Chapter 15
Clinical Cases in Oncofertility

Clarisa Gracia

Introduction

Clarisa Gracia, editor

A case-based approach to medical education is a very effective strategy to reinforce medical concepts and demonstrate how they might be applied to clinical situations. In that vein, this chapter presents a series of actual clinical scenarios described by practitioners in the field of oncofertility. They highlight important concepts covered in the preceding chapters of this text and illustrate current strategies in the care of oncofertility patients. Because the number of complex fertility preservation cases at any single center may be limited, there is value in providing a series of cases from multiple contributors in this book. An increased awareness of the complex issues involved in oncofertility practice should help prepare clinicians for some of the challenges posed by this rapidly expanding discipline. It is important to recognize that individualized care is critical in order to minimize the risks associated with fertility preservation and maximize the future reproductive options for patients.

Case 1: Sickle Cell Disease in a Prepubertal Female

Case courtesy of Clarisa Gracia, M.D.

T.T. is an 8-year-old prepubertal female with a history of severe sickle cell disease that was initially diagnosed at 6 months of age and complicated by frequent hospital admissions for pain and vaso-occlusive crises. Given the severity of her disease, her

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hematologist suggested that she pursue autologous stem cell transplantation (SCT) as treatment. Her family was counseled extensively about the potential risks and benefits of the procedure, including the high risk of infertility and premature ovarian failure. The patient's parents had already lost a child to sickle cell disease and decided to pursue SCT. Ovarian tissue cryopreservation was discussed with the family as the only available option for fertility preservation given the patient's age and prepubertal status. After extensive counseling, her parents gave consent for the patient to participate in an experimental protocol for ovarian tissue cryopreservation. Laparoscopic ovarian biopsy was planned at the time of her scheduled surgery to place a venous access port. Ovarian biopsy was performed without complication at the children's hospital by the collaborating reproductive endocrinologist. The tissue was transported to the nearby fertility clinic in holding media for processing and cryopreservation using a slow-freeze protocol. The patient completed her SCT and is currently doing well.

This case illustrates two important issues in oncofertility. First, there are limited options available for fertility preservation in prepubertal girls. Ovarian stimulation with oocyte or embryo banking is not possible before puberty, and this patient was not a candidate for ovarian transposition surgery since she was not undergoing targeted pelvic radiotherapy. Therefore, ovarian tissue cryopreservation was the only available option for this patient. This option is an experimental technique that is currently available at a number of institutions under the auspices of the institutional IRB [1]. While studies are investigating methods to mature follicles from banked ovarian tissue in vitro, autologous transplantation after treatment is the only method that has resulted in live births to date (discussed in Chap. 5 in this volume).

Second, while many patients receiving gonadotoxic agents have a cancer diagnosis, cancer therapies, in this case SCT, are increasingly being used for the treatment of nonmalignant medical conditions [2]. Often, these diseases are rheumatologic or hematologic conditions. Because such patients are often ill, they may be at greater risk for complications from fertility preservation techniques compared with patients who have a cancer diagnosis. For example, patients with sickle cell disease may be at higher risk of vaso-occlusive crises, thrombosis, and postoperative pain. While this patient was not a candidate for ovarian stimulation with oocyte or embryo banking, ovarian stimulation associated with supraphysiologic estrogen and the potential for ovarian hyperstimulation syndrome (OHSS) may pose significant risks in postpubertal patients with sickle cell disease.

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Case 2: Breast Cancer in a Married Woman of Late Reproductive Age

Case courtesy of Lynn M. Westphal, M.D.

N.B. is a 40-year-old married gravida 1 para 0 with recently diagnosed invasive ductal breast carcinoma who expressed a desire for fertility preservation prior to chemotherapy and prophylactic bilateral salpingo-oophorectomy. The patient presented on day 16 of her menstrual cycle. Progesterone levels were checked and found to be 0.7 ng/ml, indicating that ovulation had not yet occurred. Gonadotropin-releasing hormone (GnRH) antagonist was administered on cycle day 16 through cycle day 19, with menses starting on the fourth day of antagonist treatment.

Baseline ultrasound performed on cycle day 2 noted no cysts and six antral follicles in the right ovary and four in the left ovary. Ovarian stimulation was initiated with recombinant follicle-stimulating hormone (FSH) 300 IU/day, highly purified human menopausal gonadotropins (hMGs) 150 IU/day, and tamoxifen 60 mg daily. On cycle day 6 (day 5 of stimulation), a 21-mm follicle was seen, and GnRH antagonist was started. All other follicles at that time were less than 11 mm. On cycle day 7, there was a cyst that appeared to be a corpus luteum as well as a cohort of smaller developing follicles, the largest being 13 mm. Progesterone on cycle day 7 was elevated (3.8 ng/ml) and was noted to increase further the following day (5.7 ng/ml). By cycle day 9, progesterone was persistently elevated (4.4 ng/ml), but there were multiple follicles growing, with five follicles over 17 mm.

Human recombinant chorionic gonadotropin (hCG) was given, and 35 h later, transvaginal oocyte retrieval was performed, yielding 14 normal-appearing cumulus oophorus complexes. Standard insemination with her husband's sperm was performed, and nine 2-pronuclei embryos were cryopreserved using vitrification. The patient completed therapy without complications and wanted to have a child soon after therapy was complete. Six months after cryopreservation, six 2-pronuclei embryos were thawed. Two days later, three cleavage-stage embryos (8 cell grade II, 8 cell grade III, and 3 cell grade II) were transferred to a gestational surrogate. Serum beta-hCG was positive 10 days later, and ultrasound at 8 weeks gestation showed a viable twin pregnancy.

