Fertility Challenges and Solutions in Women with Cancer

Hatem A. Azim Jr
Isabelle Demeestere
Fedro A. Peccatori
Editors

Springer

Fertility Challenges and Solutions in Women with Cancer

Hatem A. Azim Jr • Isabelle Demeestere
Fedro A. Peccatori
Editors

Fertility Challenges and Solutions in Women with Cancer

Springer

Editors
Hatem A. Azim Jr
School of Medicine
Tecnologico de Monterrey
Monterrey
Mexico

Isabelle Demeestere
CUB-Erasme, Fertility Clinic
Université Libre de Bruxelles
Brussels
Belgium

Fedro A. Peccatori
Division of Gynecologic Oncology
European Institute of Oncology
Milan
Italy

ISBN 978-3-030-24085-1 ISBN 978-3-030-24086-8 (eBook)
https://doi.org/10.1007/978-3-030-24086-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This book addresses a highly controversial and challenging subject, which is related to fertility management of young women with cancer. In light of the improvement in cancer survival and the rising trend of delaying childbearing over the past decade, an increasing number of oncologists and fertility specialists are often faced with young women with cancer inquiring into fertility-related issues in routine clinical practice.

Over the past decade, the field of fertility management of cancer patients has evolved enormously moving from managing patients based on anecdotes and perceptions to counseling based on evidence, thanks to a large amount of clinical and experimental research that has been generated and published by several groups around the globe.

This book gathers worldwide experts who have made important contributions in the field of fertility management of young cancer patients. Several subjects are discussed spanning from understanding the feasibility and safety of pregnancy in cancer survivors to the various fertility preservation methods that could be used, in addition to fertility counseling of special subgroups of patients like those with germline mutations or with endocrine sensitive tumors. The book also addresses controversies related to the role of ovarian tissue cryopreservation and LHRH analogues. We strongly believe that this book will fulfill its aim in providing busy clinicians with a valuable resource in counseling their patients in routine clinical practice.

Monterrey, Mexico — Hatem A. Azim Jr
Brussels, Belgium — Isabelle Demeestere
Milan, Italy — Fedro A. Peccatori

Contents

About the Editors

Hatem A. Azim Jr, MD, PhD is a medical oncologist and an adjunct professor at the School of Medicine of the Monterrey Institute of Technology and the American University of Beirut. He also serves as faculty for the European Society for Medical Oncology (ESMO) and the European School of Oncology. He holds a master's degree from the University of Newcastle Upon Tyne (UK) and a PhD from the Université Libre de Bruxelles (Belgium). Dr. Azim has published more than 120 peer-reviewed articles, contributed to 10 books, and been an invited speaker at the major oncology conferences. In recognition to his research in the field of breast cancer in young women and its relation to pregnancy and fertility, Dr. Azim has received the American Society of Clinical Oncology Merit Award, the ESMO Translational Research Award, and the University of Padua Breast Cancer Research Award.

Isabelle Demeestere, MD, PhD is a gynecologist at the fertility clinic in Erasme Hospital (Brussels, Belgium) and the Director of the Research Laboratory on Human Reproduction at the Université Libre de Bruxelles (ULB). After earning a PhD in fertility preservation for cancer patients, she completed her research training at McGill University, Canada, and became research associate at the FNRS. She was among the earliest innovators in the fertility preservation field and is responsible for the oncofertility unit at Erasme Hospital. She is a member of several scientific societies and author or coauthor of over 60 articles and book chapters in the field.

Fedro Alessandro Peccatori, MD, PhD is a specialist in Medical Oncology and Obstetrics & Gynecology. He acts as Director of the Fertility and Pregnancy Unit at the European Institute of Oncology (IEO) and Scientific Director of the European School of Oncology (ESO) Milan, Italy. Fertility and pregnancy issues in young women with cancer are his main research interests. He has published more than 190 peer-reviewed articles in international journals and has been the editor or author of more than 10 books on cancer and reproduction. He has been invited as speaker for ASCO, ESGO, and ESMO, where he is part of the Adolescent and Young Adults working group.

Part I

Overview on Pregnancy in Cancer Survivors and Fertility Preservation Options

1 Epidemiology and General Considerations of Pregnancy Following Cancer Diagnosis

Barbara Buonomo, Hatem A. Azim Jr, Carlo Alviggi, and Fedro A. Peccatori

Introduction

Nowadays, there is a rising trend of delaying childbearing for personal, educational, and professional reasons. Given that cancer incidence increases with age, more women inquire into the feasibility and safety of pregnancy following cancer diagnosis [1]. In addition, several concerns exist regarding the impact of cancer therapy on pregnancy outcome and the possibility of adverse effects among their offspring.

However, it is not only the oncologic treatment that may have a potential negative impact on reproductive rates among cancer survivors. These patients may choose not to start a family for concerns related to the risk of transmitting predisposing genetic mutations to offsprings, for worries about cancer relapse and for the potentially increased risks of obstetric and perinatal complications [2]. Cancer survivors often suffer sexual health problems as well, which could be partly related to psychological challenges [3]. It was shown that decreased arousal, pleasure, and

B. Buonomo (✉)
Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

Fertility and Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology IRCCS, Milan, Italy
e-mail: Barbara.Buonomo@ieo.it

H. A. Azim Jr
Tecnologico De Monterrey, School of Medicine, Monterrey, Mexico

C. Alviggi
Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

F. A. Peccatori
Fertility and Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology IRCCS, Milan, Italy

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_1

overall satisfaction with sexual function occur at an increased rate among cancer survivors than the general population [4]. This underlines that importance of offering adequate oncofertility counselling for female cancer survivors.

Prevalence of Pregnancy After Cancer

The overall probability of a first live birth is significantly lower among cancer survivors than among age-matched controls [2, 5]. On average, pregnancy rates are 40% lower among female cancer survivors compared with the general population adjusting for women's age, education level, and previous parity. This observation is highly dependent on the cancer type. Women diagnosed with melanoma or thyroid cancer have pregnancy rates highly comparable to that of the general population. On the other hand, women diagnosed with breast cancer have the lowest chance of subsequent pregnancy, which is nearly 70% lower compared to the general population. This is possibly related to the administration of gonadotoxic chemotherapy but also to a general misconception that pregnancy could stimulate cancer recurrence being a hormonally driven disease [1].

Obstetric and Fetal Outcomes

Although conceiving after a cancer diagnosis does not appear to increase the risk of cancer recurrence, the vast majority of studies on childbearing among adult cancer survivors are dealing with breast cancer [6, 7]. Survivors of malignant melanoma also seems to do well after pregnancy, but the evidence is more limited [8, 9].

It is unknown whether short intervals between treatment and conception increase the risks of poor pregnancy outcomes. It is generally advised not to conceive within 2 years of diagnosis. This would allow adequate recovery of ovarian function following anticancer therapy but also avoid the time during which the risk of recurrence is relatively higher [10]. Studies have shown that threatened miscarriage is higher in survivors diagnosed at an older age, those with a history of central nervous system (CNS) tumors, abdominopelvic tumors or those who had been treated with radiation therapy. Other factors that influence the risk of miscarriage include older maternal age, congenital uterine abnormalities, autoimmune factors, thrombophilic disorders, and maternal endocrine abnormalities like poorly controlled diabetes or polycystic ovarian syndrome. The findings of increased miscarriage in CNS tumors survivors suggest that brain irradiation may increase poor obstetrical outcomes, possibly through impairment of the hypothalamic-pituitary-ovarian axis [11].

Gestational diabetes is more frequent among CNS tumors, bone sarcoma, and carcinomas survivors, as well as in patients with tumors arising in the abdominal-pelvic region. The literature also reports that maternal diabetes is more common in females exposed to chemoradiation [11–15].

Cesarean sections are more common in females diagnosed with cancer compared with those with no history of cancer. Women exposed to chemotherapy or radiation therapy, or diagnosed with leukemia, are particularly at risk. The combination of psychological and obstetric considerations has probably led to the high frequency of cesarean delivery in this group of patients. Other reasons include physicians' concerns over medical malpractice, fear of birth trauma, and the potential risk to the child due to difficult vaginal delivery [11].

Some studies reported an increased risk of preterm birth (gestational age <37 weeks) and/or growth restriction in infants born to lymphoma, soft tissue sarcoma, and carcinoma survivors (Table 1.1) [16]. Previous investigators have hypothesized that chemotherapy might increase the risk of having an infant born preterm or with low birth weight (<2500 g) or small for gestational age (SGA). Mechanisms by which chemotherapy could cause adverse outcomes include immunosuppression,

Table 1.1 Summary of recent studies on preterm birth and low birth weight among children of female cancer survivors

	Hartnett et al. [10]	Haggar et al. [11]	Mueller et al. [17]	Signorello et al. [18]	Hartnett et al. [19]	Anderson et al. [20]
Study population	Survivors: 4203 vs. comparison group (1:25)	Survivors: 1894 Controls: 4138	Survivors: 1898 Controls: 14,278	2201 children of 1264 survivors 1175 children of 601 controls	4203 cancer survivors vs. control group (1:5)	Survivors: 2598 Controls: 12,990
Risk of preterm delivery (<37 weeks)	All cancers, ≤1 year after starting CT: – CT alone: 1.9, 1.3–2.7 – CT with RT: 2.4, 1.6–3.6	1.68, 1.21–2.08	1.54, 1.13–1.56	1.9, 1.4–2.4	Breast: 1.3, 1.0–1.8 Reproductive: 2.1, 1.6–2.9 Thyroid: 1.1, 0.8–1.4	1.52, 1.34–1.71
Risk of low birth weight (<2500 g)	All cancers, ≤1 year after starting CT: – CT alone: 2.0, 1.4–3.0; – CT with RT: 2.7, 1.7–4.2	1.51, 1.23–2.12	1.31, 1.10–1.57	6.8, 2.1–22.2	Breast: 1.4, 1.0–1.9 Reproductive: 2.7, 1.9–3.9 Thyroid: 0.9, 0.7–1.3	1.59, 1.38–1.83

Abbreviations: *CT* chemotherapy, *RT* radiotherapy

chronic anemia, cardiovascular effects, physical stress, or insufficient weight gain in pregnancy [17, 18].

Hartnett et al. presented an analysis of first subsequent pregnancy outcomes among women who were diagnosed with cancer between ages 20 and 45 years [10]. They compared pregnancy outcomes with those of matched controls without cancer history. Their main findings were that early pregnancy after cancer treatment (≤1 year from treatment start) was associated with increased risk of preterm birth after starting chemotherapy (chemotherapy alone: relative risk [RR], 1.9; 95% confidence interval [CI], 1.3–2.7; chemotherapy with radiation: RR, 2.4; 95% CI, 1.6–3.6).

However, women who had later conception, with the exception of those with a history of cervical cancer, were not at higher risk than controls. In a similar work led by Hartnett et al., pregnant survivors of cervical and breast cancer or leukemia had a higher risk of preterm birth, while those with a history of brain cancer and non-Hodgkin lymphoma were more likely to have infants that were small for gestational age [19].

In another database-linked study conducted in North Carolina, Anderson et al. showed an increased risk of preterm birth and low birth weight among babies born to diverse cancer survivors compared with controls [20]. Another large population-based analysis from Israel compared more than 15,000 women who had a history of cancer before pregnancy versus a group of non-cancer survivor controls [21]. In that study, Pillar et al. found that pregnant women with a history of cancer were at increased risk of maternal and fetal complications, including a nearly 50% increased risk of premature delivery. Fortunately, absolute rates were relatively low, particularly for the most serious increased risks, such as maternal and fetal death.

Conclusions

Pregnancy following cancer is feasible and does not appear to impact maternal prognosis. However, women are often faced with several challenges. The Society for Maternal-Fetal Medicine advises that pregnancy may stress organs that were strained by prior chemotherapy and hence extra monitoring is required to minimize the risks to mother and fetus. Survivors who successfully conceive should be monitored and managed throughout their pregnancy by a multidisciplinary team, including expert obstetricians and neonatologists.

References

1. Peccatori FA, Azim HA Jr, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi160–70.
2. Gerstl B, Sullivan E, Chong S, Chia D, Wand H, Anazodo A. Reproductive outcomes after a childhood and adolescent young adult cancer diagnosis in female cancer survivors: a systematic review and meta-analysis. J Adolesc Young Adult Oncol. 2018. [Epub ahead of print]. https://doi.org/10.1089/jayao.2018.0036.

3. Jacobs LA, Pucci DA. Adult survivors of childhood cancer: the medical and psychosocial late effects of cancer treatment and the impact on sexual and reproductive health. J Sex Med. 2013;10(Suppl):120–6.
4. Blouet A, Zinger M, Capitain O, et al. Sexual quality of life evaluation after treatment among women with breast cancer under 35 years old. Support Care Cancer. 2018. [Epub ahead of print]. https://doi.org/10.1007/s00520-018-4374-z.
5. Armuand G, Skoog-Svanberg A, Bladh M, Sydsjö G. Reproductive patterns among childhood and adolescent cancer survivors in sweden: a population-based matched-cohort study. J Clin Oncol. 2017;35(14):1577–83.
6. Azim HA Jr, Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011;47:74–83.
7. Valachis A, Tsali L, Pesce LL, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. Obstet Gynecol Surv. 2010;65:786–93.
8. Kroman N. Pregnancy after cancer, is it possible and safe to the mother and the child? Acta Obstet Gynecol Scand. 2019. [Epub ahead of print]. https://doi.org/10.1111/aogs.13596.
9. Byrom L, Olsen CM, Knight L, Khosrotehrani K, Green AC. Does pregnancy after a diagnosis of melanoma affect prognosis? Systematic review and meta-analysis. Dermatol Surg. 2015;41:875–82.
10. Hartnett KP, Mertens AC, Kramer MR, Lash TL, Spencer JB, Ward KC, Howards PP. Pregnancy after cancer: does timing of conception affect infant health? Cancer. 2018;124(22):4401–7. [Epub 7 Nov 2018]. https://doi.org/10.1002/cncr.31732.
11. Haggar FA, Pereira G, Preen D, D'Arcy Homan C, Einarsdottir K. Adverse obstetric and perinatal outcomes following treatment of adolescent and young adult cancer: a population-based cohort study. PLoS One. 2014;9(12):e113292.
12. Baker KS, Ness KK, Steinberger J, Carter A, Francisco L, Burns LJ. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. Blood. 2007;109:1765–72.
13. Taskinen M, Saarinen-Pihkala UM, Hovi L, Lipsanen-Nyman M. Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet. 2000;356:993–7.
14. Link K, Moëll C, Garwicz S, Cavallin-Stahl E, Bjork J, Thilen U. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. J Clin Endocrinol Metab. 2004;89:5003–12.
15. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys. 2009;73:1304–12.
16. Partridge AH. Pregnancy after cancer: timing is everything. Cancer. 2018;124(22):4290–1. [Epub 7 Nov 2018]. https://doi.org/10.1002/cncr.31730.
17. Mueller BA, Chow EJ, Kamineni A, et al. Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. Arch Pediatr Adolesc Med. 2009;163:879–86.
18. Signorello LB, Cohen SS, Bosetti C, et al. Female survivors of childhood cancer: preterm birth and low birth weight among their children. J Natl Cancer Inst. 2006;98:1453–61.
19. Hartnett KP, Ward KC, Kramer MR, et al. The risk of preterm birth and growth restriction in pregnancy after cancer. Int J Cancer. 2017;141:2187–96.
20. Anderson C, Engel SM, Mersereau JE, et al. Birth outcomes among adolescent and young adult cancer survivors. JAMA Oncol. 2017;3:1078–84.
21. Pillar N, Mazaki-Tovi S, Berger R, Paluch-Shimon S, Symon Z, Lawrence YR. Pregnancy outcome and survivorship in cancer patients [abstract]. J Clin Oncol. 2013;31(Suppl):1503.

2 Safety and Challenges of Pregnancy in Women with a History of Endocrine-Sensitive Breast Cancer

Hatem A. Azim Jr

Introduction

In women of reproductive age, breast cancer is the most commonly diagnosed malignancy [1]. Yet with the rising trend of delaying childbearing, increasing numbers of women are diagnosed with breast cancer before completing their families [2]. Several studies have pointed out that young breast cancer patients are rather concerned about future fertility and express willingness to become subsequently pregnant [3–5].

On the other hand, there appears to be a gap in knowledge when it comes to addressing the fertility and pregnancy concerns of young breast cancer patients. In 2018, a large survey including more than 200 breast cancer specialists in Europe and the USA have shown that around 50% of them did not consult or were even not aware of guidelines on pregnancy following breast cancer [5]. In the same study, more than one-third of breast cancer specialists believe that pregnancy following breast cancer could be detrimental, particularly in patients with a history of endocrine-sensitive disease.

Young women with endocrine-sensitive disease represent around 60% of all patients [6, 7]. Several "hormonal or endocrinal" treatments are administered as part of standard adjuvant therapy for 5–10 years to reduce or block the effect of female hormones on the breast. These treatments (e.g., tamoxifen, ovarian function suppression, aromatase inhibitors in combination with ovarian function suppression) have shown to improve long-term outcomes of young breast cancer patients [8–10]. Thus, it is understood that discussing pregnancy in women with a history of endocrine-sensitive disease could pose a lot of controversies. On one end, the massive increase in female hormones during pregnancy could potentially stimulate "at least in theory"

H. A. Azim Jr (✉)
Tecnologico de Monterrey, School of Medicine, Monterrey, NL, México

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_2

breast cancer to recur. On the other end, allowing pregnancy could result in compromising the course of endocrine treatment that could potentially have detrimental implications on cancer outcome [10].

Risk of Recurrence After Pregnancy in Women with a History of Estrogen Receptor Positive Breast Cancer

Among cancer survivors, women with a history of breast cancer have the lowest rate of pregnancy following cancer diagnosis compared to survivors of other types of malignancies [11, 12]. This is due to various reasons, including concerns on the safety of pregnancy following breast cancer diagnosis, particularly in those with endocrine-sensitive disease.

In 2011, we published a meta-analysis of all case-control and population-based studies addressing the safety of pregnancy in patients with a history of breast cancer [13]. The main result indicated that pregnancy was not detrimental. In contrast, it was actually associated with better survival. However, this study highlighted the major limitations of published literature in this domain. One limitation was the selection of control group "i.e., non-pregnant patients." Most of these studies did not account for the lead time bias. In other word, as pregnancy only occurs in patients with no evidence of relapse, it is vital to ensure that the control group was free of relapse for a minimum time that corresponds to the time between cancer diagnosis and pregnancy. Another limitation was information on estrogen receptor status. None of the included studies had such information, or performed specified analysis addressing the safety of pregnancy in patients with endocrine-sensitive disease. Taken together, it is intriguing that despite the publication of around 14 studies until 2011 that demonstrated the apparent safety of pregnancy following breast cancer, surveys showed that breast cancer patients continued to be advised against subsequent pregnancy by their treating physicians for fear that it could stimulate cancer recurrence [14].

Few years later, we published the primary results of a large multicenter trial in order to address the limitations of previous studies published in the field including understanding the safety of pregnancy in women with endocrine-sensitive disease [15]. This trial included more than 1000 patients, of whom around 200 had a pregnancy following endocrine-sensitive breast cancer. Importantly, controls were selected taken into account lead time bias. The primary results showed that at a median follow-up of 4.5 years following pregnancy, there was no difference in disease-free survival between patients who became subsequently pregnant and controls. This was observed in all patients with endocrine-sensitive disease but also those with hormone receptor negative disease as well. Neither abortion nor time to pregnancy was associated with patient outcome. An updated report with 7.2 years of median follow-up following pregnancy confirmed the same findings [16]. This study provides more refined evidence on the safety of pregnancy in breast cancer survivors, even in those with endocrine-sensitive disease.

Feasibility of Pregnancy in the Era of Long-Term Adjuvant Endocrine Therapy

Current evidence suggests that time to pregnancy has no prognostic impact [15]. A minimum of 2 years from diagnosis until pregnancy is rather preferred, as this period is associated with the highest risk of recurrence [17]. Thus, it would be rather reassuring for the patient and her physician to bypass this period before attempting to become pregnant. Furthermore, it would allow recovery of ovarian function, which is often compromised following exposure to adjuvant chemotherapy.

Patients are often treated with adjuvant endocrine therapy that lasts for 5 and up to 10 years in some cases [8–10]. This renders the feasibility of becoming pregnant following the completion of endocrine therapy rather low due to the deterioration of ovarian function as a function of age especially in those previously treated with adjuvant systemic chemotherapy. On the contrary, this situation is less challenging in patients with hormone receptor negative disease, as these women do not require treatment with endocrine therapy.

Thus, the question remains: is it safe to interrupt endocrine therapy to become pregnant? Would that increase a patient's risk of recurrence? To date, we lack data from clinical studies to address this point. This approach "i.e., temporary interruption of endocrine therapy," is being adopted in referral centers on a case-by-case basis, depending on patient prognosis, willingness to accept uncertainty, and her chances of conception should she wait to complete 5 years of endocrine therapy. But are patients willing to accept such risk? A survey published in 2015 including more than 200 patients addressed this question [18]. It showed that around 40% of patients are willing to temporarily interrupt endocrine therapy to become pregnant, mostly those women who are less than 35 years of age. Furthermore, several studies point out to the poor compliance of endocrine therapy, particularly among young women, with some studies showing that only 50% of patients manage to complete the 5-year scheduled course of endocrine therapy [19, 20]. One would argue that this would be even lower with the 10-year schedule. Main reasons behind the poor compliance were patients' willingness to resume normal life, and poor tolerance to long-term side effects of such therapies, including but not restricted to impact on fertility. This underscored the need to define customized approaches to help counseling young women with a history of endocrine-sensitive breast cancer who are willing to become pregnant.

These considerations, coupled with the mounting evidence of safety of pregnancy in young women, led to the initiation of a large international clinical trial (POSITIVE; clinicaltrials.org: NCT02308085) aiming to evaluate the safety of temporary interruption of endocrine therapy to become pregnant. This is a prospective phase 2 trial, and includes patients <42 years of age, with estrogen receptor positive breast cancer and willing to become pregnant. Patients should receive a minimum of 18–30 months of endocrine therapy before interruption. Interruption period is a maximum of 2 years, to allow for pregnancy and possible breastfeeding before resuming endocrine therapy. The choice of adjuvant systemic treatment and

duration of endocrine treatment is left to the treating physician, yet a minimum of 5 years is highly recommended by the trial. Several translational research endpoints are being evaluated in this study, including effect of endocrine therapy on ovarian function parameters, and impact of interrupting therapy on circulating biomarkers including circulating tumor DNA. The trial aims to recruit around 500 patients by the end of 2019. This trial holds great promise to provide robust evidence on the safety of temporary interruption of endocrine therapy in young breast cancer patients willing to become pregnant, which would refine counseling of these patients in daily clinical practice.

Obstetric Outcome in Women with a History of Breast Cancer

Many reports were published on birth outcomes of women with a history of breast cancer (Table 2.1) [21–24]. These studies show that the rate of congenital anomalies in young survivors of breast cancer appears to be similar to that of the general population. However, older series reported a higher abortion rate (in the range of 35%) in women with a history of breast cancer; this probably also reflects the fear of physicians and patients toward the safety of pregnancy after breast cancer [15, 22]. More recent studies report spontaneous and induced abortion in the range of 12%, and congenital malformation in the range of 2–3% [2, 13]. This is rather reassuring and in line with what is observed in the general population with no prior exposure to anticancer treatments (approximately 17% rate of spontaneous abortion and 3% rate of congenital anomalies) [25].

Table 2.1 Key studies addressing birth outcome in women with a history of breast cancer

	Langagergaard et al. [21]	Dalberg et al. [22]	Azim et al. [23]	Lambertini et al. [24]
Year of publication	2005	2006	2012	2018
Number of pregnancies	216	331	45	80
Mean age at pregnancy	34.4	34	34	34
Type of study	Population-based	Population-based	Prospective cohort	Prospective cohort
Previous treatment				
– Chemotherapy – Endocrine therapy – HER2+ therapy	NA	NA	100% NA 100%	100% 60% 100%
Mean GW at delivery	39	37–42 (88%)	39	39
Fetal outcome				
– Mean weight (g)	3411	2500–4400 (88%)	3397	3345
– Median Apgar score at 10 min	NA	7–10 (92%)	9	9
– Congenital malformations	3.4%	7%	2.2%	1.7%

Managing Pregnancies Occurring Accidentally During Adjuvant Endocrine Therapy

Accidental pregnancy during adjuvant endocrine therapy is not rare.

The majority of women develop amenorrhea while on adjuvant chemotherapy [26]. This effect is reversible in a large fraction depending mostly on their age. Following chemotherapy, adjuvant endocrine therapy is started within few weeks. In such period, in most cases, it is not yet clear if amenorrhea induced by chemotherapy is permanent or patient could resume ovarian function gradually. On the other hand, tamoxifen, which is the mainstay adjuvant endocrine therapy for young breast cancer patients, could impact menstrual flow; however, it improves ovulation [27]. Thus, women who developed temporary amenorrhea secondary to chemotherapy may resume ovarian function while on tamoxifen, yet this might not necessarily result in regular menstrual cycles. This may result in women becoming pregnant on tamoxifen despite being in "amenorrhea" for long time.

Several reports exist on pregnancy outcome of women who were exposed to tamoxifen during pregnancy [28]. In a prevention trial, no single congenital malformation was reported among 85 pregnancies that were reported [28]. On the other hand, the AstraZeneca (manufacturer of tamoxifen) safety database reports 11 babies with congenital malformations out of 44 reported live births. In addition, there were six terminations of pregnancy for fetal defects. Other sporadic cases on congenital malformations were reported in the literature as well [29–31]. In total, around 138 live births are reported in the literature to have been exposed to tamoxifen during pregnancy. Of those, 16 had experienced congenital malformations. It is hard to accurately estimate the risk and incidence of malformations secondary to tamoxifen exposure. Nevertheless, it appears that exposure is problematic and associated with an important risk for congenital malformations.

Hence, it is vital that physicians discuss adequate contraceptive methods before starting endocrine therapy with tamoxifen alone for women who develop temporary amenorrhea on chemotherapy. After completion of treatment with tamoxifen, it is important to allow a minimum of 3 months washout period before attempting pregnancy.

Conclusions

Young women with a history of endocrine-sensitive breast cancer face several challenges regarding future pregnancy. In recent years, researches have demonstrated that pregnancy is safe and could be considered even in women with a history of endocrine-sensitive breast cancer. Physicians caring for these women should allow adequate counseling and time to discuss these issues with their patients. These concerns are of paramount importance for the majority of them and hence a one-size-fits-all approach is not possible. A customized approach for each patient taking into account her cancer history, family situation, and age among other factors would help to define a treatment decision which would be more adapted for each case.

References

1. Rosenberg SM, Newman LA, Partridge AH. Breast cancer in young women: rare disease or public health problem? JAMA Oncol. 2015;1:877–8.
2. Azim HA Jr, Peccatori FA, de Azambuja E, et al. Motherhood after breast cancer: searching for la dolce vita. Expert Rev Anticancer Ther. 2011;11:287–98.
3. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol. 2004;22:4174–83.
4. Ruddy KJ, Gelber SI, Tamimi RM, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol. 2014;32:1151–6.
5. Lambertini M, Di Maio M, Pagani O, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast. 2018;42:41–9.
6. Collins LC, Marotti JD, Gelber S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. Breast Cancer Res Treat. 2012;131:1061–6.
7. Azim HA Jr, Michiels S, Bedard PL, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clin Cancer Res. 2012;18:1341–51.
8. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371:107–18.
9. Francis PA, Regan MM, Fleming GF. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:1673.
10. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805–16.
11. Stensheim H, Cvancarova M, Moller B, et al. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. Int J Cancer. 2011;129:1225–36.
12. Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi160–70.
13. Azim HA Jr, Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011;47:74–83.
14. Biglia N, Torrisi R, D'Alonzo M, et al. Attitudes on fertility issues in breast cancer patients: an Italian survey. Gynecol Endocrinol. 2015;31:458–64.
15. Azim HA Jr, Kroman N, Paesmans M, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol. 2013;31:73–9.
16. Lambertini M, Kroman N, Ameye L, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J Natl Cancer Inst. 2018;110:426–9.
17. Metzger-Filho O, Sun Z, Viale G, et al. Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. J Clin Oncol. 2013;31:3083–90.
18. Pagani O, Ruggeri M, Manunta S, et al. Pregnancy after breast cancer: are young patients willing to participate in clinical studies? Breast. 2015;24:201–7.
19. Huiart L, Bouhnik AD, Rey D, et al. Early discontinuation of tamoxifen intake in younger women with breast cancer: is it time to rethink the way it is prescribed? Eur J Cancer. 2012;48:1939–46.
20. Cluze C, Rey D, Huiart L, et al. Adjuvant endocrine therapy with tamoxifen in young women with breast cancer: determinants of interruptions vary over time. Ann Oncol. 2012;23:882–90.
21. Langagergaard V, Gislum M, Skriver MV, et al. Birth outcome in women with breast cancer. Br J Cancer. 2006;94:142–6.
22. Dalberg K, Eriksson J, Holmberg L. Birth outcome in women with previously treated breast cancer—a population-based cohort study from Sweden. PLoS Med. 2006;3:e336.

23. Azim HA Jr, Metzger-Filho O, de Azambuja E, et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). Breast Cancer Res Treat. 2012;133:387–91.
24. Lambertini M, Martel S, Campbell C, et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Cancer. 2019;125:307–16.
25. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol. 2010;686:349–64.
26. Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016;14:1.
27. Sharma S, Rani G, Bose G, et al. Tamoxifen is better than low-dose clomiphene or gonadotropins in women with thin endometrium (<7 mm) after clomiphene in intrauterine insemination cycles: a prospective study. J Hum Reprod Sci. 2018;11:34–9.
28. Braems G, Denys H, De Wever O, et al. Use of tamoxifen before and during pregnancy. Oncologist. 2011;16:1547–51.
29. Tewari K, Bonebrake RG, Asrat T, et al. Ambiguous genitalia in infant exposed to tamoxifen in utero. Lancet. 1997;350:183.
30. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. JAMA. 1994;271:1905–6.
31. Berger JC, Clericuzio CL. Pierre Robin sequence associated with first trimester fetal tamoxifen exposure. Am J Med Genet A. 2008;146A:2141–4.

Pregnancy After Gynecological Cancer

3

Marieke van der Zalm, Frederic Amant, and Joris van Drongelen

General Introduction

Pregnancy after a gynecological cancer is relatively rare, although the chance that an obstetrician will be confronted with this kind of problem is increasing. This makes it necessary that obstetricians are familiar with the risks and obstetric management strategies of pregnancies after a gynecological cancer. This chapter will systematically describe fertility issues, pregnancy outcomes, and obstetric management in women with a history of cervical, ovarian, and vulvar malignancies.

Pregnancy After Cervical Cancer

Introduction

Almost 50% of cervical cancer cases are diagnosed in women less than 45 years of age. Therefore, fertility issues play an important role in this group of patients. Although radical hysterectomy is the standard treatment for early stage cervical

M. van der Zalm · J. van Drongelen
Department of Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, The Netherlands

F. Amant (✉)
Department Obstetrics and Gynaecology, Amsterdam UMC, University of Amsterdam, Gynaecologic Oncology, Amsterdam, The Netherlands

Department of Gynaecology, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Gynaecologic Oncology Research Unit, Department of Oncology, KU Leuven, Leuven, Belgium
e-mail: frederic.amant@uzleuven.be

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_3

cancer, women of reproductive age with stage 1A1, 1A2, or small 1B1 disease (without high-risk features) can be candidates for fertility-preserving surgery. Surgical options for fertility preservation are: cervical conization, simple trachelectomy, and (vaginal, abdominal, or laparoscopic) radical trachelectomy [1–5]. More advanced stages of cervical cancer are treated by chemoradiation, after which pregnancy is not an option anymore. When the wish to preserve fertility is very strong in women with larger cervical tumors, some hospitals also offer neo-adjuvant chemotherapy, followed by radical trachelectomy [6].

However, fertility-preserving surgery can lead to conception problems and obstetric complications, such as preterm labor. Unfortunately only little is known about optimal obstetric management in pregnancies after radical trachelectomy.

This chapter provides an overview of fertility issues and pregnancy outcome after fertility-preserving surgery for cervical cancer and some guidance as to how these patients should be managed obstetrically.

Pregnancy After LLETZ, Conization, or Simple Vaginal Trachelectomy

Early stage cervical carcinoma can be treated by cold knife conization or by simple trachelectomy, in which most of the cervix is removed in a cylinder shape (instead of a cone shape) without parametrial tissue. Depending on the amount of cervix that is removed, a cerclage can be placed after simple trachelectomy.

Fertility

Only few studies have focused on the impact of limited cervical surgery (mainly conization and large loop excision of the transformation zone: LLETZ) on a woman's fertility. Theoretical effects are: cervical stenosis preventing sperm entry, secondary ascending infection with tubal damage, and changes in cervical mucus [7]. However, most studies do not show a delay in conception or an increased incidence of other fertility problems [7–9]. One study did report a longer time to conceive in the treatment group [10]. It is important to notice that all these studies mainly included patients with premalignant lesions in which the majority was treated by LLETZ.

Simple trachelectomy also does not seem to negatively influence fertility in a small case series in which all patients attempting to conceive have become pregnant successfully [11].

Pregnancy Outcome

Cervical conization and LLETZ are associated with an increased risk of preterm delivery, premature rupture of membranes, a shorter cervical length in the first trimester, and a lower birth weight [12–14]. Moreover, the frequency and severity of prematurity increases with increasing cone depth, especially if the depth of excision is greater than 10–12 mm [15, 16]. Interestingly, women with cervical dysplasia are at increased baseline risk for preterm birth, and surgical treatment further increases that risk [15, 16]. The rate of 17% preterm delivery and 7% second trimester loss after simple trachelectomy is comparable to pregnancy outcome after radical

vaginal trachelectomy. It is unclear if routine cerclage after simple trachelectomy would improve these results [11].

Obstetric Management

The increased rate of preterm delivery after LLETZ, conization, and simple trachelectomy indicates that these pregnancies should be considered as potential high-risk pregnancies [11]. Serial cervical length measurement is recommended to estimate the risk of spontaneous preterm birth in post LLETZ and conization pregnancies. A midpregnancy cervical length under 25 mm is considered a strong predictor of preterm birth. Furthermore, a lower maximal cervical length measurement (measured around 13, 16, and 20 weeks) and a higher cervical length difference between 13 and 20 weeks seem to be predictors of spontaneous preterm birth [17].

Pregnancy After Radical Trachelectomy (Vaginal, Abdominal, or Laparoscopic)

Radical trachelectomy involves resection of the cervix, along with a vaginal manchet and parametrial tissue. The procedure is always combined with a complete bilateral pelvic lymphadenectomy, which precedes the radical trachelectomy in case of a vaginal approach. The majority of the surgeons prophylactically place a cervical cerclage in order to reduce preterm delivery, although there is no clear consensus on this issue [6, 18].

Fertility

Radical trachelectomy is associated with increased risk of subfertility. The fertility rates following abdominal and laparoscopic radical trachelectomies are reported to be lower (53–59% and 50–56%) than after a vaginal approach (67–80%) [3, 11, 19]. The most important cause of subfertility is cervical stenosis, which is reported in 8–11% of all cases and occurs most frequently after an abdominal radical trachelectomy [3, 6]. Interestingly, a small majority of the patients never tries to conceive after radical trachelectomy [20].

Pregnancy Outcome

The rate of first trimester loss after radical trachelectomy is comparable to the general population [2, 6, 20, 21]. Although there is considerable variation in obstetric outcomes across series, the rate of second trimester loss and preterm birth is clearly increased. Overall, the risk of preterm birth after radical trachelectomy is 38% and the life birth rate 70% [19]. The obstetrical outcome after vaginal radical trachelectomy appears to be somewhat better compared to abdominal radical trachelectomy [6]. After vaginal radical trachelectomy, a preterm birth rate of 25–33% is reported [18, 21, 22], which is slightly better than the preterm birth rate after abdominal radical trachelectomy [4]. Two-third of the pregnancies after vaginal radical trachelectomy reaches the third trimester compared to 40–52% after abdominal radical trachelectomy [4, 6, 23]. The rate of second trimester losses is also higher in the abdominal radical trachelectomy group (19% versus 8%) [6]. The reported obstetric outcome after laparoscopic radical trachelectomy is limited, but the premature delivery rate appears to be high: 48–60% are reported to deliver prematurely [5, 24].

