of life has gained increased attention [1]. Among this growing population with life-threatening illness and greater survival expectation are women of reproductive age, and for that reason, an increasing number of such patients seek fertility treatment [2]. Oocyte and embryo cryopreservation prior to chemotherapy for fertility preservation have been associated with improved quality of life [3]. Thus, the American Society for Reproductive Medicine advises that all women recommended potentially gonadotoxic therapies should be counseled on the impact of these treatments on their future fertility and their options for fertility preservation prior to initiation of gonadotoxic treatment [4].

Fertility preservation is increasingly accepted as an independent discipline within oncology and reproductive medicine [5]. Approximately 1000 research papers will be published this year on the topics of oncofertility and fertility preservation [6]. Previous studies have demonstrated that these preservation methods can be completed without significant delays in cancer treatment when a random-start approach is used [7]. There is a single publication discussing the potentially serious complications that can occur in sickle cell patients undergoing ovarian stimulation [8]. Few, if any papers, have ever focused on medical complications that have arisen during ovarian stimulation or oocyte retrieval related to an underlying cancer. Nor has any prior publication, to our knowledge, addressed the unique considerations and challenges physicians must address in this population to assure a safe and successful treatment. Addressing these challenges is crucial in maximizing each patient's chance for future family building, avoiding delay in the treatment of disease, and most importantly in doing no harm to this unique patient population.

Case presentations

Case 1: Thrombocytopenia

A 35-year-old female developed aplastic anemia 8 months following delivery of her first baby, a healthy term male, after an uncomplicated pregnancy. At the time of aplastic anemia diagnosis, platelet count ranged between 7 and 20 × 10E9, and recommendations were made for treatment with antithymocyte globulin, cyclosporine, and prednisone, followed by future bone marrow transplantation. After

✉ Kaitlyn Wald
Kaitlyn.Wald@ucsf.edu

[1] Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, 499 Illinois Street, 6th Floor, San Francisco, CA 94158, USA

[2] University of Utah Center for Reproductive Medicine, Salt Lake City, UT, USA

[3] Department of Anesthesia, University of California, San Francisco, San Francisco, CA, USA

receiving counseling on the possible impact of such treatment on future fertility, she elected to proceed with embryo cryopreservation.

She underwent preoperative evaluation at the anesthesia-directed preoperative clinic at the start of her stimulation cycle, where she was noted to be transfusion dependent, requiring frequent platelet and packed red blood cell transfusions. She had begun treatment with eltrombopag, corticosteroids, and blood component therapy to maintain hemoglobin > 7.0 g/dl and platelet count > 10 × 10E9. Two days prior to preoperative evaluation, hemoglobin was 6.7 g/dl, platelet count was 12 × 10E9, and ANC was 1.25 × 10E9/L. Her other past medical history was reviewed in detail and was notable for hypertension, well controlled with a calcium channel blocker, and gastroesophageal reflux, managed with a proton pump inhibitor.

The presenting symptom of aplastic anemia had been fatigue, but at the time of anesthesia evaluation, she still endorsed the ability to climb one flight-of-stairs without pausing to rest and denied other specific symptoms attributable to anemia, including exertional dyspnea, palpitations, or chest pain. She reported easy bruising, but denied any other unusual bleeding sequelae. Coagulation studies had remained within normal limits. Laboratory data revealed a recent transaminitis with a peak ALT of 511 U/L (decreased to 52) and AST of 271 U/L (decreased to 32). This was attributed to liver injury as a side effect from recent immunosuppressive treatment.

Following thorough evaluation by anesthesia and consultation with the UCSF Hematology service, a plan was made for Monitored Anesthesia Care sedation at the time of oocyte retrieval, with a specific anesthesiologist selected by the preoperative clinic, who once familiarized with the case, agreed to provide care for the procedure. Platelet transfusion was planned for the morning of the procedure, with a goal of raising the platelet count to ≥ 50 × 10E9 per microliter.

She underwent stimulation using an IVF antagonist protocol, with 150 IU rFSH (Gonal-F, Serono) and 150 IU HMG (Menopur, Ferring) as starting medications. By day 9 of the stimulation, with 10 follicles ≥ 13 mm in size, and E2 = 757 pg/mL, the decision was made to administer a trigger shot of 10,000 units hCG subcutaneous, with scheduled oocyte retrieval 36 h later.

