Preserving future fertility of young women with cancer

H. Irene Su, MD MSCE

Introduction

In the United States, more than 60,000 girls and adolescent and young adult women younger than age 39 are diagnosed with cancer each year.[1] Because long-term survival is high, 82% at 5 years, there are nearly 600,000 female cancer survivors who are currently of reproductive age younger than age 40.[1,2] These individuals undergo a range of therapies for cancer cure, and might be at risk of treatment-related infertility and other reproductive health late effects.

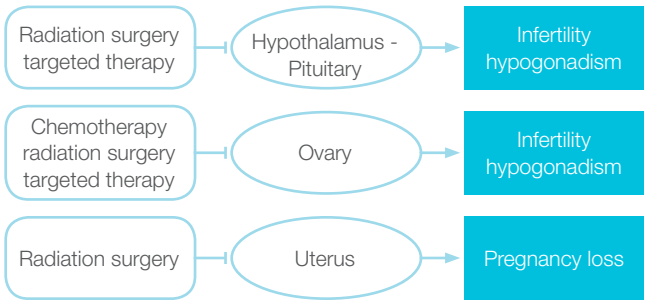
Future fertility is important to young female survivors, and infertility is preventable. Hence, major professional organizations including the American Society of Clinical Oncology (ASCO), American Society of Reproductive Medicine, American Academy of Pediatrics and the National Comprehensive Cancer Network recommend that healthcare providers discuss the possibility of infertility with patients who will undergo cancer treatment before or during their reproductive years.[3-6] Clinical guidelines also advise addressing fertility for cancer survivors who have completed treatment, as fertility concerns span the cancer continuum, from diagnosis through survivorship.[6]

Yet, there remains a significant care gap in high-quality fertility care for young cancer survivors. At cancer diagnosis, the national average for fertility care is 40-50%, with a low of 6%.[7] It is critical to improve knowledge and awareness of fertility preservation among clinical providers for children and young adults with cancer. What that in mind, this article discusses cancer treatment in females, known and unknown risks to fertility, strategies for fertility preservation, and common barriers to implementation of fertility care.

Fertility risks of cancer treatments

Chemotherapy, radiation, surgery and targeted therapy pose differential threats to fertility by disrupting the hypothalamic-pituitary-ovarian (HPO) axis, incurring toxicity to oocytes and supporting cells and impairing uterine function (Figure). Ovarian follicle development and generation of a mature oocyte requires an intact HPO axis. Surgery and radiation to the brain can disrupt this axis. Cumulative cranial radiation doses greater than 30 Gray (Gy) results in follicle-stimulating hormone/luteinizing hormone (FSH/LH) deficiency. This is also known as hypogonadotropic hypogonadism, and it manifests clinically as both amenorrhea and infertility.[8,9]

Figure: Cancer therapies incur female fertility risks



Fortunately, it is possible to overcome infertility with exogenous gonadotropins. This is because ovarian reserve, or the finite pool of oocytes in a female, is not disturbed by cranial radiation or surgery. Hysterectomy or bilateral oophorectomy will limit reproductive options of young survivors. However, unilateral oophorectomy has only a modest effect on timing of menopause, so is likely of limited reproductive risk.[10] With an intact ovary, a young woman may undergo gestational surrogacy with her autologous oocytes.

Uterine radiation, ovarian radiation and alkylating chemotherapy are known risk factors for infertility, as these treatments decrease or eliminate the pool of remaining oocytes in an individual. The risks are dependent on cumulative dose and age at treatment. The younger the female, the larger the ovarian reserve. This means gonadotoxic cancer treatment would pose less of a risk of infertility in a younger woman compared with an older woman. For example, a dose of 20 Gy or greater is estimated to cause ovarian insufficiency in infants. However, threshold doses that result in ovarian insufficiency for older girls and young women are progressively lower.[11]