A small series of pregnancies after robotic radical trachelectomy reports a term birth rate of 71% [3]. Almost all cases of preterm delivery after radical trachelectomy are proceeded by premature rupture of membranes (PPROM), which is thought to be the consequence of mechanical and functional cervical incompetence with subclinical infection [18, 19, 25].

Obstetric Management

Pregnancies after radical trachelectomy are associated with a higher risk of complications, mainly preterm birth. Therefore, a specialist in fetal maternal medicine should be involved early in patient care. Pregnancies after radical trachelectomy should be managed similar to that in other patients with cervical incompetence, including cervical length follow-up with serial ultrasounds, although the value of ultrasound in predicting preterm labor in this group of patients is controversial. Routine bed rest, routine prophylactic use of antibiotics, and routine antenatal corticosteroids are not recommended. Early screening for bacterial vaginosis and guided treatment may be performed [2, 18, 21, 26]. Attention must be paid to signs of cerclage erosion, which appears to be more common after abdominal radical trachelectomy [6].

Cesarean section is highly recommended after radical trachelectomy. Naturally, the presence of a cerclage necessitates cesarean section. However, also in the absence of a cerclage, vaginal delivery is risky, since the short scarred cervix may not adequately dilate but instead tear laterally with the risk of uterine artery bleeding [6].

Literature regarding practice guidelines for patients with PPROM in the presence of a cerclage is scarce. However, since the preferred mode of delivery after radical trachelectomy is a cesarean section, it seems justified to leave the cerclage in place with close observation for signs of imminent infection [18].

Pregnancy After Ovarian Cancer

Introduction

Fertility sparing treatment of ovarian cancers has gained more interest over the recent years [27, 28]. Up to 14% of women with an epithelial ovarian cancer (EOC) and 30% with borderline ovarian tumors (BOT) are diagnosed in the fertile period, while most non-epithelial ovarian cancers (nEOC) are diagnosed at a young age [29–32].

Pregnancy Outcome

Large cohorts of pregnancies after fertility sparing surgery lack, although case series and relatively small cohorts do not suggest high risk for adverse pregnancy outcomes [28, 32–53]. In a systematic review of literature, the rate for term delivery

for women that conceived varies between 64% and 77% in women with a history of fertility sparing surgery for ovarian cancer [54]. Recent studies report even higher live birth rates, varying between 80% and 95% [32, 33, 55]. Negative effects of adjuvant chemotherapy in both EOC and nEOC on adverse pregnancy outcomes have not been reported [56]. The available evidence suggests that women with a history of ovarian cancer that become pregnant are likely to experience uneventful pregnancies with a good neonatal outcome. Therefore, no specific recommendations for obstetric management seem to be in place.

Pregnancy After Vulvar Cancer

Introduction

Reports of pregnancy following treatment for vulvar carcinoma are scarce, mainly because carcinoma of the vulva is extremely uncommon in young women [57]. Treatment for vulvar cancer usually exists of surgery (wide local excision or radical vulvectomy) with or without inguinal lymph node dissection, sometimes with adjuvant radiotherapy. Because of the rarity of a pregnancy after vulvar cancer, all available literature consists of case reports.

Pregnancy Outcome

Pregnancy after completed therapy for vulvar cancer does not seem to increase the risk of recurrence, nor are there any reported deleterious effects in the prenatal period. In the majority of the cases, cesarean section was performed because of vulvar scarring. However, literature reports four multiparous women that delivered vaginally [58–63].

Obstetric Management

In case of a pregnancy after vulvar cancer, the mode of delivery should be individualized, depending on the extent of prior surgical treatment, the use of radiotherapy, and the parity of the woman in question.

References

1. Plante M, Renaud MC, Sebastianelli A, Gregoire J. Simple vaginal trachelectomy: a valuable fertility-preserving option in early-stage cervical cancer. Int J Gynecol Cancer. 2017;27(5):1021–7.
2. Plante M, Renaud MC, Hoskins IA, Roy M. Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature. Gynecol Oncol. 2005;98(1):3–10.

3. Johansen G, Lonnerfors C, Falconer H, Persson J. Reproductive and oncologic outcome following robot-assisted laparoscopic radical trachelectomy for early stage cervical cancer. Gynecol Oncol. 2016;141(1):160–5.
4. Pareja R, Rendon GJ, Sanz-Lomana CM, Monzon O, Ramirez PT. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy—a systematic literature review. Gynecol Oncol. 2013;131(1):77–82.
5. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Reproductive outcomes after laparoscopic radical trachelectomy for early-stage cervical cancer. J Gynecol Oncol. 2014;25(1):9–13.
6. Plante M. Evolution in fertility-preserving options for early-stage cervical cancer: radical trachelectomy, simple trachelectomy, neoadjuvant chemotherapy. Int J Gynecol Cancer. 2013;23(6):982–9.
7. Martyn FM, McAuliffe FM, Beggan C, Downey P, Flannelly G, Wingfield MB. Excisional treatments of the cervix and effect on subsequent fertility: a retrospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2015;185:114–20.
8. Bigrigg A, Haffenden DK, Sheehan AL, Codling BW, Read MD. Efficacy and safety of large-loop excision of the transformation zone. Lancet. 1994;343(8888):32–4.
9. Turlington WT, Wright BD, Powell JL. Impact of the loop electrosurgical excision procedure on future fertility. J Reprod Med. 1996;41(11):815–8.
10. Spracklen CN, Harland KK, Stegmann BJ, Saftlas AF. Cervical surgery for cervical intraepithelial neoplasia and prolonged time to conception of a live birth: a case-control study. BJOG. 2013;120(8):960–5.
11. Plante M, Gregoire J, Renaud MC, Sebastianelli A, Grondin K, Noel P, et al. Simple vaginal trachelectomy in early-stage low-risk cervical cancer: a pilot study of 16 cases and review of the literature. Int J Gynecol Cancer. 2013;23(5):916–22.
12. Pils S, Eppel W, Seemann R, Natter C, Ott J. Sequential cervical length screening in pregnancies after loop excision of the transformation zone conisation: a retrospective analysis. BJOG. 2014;121(4):457–62.
13. Zhuang H, Hong S, Zheng L, Zhang L, Zhuang X, Wei H, et al. Effects of cervical conisation on pregnancy outcome: a meta-analysis. J Obstet Gynaecol. 2019;39(1):74–81.
14. Crane JM. Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. Obstet Gynecol. 2003;102(5 Pt 1):1058–62.
15. Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ. 2016;354:i3633.
16. Gatta LA, Kuller JA, Rhee EHJ. Pregnancy outcomes following cervical conization or loop electrosurgical excision procedures. Obstet Gynecol Surv. 2017;72(8):494–9.
17. Wang L. Value of serial cervical length measurement in prediction of spontaneous preterm birth in post-conization pregnancy without short mid-trimester cervix. Sci Rep. 2018;8(1):15305.
18. Bernardini M, Barrett J, Seaward G, Covens A. Pregnancy outcomes in patients after radical trachelectomy. Am J Obstet Gynecol. 2003;189(5):1378–82.
19. Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil Steril. 2016;106(5):1195–211 e5.
20. Boss EA, van Golde RJ, Beerendonk CC, Massuger LF. Pregnancy after radical trachelectomy: a real option? Gynecol Oncol. 2005;99(3 Suppl 1):S152–6.
21. Jolley JA, Battista L, Wing DA. Management of pregnancy after radical trachelectomy: case reports and systematic review of the literature. Am J Perinatol. 2007;24(9):531–9.
22. Plante M, Gregoire J, Renaud MC, Roy M. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. Gynecol Oncol. 2011;121(2):290–7.
23. Kim CH, Abu-Rustum NR, Chi DS, Gardner GJ, Leitao MM Jr, Carter J, et al. Reproductive outcomes of patients undergoing radical trachelectomy for early-stage cervical cancer. Gynecol Oncol. 2012;125(3):585–8.
24. Ebisawa K, Takano M, Fukuda M, Fujiwara K, Hada T, Ota Y, et al. Obstetric outcomes of patients undergoing total laparoscopic radical trachelectomy for early stage cervical cancer. Gynecol Oncol. 2013;131(1):83–6.

25. Shepherd JH, Mould T, Oram DH. Radical trachelectomy in early stage carcinoma of the cervix: outcome as judged by recurrence and fertility rates. BJOG. 2001;108(8):882–5.
26. Petignat P, Stan C, Megevand E, Dargent D. Pregnancy after trachelectomy: a high-risk condition of preterm delivery. Report of a case and review of the literature. Gynecol Oncol. 2004;94(2):575–7.
27. Morice P, Denschlag D, Rodolakis A, Reed N, Schneider A, Kesic V, et al. Recommendations of the Fertility Task Force of the European Society of Gynecologic Oncology about the conservative management of ovarian malignant tumors. Int J Gynecol Cancer. 2011;21(5):951–63.
28. Cromi A, Bogani G, Uccella S, Casarin J, Serati M, Ghezzi F. Laparoscopic fertility-sparing surgery for early stage ovarian cancer: a single-centre case series and systematic literature review. J Ovarian Res. 2014;7:59.
29. Bergamini A, Petrone M, Rabaiotti E, Pella F, Cioffi R, Rossi EG, et al. Fertility sparing surgery in epithelial ovarian cancer in Italy: perceptions, practice, and main issues. Gynecol Endocrinol. 2018;34(4):305–8.
30. Trope CG, Kaern J, Davidson B. Borderline ovarian tumours. Best Pract Res Clin Obstet Gynaecol. 2012;26(3):325–36.
31. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER cancer statistics review, 1975–2010. Bethesda, MD: National Cancer Institute; 2013. http://seer.cancer.gov/csr/1975_2010/ based on November 2012 SEER data submission, posted to the SEER website.
32. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Analysis of outcomes and prognostic factors after fertility-sparing surgery in malignant ovarian germ cell tumors. Gynecol Oncol. 2017;145(3):513–8.
33. Ratanasrithong P, Benjapibal M. Pregnancy outcomes after conservative surgery for early-stage ovarian neoplasms. Asian Pac J Cancer Prev. 2017;18(8):2083–7.
34. Colombo N, Chiari S, Maggioni A, Bocciolone L, Torri V, Mangioni C. Controversial issues in the management of early epithelial ovarian cancer: conservative surgery and role of adjuvant therapy. Gynecol Oncol. 1994;55(3 Pt 2):S47–51.
35. Zanetta G, Bonazzi C, Cantu M, Binidagger S, Locatelli A, Bratina G, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. J Clin Oncol. 2001;19(4):1015–20.
36. Duska LR, Chang YC, Flynn CE, Chen AH, Goodman A, Fuller AF, et al. Epithelial ovarian carcinoma in the reproductive age group. Cancer. 1999;85(12):2623–9.
37. Morice P, Camatte S, El Hassan J, Pautier P, Duvillard P, Castaigne D. Clinical outcomes and fertility after conservative treatment of ovarian borderline tumors. Fertil Steril. 2001;75(1):92–6.
38. Schilder JM, Thompson AM, DePriest PD, Ueland FR, Cibull ML, Kryscio RJ, et al. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecol Oncol. 2002;87(1):1–7.
39. Raspagliesi F, Fontanelli R, Paladini D, di Re EM. Conservative surgery in high-risk epithelial ovarian carcinoma. J Am Coll Surg. 1997;185(5):457–60.
40. Lim-Tan SK, Cajigas HE, Scully RE. Ovarian cystectomy for serous borderline tumors: a follow-up study of 35 cases. Obstet Gynecol. 1988;72(5):775–81.
41. Boran N, Tulunay G, Caliskan E, Kose MF, Haberal A. Pregnancy outcomes and menstrual function after fertility sparing surgery for pure ovarian dysgerminomas. Arch Gynecol Obstet. 2005;271(2):104–8.
42. Fauvet R, Poncelet C, Boccara J, Descamps P, Fondrinier E, Darai E. Fertility after conservative treatment for borderline ovarian tumors: a French multicenter study. Fertil Steril. 2005;83(2):284–90; quiz 525–6.
43. Donnez J, Munschke A, Berliere M, Pirard C, Jadoul P, Smets M, et al. Safety of conservative management and fertility outcome in women with borderline tumors of the ovary. Fertil Steril. 2003;79(5):1216–21.
44. Seracchioli R, Venturoli S, Colombo FM, Govoni F, Missiroli S, Bagnoli A. Fertility and tumor recurrence rate after conservative laparoscopic management of young women with early-stage borderline ovarian tumors. Fertil Steril. 2001;76(5):999–1004.

45. Camatte S, Morice P, Pautier P, Atallah D, Duvillard P, Castaigne D. Fertility results after conservative treatment of advanced stage serous borderline tumour of the ovary. BJOG. 2002;109(4):376–80.
46. Gotlieb WH, Flikker S, Davidson B, Korach Y, Kopolovic J, Ben-Baruch G. Borderline tumors of the ovary: fertility treatment, conservative management, and pregnancy outcome. Cancer. 1998;82(1):141–6.
47. Morris RT, Gershenson DM, Silva EG, Follen M, Morris M, Wharton JT. Outcome and reproductive function after conservative surgery for borderline ovarian tumors. Obstet Gynecol. 2000;95(4):541–7.
48. Gershenson DM. Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumors. J Clin Oncol. 1988;6(2):270–5.
49. Kanazawa K, Suzuki T, Sakumoto K. Treatment of malignant ovarian germ cell tumors with preservation of fertility: reproductive performance after persistent remission. Am J Clin Oncol. 2000;23(3):244–8.
50. Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. Cancer. 2000;89(2):391–8.
51. Gershenson DM. Clinical management potential tumours of low malignancy. Best Pract Res Clin Obstet Gynaecol. 2002;16(4):513–27.
52. Perrin LC, Low J, Nicklin JL, Ward BG, Crandon AJ. Fertility and ovarian function after conservative surgery for germ cell tumours of the ovary. Aust N Z J Obstet Gynaecol. 1999;39(2):243–5.
53. Tangir J, Zelterman D, Ma W, Schwartz PE. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. Obstet Gynecol. 2003;101(2):251–7.
54. Maltaris T, Boehm D, Dittrich R, Seufert R, Koelbl H. Reproduction beyond cancer: a message of hope for young women. Gynecol Oncol. 2006;103(3):1109–21.
55. Zhang N, Chen R, Hua K, Zhang Y. A retrospective study of reproductive outcomes after fertility-sparing surgery and postoperative adjuvant chemotherapy in malignant ovarian germ cell tumors and sex cord-stromal tumors. J Ovarian Res. 2017;10(1):52.
56. Ceppi L, Galli F, Lamanna M, Magni S, Dell'Orto F, Verri D, et al. Ovarian function, fertility, and menopause occurrence after fertility-sparing surgery and chemotherapy for ovarian neoplasms. Gynecol Oncol. 2019;152(2):346–52.
57. Toriyabe K, Taniguchi H, Senda T, Nakano M, Kobayashi Y, Izawa M, et al. Pregnancy and cesarean delivery after multimodal therapy for vulvar carcinoma: a case report. Mol Clin Oncol. 2016;5(5):583–6.
58. Palmer JE, Tidy JA. Pregnancy following vulvar squamous cell carcinoma: a report of two cases. J Gynecol Oncol. 2009;20(4):254–6.
59. Dahle T. Carcinoma of the vulva and subsequent succesful pregnancy. Acta Obstet Gynecol Scand. 1959;38:448–52.
60. Collins JH, Birch HW, Pailet M, Avent JK. Pregnancy and delivery following extensive vulvectomy. Am J Obstet Gynecol. 1960;80:167–71.
61. Gemmell AA, Haines M. Pregnancy following radical vulvectomy for carcinoma of the vulva. J Obstet Gynaecol Br Emp. 1960;67:199–207.
62. Arjona JE, Velasco E, Cervelo P, Espejo E, Pizarro I, Carrasco S, et al. Pregnancy following radical vulvectomy for carcinoma of the vulva: a case report and literature review. Eur J Obstet Gynecol Reprod Biol. 2011;158(1):113–4.
63. Rubin A, Lewis GC Jr. Pregnancy and vaginal delivery following radical surgery for cancer of the vulva; review of the literature and case report. Am J Obstet Gynecol. 1953;65(6):1347–9.

Overview of Fertility Preservation Approaches in Cancer Patients

4

Isabelle Demeestere

Introduction

Recent improvements in long-term survival among cancer patients have made quality of life a major issue for young patients and their oncologists. Several anticancer treatments, such as alkylating agents and irradiation, are gonadotoxic and induce an acute depletion of the follicular pool in the ovary, leading to premature ovarian insufficiency (POI). The risk of POI and infertility after treatment depends on the age of the patient, the type and total dose of chemotherapy, the use of adjuvant pelvic or total body irradiation, and the ovarian reserve [1–3]. The risk can be classified as low (<20%), medium, or high (>80%) according to the Edinburgh criteria [4]. As ovarian dysfunction induced by anticancer treatment can be transient, posttreatment POI has been defined as amenorrhea for >2 years, a postmenopausal hormonal profile, and nonfunctional ovaries at vaginal ultrasound [5]. However, all of these criteria are usually not taken into consideration in clinical trials and posttreatment amenorrhea alone is commonly used as the primary objective to evaluate posttreatment ovarian function. Therefore, further prospective studies are needed to address the risk of POI after treatment and provide accurate information for each individual situation [6].

Overall, cancer survivors achieve a lower number of pregnancies compared to the general population (SIR 0.62; 95% CI: 0.60, 0.63) [7]. For some diseases, such as Hodgkin lymphoma and breast and cervical cancers, the chances of achieving pregnancy after treatment have progressively increased in the past few decades due to changes in therapeutics approaches (reduction of the use of radiotherapy, fertility-sparing surgery) and fewer concerns regarding the potential impact of pregnancy on recurrence in breast cancer patients. Nonetheless, patients treated with current

I. Demeestere (✉)
Research Laboratory on Human Reproduction and Fertility Clinic, Université Libre de Bruxelles, CUB-Hôpital Erasme, Brussels, Belgium
e-mail: idemeest@ulb.ac.be

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_4

standard chemotherapy, such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) in advanced lymphoma and anthracycline- or taxane-based regimens in breast cancer, remain at high or moderate risk of POI depending on their age [8–10]. For others, such as leukemia patients, the risk remains high, primarily due to the gonadotoxicity of conditioning regimens used in bone marrow transplantation, which is still the most effective treatment for advanced hematological disease [7].

The possibility of conceiving with their own gametes and building a family after being cured represents a top priority for young cancer patients at diagnosis [11–13]. In a large cohort of more than 1000 women less than 40 years of age at the time of diagnosis, 47–63% reported having a desire to have children after cancer, especially women with Hodgkin or non-Hodgkin lymphoma [13]. In another prospective study, the authors reported that more than 90% of young breast cancer patients were concerned by the consequences of chemotherapy-induced ovarian damage [11]. This concern may also be aggravated in the future by age-related infertility issues considering the increase in the average age of first-time mothers (OECD Family Database 2017, http://www.oecd.org/els/family/database.htm).

Therefore, infertility risk related to the gonadotoxicity of anticancer treatments might cause severe psychological distress and even affect treatment decisions [14]. Considering this dramatic impact of treatment-induced ovarian damage on the quality of life, medical oncological societies and expert committees have included fertility issues in their guidelines (Table 4.1). They have recommended that all young cancer patients be informed about the risk of POI due to treatment and that those who are interested in fertility preservation be referred to an oncofertility specialist. Despite these guidelines, continuous efforts are needed to improve the current knowledge and practices of oncologists regarding fertility issues and to

Table 4.1 Key recommendations

	Key recommendations
ESMO (2013) [107]	Young women desiring future fertility **should be counseled** on available fertility preserving options before starting anticancer treatment. Counseling should be implemented soon after diagnosis to allow prompt referral to fertility specialists.
St Gallen (2015) [108]	The Panel considered that **fertility preservation by ovarian tissue or oocyte conservation should be offered** upon request for patients aged <40.
ESHRE-ASRM (2015) [109]	Several oncological and nononcological diseases may affect current or future fertility, either due to the disease itself or to gonadotoxic treatment, and need an adequate FP approach. These patients **should be counseled regarding potential fertility loss and should be referred to fertility specialists** to discuss options for FP and current results. .
BCY3 (2017) [5]	All young women **should be referred** for special counseling/consultation if interested in fertility preservation prior to commencement of any therapy.
ASCO (2018) [47]	All oncologic health care providers **should be prepared to discuss infertility as a potential risk of therapy**. This discussion should take place as soon as possible once a cancer diagnosis is made and can occur simultaneously with staging and the formulation of a treatment plan.

reinforce the collaboration between oncologists and oncofertility centers [15, 16]. Currently available fertility preservation options include oocyte and embryo cryopreservation, ovarian tissue cryopreservation, and pharmacological protection with GnRH analogs.

Oocyte and Embryo Cryopreservation Procedures

Cryopreservation of embryos is the most established procedure for fertility preservation as it has been routinely available for ART treatments since the 1980s [17]. However, it requires the patient to have a partner to provide sperm or the use of donor sperm and it has raised several ethical and legal concerns that have restricted its application in different countries (i.e., Germany, Switzerland, Italy, Austria) [18] (Table 4.2). One way to circumvent this issue was to develop oocyte cryopreservation techniques. Since 2013, oocyte cryopreservation has no longer been considered to be experimental and has become a standard procedure available in many IVF laboratories

Table 4.2 Advantages and disadvantages of fertility preservation procedures

Procedure	Benefit	Disadvantages/risks
Embryo cryopreservation	• Established procedure • Well-known efficiency and outcomes	• 2–3 weeks delay • Requires partner or donor sperm • Limited number of embryos cryopreserved • Legal and ethical issues
Oocyte cryopreservation	• Established procedure • Well-known efficiency and outcomes	• 2–3 weeks delay • Limited number of oocytes cryopreserved • Appropriate expertise required
Ovarian tissue cryopreservation and transplantation	• Fertility restoration and possibility to achieve spontaneous pregnancy • Ovarian function restoration • No delay	• Experimental procedure[a] • Appropriate expertise required • Risks due to surgery (laparoscopy) and anesthesia • Risk of recurrence of the disease after graft in malignant diseases with possible ovarian involvement • Theoretical risk of increasing POI rate due to ovarian tissue collection (no evidence)
Oocyte cryopreservation after IVM	• Experimental procedure • No delay	• Very limited number of oocytes cryopreserved • Low developmental competence and success rates
Pharmacological protection (GnRHa)	• Noninvasive • Spontaneous ovarian function recovery • 10-day delay recommended but not mandatory	• Efficiency only demonstrated in breast cancer patients • Should not replace gamete or embryo storage • Lack of data on fertility restoration rate

[a]No longer experimental in Israel, status subjected to discussion in EU and the USA

[19]. While the success rate was not optimal with slow-freezing methods, the development of vitrification techniques has significantly improved clinical outcomes. A recent meta-analysis confirmed improved pregnancy rates per cycle using oocyte vitrification compared to slow freezing (RR = 2.81, 95% CI: 1.05–7.51; $P = 0.039$) [20]. Compared to fresh oocytes, no difference was observed in the live birth rate per cycle when vitrification was exclusively used (RR = 1.04, 95% CI: 0.61–1.76, $P = 0.892$). Overall, each vitrified oocyte has around an 8% chance of resulting in pregnancy and a 5% chance of resulting in a delivery [20, 21].

Efficiency and Outcomes of Oocyte Cryopreservation

Thanks to these achievements, the vitrification of mature oocytes has become the standard approach for fertility preservation in cancer patients when performed in centers with the necessary expertise. However, pregnancy outcome highly depends on the number of stored oocytes and the age of the patient. It has been reported that a mean of 12 versus 29 vitrified oocytes are required to achieve a live birth in patients aged between 30 and 36 years old versus those who are older, respectively [22]. The total number of oocytes vitrified is crucial for the future success of the procedure, with delivery rates increasing from 22.6% to 46.4% when more than eight vitrified oocytes are available for IVF [23]. Pregnancy rate per cycle also decreases with advanced age. Delivery rates per IVF/ICSI cycle in women older than 39 years of age do not exceed 10%, and the live birth rate per cycle falls to less than 2% after age 43 [24, 25]. Therefore, embryo or oocyte cryopreservation procedures are usually not recommended in patients older than 40 years of age.

However, these data were obtained from cohorts of nononcological patients, as only a few pregnancies have been reported after using cryopreserved oocytes in oncological patients [23]. In the recent largest series of 80 oncological patients who attempted pregnancy using their vitrified oocytes, the authors reported a lower implantation rate in this cohort compared to women who cryopreserved oocytes for age-related fertility decline (32.5% versus 42.6%, respectively; $P < 0.05$) [26]. Despite the fact that the number of oocytes vitrified per patient was similar in both groups, the cumulative live birth rate was also lower in the oncofertility group (42.1% versus 68.8%) but the difference was observed only for the patients less than 35 years old at the time of the fertility preservation procedure. Nonetheless, the impact of the disease on reproductive outcomes was not confirmed by adjusting OR and remains unclear. Overall, cumulative live birth rates per patient are 45.1% and 29% in patients less than 35 years old and older than 35, respectively [26]. The probability of achieving pregnancy also increases with the number of oocytes collected. In oncological patients, a mean number of 6–10 oocytes are vitrified per cycle [23, 27–29]. As at least 2 weeks is required to complete a controlled ovarian stimulation (COS) cycle and collect the mature oocytes, only one cycle can usually be offered before the beginning of oncological treatment. Moreover, COS cannot be proposed after the start of chemotherapy [30]. Early referral is, therefore, essential to avoid any delay in anticancer treatment while optimizing the efficiency of the

procedure by performing multiple cycles when feasible [31]. COS protocols have been adapted to take into consideration the timing limitations of cancer patients. Ovarian stimulation can start rapidly after counseling, irrespective of cycle phase, without impairing the efficacy of the procedure [32–35]. Based on the concept of multiple follicular waves, a second cycle can be proposed following the first one, offering the possibility of accumulating vitrified oocytes [36]. Double ovarian stimulation (DuoStim) has been performed with success in cancer patients, leading to the vitrification of around 16 oocytes per patient (range: 6–32; $n = 10$) [37].

Impacts of the Disease on Efficiency

The impact of the disease on the ovarian response remains controversial. Several studies have not shown any difference in the number of oocytes collected between oncological and nononcological patients or according to disease types [26, 37–40]. Others have reported lower fertility preservation performance in patients with breast cancer [29] and BRCA-mutated breast cancer [41], lymphoma [42], and ovarian cancer [39].

Standard COS protocols for fertility preservation include around 10 days of ovarian stimulation with gonadotrophins before ovulation trigger with hCG or GnRH analogs. GnRH antagonists are added to avoid premature LH peak during stimulation. As a consequence of ovarian stimulation, estradiol increases at supraphysiological levels (10–20 times higher than spontaneous cycle) which might negatively affect oncological outcomes in hormone-sensitive diseases by stimulating tumor cell proliferation [10]. Adapted protocols have been implemented to maintain steroids at physiological levels using aromatase inhibitors (letrozole) or selective estrogen receptor modulators (SERMs-tamoxifen) during stimulation in breast cancer patients [43, 44]. Oktay et al. reported the only prospective study showing no detrimental effect of COS associated with letrozole on disease-free survival rates in breast cancer patients [43, 45]. Others also have not observed differences in recurrence or in mortality rates between breast cancer patients who underwent COS without letrozole for fertility preservation compared to patients who did not undergo fertility preservation procedures [46]. However, these studies have several biases and the large majority of the centers used an adapted protocol in hormone-sensitive diseases to avoid any potential detrimental effect of the steroids. Therefore, the American Society of Clinical Oncology (ASCO) recently recommended the use of COS associated with aromatase inhibitors for oocyte/embryo cryopreservation in hormonal-sensitive diseases [47].

In Vitro Oocyte Maturation

Immature oocytes can be harvested from the cohort of small antral follicles at any phase of the menstrual cycle, without previous ovarian stimulation, and subsequently in vitro matured (IVM) before vitrification [48]. This method reduces the

delay before oncological treatment and the incidence of ovarian hyperstimulation syndrome (OHSS) in high-risk responder patients [49]. However, the procedure is experimental and its efficiency, in terms of number of oocytes collected and implantation rates after fertilization, remains significantly lower than conventional COS cycles [50]. Although very limited, data available in cancer patients have confirmed this observation, with a live birth rate per cycle not exceeding 7% [51]. Therefore, IVM procedures should be offered only in very specific situations when other options are not available.

Ovarian Tissue Cryopreservation Procedures

The cryopreservation of ovarian tissue emerged in the 1990s as an alternative to established embryo cryopreservation procedures [52–56]. Ovarian biopsies or a whole ovary are usually harvested by laparoscopy or, more rarely, by laparotomy under general anesthesia and dissected into fragments of, maximum, 1–2 mm thickness before cryopreservation in separated cryotubes. Complications of the procedure are rarely reported with an incidence rate varying from 0.2% to 3.3% [57, 58]. The cryopreservation process for ovarian tissue is more complex than that for gametes as the tissue contains various cell types. Nevertheless, the slow-freezing technique is now well established and results in high follicular survival rates after thawing. Recently, vitrification of ovarian tissue has been attempted, with success in humans, but almost all pregnancies obtained so far have been from slow-freezing cryopreserved ovarian tissue [59].

The main advantage of the technique is its rapidity, as it does not require any previous COS treatment (Table 4.2). It is also the only fertility preservation procedure that can be proposed for prepubertal patients. Finally, the transplantation of thawed ovarian tissue allows restoration of natural cycles and spontaneous pregnancy [60]. When feasible, the procedure should be performed before starting oncological treatment but it can also be offered to patients who already received a first-line regimen or low-gonadotoxic chemotherapy such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin lymphoma without impairing the future chances of pregnancy using preserved tissue [61].

The human cortex contains mainly non-growing follicles (NGF) at the primordial stage. This constitutes the ovarian reserve. The density of the follicles within each ovarian fragment depends on patient age and the ovarian reserve [62, 63]. A predictive model has been developed to evaluate follicular density according to age and has been validated by clinical observation [64]. Using this model, we have shown that follicular density decreases from approximately 100 to 16 NGF/mm^3 between 16 and 33 years old. Therefore, several quiescent follicles can be expected to be stored within each fragment of cryopreserved ovarian tissue in young patients but this number rapidly declines with age (Fig. 4.1).

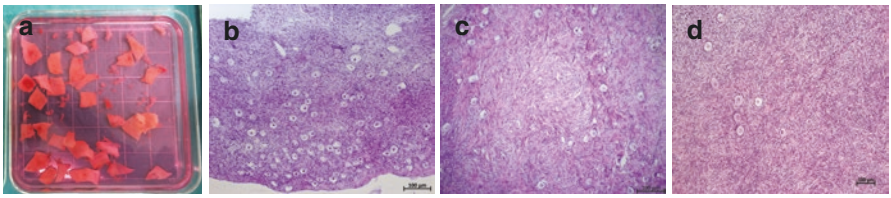

Fig. 4.1 Follicular density within ovarian fragments (**a**) according to age: histological section of ovarian cortex from (**b**) 3-year-old, (**c**) 15-year-old, and (**d**) 30-year-old patients

Efficiency and Outcomes of Ovarian Tissue Cryopreservation

At present, the only available approach to restoring fertility using cryopreserved ovarian cortex is the transplantation of the ovarian tissue [60]. Restoration of ovarian function was first demonstrated after transplantation of a fresh ovary into the forearm with vascular anastomosis in a lymphoma patient treated with pelvic irradiation [65]. Later, follicular development was observed after accidental transplantation of ovarian fragments without vascular anastomosis [66]. The first case of ovarian function restoration using cryopreserved human ovarian fragments was reported in 2000 [67]. A few years later, the first live births were obtained, providing evidence that human cryopreserved ovarian tissue can restore fertility after grafting [61, 68, 69].

Different techniques of ovarian tissue transplantation have been described. After thawing, the fragments can be grafted onto the remaining ovaries or into a pelvic peritoneum pocket in the ovarian fossa (orthotopic sites), or at distance from the ovary, such as subcutaneous sites (heterotopic sites) (Fig. 4.2). While follicular development has been observed at both orthotopic and heterotopic sites, all the pregnancies and live births except one [70] have been reported after transplantation into an orthotopic site, which remains the first option when feasible [63, 71, 72]. At present, more than 100 babies have been born worldwide following the procedure. The ovarian function recovery rate exceeds 90% with a live birth rate per patient around 40% after up to three transplantation procedures [71, 73]. Most of the pregnancies were obtained spontaneously. Recently, two women have been successfully transplanted with ovarian tissue cryopreserved before puberty or menarche, leading to live births and representing an important achievement for all the children who have undergone the procedure [74, 75]. Only one congenital abnormality was reported but it was a case of arthrogryposis in a family with a history of limb malformations [76]. In light of the considerable achievements in the field during the last decade, a debate is ongoing regarding the view that cryopreservation and transplantation procedures are experimental. Ovarian tissue cryopreservation is no longer considered experimental in Israel and will likely be reconsidered in Europe and the USA soon [76, 77].

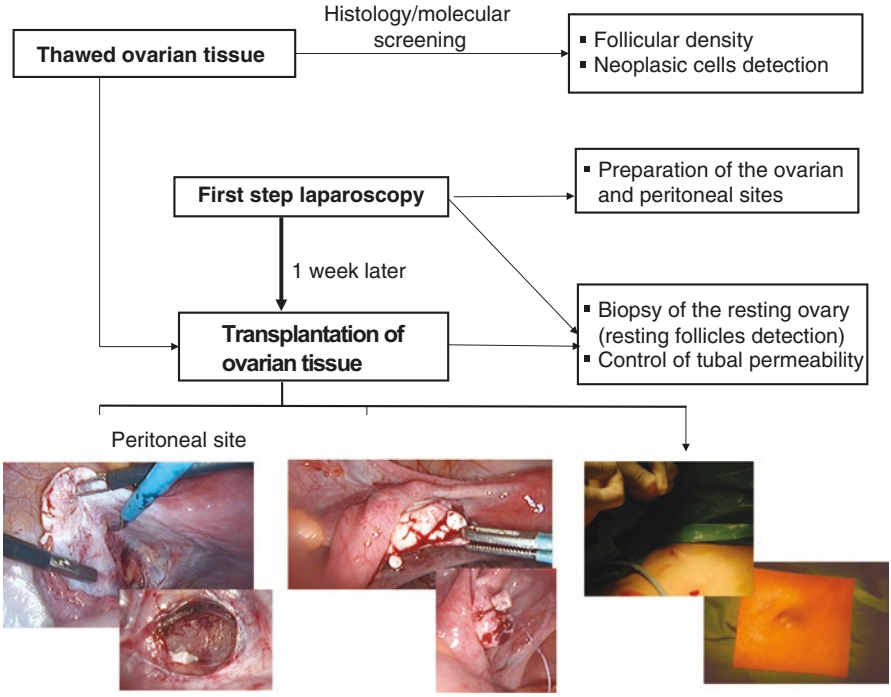

Fig. 4.2 Ovarian tissue transplantation procedure (modified from [60])

One of the main issues regarding the procedure remains the risk of reintroducing cancer cells by using ovarian tissue collected before oncological treatment. This risk varies depending on cancer stage, the localization of the disease, and the type of the disease, and is highest in leukemia, neuroblastoma, ovarian cancer, and Burkitt lymphoma [78, 79]. Experiments using specific PCR markers have revealed that more than 30% of the ovarian tissue from chronic myeloid leukemia (CML) and 70% of acute lymphoblastic leukemia (ALL) patients were contaminated by neoplastic cells. Moreover, contaminated human ovarian tissue is able to transmit the disease after xenograft into mice [80]. In order to avoid this risk, ovarian tissue is harvested after the first-line chemotherapy regimen when complete remission is observed. Despite the fact that the ovarian tissue remained positive for detection of leukemia cells by molecular techniques, these ovarian fragments collected after first-line chemotherapy were negative after xenograft into mice and none of the animals developed the disease [81]. Based on these reassuring data, the first live births after transplantation of cryopreserved ovarian tissue in leukemia patients were reported [82]. Nevertheless, the safety of the procedure should be evaluated with caution in these cases.

Experimental alternatives to the transplantation procedure have been developed to increase the safety of the procedure, including the purging of tumor cells [83], the isolation of follicles to obtain disease-free follicle suspensions that are grafted as an

artificial ovary [84–86], and in vitro follicular culture systems [87]. While important progress has been made in this field, none of these procedures have been applied yet in the clinic.