She presented for her scheduled day of procedure platelet transfusion with a platelet count of 11 × 10E9. After the planned transfusion of 1 unit apheresis platelets, the count increased to 15 × 10E9 per microliter. This was significantly lower than expected based on her prior transfusions and felt to be related to quick consumption secondary to her disease. At that time, the decision was made to complete a second transfusion of 1 unit apheresis platelets, after which her platelets increased to 27 × 10E9. Several additional hours would be required to complete further platelet transfusions. Given the critical timing of retrieval following administration of the trigger shot, to avoid ovulation, additional transfusions prior to retrieval were not possible. The risk for significant bleeding from egg retrieval with platelets less than 30–50 × 10E9 was too great and the patient's scheduled retrieval was canceled.

In discussion with the patient's hematology/oncology team, the ability to successfully transfuse platelets to reach greater than 30 × 10E9, a level considered safe for embryo retrieval, was low based on her transfusion response the day of planned retrieval and her very low baseline platelet counts. The decision was made to work towards disease stabilization and an improved baseline platelet count before attempting another preservation cycle.

Following the cancelation, she experienced significant bloating which resolved within 1–2 weeks, but no other serious symptoms warranting intervention.

Case 2: Pericardial and pleural effusions

A 38-year-old nulliparous female sought fertility preservation consultation following a diagnosis of stage 2 B cell lymphoma. The lymphoma was diagnosed in the setting of an enlarged supraclavicular lymph node, unexplained fevers, night sweats, and unintentional weight loss. Chest x-ray at the time of diagnosis was notable for small pleural effusions, left greater than right, and no consolidations. She did not endorse respiratory symptoms at the time of presentation for fertility preservation consultation. Her proposed treatment plan was the combination chemotherapy regimen EPOCH (Etoposide, Prednisolone, Onvocin, Cyclophosphamide, Hydroxydaunorubicin).

She was counseled on the possible impact of lymphoma treatment on her future fertility and options for fertility preservation. She elected to proceed with egg cryopreservation, which was initiated within 11 days of her lymphoma diagnosis.

She underwent excisional biopsy of an enlarged cervical lymph node in the operating room under general endotracheal anesthesia, with sevoflurane induction to facilitate maintenance of spontaneous ventilation in an effort to minimize the risk of tracheobronchial or circulatory collapse. The patient remained hemodynamic stable throughout the procedure.

She was subsequently evaluated in anesthesia department-directed preoperative clinic at the start of her stimulation cycle, 1 day after the biopsy, endorsing decreased appetite, pruritus, mid-back pain, dry cough, pleuritic pain, and shortness-of-breath that were improving since the initiation of a course of prednisone prescribed by her oncologist a few days earlier. Following thorough evaluation by anesthesia and communication with the UCSF Hematology-Oncology team, a plan was made for Monitored Anesthesia Care sedation at the time of oocyte retrieval.

She underwent ovarian stimulation using an antagonist random-start protocol, with 150 IU rFSH (Gonal-F, Serono)

and 150 IU HMG (Menopur, Ferring) given throughout the cycle. Baseline antral follicle count was 12. By day 11 of stimulation, with 11 follicles ≥ 13 mm and E2 = 3591 pg/mL, she took a 10,000 IU hCG subcutaneous trigger shot. The day following the hCG trigger, she developed dyspnea, and presented to the emergency department where she was found to have large pleural and pericardial effusions. A CT of the chest was notable for extensive lymphadenopathy, a moderate to large pericardial effusion, moderate left and small right pleural effusions, right lower lobe passive atelectasis, and near complete collapse of the left lower lobe. Due to concerns for worsening respiratory status, the patient was admitted to the hospital. Admission labs included a normal basic metabolic panel and a complete blood count notable for a white blood cell count of 12.1 and a hemoglobin of 10.3. Further, she felt unsafe to undergo egg retrieval in an outpatient venue. Due to the need for close proximity of the embryology lab immediately following retrieval, it was not logistically possible in our setting to coordinate the retrieval in the hospital, and her cycle was canceled.

Following admission to the hospital, she underwent thoracentesis for the right pleural effusion felt to be primarily related to rapid disease progression and received cabergoline orally for 8 days to minimize the risk of developing ovarian hyperstimulation syndrome (OHSS), and Lupron 3.75 mg for ovarian suppression. She was started on daily prophylactic Lovenox, as routine for all cancer patients admitted to the hospital. Chemotherapy was initiated during the 2-week admission, and continued over subsequent weeks after hospital discharge, produced gradual symptomatic improvement.