The main known risk factors for gonadotoxicity are pelvic radiation and alkylating chemotherapy, a class of chemotherapy that includes drugs such as cyclophosphamide and procarbazine. The general risk of infertility in the United States is around 1 in 10 couples. More than 5 Gy radiation to the uterus increases that risk more than twofold.[12] For alkylating

chemotherapy, there is a formula to combine cumulative doses of different drugs in this class into a cyclophosphamide equivalent dose (CED). In general, the higher the alkylating dose, the higher the risk of infertility. For example, the highest tertile in alkylating chemotherapy exposure in the Childhood Cancer Survivor Study resulted in a 1.5-fold (95% CI 1.1-2.0) increased risk of infertility in girls, compared with no alkylating chemotherapy exposure.[12] To date, there is no well-validated threshold for risk of infertility based on the CED.[13-15]

There is a great deal of clinically relevant information on infertility risk that would help patients. However, most of it remains unknown because of a lack of high-quality translational and clinical research on reproductive risks. Beyond alkylating chemotherapy and radiation, little is known about whether additional chemotherapy given concurrently or in sequence might negatively affect ovarian reserve.

As novel targeted cancer therapies continue to emerge in the era of precision medicine, human data on associated reproductive risks are extremely limited. Preclinical laboratory data show expression of targets in reproductive organs, and animal data show abnormal ovarian follicular development, decreased ovarian and uterine weights and nearly uniform teratogenicity.[16-20] As these new drugs move to phase III trials, if not sooner, it is important to advocate for appropriate studies to quantify their reproductive risks.

Fertility preservation strategies

Current standard of care methods for fertility preservation include controlled ovarian stimulation (COS) with embryo or oocyte banking. Additionally, ovarian transposition out of the radiation field and gonadal shielding help minimize radiation exposure to ovaries.[3] Recent ASCO clinical guidelines for fertility preservation delineate gonadotropin-releasing hormone (GnRH) agonist use for ovarian suppression during chemotherapy as a potential fertility preservation method to offer young women with breast cancer, if more proven methods such as oocyte or embryo cryopreservation are not feasible.[3] Ovarian tissue freezing and in vitro maturation of oocytes or ovarian follicles are currently considered experimental.

COS uses injectable gonadotropins (FSH and LH) to support growth of multiple ovarian follicles over approximately two weeks, culminating in oocyte retrieval that is most commonly transvaginal. The premise of COS is that females develop multiple ovarian follicles to the antral stage in waves. In each natural menstrual cycle, the lead of these antral follicle responds to a finite amount of FSH from the pituitary to mature and ovulate, and the remaining antral follicles undergo atresia. In COS, supraphysiologic levels of FSH and LH are administered to “rescue” some of the antral follicles otherwise destined for atresia. Once retrieved, mature oocytes may be frozen or fertilized and cultured to embryos prior to freezing.

After thaw, frozen oocytes exhibit lower survival than frozen embryos, although an embryo derived from a frozen oocyte appears to have similar fertility potential to an embryo derived from a fresh oocyte.[21] For example, if fertilization of mature oocytes is at least 67%, and development of blastocysts is 50% of fertilized oocytes, then 10 oocytes undergoing fertilization will yield three to four blastocyst embryos to freeze. In vitrification (flash-freezing) protocols, more than 95% of blastocysts survive the thaw, yielding a final three to four blastocysts to transfer.

In comparison, if the thaw rate of frozen oocytes is 80 to 90%,[21,22] then the same 10 oocytes that are initially frozen would yield eight thawed oocytes, and subsequently two to three blastocysts, given the same attrition with fertilization and embryo culture. The live birth rate of each transferred blastocyst is dependent on oocyte age. Importantly, the survival, implantation and live birth rates of oocytes, embryos and embryo transfers vary considerably by clinic. Fortunately, most assisted reproductive technology centers in the United States report their center-specific outcomes through the Centers for Disease Control and Prevention and the Society for Assisted Reproductive Technology.