For a patient presenting for fertility preservation in the luteal phase of her cycle, often, there is not sufficient time to allow for a spontaneous menses before commencing a conventional regimen of ovarian stimulation in the early follicular phase. A time-saving alternative is immediate initiation of a GnRH antagonist prior to ovarian stimulation or concomitantly with stimulation. This case differs from standard luteal phase stimulation in that ovulation occurred during ovarian stimulation prior to the hCG trigger. With evidence of a cohort of smaller follicles growing despite premature ovulation, we continued our stimulation protocol to encourage the growth of this second wave of follicles. Elevated progesterone concentrations do not appear to have been detrimental to oocyte quality in this case, as the cycle yielded embryos that resulted in an ongoing twin pregnancy. Thus, ovulation prior to retrieval need not uniformly necessitate cycle cancellation, especially in the case of urgent fertility preservation [1].

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Case 3: ALL in an Adolescent Boy

Case courtesy of Jill P. Ginsberg, M.D.

J.B. is a 15-year-old boy diagnosed with high-risk acute lymphoblastic leukemia (ALL). He began treatment on a protocol that contained 2 g/m^2 of cyclophosphamide. Because of the low risk of gonadotoxicity of this regimen, his treating physician did not offer him the opportunity to cryopreserve sperm. Unfortunately, the patient relapsed while on maintenance therapy. At that time, it was recommended that he restart more aggressive chemotherapy and then be considered for hematopoietic SCT. The patient was approached about the possibility of sperm banking. Unfortunately, because he was in the middle of therapy, he was azoospermic and was unable to cryopreserve sperm prior to starting the more aggressive and gonadotoxic regimen.

This case highlights the importance of approaching all teenage boys about sperm banking at diagnosis, regardless of the perceived gonadotoxicity of the planned therapeutic regimen [1, 2]. It is very possible that if the patient should relapse, they will do so on therapy or shortly after completing therapy. At that time, they may not have recovered their sperm count to then have an adequate specimen to cryopreserve. Therefore, we recommend asking all teenage boys newly diagnosed with cancer to cryopreserve sperm before any treatment is delivered (see Chaps. 2 and 3 in this volume for in-depth discussions of these topics).

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Case 4: Cervical Cancer in a Young Adult

Case courtesy of Jennifer Mersereau, M.D., M.S.C.I.

S.G. is a 25-year-old gravida 0 married female with a diagnosis of stage IB poorly differentiated squamous cell carcinoma of the cervix. Approximately 1 month before her fertility preservation consultation, she had undergone surgery with her

gynecologic oncologist. Specifically, she had a robotic radical hysterectomy with pelvic lymph node dissection and bilateral oophoropexy, where each ovary was fixed to the paracolic gutter out of the pelvis. She was referred to a reproductive endocrinologist for consultation after surgery but prior to her planned treatment with whole pelvic radiation and cisplatin chemotherapy. It was anticipated that treatment would be initiated a few weeks later. On examination with transvaginal ultrasound, her ovaries were difficult to visualize. Her body mass index was 19 kg/m^2 and her anti-Müllerian hormone (AMH) level was 1.9 ng/ml. She underwent ovarian stimulation with an antagonist protocol and her peak estradiol level was 898 pg/ml on cycle day 10. Transabdominal oocyte retrieval yielded nine oocytes, and three embryos were available to be frozen on day 3. Approximately 1 year after she had completed therapy, she experienced vasomotor symptoms, and her AMH level was <0.1 pg/ml. She attempted pregnancy using the previously frozen embryos with a gestational carrier. Unfortunately, two frozen embryo transfer cycles did not result in pregnancy.

This case highlights some important challenges that arise when considering fertility preservation in women with carcinoma of the cervix. One of the biggest challenges in this case was that ovarian stimulation and oocyte retrieval were difficult after ovarian transposition surgery. Whenever possible, it is preferable to perform ovarian stimulation and oocyte retrieval prior to ovarian transposition surgery. Therefore, early consultation with a fertility specialist is especially important so the entire team can decide on the timing of events and whether ovarian transposition is appropriate at the time of her primary surgery. The benefit of oophoropexy is that it moves the ovaries away from the radiation field, thereby minimizing damage to the ovaries (see Chap. 7 in this volume for further discussion) [1, 2]; however, this needs to be weighed against the increased difficulty of oocyte retrieval using a transabdominal (vs. transvaginal) approach, which may compromise egg yield. Also, even if the patient undergoes ovarian transposition, the ovarian reserve may still be affected by radiation scatter or vascular compromise. If the patient does require transabdominal oocyte retrieval, this can be technically challenging, especially in obese patients. This procedure can be made easier by using a transabdominal ultrasound probe with a needle guide and by having at two reproductive specialists present for the case. A final consideration for women with cervical cancer who have undergone radical hysterectomy is the need for a surrogate to carry the future pregnancy. For this reason, the patient (and her partner, if applicable) should be evaluated as rigorously as "donors," with the appropriate donor questionnaires and infectious disease laboratory testing in compliance with FDA guidelines.

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Case 5: Breast Cancer in a Young Single Female

Case courtesy of Nicole Noyes, M.D.

S.C. is a single 24-year-old gravida 0 who sought fertility preservation 7 days after receiving a diagnosis of estrogen receptor (ER)-positive, invasive intraductal breast carcinoma. She denied other medical, surgical, or gynecologic issues and gave a 4-year history of oral contraceptive use. Her father was a known BRCA1 gene mutation carrier. The patient's physical exam was significant only for a 1.5-cm, firm right breast mass. After extensive counseling regarding options for fertility preservation in accordance with the American Society for Reproductive Medicine (ASRM) guidelines, as well as discussion with the patient's surgical and medical oncologists, the patient elected to proceed with oocyte cryopreservation [1]. At the time of initial presentation to the reproductive endocrinologist, the patient had not yet undergone surgical treatment. The decision was made to begin ovarian stimulation following mastectomy and axillary lymph node dissection, which was scheduled 4 days after the initial consultation with the reproductive endocrinologist. Ovarian stimulation using a letrozole-based protocol was initiated on postoperative day 1. On ovarian stimulation day 9, the patient engaged in sexual intercourse noting that the "condom broke." She presented to the office the following morning requesting emergency contraception. A nonhormonal (ParaGard®) intrauterine contraceptive device (IUD) was placed. The remainder of the patient's fertility preservation cycle was uncomplicated. Twenty-eight oocytes were retrieved and 24 mature (metaphase II) oocytes were cryopreserved [2]. She tolerated the treatment without incident and was discharged to home approximately 1 h post-retrieval. She was evaluated 14 days post-retrieval and denied any reproductive complaints.