Case 3: Large mediastinal mass

31-year-old nulliparous female presented for fertility preservation consultation following a diagnosis of primary mediastinal large B cell lymphoma. The lymphoma diagnosis was made after 2-week onset of chest pain and fatigue. A CT scan showed a 6.5 × 4.4 cm anterior mediastinal mass that on biopsy was confirmed to be large B cell lymphoma. Her proposed treatment plan was the combination chemotherapy regimen EPOCH-R (Etoposide, Prednisolone, Onvocin, Cyclophosphamide, Hydroxydaunorubicin). After receiving counseling on the possible impact of cancer treatment on future fertility status, she elected to proceed with egg cryopreservation.

She underwent ovarian stimulation using an antagonist, random-start protocol, with 150 IU rFSH (Gonal-F, Serono) and 150 IU HMG (Menopur, Ferring) throughout the cycle. On cycle day 8, she developed worsening pleuritic chest pain and presented to the emergency room for evaluation, where CT imaging showed increased size of her anterior mediastinal mass, measuring 7.3 × 5.0 cm, compared with 6.5 × 4.4 cm previously, and increased mass effect on the right ventricular outflow tract and main pulmonary artery. Mediastinal lymph nodes had increased in size, and fluid was newly visible in the left pleural space. After receiving a single dose of oxycodone for symptomatic relief, she experienced profound oxyhemoglobin desaturation.

Urgent anesthesia preoperative evaluation was requested in the setting of her changing clinical picture. She was evaluated in the anesthesia department-directed preoperative clinic, and her emergency room evaluation was reviewed in detail. She reported that her symptoms had decreased significantly after treatment with hydrocodone/acetaminophen, but that she was still sleeping with 3 pillows to relieve the pleuritic chest pain. Vital signs were unremarkable, aside from resting heart rate of 106. She did not appear dyspneic on the exam and was able to tolerate the supine position for 5 min without distress. Despite reassuring exam, the location and growing size of the mass, recent increase in symptom severity, and desaturation after administration of narcotic, both the anesthesiologists and fertility physicians, were concerned about the safety of sedation in an outpatient, non-hospital setting. Chief among these concerns were the risks of ventilatory compromise, distress, or irreversible cardiorespiratory collapse. In light of these concerns, the patient's ovarian stimulation cycle was canceled.

Case 4: Seizures

A 41-year-old nulliparous female presented for fertility consultation following a diagnosis of grade 3 anaplastic astrocytoma. This tumor, a 3.8 × 2.7 × 2.3 cm frontal lobe mass, was discovered after she suffered a grand mall seizure.

After receiving counseling on the possible impact of treatment on her future fertility, she elected to proceed with embryo cryopreservation. Fertility treatment was initiated prior to undergoing anesthetic preoperative evaluation. Ovarian stimulation was performed using an antagonist, random-start protocol, with 225 IU rFSH (Gonal-F, Serono) and 150 IU HMG (Menopur, Ferring) throughout the cycle. On day 9 of stimulation, there were 7 follicles ≥ 13 mm and E2 was 1589 pg/mL, at which point she received a 10,000 IU subcutaneous hCG trigger shot.

Despite continuation of levetiracetam during her stimulation cycle, she suffered another grand mall seizure the evening of her trigger shot and her retrieval was canceled.

Discussion

Over the past 10 years, we have had over 2000 consults for emergent fertility preservation and have a system in place to manage patients at high risk, which includes several unique steps for avoiding complications and maintaining patient safety (see Table 1). Our program activates a team of anesthesiologists, oncologists, and reproductive endocrinologists for co-

Table 1 Several unique steps for avoiding complications and maintaining patient safety

Ovarian stimulation in the acutely ill; essential steps for avoiding complications
• Regular and frequent communication between ALL members of the care team (oncologist, anesthesiologist, reproductive endocrinologist, internist)
• In-person anesthesiology evaluation
• Conservative dosing of gonadotropins
• Required labs: CBC
• Labs to consider: BMP, AST/ALT, coagulation studies
• Imaging to consider: chest x-ray, ECHO
• Close monitoring by physicians of symptoms during stimulation
• Consideration of low dose hCG and FSH or Lupron for trigger
• Retrieval kit and setup for retrieval in main operating room if necessary
• Close monitoring by physicians of symptoms following stimulation, with low threshold for OHSS evaluation

management during fertility preservation treatment. In this setting, we present 4 different scenarios with serious medical conditions that highlight the high-risk nature, and why ongoing multidisciplinary management is required during ovarian stimulation to prevent further sequela. Our experience, however, supports the need for a broad, multidisciplinary approach for all patients presenting with a cancer diagnosis. Practitioners taking care of these patients, particularly in an outpatient setting, should be aware, take proper precautions and have a system in place to decrease risk. In addition, programs taking care of these patients should have alternative options to offer, such as an ability to do "in hospital" oocyte retrievals, and/or ovarian tissue cryopreservation.