As the standard procedure consists of the transplantation of ovarian fragments in the absence of vascular anastomosis, the second issue is the dramatic loss of follicles observed after transplantation due to ischemic processes. Revascularization after graft requires around 7 days, during which up to 65% of the follicular pool is lost [78, 88]. Although ovarian function restoration has been observed in the large majority of the patients after 5 months, follicular depletion might dramatically reduce the life span of the graft and limit the success of the procedure. The longevity of the tissue graft varies from less than 1 year to more than 10 years [63, 89]. As a consequence of follicular losses after grafting, the ovarian reserve at the time of the cryopreservation procedure is a crucial factor for success. Women who are younger at the time of the cryopreservation procedure have a higher chance of pregnancy after graft than older patients [71, 90]. Most patients older than 36 years of age at the time of cryopreservation do not succeed, justifying the recommendation of an age limit of 35 years for undergoing the procedure [4, 61, 91]. Several attempts to reduce the ischemic process have been made, with limited clinical application (Table 4.3). Most of these are experimental and have never been used in clinical application. The simplest way to promote neovascularization is to induce granulation at the site of transplantation. The first live birth was obtained after two-step laparoscopy in order to create a peritoneal pocket and induce neovascularization 1 week before the transplantation of the ovarian tissue [68]. Recently, the first pregnancies and live births have been reported after ovarian tissue transplantation with a decellularized extracellular tissue matrix to promote revascularization [92]. Nonetheless, the clinical advantages of these procedures have not been demonstrated.

Table 4.3 Methods to increase vascularization processes and follicular survival after graft of human ovarian tissue

Models	Graft process or treatment	References
Clinical application	Decellularized human extracellular tissue matrix (ECTM)	[92]
Clinical application	Granulation (two-step transplantation)	[68]
Xenograft of human ovarian tissue into mice	VEGF, bFGF, vitE, hyaluran	[110, 111]
Xenograft of human ovarian tissue into mice	Exogenous endothelial cells	[112]
Xenograft of human ovarian tissue into mice	Mesenchymal stem cells	[113]
Xenograft model of human ovarian tissue into mice	Human adipose tissue-derived stem cells (fibrin scaffold)	[114, 115]
Xenograft model of human ovarian tissue into mice	Caspase inhibitors (Z-VAD-FMK)	[116]

Pharmacological Options

The concept of pharmacological protection of the ovary against chemotherapy-induced damage is very attractive. It allows for a reduction in the risk of POI after treatment and increases the chances of spontaneous ovarian recovery and pregnancy. However, only one drug therapy has been tested in humans so far, the concomitant administration of gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy. After several years of intense debate regarding the efficiency of this approach and its mechanism of ovarian protection, recent large randomized studies in breast cancer patients have demonstrated a significant reduction in amenorrhea rates in breast cancer patients who received GnRHa during chemotherapy compared to patients who received chemotherapy alone after 2 years of follow-up [93]. Therefore, the most recent ASCO guidelines state that "GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. GnRHa should not be used in place of proven fertility preservation methods." However, this recommendation is restricted to breast cancer patients as treatment efficacy has not been demonstrated in hematological patients [94].

Drug-based fertility preservation is an emerging approach that is being widely investigated in experimental research to reduce chemotherapy-induced ovarian damage (Table 4.4). Most of the drugs have been tested in animals or human xenograft models and are not yet used for human application in this indication. These proposed therapies target direct mechanisms of chemotherapy-induced ovarian damage such as follicular apoptosis, follicular activation, and vascular injury in the ovary. Chemotherapeutic components like cyclophosphamide, doxorubicin, and their metabolites have been shown to cause human primordial follicle apoptosis. Specifically, cyclophosphamide interferes with cell division by altering DNA base pairs which leads to cross-linking with DNA and to single- or double-strand DNA breaks. The inability to repair these breaks results in cell death. Growing follicles and, more specifically, granulosa cells are the most sensitive to

Table 4.4 Experimental pharmacological approaches to prevent chemotherapy-induced ovarian damage

Targeted mechanisms of ovarian damage	Agents	References
Follicular activation	Immunomodular (AS201) mTOR inhibitors AMH	[99–101]
Apoptosis	Sphingosine-1 phosphate Ceramide-1 phosphate Imatinib Dexrazoxane	[95, 96, 117–120]
Vascular injury	Granulocyte colony-stimulating factor (G-CSF)	[103]
Drug nuclear accumulation	Proteasome inhibitors (Bortezomib)	[121]
Multiple targets	miRNAs	[104, 105]
Unclear	SERMs (tamoxifen)	[106]

chemotherapy-induced apoptosis but quiescent follicles can be also affected [2]. Several drugs have been tested to reduce chemotherapy-induced apoptosis and, for some of them, like imatinib, the results were controversial [95, 96]. Manipulation of the sphingosine pathway, which leads to apoptosis in follicles, has been investigated for the prevention of chemotherapy- and radiotherapy-induced apoptosis in animals with encouraging results [97]. While these approaches are interesting, questions have been raised regarding the possible interaction of these drugs with chemotherapeutic efficiency.

Chemotherapeutic agents, such as alkylating agents, can also induce the massive activation of quiescent follicles through a direct effect on PI3K/Akt pathway and an indirect effect on the growing follicles that negatively regulate quiescent follicle activation by secreting anti-Mullerian hormone (AMH). Altogether, the activation of the PI3K/Akt pathway and the reduction of AMH trigger a follicular "burn-out" effect leading to follicular loss [98]. By co-administration of PI3K/Akt inhibitors during cyclophosphamide treatment in mice, Goldman et al. recently succeed in preserving fertility [99]. Massive follicle activation has also been prevented by the administration of AMH or an immunomodulatory agent, such as AS101, that acts on the PI3K pathway [100, 101]. Finally, vascular injury can also be targeted to reduce ovarian damage. By decreasing microvascularization networks, chemotherapy drugs like doxorubicin induce focal ischemia that contributes to follicular loss [102]. In this regard, G-CSF, already used in cancer therapy, might reduce this vascular effect and, therefore, follicular losses [103].

As chemotherapy-induced damage in the ovary occurs through several mechanisms, the use of microRNAs, noncoding small RNAs that regulate many biological processes such as growth, differentiation, and apoptosis, have emerged as a potential interesting pharmacological approach. Advances in the field of oncology have brought microRNAs into the spotlight as potential therapeutic options. As therapeutic tools, miRNAs can be used to modulate and increase the sensitivity of neoplastic cells to chemotherapy and miRNAs are themselves modulated by chemotherapy. Therefore, they have recently been tested as potential ovarian protective drugs during chemotherapy administration in animal models [104, 105].

Finally, it has been shown that tamoxifen may prevent ovarian damage during chemotherapy. However, this effect has been questioned as the mechanism of action remains unclear [106].

Conclusion

Fertility preservation is considered to be an essential step in the management of young cancer patients in order to improve their long-term quality of life. When feasible, the first option that should be offered is the cryopreservation of embryos or oocytes, as this is the only established procedure. Nevertheless, cryopreservation of ovarian tissue has proven to be efficient for restoration of ovarian tissue and fertility after transplantation and is an interesting alternative, especially for very young patients with low risk of ovarian involvement by tumoral cells. Alternatives to

transplantation might be available in the future due to safety concerns that have been raised regarding the risk of transplanting malignant cells with the ovarian tissue. Finally, GnRHa can be offered as an additional fertility preservation procedure in breast cancer patients but should not replace the cryopreservation of gametes. Several other pharmacological options have been investigated in preclinical settings and offer promise for future clinical use.

References

1. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncol. 2016;12(20):2333–44.
2. Morgan S, Anderson RA, Gourley C, Wallace WH, Spears N. How do chemotherapeutic agents damage the ovary? Hum Reprod Update. 2012;18(5):525–35.
3. Anderson RA, Rosendahl M, Kelsey TW, Cameron DA. Pretreatment anti-Mullerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer. Eur J Cancer. 2013;49(16):3404–11.
4. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;6(4):209–18.
5. Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso MJ, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast (Edinburgh, Scotland). 2017;35:203–17.
6. Lambertini M, Demeestere I. Another step towards improving oncofertility counselling of young women with Hodgkin's lymphoma. Lancet Oncol. 2018;19(10):1264–6.
7. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW, et al. The impact of cancer on subsequent chance of pregnancy: a population-based analysis. Hum Reprod (Oxford, England). 2018;33(7):1281–90.
8. Behringer K, Mueller H, Goergen H, Thielen I, Eibl AD, Stumpf V, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. J Clin Oncol. 2013;31(2):231–9.
9. Anderson RA, Remedios R, Kirkwood AA, Patrick P, Stevens L, Clifton-Hadley L, et al. Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial. Lancet Oncol. 2018;19(10):1328–37.
10. Lambertini M, Goldrat O, Clatot F, Demeestere I, Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol. 2017;29(4):243–52.
11. Lambertini M, Fontana V, Massarotti C, Poggio F, Dellepiane C, Iacono G, et al. Prospective study to optimize care and improve knowledge on ovarian function and/or fertility preservation in young breast cancer patients: results of the pilot phase of the PREgnancy and FERtility (PREFER) study. Breast (Edinburgh, Scotland). 2018;41:51–6.
12. Reh AE, Lu L, Weinerman R, Grifo J, Krey L, Noyes N. Treatment outcomes and quality-of-life assessment in a university-based fertility preservation program: results of a registry of female cancer patients at 2 years. J Assist Reprod Genet. 2011;28(7):635–41.
13. Letourneau JM, Melisko ME, Cedars MI, Rosen MP. A changing perspective: improving access to fertility preservation. Nat Rev Clin Oncol. 2011;8(1):56–60.
14. Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol. 2014;32(11):1151–6.
15. Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, Del Mastro L, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility

and pregnancy-related issues in young breast cancer patients. Breast (Edinburgh, Scotland). 2018;42:41–9.
16. Sallem A, Shore J, Ray-Coquard I, Ferreux L, Bourdon M, Maignien C, et al. Fertility preservation in women with cancer: a national study about French oncologists awareness, experience, and feelings. J Assist Reprod Genet. 2018;35(10):1843–50.
17. Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. Nature. 1983;305(5936):707–9.
18. Gianaroli L, Ferraretti AP, Magli MC, Sgargi S. Current regulatory arrangements for assisted conception treatment in European countries. Eur J Obstet Gynecol Reprod Biol. 2016;207:211–3.
19. 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.
20. Rienzi L, Gracia C, Maggiulli R, LaBarbera AR, Kaser DJ, Ubaldi FM, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum Reprod Update. 2017;23(2):139–55.
21. Rienzi L, Cobo A, Paffoni A, Scarduelli C, Capalbo A, Vajta G, et al. Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentric study. Hum Reprod (Oxford, England). 2012;27(6):1606–12.
22. Chang CC, Elliott TA, Wright G, Shapiro DB, Toledo AA, Nagy ZP. Prospective controlled study to evaluate laboratory and clinical outcomes of oocyte vitrification obtained in in vitro fertilization patients aged 30 to 39 years. Fertil Steril. 2013;99(7):1891–7.
23. Cobo A, Garcia-Velasco JA, Domingo J, Remohi J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril. 2013;99(6):1485–95.
24. European IVFmC, European Society of Human Reproduction and Embryology, Calhaz-Jorge C, De Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. Hum Reprod (Oxford, England). 2017;32(10):1957–73.
25. Raz N, Shalev A, Horowitz E, Weissman A, Mizrachi Y, Ganer Herman H, et al. Cumulative pregnancy and live birth rates through assisted reproduction in women 44-45 years of age: is there any hope? J Assist Reprod Genet. 2018;35(3):441–7.
26. Cobo A, Garcia-Velasco J, Domingo J, Pellicer A, Remohi J. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod (Oxford, England). 2018;33:2222–31.
27. Garcia-Velasco JA, Domingo J, Cobo A, Martinez M, Carmona L, Pellicer A. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. Fertil Steril. 2013;99(7):1994–9.
28. Goldrat O, Gervy C, Englert Y, Delbaere A, Demeestere I. Progesterone levels in letrozole associated controlled ovarian stimulation for fertility preservation in breast cancer patients. Hum Reprod (Oxford, England). 2015;30(9):2184–9.
29. Decanter C, Robin G, Mailliez A, Sigala J, Morschhauser F, Ramdane N, et al. Prospective assessment of follicular growth and the oocyte cohort after ovarian stimulation for fertility preservation in 90 cancer patients versus 180 matched controls. Reprod Biomed Online. 2018;36(5):543–51.
30. Dolmans MM, Demylle D, Martinez-Madrid B, Donnez J. Efficacy of in vitro fertilization after chemotherapy. Fertil Steril. 2005;83(4):897–901.
31. Lee S, Ozkavukcu S, Heytens E, Moy F, Oktay K. Value of early referral to fertility preservation in young women with breast Cancer. J Clin Oncol. 2010;28:4683–6.
32. Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100(6):1673–80.
33. Muteshi C, Child T, Ohuma E, Fatum M. Ovarian response and follow-up outcomes in women diagnosed with cancer having fertility preservation: comparison of random start

and early follicular phase stimulation—cohort study. Eur J Obstet Gynecol Reprod Biol. 2018;230:10–4.
34. 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 (Oxford, England). 2017;32(10):2123–9.
35. von Wolff M, Capp E, Jauckus J, Strowitzki T, Germeyer A, FertiPROTEKT Study Group. Timing of ovarian stimulation in patients prior to gonadotoxic therapy: an analysis of 684 stimulations. Eur J Obstet Gynecol Reprod Biol. 2016;199:146–9.
36. Sighinolfi G, Sunkara SK, La Marca A. New strategies of ovarian stimulation based on the concept of ovarian follicular waves: from conventional to random and double stimulation. Reprod Biomed Online. 2018;37(4):489–97.
37. Tsampras N, Gould D, Fitzgerald CT. Double ovarian stimulation (DuoStim) protocol for fertility preservation in female oncology patients. Hum Fertil (Cambridge, England). 2017;20(4):248–53.
38. Quinn MM, Cakmak H, Letourneau JM, Cedars MI, Rosen MP. Response to ovarian stimulation is not impacted by a breast cancer diagnosis. Hum Reprod (Oxford, England). 2017;32(3):568–74.
39. von Wolff M, Bruckner T, Strowitzki T, Germeyer A. Fertility preservation: ovarian response to freeze oocytes is not affected by different malignant diseases-an analysis of 992 stimulations. J Assist Reprod Genet. 2018;35(9):1713–9.
40. Lefebvre T, Mirallie S, Leperlier F, Reignier A, Barriere P, Freour T. Ovarian reserve and response to stimulation in women undergoing fertility preservation according to malignancy type. Reprod Biomed Online. 2018;37(2):201–7.
41. Lambertini M, Goldrat O, Ferreira AR, Dechene J, Azim HA Jr, Desir J, et al. Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients. Ann Oncol. 2018;29(1):237–43.
42. Lekovich J, Lobel ALS, Stewart JD, Pereira N, Kligman I, Rosenwaks Z. Female patients with lymphoma demonstrate diminished ovarian reserve even before initiation of chemotherapy when compared with healthy controls and patients with other malignancies. J Assist Reprod Genet. 2016;33(5):657–62.
43. Oktay K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol. 2005;23(16):3858–9.
44. Rodgers RJ, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, et al. The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: a systematic review. Hum Reprod (Oxford, England). 2017;32(5):1033–45.
45. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol. 2008;26(16):2630–5.
46. Moravek MB, Confino R, Smith KN, Kazer RR, Klock SC, Lawson AK, et al. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. Fertil Steril. 2018;109(2):349–55.
47. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(19):1994–2001.
48. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. Lancet. 2014;384(9950):1302–10.
49. Walls ML, Hunter T, Ryan JP, Keelan JA, Nathan E, Hart RJ. In vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. Hum Reprod (Oxford, England). 2015;30(1):88–96.
50. Cohen Y, St-Onge-St-Hilaire A, Tannus S, Younes G, Dahan MH, Buckett W, et al. Decreased pregnancy and live birth rates after vitrification of in vitro matured oocytes. J Assist Reprod Genet. 2018;35(9):1683–9.

51. 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):583–92.
52. Demeestere I, Simon P, Englert Y, Delbaere A. Preliminary experience of ovarian tissue cryopreservation procedure: alternatives, perspectives and feasibility. Reprod Biomed Online. 2003;7(5):572–9.
53. Oktay K, Newton H, Aubard Y, Salha O, Gosden RG. Cryopreservation of immature human oocytes and ovarian tissue: an emerging technology? Fertil Steril. 1998;69(1):1–7.
54. Gosden RG, Mullan J, Picton HM, Yin H, Tan SL. Current perspective on primordial follicle cryopreservation and culture for reproductive medicine. Hum Reprod Update. 2002;8(2):105–10.
55. Newton H, Aubard Y, Rutherford A, Sharma V, Gosden R. Low temperature storage and grafting of human ovarian tissue. Hum Reprod (Oxford, England). 1996;11(7):1487–91.
56. Nugent D, Meirow D, Brook PF, Aubard Y, Gosden RG. Transplantation in reproductive medicine: previous experience, present knowledge and future prospects. Hum Reprod Update. 1997;3(3):267–80.
57. Beckmann MW, Dittrich R, Lotz L, van der Ven K, van der Ven HH, Liebenthron J, et al. Fertility protection: complications of surgery and results of removal and transplantation of ovarian tissue. Reprod Biomed Online. 2018;36(2):188–96.
58. Mayerhofer K, Ott J, Nouri K, Stoegbauer L, Fischer EM, Lipovac M, et al. Laparoscopic ovarian tissue harvesting for cryopreservation: an effective and safe procedure for fertility preservation. Eur J Obstet Gynecol Reprod Biol. 2010;152(1):68–72.
59. Shi Q, Xie Y, Wang Y, Li S. Vitrification versus slow freezing for human ovarian tissue cryopreservation: a systematic review and meta-anlaysis. Sci Rep. 2017;7(1):8538.
60. Demeestere I, Simon P, Emiliani S, Delbaere A, Englert Y. Orthotopic and heterotopic ovarian tissue transplantation. Hum Reprod Update. 2009;15(6):649–65.
61. Demeestere I, Simon P, Emiliani S, Delbaere A, Englert Y. Fertility preservation: successful transplantation of cryopreserved ovarian tissue in a young patient previously treated for Hodgkin's disease. Oncologist. 2007;12(12):1437–42.
62. Poirot C, Vacher-Lavenu MC, Helardot P, Guibert J, Brugieres L, Jouannet P. Human ovarian tissue cryopreservation: indications and feasibility. Hum Reprod (Oxford, England). 2002;17(6):1447–52.
63. Imbert R, Moffa F, Tsepelidis S, Simon P, Delbaere A, Devreker F, et al. Safety and usefulness of cryopreservation of ovarian tissue to preserve fertility: a 12-year retrospective analysis. Hum Reprod (Oxford, England). 2014;29:1931–40.
64. McLaughlin M, Kelsey TW, Wallace WH, Anderson RA, Telfer EE. An externally validated age-related model of mean follicle density in the cortex of the human ovary. J Assist Reprod Genet. 2015;32(7):1089–95.
65. Leporrier M, von Theobald P, Roffe JL, Muller G. A new technique to protect ovarian function before pelvic irradiation. Heterotopic ovarian autotransplantation. Cancer. 1987;60(9):2201–4.
66. Marconi G, Quintana R, Rueda-Leverone NG, Vighi S. Accidental ovarian autograft after a laparoscopic surgery: case report. Fertil Steril. 1997;68(2):364–6.
67. Oktay K, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. N Engl J Med. 2000;342(25):1919.
68. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004;364(9443):1405–10.
69. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med. 2005;353(3):318–21.
70. Stern CJ, Gook D, Hale LG, Agresta F, Oldham J, Rozen G, et al. First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy. Hum Reprod (Oxford, England). 2013;28(11):2996–9.

71. Gellert SE, Pors SE, Kristensen SG, Bay-Bjorn AM, Ernst E, Yding AC. 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):561–70.
72. 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):325–36.
73. Pacheco F, Oktay K. Current success and efficiency of autologous ovarian transplantation: a meta-analysis. Reprod Sci. 2017;24(8):1111–20.
74. Demeestere I, Simon P, Dedeken L, Moffa F, Tsepelidis S, Brachet C, et al. Live birth after autograft of ovarian tissue cryopreserved during childhood. Hum Reprod (Oxford, England). 2015;30(9):2107–9.
75. Matthews SJ, Picton H, Ernst E, Andersen CY. Successful pregnancy in a woman previously suffering from beta-thalassemia following transplantation of ovarian tissue cryopreserved before puberty. Minerva Ginecol. 2018;70(4):432–5.
76. Meirow D, Ra'anani H, Shapira M, Brenghausen M, Derech Chaim S, Aviel-Ronen S, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril. 2016;106(2):467–74.
77. von Wolff M, Sanger N, Liebenthron J. Is ovarian tissue cryopreservation and transplantation still experimental? It is a matter of female age and type of cancer. J Clin Oncol. 2018;36:JCO1800425.
78. Oktay K. Ovarian tissue cryopreservation and transplantation: preliminary findings and implications for cancer patients. Hum Reprod Update. 2001;7(6):526–34.
79. Dolmans MM, Luyckx V, Donnez J, Andersen CY, Greve T. Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue. Fertil Steril. 2013;99(6):1514–22.
80. Dolmans MM, Marinescu C, Saussoy P, Van Langendonckt A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood. 2010;116(16):2908–14.
81. Greve T, Clasen-Linde E, Andersen MT, Andersen MK, Sorensen SD, Rosendahl M, et al. Cryopreserved ovarian cortex from patients with leukemia in complete remission contains no apparent viable malignant cells. Blood. 2012;120(22):4311–6.
82. Shapira M, Raanani H, Barshack I, Amariglio N, Derech-Haim S, Marciano MN, 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.
83. Schroder CP, Timmer-Bosscha H, Wijchman JG, de Leij LF, Hollema H, Heineman MJ, et al. An in vitro model for purging of tumour cells from ovarian tissue. Hum Reprod (Oxford, England). 2004;19(5):1069–75.
84. Soares M, Saussoy P, Maskens M, Reul H, Amorim CA, Donnez J, et al. Eliminating malignant cells from cryopreserved ovarian tissue is possible in leukaemia patients. Br J Haematol. 2017;178(2):231–9.
85. Chiti MC, Dolmans MM, Mortiaux L, Zhuge F, Ouni E, Shahri PAK, et al. A novel fibrin-based artificial ovary prototype resembling human ovarian tissue in terms of architecture and rigidity. J Assist Reprod Genet. 2018;35(1):41–8.
86. Telfer EE, Fauser BC. Important steps towards materializing the dream of developing an artificial ovary. Reprod Biomed Online. 2016;33(3):333–4.
87. McLaughlin M, Albertini DF, Wallace WHB, Anderson RA, Telfer EE. Metaphase II oocytes from human unilaminar follicles grown in a multi-step culture system. Mol Hum Reprod. 2018;24(3):135–42.
88. Baird DT, Webb R, Campbell BK, Harkness LM, Gosden RG. Long-term ovarian function in sheep after ovariectomy and transplantation of autografts stored at −196 C. Endocrinology. 1999;140(1):462–71.
89. Jensen AK, Kristensen SG, Macklon KT, Jeppesen JV, Fedder J, Ernst E, et al. Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. Hum Reprod (Oxford, England). 2015;30(12):2838–45.

90. Van der Ven H, Liebenthron J, Beckmann M, Toth B, Korell M, Krussel J, et al. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. Hum Reprod (Oxford, England). 2016;31(9):2031–41.
91. Diaz-Garcia C, Domingo J, Garcia-Velasco JA, Herraiz S, Mirabet V, Iniesta I, et al. Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study. Fertil Steril. 2018;109(3):478–85.e2.
92. Oktay K, Bedoschi G, Pacheco F, Turan V, Emirdar V. First pregnancies, live birth, and in vitro fertilization outcomes after transplantation of frozen-banked ovarian tissue with a human extracellular matrix scaffold using robot-assisted minimally invasive surgery. Am J Obstet Gynecol. 2016;214(1):94.e1–9.
93. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol. 2018;36(19):1981–90.
94. Demeestere I, Brice P, Peccatori FA, Kentos A, Dupuis J, Zachee P, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. J Clin Oncol. 2016;34(22):2568–74.
95. Gonfloni S, Di Tella L, Caldarola S, Cannata SM, Klinger FG, Di Bartolomeo C, et al. Inhibition of the c-Abl-TAp63 pathway protects mouse oocytes from chemotherapy-induced death. Nat Med. 2009;15(10):1179–85.
96. Kerr JB, Hutt KJ, Cook M, Speed TP, Strasser A, Findlay JK, et al. Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. Nat Med. 2012;18(8):1170–2; author reply 2–4.
97. Roness H, Kalich-Philosoph L, Meirow D. Prevention of chemotherapy-induced ovarian damage: possible roles for hormonal and non-hormonal attenuating agents. Hum Reprod Update. 2014;20(5):759–74.
98. Gavish Z, Spector I, Peer G, Schlatt S, Wistuba J, Roness H, et al. Follicle activation is a significant and immediate cause of follicle loss after ovarian tissue transplantation. J Assist Reprod Genet. 2018;35(1):61–9.
99. Goldman KN, Chenette D, Arju R, Duncan FE, Keefe DL, Grifo JA, et al. mTORC1/2 inhibition preserves ovarian function and fertility during genotoxic chemotherapy. Proc Natl Acad Sci U S A. 2017;114:3186.
100. Kalich-Philosoph L, Roness H, Carmely A, Fishel-Bartal M, Ligumsky H, Paglin S, et al. Cyclophosphamide triggers follicle activation and "burnout"; AS101 prevents follicle loss and preserves fertility. Sci Transl Med. 2013;5(185):185ra62.
101. Sonigo C, Beau I, Grynberg M, Binart N. AMH prevents primordial ovarian follicle loss and fertility alteration in cyclophosphamide-treated mice. FASEB J. 2019;33:1278–87.
102. Ben-Aharon I, Shalgi R. What lies behind chemotherapy-induced ovarian toxicity? Reproduction (Cambridge, England). 2012;144(2):153–63.
103. Skaznik-Wikiel ME, McGuire MM, Sukhwani M, Donohue J, Chu T, Krivak TC, et al. Granulocyte colony-stimulating factor with or without stem cell factor extends time to premature ovarian insufficiency in female mice treated with alkylating chemotherapy. Fertil Steril. 2013;99(7):2045–54.e3.
104. Jiajie T, Yanzhou Y, Hoi-Hung AC, Zi-Jiang C, Wai-Yee C. Conserved miR-10 family represses proliferation and induces apoptosis in ovarian granulosa cells. Sci Rep. 2017;7:41304.
105. Fu X, He Y, Wang X, Peng D, Chen X, Li X, et al. Overexpression of miR-21 in stem cells improves ovarian structure and function in rats with chemotherapy-induced ovarian damage by targeting PDCD4 and PTEN to inhibit granulosa cell apoptosis. Stem Cell Res Ther. 2017;8(1):187.
106. Ting AY, Petroff BK. Challenges and potential for ovarian preservation with SERMs. Biol Reprod. 2015;92(5):133.

107. Peccatori FA, Azim HA Jr, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi160–70.
108. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26(8):1533–46.
109. Martinez F. Update on fertility preservation from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives. Hum Reprod (Oxford, England). 2017;32(9):1802–11.
110. Kang BJ, Wang Y, Zhang L, Xiao Z, Li SW. bFGF and VEGF improve the quality of vitrified-thawed human ovarian tissues after xenotransplantation to SCID mice. J Assist Reprod Genet. 2016;33(2):281–9.
111. Friedman O, Orvieto R, Fisch B, Felz C, Freud E, Ben-Haroush A, et al. Possible improvements in human ovarian grafting by various host and graft treatments. Hum Reprod (Oxford, England). 2012;27(2):474–82.
112. Man L, Park L, Bodine R, Ginsberg M, Zaninovic N, Man OA, et al. Engineered endothelium provides angiogenic and paracrine stimulus to grafted human ovarian tissue. Sci Rep. 2017;7(1):8203.
113. Zhang Y, Xia X, Yan J, Yan L, Lu C, Zhu X, et al. Mesenchymal stem cell-derived angiogenin promotes primodial follicle survival and angiogenesis in transplanted human ovarian tissue. Reprod Biol Endocrinol. 2017;15(1):18.
114. Manavella DD, Cacciottola L, Desmet CM, Jordan BF, Donnez J, Amorim CA, et al. Adipose tissue-derived stem cells in a fibrin implant enhance neovascularization in a peritoneal grafting site: a potential way to improve ovarian tissue transplantation. Hum Reprod (Oxford, England). 2018;33(2):270–9.
115. Manavella DD, Cacciottola L, Pomme S, Desmet CM, Jordan BF, Donnez J, et al. Two-step transplantation with adipose tissue-derived stem cells increases follicle survival by enhancing vascularization in xenografted frozen-thawed human ovarian tissue. Hum Reprod (Oxford, England). 2018;33(6):1107–16.
116. Fransolet M, Noel L, Henry L, Labied S, Blacher S, Nisolle M, et al. Evaluation of Z-VAD-FMK as an anti-apoptotic drug to prevent granulosa cell apoptosis and follicular death after human ovarian tissue transplantation. J Assist Reprod Genet. 2019;36(2):349–59.
117. Pascuali N, Scotti L, Di Pietro M, Oubina G, Bas D, May M, et al. Ceramide-1-phosphate has protective properties against cyclophosphamide-induced ovarian damage in a mice model of premature ovarian failure. Hum Reprod (Oxford, England). 2018;33(5):844–59.
118. Roti Roti EC, Salih SM. Dexrazoxane ameliorates doxorubicin-induced injury in mouse ovarian cells. Biol Reprod. 2012;86(3):96.
119. Meng Y, Xu Z, Wu F, Chen W, Xie S, Liu J, et al. Sphingosine-1-phosphate suppresses cyclophosphamide induced follicle apoptosis in human fetal ovarian xenografts in nude mice. Fertil Steril. 2014;102(3):871–7.e3.
120. Morita Y, Tilly JL. Sphingolipid regulation of female gonadal cell apoptosis. Ann N Y Acad Sci. 2000;905:209–20.
121. Roti Roti EC, Ringelstetter AK, Kropp J, Abbott DH, Salih SM. Bortezomib prevents acute doxorubicin ovarian insult and follicle demise, improving the fertility window and pup birth weight in mice. PLoS One. 2014;9(9):e108174.

Fertility Preservation in Women with Hematological Malignancies

5

Javier Domingo and Antonio Pellicer

Introduction

Hematological tumors are the most frequent cancers in children and young adults, with high survival rates that can even reach 95% in children and teenagers affected by Hodgkin lymphoma.

One of the factors affecting quality of life in cancer survivors during reproductive age is the possibility of childbearing. Radiotherapy and chemotherapy may affect the gonadal function and therefore cause infertility. In this context, it is important to define ways to improving the quality of life of our patients and help them along the process of assuming the consequences of their treatments, even in cases in which fertility preservation options cannot be performed.

Considering the demography of hematological cancers, most of the patients suffering from acute lymphoid leukemia and Hodgkin lymphoma are at risk of infertility. Hodgkin lymphoma is one of the cancers with the highest survival rate, but the incidence of premature ovarian failure has been described to increase up to 3 times in those patients undergoing chemotherapy, which is a dose-dependent effect, and up to 30 times in those patients undergoing also pelvic radiotherapy [1]. In addition, though a younger age at the time of treatment may delay the appearance of ovarian failure, this will not, however, diminish their cumulative risk.

Gonadotoxicity of the different chemotherapeutic regiems are described in Table 5.1. Although chemotherapy regimens for lymphomas and leukemias have

J. Domingo (✉)
IVI Las Palmas, Las Palmas, Spain
e-mail: javier.domingo@ivirma.com

A. Pellicer
IVI Roma, Rome, Italy
e-mail: apellicer@ivirma.com

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_5

Table 5.1 Gonadotoxicity based on the polychemotherapy regimen

High risk (>80% permanent amenorrhea)
– Busulphan
– BEACOPP (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, procarbazine) (age >30)
– COPP/MOPP (cyclophosphamide or nitrogen mustard, vincristine, procarbazine, prednisone)
– Chlorambucil
– Cyclophosphamide
Moderate risk (40–60% permanent amenorrhea)
– BEACOPP (age <30)
Low risk (<20% permanent amenorrhea)
– ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine)
– CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)
– CVP (cyclophosphamide, vincristine and prednisone)
– Anthracycline and cytarabine
Very low risk
– ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) (age <32)
– Methotrexate
Unknown risk
– Tyrosine kinase inhibitors (imatinib)
– Oxaliplatin

been optimized in order to minimize the side effects of alkylating agents, fertility counseling, a discipline whose interest is increasing among professionals and patients themselves, should be considered as soon as the diagnosis is confirmed.

Gonadotoxicity in Hematological Cancers

Chemotherapeutic agents may cause depletion of the ovarian reserve and mutations and DNA structural damage in somatic and germ cells [2, 3]. A quick decline in anti-Müllerian hormone (AMH) has been recorded during chemotherapy [4]; however, the number of surviving primordial follicles following chemotherapy depends on different factors such as age, type of agent, and cumulative doses received [3].

Granulosa cells appear to be crucially affected after chemotherapy, leading to premature ovarian failure [5]. Cellular edema of pregranulosa cells and keratin deposits as well as edema of the nucleus of the cells will damage the morphology of the oocyte. Similarly, vascular alterations and fibrosis of the ovarian cortex may contribute to the reduction of follicles [6, 7].

Lymphoid neoplasms are highly radiosensitive, especially B-cell lymphomas. Irradiation of the ovaries may cause direct damage to the DNA of the follicles causing follicular atrophy and decreased ovarian reserve. Primordial follicles are the most radioresistant while the oocytes are the most radiosensitive [8]. The effect of radiotherapy on the ovarian function depends as well on such factors as age, cumulative doses, fractioned doses, and irradiation area [9]. The dose needed to destroy oocytes in humans is 2 Gy [10]. Ninety-seven percent of women treated with

Table 5.2 Radiotherapy doses associated with premature ovarian failure according to the age

Age	Doses (Gy)
Prepuberty	10
20–25 years	4–5
30 years	3
40 years	1.5

5–10 Gy will subsequently undergo ovarian failure, depending on age [11] (Table 5.2).

The doses affecting the ovaries vary contingent upon the stage and location of the disease. For supradiaphragmatic irradiations, the average dose on the ovaries is less than 0.2 Gy [12]. Risk is higher in subdiaphragmatic irradiations; however, in abdominal irradiations of the para-aortic lymph nodes, the doses received are about 1.2 Gy, still low to cause infertility. The risk of infertility is much higher in case of pelvic irradiations. It is important to remember that the use of cytostatics has a synergistic effect with radiotherapy, so the risk of infertility increases with these combined protocols.

The irradiation area has also been associated with alterations of the uterine function due to the reduction of vascular flow, endometrial thickness, and uterine volume [13]. Cranial irradiation with 35–45 Gy can damage the hypothalamus-pituitary-gonadal axis, yet, since gonads are not affected, they usually may recover their function with gonadotropin replacement.

ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and escalated BEACOPP (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, procarbazine) are the two chemotherapy regimens usually used for the treatment of Hodgkin lymphoma (HD). BEACOPP escalated is more toxic due to the presence of alkylating agents and therefore is associated with a higher incidence of long-term side effects such as second malignancies or infertility [14].

Regimens in young people have recently been modified by adding etoposide and cyclophosphamide instead of procarbazine and bleomycin with the aim of increasing the antineoplastic activity and decreasing gonadotoxicity, trying as well to avoid radiotherapy in those low-risk patients with an early response and negative PET result after completing their treatment.

The treatment for non-Hodgkin lymphomas (NHL) is quite variable depending on the histological subtype and risk factors, and is based on polychemotherapy regimens such as CHOP (cyclophosphamide, vincristine, adriamycin, prednisone), radiotherapy, and monoclonal antibodies; however, immunochemotherapy is often used in diffuse large-cell B lymphoma, as gonadotoxicity effects are lower when combining the monoclonal antibody rituximab and CHOP.

Acute lymphoblastic leukemia is the most common neoplasm among children, and the polychemotherapy now commonly used is considered of low risk for infertility. Only patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) will be related to infertility and fertility preservation should be considered in high-risk patients or those with recurrences about to undergo an allo-HSCT.