Multiple advances in COS for fertility preservation in cancer patients have improved safety and minimized delay to start of cancer treatment. First, the ability to begin COS on any day of a menstrual cycle decreases the time to start cancer treatment.[23-26] Compared with follicular phase starts for COS, luteal phase starts appear to take one to two days longer for COS but result in similar oocyte and embryo numbers while minimizing delays to start of cancer treatment. Second, some studies have reported consecutive COS cycles during which a second cycle is begun within a few days following the first oocyte retrieval. This approach results in two stimulations within one menstrual cycle to increase the number of oocytes retrieved within the same menstrual cycle.[27-29] Third, aromatase-inhibitor- or tamoxifen-based COS protocols are commonly used to reduce estradiol exposure in cancer patients with estrogen-sensitive tumors with early evidence of safety.[30-32] There is little data on risk of recurrence following tamoxifen plus gonadotropin COS in breast cancer patients, but a randomized controlled trial is under way (NTR4108). Fourth, use of GnRH agonists to induce ovulation greatly reduces the risk of ovarian

hyperstimulation syndrome, rendering COS safer.[33] Fifth, case reports suggest it is possible to retrieve mature oocytes through COS in premenarchal girls who have initiated puberty.[34] Of note, there are also mixed reports regarding whether COS immediately following a termination of pregnancy can result in retrieval of mature oocytes.[35,36]

Though limited in sample size (28 to 131 women), reports on use of frozen oocytes and embryos found between 19 and 43% of women who froze gametes or embryos returned to use them, and ongoing pregnancy or live birth ranges from 25 to 50% per patient.[37-41] It is not clear why more survivors have not returned, though possible reasons might include no loss of fertility, cancer-related considerations such as relapse, lack of prolonged follow-up or psychosocial concerns such as worries about health during pregnancy or financial burdens after cancer.[12,42]

Ovarian tissue freezing involves partial or complete removal of an ovary and cryopreservation of the ovarian cortex. Currently, the utility of this experimental method is for retransplantation. Some women might conceive spontaneously after retransplantation, but around 40% still require further assisted reproductive technology.[43] The most frequent application of this method is in prepubertal children, women whose treatment timelines do not allow for COS and women with concerns about elevated estradiol levels during COS. To date, there are more than 86 births from retransplantation of frozen ovarian tissue, one from a postpubertal but premenarchal girl.[44-47] There are no reported pregnancies or live births from transplantation of ovarian tissue frozen during prepubertal years. Most transplants are orthotopic, with ovarian tissue sewn back into the ovarian fossa. However, there is a reported ongoing pregnancy from heterotopic transplantation into the abdominal wall.46 Safety considerations include the risk of cancer cells in ovarian tissue in cases of leukemia or ovarian cancer. Some work now focuses on using histology or molecular markers to decrease the risk of reintroducing cancer cells.[48]

In vitro maturation (IVM) is the retrieval of oocytes with minimal to no reliance on COS. For women with cancer, the process requires little or no ovarian stimulation, takes less time to oocyte retrieval and facilitates an earlier start of cancer therapy. Once retrieved, oocytes undergo maturation in vitro. Mature oocytes may similarly undergo freezing or fertilization followed by embryo freezing. Compared with standard COS, IVM yields fewer oocytes and embryos, and implantation rates are exceedingly low.[49,50] Hence, IVM remains an experimental fertility preservation method.

Identifying and overcoming barriers

Understanding fertility risk is important to young survivors, as treatment-related infertility is preventable. However, the evidence-based practice of fertility care prior to cancer treatment still has limited uptake. In 2017-2018, Connecticut, Delaware and Maryland have passed mandates for insurance coverage of fertility preservation for iatrogenic infertility risk. However, single-care settings continue to report barriers to fertility preservation that leave a gap in care. Examples include inadequate recognition of reproductive health needs by both patients and providers,[51,52] confusion regarding whether oncology providers or fertility providers are the main source of fertility counseling,[53-56] absence of referral pathways between oncology and reproductive services,[57-59] lack of access to fertility care programs,[60] and financial barriers. These multilevel barriers pose opportunities for multicomponent strategies that implement fertility care more systematically across care settings.