This case highlights the importance of effective contraception in young, sexually active, cancer patients during fertility preservation and cancer therapy. Contraceptive counseling is very important in patients diagnosed with cancer since an unplanned pregnancy in the setting of a cancer diagnosis can be devastating. Making a decision to continue or terminate an unplanned pregnancy in such cases can be very difficult. In addition, pregnancy makes treatment decisions more complex and puts the patient and pregnancy at high risk (see Chap. 10 in this volume for more information). Even after cancer treatment is completed, oncologists often recommend waiting at least 2 years before pursuing pregnancy in order to minimize the risk of developing recurrent cancer during pregnancy. For these reasons, discussion of contraceptive options should be a priority soon after the diagnosis of cancer [3]. While these options are limited in patients with breast cancer since hormonal contraceptives are contraindicated, barrier methods are reasonable for such patients, and effective methods include a reversible nonhormonal IUD and/or permanent sterilization for those who do not wish to conceive in the future.

This case also recounts the use of emergency contraception in an ER-positive breast cancer patient. Available methods in the USA include progestin-only (Plan B), combined estrogen/progestin, and nonhormonal IUD. In this patient, the IUD was the optimal choice because, unlike a hormonal option, it does not have an

effect on ovarian stimulation and poses no known risk to hormone-sensitive tumors. In addition, it provides excellent reversible contraceptive efficacy (99%) for up to 10 years. When used for emergency contraception, studies show that a nonhormonal IUD is a safe and effective option [4].

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Case 6: Ovarian Cancer in a Young Married Adult

Case courtesy of Steven T. Nakajima, M.D.

P.N. is a 23-year-old gravida 0 female with an 8×7-cm left ovarian multicystic mass. She had a history of a right oophorectomy 2 years prior for a stage IA low-malignant potential mucinous cystadenoma. She was referred by her gynecologic oncologist for counseling on her fertility options in conjunction with her planned operative evaluation. The patient had been previously prescribed 25 μg ethinyl estradiol oral contraceptive pills (OCPs), which she used inconsistently. The patient was instructed to ingest only the active combination OCPs, but the cystic mass persisted despite 10 weeks of medication. The patient and her husband were counseled extensively on their fertility options, which included (1) left cystectomy and preservation of any residual ovarian tissue or (2) left oophorectomy and in vitro maturation (IVM) of immature oocytes. The patient opted for the latter and discontinued the use of her combination OCPs 8 days prior to her anticipated operative procedure. The patient had an exploratory laparotomy, left oophorectomy, lysis of extensive adhesions, and appendectomy. The frozen section and final pathology revealed a benign mucinous cystadenoma. The left ovary was transferred to the embryology laboratory in a container with a small amount of modified human tubal fluid media to keep the tissue moist. There were multiple follicles visible on the ovarian surface, and these were aspirated. Ten immature oocytes were recovered and four MII oocytes were identified after 24 h of IVM. Three zygotes resulted after intracytoplasmic sperm injection (ICSI), and these were cryopreserved. After 48 h of IVM, none of the remaining oocytes had reached the MII stage (two were atretic, two had germinal vesicles, and two were at the MI stage). At this point, the remaining six oocytes were removed from culture.

This case study illustrates a number of key principles of IVM of immature oocytes in the clinical setting of an enlarged ovarian multicystic mass. Despite the size of the tumor, the remaining ovary still provided a number of follicles that could be aspirated just 8 days after discontinuing OCPs. This period of time allowed for early folliculogenesis without augmentation with fertility medication. The patient's young age may have also contributed the ability to retrieve ten immature oocytes. In women 30 years of age or older, the density of immature oocytes often appears diminished compared with women less than 30 years of age. Using an 18-gauge butterfly infusion set needle attached to a vacuum pump (as described in Chap. 3 of this volume), the immature oocytes were readily identified [1]. It has been our observation that the majority of oocytes will mature within 24 h and that these are the most likely to yield zygotes [2]. We culture the immature oocytes to 48 h to ensure an adequate time to elapse for IVM. The percentage of oocytes that mature at 48 h is low, but if an MII oocyte is present, a second ICSI procedure would be performed. These steps are routinely followed since the presence of any mature oocyte provides hope for these patients, who may have a limited opportunity to conceive with their own gametes.

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Case 7: BRCA Mutation Detected in a Single Female

Case courtesy of Janet McClaren, M.D., M.S.C.E.

Z.F. is a 29-year-old gravida 0 female who presents for counseling regarding future fertility. She had a family history notable for breast cancer in her mother and maternal aunt at 51 and 45 years of age, respectively, and ovarian cancer in her maternal grandmother at age 42. She recently discovered that she carries a BRCA1 mutation. She planned to undergo a prophylactic mastectomy in the next few weeks and was considering a prophylactic salpingo-oophorectomy. Her gynecologic and medical history was otherwise unremarkable. She was single and expressed interested in having children in the future. Evaluation of ovarian reserve with anti-Müllerian hormone (AMH) levels and antral follicle counts demonstrated normal ovarian reserve.