Chronic myeloid leukemia is currently being treated with tyrosine kinase inhibitors, something which has increased the survival rates of these patients. Around 25% of patients affected by CML are less than 50 years old. Gonadotoxicity is low for tyrosine kinase inhibitors, but teratogenic effects have been described, so pregnancy in CML patients needs a specific management. Fertility preservation should be considered in those patients who have failed treatment with tyrosine kinase inhibitors and will be undergoing therefore an allogeneic hematopoietic stem cell transplantation.

According to the European Society of Blood and Marrow Transplantation (EBMT) Registry of HSCT, 60% of the young patients receiving a HSCT survive, with high risk of ovarian failure and infertility and other late effects. Candidates for HSCT and therefore for fertility preservation included 10% of children diagnosed with acute lymphoblastic leukemia and 50% of those with recurrences, 10% of the patients with lymphoma, <50% with acute myeloid leukemia and most of those affected of myelodysplastic syndrome [15].

Fertility Preservation in Hematological Cancers

Several strategies have been proposed to protect or preserve the ovarian function in patients undergoing chemotherapy [2]. Oocyte and embryo vitrification are the only ones currently not being considered experimental [16]. Ovarian cortex cryopreservation plays an important role for fertility preservation treatments in hematological neoplasms since these types of tumors are very frequent in prepubertal girls.

Oocyte and Embryo Vitrification

According to the available evidence, oocyte vitrification is a reproducible, safe, and effective technique. It is an established approach that provides excellent clinical results, similar to fresh, although survival rate depends on age and quality of the oocytes and clinical outcome is strongly related to the number of oocytes [17].

Rather than resorting to other techniques, the current tendency in fertility preservation is to vitrify oocytes, even if it needs an ovarian stimulation that could delay the start of chemotherapy. The limitation is that there will be a limited number of available oocytes and, therefore, a limited number of IVF attempts. Pregnancy of course is not guaranteed. Ovarian tissue cryopreservation is the option available in the case of girls or in cases in which chemotherapy has to be started immediately.

Embryo vitrification is another possible option to preserve fertility, but it is less considered due to its ethical dilemmas and, often, the lack of partner in patients so young.

Whether ovarian response to stimulation decreases or not in cancer patients remains still a controversial issue. Different authors have found no significant

differences in antral follicle count according to the type of cancer [18], and recently Von Wolff reported no significant differences in the ovarian response for hematological malignancies, even in cases of a better response with more mature oocytes and embryos cryopreserved [19]. Response may ultimately depend on the age of the patients [18].

Oocyte vitrification has been proved effective for safeguarding fertility. Age is revealed as the most powerful confounding factor, and the number of oocytes consumed per patient is closely linked to success. Poorer outcomes in cancer patients have been described, in comparison to those who vitrified electively, although these data need still to be confirmed [20]. In this study, 65% were breast cancer patients and only 17.8% hematological cancers. Further research is mandatory to rule out the role of cancer disease in IVF outcomes. This can be effectively done by also considering malignancy type, especially taking into account that breast cancer is the most frequent type of cancer in most of the studies [20].

Gonadal Medical Protection

Gonadotropin-Releasing Hormone Agonists (GnRHa)

The efficiency of GnRH agonists in preventing premature ovarian failure in women with hematological malignancies is still controversial [21]. GnRH agonists would act by inhibiting the secretion of FSH that enables the recruitment of the primordial follicles that will be subjected to apoptosis after exposition to chemotherapy and decreasing the perfusion flow of the uterus and ovaries. Thus, a decreased number of primordial follicles will be exposed to chemotherapy.

The potential mechanisms of action for the protective effects of GnRHa during chemotherapy are not clearly identified. A reduction in the mitotic activity of the granulosa cells has been described in animals after the administration of GnRHa, though GnRHa could also prevent follicles from reaching their sensitivity threshold to chemotherapy. FSH suppression after GnRHa administration could prevent chemotherapy-induced damage on the early growing follicles by slowing down the proliferation of follicular cells, and therefore preventing an accelerated recruitment of the quiescent follicular pool [22].

The American Society of Clinical Oncology (ASCO) refers insufficient evidence about the effectiveness of GnRH agonists and ovarian suppression drugs for fertility preservation; although they can provide some beneficial effects, such as the prevention of the metrorrhagia due to the associated thrombocytopenia, they do not recommend them as a reliable method for hematological diseases instead of proven fertility preservation methods. However, the use of GnRHa is supported in breast cancer patients [23]. The Spanish Society of Medical Oncology (SEOM) considers GnRH agonists an option for negative-ER breast cancers, whenever other procedures are not available, but doesn't recommend them for other type of tumors [24].

There are studies in favor and against the use of GnRH agonists with the aim of fertility preservation [25, 26], although most of them are limited due to the heterogeneity of the follow-up: type of cancer, type of chemotherapy, sample, control groups or the definition of ovarian function or ovarian failure. Furthermore, many studies limit their analysis to the ovarian function or to patients with menopause but very few analyze the future fertility. Since the recovery of ovarian function doesn't necessarily entail fertility, only pregnancy rate would serve as a marker of GnRHa as a procedure for fertility preservation. In addition, evidence in hematological diseases is rather scarce, since most of the studies are performed in breast cancer patients.

Demeestere et al. in 2016 didn't find any significant difference when adding GnRH agonists in patients diagnosed with lymphoma; on the other hand, Gris-Martínez et al. didn't find any protection for fertility in patients with cancer or autoimmune diseases, while side effects such as decreased bone mineral density, headache or vaginal atrophy increased [27, 28]. Behringer et al. compared the administration of oral contraceptives and GnRHa in Hodgkin lymphoma patients receiving BEACOPP with no benefit found in terms of ovarian reserve or AMH determination [29]. In this sense, it has been proposed the use of agonists when attempting to maintain ovarian function, but oocyte vitrification when the objective is to preserve fertility, regardless of the use of agonists [29].

There are also some additional publications that have found significant differences, but mostly referred to the ovarian function, no to fertility [30, 31]. In 2016, Huser et al. assessed the fertility status in young patients receiving GnRH analogs in Hodgkin lymphoma patients treated with chemotherapy to preserve their ovarian function determining FSH measurement and pregnancy achievement. Ovarian function was reported in 82.4% of patients. During the 2 years follow-up period, 90% of patients retained their ovarian function and 21% achieved clinical pregnancy [32]. In 2017, Senra et al. published a meta-analysis and found significant benefits concerning the risk of ovarian failure and amenorrhea in patients using GnRHa, but only for breast cancer patients, not for patients with lymphoma. They also found a higher rate of spontaneous pregnancies [33]. The 2018 ASCO Guidelines found significant higher pregnancy rates in two out of four systematic reviews in patients treated with chemotherapy and GnRHa [23]. Similarly in breast cancer patients, Lambertini et al. published a systematic review of five randomized studies, three of them analyzing pregnancy rates, showing a higher number of pregnancies in those patients receiving GnRHa [34].

GnRH Antagonists

GnRH antagonists suppress gonadotrophin levels immediately after their administration by acting on the GnRH receptor through competitive inhibition [35], thus avoiding the initial flare-up effect on pituitary FSH and LH secretion of the

agonists. Their daily administration is a limitation if compared to the long-acting effect of the agonists.

As shown in mice, the extent of protection is dose-dependent and therefore not absolute: its efficacy decreases with higher doses of cyclophosphamide [36]. Other studies have not found long-term effectiveness; another study suggests that GnRH antagonists could reduce ovarian follicles through a direct effect on the ovary of murines [37]. The addition of a GnRH antagonist to a GnRH agonist may provide a faster downregulation by diminishing the number of receptors, but does not confer a greater protective effect [38]. Wen et al. observed that the use of GnRH antagonists provided benefit on human multiple myeloma in mice by inducing cytotoxicity and apoptosis in myeloma cells [39].

Other Experimental Strategies

There are some experimental and still nontested in human possibilities that may avoid the primordial follicles consumption related to chemotherapy. These are:

Tyrosine Kinase Inhibitors

Imatinib and other tyrosine kinase inhibitors such as nilotinib or dasatinib act by blocking the apoptotic pathway activated by cisplatin in ovarian germ cells. Cisplatin induces DNA damage by activating the c-Abl–TAp63 pathway, leading to cell death. In cell lines, c-Abl phosphorylates TAp63 induce the activation of proapoptotic cells. Treatment with the c-Abl kinase inhibitor imatinib blocks these effects [40].

First generation tyrosine kinase inhibitor imatinib is used for the treatment of chronic myeloid leukemia and acute lymphoblastic leukemia. Its gonadotoxicity is low, although not excluded completely, and has important teratogenic effects on the fetus [41].

AS101

In vivo treatment of mice with the immunomodulator AS101 reduced cyclophosphamide induced loss of primordial follicles as well as reduced apoptosis in granulosa cells of growing follicles by inhibiting the PI3K/PTEN/Akt pathway, which induces the activation of primordial follicles. It has also shown no interference with the primary antineoplastic activity of cyclophosphamide but also a synergistic anticancer activity with it [42].

Sphingosine-1-phosphate (S1P)

In vivo treatment of human ovarian tissue xenografts in mice with S1P, an inhibitor of the ceramide-promoted apoptotic pathway, increased vascular density and angiogenesis, and reduced follicle apoptosis [43]. In different studies, a dose-dependent preservation effect has been observed, reducing irradiation-induced primordial follicle depletion and even a complete preservation of both primordial and growing follicles when administered at high doses [42, 44].

Different studies have shown that it also protects against the effect of chemotherapy induced follicle loss [42] although results have not been uniformly positive [44]. Its short half-life is an important limitation, as it would require continuous administrations or even directly in the ovary.

Anti-Müllerian Hormone

AMH is a negative regulator of primordial follicle activation that inhibits primordial follicle recruitment and growth, regulating the proportion of primordial follicles being activated in each cycle, and therefore protecting the dormancy of the ovarian follicle pool. Adding recombinant human AMH in mice resulted in higher number of primordial follicles and lower loss of follicles compared to those ovaries exposed only to chemotherapy [42]. Its low possibility of side effects due to its activity being limited to the ovary is an interesting point.

Ovarian Transposition

Ovarian transposition is a surgical procedure, which aims to avoid direct exposure of the ovaries to radiotherapy by moving them away from the field of irradiation, although indirect exposure may also cause gonadotoxicity. It should be considered for any pathology requiring pelvic radiotherapy treatment with reasonable prognosis and good ovarian reserve. To render ovarian transposition useful, the ovaries should be placed at least 2–5 cm from the limit of the irradiation volume [45, 46].

Currently there are more efficient fertility preservation procedures; ovarian transposition should be, however, considered only in those patients who are going to be treated with pelvic radiotherapy alone, without chemotherapy, or with chemotherapy linked to a low risk of gonadotoxicity. It can also be considered as a complementary treatment to ovarian cortex cryopreservation or oocyte vitrification. Scatter radiotherapy can cause considerable damage even if the gonads are outside the radiation field [47].

The ovarian function has been shown to be preserved in 50–80% of the patients having undergone this treatment [48]. It is important to avoid any injury in the vascular flow when moving out the ovaries since this may condition the results as well as the residual radiation effect [48, 49]. The endometrial damage will also play an important role in the prognosis of future fertility.

Although spontaneous pregnancies have been described as a migration of the ovary can exist [50], the extrapelvic location of the ovaries will hinder the access to them in case of an ovarian stimulation for IVF. It is not recommended to place again the ovaries in its original place [51].

In Vitro Maturation

Immature egg retrieval for further in vitro oocyte maturation and vitrification is a promising option for the future but still under evaluation and regarded as experimental [26, 52]. The combination of successful cryopreservation of ovarian tissue

and follicle culture is an emerging option for those patients who need to start chemotherapy soon after diagnosis and for those who cannot undergo ovarian stimulation. The immature oocytes will be isolated from the antral follicles of either fresh or cryopreserved ovarian tissues for subsequent in vitro maturation and vitrification.

Immature oocytes can be retrieved through transvaginal aspiration at any stage of the menstrual cycle from the small antral follicles in the ovarian cortex, but also at the time of ovarian cortex processing before cryopreservation. The absence of stimulation is the main benefit, but results are not consistent enough and still need to be improved. The fertilization potential of in vitro matured oocytes might be compromised by the cryopreservation process [53], and vitrification of mature oocytes is preferred over cryopreservation of immature oocytes [54]. Pregnancy and implantation rates are therefore lower than those after conventional IVF [52], and higher clinical miscarriage rate has been also observed [55]. Many children have been born after fertilization of fresh in vitro maturation oocytes, but very few livebirths have been reported with the use of in vitro maturation oocytes that have been cryopreserved and thawed or warmed, related to the worse outcome of those oocytes [53]. Although the viability, development capability, and fertilization potential of oocytes from prepubertal pediatric patients are unknown, vitrified-in vitro-matured oocytes collected ex vivo during ovarian tissue cryopreservation procedure may have special relevance for those patients in whom autografting cryopreserved-thawed ovarian tissue poses high risk of reseeding the malignancy [56].

This method may be suitable for patients in an urgent need to start cytotoxic therapy, for prepubertal girls who cannot undergo ovarian stimulation, for patients with polycystic ovaries (PCO), or, finally, whenever we want to avoid an ovarian stimulation.

In conclusion, young patients diagnosed with hematological cancers who will be treated with chemotherapy and radiotherapy should be counseled for fertility preservation. Oocyte and embryo vitrification are the only procedures not considered experimental. Ovarian response is not affected by the type of cancer, and prognosis is highly dependent on age and the ovarian reserve.

References

1. Harel S, Fermé C, Poirot C. Management of fertility in patients treated for Hodgkin's lymphoma. Haematologica. 2011;96:1692–9.
2. Larsen EC, Müller J, Schmiegelow K, et al. Reduced ovarian function in long-term survivors of radiation and chemotherapy-treated childhood cancer. J Clin Endocrinol Met. 2003;88:5307–14.
3. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update. 2001;7:535–43.
4. Anderson RA, Themmen AP, Al-Qahtani A, et al. The effects of chemotherapy and long term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. Hum Reprod. 2006;21:2583–92.
5. Marcello MF, Nuciforo G, Romeo R, et al. Structural and ultrastructural study of the ovary in childhood leukemia after succesful treatment. Cancer. 1990;66:2099–104.

6. Familiari G, Caggiati A, Nottola SA, et al. Ultrastructure of human primordial follicles after combination chemotherapy for Hodgkin's disease. Hum Reprod. 1993;8:2080–7.
7. Meirow D, Dor J, Kaufman B, et al. Cortical fibrosis and blood-vessels damage in human ovaries exposed to chemotherapy. Potential mechanisms of ovarian injury. Hum Reprod. 2007;22:1626–33.
8. Wo JY, Viswanathan AN. The impact or radiotherapy on fertility, pregnancy and neonatal outcomes of female cancer patients. Int J Radiat Oncol Biol Phys. 2009;73:1304–12.
9. Irtan S, Orbach D, Helfre S, Sarnacki S. Ovarian transposition in prepubescent and adolescent girls with cancer. Lancet Oncol. 2013;14:e601–8.
10. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of human oocyte. Hum Reprod. 2003;18:117–21.
11. Howell SJ, Shalet S. Gonadal damage from chemotherapy and radiotherpy. Endocrinol Metab Clin. 1998;27:927–43.
12. De Bruin ML, Huisbrink J, Hauptmann M, et al. Treatment-related risk factors for premature menopause following Hodgkin lymphoma. Blood. 2008;111:101–8.
13. Patrick K, Wallace WH, Critchley H. Late reproductive effects of cancer treatment in female survivors of childhood malignancy. Curr Obstet Gynecol. 2003;13:369–72.
14. Skoetz N, Will A, Monsef I, et al. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma. Cochrane Database Syst Rev. 2017;(5):CD007941.
15. Loren AW, Chow E, Jacobsohn DA, Gilleece M, Halter J, Joshi S, et al. Pregnancy after hematopoietic cell transplantation: a report from the late effects working committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). Biol Blood Marrow Transplant. 2011;17:157–66.
16. Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99:37–43.
17. Cobo A, García-Velasco JA, Coello A, et al. Oocyte vitrification as an efficient option for elective fertility preservation (EFP). Fertil Steril. 2016;105:755–64.
18. Alvarez RM, Ramanathan P. Fertility preservation in female oncology patients: the influence of the type of cancer on ovarian stimulation response. Hum Reprod. 2018;33:2051–9.
19. von Wolff M, Bruckner T, Strowitzki T, Germeyer A. Fertility preservation: ovarian response to freeze oocytes is not affected by different malignant diseases-an analysis of 992 stimulations. J Assist Reprod Genet. 2018;35:1713–9.
20. Cobo A, García-Velasco J, Domingo J, et al. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod. 2018;33:2222–31.
21. American Society of Clinical Oncology. Recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917–31.
22. Lambertini M, Horicks F, Del Mastro L, et al. Ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy in cancer patients: from biological evidence to clinical application. Cancer Treat Rev. 2019;72:65–77.
23. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994–2001.
24. Muñoz M, Santaballa A, Seguí MA, et al. SEOM clinical guideline of fertility preservation and reproduction in cancer patients (2016). Clin Transl Oncol. 2016;18:1229–36.
25. Blumenfeld Z, Evron A. Endocrine prevention of chemotherapy-induced ovarian failure. Curr Opin Obstet Gynecol. 2016;28:223–9.
26. Elgindy E, Sibai H, Abdelghani A, et al. Protecting ovaries during chemotherapy through gonad suppression: a systematic review and metaanalysis. Obstet Gynecol. 2015;126: 187–95.
27. Demeestere I, Brice P, Peccatori FA, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. J Clin Oncol. 2016;34:2568–74.

28. Gris-Martínez JM, Trillo-Urrutia L, Gómez-Cabeza JJ, et al. Protective effect of GnRH analogues on the reproductive capacity of women with neoplasia or autoimmune disease who require chemotherapy. Final results of a phase II clinical trial. Med Clin. 2016;146:97–103.
29. Behringer K, Thielen I, Mueller H, et al. Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial. Ann Oncol. 2012;23:1818–25.
30. Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016;14(1):1.
31. Blumenfeld Z, Evron A. Preserving fertility when choosing chemotherapy regimens—the role of gonadotropin-releasing hormone agonists. Expert Opin Pharmacol. 2015;16:1009–20.
32. Huser M, Smardova L, Janku P, et al. Fertility status of Hodgkin lymphoma patients treated with chemotherapy and adjuvant gonadotropin-releasing hormone analogues. J Assist Reprod Genet. 2015;32:1187–93.
33. Senra JC, Roque M, Talim MCT, et al. Gonadotropin-releasing hormone agonist for ovarian protection during cancer chemotherapy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51:77–86.
34. Lambertini M, Dellepiane C, Viglietti G, et al. Pharmacotherapy to protect ovarian function and fertility during cancer treatment. Expert Opin Pharmacother. 2017;18:739–42.
35. Rabinovici J, Rothman P, Monroe SE, et al. Endocrine effects and pharmacokinetic characteristics of a potent new gonadotropin-releasing hormone antagonist (Ganirelix) with minimal histamine-releasing properties: studies in postmenopausal women. J Clin Endocrinol Metab. 1992;75:1220–5.
36. Meirow D, Assad G, Dor J, et al. The GnRH antagonist cetrorelix reduces cyclophosphamide-induced ovarian follicular destruction in mice. Hum Reprod. 2004;19:1294–9.
37. Danforth DR, Arbogast LK, Friedman CI. Acute depletion of murine primordial follicle reserve by gonadotropin-releasing hormone antagonists. Fertil Steril. 2005;83:1333–8.
38. Knudtson JF, Tellez M, Failor CM, et al. A combination of a GnRH antagonist and agonist for fertility preservation in an adolescent female murine model. Reprod Sci. 2017;24:1280–3.
39. Wen J, Feng Y, Bjorklund CC, et al. Luteinizing hormone-releasing hormone (LHRH)-I antagonist cetrorelix inhibits myeloma cell growth in vitro and in vivo. Mol Cancer Ther. 2011;10:148–58.
40. Gougeon A. Regulation of ovarian follicular development in primates: facts and hypotheses. Endocr Rev. 1996;17:121–55.
41. Bildik G, Acılan C, Sahin GN, et al. C-Abl is not actıvated in DNA damage-induced and Tap63-mediated oocyte apoptosıs in human ovary. Cell Death Dis. 2018;20(9):943.
42. Roness H, Kashi O, Meirow D. Prevention of chemotherapy-induced ovarian damage. Fertil Steril. 2016;105:20–9.
43. Morita Y, Perez GI, Paris F, et al. Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. Nat Med. 2000;6:1109–14.
44. Kaya H, Desdicioglu R, Sezik M, et al. Does sphingosine-1-phosphate have a protective effect on cyclophosphamide and irradiation-induced ovarian damage in the rat model? Fertil Steril. 2008;89:732–5.
45. Gross E, Champetier C, Pointreau Y, et al. Normal tissue tolerance to external beam radiation therapy: ovaries. Cancer Radiothér. 2010;14:373–5.
46. Haie-Meder C, Mlika-Cabanne N, Michel G, et al. Radiotherapy after ovarian transposition: ovarian function and fertility preservation. Int J Radiat Oncol Biol Phys. 1993;25:419–24.
47. Kimler BF, Briley SM, Johnson BW, et al. Radiation-induced ovarian follicle loss occurs without overt stromal changes. Reproduction. 2018;155:553–62.
48. Gubbala K, Laios A, Gallos J, et al. Outcomes of ovarian transposition in gynaecological cancers; a systematic review and meta-analysis. J Ovarian Res. 2014;7:69.
49. Mossa B, Schimberni M, di Benedetto L, et al. Ovarian transposition in young women and fertility sparing. Eur Rev Med Pharmacol Sci. 2015;19:3418–25.
50. Morice P, Thiam-Ba R, Castaigne D, et al. Fertility results after ovarian transposition for pelvic malignancies treated by external irradiation or brachytherapy. Hum Reprod. 1998;13:660–3.

51. Salih S, Albayrak S, Seo S, Stewart S, Bradley K, Kushner D. Diminished utilization of in vitro fertilization following ovarian transposition in cervical cancer patients. J Reprod Med. 2015;60:345–53.
52. De Vos M, Smitz J, Woodruff T. Fertility preservation in women with cancer. Lancet. 2014;384:1302–10.
53. Cohen Y, St-Onge-St-Hilaire A, Tannus S, et al. Decreased pregnancy and live birth rates after vitrification of in vitro matured oocytes. J Assist Reprod Genet. 2018;35:1683–9.
54. Brambillasca F, Guglielmo MC, Coticchio G, et al. The current challenges to efficient immature oocyte cryopreservation. J Assist Reprod Genet. 2013;30:1531–9.
55. Buckett WM, Chian RC, Dean NL, et al. Pregnancy loss in pregnancies conceived after in vitro oocyte maturation, conventional in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril. 2008;90:546–50.
56. Abir R, Ben-Aharon I, Garor R, et al. Cryopreservation of in vitro matured oocytes in addition to ovarian tissue freezing for fertility preservation in paediatric female cancer patients before and after cancer therapy. Hum Reprod. 2016;31:750–62.

Part II

Challenges to Fertility Preservation in Women with Cancer

6 Organizational Strategies to Overcome Barriers to Addressing Fertility Preservation in the Oncology Setting

Joanne Frankel Kelvin

Introduction

Many young adult women (aged 20–39) are diagnosed with cancer each year—more than 30,000 in the United States [1] and more than 194,000 worldwide [2]. Unfortunately, many cancer treatments used in this population have the potential to impair fertility, and after treatment these women may not be able to achieve a natural pregnancy, have a biologic child, and/or carry a pregnancy. For survivors who had not started or completed building their family at the time of diagnosis, these treatment-related fertility risks can cause significant reproductive concerns [3].

A large body of evidence, summarized in three recent systematic reviews, attests to the unmet needs among many young women for fertility-related information and support at the time of diagnosis and after completing treatment. Goossens et al. [4], summarizing results from 21 articles published in English, Dutch, German, and French between January 2001 and March 2012, found that 66% to 100% of young cancer patients desire information related to fertility. However, there was a wide range in their receipt and satisfaction with the information provided. Anywhere from 0% to 85% reported having received information, and 11% to 90% reported that the information was sufficient. Patients were more likely to want information if they were younger, childless, and had plans for childbearing, and they were more likely to report dissatisfaction with the information received if they were female and older than 35 years of age. Patients desired an open and honest conversation about fertility, occurring early enough before treatment so they had enough time to make decisions about pursuing fertility preservation. They also wanted information about fertility, menses, and family planning after treatment was completed. Bibby et al. [5], summarizing results from 45 English-language articles published from 1990 to

J. F. Kelvin (✉)
Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: kelvinj@mskcc.org

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_6

2015, found that fertility was the most common unmet need among adolescents and young adults with cancer. Women in particular felt they received insufficient information about the impact of treatment on fertility and their options for fertility preservation, and for many, this was associated with distress and affected their decision-making. Women also reported an unmet need for information and support around fertility issues after treatment was completed. Anazodo et al. [6], summarizing results from 147 English-language articles from 17 countries published from 2007 to 2016, found that many patients report receiving incomplete fertility-related information that is given too quickly, without accompanying written material. Females are generally less satisfied than males with the information received. Patients want communication about fertility to be initiated by clinicians around the time of diagnosis, tailored to their age and life stage.

Recognizing the importance of fertility and family building among adolescents and young adults with cancer, a number of professional organizations, including the American Society of Clinical Oncology [7–9], the National Comprehensive Cancer Network [10], the European Society for Medical Oncology [11], the American Society of Reproductive Medicine [12, 13], and the European Menopause and Andropause Society [14], have developed guidelines related to fertility preservation. These highlight the need for oncology clinicians to address fertility before treatment begins by informing patients about the potential risks to fertility from treatment, discussing options for fertility preservation, and referring interested patients to reproductive specialists.

Barriers to Addressing Fertility Preservation

Despite the fact that guidelines have been in place for over 10 years, patients continue to report unmet fertility-related informational needs. This is not surprising as oncology clinicians have identified a number of organizational and personal barriers that make it difficult to address fertility in their clinical practice. These have been described in institution-specific and national surveys, and findings from these and other studies have been reviewed in four recent publications [4, 15–17] and are discussed below.

A lack of knowledge about treatment-related fertility risks is a fundamental problem, leading to uncertainty about which patients need this information and how to quantify the risk of impaired fertility. Most of the data available on risk is based on older chemotherapy regimens. However, chemotherapy agents are being used now in new combinations and at varying doses, and there is an increasing use of targeted and immunologic therapies. We have limited data on the reproductive effects of most of these new treatments. Furthermore, in women there can be significant differences in risk based on age at the time treatment begins, how long treatment continues, and the length of time the patient must wait after treatment before being cleared to attempt pregnancy. The reality is that the risk of infertility cannot be predicted with certainty in any individual patient.

A lack of knowledge about fertility preservation options is another widely reported barrier, potentially leading to misconceptions about what may or may not be feasible for any given patient. Oncology clinicians may not know of recent advances, such as the availability of and indications for oocyte and ovarian tissue cryopreservation. They also may not be aware of measures frequently used in women with cancer to optimize safety during fertility preservation. These include the use of random start protocols, enabling ovarian stimulation to begin at any point in the menstrual cycle, thus minimizing delays in the start of cancer treatment, and the use of aromatase inhibitors to lower estrogen levels during stimulation in women with hormone-sensitive disease. Furthermore, few women who underwent fertility preservation prior to cancer treatment have gone on to use their frozen oocytes, embryos, or ovarian tissue, so there is little known about the success rates in this population. A *lack of relevant fertility-related patient education resources* to build on the limited information discussed during a clinic visit can be an additional barrier, particularly for clinicians who are uncomfortable in their own knowledge about fertility preservation.

Another significant barrier for many oncology clinicians is *not knowing of reproductive specialists to whom they can refer interested patients* to get additional information about their options and to safely pursue fertility preservation if they so desire. This is particularly challenging for clinicians who work in centers or practices without an affiliated reproductive endocrinology service or department.

A lack of time to discuss fertility during clinic visits is reported by many oncology clinicians. Their primary responsibility during the visit is to address the informational and support needs of patients as they explain the cancer diagnosis and describe the proposed treatment plan. If pressed for time, fertility issues may be forgotten if the patient doesn't bring this up, and for some clinicians, a fear of overloading patients with information may contribute to a reluctance to initiate a discussion about fertility.

Clinician assumptions about patient interest can also create barriers. Some clinicians may assume that patients who don't ask about fertility are not interested. Other assumptions about interest may be based on the woman's age, partnership status, prior children, gender identity, sexual orientation, religion, socioeconomic status, or clinical presentation. Financial concerns are particularly significant in countries or states where patients do not have insurance coverage for fertility preservation. If concerned that a patient does not have the financial resources to pay for fertility preservation, clinicians may not bring this up in an effort to protect them from the distress of not being able to pursue this. In addition, clinicians may not be comfortable discussing fertility preservation, with the implication of future parenthood, in patients with a poor prognosis for fear of sending mixed messages. There may also be valid clinical constraints, for example, the patient who is acutely ill and must start treatment urgently, or a situation in which pursing fertility preservation would put the patient's health at risk. As in patients with limited financial resources, clinicians may not introduce a discussion

of fertility with their acutely ill patients to protect them from the distress of not being able to pursue fertility preservation.

Organizational Strategies to Overcome Barriers

Creating organizational policies mandating fertility discussions with newly diagnosed patients is not enough to change practice and ensure patients receive the information they need early enough before starting treatment to have time to decide on and pursue fertility preservation. Oncology care settings must respect the challenges clinicians face in discussing fertility with their patients and develop organization-wide strategies to overcome the barriers that exist.

The nonprofit organization Fertile Hope (acquired by the LIVESTRONG Foundation in 2010) was established to address unmet needs associated with cancer-related infertility and undertook the first effort in the United States to outline the strategies needed. In 2005, they launched the Fertile Hope Centers of Excellence Program,

Table 6.1 Organizational strategies for overcoming barriers to discussing fertility preservation

Barriers to discussing fertility preservation	Organizational strategies
Lack of knowledge about fertility risks and fertility preservation options	Education of oncology clinicians on treatment-related fertility risks and fertility preservation options • Lectures with annual reviews (e.g., grand rounds, disease-specific service meetings, orientations) • Case presentations • Internal website with need to know content accessible at any clinical site within the organization
Lack of fertility-related patient education resources	Ensuring the availability of patient education resources • Written booklets or brochures • Animated or live videos • List of relevant internet sites
Not knowing of reproductive specialists to whom they can refer interested patients	Establishing a network of collaborating reproductive specialists • Locate local reproductive specialists • Use criteria for selecting specialists to affiliate with • Establish a process for making referrals
Lack of time to discuss fertility in clinic	Promoting multidisciplinary responsibility for fertility discussions • Clarify roles, designating individuals to educate and refer • Schedule fertility-focused sessions after the oncology consultation, in person or by phone
Assumptions about patient interest based on whether they ask about fertility, as well as their age, partnership status, prior children, gender identity, sexual orientation, religion, socioeconomic status, and clinical presentation	Creating prompts reminding clinicians to provide information to all patients of reproductive potential • Electronic flags or reports generated by the scheduling system of new patients of reproductive potential • Patient intake forms • Electronic documentation forms

listing specific criteria for cancer centers to be recognized as having effectively institutionalized their approach to fertility [18]. Since then various approaches have been described in the literature to improve fertility-related services for cancer patients [6, 19–22], and common strategies have emerged. These are summarized in Table 6.1, and organized in the discussion below, to illustrate how they may overcome each of the previously described barriers.

Education of oncology clinicians about fertility risks and fertility preservation options is an essential first step to helping them feel more comfortable with and willing to discuss these issues with their patients. Education can be provided by an internal expert if one is available in the setting, or by an invited reproductive endocrinologist from the community. The target audience should include clinicians of all relevant disciplines, including medical, surgical and radiation oncology attending physicians and fellows, advanced practice providers, clinical and research nurses, clinical psychologists, social workers, and genetic counselors. Lectures can be presented at grand rounds, disease-specific service meetings, and staff orientations, with annual reviews and updates on reproductive techniques and clinical outcomes. Case presentations focusing on patient scenarios relevant to particular clinical specialties can create meaningful teachable moments, going beyond general principles and allowing for discussion and sharing of personal experiences in discussing fertility issues with patients. However, clinicians also need access to information during patient encounters in the clinical setting. With most organizations now having some type of intranet system available, creating an institution-specific internal cancer and fertility website can be quite useful. This should be accessible from any workstation at any location in the organization. The site can include links to tables outlining fertility risks, algorithms to clarify fertility preservation options for subsets of patients, tips for discussing fertility, steps for making referrals, copies of guidelines and key references, links to external resources, and printable patient education materials.

Ensuring the availability of patient education resources, with accurate and up-to-date information on fertility risks and fertility preservation options, is also important. Knowing these are on hand to reinforce and supplement the information they provide can increase clinician comfort and willingness to discuss these issues with their patients. These can be in the form of written booklets or brochures, or animated or live video presentations, and can be developed by internal experts or by affiliated reproductive endocrinologists. Alternatively, patients can be given a printed list of relevant external websites they can access to obtain accurate information. Examples are listed below.

- Cancer.Net, developed by ASCO (https://www.cancer.net/navigating-cancer-care/dating-sex-and-reproduction/fertility-concerns-and-preservation-women)
- American Cancer Society (https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/fertility-and-women-with-cancer.html)
- SaveMyFertility, developed by the Oncofertility Consortium (https://www.savemyfertility.org)
- Livestrong Fertility (https://www.livestrong.org/we-can-help/livestrong-fertility)

Whatever educational resources are used can be posted on the organization's internet site for patients to access.

Establishing a network of collaborating reproductive specialists to partner with in providing care is essential. Without this clinicians will not know where to refer patients interested in learning more and/or pursuing fertility preservation. If there are no internal or affiliated reproductive specialists in your organization, there are several ways to find local groups. Examples for finding reproductive specialists in the United States are listed below.

- Fertility Scout, an online tool for finding fertility preservation services established by the Alliance for Fertility Preservation (http://www.allianceforfertilitypreservation.org/get-involved/fertility-scout)
- Society for Assisted Reproductive Technology (https://www.sart.org/clinicpages/find-a-clinic)
- American Society for Reproductive Medicine (https://www.reproductivefacts.org/resources/find-a-health-professional)
- LIVESTRONG Fertility (https://www.livestrong.org/we-can-help/livestrongfertility)

Melan et al. [23] recently described the paucity of networks to facilitate fertility preservation referrals throughout the world. Two resources from outside of the USA are listed below.

- FertiPROTEKT [Germany, Austria, and Switzerland] (https://fertiprotekt.com).
- Oncofertility Referral Network [Canada] (https://cancerkn.com/oncofertilityreferral-network).

To ensure patients receive optimal care, use defined criteria to select which reproductive endocrinology practices to affiliate with. Examples of criteria to consider are listed below.

- Expertise in the techniques of embryo and oocyte cryopreservation (and ideally ovarian tissue cryopreservation).
- Willingness to see patients within 24 to 48 hours.
- Availability of a single point of contact for referring and scheduling patients.
- Experience caring for cancer patients, who have emotional and financial concerns that will be different than those they more commonly see in women seeking treatment for infertility.
- Being prepared to use strategies such as random start protocols to minimize treatment delays and administration of letrozole in patients with hormonesensitive tumors.
- Readiness to communicate and collaborate with the referring oncology team to ensure patients receive safe and effective care.
- Willingness to provide discounted rates and to affiliate with programs that provide free medication for ovarian stimulation.

- Availability of information on their website about the fertility preservation options they offer and how clinicians can refer (or how patients can self-refer) to ensure timely consultations.

Once reproductive specialists have been identified, a simple process for making referrals with communication of relevant medical information must be established, for example, using an electronic order, a secure email, or a phone call.

Promoting multidisciplinary responsibility for fertility discussions, with clarification of roles among team members, can help in overcoming time constraints in clinic. The oncologist would generally be responsible to initiate the discussion, describing the risk of infertility from treatment, just as he or she would describe other potential side effects or risks of the recommended treatment. The nurse, nurse practitioner, or physician assistant on the team could be responsible for following up, outlining the available fertility preservation options, providing relevant educational materials, and referring interested patients. If the patient is overwhelmed during the visit by the information received regarding their cancer diagnosis and the planned treatment, a discussion focused on fertility can be scheduled for the following day, either by phone or at a follow-up clinic visit.

Creating prompts reminding clinicians to provide relevant fertility-related information may help overcome the potential for withholding of information based on assumptions about patient interest. Examples of prompts include: electronic flags or reports generated by the scheduling system of new patients of reproductive age; a question on new patient intake forms asking about interest in receiving fertility information; and electronic documentation forms with fields to document discussion of fertility risks and fertility preservation options.