Conclusion

Sound strategies for fertility preservation in cancer are available but underutilized. Effective technology is only part of the equation. It is also necessary for oncology practice to include equitable and systematic implementation of fertility care to anticipate and improve the reproductive future of young cancer patients.

About the author

Dr. H. Irene Su is a reproductive endocrinologist and epidemiologist at the University of California, San Diego. She is an associate professor of Obstetrics, Gynecology and Reproductive Sciences and the director of the Fertility Preservation Program at UC San Diego Health. Dr. Su's research focuses on improving reproductive health in young female cancer survivors, and her work includes a collaboration with the Ferring Pharmaceuticals Heart Beat Program to follow long-term reproductive outcomes after fertility preservation. An exciting project in her group focuses on using anti-Mullerian hormone and other endocrine biomarkers of ovarian reserve to estimate the post-treatment reproductive window in young adult cancer survivors.

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References

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973-2014 varying) - Linked To County Attributes - Total U.S., 1969-2015 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2017, based on the November 2016 submission.
2. American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2016-2017. Atlanta: American Cancer Society; 2016.
3. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(19):1994-2001.
4. Practice committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2013;100(5):1214-1223.
5. Fallat ME, Hutter J, American Academy of Pediatrics Committee on Bioethics, American Academy of Pediatrics Section on Hematology/Oncology, American Academy of Pediatrics Section on Surgery. Preservation of fertility in pediatric and adolescent patients with cancer. Pediatrics. 2008;121(5):e1461-1469.
6. Adolescent and Young Adult Oncology, NCCN Clinical Practice Guidelines in Oncology. 2017. https://www.nccn.org/professionals/physician_gls/pdf/aya.pdf. Accessed June 20, 2018.
7. Neuss MN, Malin JL, Chan S, et al. Measuring the improving quality of outpatient care in medical oncology practices in the United States. J Clin Oncol. 2013;31(11):1471-1477.
8. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med. 1993;328(2):87-94.
9. Crowne E, Gleeson H, Benghiat H, Sanghera P, Toogood A. Effect of cancer treatment on hypothalamic-pituitary function. Lancet Diabetes Endocrinol. 2015;3(7):568-576.
10. Bjelland EK, Wilkosz P, Tanbo TG, Eskild A. Is unilateral oophorectomy associated with age at menopause? A population study (the HUNT2 Survey). Hum Reprod. 2014;29(4):835-841.
11. Anderson RA, Mitchell RT, Kelsey TW, Spears N, Telfer EE, Wallace WH. Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. Lancet Diabetes Endocrinol. 2015;3(7):556-567.
12. Barton SE, Najita JS, Ginsburg ES, et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2013;14(9):873-881.
13. Chow EJ, Stratton KL, Leisenring WM, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2016;17(5):567-576.
14. Levine JM, Whitton JA, Ginsberg JP, et al. Nonsurgical premature menopause and reproductive implications in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer. 2018;124(5):1044-1052.
15. Chemaitilly W, Li Z, Krasin MJ, et al. Premature ovarian insufficiency in childhood cancer survivors: a report from the St. Jude Lifetime Cohort. J Clin Endocrinol Metab. 2017;102(7):2242-2250.
16. The Human Protein Atlas Web site. www.proteinatlas.org. Accessed October 1, 2017.
17. Okano Y, Satoh T, Horiguchi K, et al. Nivolumab-induced hypophysitis in a patient with advanced malignant melanoma. Endocr J. 2016;63(10):905-912.
18. Seshadri T, Seymour JF, McArthur GA. Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. N Engl J Med. 2004;351(20):2134-2135.
19. Mariani S, Basciani S, Fabbri A, et al. Severe oligozoospermia in a young man with chronic myeloid leukemia on long-term treatment with imatinib started before puberty. Fertil Steril. 2011;95(3):1120.e15-1120e.17.
20. Strasswimmer J, Latimer B, Ory S. Amenorrhea secondary to a vismodegib-induced blockade of follicle-stimulating hormone-receptor activation. Fertil Steril. 2014;102(2):555-557.
21. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod. 2010;25(9):2239-2246.
22. Practice committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99(1):37-43.
23. Boots CE, Meister M, Cooper AR, Hardi A, Jungheim ES. Ovarian stimulation in the luteal phase: systematic review and meta-analysis. J Assist Reprod Genet. 2016;33(8):971-980.
24. Martínez F, Clua E, Devesa M, et al. Comparison of starting ovarian stimulation on day 2 versus day 15 of the menstrual cycle in the same oocyte donor and pregnancy rates among the corresponding recipients of vitrified oocytes. Fertil Steril. 2014;102(5):1307-1311.
25. von Wolff M, Thaler CJ, Frambach T, et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril. 2009;92(4):1360-1365.
26. Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100(6):1673-1680.
27. Turan V, Bedoschi G, Moy F, Oktay K. Safety and feasibility of performing two consecutive ovarian stimulation cycles with the use of letrozole-gonadotropin protocol for fertility preservation in breast cancer patients. Fertil Steril. 2013;100(6):1681.e1-1685.e1.
28. Tsampras N, Gould D, Fitzgerald CT. Double ovarian stimulation (DuoStim) protocol for fertility preservation in female oncology patients. Hum Fertil (Camb). 2017;20(4):248-253.