Preoperative evaluation

The objective of the preoperative evaluation is to identify and optimize a patient's comorbidities as well as to assess and, where possible, reduce perioperative risk. Preoperative evaluation has been associated with decreased surgical complications, delays, and cancelations [9]. Although both benefits and risks are weighed before any surgical procedure, the ovum harvest cases are unique in two respects. First, these procedures may be performed in a remote, non-clinical venue, neither in nor near a hospital or accredited outpatient surgical facility. For the patient who becomes clinically unstable, the only practical option for the clinician may be to call 911, since resources such as urgent labs, pharmacy, blood bank, respiratory therapy, and surgical equipment may not be available on site. Second, when fertility treatment is offered to these patients, the cycle becomes time sensitive in nature. Any cycle delays could be accompanied by disease progression and/or detrimental delay in receiving life-saving or life-extending disease treatment. Although these procedures can never be risk-free, providers must, whenever possible, identify patients at an especially elevated risk for complications and determine whether the risks are acceptable.

Patients at elevated risk for cardiovascular, pulmonary, hematologic, or neurologic instability must be identified prior to initiation of fertility treatment. Preoperative evaluation should take place in-person, with history, complete physical examination, review of laboratory results and imaging, and consultation with any specialist as indicated. Symptoms that should raise concern include exertional or positional dyspnea, chest pain, presyncope or syncope, and progressive fatigue. Physical findings warranting concern include oxyhemoglobin desaturation at rest or with exercise, tachycardia, tachypnea, distant heart sounds, jugular venous distention, diminished or adventitial breath sounds, and wheezing or stridor. Further, the inability to climb two flights of stairs or walk four blocks has been associated with an increased risk of postoperative cardiopulmonary complications [10].

Conditions that may lead to clinical instability during an oocyte retrieval procedure under sedation include but are not limited to mediastinal mass, accumulating pleural or pericardial effusions, intracranial masses, and severe hematologic abnormality with profound impairment of coagulation. In addition, it is important to remember that there are numerous other clinical conditions that are beyond the scope of this case series that can still pose significant risk among the fertility preservation population. This includes acquired or congenital heart disease, morbid obesity, difficult airway, and sleep-disordered breathing [11–13].

Intra-operative risks and precautions

Propofol is the anesthetic most commonly used for oocyte retrieval procedures. In addition, midazolam is often given for anxiolysis, and usually some quantity of fentanyl to decrease likelihood of movement during the procedure and to offset acute post-procedural pain. These medications all impair respiratory and cardiovascular function to varying degrees. Hemodynamic instability can result from decreased preload and decreased afterload. These effects may be amplified in patients with acute conditions, vascular disease, intrathoracic and mediastinal masses, and pericardial disease, all of which have been associated with an elevated risk of developing hemodynamic instability [14–16]. Pharmacologic respiratory depression in patients with increased work of breathing, airway compression, and V/Q mismatch can lead to rapid decrease in ventilation and oxygenation. Severe anemia can further limit oxygen delivery. Patients with mediastinal masses can present unique anesthetic challenges, with unpredictable changes in airway and vascular compression and alterations in chest wall compliance leading to respiratory or cardiovascular collapse [15, 17]. Unfortunately, for those patients in whom Monitored Anesthesia Care sedation is of high

risk, conscious sedation also carries similar risks due to muscle relaxation which can also lead to oxygen desaturation, compromised right heart filling, and decreased systolic blood pressure. While local anesthetic may not carry these same risks, it does not provide adequate pain control for aspiration of multiple ovarian follicles.

Limited resources in remote and outpatient surgery settings can render the anesthesiologist unable to treat some of the above discussed alterations. Necessary interventions may include transfusion of blood products, invasive monitoring, echocardiography, advanced airway techniques including tracheal intubation, administration of vasopressor and/or inotropic agent, electrical cardioversion, defibrillation, or advanced circulatory support. Readily available backup by a second anesthesiologist or intensivist may not be available. Adequate postoperative care may not be available for patients at increased risk of post-procedure pulmonary complications or requiring post-procedure labs, imaging, blood products, or medications. While it is best to make the above resources available whenever possible, it is also critical to complete a thorough preoperative evaluation to avoid such situations and to appropriately prepare. Facilities unable to make the above resources available when necessary should consider having a kit and setup available to complete retrievals in a main operating room setting.