Implementation and Evaluation

Success in implementing these strategies within the oncology setting, and ensuring they are institutionalized throughout the organization and sustainable over time, is optimized by using a centralized programmatic approach [19–22]. Issues to consider are discussed below.

Establishing an advisory group to provide direction as the program is planned and implemented can be of tremendous value. The group should include oncology clinicians of various disciplines and specialties, particularly those that treat a high volume of patients of reproductive potential, as well as one or two cancer survivors. This will ensure that those who are to be served by the program can provide advice and input as educational sessions are planned and as resources and services are developed and refined. Clinicians can later serve as champions in the clinical setting after the program is launched to disseminate information to their colleagues.

A key component of several programs described in the literature is the establishment of an internal consult service [19–22]. Any oncology clinician can refer interested patients for individualized education on risks and options, counseling to facilitate decision-making, and referral of interested patients to reproductive specialists where they can learn more and/or pursue fertility preservation. In addition,

the individual or team providing this consult service can serve as a liaison between the oncology clinicians and reproductive specialists to ensure coordination of care and optimal communication. They may also provide or arrange multidisciplinary clinician education, answer clinicians' fertility-related questions, develop patient education materials, and participate in or lead fertility-related improvement and research initiatives. An alternative approach to developing expertise internally is to bring a reproductive endocrinologist on site, within the cancer center [24], potentially reducing logistical barriers to making referrals to outside providers.

It is challenging to evaluate the effectiveness of organizational strategies designed to ensure that patients receive timely information about their fertility risks and fertility preservation options. Metrics used to evaluate practice have included medical record documentation of fertility-related discussions [25–28], referrals to a centralized fertility team [22], and referrals for sperm banking or oocyte or embryo cryopreservation [19, 22, 24, 26, 29, 30]. However, documentation may not accurately reflect clinical practice, and referral numbers without meaningful denominators to track rates over time is limited in its usefulness and may not capture referrals that were made without going through a centralized individual or team, or patients who declined a referral. Tracking the number of patients who decide to pursue fertility preservation is another metric that is sometimes used, but this does not account for the various reasons patients decline fertility preservation. Another, more meaningful, metric may be patient satisfaction with fertility-related information received [22]. Regardless of the decisions patients make about obtaining a referral or pursuing fertility preservation, it is their perception of the experience that is perhaps most important in minimizing later regret. Developing a valid and reliable instrument to measure satisfaction with information received could be of use to all oncology organizations as they strive to improve practice in this area.

Conclusion

It is widely accepted that oncology clinicians have a responsibility to inform young patients about the potential risks to fertility from treatment, discuss options for fertility preservation, and refer interested patients to reproductive specialists. To ensure patients receive the information and referrals they want and need, organizations must acknowledge the barriers clinicians face in addressing fertility in their clinical practice. Regardless of its structure—comprehensive cancer center, academic center, or private practice—any organization providing cancer care can benefit by using a centralized programmatic approach to developing strategies to overcome these barriers.

Acknowledgment
Funding: Funded in part through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30CA008748.

References

1. American Cancer Society. Key statistics for cancers in young adults. 2018.
2. Fidler MM, Gupta S, Soerjomataram I, Ferlay J, Steliarova-Foucher E, Bray F. Cancer incidence and mortality among young adults aged 20–39 years worldwide in 2012: a population-based study. Lancet Oncol. 2017;18(12):1579–89.
3. 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):935–42.
4. Goossens J, Delbaere I, Van Lanker A, Beeckman D, Verhaeghe S, Van Heck A. Cancer patients' and professional caregivers' needs, preferences and factors associated with receiving and providing fertility-related information: a mixed-methods systematic review. Int J Nurs Stud. 2014;51:300–19.
5. Bibby H, White V, Thompson K, Anazodo A. What are the unmet needs and care experiences of adolescents and young adults with cancer? A systematic review. J Adolesc Young Adult Oncol. 2017;6(1):6–30.
6. Anazodo A, Laws P, Logan S, Saunders C, Travaglia J, Gerstl B, et al. How can we improve oncofertility care for patients? A systematic scoping review of current international practice and models of care. Hum Reprod Update. 2019;25(2):159–79.
7. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24(18):2917–31.
8. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500–10.
9. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(19):1994–2001.
10. Coccia PF, Pappo AS, Altman J, Bhatia S, Borinstein SC, Flynn J, et al. Adolescent and young adult oncology, version 2.2014. J Natl Compr Cancer Netw. 2014;12(1):21–32.
11. Pentheroudakis G, Orecchia R, Hoekstra HJ, Pavlidis N, ESMO Guidelines Working Group. Cancer, fertility and pregnancy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v266–v73.
12. American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2013;100(5):1214–23.
13. American Society for Reproductive Medicine. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril. 2018;110(3):380–6.
14. Mintziori G, Lambrinoudaki I, Ceausu I, Depypere H, Erel CT, Perez-Lopez FR, et al. EMAS position statement: fertility preservation. Maturitas. 2014;77(1):85–9.
15. Linkeviciute A, Boniolo G, Chiavari L, Peccatori FA. Fertility preservation in cancer patients: the global framework. Cancer Treat Rev. 2014;40(8):1019–27.
16. Panagiotopoulou N, Ghuman N, Sandher R, Herbert M, Stewart JA. Barriers and facilitators towards fertility preservation care for cancer patients: a meta-synthesis. Eur J Cancer Care (Engl). 2018;27(1) https://doi.org/10.1111/ecc.12428.
17. Vindrola-Padros C, Dyer KE, Cyrus J, Lubker IM. Healthcare professionals' views on discussing fertility preservation with young cancer patients: a mixed method systematic review of the literature. Psycho-Oncology. 2017;26(1):4–14.
18. Reinecke JD, Kelvin JF, Arvey SR, Quinn GP, Levine J, Beck LN, et al. Implementing a systematic approach to meeting patients' cancer and fertility needs: a review of the Fertile Hope Centers Of Excellence program. J Oncol Pract. 2012;8(5):303–8.
19. Carlson CA, Kolon TF, Mattei P, Hobbie W, Gracia CR, Ogle S, et al. Developing a hospital-wide fertility preservation service for pediatric and young adult patients. J Adolesc Health. 2017;61(5):571–6.

20. Kelvin JF, Reinecke J. Institutional approaches to implementing fertility preservation for cancer patients. Adv Exp Med Biol. 2012;732:165–73.
21. Smith K, Efymow B, Gracia C. Patient navigation and coordination of care for the oncofertility patient: a practical guide. In: Gracia C, Woodruss TK, editors. Oncofertility medical practice: clinical issues and implementation. New York: Springer Science+Business Media; 2012.
22. Kelvin JF, Thom B, Benedict C, Carter J, Corcoran S, Dickler MN, et al. Cancer and fertility program improves patient satisfaction with information received. J Clin Oncol. 2016;34(15):1780–6.
23. Melan K, Amant F, Veronique-Baudin J, Joachim C, Janky E. Fertility preservation healthcare circuit and networks in cancer patients worldwide: what are the issues? BMC Cancer. 2018;18(1):192.
24. Peavey M, Arian S, Gibbons W, Lu K, Gershenson D, Woodard T. On-site fertility preservation services for adolescents and young adults in a comprehensive cancer center. J Adolesc Young Adult Oncol. 2017;6(2):229–34.
25. Salsman JM, Yanez B, Smith KN, Beaumont JL, Snyder MA, Barnes K, et al. Documentation of fertility preservation discussions for young adults with cancer: examining compliance with treatment guidelines. J Natl Compr Cancer Netw. 2016;14(3):301–9.
26. Grover NS, Deal AM, Wood WA, Mersereau JE. Young men with cancer experience low referral rates for fertility counseling and sperm banking. J Oncol Pract. 2016;12(5):465–71.
27. Lewin J, Ma JMZ, Mitchell L, Tam S, Puri N, Stephens D, et al. The positive effect of a dedicated adolescent and young adult fertility program on the rates of documentation of therapy-associated infertility risk and fertility preservation options. Support Care Cancer. 2017;25(6):1915–22.
28. Quinn GP, Block RG, Clayman ML, Kelvin J, Arvey SR, Lee JH, et al. If you did not document it, it did not happen: rates of documentation of discussion of infertility risk in adolescent and young adult oncology patients' medical records. J Oncol Pract. 2015;11(2):137–44.
29. Quinn GP, Vadaparampil ST, Gwede CK, Reinecke JD, Mason TM, Silva C. Developing a referral system for fertility preservation among patients with newly diagnosed cancer. J Natl Compr Cancer Netw. 2011;9(11):1219–25.
30. Sheth KR, Sharma V, Helfand BT, Cashy J, Smith K, Hedges JC, et al. Improved fertility preservation care for male patients with cancer after establishment of formalized oncofertility program. J Urol. 2012;187(3):979–86.

Impact of Systemic Anticancer Therapy on Fertility

7

Antonio Di Meglio, Ines Vaz-Luis, and Barbara Pistilli

Introduction

Each year, thousands of young women in reproductive age are diagnosed with cancer worldwide. Frequent cancers in this population of young women include, among others, breast cancer and childhood cancers such as hematological malignancies, sarcomas, and germinal cell tumors. Given the recent trend toward delayed childbearing age, many young women diagnosed with cancer have not yet completed their family plans at the time of cancer diagnosis [1–4]. Due to improvements in local and systemic cancer therapy, cure rates of these cancers at such young age increased significantly over the past decades. However, one of the potential long-term consequences of systemic therapy is the early loss of ovarian function leading to loss of fertility and risk for menopause-related complications at a very young age [5, 6].

In this chapter, we review the impact of systemic anticancer therapy on fertility in women with cancer, including the impact on fertility of chemotherapy, endocrine therapy, trastuzumab, and other novel targeted therapies.

Impact of Specific Systemic Treatments on Fertility in Women with Cancer

Chemotherapy

For many patients with cancer, chemotherapy still represents the cornerstone of their oncologic treatment. Human ovaries have a fixed and not replaceable number of primordial follicles, which are progressively lost with age. The number of oocytes

A. Di Meglio (✉) · I. Vaz-Luis · B. Pistilli
Institut Gustave Roussy, INSERM Unit 981, Villejuif, France
e-mail: Antonio.DI-MEGLIO@gustaveroussy.fr;
INES-MARIA.VAZ-DUARTE-LUIS@gustaveroussy.fr;
BARBARA.PISTILLI@gustaveroussy.fr

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_7

starts to decline around age 37 when there are about 25,000 primordial oocytes remaining, and precedes menopause by 12–14 years, when roughly 1,000 oocytes are left. Cytotoxic agents can lead to early oocyte depletion; after cytotoxic treatment, the ovaries show a spectrum of lesions that spans from a decreased number of secondary follicles to complete absence of follicles, associated with ovarian fibrosis, often with histologic sections that are identical to those seen in postmenopausal ovaries [7–11]. These morphological alterations associated with the use of chemotherapeutics mirror a premature follicular depletion that in some cases may lead to an irreversible ovarian damage, and to premature ovarian failure [7–11]. In addition, a phenomenon termed "burn-out of follicle reserve" has been recently described, consisting of imbalanced follicle recruitment and growth induced by chemotherapeutic agents, which ultimately can lead to accelerated depletion of the follicular stock [12].

Ovarian failure that follows chemotherapy has been well described. Chiarelli and colleagues [13] nicely demonstrated that after following up women treated for childhood cancer before the age of 20 years, those treated with radiotherapy and chemotherapy had an increased risk of ovarian failure of 2.58 (95% confidence interval: 1.14–5.80) when compared with those only treated with surgery. Mackie et al. also reported that half of patients treated with chlorambucyl, vinblastine, procarbazine, and prednisolone presented ovarian failure [14].

There are several contributors to ovarian failure after chemotherapy, and the single effect of each of them is hard to quantify. The degree of ovarian failure associated with each chemotherapy regimen ranges from 0% to 100% and greatly varies mainly according to (1) *drug exposure* (type of drug, duration, and dose of chemotherapy) and (2) *patient age* (being particularly related with the ovarian function before treatment—see relative chapter) [7, 10, 11, 14, 15]. These aspects are detailed below.

Drug Exposure

Type of drug. Different cytotoxic drugs have been associated with different degrees of gonadal damage. Table 7.1 summarizes the estimated risk of each individual drug of inducing ovarian failure across several studies [6, 7, 14–33]. In addition, since treatment protocols for different malignant diseases are continuously evolving, the expected impact of current curative treatment regimens by disease is also reported in Table 7.1.

Dose, duration, schedule. For agents such as cyclophosphamide, risk of treatment-induced amenorrhea is usually dose-dependent [10, 11]. Nevertheless, assessing the impact of dose, duration, and schedule of treatment on risk of amenorrhea is challenging, particularly when using poly-chemotherapy regimens [34–36]. For example, among premenopausal women with breast cancer enrolled in a Cancer and Leukemia Group B (CALGB) trial that received six cycles of cyclophosphamide, doxorubicin, and fluorouracil with varied doses of doxorubicin, 51% achieved amenorrhea, but no association with dose intensity emerged [36]. In parallel, in the study by Venturini and colleagues, focusing on breast cancer patients treated with

Table 7.1 Risk of ovarian failure according to single chemotherapeutic drug and by current treatment for common cancers

Low risk (<20%)	Moderate risk (20–80%)	High risk (>80%)
Single drugs		
Vincristine	Cisplatin	Cyclophosphamide
Methotrexate	Carboplatin	Ifosphamide
Dactonomycin	Doxorubicine	Busulfan
Bleomycin		Melphalan
Mercaptopurine		Procarbazine
Vinblastine		Chlorambucil
5-FU		Nitrogen Mustard
Current treatment for common cancers		
Acute lymphoblastic leukemia	Acute myeloblastic leukemia (difficult to quantify)	Chemotherapy conditioning for bone-marrow transplantation
Wilms' tumor	Hepatoblastoma	Hodgkin's disease: treatment with alkylating-drugs
Soft-tissue sarcoma: stage I	Osteosarcoma	Soft-tissue sarcoma: stage IV (metastatic)
Germ-cell tumors (with gonadal preservation and no radiotherapy)	Ewing's sarcoma: non-metastatic	Ewing's sarcoma: metastatic
Retinoblastoma	Soft-tissue sarcoma: stage II or III	Breast cancer treated with 6 CMF, FEC, FAC >39 years of age
Breast cancer treated with 6 FEC and FAC <30 years of age	Neuroblastoma	
Breast cancer treated with AC 30–39 years of age	Non-Hodgkin lymphoma	
	Hodgkin's disease: alternating treatment	
	Brain tumors: craniospinal radiotherapy, cranial irradiation >24 Gy	
	Breast cancer treated with 6 CMF, FEC, FAC 30–39 years of age	
	AC > 39 year	

Taxanes: Unknown risk [11, 97, 98]. Some data on the combined impact of taxanes on fertility are provided in section "Trastuzumab and Other Anti-HER2 Therapies" (in combination with trastuzumab in the APT trial [69]).

AC Doxorubicin (adriamycin) cyclophosphamide, *CMF* Cyclophosphamide methrotrexate fluorouracil, *FAC* Fluorouracil doxorubicin (adriamycin) cyclophosphamide, *FEC* Fluorouracil epirubicin cyclophosphamide.

Adapted from: [6, 7, 10, 14–32, 99].

cyclophosphamide, epirubicin, and fluorouracil, rates of amenorrhea were 64%, independently of dose dense scheduling [35]. Findings from other studies focused on the same patient population and impact of dose, duration, and schedule were inconsistent [34]. Among these, the French Adjuvant Study Group (FASG) retrospectively evaluated the impact of anthracycline dose and duration in women who received epirubicin-containing regimens in eight adjuvant trials and had shown statistically significant differences regarding dose and duration of similar regimens [37]. Evaluated regimens included three to six cycles of cyclophosphamide, epirubicin, and fluorouracil with increasing doses of epirubicin (50, 75, or 100 mg/m^2) or six cycles of epirubicin 50 mg/m^2 in association with vinorelbine. 52%, 58%, and 69% women who received cumulative doses of less than 300 mg/m^2, 300–450 mg/m^2, and greater than 450 mg/m^2 achieved amenorrhea, respectively. Additionally, 60% of women who received four to six cycles experienced amenorrhea versus 49% among those treated with one to three cycles of chemotherapy [37]. Finally, other studies suggested higher rates of amenorrhea in those who were treated with dose-intensive or high-dose regimens compared with regimens with conventional doses [34, 38, 39].

Age

Younger patients have a higher number of oocytes, and thus gonadal damage seems to be less severe than that in older patients because the ovary can still support regular ovulatory cycles even with a small numbers of follicles [8, 9].

The average prevalence of ovarian dysfunction among women receiving alkylating agent-based regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF) is 40% for women <40 years and around 80% for those older than 40. The median time to ovarian failure varies from 6 to 16 months in the younger age group and from 2 to 4 months among older women [7, 10, 11].

Further data on the combined effect of systemic therapy and age on fertility comes from the work of Goodwin et al., who examined predictors of menopause by different adjuvant treatments among 183 patients [33]. The majority of women received adjuvant chemotherapy (45.4%, CMF; 13.7%, cyclophosphamide, epirubicin, and fluorouracil [CEF]). In this study, age was among the most important predictors of early menopause. Although the risk of menopause was low in many of the treatment groups before the age of 35, beyond that age there was a clear separation of risk in those receiving chemotherapy and those not receiving chemotherapy; in women over the age of 35, 95% confidence intervals for those receiving chemotherapy did not overlap the 95% confidence intervals for those not receiving chemotherapy [33].

Chemotherapy is highly likely to cause irregular menstrual patterns and amenorrhea, which may last long after its completion. Nevertheless, it is common occurrence for many patients to return to prechemotherapy menstrual patterns [15, 40, 41]. Particularly, younger patients are more prone to reversal from a hypergonadotropic hypogonadal state that commonly occurs during the course of chemotherapy to a normogonadotropic state following completion of chemotherapy [23, 25, 42, 43], although they seem to keep at increased risk of developing premature menopause later on over the course of their reproductive life [44, 45].

Impact of Endocrine Therapy on Fertility

An average 65–70% of early breast cancers occurring in patients younger than 40 years of age is hormone receptor-positive [46]. In patients with hormone receptor-positive breast cancer, 5 years of adjuvant endocrine therapy reduce recurrence rate by 50% and mortality by a third [47, 48]. As a result, a substantial proportion of younger patients with breast cancer are prescribed adjuvant endocrine therapy, either consisting of tamoxifen (a nonsteroidal, selective estrogen receptor modulator) with or without luteinizing hormone-releasing hormone agonists or aromatase inhibitors in association with luteinizing hormone-releasing hormone agonists for 5–10 years.

Tamoxifen

Use of tamoxifen may negatively impact fertility potential both directly, by causing drug-related ovarian function impairment, and indirectly, increasing the odds of loss of ovarian reserve linked to aging. Indeed, its potential teratogenicity forces patients to postpone the time of conception until the completion of adjuvant endocrine therapy, which may last up to 10 years. When premenopausal women recover menses while on tamoxifen treatment, menstrual cycles are generally irregular. Some evidence suggests that the effect of tamoxifen on ovarian function is reversible, and that it may be related to an increased concentration of plasma estradiol induced by tamoxifen, which leads to an unbalanced hypothalamic-ovarian feedback loop [49].

Many studies showed that tamoxifen was independently associated to decreased likelihood of menses recovery and longer duration of amenorrhea when given after adjuvant or neoadjuvant chemotherapy, regardless of type of chemotherapy [33, 50–52]. A large meta-analysis of 75 studies assessing the rate of chemotherapy-induced amenorrhea found that sequential use of tamoxifen significantly predicted a higher risk of chemotherapy-induced amenorrhea, being associated to a twofold increased risk [53]. However, it remains unclear what direct role might tamoxifen have on ovulatory function when administered alone and not as part of a sequential chemotherapy-endocrine therapy regimen.

In the study about the combined effect of chemo- and endocrine-therapy on menopause status by Goodwin et al. [33], just over 25% (47 women) received adjuvant tamoxifen; of these, 25 (53.2%) received combined chemotherapy and tamoxifen. Use of either CMF or CEF, whether in combination with tamoxifen or not, increased the risk of menopause in 40-year-old women from less than 5% to more than 40%. In the same study, onset of menopause was reported among 13.6% of women who received tamoxifen alone and use of hormone therapy was significantly and independently associated with menopause onset in multivariate analyses. Addition of tamoxifen to either type of chemotherapy (CMF or CEF) determined a small but significant increase in the risk of menopause [33].

In addition, a recent retrospective analysis showed that breast cancer survivors who were on tamoxifen were less likely to have a child following cancer diagnosis compared to breast cancer patients who did not take tamoxifen, but this difference did not seem associated to a decreased ovarian function. Indeed, in patients on

tamoxifen the mean concentration of anti-Mullerian hormone was consistently higher than tamoxifen nonusers. Similarly, antral follicle count was higher in survivors who took tamoxifen compared to those who did not. As a result, it was hypothesized that the reduced birth rate among tamoxifen users may be related to the shorter reproductive window [54].

Finally, pursuit of fertility was found to be one of the most common reported reasons for tamoxifen noninitiation or discontinuation in younger breast survivors [55]. Therefore, fertility concerns related to tamoxifen utilization and need to postpone conception should be deeply discussed with patients willing to have pregnancy after breast cancer. Some evidence suggests that patients might consider the possibility to interrupt temporarily tamoxifen therapy to pursue a pregnancy and to resume the treatment upon childbearing in order to complete the preplanned endocrine therapy course [56–58]. The safety of this option is currently being investigated in the prospective Positive trial [59]

Aromatase Inhibitors

Data regarding the impact of aromatase inhibitors on fertility are scarce. Recently, the combined analysis of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT) confirmed that the association of aromatase inhibitors with ovarian function suppression represents a valid option for premenopausal patients with hormone receptor-positive breast cancer [60]. Nevertheless, as compared to tamoxifen alone, this combination determines a greater burden of endocrine and sexual-functioning related side effects, especially during the first 2 years of treatment, and its potential long-term effect on fertility is still unknown [61].

Ovarian Suppression

Substantial data is now available demonstrating the protective role of temporary ovarian function suppression administered during adjuvant chemotherapy in preserving ovarian function, both reducing rates of premature ovarian failure and increasing rates of pregnancies [62–64]. These data led to recommendations and guidelines acknowledging the clinical utility of temporary ovarian function suppression in breast cancer patients interested in preserving fertility and ovarian function [65]. Utilization of short-term course of ovarian suppression as a strategy for fertility preservation is discussed elsewhere in this book.

Recently, updated results of two large trials investigating the addition of longer courses of ovarian function suppression to adjuvant tamoxifen or exemestane became available: the SOFT and the TEXT trials, involving premenopausal women with hormone receptor-positive early breast cancer. Results showed significantly higher rates of disease-free and overall survival with the combination of ovarian suppression and tamoxifen than with tamoxifen alone and even higher rates of disease-free survival with exemestane plus ovarian suppression versus tamoxifen alone. Effects were similar regardless of receipt of chemotherapy, but the absolute benefits were larger in the cohort of patients who remained premenopausal after previous chemotherapy, who also had worse clinicopathological features [60].

Based on such results, guidelines now recommend to consider and discuss with the patients the addition of ovarian suppression to tamoxifen or aromatase inhibitors for premenopausal women at high risk of recurrence, namely the younger ones. Data on the effects of long-term ovarian suppression on fertility among this population of women that may still be pursuing pregnancies and completing family plans are still not available.

Impact of Other Targeted Therapies on Fertility

Over the last decades, systemic therapy started to be populated by several targeted therapies. Data on fertility for most of these agents is limited. We present a non-extensive review of the impact on fertility of some of targeted agents that are now being used in the treatment of young women with cancer.

Trastuzumab and Other Anti-HER2 Therapies

Around 20% of breast cancers diagnosed in patients younger than 40 years are human epidermal growth factor receptor 2 (HER2)-positive [46]. In the subgroup of patients with HER2-positive breast cancer, the addition to (neo) adjuvant chemotherapy of 1 year of adjuvant trastuzumab, a recombinant humanized monoclonal antibody targeting HER2, demonstrated a high and consistent benefit in terms of disease-free survival [hazard ratio = 0.60; 95% confidence interval, 0.50–0.71] and overall survival (hazard ratio = 0.66; 95% confidence interval, 0.57–0.77) across several clinical trials [66–68].

Few studies assessed the impact of trastuzumab on fertility. A retrospective analysis conducted on 431 premenopausal patients treated with anthracycline- and taxane-based chemotherapy +/− trastuzumab showed that 55% of patients remained amenorrheic at 3 years; however, the addition of trastuzumab did not appear to be detrimental on the likelihood of recovery of menses. The rate of amenorrhea at 1 year was substantially lower in patients treated with a combination containing paclitaxel and trastuzumab without any alkylating agent or anthracyclines. In a retrospective analysis among the premenopausal patients in the APT trial (the Adjuvant Paclitaxel Trastuzumab trial) only 28% patients remained amenorrheic at 1 year, suggesting that both paclitaxel and trastuzumab have a limited impact on fertility. Authors conclude that regimen employed in the APT trial may be considered as a valid option for premenopausal patients with small HER2+ breast cancer willing to pursue their family plans [69].

Moreover, pertuzumab is another anti-HER2 agent that has been tested in the neoadjuvant and adjuvant setting in phase II and III clinical trials and now it is an approved available option in some countries [70, 71]. No specific studies in animals have been performed to evaluate the effect of pertuzumab on fertility. However, no adverse effects on reproductive organs were reported in animal studies in repeat-dose toxicity studies [72, 73]. Finally, neratinib, a small orally available molecule that irreversibly inhibits HER1, HER2, and HER4 at the intracellular level, provided promising results in the early breast cancer setting, showing improved

disease-free survival as compared to placebo in patients who had already completed one year of trastuzumab [74]. In animal studies, neratinib did not show to reduce the ability of animals to become pregnant [75]. Dedicated studies with longer follow-up time will better elucidate the impact of these novel HER-2 targeted compounds on fertility.

Rituximab

Rituximab is a monoclonal antibody targeting the CD20 antigen approved for the treatment of chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide or chlorambucil as well as for other hematologic malignancies [76, 77]. The addition of rituximab to chemotherapy does not increase the risk of impaired ovarian function, especially in women younger than 40 years old [78].

BRAF Inhibitors and MEK Inhibitors

Approximately 50% of melanomas harbor activating *BRAF* mutations. *BRAF* is a member of the RAF kinase family, acting in the ERK/MAP kinase pathway that regulates cell proliferation, differentiation, and survival [79]. FDA has recently approved the combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) for the adjuvant treatment of patients with *BRAF*-positive stage III melanoma [80]. This combination demonstrated to reduce the risk of death by 53% compared with placebo in patients with BRAF-mutated stage III melanoma; however, little is known about their impact on the fertility of treated younger women. As a result, before treatment initiation, fertility preservation options should be discussed with patients that have indication to start such regimen and wishing to complete their family plans [81].

Immune Checkpoint Inhibitors (CTLA-4 Inhibitors, PD-1/PD-L1 Inhibitors)

The development of immune checkpoint inhibitors is dramatically changing the natural history of several cancer types. Ipilimumab is a monoclonal antibody binding the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and preventing it from interacting with its ligands. In a phase III study ipilimumab significantly improved the overall survival of patients with stage III melanoma after complete surgical resection, so leading to FDA approval for the adjuvant therapy of melanoma [82]. More recently, the programmed death 1 (PD-1) inhibitor pembrolizumab has been found to prolong overall survival in patients with resected, high-risk stage III melanoma [83], as well as several other cancer types, including advanced non-small cell lung carcinoma [84] and renal cell carcinoma [85]. The impact of immune checkpoint inhibitors on fertility is still unclear. These drugs appear not to have a direct impact on ovarian function. In animals treated with ipilimumab, exposure has been associated to histopathological changes in ovary tissue. Nevertheless, immune checkpoint inhibitors determine a higher risk of hypophysitis, which may eventually lead to a reduction in the gonadotropin production.

Bcr-Abl Inhibitors

Imatinib mesylate was the first Bcr-Abl, c-Kit, and platelet-derived growth factor receptor (PDGFR) inhibitor approved for the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors [86]. More recently, two other more potent Bcr-Abl inhibitors have been approved for patients with CML: nilotinib and dasatinib [87, 88]. Little is known about the effects of these tyrosine-kinase inhibitors on women's fertility. In women, both c-Kit and PDGF are expressed by early follicles and play a central role in ovarian follicular development. Preclinical data showed that the exposure of human ovarian cortical tissue to anti-c-Kit antibody significantly increased the rate of follicular atresia [89, 90]. However, a study conducted on mouse models showed that imatinib at therapeutic doses, given for 2 months, did not seem to affect folliculogenesis [91]. Also, in women treated with imatinib, some successful conceptions have been reported.

Bevacizumab

Bevacizumab, a humanized anti-VEGF (vascular endothelial growth factor) monoclonal antibody, is approved, in combination with chemotherapy, for the treatment of many advanced solid tumors, including ovarian cancer and cervical cancer [92, 93]. In animal models, the prolonged administration of bevacizumab showed to reduce follicular maturation and number of menstrual cycles [94]. A detrimental effect of bevacizumab on ovarian function has been observed also in premenopausal women receiving adjuvant chemotherapy + bevacizumab for stage II or III colorectal cancer. In the phase III NSABP C-08 trial the rate of ovarian failure, defined as amenorrhea for ≥3 months with blood follicle-stimulating hormone (FSH) levels ≥30 mIU/mL, was 34% vs. 2.6% in women receiving and non-receiving adjuvant bevacizumab, respectively, with only 22% of women recovering ovarian function after treatment cessation [95].

Olaparib

Olaparib is an oral PARP inhibitor approved for the treatment of patients with germline BRCA-mutated advanced ovarian cancer. Olaparib does not appear to cause infertility. However, pregnancy should be avoided during olaparib treatment for at least 6 months after the last dose, since it demonstrated major teratogenic and embryotoxic effects in rats exposed at lower doses of those used in clinical practice [96]. During olaparib therapy, women should be appropriately advised about contraception and reproductive risks.

References

1. Mills M, Rindfuss RR, McDonald P, te Velde E. ESHRE Reproduction and Society Task Force. Why do people postpone parenthood? Reasons and social policy incentives. Hum Reprod Update. 2011;17(6):848–60.
2. Trivers KF, Fink AK, Partridge AH, Oktay K, Ginsburg ES, Li C, et al. Estimates of young breast cancer survivors at risk for infertility in the U.S. Oncologist. 2014;19(8):814–22.

3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225–49.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
5. Green DM. Late effects of treatment for cancer during childhood and adolescence. Curr Probl Cancer. 2003;27(3):127–42.
6. Sonmezer M, Oktay K. Fertility preservation in female patients. Hum Reprod Update. 2004;10(3):251–66.
7. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 1996;14(5):1718–29.
8. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effect of combination chemotherapy on ovarian function in women treated for Hodgkin's disease. Cancer. 1983;52(6):988–93.
9. Familiari G, Caggiati A, Nottola SA, Ermini M, Di Benedetto MR, Motta PM. Ultrastructure of human ovarian primordial follicles after combination chemotherapy for Hodgkin's disease. Hum Reprod Oxf Engl. 1993;8(12):2080–7.
10. Wallace WHB, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol. 2005;6(4):209–18.
11. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(36):5769–79.
12. Roness H, Gavish Z, Cohen Y, Meirow D. Ovarian follicle burnout: a universal phenomenon? Cell Cycle Georget Tex. 2013;12(20):3245–6.
13. Chiarelli AM, Marrett LD, Darlington G. Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964–1988 in Ontario, Canada. Am J Epidemiol. 1999;150(3):245–54.
14. Mackie EJ, Radford M, Shalet SM. Gonadal function following chemotherapy for childhood Hodgkin's disease. Med Pediatr Oncol. 1996;27(2):74–8.
15. Wallace WH, Shalet SM, Crowne EC, Morris-Jones PH, Gattamaneni HR, Price DA. Gonadal dysfunction due to cis-platinum. Med Pediatr Oncol. 1989;17(5):409–13.
16. Warne GL, Fairley KF, Hobbs JB, Martin FI. Cyclophosphamide-induced ovarian failure. N Engl J Med. 1973;289(22):1159–62.
17. Koyama H, Wada T, Nishizawa Y, Iwanaga T, Aoki Y. Cyclophosphamide-induced ovarian failure and its therapeutic significance in patients with breast cancer. Cancer. 1977;39(4):1403–9.
18. Fisher B, Sherman B, Rockette H, Redmond C, Margolese R, Fisher ER. 1-phenylalanine mustard (L-PAM) in the management of premenopausal patients with primary breast cancer: lack of association of disease-free survival with depression of ovarian function. National Surgical Adjuvant Project for Breast and Bowel Cancers. Cancer. 1979;44(3):847–57.
19. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. Eur J Cancer Clin Oncol. 1985;21(5):601–5.
20. Teinturier C, Hartmann O, Valteau-Couanet D, Benhamou E, Bougneres PF. Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. Bone Marrow Transplant. 1998;22(10):989–94.
21. Legault L, Bonny Y. Endocrine complications of bone marrow transplantation in children. Pediatr Transplant. 1999;3(1):60–6.
22. Meirow D, Lewis H, Nugent D, Epstein M. Subclinical depletion of primordial follicular reserve in mice treated with cyclophosphamide: clinical importance and proposed accurate investigative tool. Hum Reprod Oxf Engl. 1999;14(7):1903–7.
23. Blumenfeld Z, Shapiro D, Shteinberg M, Avivi I, Nahir M. Preservation of fertility and ovarian function and minimizing gonadotoxicity in young women with systemic lupus erythematosus treated by chemotherapy. Lupus. 2000;9(6):401–5.

24. Kenney LB, Laufer MR, Grant FD, Grier H, Diller L. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer. 2001;91(3):613–21.
25. Tauchmanovà L, Selleri C, Rosa GD, Pagano L, Orio F, Lombardi G, et al. High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. Cancer. 2002;95(5):1076–84.
26. Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. NCI Monogr Publ Natl Cancer Inst. 1986;(1):105–9.
27. Maneschi F, Benedetti-Panici P, Scambia G, Salerno MG, D'Agostino G, Mancuso S. Menstrual and hormone patterns in women treated with high-dose cisplatin and bleomycin. Gynecol Oncol. 1994;54(3):345–8.
28. Tangir J, Zelterman D, Ma W, Schwartz PE. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. Obstet Gynecol. 2003;101(2):251–7.
29. Van Thiel DH, Ross GT, Lipsett MB. Pregnancies after chemotherapy of trophoblastic neoplasms. Science. 1970;169(3952):1326–7.
30. Shamberger RC, Sherins RJ, Ziegler JL, Glatstein E, Rosenberg SA. Effects of postoperative adjuvant chemotherapy and radiotherapy on ovarian function in women undergoing treatment for soft tissue sarcoma. J Natl Cancer Inst. 1981;67(6):1213–8.
31. Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, et al. Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol. 1981;139(1):62–6.
32. Sudman PD, Rutledge JC, Bishop JB, Generoso WM. Bleomycin: female-specific dominant lethal effects in mice. Mutat Res. 1992;296(1–2):143–56.
33. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol Off J Am Soc Clin Oncol. 1999;17(8):2365–70.
34. International Breast Cancer Study Group, Basser RL, O'Neill A, Martinelli G, Green MD, Peccatori F, et al. Multicycle dose-intensive chemotherapy for women with high-risk primary breast cancer: results of International Breast Cancer Study Group Trial 15-95. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(3):370–8.
35. Venturini M, Del Mastro L, Aitini E, Baldini E, Caroti C, Contu A, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. J Natl Cancer Inst. 2005;97(23):1724–33.
36. Budman DR, Berry DA, Cirrincione CT, Henderson IC, Wood WC, Weiss RB, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst. 1998;90(16):1205–11.
37. Borde F, Chapelle-Marcillac I, Fumoleau P, Hery M, Bonneterre J, Kerbrat P, Namer M, Fargeot P, Roche H. Role of chemo-induced amenorrhea in premenopausal, node-positive, operable breast cancer patients: 9-year follow-up results of French Adjuvant Study Group (FASG) data base. Breast Cancer Res Treat. 2003;82:138.
38. Nitz UA, Mohrmann S, Fischer J, Lindemann W, Berdel WE, Jackisch C, et al. Comparison of rapidly cycled tandem high-dose chemotherapy plus peripheral-blood stem-cell support versus dose-dense conventional chemotherapy for adjuvant treatment of high-risk breast cancer: results of a multicentre phase III trial. Lancet Lond Engl. 2005;366(9501):1935–44.
39. Rodenhuis S, Bontenbal M, Beex LVAM, Wagstaff J, Richel DJ, Nooij MA, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. N Engl J Med. 2003;349(1):7–16.
40. Brewer M, Gershenson DM, Herzog CE, Mitchell MF, Silva EG, Wharton JT. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. J Clin Oncol Off J Am Soc Clin Oncol. 1999;17(9):2670–5.
41. Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. Cancer. 2000;89(2):391–8.