This patient was referred for consultation with an oncologist and a reproductive endocrinologist to discuss how to minimize the risk of cancer and maximize her

reproductive options and long-term quality of life. It was explained that while a risk-reducing salpingo-oophorectomy (RRSO) provides significant protection against cancer in BRCA1/2 carriers, this surgery results in sterility and in risks and symptoms associated with estrogen deficiency. Since the risk of ovarian cancer increases in women over the age of 35, it would be reasonable for this patient to undergo RRSO by age 35 or as soon as she completes her family [1, 2]. In the meantime, surveillance with ultrasound and CA125 may be employed to monitor for signs of ovarian cancer, and ovulation suppression with oral contraceptives should be prescribed to reduce the risk of ovarian cancer while she is not attempting conception. Given that this patient was not in a relationship and not ready to conceive on her own, options of embryo crypopreservation (using donor sperm) and oocyte cryopreservation were discussed as ways to preserve her reproductive potential for the future, especially if she wishes to purse RRSO at an earlier age. These options might also provide an opportunity for preimplantation genetic testing of embryos for the BRCA mutation. After discussing the potential risks and benefits, the patient decided to delay RRSO and proceed with surveillance for ovarian cancer. She plans to reconsider her options surrounding fertility preservation in a few years if she still does not have biological children.

The majority of hereditary breast and ovarian cancers are due to mutations in two genes, BRCA1 and BRCA2. It is estimated that a BRCA1 mutation carries a 60% risk of breast cancer and a 40% risk of ovarian cancer, while the BRCA2 mutation carries a 50% risk of breast and 20% risk of ovarian cancer [3]. While hereditary forms of breast and ovarian cancer account for less than 10% of breast cancers and less than 15% of ovarian cancers, the earlier age of onset of cancer in these women and the treatments employed to prevent or treat these cancers often threaten future fertility. In particular, women who test positive for BRCA1/2 are provided increased surveillance (including mammograms, breast MRI, pelvic ultrasounds, and CA125 levels) and/or interventions to reduce the risk of breast and ovarian cancer. Risk-reducing surgeries include prophylactic mastectomy and bilateral salpingo-oophorectomy, which can reduce the risk of breast cancer by 90% and ovarian cancer by 80–90% [1, 4, 5]. While a risk-reducing salpingo-oophorectomy (RRSO) provides significant protection against cancer in BRCA1/2 carriers, this surgery also results in sterility. Therefore, young women who carry the mutation benefit from reproductive counseling and should be made aware of the options for fertility preservation and PGD.

Traditional management has been to encourage young women who are found to carry a BRCA1/2 mutation to undergo RRSO by age 35 or as soon as they complete their family [1, 2]. For women not willing to undergo surgery, surveillance with ultrasound and CA125 can be employed. Ovulation suppression with oral contraceptive use has also been shown to reduce the risk of ovarian cancer in BRCA carriers by 50% [6]. Thankfully, advances in assisted reproductive technology (ART) and fertility preservation now provide these women with additional options. Embryo or oocyte banking may be optimal for women who desire biologic children but do not currently have a partner or wish to prioritize an RRSO to reduce cancer risk (these options are described in Chap. 4 of this volume). By banking oocytes or undergoing

in vitro fertilization (IVF) and banking embryos, patients can undergo RRSO and then return to use the oocytes and/or embryos at a later date. Ovarian tissue cryopreservation for autologous transplantation at a later date is a third option for fertility preservation (see Chap. 5 in this volume), but this procedure is experimental and is not ideal for women who are BRCA carriers, as it would negate the benefits of RRSO. Ovarian tissue cryopreservation may become an option for BRCA carriers if laboratory techniques improve and allow us to isolate follicles from the cryopreserved ovarian tissue for growth in vitro to obtain mature oocytes to be used for ART.

Until recently, it had not been thought that there was an association between BRCA status and fertility. A large case-control study of BRCA carriers did not reveal an increased risk of infertility or the use of fertility medications in these women [7]. However, a recent cohort study of BRCA carriers undergoing ovarian stimulation for oocyte or embryo cryopreservation noted a higher prevalence of poor response in BRCA1 carriers (≤4 oocytes retrieved) [8]. Further investigation is needed to support this finding and help counsel these patients with regard to their fertility preservation options. Ovarian reserve testing, as was done in this case, may be appropriate to help guide decisions regarding fertility preservation in this population.

Further complicating the reproductive choices facing BRCA carriers is the decision to have a biologic child and risk transmission of the BRCA mutation. Preimplantation genetic diagnosis (PGD) is an option for BRCA carriers to minimize the risk of having offspring with the mutation. Studies have shown that a large percentage of women are not aware of the option of PGD and desire both more education regarding their reproductive options and assistance in decision-making [9]. In addition, the effects of RRSO go beyond reproductive concerns. A survey of BRCA carriers after RRSO revealed that women were very satisfied with their decision to undergo surgery and would recommend surgery to others; however, they also wished they had known more about the effect on the surgery on sexual function and impact of surgical menopause on cardiovascular and bone health [10]. Thus, for BRCA carriers, the choice of undergoing RRSO is complicated, with reproductive concerns being only one of many considerations.

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Case 8: Cervical Cancer in a Married Female

Case courtesy of Clarisa Gracia, M.D., M.S.C.E.

J.G. is a 32-year-old married female who had an abnormal pap smear on routine screening. Follow-up colposcopy was notable for small cell cervical cancer, and a cervical conization revealed invasive cancer. It was recommended that she undergo hysterectomy and bilateral salpingo-oophorectomy and lymph node dissection, followed by chemotherapy and pelvic radiotherapy. The patient had one daughter but expressed interest in having additional biologic children, and she was referred for consultation regarding her fertility preservation options. A patient navigator at the institution rapidly coordinated an appointment with a reproductive endocrinologist.