Blood dyscrasias and electrolyte abnormalities

Abnormal blood counts are not uncommon in cancer patients and patients with chronic disease. Thrombocytopenia, anemia, and leukopenia are all commonly encountered dyscrasias in this population. These lab disturbances, when severe and transfusion dependent, can alter oxygen delivery and hemostasis and may require repeated laboratory evaluation as well as planning by anesthesia.

For a major surgery, platelet transfusion is generally recommended for a platelet count < 50 × 10E9. For minor procedures, the threshold for transfusion is typically < 20 × 10E9 [18]. Egg retrieval is considered a minor procedure, although a 17-gauge needle is placed vaginally to collect the oocytes. Given the inability to directly visualize internal bleeding and the significant vascularity of vaginal tissue and the ovary, we recommend considering platelet transfusion for a platelet count < 50 × 10E9. When platelets are below or near this threshold, a multidisciplinary approach should be used to coordinate pre-procedure transfusion of platelets and a target platelet count should be agreed upon in advance by the patient's hematologist, anesthesiologist, and fertility specialist. The patient's prior response to transfusions should be considered; however in general, following a single unit platelet transfusion, the platelet count is expected to rise by approximately 35,000/microL within 10 min of the infusion and gradually decline over 72 h [19]. Planning must account for the critical timing of oocyte retrieval following administration of the trigger shot, ideally allowing for additional transfusions to be completed in the setting of an unexpected response. In the case one discussed above, the patient had an abnormal and unexpectantly poor response to platelet transfusion based on her prior responses, with a quick consumption of platelets related to her disease process. Unfortunately, there was no sufficient time to complete additional transfusions prior to retrieval.

Anemia is another common blood dyscrasia in patients undergoing emergency fertility preservation. In general, a restrictive transfusion threshold of 7 g/dL is recommended in hemodynamically stable patients [20]. Exceptions to this threshold include symptomatic patients, patients with hematologic or oncologic diseases at risk of bleeding and chronic transfusion-dependent anemia. As discussed with platelets above, when a patient's hemoglobin is at or near this threshold, a multidisciplinary approach should be used to coordinate pre-procedure transfusion of packed red blood cells and a target hemoglobin level should be agreed upon in advance by the patient's hematologist, anesthesiologist, and fertility specialist.

Leukopenia is a common presenting dyscrasia in patients with leukemia. These patients are often in need of immediate chemotherapy, which can limit their ability to undergo ovarian stimulation. When timing does allow for ovarian stimulation, one must carefully consider the risk of infection and safety of stimulation and retrieval with a low white blood cell count. Providers should also strongly consider the use of prophylactic antibiotics at the time of retrieval, if not already a standard practice at their clinic. Alternatively, it may be reasonable to consider ovarian stimulation after induction chemotherapy as previously shown successful [21]. Ideally, however, patients complete fertility preservation prior to chemotherapy and in our practice, we consider it best not to harvest eggs or embryos within 1 year of exposure to chemotherapy due to the theoretical risk of teratogenic exposure of the oocytes as previously shown in animal studies [22].

Electrolyte abnormalities are also commonly observed in patients with malignancy. This is particularly common following cancer debulking surgery. Postoperative electrolyte derangements occur secondary to loss of blood and body fluids, stress response to surgery, intravenous fluid administration, and blood transfusion [23]. To avoid delays in treatment, patients often undergo fertility preservation cycles following surgery while awaiting initiation of chemotherapy. It is therefore particularly important to monitor closely for electrolyte abnormalities in this patient population. Further, although rare, tumor lysis syndrome can occur and result in life-threatening electrolyte abnormalities [24]. It is most commonly observed in patients with high-grade lymphomas and acute lymphoblastic leukemia, following the initiation of chemotherapy [24, 25]. It can, however, be observed in all cancer

types, and rarely occurs following tumor debulking surgery, prior to initiation of chemotherapy. We therefore recommend strong consideration of a complete metabolic panel prior to cycle imitation in any of these higher risk patient populations.