29. Kuang Y, Chen Q, Hong Q, et al. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). Reprod Biomed Online. 2014;29(6):684-691.

30. Kim J, Turan V, Oktay K. Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer. J Clin Endocrinol Metab. 2016;101(4):1364-1371.

31. Chien AJ, Chambers J, McAuley F, et al. Erratum to: Fertility preservation with ovarian stimulation and time to treatment in women with stage II-III breast cancer receiving neoadjuvant therapy. Breast Cancer Res Treat. 2017;165(1):161.

32. Chien AJ, Chambers J, McAuley F, et al. Fertility preservation with ovarian stimulation and time to treatment in women with stage II-III breast cancer receiving neoadjuvant therapy. Breast Cancer Res Treat. 2017;165(1):151-159.

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):944-951.

34. Reichman DE, Davis OK, Zaninovic N, Rosenwaks Z, Goldschlag DE. Fertility preservation using controlled ovarian hyperstimulation and oocyte cryopreservation in a premenarcheal female with myelodysplastic syndrome. Fertil Steril. 2012;98(5):1225-1228.

35. Cohade C, Moreau J, Gatimel N, Gladieff L, Parinaud J, Leandri R. Follicular growth but absence of oocyte and cumulus maturation during ovarian stimulation in the days following surgical abortion: a case report. Gynecol Endocrinol. 2017;33(9):680-681.

36. Goeckenjan M, Rosner S, Toth B, Strowitzki T, Germeyer A. Successful controlled ovarian stimulation despite elevated hCG levels after first-trimester abortion in the context of fertility preservation. Gynecol Endocrinol. 2013;29(11):960-962.

37. Oktay K, Turan V, Bedoschi G, Pacheco FS, Moy F. Fertility preservation success subsequent to concurrent aromatase inhibitor treatment and ovarian stimulation in women with breast cancer. J Clin Oncol. 2015;33(22):2424-2429.

38. Sabatini ME, Wolkovich AM, Macklin EA, Wright DL, Souter I, Toth TL. Pronuclear embryo cryopreservation experience: outcomes for reducing the risk of ovarian hyperstimulation syndrome and for fertility preservation in cancer patients. J Assist Reprod Genet. 2011;28(3):279-284.

39. Courbiere B, Decanter C, Bringer-Deutsch S, et al; for French Study Group for Ovarian and Testicular Cryopreservation (GRECOT). Emergency IVF for embryo freezing to preserve female fertility: a French multicentre cohort study. Hum Reprod. 2013;28(9):2381-2388.

40. Dolmans MM, Hollanders de Ouderaen S, Demylle D, Pirard C. Utilization rates and results of long-term embryo cryopreservation before gonadotoxic treatment. J Assist Reprod Genet. 2015;32(8):1233-1237.