After extensive consultation with the reproductive endocrinologist, psychosocial counselor, and financial counselor, the patient elected to pursue ovarian stimulation and IVF for embryo banking. A nursing consultation was completed. The patient had been taking the combined birth control pill, and this was stopped. Her husband underwent semen analysis, which was normal. On the second day of her menstrual cycle, an ultrasound was performed, and hormone levels were measured to assess her ovarian reserve. Her FSH was 7.8 mIU/ml, estradiol was 45 pg/ml, and antral follicle count was 15. Ovarian stimulation was carried out using an antagonist protocol and recombinant FSH starting at 225 IU daily. Her response was brisk. When the lead follicle was 14 mm in size, daily cetrorelix was recommended. When the lead follicle was 18 mm in size, GnRH agonist (GnRHa) was administered for triggering oocyte maturation (given the risk of OHSS), and oocyte retrieval was performed 36 h later. A total of 10 oocytes were retrieved and were conventionally inseminated with her husband's sperm. Seven 2-pronuclear embryos were cryopreserved. The patient had no complications and did not experience OHSS. The time from initial fertility preservation consultation to oocyte retrieval was 18 days. The patient subsequently underwent surgery, chemotherapy, and radiotherapy as planned.

Two years after treatment, she continued to have no evidence of recurrence and wanted to use the embryos to have a biological child. She and her husband were referred to a reproductive surrogacy lawyer and identified a gestational carrier to carry the pregnancy. The carrier underwent a programmed frozen embryo cycle. Three embryos were thawed, and two were transferred to the carrier. One embryo successfully implanted, and the gestational carrier delivered a healthy baby boy at term.

This clinical scenario highlights several important points. Coordination of care through a patient navigator facilitated a rapid appointment and minimal delay in pursuing fertility preservation ([1]; and also see Chap. 13 in this volume). A team approach was utilized in this patient's care, with a variety of different providers providing unique services and perspectives to the patient and her husband. In particular, it is important that psychosocial counseling be provided to all patients.

GnRH antagonist cycles are often employed for ovarian stimulation in the setting of a cancer diagnosis to expedite the process of ovarian stimulation since long luteal phase leuprolide acetate protocols can delay oocyte retrieval. In addition, this case also demonstrates how GnRHa may be used during such protocols as an alternative to traditional hCG administration to simulate the natural midcycle luteinizing hormone (LH) surge. Studies have reported that GnRHa administration successfully induces final oocyte maturation and essentially eliminates the risk of OHSS [2, 3]. This technique is particularly convenient in cancer patients who are pursuing oocyte or embryo banking but whose response to stimulation may be unpredictable and in whom luteal support is not needed to sustain a pregnancy.

Finally, it is important to keep in mind that a gestational carrier is a possible option for women requiring hysterectomy to have a biological child in the future. It can be expensive to use an unrelated carrier, with known carriers less expensive. It is important to refer patients to surrogacy lawyers and agencies who can assist them in this process.

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Case 9: Young Married Male with Testicular Cancer

Case courtesy of Robert E. Brannigan, M.D.

A 30-year-old male business executive recently found a hard, painless lump involving the majority of his right testicle during a routine, monthly scrotal self-examination. His internist confirmed this finding upon physical examination, and the patient was referred for a scrotal ultrasound that revealed a heterogeneous, 4×3×3-cm testicular mass replacing nearly all of the normal right testicular tissue. The lesion was noted to be very suspicious for cancer. The patient was sent to a urologist for

evaluation. Serum tumor markers, including alpha fetoprotein, beta-hCG, and lactate dehydrogenase (LDH), were measured, revealing elevated alpha fetoprotein. Imaging studies were also ordered to provide tumor staging information. A chest x-ray revealed no evidence of pulmonary lesions, but a CT scan of the abdomen and pelvis showed significant, bulky, right retroperitoneal lymphadenopathy in the inter-aortocaval region, the landing zone for right testicular cancer metastases.

The patient reported that he was newly married, and he expressed a desire to have children in the near future. His urologist sent him for semen analysis, which showed normal ejaculate volume azoospermia. A second semen sample showed similar findings. The patient was counseled that there was another fertility preservation option available, "onco-TESE" (oncologic testicular sperm extraction), which could be performed on the left testicle at the time of the right orchiectomy. He was counseled that there was an approximately 50–60% likelihood of successful sperm extraction using this approach. The patient agreed to undergo onco-TESE. He had an uneventful right radical orchiectomy, and the operating microscope was then brought into the field, and a left micro-TESE procedure was performed. The majority of the seminiferous tubules within the left testicle were thin and relatively translucent, findings not suggestive of presence of active spermatogenesis. In the lateral aspect of the upper pole of the left testicle, several regions of full and opaque seminiferous tubules were found. Samples of this tissue were excised, and wet preparation slides were made. Upon inspection of the slides under a phase contrast microscope, 1–2 whole motile sperm per high power field were found. This tissue was cryopreserved for future use in the setting of IVF/ICSI.

The pathology from the right testicle orchiectomy specimen revealed a nonseminomatous, mixed germ cell tumor. The patient's postorchiectomy alpha fetoprotein remained elevated. Therefore, he received three cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy. Concurrently, he and his wife pursued IVF/ICSI. On their first IVF attempt, five oocytes were fertilized. Two embryos were transferred on day 5, yielding a singleton pregnancy. A healthy male offspring was born at 40 weeks gestational age by spontaneous vaginal delivery. At the time of his son's birth, the father's tumor markers had normalized, and his follow-up CT scan imaging showed no evidence of residual retroperitoneal lymphadenopathy.