Mediastinal masses

Mediastinal tumors are not uncommon in patients with lymphoma, one of the more common cancers in women of reproductive age. They can result in the compression of anterior mediastinal structures, including the right ventricle, pulmonary artery, and superior vena cava. Patients with a mediastinal mass therefore must undergo a detailed preoperative anesthesia assessment, including consideration of potential for airway or respiratory compromise and/or hemodynamic instability.

Typically, patients must be stable enough to receive anesthesia in an outpatient procedure center, as previously discussed. At centers regularly providing emergency stimulation cycles to this patient population, it may be reasonable to have a protocol in place that allows for retrieval in a hospital setting. This would involve the development of a specialized procedure for ovum transport back to the embryology lab.

Estrogen elevation and thromboembolic risk

Cancer is a known hypercoagulable state with venous thromboembolism (VTE) occurring in 8–15% of all cancer patients [26, 27]. Demographic characteristics (age, race, ethnicity) and cancer type and stage are factors known to influence the risk of VTE within this population. African-American patients, aggressive tumors (pancreas, lung, ovarian), and metastatic disease all being associated with a particularly elevated VTE risk [28]. Further, the incidence of VTE appears to be greatest in the first 3–12 months following diagnosis [28].

Ovarian stimulation results in elevated systemic estrogen levels, which is a known thrombogenic agent as it increases a number of procoagulant factors, including fibrinogen, von Willebrand factor, and factors VIII and V [29]. Further, it is associated with increased activated protein C resistance, reduced antithrombin, protein C, and S activity [29]. The prevalence of VTE in patients undergoing ovarian stimulation is low at 0.1–0.2%; however, it is still ten times higher than that of the general population [30, 31]. Both OHHS and pregnancy immediately following ovarian hyperstimulation dramatically increase the thromboembolic risk [32].

Given the thromboembolic risks associated with cancer and with ovarian stimulation, one must consider the risk in our patient population; cancer patients undergoing ovarian stimulation. While they are not attempting immediate pregnancy, they are recently diagnosed and at potentially greater risk for the development of OHSS (see section on post-retrieval complications). There is little available data on this specific risk; however, epidemiological data has been reassuring [33]. As such, there is currently no recommendation for antithrombotic prophylaxis during fertility preservation in cancer patients. All patients, however, should be counseled on the potential risk and prophylaxis should be strongly considered in those developing early OHSS, with diagnosis of a high-risk cancer type, or advanced stage disease. Ultimately, the decision for or against prophylaxis should be individualized and made together with the patient's primary oncologist. For our patients requiring prophylaxis, we most commonly use prophylactic dosing of low molecular weight heparin, with discontinuation 24 h prior to retrieval and re-initiation 24 h following retrieval.

Elevated estrogen levels are also an important consideration in women with estrogen-sensitive cancers, undergoing fertility preservation. Most commonly, this is women with estrogen receptor-positive breast cancer, as this is one of the most common cancer types in women of reproductive age. In our clinic, we routinely prescribe this patient population 5 mg Letrozole from the start of stimulation and through 10 days post-retrieval or start of chemotherapy, whichever occurs first. This dose is uptitrated as needed to keep the estradiol level below 500 pg/mL. It is possible that Letrozole may be of benefit for other indications in this patient population, including decreased thromboembolic risk; however, this is an area that requires further research.

Post-retrieval complications

Ovarian hyperstimulation syndrome occurs in 1–5% of ovarian stimulation cycles [34]. Symptoms include ovarian enlargement, ascites, hemoconcentration, hypercoagulability, and electrolyte imbalances. These symptoms are largely secondary to increased capillary permeability and vasodilation [35]. Vascular endothelial growth factor (VEGF) has also been shown to play a role in the increased vascular permeability and is produced by granulosa cells after stimulation by hCG [36]. The result of these changes is often abnormal fluid collections in extravascular spaces.

Inflammation and malignant tumors are associated with vascular instability and increased vascular leakage [37]. As such, one must be particularly cautious about the development of OHSS or third spacing during emergency fertility preservation in cancer patients. It is also important to remember that in the event a patient's cycle must be canceled after the development of multiple mature follicles, they may be at an even greater risk of developing OHSS due to the prolonged presence of granulosa cells, typically aspirated during the oocyte retrieval process, which produce VEGF [36].