42. Zanetta G, Bonazzi C, Cantù M, Binidagger S, Locatelli A, Bratina G, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. J Clin Oncol Off J Am Soc Clin Oncol. 2001;19(4):1015–20.
43. Wikström AM, Hovi L, Dunkel L, Saarinen-Pihkala UM. Restoration of ovarian function after chemotherapy for osteosarcoma. Arch Dis Child. 2003;88(5):428–31.
44. Byrne J, Fears TR, Gail MH, Pee D, Connelly RR, Austin DF, et al. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol. 1992;166(3):788–93.
45. Larsen EC, Müller J, Rechnitzer C, Schmiegelow K, Andersen AN. Diminished ovarian reserve in female childhood cancer survivors with regular menstrual cycles and basal FSH <10 IU/l. Hum Reprod Oxf Engl. 2003;18(2):417–22.
46. Sabiani L, Houvenaeghel G, Heinemann M, Reyal F, Classe JM, Cohen M, et al. Breast cancer in young women: pathologic features and molecular phenotype. Breast Edinb Scotl. 2016;29:109–16.
47. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377(19):1836–46.
48. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet Lond Engl. 2011;378(9793):771–84.
49. Jordan VC, Lieberman ME, Cormier E, Koch R, Bagley JR, Ruenitz PC. Structural requirements for the pharmacological activity of nonsteroidal antiestrogens in vitro. Mol Pharmacol. 1984;26(2):272–8.
50. Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftalis EZ, Singletary SE, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(7):1045–51.
51. Pistilli B, Mazouni C, Zingarello A, Faron M, Saghatchian M, Grynberg M, et al. Individualized prediction of menses recovery after chemotherapy for early-stage breast cancer: a nomogram developed from UNICANCER PACS04 and PACS05 trials. Clin Breast Cancer. 2019;19(1):63–70.
52. Lee S, Kil WJ, Chun M, Jung Y-S, Kang SY, Kang S-H, et al. Chemotherapy-related amenorrhea in premenopausal women with breast cancer. Menopause N Y N. 2009;16(1):98–103.
53. Zavos A, Valachis A. Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. Acta Oncol Stockh Swed. 2016;55(6):664–70.
54. Shandley LM, Spencer JB, Fothergill A, Mertens AC, Manatunga A, Paplomata E, et al. Impact of tamoxifen therapy on fertility in breast cancer survivors. Fertil Steril. 2017;107(1):243–252.e5.
55. Llarena NC, Estevez SL, Tucker SL, Jeruss JS. Impact of fertility concerns on tamoxifen initiation and persistence. J Natl Cancer Inst. 2015;107(10)
56. Gradishar WJ, Hellmund R. A rationale for the reinitiation of adjuvant tamoxifen therapy in women receiving fewer than 5 years of therapy. Clin Breast Cancer. 2002;2(4):282–6.
57. Delozier T, Switsers O, Génot JY, Ollivier JM, Héry M, Namer M, et al. Delayed adjuvant tamoxifen: ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial). Ann Oncol Off J Eur Soc Med Oncol. 2000;11(5):515–9.
58. Love RR. Adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med. 2018;379(17):1683.
59. http://www.ibcsg.org/Public/Health_Professionals/Open_Trials/ibcsg_48-14_positive/Pages/IBCSG48-14POSITIVE.aspx.
60. Francis PA, Pagani O, Fleming GF, Walley BA, Colleoni M, Láng I, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med. 2018;379(2):122–37.
61. Ribi K, Luo W, Bernhard J, Francis PA, Burstein HJ, Ciruelos E, et al. Adjuvant tamoxifen plus ovarian function suppression versus tamoxifen alone in premenopausal women with early breast cancer: patient-reported outcomes in the suppression of ovarian function trial. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34(14):1601–10.

62. Moore HCF, Unger JM, Phillips K-A, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372(10):923–32.
63. Lambertini M, Peccatori FA, Azim HA. Targeted agents for cancer treatment during pregnancy. Cancer Treat Rev. 2015;41(4):301–9.
64. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(19):1981–90.
65. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies: improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol Off J Eur Soc Med Oncol. 2015;26(8):1533–46.
66. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659–72.
67. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673–84.
68. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
69. Ruddy KJ, Guo H, Barry W, Dang CT, Yardley DA, Moy B, et al. Chemotherapy-related amenorrhea after adjuvant paclitaxel-trastuzumab (APT trial). Breast Cancer Res Treat. 2015;151(3):589–96.
70. Gianni L, Pienkowski T, Im Y-H, Tseng L-M, Liu M-C, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791–800.
71. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377(2):122–31.
72. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125409s113s118lbl.pdf.
73. Hoffmann-La Roche Limited. PERJETA® product monograph. Mississauga, Ontario; 12 April 2013. http://www.rochecanada.com/content/dam/roche_canada/en_CA/documents/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Perjeta/Perjeta_PM_E.pdf.
74. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016;17(3):367–77.
75. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf.
76. McLaughlin P. Progress and promise in the treatment of indolent lymphomas. Oncologist. 2002;7(3):217–25.
77. Pfreundschuh M, Schubert J, Ziepert M, Schmits R, Mohren M, Lengfelder E, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008;9(2):105–16.
78. Gharwan H, Lai C, Grant C, Dunleavy K, Steinberg SM, Shovlin M, et al. Female fertility following dose-adjusted EPOCH-R chemotherapy in primary mediastinal B-cell lymphomas. Leuk Lymphoma. 2016;57(7):1616–24.
79. Wellbrock C, Arozarena I. The complexity of the ERK/MAP-kinase pathway and the treatment of melanoma skin cancer. Front Cell Dev Biol. 2016;4:33.

80. Long GV, Eroglu Z, Infante J, Patel S, Daud A, Johnson DB, et al. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(7):667–73.
81. Walter JR, Xu S, Paller AS, Choi JN, Woodruff TK. Oncofertility considerations in adolescents and young adults given a diagnosis of melanoma: Fertility risk of Food and Drug Administration-approved systemic therapies. J Am Acad Dermatol. 2016;75(3):528–34.
82. Eggermont AMM, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage iii melanoma with ipilimumab adjuvant therapy. N Engl J Med. 2016;375(19):1845–55.
83. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med. 2018;378(19):1789–801.
84. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
85. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1116–27.
86. Kantarjian HM, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood. 2002;99(10):3547–53.
87. Hochhaus A, Rosti G, Cross NCP, Steegmann JL, le Coutre P, Ossenkoppele G, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. Leukemia. 2016;30(1):57–64.
88. Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2012;119(5):1123–9.
89. Carlsson IB, Laitinen MPE, Scott JE, Louhio H, Velentzis L, Tuuri T, et al. Kit ligand and c-Kit are expressed during early human ovarian follicular development and their interaction is required for the survival of follicles in long-term culture. Reprod Camb Engl. 2006;131(4):641–9.
90. Nilsson EE, Detzel C, Skinner MK. Platelet-derived growth factor modulates the primordial to primary follicle transition. Reprod Camb Engl. 2006;131(6):1007–15.
91. Schultheis B, Nijmeijer BA, Yin H, Gosden RG, Melo JV. Imatinib mesylate at therapeutic doses has no impact on folliculogenesis or spermatogenesis in a leukaemic mouse model. Leuk Res. 2012;36(3):271–4.
92. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473–83.
93. Tewari KS, Sill MW, Long HJ, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370(8):734–43.
94. https://www.ema.europa.eu/documents/scientific-discussion/avastin-epar-scientific-discussion_en.pdf.
95. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(1):11–6.
96. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf.
97. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla J-P, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005;352(22):2302–13.
98. Davis AL, Klitus M, Mintzer DM. Chemotherapy-induced amenorrhea from adjuvant breast cancer treatment: the effect of the addition of taxanes. Clin Breast Cancer. 2005;6(5):421–4.
99. Association Francophone pour les Soins Oncologiques de Support (AFSOS). www.afsos.org.

Fertility Counseling in Routine Practice: Why, When, and How?

8

Sukhkamal B. Campbell and Terri L. Woodard

Cancer Survivorship and Fertility

In the United States, there are approximately 900,000 female cancer cases diagnosed annually [1]. Due to earlier diagnosis and advancements in therapies, the 5-year survival rate among women less than 45 years old was found to be 83% from 2003 to 2009 [2]. Additionally, the National Cancer Institute reports that there are currently 8.8 million females in the United States with a history of cancer, and 48,000 of survivors are in the 15–19-year-old subgroup of adolescents and young adults (AYAs), AYA being defined as 15–39-year-old patients [3, 4]. Emerging data shows that survival rates among AYAs are overall the best they have been, despite room for continued improvement [5]. By January 2026, it is estimated that the population of cancer survivors in the United States will increase to 20.3 million with 10.3 million of them being female [6]. Further, based on recent United States census data, 2.5 million adults of childbearing age are cancer survivors. As survivorship improves and delayed childbearing continues to become more commonplace, more women face potential interrupted childbearing potential due to cancer and its treatment. There is a need for greater focus on the long-term effects of cancer treatment for survivors, including the risk of infertility or subfertility [7].

While any type of cancer can affect women of reproductive age, adolescents are more prone to specific cancer types including Hodgkin's lymphoma, leukemia, thyroid cancer, brain and spinal cord cancers, bone cancers (osteosarcoma and Ewing's sarcoma), soft tissue cancers (sarcoma and rhabdomyosarcoma), and ovarian cancer

S. B. Campbell
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, USA
e-mail: Sukhkamal.Campbell@bcm.edu

T. L. Woodard (✉)
MD Anderson Cancer Center, Houston, TX, USA
e-mail: TLWoodard@mdanderson.org

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_8

[8]. Young adults are more prone to malignancies such as breast cancer, lymphoma, melanoma, soft tissue cancers (sarcomas), cervical and ovarian cancer, thyroid cancer, colorectal cancer, and brain and spinal cord cancers [8]. The 5-year survival rates for young women with the abovementioned cancers approach 90–95% [9]. The unfortunate trade-off is that treatments that result in such promising survival rates often lead to greater risk of future infertility due to gonadotoxicity—including treatments for Hodgkin's lymphoma, leukemias, and ovarian cancers [8]. The possibility of impending infertility can lead to significant distress and impact quality of life for many young female cancer survivors for many years following treatment completion [10]. Of 7500 women aged 15–44 years old interviewed in the National Survey of Family Growth, nearly 50% were bothered a great deal by the possibility of never having a child due to their cancer therapy and 75% expressed wanting children in the future [11].

Female Reproductive Physiology

Once a girl has started puberty, approximately 400,000 of the initial one million primordial follicles remain in the ovaries. These follicles will mature based on hormonal regulation from the hypothalamic–pituitary–ovarian (HPO) axis. Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and induces release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. During each cycle, multiple follicles mature and a rise in FSH causes one dominant follicle to be chosen for ovulation. This follicle will in turn make estradiol which triggers an LH surge that consequently causes ovulation, or release of the mature follicle near the fallopian tube to be picked up for fertilization. The remaining unselected follicles undergo apoptosis, or self destruction [12]. As women age, there is a natural depletion of available follicles and cancer therapies can expedite this process significantly, often resulting in premature ovarian insufficiency or failure (Fig. 8.1) [13].

Cancer Treatment and Effects on Fertility

Ultimately, treatment-related infertility can result from chemotherapy, surgery, and/or radiation [10]. Chemotherapeutic agents specifically function by interrupting cell division, and therefore can impact the maturation and viability of ovarian follicles [12]. Alkylating agents (including cyclophosphamide, ifosfamide, and chlorambucil) are often used for the treatment of cancers such as non-Hodgkin lymphoma, acute lymphoblastic leukemia, and sarcoma. They cause both single- and double-strand DNA breaks, disrupting both actively dividing and dormant cells in the ovary—leading to significant acute and long-term toxicity [12]. Anthracyclines (i.e., doxorubicin), which are used in the treatment of breast, lung, thyroid, and blood cancers, inhibit DNA and RNA synthesis by intercalating between base pairs [12]. Platinums (cisplatin and carboplatin), which are often used in the treatment of ovarian and colorectal cancers, induce apoptotic cell death and inhibit transcription [12].

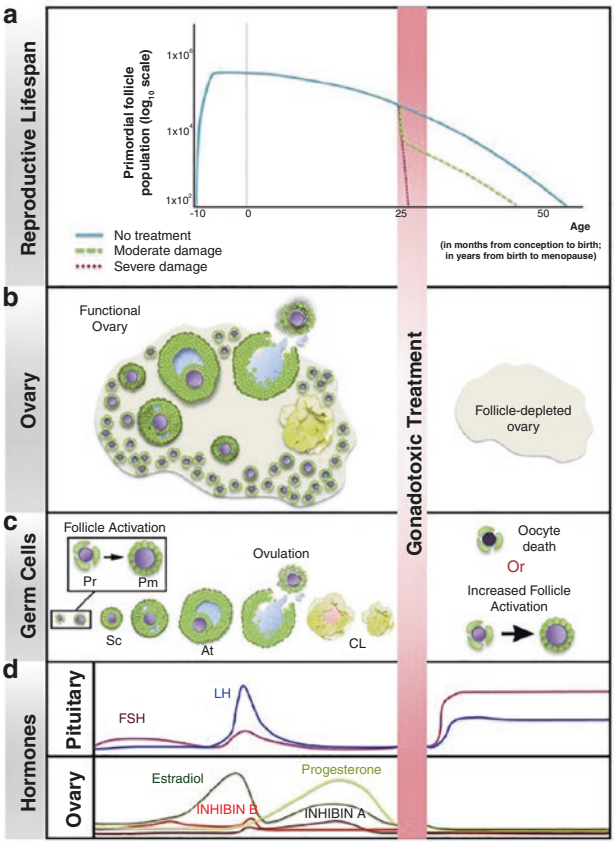

Fig. 8.1 Female menstrual cycle and consequences of gonadotoxic treatment in reproductive-aged women [13]

Chemotherapeutic agents are divided into several risk categories, based on their potential for inducing amenorrhea. "High-risk" agents are those that cause more than 80% of women to develop amenorrhea posttreatment. Alkylating agents are considered to be in a "high-risk category." Whole abdominal or pelvic radiation at doses greater than or equal to 6 Gray (Gy) in adult women, greater than or equal to 15 Gy in prepubertal girls, and greater than or equal to 10 Gy in postpubertal girls are also considered to be in the "high-risk" category. In addition, cranial/brain radiation greater than or equal to 40 Gy is also in the "high-risk" category given that it can cause hypogonadism by disrupting the HPO axis. Low doses of whole abdominal and pelvic radiation or chemotherapeutic agents such as vincristine or methotrexate, in contrast to alkylating agents, are in the "low-risk to very-low-risk/negligible-risk" category. Newer treatments often do not have any data on fertility risk and patients should be counseled accordingly. Finally, surgical treatment via resection of reproductive organs (hysterectomy and/or oophorectomy) has obvious

implication on future fertility and clear pretreatment counseling of these effects is essential. Ultimately, the overall impact of cancer treatment on fertility depends not only on treatment type but also on duration of treatment, total dose administered, patient age at the time of treatment, and other patient-specific factors (such as baseline ovarian reserve) that should all be individually assessed [12]. Also, it should be stressed that menstrual function does not serve as an accurate surrogate marker for fertility, even though historically it has been used to estimate fertility risk.

Age is one of the most important factors that helps determine the risk for premature ovarian failure and cancer-related infertility. The risk for ovarian failure increases tenfold for women that are diagnosed and receive treatment in their late thirties [11]. Ultimately, up to 90% of women aged 40 and older experience permanent ovarian failure and sterility [11]. Similarly, the effective sterilizing dose of radiation to the ovaries is 20.3 Gy for newborns, 18.4 Gy for 10-year-old girls, 16.5 Gy for 20-year-old women, and 14.3 Gy for 30-year-old women; however, there is of course variation in ovarian reserve for each patient in each age range [14].

Fertility Preservation Guidelines

In July of 2018, The American Society of Clinical Oncology (ASCO) published a clinical practice guideline update with the goal of providing all healthcare providers caring for reproductive-aged individuals at risk for cancer-related infertility with recommendations regarding fertility preservation [15]. This guideline was an update to practice guidelines initially published in 2006 [16] and serves to promote discussion of fertility risks and early referral to reproductive specialists, if indicated [15]. Importantly, the most recent update recommends that all discussions be documented in the medical record and addresses concerns about disparities and access to fertility preservation services, especially with regard to cost [15].

The American Society of Reproductive Medicine (ASRM) ethics committee opinion echoes many of the recommendations made by ASCO [17]. It encourages a multidisciplinary approach to fertility preservation counseling and treatment [17]. In addition, it comments on the use of preimplantation genetic testing for monogenic diseases (PGT-M) for those patients with hereditary cancers who wish to avoid having a child with a genetic mutation that predisposes them to malignancy [17]. Internationally, there are multiple guidelines that have been developed to address fertility issues in reproductive-aged women with cancer such as the European Menopause and Andropause Society (EMAS) position statement (2014), Oncofertility in Canada: options for future parenthood (2014), Germany/Switzerland/Austria practical recommendations for fertility preservation in women by the FertiPROTEKT network (2018), International Society for Fertility Preservation (ISFP) update on ESHRE/ASRM expert meeting (2017), and the Sociedad Espanola de Oncologia Medica guidelines on reproduction in cancer patients (2016), among many more from the UK, Japan, Singapore, and New Zealand [18].

Barriers to Fertility Preservation Counseling and Referral

Most young cancer survivors have an interest in future fertility and are concerned about the impact of their cancer therapy on their future ability to have children [19]. However, it has been shown that many AYAs have not participated/engaged in meaningful fertility preservation counseling at the time of diagnosis [19]. Unique barriers exist for this population, including their developmental stage of life—which is often characterized by uncertainty about future goals [19]. Although AYAs are developing autonomy at this age, they often depend heavily on their parents to help them make major decisions—including those about their cancer care as well as future fertility goals [19]. Studies cite "parental protective buffering" and "clinicians' discomfort" as barriers to addressing fertility with AYAs [19]. However, a lack of fertility counseling is not limited to the AYA population. Unfortunately, fertility preservation counseling and therapies remain underutilized by women of all age ranges.

Despite multiple guidelines and recommendations for both pre- and posttreatment counseling, literature shows that only 34–72% of reproductive-age female survivors recall having fertility preservation discussions [20]. Of those who are eligible for referral to fertility specialists, only 21% are actually referred, with trends toward greater referral for younger women (age less than 35 years old), nulliparous women, and those with breast cancer [21]. There are several patient and provider barriers that prevent fertility preservation discussions and referral to reproductive specialists. Patient barriers include fear of delaying cancer therapy, fear of birth defects related to their cancer or treatment, concerns about the safety of fertility treatment, and the prohibitive costs of fertility preservation [21, 22]. Additionally, stress and anxiety related to their new life-altering cancer diagnosis often puts survival at the forefront of their mind above all other concerns, including fertility. Physician barriers also exist—including time constraints, lack of knowledge, and personal biases/assumptions [23]. Physicians often report not having enough time in a busy clinic to stop and discuss fertility [23]. Discussions may also be avoided if they feel they lack the necessary knowledge to educate patients on fertility preservation options [23]. Finally, provider assumptions and biases at the time of diagnosis about patient characteristics such as age, partnership status, perceived ability to afford fertility preservation, and parity can influence whether fertility preservation is addressed or not [23].

Timing of Fertility Preservation Discussions

The timing of fertility preservation discussions is crucial to ensure that a patient's fertility needs are met. Once a woman has been diagnosed with cancer and it has been determined that she will receive treatment that may cause infertility, she should be asked if she is interested in having children in the future and informed of her risk for infertility. The potential of future, treatment-related infertility should be addressed as early as possible after diagnosis and prior to treatment initiation [15]. If patients are interested or ambivalent about pursuing fertility preservation, they

should be offered referral to reproductive specialists as early as possible to further explore options and receive formal counseling about which treatments may be appropriate for them [15]. A reproductive specialist can conduct an in-depth evaluation of current fertility status, provide estimates of expected success rates as well as risks, and discuss strategies for future pregnancy. Early referral gives patients more time for information gathering, decision-making and improves the odds that the full range of fertility preservation options is available to the patient [15]. In addition, once cancer therapy has been completed, another referral may be indicated if/when a patient returns for follow-up and has fertility concerns and/or if pregnancy is being considered [15].

Fertility Preservation Options

When discussing the various fertility preservation options available, it is important to provide patients with all suitable options (including not pursuing fertility preservation) to help them choose what is most appropriate for their lifestyle. Some options are available to only postpubertal women, whereas others are available to prepubertal girls.

Currently, both embryo and oocyte cryopreservation are first-line fertility preservation options [17]. Embryo cryopreservation is the most established method of fertility preservation for women and is widely available, and frequently utilized, particularly by those with partners or who choose to use donor sperm [17]. In addition, preimplantation genetic testing can be performed on embryos, if desired. Survival rates per thawed embryo range between 35% and 90%, implantation rates between 8% and 30%, and cumulative pregnancy rates above 60%, though this is largely dependent on age and ovarian reserve [17].

Oocyte cryopreservation became a first-line fertility preservation method when its experimental label was removed in 2013 [24]. The benefits of oocyte cryopreservation are that it provides women with reproductive autonomy (does not require a partner), bypasses some of the moral and religious objections surrounding embryo cryopreservation and is usually less expensive, initially [24]. Compared with use of cryopreserved embryos, less pregnancy rate data is available [24]. However, it has been reported that the clinical pregnancy rate per thawed oocyte ranges from 4.5% to 12% [24]. Overall, oocytes survive vitrification at a rate of 90–97% and fertilization rates are between 71% and 79% [24]. A compilation of studies of over 900 cryopreserved oocyte babies showed no increased risk of congenital anomalies compared to naturally conceived infants for both vitrified and slow-frozen oocytes [25]. Additionally, studies show no difference in live birth rates as compared to age-matched fresh controls [26]. However, the likelihood of success is likely dependent upon several factors including ovarian reserve, the woman's age at the time of oocyte cryopreservation, and clinic/lab-specific successful thaw rates.

Both oocyte and embryo cryopreservation require controlled ovarian stimulation with exogenous gonadotropins, for approximately 10–15 days followed by transvaginal oocyte retrieval. The entire process should be completed prior to initiation

of cancer therapy agents. While COH does not cause recurrence of cancer, increased levels of estradiol during stimulation could, in theory, impact hormonally sensitive cancers [27]. Aromatase inhibitors, such as letrozole, are often used in conjunction with gonadotropins to suppress peak estradiol levels without impacting oocyte yield [27]. However, this topic is debatable and a recent study of 45 young breast cancer patients undergoing COH with recombinant FSH with GnRH agonist triggers and without the use of letrozole prior to initiating adjuvant chemotherapy showed a peak estradiol ranging from 149 to 5300 with an average of 10 oocytes retrieved and no recurrences observed during a study period of 10 months post-chemotherapy [28].

Another study sought to quantify the delay to treatment for patients who elect to pursue fertility preservation and determine whether there is any association between COH and cancer recurrence and mortality [29]. Approximately 500 women with various cancer types (including breast, gynecologic, and hematologic malignancies) were studied with about 200 undergoing fertility preservation and 300 not undergoing fertility preservation [29]. When compared to those who did not pursue fertility preservation, patients who had COH had an approximately 2 week delay to initiation of cancer treatment and this time period was not considered to be clinically significant or impactful on long-term outcomes [29].

One fertility preservation option that is readily available in other countries but remains experimental in the United States is ovarian tissue cryopreservation (OTC). This is an option for women who do not have time to pursue egg or embryo freezing and it is the only option that is suitable for prepubertal girls. OTC does not require COH and allows for more urgent initiation of cancer therapy [30]. Ovarian tissue is removed surgically (often concurrently with other surgical procedures, such as chemotherapy port placements, to reduce overall cost), and cryopreserved using slow-freeze or vitrification methods. If a patient is found to have ovarian insufficiency or failure post-cancer treatment, the tissue can be thawed or warmed and reimplanted in the pelvic cavity (orthotopic) or elsewhere in the body (heterotopic). Reimplantation is typically done via a minimally invasive approach such as laparoscopically or using robotic assistance [30]. Reimplantation may restore ovarian hormone secretion and ultimately lead to ovulation [30]. To date, 87 live births and 9 ongoing pregnancies have been reported from OTC [31].

Experimental fetoprotective agents are fertility preservation options that can be used when any of the above options are not desired by the patient or are not clinically feasible [32]. GnRH agonists can be given cyclically in depot injection formulation to protect follicles from destruction during chemotherapy by suppression of gonadotropin levels and reduction of perfusion to ovarian tissue [32]. The mechanism of action and efficacy of GnRH agonists is highly controversial. The protective effects of GnRH agonists may vary based on the type of cancer present—for example, while they may be effective in buffering the effects of ovarian failure in some breast cancer patients, they will have no such effect or benefit in patients with ovarian cancer getting chemotherapy or surgery that is innately damaging to the ovary [32]. Newer fetoprotective agents that are currently under investigation focus on agents with anti-apoptotic properties (imantinib, thyroid hormone T3, granulocyte colony stimulating factor, and tamoxifen) that have shown promise in reducing

follicle loss in animal models alongside agents that prevent dormant follicle activation such as AS101 (immune modulator acting on P13K/PTEN/AKT follicle activation pathways) and AMH (anti-Mullerian hormone) [33].

For women and girls receiving pelvic radiation, ovarian transposition or oophoropexy is another fertility preservation option [34]. Oophoropexy involves movement and fixation of the ovary outside of the radiation field [35]. These surgeries are typically performed using minimally invasive surgical techniques [35]. The left ovary is usually placed at the level of the aortic bifurcation and the right ovary is often placed above the pelvic brim [35]. Few cases have shown successful return of ovarian function upon reversal of ovarian transposition with rates varying from 16% to 90% [35].

Due to personal beliefs or concerns, many patients may not choose to pursue fertility preservation or may not desire future pregnancy. It is imperative to keep an open mind during all counseling sessions, and to also introduce other options that may be available posttreatment, such as gestational carriers (surrogacy), donor gametes (donor eggs, donor sperm, and donor embryos), and adoption [36].

Strategies and Tools for Encouraging and Optimizing Fertility Preservation Discussions

Data shows that timely discussion of fertility preservation options improves long-term outcomes such as quality of life after cancer and decisional regret and that women reap the benefits of these discussions with their providers regardless of whether they ultimately pursue fertility preservation or not [37]. While many providers desire addressing fertility preservation with their patients at the time of initial diagnosis, they lack the tools or communication techniques to share this knowledge.

Effective communication of complex information is critical to patient satisfaction and decision-making, especially during the emotionally charged and stressful time period between diagnosis and initiation of treatment [37]. In order to facilitate patient understanding of the key concepts about fertility preservation, it is important to deliver evidenced-based information in an understandable and easy-to-absorb manner [37]. Patient decision aids are effective tools designed to deliver structured medical information and decision support. They can help address areas where patients experience decisional conflict—which includes feeling uninformed, unclear, unsupported, and uncertain—all of which have been shown to lead to delay in decision-making [37]. There is a plethora of data citing the benefits of decision aids, which include improved knowledge and increased patient engagement [37]. Existing fertility preservation decision aids are available to facilitate discussions with parents of adolescents or women with breast cancer, but few decision aids existed for women of reproductive age that addressed all cancer types until the very recent past [37]. Pathways is an interactive fertility preservation website that provides up-to-date information on fertility preservation options (include pros, cons, and costs) and posttreatment family building strategies along with values

clarification exercises and structured support to help women prepare for fertility discussions with their providers [37]. It has been shown to improve patient knowledge about fertility preservation and facilitate decision-making [37]. This tool is being pilot tested with plans for release for public use in the future [37].

In addition to patient decision aids, many other decision tools are available for fertility preservation counseling for both adolescents/young adults and postpubertal women [38]. The Adolescent Fertility Values Clarification Tool (AFVCT) can be used for patients aged 12–18 years old and has been validity-tested with teenage oncology patients and their parents [39]. AFVCT guides discussion of future quality of life, fertility preservation options, and the value of parenthood in an easy-to-understand format for teens and young adults [39]. Published decision trees are also available, such as the "Female Fertility Preservation Decision Tree" [40] and "Potential future decisions regarding fertility preservation" [41]. Both can be used to visually guide patients through the decision of pursuing fertility preservation pretreatment versus options available posttreatment in the event fertility preservation is not chosen (including adoption and donor gametes) [40, 41]. Religious, social, and familial influences as well as the patients' feelings are all taken into consideration as part of the decision [41].

Organizations such as LIVESTRONG also provide patients with printed and online educational materials on fertility risks, fertility preservation options, and their costs. These pamphlets can be provided directly to patients or used by providers as part of the counseling session to guide patient decisions [42]. The Oncofertility Consortium at Northwestern University (Chicago, IL, USA) hosts the "Save My Fertility: An Online Fertility Preservation Toolkit for Patients and Their Providers" resource that summarizes available fertility preservation options and provides further materials for reading and education on the topic [36]. Many tools are available in a variety of translations including Spanish, Arabic, French, Italian, and Chinese for international use and distribution.

For women who carry hereditary gene mutations that predispose them to cancer (such as those carrying BRCA1/2 mutations), specific guidelines are available that outline the steps to follow for referral as well as recommendations for ordering baseline labs that would be helpful for fertility specialists [43]. In addition, the impact of relevant therapies on fertility is specifically outlined (such as tamoxifen use and sequelae of prophylactic oophorectomy) [43].

In addition to oncologists, there are several key members such as nurses, advanced practice providers (nurse practitioners and physician assistants), and patient navigators/advocates who can play a large role in facilitating fertility preservation discussions and referrals. By approaching the topic of fertility preservation as a team, barriers such as physician time in clinic or lack of knowledge regarding fertility preservation can be overcome. Current literature reports the benefit of using patient navigators and/or advocates to help patients initially engage in fertility preservation discussion after diagnosis [44]. The main role of patient navigators has been to triage patients based on their oncologic timelines, provide general information about fertility preservation, and help facilitate referral during the brief window of time before treatment [44]. Patient navigators also help coordinate services

between various providers (oncology, urology, and reproductive endocrinology, for example) and direct patients to financial support resources [44]. The navigator serves as a resource not only for patients but also for physicians and patient supporters as the patient progresses through the fertility preservation process [44].

Conclusion

Cancer-related infertility is a significant cause of emotional distress that may persist many years after successful cancer treatment. As the number of young cancer survivors continues to grow, the importance of addressing fertility and family building concerns in a timely manner is becoming increasingly recognized. Women should be informed of their risk for treatment-related infertility and options for fertility preservation as soon as possible after diagnosis and prior to initiating treatment. Multiple options for fertility preservation exist and there are tools and resources that can be utilized to help facilitate patient education and decision-making. Fertility counseling improves women's quality of life, whether they pursue fertility preservation or not and is a component of quality, comprehensive cancer care that should be made available to all patients with a cancer diagnosis.

References

1. American Cancer Society. Cancer facts and figures 2019. Atlanta: American Cancer Society; 2019.
2. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER cancer statistics review, 1975–2010. Bethesda, MD: National Cancer Institute; 2013. https://seer.cancer.gov/archive/csr/1975_2010. based on November 2012 SEER data submission, posted to the SEER web site.
3. Miller KD, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019; https://doi.org/10.3322/caac.21565.
4. National Cancer Institute. Adolescents and young adults with cancer. Updated 2018. https://www.cancer.gov/types/aya.
5. Keegan THM, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. Cancer. 2016;122(7):1029–37.
6. National Cancer Institute. Cancer statistics. Updated 2018. https://www.cancer.gov/about-cancer/understanding/statistics.
7. Schover L. Motivation for parenthood after cancer: a review. J Natl Cancer Inst. 2005;2005(34):2–5.
8. American Cancer Society. When adolescents and young adults get cancer. Atlanta: American Cancer Society; 2018.
9. American Cancer Society. Adolescent and young adult cancer survival rates increase when re-evaluated. Atlanta: American Cancer Society; 2018.
10. Woodard TL, et al. The pathways fertility preservation decision aid website for women with cancer: development and field testing. J Cancer Surviv. 2018;12(1):101–14.
11. Canada AL, Schover LR. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psycho-Oncology. 2012;21(2):134–43.

12. Levine J. Gonadotoxicity of cancer therapies in pediatric and reproductive-age females: Chapter 1. In: Gracia C, Woodruff TK, editors. Oncofertility medical practice: clinical issues and implementation. New York: Springer Science; 2012.
13. Kim SY, et al. Toward precision medicine for preserving fertility in cancer patients: existing and emerging fertility preservation options for women. J Gynecol Oncol. 2016;27(2):e22.
14. Biedka M, et al. Fertility impairment in radiotherapy. Contemp Oncol (Pozn). 2016;20(3):199–204.
15. Oktay K, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;14(6):381–5.
16. Lee SJ, et al. American Society of Clinical Oncology recommendations on fertility preservation in patients. J Clin Oncol. 2006;24(18):2917–31.
17. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril. 2018;110(3):380–6.
18. Geneva Foundation for Medical Education and Research. Obstetric and gynecology guidelines: fertility preservation resources. 2018.
19. Benedict C, et al. Fertility issues in adolescent and young adult cancer survivors. J Adolesc Young Adult Oncol. 2016;5(1):48–57.
20. Letourneau JM, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118(6):1710–7.
21. Goodman LR, et al. Trends of socioeconomic disparities in referral patterns for fertility preservation consultation. Hum Reprod. 2012;27(7):2076–81.
22. Takeuchi E, et al. Physicians' practice of discussing fertility preservation with cancer patients and the associated attitudes and barriers. Support Care Cancer. 2017;25(4):1079–85.
23. Fritz R, et al. Counseling patients on reproductive aging and elective fertility preservation: a survey of obstetricians and gynecologists' experience, approach, and knowledge. J Assist Reprod Genet. 2018;35(9):1613–21.
24. Practice Committee of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99(1):37–43.
25. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online. 2009;18(6):769–76.
26. Grifo JA, Noyes N. Delivery rate using cryopreserved oocytes is comparable to conventional in vitro fertilization using fresh oocytes: potential fertility preservation for female cancer patients. Fertil Steril. 2009;93(2):391–6.
27. Reddy J, Oktay K. Ovarian stimulation and fertility preservation with the use of aromatase inhibitors in women with breast cancer. Fertil Steril. 2012;98(6):1363–9.
28. Decanter C, et al. Fertility preservation by controlled ovarian hyperstimulation (COH) without letrozole in young breast cancer patients before adjuvant chemotherapy: preliminary results. Fertil Steril. 2013;100(3):S169. 8 Fertility Counseling in Routine Practice: Why, When, and How?
29. Moravek MB, et al. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. Fertil Steril. 2018;109(2):349–55.
30. Devi L, Goel S. Fertility preservation through gonadal cryopreservation. Reprod Med Biol. 2016;15(4):235–51.
31. Kim S, et al. Ovarian tissue cryopreservation and transplantation in patients with cancer. Obstet Gynecol Sci. 2018;61(4):431–42.
32. Falcone T, et al. GnRH agonist for gondal protection during chemotherapy. Hum Reprod. 2015;30(12):2711–2.
33. Hadassa R, et al. Prevention of chemotherapy-induced ovarian damage: possible roles for hormonal and non-hormonal attenuating agents. Hum Reprod Update. 2014;20(1):759–74.
34. The Oncofertility Consortium. Resources: fertility preservation options for pediatric and adolescent females. Chicago: The Oncofertility Consortium; 2018.