41. Robertson AD, Missmer SA, Ginsburg ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. Fertil Steril. 2011;95(2):588-591.

42. Gorman JR, Su HI, Roberts SC, Dominick SA, Malcarne VL. Experiencing reproductive concerns as a female cancer survivor is associated with depression. Cancer. 2015;121(6):935-942.

43. Gellert SE, Pors SE, Kristensen SG, Bay-Bjorn AM, Ernst E, Yding Andersen C. Transplantation of frozen-thawed ovarian tissue: an update on worldwide activity published in peer-reviewed papers and on the Danish cohort. J Assist Reprod Genet. 2018;35(4):561-570.

44. Jensen AK, Macklon KT, Fedder J, Ernst E, Humaidan P, Andersen CY. 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. J Assist Reprod Genet. 2017;34(3):325-336.

45. Donnez J, Dolmans MM, Diaz C, Pellicer A. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. Fertil Steril. 2015;104(5):1097-1098.

46. Stern CJ, Gook D, Hale LG, et al. First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy. Hum Reprod. 2013;28(11):2996-2999.

47. Demeestere I, Simon P, Dedeken L, et al. Live birth after autograft of ovarian tissue cryopreserved during childhood. Hum Reprod. 2015;30(9):2107-2109.

48. Shapira M, Raanani H, Barshack I, et al. First delivery in a leukemia survivor after transplantation of cryopreserved ovarian tissue, evaluated for leukemia cells contamination. Fertil Steril. 2018;109(1):48-53.

49. Kedem A, Yerushalmi GM, Brengauz M, et al. Outcome of immature oocytes collection of 119 cancer patients during ovarian tissue harvesting for fertility preservation. J Assist Reprod Genet. 2018;35(5):851-856.

50. Creux H, Monnier P, Son WY, Buckett W. Thirteen years' experience in fertility preservation for cancer patients after in vitro fertilization and in vitro maturation treatments. J Assist Reprod Genet. 2018;35(4):583-592.

51. Gorman JR, Bailey S, Pierce JP, Su HI. How do you feel about fertility and parenthood? The voices of young female cancer survivors. J Cancer Surviv. 2012;6(2):200-209.

52. Quinn GP, Vadaparampil ST, Lee JH, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. J Clin Oncol. 2009;27(35):5952-5957.

53. Johnson RH, Kroon L. Optimizing fertility preservation practices for adolescent and young adult cancer patients. J Natl Compr Canc Netw. 2013;11(1):71-77.

54. Duffy C, Allen SM, Dube C, Dickersin K. Oncologists' confidence in knowledge of fertility issues for young women with cancer. J Cancer Educ. 2012;27(2):369-376.

55. Overbeek A, van den Berg M, Louwé L, et al. Practice, attitude and knowledge of Dutch paediatric oncologists regarding female fertility. Neth J Med. 2014;72(5):264-270.

56. Ghorbani B, Madahi P, Shirazi E, Ardekani HS, Kamali K. Iranian oncologists' attitude towards fertility preservation in a sample group. J Reprod Infertil. 2011;12(1):33-36.

57. Loren AW, Brazauskas R, Chow EJ, et al. Physician perceptions and practice patterns regarding fertility preservation in hematopoietic cell transplant recipients. Bone Marrow Transplant. 2013;48(8):1091-1097.

58. Clayman ML, Harper MM, Quinn GP, Reinecke J, Shah S. Oncofertility resources at NCI-designated comprehensive cancer centers. J Natl Compr Canc Netw. 2013;11(12):1504-1509.

59. Warner E, Yee S, Kennedy E, et al. Oncofertility knowledge, attitudes, and practices of Canadian breast surgeons. Ann Surg Oncol. 2016;23(12):3850-3859.

60. Rabah DM, Wahdan IH, Merdawy A, Abourafe B, Arafa MA. Oncologists' knowledge and practice towards sperm cryopreservation in Arabic communities. J Cancer Surviv. 2010;4(3):279-283.

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