This case brings to light several interesting points. First, impaired spermatogenesis is commonly found in men with various types of cancer, including testicular cancer, at the time of diagnosis [1–3]. Secondly, azoospermia at the time of sperm banking need not be an end point for fertility preservation efforts [4]. As is highlighted in this case, onco-TESE procedures can facilitate sperm cryopreservation, even in the absence of sperm in the ejaculate ([5]; see Chap. 3 in the volume for more information). Finally, some clinicians may presume that a male who is actively undergoing cancer treatment would not be interested in pursuing efforts for parenthood. As is clearly demonstrated by this case, some patients *do* indeed have such paternal aspirations. This patient reported that the prospect of becoming a father was a significant motivating factor to him during his ongoing cancer therapy. After his son was born, he stated, "I feel like I am moving ahead with my life, not living life on the sidelines."

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Case 10: Breast Cancer in a Married Female

Case courtesy of Clarisa Gracia, M.D., M.S.C.E.

M.B. is a 34-year-old married, gravida 0 female who noted a right breast lump. Biopsy and imaging revealed a 2-cm estrogen- and progesterone-sensitive invasive ductal carcinoma of the breast. Sentinel lymph node biopsy was negative. After consultation with a breast oncologist, her planned treatment included right mastectomy and reconstruction followed by multi-agent chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel; radiotherapy to the right breast; and tamoxifen for 5 years. She was referred for consultation regarding her options for having children in the future. During the consultation with the reproductive endocrinologist, a number of topics were reviewed with the patient and her husband. The risk of amenorrhea and infertility were discussed. The risks and benefits of several fertility-preserving techniques were reviewed, including ovarian stimulation with embryo or oocyte cryopreservation, IVM with embryo or oocyte cryopreservation, ovarian tissue cryopreservation, and the use of GnRHa to potentially protect the ovaries during chemotherapy. The options of using an oocyte donor or adopting a baby after cancer therapy were also discussed with the couple. Given that the patient was married, she elected to bank embryos. She applied for financial assistance through Fertile Hope and qualified for a discounted IVF cycle. Her last menstrual period occurred 2 weeks prior, and ultrasound and blood work revealed evidence of recent ovulation. In order to expedite the onset of her menstrual cycle, cetrorelix 3-mg injection was administered. A menstrual cycle began 3 days later, and ovarian stimulation was carried out using a combination of letrozole and recombinant FSH. GnRH antagonist was initiated when the largest follicle reached 14 mm in diameter. After 10 days of ovarian stimulation, the peak estradiol level was 329 pg/ml, and she had a total of 15 follicles greater than 10 mm in diameter, with the dominant follicle measuring 20 mm. The final maturation of the oocyte was triggered with hCG, and oocyte retrieval was performed 36 h later. A total of 10 oocytes were retrieved, and they were conventionally inseminated, as her husband's semen parameters were within normal limits.

A total of seven embryos were cryopreserved at the 2-pronuclear stage. Three years after her initial consultation, the patient reported that she is divorced and has no plans on pursuing pregnancy at this time.

Unfortunately, the majority of data regarding the reproductive risks of cancer therapies in women relies on menstrual status, which is not equivalent to fertility (see Chap. 1 in this volume for more information on this topic). Nonetheless, these data are used to some extent for counseling women about the reproductive risks of therapy. For example, according to a large prospective study of menstrual function after multi-agent chemotherapy for breast cancer, one could inform the above patient that she is likely to resume menses after therapy [1]. Indeed, 90% of women less than 35 years of age will resume menses after chemotherapy for breast cancer. However, the risk of infertility may be high—despite the return of menses—since ovarian reserve will be impaired from treatment. The patient may therefore be advised to delay pregnancy for 5 years in order to complete tamoxifen therapy.

In this case, the patient elected to cryopreserve embryos. Because she has an estrogen-sensitive tumor, there is a theoretical concern that tumor cells may be stimulated by the supraphysiologic estrogen levels associated with ovarian stimulation (discussed further in Chap. 4 of this volume). Several alternative stimulation protocols have been developed to suppress estrogen levels during stimulation. These protocols use recombinant FSH in combination with aromatase inhibitors like letrozole or selective estrogen receptor modulators such as tamoxifen. While the available data are limited, early studies suggest that ovarian stimulation with letrozole-FSH is unlikely to cause a substantially increased risk of cancer recurrence [2, 3].

Finally, it is important to recognize that cancer patients may delay childbearing for years after banking embryos. Therefore, separation and divorce of couples who created the embryos together is a real possibility. It is critical that the disposition of embryos should be discussed at length with the couple, and it should be made clear that consent of both parties is generally required for the use of the embryos (this topic is discussed in Chap. 9 of this volume). In addition, psychosocial counseling should always be provided to patients pursuing fertility preservation services, and consideration should be given to cryopreservation of gametes rather than embryos if appropriate.

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Case 11: Leukemia in a Single Young Adult Female

Case courtesy of Clarisa Gracia, M.D., M.S.C.E.

K.B. is a 23-year-old female who was diagnosed with ALL after she presented to her local physician's office for fatigue and bruising. Her hemoglobin was noted to be 6 g/dl, and her platelets were 20 cells/mm^3. She was admitted to the hospital for further evaluation and treatment. She received transfusions of red blood cells and platelets, and a bone marrow biopsy was performed that revealed an aggressive form of leukemia associated with a poor prognosis. The oncology team recommended immediate treatment with chemotherapy followed by hematopoietic SCT in the near future. The patient was counseled about the risks of therapy, including the high risk of infertility and premature ovarian failure after SCT. Given the recommended timing of treatment, ovarian stimulation was not possible. Ovarian tissue cryopreservation was offered, but it was explained that future transplantation of ovarian tissue would not be recommended given the risk of reseeding leukemic cells. The patient and her family were not interested in pursuing this experimental procedure and wanted to focus instead on treating her disease. Given the risks of irregular heavy menstrual bleeding during therapy, it was recommended that she receive GnRHa therapy for menstrual suppression. The controversial data regarding the ability of this medication to protect the ovaries from gonadotoxic therapy was discussed with the patient. She elected to be treated with GnRHa therapy for 6 months during therapy and 2 years after SCT continued to be amenorrheic consistent with acute ovarian failure.