35. Phillippe M, et al. Laparoscopic ovarian transposition for pelvic malignancies: indications and functional outcomes. Fertil Steril. 1998;70(5):956–60.
36. Save My Fertility. Provider pocket guides: fertility preservation for women diagnosed with cancer. Chicago: The Oncofertility Consortium; 2018.
37. Woodard TL, et al. Pathways: patient centered decision counselling for women at risk of cancer-related infertility: a protocol for a comparative effectiveness cluster randomized trial. Br Med J Open. 2018;8(2):e019994.
38. The Oncofertility Consortium. Oncofertility decision tool web portal: decision tools. Chicago: The Oncofertility Consortium; 2018.
39. The Oncofertility Consortium. Adolescent fertility values clarification tool (AFVCT). 2012 Moffitt Cancer Center. Chicago: The Oncofertility Consortium; 2018.
40. Gardino SL, et al. Using decision trees to enhance interdisciplinary team work: the case of oncofertility. J Assist Reprod Genet. 2010;27(5):227–31.
41. Quinn GP, et al. More research, more responsibility: the expansion of duty to warn in cancer patients considering fertility preservation. Am J Obstet Gynecol. 2013;209(2):98–102.
42. LIVESTRONG Fertility. Understand the risks, explore your options, and plan for your future. Austin: LIVESTRONG Fertility; 2013.
43. Woodruff TK, et al., editors. Oncofertility communication: sharing information and building relationships across disciplines. New York: Springer Science; 2014.
44. The Oncofertility Consortium. Resources: patient navigators. Chicago: The Oncofertility Consortium; 2018.

9 Challenges in Fertility Counseling of Cancer Patients: A Developing Nation Perspective

Ghina Ghazeeri and Dalia Khalife

Introduction

The number of cancer survivors has been increasing in developing countries due to the continuous improvement in cancer treatment [1–3]. This raises the hope for long-term survival in reproductive age patients and raises concern about the effect of cancer treatment on their fertility [4]. The effects might be permanent or transient depending on the treatment protocols, the age of the patient, and the genetic predisposition to reproductive damage [5, 6]. Discussing reproductive choices at the time of cancer diagnosis when patients and families are extremely vulnerable requires certain expertise and knowledge. Patients are usually uncertain about their future and many may still wish to have children after cancer treatment. During this stressful time, physicians are required to advise women on taking long-term decisions and weigh their desire to maintain their reproductive potential against starting cancer treatments immediately [7].

The loss of fertility is devastating for patients in the reproductive age group. The American Society of Clinical Oncologists (ASCO) and the American Society for Reproductive Medicine (ASRM) recommend discussing the risks of infertility with all cancer patients in the reproductive age. All patients should be provided with the option of a referral to reproductive endocrinologists for further discussion about possible fertility preservation (FP) options. Since FP options are not widely available in all developing countries, and some are still under investigation, many oncologists find it difficult to counsel patients about different options when only fifty percent of cancer patients are informed about FP necessity from their health care providers at the time of diagnosis [8]. In addition, finding fertility specialists with expertise in managing cancer patients is difficult to find even in developed countries [9]. Management requires a multidisciplinary approach among oncologists,

G. Ghazeeri (✉) · D. Khalife
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Beirut, Lebanon
e-mail: gg02@aub.edu.lb; dk41@aub.edu.lb

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_9

fertility experts, psychologists, and gynecologists to provide the best medical care for such patients. Yet, this is not always the case, and many patients lack adequate support whether psychologically, medically, or financially.

Deciding on the different FP options available is extremely important before proceeding to treatment. Unfortunately, counseling about FP varies extensively in developing countries. Awareness of the damaging effect of cancer treatments on fertility is growing, yet counseling patients is still complex and bounded by many challenges. Recommending FP options raises many technical, ethical, and legal issues for both experts in this field and cancer survivors. The ASRM and the ASCO recommend offering oocyte collection for adolescent and adult female patients receiving cancer treatment at high risk of infertility [2, 10]. Despite the remarkable progress in oocyte cryopreservation, it is still not widely available in many developing countries due to multiple factors that will be discussed below. Cryopreservation of spermatozoa and embryos is already established. The advent of ovarian tissue cryopreservation has improved counseling for prepubertal patients, yet it is still experimental and its potential use in FP is still not well defined.

Providing optimal information about FP options is challenging for health care providers, when both patients and their families are overwhelmed by the diagnosis. Appropriate counseling includes evaluation of costs, time, and alternatives. Services in some developing countries are not offered because of religious and cultural beliefs [11]. More importantly, the legal requirements in various countries are also to be considered for each patient [12].

All possibilities after cancer treatment are to be discussed during the fertility consult to ensure that patients and families are well informed. For instance, third-party parenting is one of the alternative options to be discussed in case of uterine dysfunction after chemotherapy/radiotherapy. A survey in 28 countries was conducted to assess the global experiences on FP and third-party parenting. Surrogacy is practiced in Iran in the absence of any laws or regulations. Adoption is also another option. It is permitted by law, yet it is bounded by cultural and legal challenges, especially in developing countries [11].

We herein review in this chapter the unique challenges faced by health care providers in developing nations while discussing FP options and cancer-related fertility issues (Table 9.1).

Table 9.1 Challenges faced when counseling cancer patients in developing countries

Challenges
Lack of communication between fertility experts and oncologists
Few data on experimental studies (ovarian tissue cryopreservation)
Few centers available for oocyte cryopreservation and ovarian tissue cryopreservation
Costs and lack of insurance coverage
Cultural differences and religious concerns
Fear of delay in treatment
Fear of hormonal stimulation side effects on cancer treatment
Ethical and legal challenges after cancer: disposal of gametes

Initiation of Discussion of Oncofertility Options

Multiple surveys on the awareness and knowledge of oncologists about FP were conducted, at two tertiary care centers in the Middle East. The majority of oncologists claimed discussing the issue with their patients but do not refer them to pursue FP prior to cancer treatment for many reasons, among which is the absence of well-developed fertility centers with the necessary expertise to perform oocyte cryopreservation [13, 14].

Fertility preservation centers are not widely available in developing countries. Data regarding the success of the different procedures is unavailable, making it hard to counsel patients on the advantages of FP. In Saudi Arabia, less than 20% of males are referred to reproductive endocrinologists prior to cancer treatment for sperm cryopreservation, 80% believe that FP is a complicated process [13, 15]. Despite the published guidelines by the ASCO in 2006 regarding FP recommendations [1], referral of eligible patients to specialists by health care providers in developed countries stayed less than 50% [16], expecting the percentage to be much less in developing countries.

We face many challenges when discussing FP options with cancer patients. The first challenge is related to the health care system. Oncologists in developing countries still face knowledge barriers that prevent a cancer patient of childbearing age to have a FP discussion. They have difficulties in referring patients as well as explaining the most up-to-date fertility treatment options [14]. Communication barriers are another issue secondary to high rates of low literacy and different religions being not supportive of some assisted reproductive techniques.

Challenges Encountered in Developing Nations

Institutional Barriers and Late Referrals

Ideally, the discussion about various FP options should take place with a multidisciplinary team involving oncologists, surgeons, psychologists, and fertility experts upon cancer diagnosis and before any treatment plan. This is not the case in some countries where large specialized centers with necessary expertise are not available to all patients. Fertility specialists interested in FP are rare and are not always available due to time and geographical constraints. Some patients might need to travel 5–6 h before reaching a fertility preservation center. Thus, oncologists are not always in the best position to provide patients with various alternatives and make appropriate decisions and referrals. In addition, there are no referral standards or care plans among different pillars of FP team. Delayed referrals are very common in developing countries, usually within 1–2 days before starting chemotherapy. Counseling these patients when options are no longer valid is very challenging.

Fear of Delay in Treatment

Oncologists do not recommend delaying cancer treatment and frequently act as a barrier to discussing FP options. Male patients can normally have their sperm cryopreserved in available facilities within a day of diagnosis. However, female patients require at least 2–3 weeks of ovarian stimulation to be able to cryopreserve their oocytes. There's a continuous debate between oncologists and fertility experts about the effect of delaying treatment on worsening the clinical outcome and cancer mortality. Moravek reported on long-term outcomes of cancer patients with respect to FP. Forty-one percent of patients pursued FP with a delay of 33 days to cancer treatment compared to 19 days in patients who did not undergo FP with no significant difference in mortality or recurrence rates concluding about the safety and efficacy of the procedure and encouraging oncologists to consider and advocate FP options [17].

Moreover, various options are now available in order to decrease the delay in treatment. Patients are counseled about the use of random start ovarian stimulation protocols rather than day 3 of the period, to avoid any delays. Studies have shown that FP with random start protocols was not correlated with delay in treatment of cancer (38.1 ± 11.3 in patients who underwent FP versus 39.4 ± 18.5 days in patients who did not, $p = 0.672$) [18]. In preparation for FP, a retrospective study revealed no difference in oocyte yield and fertilization rates in patients undergoing random start ovarian stimulation versus conventional stimulation [19]. Patients are usually anxious and concerned about delaying their treatment. Hence, counseling patients must include uncovering available data in order to avoid unnecessary nervousness due to delays in treatment. Oncology teams' knowledge about random start protocols is necessary in order to refer patients when applicable without the fear of delaying cancer treatment.

Fear of Effect of Hormonal Stimulation on Cancer Treatment

Fertility preservation specialists are challenged with questions about the effect of hormonal stimulation on cancer treatment. Literature data is incomplete and based on observational and small sample size studies. Fertility experts need to be more vigilant before counseling their patients on their fertility outcomes after specific treatments and must tailor the consult according to each patient's plan and risk factors for infertility.

Patients apprehend FP because of the fear that hormonal stimulation may have an impact on their cancer treatment [13]. Cancer patients with estrogen sensitive tumors such as breast cancer are not usually offered FP before chemotherapy because of concerns about the potential risks associated with the harmful supraphysiologic estradiol levels after controlled ovarian stimulation. However, Moraveck and colleagues have shown that in patients pursuing FP, hormonal stimulation did not have any impact on the mortality or recurrence of their disease compared to those who did not [17]. Protocols using aromatase inhibitors are now available in case of estrogen sensitive tumors [19]. The use of letrozole in combination with

gonadotropin treatment results in significantly lower peak estradiol levels (483.4 ± 278.9 versus 1464.6 ± 644.9 pg/mL, $p < 0.001$) with similar length of days of stimulation, number of embryos obtained, and fertilization rates [20]. Patients are now safely counseled about the effectiveness of different stimulation protocols in order to optimize their care and quality of life.

In addition, physicians are challenged when patients ask about the safety of this procedure, the thaw-survival rate for oocytes, the total number of patients who have previously cryopreserved in the facility as well as the survival, fertilization, and live birth rate per oocyte thawed for which most of the time, physicians don't have enough data due to the unavailability of dedicated FP units. Furthermore, follow-up data is unavailable regarding the risk of congenital anomalies in children from frozen oocytes. More research is needed in this regard to be able to counsel patients adequately.

Lack of Insurance Coverage

Discussing the costs of FP is very challenging in this vulnerable population that might lack health insurance coverage [21]. Access to FP services in the developing world can be hindered by social, cultural, and financial constraints [22]. Fertility is an important issue, where sterility is stigmatized leading to social suffering for infertile patients. Most centers are private centers, with no health insurance coverage. Some insurance companies cover infertility treatments for highly educated couples who can provide themselves with these therapies leading to socioeconomic inequities in health care. A large survey conducted throughout the globe provided information on barriers and challenges faced by centers, including developing countries. For instance, lack of insurance coverage predominates in Egypt, with few resources supporting patients. As for Tunisia, insurance coverage only applies to patients with demonstrated infertility [23].

Unfortunately, when confronted with cancer diagnosis, many patients face the difficult diagnosis with a lack of financial support and insurance coverage [24]. A systematic review by Jones et al. found that the prohibitive cost is one of the limiting factors for not pursuing FP [24]. The reproductive needs of many young cancer patients remain unmet for economic reasons. ASCO recommends that any patient, regardless of her socioeconomic status, age, prognosis, or parity, should be advised and counseled for FP. Disparities in access to care should be made aware by health care providers including oncologists and fertility experts who are committed to provide the highest level of treatment to this helpless population [2].

Ethical and Legal Challenges After Cancer: Disposal of Gametes

Preservation of fertility raises ethical issues for fertility specialists and legal concerns for the society. The disposition of cryopreserved oocytes and embryos in the case they are not used or in the event of death is another challenge. In the absence

of well-established policies and laws, patients may need to make important life decisions before undergoing this intervention. Discussing the disposition of banked embryos, oocytes, and/or ovarian tissue in the event of changing relationships, divorce, or death in order to protect patients and their partners is not consistently accomplished. Standardized consents are not yet well defined. Posthumous use is not regularly discussed with the patient because of the delicate matter influenced by religion. Policies and laws are not well clear to guide the management. This falls into the legal system of each country, where in such cases the wishes of the person about disposition are honored. Many patients object specifically to embryo cryopreservation for religious reasons [1].

As fertility specialists practicing in a multisectoral country, we encounter families with different beliefs; hence performing reproductive techniques should be undertaken according to the different religious perspectives which respect those beliefs. These religious parties influence the public regarding decisions related to procreation and infertility treatment.

For instance, ethical issues we face in Lebanon may include the process of obtaining an informed consent which is critical to address before any procedure to avoid any ethical dilemmas in the upcoming future. Yet, patients become reluctant at the time of consenting especially with relation to discarding the embryos in case of death, positions influenced by their religious beliefs. Posthumous assisted reproduction is thus the most challenging to discuss in an ethical and religious way. Cryopreservation of embryos is permitted by Islamic figures in Iran as long as it happens in the contract of marriage [25]. Yet, acceptance is confronted with major concerns regarding ownership of gametes after death. From an Islamic vision, the use of previously frozen gametes or embryos is unacceptable [26]. However, no official regulations, policies, or laws exist to ban these procedures. Christian scholars have different attitudes. Assisted reproduction is forbidden by Vatican since moral status begins at the embryo stage, yet it is practiced by Protestant [27]. Cryopreserving human embryos provokes discussions about the moral status of the embryo according to Christian ethical norms. Yet, the different Christian Churches do not have specific positions on this specific issue. Thus, it is important to tailor the fertility consult according to the patients' religious views in order to facilitate the decision-making of the individual. Religious factors shape the practice too in other developing countries such as in Indonesia. As an Islamic community, concerns about the different procedures are faced, in addition to the poor economic status of the country that prohibits most Indonesians from accessing health care [28].

Thus, respecting the autonomy of the patient and the freedom of choice may be important in order to provide accurate information.

While oocyte and embryo cryopreservation have been recommended as the standard options by the ASRM and ASCO, ovarian suppression, gonadal tissue cryopreservation should be offered as part of an institutional review board protocol [1, 29]. This is not the practice in developing nations, where these techniques are suggested and advertised without a prior informed consent. Another barrier to counseling about ovarian tissue cryopreservation is the hypothetical concern of reintroducing cancer cells and thus

inability to obtain healthy mature oocytes. Experts need to fully disclose the risks of this procedure and the uncertainty of the outcome [30].

It is complicated in view of the scarcity of true options and the short time available to take any decision. Moreover, few centers have validated their technique of oocyte cryopreservation and many are still considering it as experimental. In view of the above challenges, patients need to cope with these technical uncertainties which might interfere with their decision.

Cultural Barriers in Counseling

The complexity of consultations involving counseling about FP is magnified by the cultural beliefs.

One of the cultural challenges faced in developing countries is the ovum pick-up being an invasive procedure, done vaginally under ultrasound guidance. In many developing countries, vaginal examination in non-sexually active patients is prohibited for cultural and religious reasons [31]. This makes it challenging for physicians to discuss the potential loss of hymeneal integrity in favor of freezing their eggs. In Egypt, reproductive endocrinologists counsel non-sexually active patients about trans-rectal egg collection, despite the risk of infection and bleeding just to avoid the disruption of the hymen *(Unpublished data, Hesham Al-Inany, Middle East Fertility Society 2018).* In addition, Tunisian female patients are hesitant in pursuing egg cryopreservation because of the fear of loss of virginity [11]. This is one of the observed challenges we have seen in our center; however, there is no available scientific data to support it.

In addition, the emotional state of the parents upon the cancer diagnosis may affect their judgement about the importance of FP focusing on survivorship instead of quality of life. The seriousness of the topic may necessitate several consultations with the family. Selecting appropriate terminology is always challenging for experts and essential in influencing decision's making of adolescents and their parents.

Conclusion

Counseling cancer patients for FP options requires dedication, expertise, as well as economic support and adequate institutional facilities. The main objective is to improve the quality of life for cancer survivors by coordinating the work of a multidisciplinary team. Oncologists are still slow in referring patients for FP discussions. In developing nations, many physicians are not used to involving patients in the decision-making process, where the whole family might be involved in the consultation. Consequently, reproductive concerns are not always addressed. In addition, dedicated fertility clinics are not widely available because of economic reasons. Considerable efforts and resources are needed to these communities in order to train oncology professionals and health care providers regarding fertility issues with patients, emphasizing open communication and early disclosure. Institutional

practices, insurance coverage, and health care policies affect FP discussion with cancer patients. Young cancer patients need to have adequate financial aid to cover FP services including expensive hormonal stimulation and technical procedures; oocyte collection and egg freezing. The ultimate goal is to improve the quality of life in cancer survivors by improving the access to FP options, coordination between the different medical teams, while paying special attention to ethical and legal issues set by national and institutional laws.

Writing this chapter was a real challenge since FP options were recently introduced in this area of the world. In view of the fact that few studies were conducted in developing countries showing lack of awareness and knowledge toward FP, adequate research and structured serious awareness campaigns are urgently needed.

References

1. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24(18):2917–31.
2. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, Quinn G, Wallace WH, Oktay K. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500.
3. Becht LC, Forman EJ. Navigating the complex challenges of fertility preservation. Fertil Steril. 2018;109(2):252–3.
4. Connell S, Patterson C, Newman B. A qualitative analysis of reproductive issues raised by young Australian women with breast cancer. Health Care Women Int. 2006;27(1):94–110.
5. Blumenfeld Z, Haim N. Prevention of gonadal damage during cytotoxic therapy. Ann Med. 1997;29(3):199–206.
6. Peate M, Meiser B, Hickey M, Friedlander M. The fertility-related concerns, needs and preferences of younger women with breast cancer: a systematic review. Breast Cancer Res Treat. 2009;116(2):215.
7. Kirkman M, Winship I, Stern C, Neil S, Mann GB, Fisher JR. Women's reflections on fertility and motherhood after breast cancer and its treatment. Eur J Cancer Care. 2014;23(4):502–13.
8. Hewitt M, Greenfield S, Stovall E. From cancer patient to cancer survivor: lost in transition. Washington, DC: Committee on Cancer Survivorship: Improving Care and Quality of Life, National Cancer Policy Board, Institute of Medicine, and National Research Council; 2006.
9. Davis M. Fertility considerations for female adolescent and young adult patients following cancer therapy: a guide for counseling patients and their families. Clin J Oncol Nurs. 2006;10(2):213.
10. Centers for Disease Control and Prevention. American Society for Reproductive Medicine, and Society for Assisted Reproductive Technology. 2006 Assisted reproductive technology success rates: National summary and fertility clinic reports; 2008
11. Rashedi AS, SFD R AL, Edmonds ME. Survey of third-party parenting options associated with fertility preservation available to patients with cancer around the globe. J Glob Oncol. 2017; https://doi.org/10.1200/JGO.2017.009944.
12. Whitworth A. Freezing embryos—a woman's best option, but is it legal? J Natl Cancer Inst. 2006;98(19):1359.
13. Rabah DM, El-Nimr N, Rafe BA, Arafa MA. Fertility cryopreservation for female cancer patients: attitudes and clinical practices of oncologists in Riyadh, Saudi Arabia. J Reprod Med. 2012;57(9-10):431–4.

14. Ghazeeri G, Zebian D, Nassar AH, Harajly S, Abdallah A, Hakimian S, Skaiff B, Abbas HA, Awwad J. Knowledge, attitudes and awareness regarding fertility preservation among oncologists and clinical practitioners in Lebanon. Hum Fertil. 2016;19(2):127–33.
15. 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):279–83.
16. Quinn GP, Vadaparampil ST. Fertility preservation and adolescent/young adult cancer patients: physician communication challenges. J Adolesc Health. 2009;44(4):394–400.
17. Moravek MB, Confino R, Smith KN, Kazer RR, Klock SC, Lawson AK, Gradishar WJ, Pavone ME. Long-term outcomes in cancer patients who did or did not pursue fertility preservation. Fertil Steril. 2018;109(2):349–55.
18. Letourneau JM, Sinha N, Wald K, Harris E, Quinn M, Imbar T, Mok-Lin E, Chien AJ, Rosen M. 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.
19. Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100(6):1673–80.
20. Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, Bang H. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab. 2006;91(10):3885–90.
21. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 405: ovarian tissue and oocyte cryopreservation. Obstet Gynecol. 2008;111(5):1255–6.
22. Nachtigall RD. International disparities in access to infertility services. Fertil Steril. 2006;85(4):871–5.
23. Rashedi AS, de Roo SF, Ataman LM, Edmonds ME, Silva AA, Scarella A, Horbaczewska A, Anazodo A, Arvas A, Ramalho de Carvalho B, Sartorio C. Survey of fertility preservation options available to patients with cancer around the globe. J Glob Oncol. 2017;4:1–6.
24. Jones G, Hughes J, Mahmoodi N, Smith E, Skull J, Ledger W. What factors hinder the decision-making process for women with cancer and contemplating fertility preservation treatment? Hum Reprod Update. 2017;23(4):433–57.
25. Larijani B, Zahedi F. Ethical and religious aspects of gamete and embryo donation and legislation in Iran. J Relig Health. 2007;46(3):399–408.
26. Samani RO, Ashrafi M, Alizadeh L, Mozafari M. Posthumous assisted reproduction from Islamic perspective. Int J Fertil Steril. 2008;2(2)
27. Schenker JG. Assisted reproduction practice: religious perspectives. Reprod Biomed Online. 2005;10(3):310–9.
28. Purvis TE. Assisted reproduction in Indonesia: policy reform in an Islamic culture and developing nation. Reprod Biomed Online. 2015;31(5):697–705.
29. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril. 2018;110(3):380–6.
30. Crockin SL. Legal issues related to parenthood after cancer. JNCI Monogr. 2005;(34):111–3.
31. Robertson JA. Cancer and fertility: ethical and legal challenges. JNCI Monogr. 2005;(34):104–6.

Part III

Controversial Topics in Fertility Counseling of Breast Cancer Patients

Ovarian Stimulation in Women with Breast Cancer

10

Volkan Turan and Kutluk Oktay

Introduction

Breast cancer is the most common malignant tumor diagnosed in women, with 7–10% of cases before the age of 40 years [1]. Every year, an increasing number of women with breast cancer is successfully treated with cytotoxic chemotherapy and/or radiotherapy. Although the treatments significantly reduce the mortality rates, the long-term consequences of gonadal toxicity include premature ovarian insufficiency and infertility [2]. In addition to the gonadotoxicity of chemotherapy, women who are on tamoxifen treatment are now asked to delay childbearing for the duration of treatment which could be as long as 10 years. Adding the aging-related decline in ovarian reserve to chemotherapy-induced damage, most women with breast cancer are at risk of living childless or not having reached the size of family that they have desired [3]. As a result, fertility preservation gains utmost importance in these patients.

Cancer Treatment and Ovary

The impact of the treatment on ovarian function depends on the age, ovarian reserve, and the type and dose of the chemotherapeutic agents. Alkylating agents are associated with highest risk of gonadotoxicity, which is widely used in combination with other chemotherapeutic agents for the treatment of breast cancer. While

V. Turan
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Yeni Yuzyil University School of Medicine, Istanbul, Turkey

K. Oktay (✉)
Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA
e-mail: kutluk.oktay@kutlukoktay.com

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_10

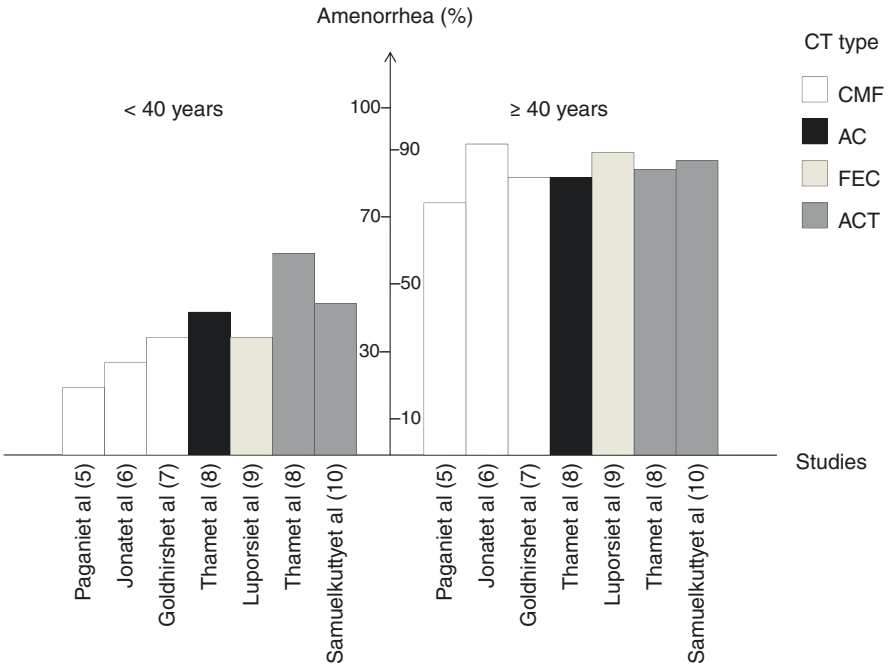

Fig. 10.1 Amenorrhea risk according to age and different chemotherapy regimens in women with breast cancer. Please note that treatment with chemotherapy regimens was given for 3–6 cycles

anthracyclines have a moderate risk, antimetabolites such as 5-fluorouracil is associated with low gonadal toxicity [4]. The rates of acute premature ovarian failure according to chemotherapy protocol used and women age in breast cancer were shown in Fig. 10.1. While acute premature ovarian failure rate was between 18% and 61% under the age of 40, more than 74% of the women over the age of 40 has been shown to be amenorrheic after the treatment [5–10].

Although most of the studies assessed the ovarian function based on the menstrual pattern, the resumption of menstruation is not associated with intact ovarian reserve and these women will always have a high risk of developing premature menopause during their later reproductive life. Therefore, studies have been performed to find out the best marker to show the long-term ovarian function following chemotherapy. Although serum anti-Müllerian hormone (AMH) levels are predictive of ovarian function postchemotherapy and age at menopause, more research is required to find out their predictive value on pregnancy rates [11].

Fertility Preservation Options

The options for fertility preservation in women vary depending on the patient's age, ovarian reserve, window of time available before treatment starts, and marriage status. Controlled ovarian stimulation followed by in vitro fertilization (IVF)

for embryo and oocyte cryopreservation are the established methods recommended by American Society of Clinical Oncology (ASCO), although ovarian tissue cryopreservation is currently being removed from experimental category for fertility preservation around the world [12]. Fertility preservation strategies have been well covered in the recent update of ASCO Clinical Guidelines for Fertility Preservation and they will not be detailed here. We will only briefly touch upon ovarian cryopreservation before focusing on ovarian stimulation for oocyte/embryo cryopreservation.

Ovarian Tissue Cryopreservation

Since the performance of first successful ovarian transplantation procedure by Oktay and Karlikaya, more than 100 children have been born worldwide after this technique [13, 14]. Ovarian tissue cryopreservation is a strong alternative to oocyte/embryo cryopreservation, given that it does not require a delay for ovarian stimulation and can be performed as an outpatient laparoscopic procedure. Breast cancer metastasis to ovarian tissue is extremely unlikely in stage III or earlier breast cancer and hence this is not a real concern [15]. One concern is risk of ovarian cancer in cryopreserved and transplanted ovarian tissue in women carrying BRCA and other mutations of the genes from the same DNA repair pathway, especially if these mutations were also associated with increased ovarian cancer risk. However, it is probable that if the ovarian tissue was cryopreserved at a young age when the risk of cancer was low, the risk will be similarly low when the tissue transplanted back. In that case, the tissue can be removed as soon as the desired outcome is achieved in the transplant recipient, similar to performing an RRSO in women carrying high-risk mutations [16].

Embryo and Oocyte Cryopreservation

Although embryo cryopreservation has been used worldwide at least for more than 30 years, oocyte cryopreservation was removed from the experimental category in 2013 by the American Society of Reproductive Medicine [17]. Controlled ovarian stimulation is typically required before the oocyte retrieval for both approaches, which lasts for about 2 weeks. Given that the women with breast cancer typically have an interval of 6–8 weeks between surgery and the initiation of adjuvant chemotherapy, and that random start ovarian stimulation methods enable initiation of the treatment at any time during the menstrual cycle, ovarian stimulation is practical in most women with breast cancer. Although historically embryo cryopreservation has been preferred for women with partners, because of the flexibility and autonomy that it offers to women and given its rising success rates, egg freezing is also considered as a nearly equivalent option even among those who are not single. Most studies have shown significantly high post-thaw survival rates (more than 90%) for embryos and oocytes with the development of cryopreservation techniques [18]

though blastocyst embryo development rates and pregnancy rates still remain lower for egg freezing than embryo freezing [19]. Hence, even women with partners should be counseled on both egg and embryo freezing.

Ovarian Stimulation in Women with Breast Cancer

Conventional ovarian stimulation protocols lead to a significant increase in peak serum estradiol levels, which can induce breast cancer cell proliferation and dissemination [20]. Until about a decade ago, women with breast cancer were usually offered natural cycle IVF, which resulted on average 0.6 embryos per cycle [21]. As an improvement to natural cycle stimulation, Oktay et al. first used tamoxifen, a selective estrogen receptor blocker, for ovarian stimulation which resulted in increased number of embryo recovery per patient [21]. Subsequently, Oktay et al. combined tamoxifen with gonadotropins and later introduced the aromatase inhibitor protocol with gonadotropins [22]. The latter protocol in general resulted in larger number of oocytes and embryos being cryopreserved and hence become the protocol of choice [22]. However, we still use tamoxifen protocol in patients who cannot tolerate aromatase inhibitors or who are already on tamoxifen for breast cancer treatment and wish to preserve oocytes and embryos without discontinuing them.

Later, the letrozole-gonadotropin stimulation protocol was further improved by the substitution of hCG trigger with GnRH analog trigger, further reducing the risk of estrogen exposure, ovarian hyperstimulation, and false positive pregnancy tests before chemotherapy. In this protocol, letrozole 5 mg/day is initiated on cycle day 2 followed by gonadotropins, 150–450 IU/day on cycle day 4 (Fig. 10.2). The letrozole treatment is then continued throughout the stimulation. To prevent a premature luteinizing hormone (LH) surge, patients are given 0.25 mg/day of a GnRH

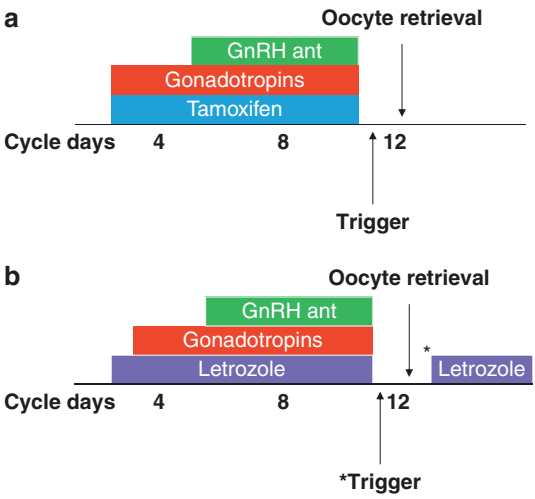

Fig. 10.2 Ovarian stimulation with tamoxifen-gonadotropin (**a**) and letrozole-gonadotropin (**b**) in women with breast cancer. ∗ If using a GnRHa trigger, there is no need to restart letrozole in the luteal phase

antagonist when the lead follicle size reached ≥13 mm mean diameter; this dose is continued until the trigger day. When at least two follicles reached at least 20–21 mm in diameter, oocyte maturation is triggered with leuprolide acetate. Letrozole is discontinued on the day of trigger. Transvaginal ultrasound-guided oocyte retrieval is performed 35 h after the trigger. If an hCG trigger is used instead of the GnRHa, the estradiol (E2) measurement is repeated 3 days after oocyte retrieval in patients triggered by hCG and if the E2 level is >250 pg/mL, letrozole is continued for approximately 3–6 days until the E2 levels decreased to <50 pg/mL. Post retrieval E2 monitoring and letrozole treatment are not necessary for women who are triggered with GnRHa as this results in a sharp decline in E2 levels within 48 h.

There are some differences in letrozole protocols compared to standard, as the follicle size for trigger needs to be about 2–3 mm larger as we have found to avoid retrieving high percentage of immature oocytes [22, 23]. This difference in trigger size is due to the fact that letrozole results in the earlier antral space formation and hence the length of stimulation is similar to standard protocols [24]. The cycle outcomes from letrozole protocols are in fact equal or better than standard protocols in cancer patients. In a one-of-a-kind study assessing the impact of letrozole on cycle outcomes in cancer patients, we compared the cycle outcomes in 145 patients stimulated with an antagonist protocol either using letrozole combined with gonadotropins (breast cancer, $n = 118$) or gonadotropin alone (other cancer types, $n = 24$). After adjusting for age, body mass index, baseline FSH level, and BRCA status, letrozole combined with gonadotropin protocol resulted in higher number of total oocytes (95% confidence interval [CI]: 1.9–3.6; $p = 0.002$), mature oocyte (95% CI: 0.3–1.4; $p = 0.028$), and embryo yield (95% CI: 0.7–1.4; $p = 0.015$) [25].

hCG trigger carries the risk of ovarian hyperstimulation syndrome (OHSS) which may delay the initiation of chemotherapy in cancer patients. In addition, due to its longer half-life compared with endogenous LH, it can induce endogenous production of estrogen which is not desirable in breast cancer patients. Therefore in recent years, GnRH agonist was widely used by clinicians to achieve a greater and faster decline in estradiol levels without effecting cycle outcomes [26]. In a recent study [27], we analyzed the cycle outcomes and the incidence of ovarian hyperstimulation syndrome (OHSS) when oocyte maturation was triggered by GnRH agonist versus hCG in breast cancer patients undergoing fertility preservation and concluded that GnRH agonist trigger improved cycle outcomes via increasing number of mature oocytes, while significantly reducing the risk of OHSS in breast cancer patients undergoing fertility preservation.

Early counseling and referral for ovarian stimulation may further enhance success rates. We analyzed cycle outcomes based on referral before or after breast surgery [28]. We found that women who were referred pre-breast surgery initiated chemotherapy on average 24 days earlier compared to those referred post-surgery. In addition, earlier counseling and initiation of cryopreservation cycles enabled us to perform two consecutive ovarian stimulation cycles without any delay in chemotherapy treatment in a larger number of women referred before surgery, resulting in higher yield of embryos/oocytes cryopreserved [28, 29].

In setting of a late referral, to prevent delay in cancer treatment, we developed random start ovarian stimulation protocols, where the ovarian stimulation can be initiated regardless of the menstrual cycle day [30]. This approach is based on the fact that there is a cohort of follicles developing at any given day of the cycle, follicular or luteal phase, for most women which can be stimulated [31]. Gonadotropins are started randomly with or without antagonists depending on the stage of the cycle and presence or absence of a large preovulatory follicle. In addition, luteal phase start ovarian stimulation can be performed after the retrieval of dominant follicle in patients whose initial visit is during late follicular phase. Cycle outcomes after random start ovarian stimulation protocol was found as effective as conventional protocol in the studies [30, 32].

Ovarian Response to Stimulation

Because cancer is associated with increased states of catabolism and malnutrition, it has been hypothesized that ovarian response to stimulation may be altered [33–36]. Although some reports have suggested a lower response to ovarian stimulation in cancer patients compared to controls [33, 34], others could not confirm those finding [35, 36]. We have recently performed a meta-analysis of ten case-controlled studies and concluded that a cancer diagnosis is not associated with reduced response to ovarian stimulation. Subgroup analysis of women with breast cancer also yielded similar results. While, other than in women with BRCA mutations, a cancer diagnosis does not seem to result in poorer fertility preservation outcomes, further research may be required due to heterogeneity among the studies analyzed in our meta-analysis [37].