There is increasing evidence that cabergoline results in a decreased production of VEGF and thus decreases the risk of OHSS [34]. Strong consideration should be given to the use of cabergoline in these situations. In our practice, we typically

use a regimen of 0.5 mg/day starting the day of trigger and continuing for 8 days. Further, in patients who are already known to have abnormal fluid collections or electrolyte abnormalities at the time of fertility consultation, physicians must carefully consider the safety of moving forward with ovarian stimulation. If stimulation is pursued, a lower dose of gonadotropins should be considered. A lower dose hCG trigger in combination with FSH or a GnRH agonist may be safer as a trigger, as previous studies have shown a reduction in OHSS following their use [34, 38–40]. This is felt to be secondary to the shorter half-life and decreased duration of LH-like activity on post-retrieval corpora lutea [34]. While all four cases above used hCG trigger, these are cases resulted in a suboptimal outcome from which we have improved our management of fertility preservation and the basis for our recommendation Further, a plan must be developed for careful and regular monitoring of fluid shifts and the patient needs to be counseled on the potential risk of cycle cancelation.

Summary

Patients with cancer or a severe medical condition represent a unique population for fertility care. For all patients, a collaborative multidisciplinary approach including all providers involved a patient's medical treatment is critical. At a minimum, this should include regular discussion between the patient's reproductive endocrinologist, oncology team, and anesthesiologists. This communication, in addition to the summarized guidelines below, is the most critical aspect to providing safe and successful care to this unique patient population.

Management guidelines:

1. Pre-anesthesia evaluation prior to initiation of fertility treatment in patients in whom a high-risk condition is known or suspected. Detailed physical examination with close attention to vitals and heart and lung exam should be performed and documented by an anesthesiologist. Preoperative laboratory data should include complete blood count, basic metabolic panel, and any other labs indicated based upon clinical considerations relevant to the individual patient.
2. Direct communication should take place between the primary cancer team and reproductive endocrinology team regarding a patient's overall health, timeline of stimulation, and treatment initiation.
3. Ongoing medical evaluation during ovarian stimulation should take place, with continued communication with the oncology and anesthesia teams.
4. Greater vigilance should be maintained for recognizing symptoms of OHSS, with consideration for more conservative dosing of gonadotropins and hCG triggers and/or the use of a Lupron trigger.
5. Retrieval kit and setup for retrieval in the main operating room should be available in the setting it becomes necessary.

References

1. Centers for Disease Control. A national action plan for cancer survivorship: advancing public health strategies. 2004 12/20/2018]; Available from: https://www.cdc.gov/cancer/survivors/pdf/plan.pdf.
2. Surveillance, epidemiology, and end results program. Cancer statistics and review 1975–2015. [cited 2018; Available from: http://www.seer.cancer.gov.
3. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118(6):1710–7.
4. Ethics Committee of the American Society for Reproductive Medicine. Electronic address, A.a.o., Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril, 2018. 110(3): p. 380–386.
5. Anazodo A, Ataman-Millhouse L, Jayasinghe Y, Woodruff TK. Oncofertility-an emerging discipline rather than a special consideration. Pediatr Blood Cancer. 2018;65(11):e27297.
6. Ataman LM, Ma Y, Duncan FE, Uzzi B, Woodruff TK. Quantifying the growth of oncofertility. Biol Reprod. 2018;99(2):263–5.
7. Letourneau JM, Sinha N, Wald K, Harris E, Quinn M, Imbar T, et al. Random start ovarian stimulation for fertility preservation appears unlikely to delay initiation of neoadjuvant chemotherapy for breast cancer. Hum Reprod. 2017;32(10):2123–9.
8. Pecker LH, Maher JY, Law JY, Beach MC, Lanzkron S, Christianson MS. Risks associated with fertility preservation for women with sickle cell anemia. Fertil Steril. 2018;110(4):720–31.
9. Ferschl MB, Tung A, Sweitzer BJ, Huo D, Glick DB. Preoperative clinic visits reduce operating room cancellations and delays. Anesthesiology. 2005;103(4):855–9.
10. Reilly DF, McNeely MJ, Doerner D, Greenberg DL, Staiger TO, Geist MJ, et al. Self-reported exercise tolerance and the risk of serious perioperative complications. Arch Intern Med. 1999;159(18):2185–92.
11. Subramani Y, Wong J, Nagappa M, Chung F. The benefits of perioperative screening for sleep apnea in surgical patients. Sleep Med Clin. 2017;12(1):123–35.
12. Cartagena R. Preoperative evaluation of patients with obesity and obstructive sleep apnea. Anesthesiol Clin North Am. 2005;23(3):463–78 vi.
13. Subramani Y, Nagappa M, Wong J, Mubashir T, Chung F. Preoperative evaluation: estimation of pulmonary risk including obstructive sleep apnea impact. Anesthesiol Clin. 2018;36(4):523–38.
14. Devereaux PJ, Sessler DI. Cardiac complications in patients undergoing major noncardiac surgery. N Engl J Med. 2015;373(23):2258–69.
15. Bechard P, et al. Perioperative cardiorespiratory complications in adults with mediastinal mass: incidence and risk factors. Anesthesiology. 2004;100(4):826–34; discussion 5A.
16. Grocott HP, Gulati H, Srinathan S, Mackensen GB. Anesthesia and the patient with pericardial disease. Can J Anaesth. 2011;58(10):952–66.
17. Goh MH, Liu XY, Goh YS. Anterior mediastinal masses: an anaesthetic challenge. Anaesthesia. 1999;54(7):670–4.