Hematologic malignancies can present special challenges to fertility preservation. Because most patients with acute leukemia are quite ill with impaired blood counts at initial presentation, these patients are often hospitalized and treated with chemotherapy shortly after the diagnosis is made. Therefore, patients with acute leukemia are usually not appropriate candidates for postponing cancer therapies in order to undergo ovarian stimulation for embryo or mature oocyte banking. While ovarian tissue banking generally does not delay cancer therapy, patients may not be good candidates for undergoing laparoscopic surgery for ovarian tissue acquisition. In addition, autologous transplantation of ovarian tissue after cancer therapy is not recommended in patients with leukemia since there is a risk of reintroduction of cancer cells [1]. Hence, fertility preservation options prior to treatment are limited for this population.

The use of GnRH analogues during chemotherapy to protect the ovaries from damage is controversial (see Chap. 7 in this volume for an in-depth discussion). Several small, short-term studies suggest that menstrual function is more likely to be preserved in women who receive GnRHa during treatment compared with those who do not [2, 3]. In addition, there are some data to suggest that pregnancy rates are higher following suppression with GnRHa [2, 4]. However, studies are limited by small sample sizes, inappropriate control groups, inadequate assessment of clinically meaningful outcomes such as time to pregnancy, and limited duration of follow-up. No large, long-term randomized controlled trials have been conducted to date, and a recent meta-analysis concluded that there is still insufficient evidence

that GnRHa treatment preserves future fertility [4]. Nonetheless, GnRHa treatment has been shown to reduce menstrual bleeding during cancer therapy and may be particularly useful for that purpose in the hematopoietic SCT population [5].

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Case 12: Breast Cancer During Pregnancy

Case courtesy of Eileen Wang, M.D.

C.C. is a 36-year-old gravida 2 para 1 who presented at 9 weeks of gestation with a self-identified lump in her right breast. An assessment in her obstetrician's office suggested that the lump may be palpable milk ducts. Two months later, the area was still noticeable, and an ultrasound and mammogram were ordered for further evaluation. Imaging revealed a solid mass concerning for malignancy. A breast biopsy with axillary node fine needle aspiration (FNA) was recommended and revealed ER-positive/PR-positive/Her2-negative adenocarcinoma of the breast with positive FNA. She was diagnosed with stage II breast cancer. Standard treatment for this type of breast cancer in a nonpregnant female generally includes surgery, multi-agent chemotherapy, and radiotherapy, followed by hormonal therapy with tamoxifen.

The patient was referred for consultation with maternal-fetal medicine (MFM) to discuss management of the pregnancy in the setting of a new diagnosis of breast cancer. The impact of the pregnancy on the cancer prognosis and the impact of the therapy (surgery, chemotherapy) on the fetus were discussed. The option of pregnancy termination was discussed as well, but the patient desired to continue the pregnancy. She also met with the medical and surgical oncology teams to determine the plan of treatment with respect to surgery, chemotherapy, and timing of delivery. After obtaining a baseline echocardiogram (given the cardiac risks of doxorubicin), the patient underwent doxorubicin and cyclophosphamide chemotherapy during the third trimester of pregnancy. Steroids were administered for fetal health in case of a preterm delivery, and labor was induced at 36 weeks gestation, 3 weeks after her last chemotherapy course. She delivered a healthy girl weighing 5 lbs 10 oz. Paclitaxel

chemotherapy was planned after delivery. Long-term childbearing issues were discussed with the patient, who subsequently declined long-term contraception.

Given that breast cancer is the most common cancer identified during pregnancy, any persistent breast mass should be evaluated in a timely fashion. Ultrasound and mammogram (with very low radiation exposure to the fetus, especially with abdominal shielding) are appropriate imaging techniques. In addition, in cases of suspicious masses, patients should be referred to a surgeon. Pregnancy should NOT be a contraindication to biopsy.

When malignancy is detected, a multidisciplinary approach to cancer treatment and pregnancy management must occur (see Chap. 10 for an in-depth discussion of pregnancy in the context of oncofertility). The patient should know her own risks, often best provided by her oncologists, while the perinatologist can best discuss the likely pregnancy outcome and the option of termination if applicable. Together, the plan for timing of treatment in conjunction with timing of delivery can be made to maximize benefits and minimize risks for both the patient and her child [1, 2, 3].

A baseline echocardiogram prior to anthracycline chemotherapy (in this case, doxorubicin) is important in the context of future childbearing. The patient will need follow-up for cancer recurrence, but she should also undergo evaluation of her cardiac status, as anthracycline exposure can impact long-term cardiac function and make the patient more vulnerable to the cardiac changes of a future pregnancy. Awareness of the increased risk of cardiac failure after exposure to anthracycline chemotherapy may sway her from pursuing pregnancy in the future [4, 5].

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Case 13: Pregnancy in a Hodgkin Lymphoma Survivor

Case courtesy of Eileen Wang, M.D.

S.C. is a 40-year-old female with a history of Hodgkin lymphoma as a teenager. She was treated with mediastinal radiation and doxorubicin chemotherapy at that time. She experienced no long-term complications from therapy. In her 30s, she

exercised regularly and was an avid mountain climber and traveler. She married her husband in her late 30s, and she became less physically active. She conceived without assistance at age 40. During the first trimester of pregnancy, she began complaining of increasing fatigue, shortness of breath, and swelling of her legs. Given her previous exposure to cardiotoxic therapies, an echocardiogram was ordered. The echocardiogram demonstrated extremely concerning restrictive pericarditis/cardiomyopathy. She was counseled extensively by a cardiologist and perinatologist about the risks of pregnancy in the setting of severe cardiomyopathy. Her risk of heart failure and death due to worsening cardiomyopathy during pregnancy was discussed, and she elected to terminate the pregnancy.