18. Graetz T, N.D. Perioperative strategies to reduce bleeding and minimize transfusions. UpToDate. 2018; Available from: http://www.uptodate.com.
19. McCullough J. Overview of platelet transfusion. Semin Hematol. 2010;47(3):235–42.
20. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB red blood cell transfusion thresholds and storage. Jama-J Am Med Assoc. 2016;316(19):2025–35.
21. Ye R, et al. Timing embryo preservation for a patient with high-risk newly diagnosed acute myeloid leukemia. Case Rep Hematol. 2018;2018:9807047.
22. Meirow D, Epstein M, Lewis H, Nugent D, Gosden RG. Administration of cyclophosphamide at different stages of follicular maturation in mice: effects on reproductive performance and fetal malformations. Hum Reprod. 2001;16(4):632–7.
23. Brunicardi FC, et al. Schwartz's principles of surgery. Tenth ed. New York: McGraw-Hill Education; 2014.
24. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844–54.
25. Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. Ann Hematol. 2016;95(4):563–73.
26. Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C, et al. High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. Arterioscler Thromb Vasc Biol. 2009;29(12):2176–81.
27. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer. 2013;49(6):1404–13.
28. Mahajan A, et al. The epidemiology of cancer-associated venous thromboembolism: an update. Semin Thromb Hemost. 2019.
29. Chan WS. The 'ART' of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. Curr Opin Obstet Gynecol. 2009;21(3):207–18.
30. Rova K, Passmark H, Lindqvist PG. Venous thromboembolism in relation to in vitro fertilization: an approach to determining the incidence and increase in risk in successful cycles. Fertil Steril. 2012;97(1):95–100.
31. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):92–128.
32. Gurunath S, Vinekar S, Biliangady R. Assisted reproductive techniques in a patient with history of venous thromboembolism: a case report and review of literature. J Hum Reprod Sci. 2018;11(2):193–7.
33. Somigliana E, Peccatori FA, Filippi F, Martinelli F, Raspagliesi F, Martinelli I. Risk of thrombosis in women with malignancies undergoing ovarian stimulation for fertility preservation. Hum Reprod Update. 2014;20(6):944–51.
34. Practice Committee of the American Society for Reproductive Medicine. Electronic address, A.a.o. and M. Practice Committee of the American Society for reproductive, prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril, 2016. 106(7): p. 1634–1647.
35. Goldsman MP, Pedram A, Dominguez CE, Ciuffardi I, Levin E, Asch RH. Increased capillary permeability induced by human follicular fluid: a hypothesis for an ovarian origin of the hyperstimulation syndrome. Fertil Steril. 1995;63(2):268–72.
36. Namavar Jahromi BM, et al. Ovarian hyperstimulation syndrome: a narrative review of its pathophysiology, risk factors, prevention, classification, and management. Iran J Med Sci. 2018;43(3):248–60.
37. Claesson-Welsh L. Vascular permeability–the essentials. Ups J Med Sci. 2015;120(3):135–43.
38. Toftager M, Bogstad J, Bryndorf T, Løssl K, Roskær J, Holland T, et al. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. Hum Reprod. 2016;31(6):1253–64.
39. Youssef MA, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database Syst Rev. (2011, 1):CD008046.
40. Anaya Y, Mata DA, Letourneau J, Cakmak H, Cedars MI, Rosen MP. A novel oocyte maturation trigger using 1500 IU of human chorionic gonadotropin plus 450 IU of follicle-stimulating hormone may decrease ovarian hyperstimulation syndrome across all in vitro fertilization stimulation protocols (vol 35, pg 297, 2017). J Assist Reprod Genet. 2018;35(2):309–9.