This case illustrates the long-term cardiac risks associated with mediastinal radiotherapy and doxorubicin exposure for Hodgkin lymphoma. It is important to recognize that the physiologic changes in pregnancy increase workload on the heart due to increased circulating volume and cardiac output (see Chap. 10 in this volume for further discussion). Pregnancy may precipitate heart failure and significantly impact maternal and the fetal health. Women with a history of Hodgkin lymphoma and exposure to both radiation and chemotherapy with doxorubicin have a further increased cardiac risk, with cardiac dysfunction and risk of restrictive myocardial or pericardial disease. Medical treatment, hospitalization, and in some cases preterm delivery may be necessary in patients with cardiomyopathy during pregnancy. Ideally, before achieving pregnancy, patients should be evaluated and counseled regarding the risks of pregnancy. The American Society of Clinical Oncology (ASCO) recommends echocardiograms, multi-gated acquisition (MUGA) scans, or radionuclide angiography for assessment of left ventricular function prior to or during pregnancy. In addition, it is recommended by the American College of Radiology that asymptomatic Hodgkin lymphoma survivors with exposure to mediastinal radiation undergo periodic exercise tolerance testing and echocardiograms. When taking a patient's history, it is also important to determine the New York Heart Association (NYHA) heart failure classification, as it is predictive of outcomes during pregnancy [1, 2, 3].

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Case 14: Leukemia in a Prepubertal Female

Case courtesy of Laxmi A. Kondapalli, M.D., M.S.

R.M. is an 11-year-old female with recurrent pre-B cell ALL. She presented with her parents for consultation regarding fertility preservation and to discuss the implications of her cancer treatment on ovarian function. She was initially diagnosed at the age of 3 and underwent treatment with cyclophosphamide (2 g/m^2), cytarabine, doxorubicin, peg-asparaginase, vincristine, 6-MP, methotrexate, and dexamethasone over the course of 2 years. She was in remission for 5 years until she developed fevers, fatigue, and abdominal pain. The patient was subsequently diagnosed with relapse and immediately initiated treatment on a study protocol. Her regimen included vincristine, doxorubicin, cytarabine, and methotrexate for 6 weeks.

The patient has an older brother who recently underwent a bone marrow biopsy for possible donation. If he is an appropriate match, the patient will undergo total body irradiation (TBI) and bone marrow transplant (BMT). If he is not a match, she will continue the chemotherapy regimen for a total of 2 years. Her consolidation phase will include high-dose cyclophosphamide.

This case raises a number of fundamental issues to consider when caring for young cancer patients. First, for patients who are in relapse, a discussion regarding ovarian reserve must involve an assessment of past treatment effects and consideration of future treatment effects. For this patient, given her young age at initial diagnosis and treatment, as well as the chemotherapeutic regimen used at that time, it is likely that she has maintained most of her ovarian reserve. Most of her initial treatments are considered to be on the lower spectrum of risk to permanent ovarian failure, except for cyclophosphamide (see Chap. 1 for more information on this topic). Although she did receive cyclophosphamide at age 3, it was a low total dose of 2 g/m^2. With her recent relapse, she will receive a higher dose of this agent with the possibility of TBI and SCT. Given this multimodality therapy, the patient is at significant risk of premature menopause and ovarian failure (upward of 90% risk) [1]. At her consultation, the effect of chemotherapy, particularly alkylating agents, on ovarian reserve, infertility risk, and premature ovarian failure were discussed. In the setting of premature ovarian failure, it is also important to discuss the long-term effects of hypoestrogenism, including the increased risk of osteoporosis, cardiovascular disease, vasomotor symptoms, and genitourinary atrophy, and the potential need for hormone replacement therapy.

With regard to fertility preservation, given the patient's prepubertal status, her options are limited. Observation, ovarian tissue cryopreservation, use of third-party reproduction in the future (donor oocytes or embryos from known or anonymous donors), and adoption were discussed, in addition to ovarian tissue cryopreservation and the possible use of thawed tissue for in vitro follicle maturation (see Chaps. 5 and 6 in this volume for more information about these options). Although all the reported births from ovarian tissue cryopreservation are from subsequent transplantation of the thawed tissue, transplantation is not recommended due to potential risk of reintroduction of malignant cells in the setting of ALL. The experimental nature

of ovarian tissue cryopreservation was stressed, and that no human live births have been achieved with in vitro follicle maturation, although there are promising data emerging nationally and the technology will likely improve by the time the patient is ready to use her banked ovarian tissue. If the patient's brother is a match and she undergoes TBI and BMT, she is at significant risk of premature ovarian failure, and it would be reasonable to remove a whole ovary for cryopreservation in this setting. Her blood count recovery post-chemotherapy and before the surgical procedure to remove the tissue also need to be considered.

Finally, there is a possibility that the patient may experience delayed or absent puberty due to premature ovarian failure. For prepubertal girls at risk of permanent premature ovarian failure, parents should be aware that physiologic doses of hormone therapy should be administered to ensure optimal development of secondary sex characteristics and adult stature. It is important to monitor pubertal development closely after 10 years of age with Tanner staging and to continue to follow development closely throughout treatment [2]. After menarche, early loss of ovarian function is associated with menopausal symptoms and long-term health risks including cardiovascular disease and osteoporosis. While the optimal method of hormone replacement therapy is not clear, hormone therapy is recommended since it effectively treats menopausal symptoms and improves bone mineral density [3, 4].

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