Pregnancy and Perinatal Outcomes

The largest prospective study regarding clinical outcomes has been published by Oktay et al., suggesting that pregnancy rates of women with breast cancer were comparable to those expected in a noncancer population undergoing in vitro fertilization [38]. In that study, of the 131 women undergoing embryo cryopreservation, 33 returned to have frozen embryo transfer at a median 5.25 years (range, 2–8.2 years) after oocyte retrieval. Seventeen of the 33 women attempting pregnancy had at least one child with embryos, translating into a fertility preservation rate of 51.5% per attempting woman. Although the sample size was limited, no minor or major fetal malformations or developmental abnormalities were detected after a mean follow-up of more than 3 years. In another study using letrozole as an ovulation induction agent, the authors found no evidence that the exposure of the oocytes to letrozole increases congenital birth defects [38, 39]. Teratogenicity is not plausible in the fertility preservation setting as oocytes are retrieved and fertilized in vitro and cryopreserved. Embryos are never exposed to letrozole.

Safety of Ovarian Stimulation

We have performed several studies on the impact of letrozole-IVF protocols on relapse-free survival in women with breast cancer. In the first study, we investigated the safety of fertility preservation via controlled ovarian stimulation with letrozole in women with breast cancer after a median follow-up of 23.4 months (range, 7.5–63.6 months) and found that the survival was not compromised compared with controls [40]. In the second study [41], we investigated the long-term safety of fertility preservation via controlled ovarian stimulation with letrozole. In that study, 120 women with non-metastatic breast cancer who elected to undergo ovarian stimulation with letrozole for fertility preservation prior to chemotherapy were compared to 217 women with breast cancer who chose not to undergo any fertility preservation procedures and served as controls. No significant differences were found in the relapse-free survival and recurrence rates between the two groups after a mean follow-up of 5.0 ± 2.1 years (range 1–13 years). Neither BRCA gene mutation status nor undergoing fertility preservation before or after breast surgery affected survival outcomes. Based on these studies, ovarian stimulation with concurrent use of letrozole seems to provide a safe fertility preservation option to women with breast cancer even though longer term follow-up may strengthen these conclusions.

Special Case of Women with BRCA Mutations: Accelerated Ovarian Aging

BRCA genes play a key role in double-strand DNA break repair via homologous recombination [42]. In 2008, Oktay et al. made the first observation that women with BRCA mutations, especially those with BRCA1, may show lower response to ovarian stimulation compared to those who tested negative for those mutations [43]. Oktay laboratory also showed that women with BRCA1 mutations have lower AMH levels compared to controls [44]. The finding of diminished ovarian reserve in women with BRCA mutations was strengthened by multiple reports of earlier age at natural menopause in carriers as well as lower serum AMH levels [44–47]. Furthermore, we showed that women with BRCA mutations have lower primordial follicle counts in their ovarian tissue and their follicles accumulate significantly more DNA damage than those of controls [48]. In a recent study, we further confirmed that women with BRCA mutations and breast cancer yield fewer oocytes; those with BRCA mutations produced fewer oocytes (16.4 ± 7.7 vs. 11.0 ± 8.0; $p = 0.01$) and embryos (8.2 ± 4.7 vs. 5.1 ± 4.4, $p = 0.01$) compared to those who were BRCA negative [25].

Women with BRCA mutations may face a double whammy. First they have lower ovarian reserve to begin with, and after chemotherapy, they may be at higher risk of premature ovarian insufficiency compared to other women. Second, given both cyclophosphamide and doxorubicin damage primordial follicles by inducing double-strand DNA breaks (DSBs) in oocytes [49], a diminished DNA repair mechanism secondary to BRCA mutations may result in a higher extent of follicle reserve

loss after chemotherapy [50]. Hence, fertility preservation via embryo or oocyte cryopreservation should be further emphasized among those women. Further, if women with BRCA mutations undergo embryo cryopreservation, their embryos could be screened for those mutations to eliminate propagation of these mutations to next generations. Finally, there are more pathogenic mutations being identified in the double-strand DNA break repair pathway. Currently, we do not have any clinical data to determine if they too are associated with accelerated ovarian aging. However, our laboratory showed that essentially all genes in the same pathway play critical role in oocyte aging and future research may show that mutations in the genes such as CHK1, PALB2, BRIP1, and TP53 may also out women with breast cancer at reproductive disadvantage [51].

Conclusion

In conclusion, women with breast cancer require special attention for fertility preservation due to potential hormone sensitive nature of their neoplasm and the fact that BRCA and other pathogenic mutations may put them at reproductive disadvantage. Embryo and oocyte cryopreservation are the most common fertility preservation options but they both typically require controlled ovarian stimulation. The stimulation protocol using letrozole plus gonadotropins seems to be effective and safe in this population because it does not allow estrogen levels to rise to those seen with standard stimulation protocols. Random start ovarian stimulation protocols can be used for women who have time constraints before chemotherapy, with similar success to conventional ovarian stimulation protocols. Future areas of research should include further studies regarding pregnancy and perinatal outcomes following the transfer of embryos generated with the aromatase inhibitor protocols and the association of BRCA mutations with ovarian aging.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Turan V, Oktay K. Sexual and fertility adverse effects associated with chemotherapy treatment in women. Expert Opin Drug Saf. 2014;13:775–83.
3. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381(9869):805–16.
4. Bedoschi G, Oktay K. Current approach to fertility preservation by embryo cryopreservation. Fertil Steril. 2013;99:1496–502.
5. Pagani O, O'Neill A, Castiglione M, et al. Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the International Breast Cancer Study Group (IBCSG) Trial VI. Eur J Cancer. 1998;34:632–40.
6. Jonat W, Kaufmann M, Sauerbrei W, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. J Clin Oncol. 2002;20:4628–35.

7. Goldhirsch A, Gelber RD, Castiglione M. The magnitude of endocrine effects of adjuvant chemotherapy for premenopausal breast cancer patients. The International Breast Cancer Study Group. Ann Oncol. 1990;1:183–8.
8. Tham YL, Sexton K, Weiss H, Elledge R, Friedman LC, Kramer R. The rates of chemotherapy-induced amenorrhea in patients treated with adjuvant doxorubicin and cyclophosphamide followed by a taxane. Am J Clin Oncol. 2007;30:126–32.
9. Luporsi E, Weber B. The effects of breast cancer chemotherapy on menstrual function. Proc Am Soc Clin Oncol. 1998;17:155A.. [abstr 595]
10. Samuelkutty S, Gluz O, Mohrmann S. Chemotherapy-induced amenorrhea g(CIA) in patients treated with adjuvant CEF/CMF or EC/docetaxel: analysis from a phase III randomized EC/Doc trial. Breast Cancer Res Treat. 2005;94:S105.. [abstr 2063]
11. Anderson RA, Cameron DA. Pretreatment serum anti-Müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab. 2011;96:1336–43.
12. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, Wallace WH, Wang ET, Loren AW. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994–2001.
13. Pacheco F, Oktay K. Current success and efficiency of autologous ovarian transplantation: a meta-analysis. Reprod Sci. 2017;24:1111–20.
14. Oktay K, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. N Engl J Med. 2000;342:1919 15 17.
15. Redig AJ, McAllister SS. Breast cancer as a systemic disease: a view of metastasis. J Intern Med. 2013;274:113–26.
16. Rodriguez-Wallberg KA, Oktay K. Fertility preservation and pregnancy in women with and without BRCA mutation-positive breast cancer. Oncologist. 2012;17:1409–17.
17. Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013;99:37–43.
18. Rienzi L, Romano S, Albricci L, et al. Embryo development of fresh 'versus' vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study. Hum Reprod. 2010;25:66–73.
19. Kushnir VA, Barad DH, Albertini DF, Darmon SK, Gleicher N. Outcomes of fresh and cryopreserved oocyte donation. JAMA. 2015;314:623–4.
20. Zheng S, Huang J, Zhou K, Zhang C, Xiang Q, Tan Z, Wang T, Fu X. 17β-Estradiol enhances breast cancer cell motility and invasion via extra-nuclear activation of actin-binding protein ezrin. PLoS One. 2011;6:e22439.
21. Oktay K, et al. Fertility preservation in breast cancer patients: IVF and embryo cryopreservation after ovarian stimulation with tamoxifen. Hum Reprod. 2003;18:90–5.
22. Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, Bang H. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab. 2006;91:3885–90.
23. Garcia-Velasco JA, Moreno L, Pacheco A, Guillén A, Duque L, Requena A, Pellicer A. The aromatase inhibitor letrozole increases the concentration of intraovarian androgens and improves in vitro fertilization outcome in low responder patients: a pilot study. Fertil Steril. 2005;84:82–7.
24. Hu Y, Cortvrindt R, Smitz J. Effects of aromatase inhibition on in vitro follicle and oocyte development analyzed by early preantral mouse follicle culture. Mol Reprod Dev. 2002;61:549–59.
25. Turan V, Bedoschi G, Emirdar V, Moy F, Oktay K. Ovarian stimulation in patients with cancer: Impact of letrozole and BRCA mutations on fertility preservation cycle outcomes. Reprod Sci. 2018;25:26–32.
26. Oktay K, Türkçüoğlu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod Biomed Online. 2010;20:783–8.

27. Reddy J, Turan V, Bedoschi G, Moy F, Oktay K. Triggering final oocyte maturation with gonadotropin-releasing hormone agonist (GnRHa) versus human chorionic gonadotropin (hCG) in breast cancer patients undergoing fertility preservation: an extended experience. J Assist Reprod Genet. 2014;31:927–32.
28. Lee S, Ozkavukcu S, Heytens E, Moy F, Oktay K. Value of early referral to fertility preservation in young women with breast cancer. J Clin Oncol. 2010;28:4683–6.
29. 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;100:1681–5.e1.
30. Sönmezer M, Türkçüoğlu I, Coşkun U, Oktay K. Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles. Fertil Steril. 2011;95:2125.e9–11.
31. Oktay K, Demirtas E, Son WY, Lostritto K, Chian RC, Tan SL. In vitro maturation of germinal vesicle oocytes recovered after premature luteinizing hormone surge: description of a novel approach to fertility preservation. Fertil Steril. 2008;89:228.e19–22.
32. Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: random-start controlled ovarian stimulation. Fertil Steril. 2013;100:1673–80.
33. Domingo J, Guillen V, Ayllon Y, Martinez M, Munoz E, Pellicer A, GarciaVelasco JA. Ovarian response to controlled ovarian hyperstimulation in cancer patients is diminished even before oncological treatment. Fertil Steril. 2012;97:930–4.
34. Klock SC, Zhang JX, Kazer RR. Fertility preservation for female cancer patients: early clinical experience. Fertil Steril. 2010;94:149–55.
35. Almog B, Azem F, Gordon D, Pauzner D, Amit A, Barkan G, Levin I. Effects of cancer on ovarian response in controlled ovarian stimulation for fertility preservation. Fertil Steril. 2012;98:957–60.
36. Robertson AD, Missmer SA, Ginsbug ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. Fertil Steril. 2011;95:588–91.
37. Turan V, Quinn MM, Dayioglu N, Rosen MP, Oktay K. The impact of malignancy on response to ovarian stimulation for fertility preservation: a metaanalysis. Fertil Steril. 2018;110:1347–55. https://doi.org/10.1016/j.fertnstert.2018.08.013.
38. 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;33:2424–9.
39. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril. 2006;85:1761–5.
40. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol. 2008;26:2630–5.
41. 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;101:1364–71.
42. Oktay K, Turan V, Titus S, Stobezki R, Liu L. BRCA mutations, dna repair deficiency, and ovarian aging. Biol Reprod. 2015;93:67.
43. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol. 2010;28:240–4.
44. Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, Dickler M, Robson M, Moy F, Goswami S, Oktay K. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. Sci Transl Med. 2013;5:172ra21.
45. Rzepka-Górska I, Tarnowski B, Chudecka-Głaz A, Górski B, Zielińska D, Tołoczko-Grabarek A. Premature menopause in patients with BRCA1 gene mutation. Breast Cancer Res Treat. 2006;100:59–63.

46. Wang ET, Pisarska MD, Bresee C, Chen YD, Lester J, Afshar Y, Alexander C, Karlan BY. BRCA1 germline mutations may be associated with reduced ovarian reserve. Fertil Steril. 2014;102:1723–8.
47. Lin WT, Beattie M, Chen LM, Oktay K, Crawford SL, Gold EB, Cedars M, Rosen M. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. Cancer. 2013;119:1652–9.
48. Lin W, Titus S, Moy F, Ginsburg ES, Oktay K. Ovarian aging in women with BRCA germline mutations. J Clin Endocrinol Metab. 2017;102:3839–47.
49. Soleimani R, Heytens E, Darzynkiewicz Z, Oktay K. Mechanisms of chemotherapy-induced human ovarian aging: double strand DNA breaks and microvascular compromise. Aging (Albany NY). 2011;3:782–93.
50. Oktay K, Moy F, Titus S, Stobezki R, Turan V, Dickler M, Goswami S. Age-related decline in DNA repair function explains diminished ovarian reserve, earlier menopause, and possible oocyte vulnerability to chemotherapy in women with BRCA mutations. J Clin Oncol. 2014;32:1093–4.
51. Frey JD, Salibian AA, Schnabel FR, Choi M, Karp NS. Non-BRCA1/2 breast cancer susceptibility genes: a new frontier with clinical consequences for plastic surgeons. Plast Reconstr Surg Glob Open. 2017;5:e1564.

Role of GnRH Agonists for Fertility Preservation in Breast Cancer

11

Cynthia Villarreal-Garza, Edna A. Lopez-Martinez, and Hatem A. Azim Jr

Fertility Aspects in Young Women with Breast Cancer

Breast cancer in young women ≤40 years represents a significant proportion of breast cancer cases, ranging from 5% in countries such as the United States and Canada to 11% in Latin American countries and 26% in Sub-Saharan Africa [1]. These patients are often diagnosed with more advanced disease [2, 3] and, thus, frequently undergo aggressive and prolonged treatment regimens with considerable morbidity and psychosocial repercussions.

Premature ovarian failure (POF) represents a possible side effect of chemotherapy administration in these patients [4] and is associated with significant adverse effects such as infertility [5]. This represents a major concern, as late or delayed pregnancy is increasingly encountered nowadays among working-class women around the world [6, 7]. This issue often leads to psychological distress and anxiety [8–10] and may impact patients' choice and adherence to treatment, with

C. Villarreal-Garza
Hospital Zambrano Hellion—Breast Cancer Center, Tecnologico de Monterrey, School of Medicine, Monterrey, NL, Mexico

Research and Breast Cancer Department, Instituto Nacional de Cancerologia, Mexico City, Mexico

Joven & Fuerte, Program for Young Women with Breast Cancer in Mexico, Mexico City, Mexico

E. A. Lopez-Martinez
Hospital Zambrano Hellion—Breast Cancer Center, Tecnologico de Monterrey, School of Medicine, Monterrey, NL, Mexico

Joven & Fuerte, Program for Young Women with Breast Cancer in Mexico, Mexico City, Mexico

H. A. Azim Jr (✉)
Hospital Zambrano Hellion—Breast Cancer Center, Tecnologico de Monterrey, School of Medicine, Monterrey, NL, Mexico

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_11

subsequent suboptimal disease outcomes [11]. Recent studies have shown that approximately half of the young women with newly diagnosed breast cancer are worried about the possible treatment-related loss of fertility and ovarian function, and similarly the same proportion desire to have a future pregnancy [8, 11–13]. However, only less than 10% manage to become pregnant later on [14].

Currently approved strategies for fertility preservation in young breast cancer patients include embryo, oocyte, and ovarian tissue cryopreservation [15, 16]. However, these options are not universally available [17] and do not prevent the development of chemotherapy-induced POF. In recent years, temporary ovarian suppression with the administration of gonadotropin-releasing hormone agonists (GnRHa) concomitantly with chemotherapy emerged as a possible tool to preserve ovarian function in premenopausal patients and, thus, improve their chances of future pregnancies [18]. Although the mechanism of action for the protective effect of temporary ovarian suppression with GnRHa during chemotherapy is not completely understood, existing theories suggest a direct protective effect by preventing apoptosis [19] and an indirect effect by promoting a prepubertal hormonal state in which follicles remain quiescent and less vulnerable to chemotherapy-induced toxicity [20].

Randomized Controlled-Trials that Evaluate the Role of GnRHa on Ovarian Protection/Fertility Preservation in Breast Cancer

To date, 14 randomized controlled-trials have addressed the protective role of temporary ovarian suppression with GnRHa in young women with breast cancer. Table 11.1 summarizes these studies. Median patient age ranged from 29.9 to 46 years, with most trials having a median close to 40 years. The most commonly used chemotherapy regimens were anthracyline- and cyclophosphamide-based. Goserelin was the administered GnRHa in eight trials, triptorelin in five, and leuprolide acetate in one.

Some of the main differences between studies that have evaluated the efficacy of GnRHa as an ovarian-protection strategy are the POF definition and time-point evaluation used in each trial. Most of the studies used amenorrhea as the definition of POF, with the timing of the evaluation ranging from 6 to 36 months [21–28]. Some others defined POF as the presence of amenorrhea and postmenopausal levels of FSH ± E2 at 12–24 months [29–33], while one study extended the timing of evaluation up to 72 months [34]. Lastly, one study defined POF as amenorrhea and no resumption of ovulation at 8 months [35].

Impact of GnRHa on POF

Ten out of the 14 randomized controlled trials evaluating the impact of GnRHa on POF showed a protective effect of GnRHa on ovarian function when given along with chemotherapy in premenopausal patients. Notably, three out of four of the

Table 11.1 Randomized clinical studies evaluating temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients

Authors	POF definition and timing of evaluation	Treatment regimen	CT regimen	Cycles	Number of patients	Median age	Main results (POF, pregnancies)	Main results (DFS, OS)
Li et al. (2008)	Amenorrhea at 12 m	CT ± goserelin	AC or AC-D	4	31 32	40 39	POF 32.1% vs. 53.1% ($p = 0.027$)	
Badawy et al. (2009)	Amenorrhea and no resumption of ovulation at 8 m	CT ± goserelin	FAC	6	39 39	30 29.2	POF 11.4% vs. 66.6% ($p < 0.001$)	
Sverrisdottir A et al. 2009	Amenorrhea at up to 36 m	CT ± goserelin (± tamoxifen)	CMF	6	51 43	45 45–46	POF 64% (93%) vs. 90% (87%) ($p = 0.006$)	
Del Mastro et al. (2011) Lambertini et al. (2015) (PROMISE-GIM6)	Amenorrhea and postmenopausal levels of FSH and E2 at 12 m	CT ± triptorelin	CMF, E-CMF, EP-CMF, ED-CMF, AC, EC, FEC, AC-D, EC-D, EC-P, FEC-P, FEC-D, or ED	4–8	148 133	39 39	POF 8.9% vs. 25.9% ($p < 0.001$) Pregnancies: 8 vs. 3 ($p = 0.20$)	DFS events: 36 vs. 29 (5-y DFS 80.5% vs. 83.7%) ($p = 0.52$)
Gerber et al. (2011)	Amenorrhea at 6 m	CT ± goserelin	FEC-T, EC-T, FEC, FAC, TAC, FEC-GEM	6–8	30 30	35 38.5	POF 30% vs. 43.3% ($p = 0.142$) Pregnancies: 1 vs. 1	
Sun et al. (2011)	Amenorrhea at 12 m	CT ± goserelin	NR	NR	11 10	38 37	POF 27.3% vs. 50% ($p = 0.039$)	

(continued)

Table 11.1 (continued)

Authors	POF definition and timing of evaluation	Treatment regimen	CT regimen	Cycles	Number of patients	Median age	Main results (POF, pregnancies)	Main results (DFS, OS)
Munster et al. (2012)	Amenorrhea at 24 m	CT ± triptorelin	AC, AC-P, FEC, or FAC	4–8	27 22	39 38	POF 15% vs. 14% ($p = 0.32$) Pregnancies: 0 vs. 2	
Elgindy et al. (2013)	Amenorrhea at 12 m	CT + triptorelin ± GnRH antagonist CT	FAC	6	50 50	33 32	POF 20%/16% vs. 20%/20% ($p = 1.00$/$p = 0.71$) Pregnancies: 2 vs. 1	
Song et al. (2013)	Amenorrhea and postmenopausal levels of FSH and E2 at 12 m	CT ± leuprolide acetate	AC or AC-D	4–6	89 94	40.3 42.1	POF 16.9% vs. 28.7% ($p < 0.01$)	
Jiang et al. (2013)	Amenorrhea	CT ± triptorelin	NR	NR	10 11		POF 10.0% vs. 45.5% ($p = 0.05$)	
Karimi-Zarchi et al. (2014)	Amenorrhea at 6 m	CT ± triptorelin	TAC	NR	21 21	37	POF 9.5% vs. 66.7% ($p < 0.001$)	
Leonard et al. (2017) (OPTION)	Amenorrhea and postmenopausal levels of FSH at 12–24 m	CT ± goserelin	CAF, CAF-T, CEF, CEF-T	6–8	103 118	37.9 38.8	POF 18.5% vs. 34.8% ($p = 0.048$) Pregnancies: 7 vs. 5	OS events: 9 vs. 15

Zhang et al. (2018)	Amenorrhea and postmenopausal levels of FSH and E2 at 36–72 m	CT ± goserelin	NR	NR	108 108	37.5 39	POF 23.1% vs. 22.8% ($p = 0.969$)	DFS events: 23 vs. 17 (5-y DFS 78.2% vs. 84.5%) ($p = 0.293$) OS events: 7 vs. 5 (5-y OS 96.0% vs. 95.3%) ($p = 0.516$)
Moore et al. (2019) (POEMS/ SWOG S0230)	Amenorrhea and postmenopausal levels of FSH at 24 m	CT ± goserelin	AC, CAF, TAC, CEF, AC-T, or CMF	NR	105 113	37.6 38.7	POF 8% vs. 22% ($p = 0.04$) Pregnancies: 23.1% vs. 12.2% ($p = 0.04$)	DFS events: 12 vs. 23 (5-y DFS 88.1% vs. 78.6%) ($p = 0.09$) OS events: 8 vs. 18 (5-y OS 91.7% vs. 83.1%) ($p = 0.06$)

GnRHa gonadotropin-releasing hormone agonists, *AC* doxorubicin and cyclophosphamide, *AC-D* AC followed by docetaxel, *FAC* 5-fluorouracil, doxorubicin and cyclophosphamide, *CMF* cyclophosphamide, methotrexate and 5-fluorouracil, *E-CMF* epirubicin followed by CMF, *EP-CMF* epirubicin, paclitaxel followed by CMF, *ED-CMF* epirubicin, docetaxel followed by CMF, *EC* epirubicin and cyclophosphamide, *FEC* 5-fluorouracil, epirubicin, and cyclophosphamide, *AC/EC-D* AC or EC followed by docetaxel, *EC-P* EC followed by paclitaxel, *FEC-P* FEC followed by paclitaxel, *FEC-D* FEC followed by docetaxel, *ED* epirubicin and docetaxel, *FEC-T* FEC followed by a taxane, *EC-T* EC followed by a taxane, *TAC* docetaxel, doxorubicin, and cyclophosphamide, *FEC-GEM* FEC followed by gemcitabine, *AC-P* AC followed by paclitaxel, *CAF* cyclophosphamide, doxorubicin, fluorouracil, *CAF-T* CAF followed by a taxane, *CEF* cyclophosphamide, epirubicin, fluorouracil, *CEF-T* CEF followed by a taxane, *GnRHa* gonadotropin-releasing hormone agonists, *CT* chemotherapy, *POF* premature ovarian failure, *DFS* disease-free survival, *OS* overall survival, *NR* not reported

largest studies (more than 200 patients included) showed a significant reduction of POF in patients given GnRHa. Specifically, the three largest trials [31–33] reported very similar results, with a significant 15% reduction of POF rates, thus reducing to less than 10% the incidence of chemotherapy-induced POF in patients treated with GnRHa concurrently with chemotherapy.

Pregnancy Rates Following GnRHa Use

To date, few studies have addressed the impact of GnRHa as a fertility-preservation strategy. The scarcity of information regarding posttreatment pregnancies might be explained by the small sample sizes and short follow-up. Only six studies have reported posttreatment pregnancy rates [23, 25, 26, 31–33], with only one of them having established this outcome as a preplanned secondary endpoint [32]. Four of these studies reported more pregnancies in the GnRHa group. However, only one of them yielded statistically significant results.

In the POEMS/SWOG S0230 study, which included 218 patients, the 5-year cumulative incidence of pregnancy was 23.1% in the GnRHa group vs. 12.2% in the chemotherapy-alone group (OR 2.34; 95% CI, 1.07–5.11; $p = 0.03$). Notably, patients who became pregnant were younger than those who did not (median age 32.9 years vs. 39.6 years, $p < 0.001$). Additionally, more patients in the GnRHa group than in the chemotherapy-alone group successfully delivered one or more babies (18 vs. 12, $p = 0.05$) [32].

Long-Term Breast Cancer Outcomes Following GnRHa Use

To date, three randomized controlled trials have reported disease-free survival (DFS) events in breast cancer patients treated with GnRHa along with chemotherapy for ovarian protection. In the POEMS/SWOG S0230 trial, the 5-year DFS was 88.1% in the GnRHa group vs. 78.6% in the chemotherapy-alone group (HR 0.55; 95% CI, 0.27–1.10; $p = 0.09$). Furthermore, 5-year overall survival (OS) was 91.7% in the GnRHa group vs. 83.1% in the chemotherapy-alone group (HR, 0.45; 95% CI, 0.19–1.04; $p = 0.06$) [32]. Similar 5-year outcomes were observed in the PROMISE study [31], and the most recently randomized trial reported by Zhang et al. [34].

Critical Analysis of Current Evidence

Up to now, eight meta-analyses have been conducted to summarize the results from the existing randomized controlled trials performed to assess the clinical efficacy of temporary ovarian suppression with GnRHa during chemotherapy for ovarian protection and fertility preservation exclusively in breast cancer patients [36–43] (Table 11.2). Findings were rather consistent showing that the

Table 11.2 Meta-analyses evaluating temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients

Authors	Number of included RCT	Number of patients	Main results
Yang et al. (2013)	5	528	POF RR 0.40, 95% CI 0.21–0.75 Pregnancy RR 0.96, 95% CI 0.20–4.56
Wang et al. (2013)	7	677	POF OR 2.83, 95% CI 1.52–5.25
Shen et al. (2015)	11	1062	POF 30% vs. 45%; OR 2.57, 95% CI 1.65–4.01, $p < 0.0001$ Pregnancies 26 (9%) vs. 16 (6%); OR 1.77, 95% CI 0.92–3.40, $p = 0.09$
Lambertini et al. (2015)	12	1231	POF 19% vs. 34%; OR 0.36, 95% CI 0.23–0.57, $p < 0.001$ Pregnancies 33 (9%) vs. 19 (6%); OR 1.83, 95% CI 1.02–3.28, $p = 0.041$ DFS HR 1.00, 95% CI 0.49–2.04, $p = 0.939$
Munhoz et al. (2016)	7	856	POF at 6 months: 26% vs. 43%; OR 2.41, 95% CI 1.40–4.15 POF at 12–24 months: 26% vs. 37%; OR 1.85, 95% CI 1.33–2.59 Pregnancy OR 1.85, 95% CI 1.02–3.36
Silva et al. (2016)	7	1002	POF 26% vs. 39%; OR 2.03, 95% CI 1.18–3.47
Bai et al. (2017)	15	1540	POF 23% vs. 43%; OR 1.36, 95% CI 1.19–1.56 Pregnancies 34 (7%) vs. 19 (4%); OR 1.90, 95% CI 1.06–3.41
Lambertini et al. (2018)	5	873	POF 14% vs. 31%; OR 0.38, 95% CI 0.26–0.57 Pregnancies 37 (10%) vs. 20 (6%); IRR 1.83, 95% CI 1.06–3.15

GnRHa gonadotropin-releasing hormone agonists, *RCT* randomized controlled trials, *POF* premature ovarian failure, *RR* relative risk, *OR* odds ratio, *CI* confidence interval, *DFS* disease-free survival

coadministration of GnRHa with chemotherapy significantly reduces the risk of chemotherapy-induced POF.

In the most recent and robust meta-analysis, Lambertini et al. analyzed individual patient-level data, including five randomized controlled trials and 873 patients. They found that 51 (14.1%) of 363 patients in the GnRHa group developed POF, as compared with 111 (30.9%) of 359 in the control group (OR 0.38; 95% CI, 0.26–0.57; $p < 0.001$). Notably, only treatment with GnRHa (OR 0.38; 95% CI, 0.26–0.57; $p < 0.001$) and younger age at diagnosis (OR 0.35; 95% CI, 0.24–0.52; $p < .001$) were significantly associated with a reduced risk of developing chemotherapy-induced POF [36]. Furthermore, 10.3% of patients had at least one posttreatment pregnancy in the GnRHa group and 5.5% in the control group (IRR, 1.83; 95% CI, 1.06–3.15; $p = 0.030$) [39].

On the other hand, GnRHa administration was associated with a significantly higher incidence of hot flashes and sweating, although the majority was of grade 1 or 2 in intensity [30–32]. This should be taken into account when considering the use of these agents.

While available data support considering the use of GnRHa to reduce the risk of POF, current evidence has some limitations that should be contemplated when counseling young women on their fertility preservation methods. This includes the different definitions of POF that were used in different trials and the short length of follow-up, which hinders the reliable determination of the long-term impact of GnRHa on preservation of ovarian function and fertility. Furthermore, previous studies have shown that women who receive chemotherapy are destined to develop early menopause [44]. Whether the concomitant administration of GnRHa could avoid this phenomenon still remains unknown. Of note, in all randomized trials evaluating the role of GnRHa, the primary endpoint was based on resuming menses (i.e., one or two consecutive menstrual cycle), but no follow-up was adopted to evaluate the durability of menstruation afterwards. Finally, none of the randomized trials reported the impact of GnRHa on ovarian reserve and anti-Müllerian hormone (AMH) levels. Such data, if available, would help strengthen the role of GnRHa as a reliable method to preserve ovarian function and fertility.

International Guidelines and Recommendations

Several international guidelines have addressed the use of GnRHa as a strategy to preserve fertility in young breast cancer patients receiving chemotherapy (Table 11.3). According to the ESO-ESMO 3rd International Consensus Guidelines

Table 11.3 Current clinical guidelines and main recommendations

International guidelines	Recommendation
ESO-ESMO (BCY3) Paluch-Shimon et al. (2017)	The use of GnRHa concomitant with adjuvant chemotherapy should be discussed on a case by case basis to preserve ovarian function and possibly fertility
AIOM Lambertini et al. (2017)	Temporary ovarian suppression with GnRHa during chemotherapy should be recommended to all premenopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation
ASCO guidelines Oktay et al. (2018)	There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. GnRHa may be offered to young women with breast cancer in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible

GnRHa gonadotropin-releasing hormone agonists

for Breast Cancer in Young Women (BCY3) published in 2017, GnRHa, when used concomitantly with adjuvant chemotherapy, appear to preserve ovarian function, reducing the risk of early menopause and increasing the chances for future fertility, and should be discussed as an option with all patients interested in fertility preservation who are candidates for chemotherapy, irrespective of tumor subtype [15].

A second European organization, the Italian Association of Medical Oncology (AIOM), reached a similar conclusion after analyzing the current evidence. The AIOM stated that temporary ovarian suppression with GnRHa during chemotherapy should be recommended to all premenopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation, as this strategy reduced the risk of developing POF by approximately 50% and the possible harms of such treatment are known and clinically small in relation to the expected benefit [45].

On the other hand, the American Society of Clinical Oncology (ASCO) guidelines were rather more conservative indicating that when proven fertility preservation methods are not feasible, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency but should not be used in place of proven fertility preservation methods [16].

Physicians' Knowledge and Current Use

To date, limited information is available on physicians' attitudes and knowledge towards fertility counseling of young breast cancer patients. A large survey including around 250 breast cancer specialists mostly from Europe showed that the risk of treatment-induced POF and infertility is often discussed prior to starting therapy [46]. The same observation was reported by another survey performed in Latin America, in which nearly 80% of physicians reported taking into account patients' interests in fertility preservation for treatment planning [47].

In two European surveys, at least 80% of physicians confirmed that ovarian suppression with GnRHa during chemotherapy is the most suggested strategy for fertility preservation [46, 48]. This was not the case in a survey performed in Mexico, in which only 41% of physicians considered GnRHa application during chemotherapy as a safe procedure [47]. This highlights the discrepancy in appreciating the role of GnRHa as a reliable means to preserve fertility in different parts of the world. As for patients' preference of fertility preservation strategies, results of the pilot phase of the Italian PREgnancy and FERtility (PREFER) study reported that, among 92 interviewed patients diagnosed at 40 years, 86 (93.5%) took active steps towards the offered strategies for ovarian function and/or fertility preservation by accepting the use of temporary ovarian suppression with GnRHa during chemotherapy (75 women, 81.5%), both temporary ovarian suppression with GnRHa and cryopreservation strategies (10, 10.9%), or cryopreservation strategies alone (1, 1.1%) [49].

Challenges in the Use of GnRH in Routine Practice

Despite the evidence stating that GnRHa administered concomitantly with chemotherapy is a viable option for fertility preservation in breast cancer patients, several barriers limit its use.

Studies have demonstrated that oncologists at times do not provide patients with the information they need before administering fertility-compromising therapies [50, 51]. Possible explanations for physicians' inconsistent disclosure of infertility risks include the high proportion of advanced breast cancer cases in young women, the concern of delaying cancer treatment if fertility preservation is pursued, the lack of knowledge on the effects of systemic therapy on fertility, and the concern about the effect of pregnancy on breast cancer prognosis [17]. Another study has shown that the main factors preventing access to fertility preservation procedures were patient-related factors (including age, social status, education, relationship status, prior children, and cancer prognosis), lack of collaboration with a specialized fertility center, resistance of the medical team to potentially delay chemotherapy, poor knowledge about these techniques, and resistance of the medical team to allow pregnancy after breast cancer or to use controlled ovarian stimulation [46].

Furthermore, as the cost of administering GnRHa for 6 months during chemotherapy is approximately 1000 US dollars, this represents a significant out-of-pocket expense for patients, as fertility preservation procedures are very often not covered by healthcare insurance [17]. In a survey answered by members of the Oncofertility Consortium Global Partners Network, the most commonly identified barriers for fertility preservation were lack of insurance coverage and significant financial burden for patients (both 62%) [52]. As a consequence, in countries where fertility preservation depends on the individual capacity to afford its coverage, the access to these procedures will likely remain low [17].

Currently, the Italian Ministry of Health and the Australian Pharmaceutical Benefits Scheme have endorsed the coverage of the 6-month treatment with GnRHa during chemotherapy to preserve ovarian function and fertility [45, 49]. Furthermore, we believe that the implementation of support programs dedicated to young breast cancer patients can help address important quality of life issues, such as future pregnancies desire, and promote fertility preservation strategies among patients and providers [53–55].

Conclusion

Concomitant administration of GnRHa with chemotherapy reduced POF and could potentially increase the chance of future pregnancies. We believe that current data supports the use of GnRHa as a possible option for fertility preservation, especially when standard strategies are not readily available. However, while reported pregnancy rates in patients treated with GnRHa concomitantly with chemotherapy appear higher, absolute numbers remain low and more studies are needed to strengthen this observation.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013.. http://globocan.iarc.fr/
2. Collins LC, Marotti JD, Gelber S, Cole K, Ruddy K, Kereakoglow S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. Breast Cancer Res Treat. 2012;131(3):1061–6.
3. Partridge AH, Hughes ME, Ottesen RA, Wong YN, Edge SB, Theriault RL, et al. The effect of age on delay in diagnosis and stage of breast cancer. Oncologist. 2012;17(6):775–82.
4. Poggio F, Levaggi A, Lambertini M. Chemotherapy-induced premature ovarian failure and its prevention in premenopausal breast cancer patients. Expert Rev Quality Life Cancer Care. 2016;1(1):5e7.
5. ESHRE Guideline Group on POI, Webber L, Davies M, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926–37.
6. Sawe BE. Countries with the oldest average mother's age at first birth. 15 Aug. 2016. www.worldatlas.com/articles/countries-with-the-highest-mother-s-mean-age-at-first-birth.html.
7. Mathews TJ, Hamilton BE. Mean age of mothers is on the rise: United States, 2000–2014. NCHS Data Brief. 2016;232:1e8.. http://www.ncbi.nlm.nih.gov/pubmed/26828319.
8. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol. 2004;22(20):4174–83.
9. Villarreal-Garza C, Aguila C, Magallanes-Hoyos MC, et al. Breast cancer in young women in Latin America: an unmet, growing burden. Oncologist. 2013;18(12):1298–306.
10. Villarreal-Garza C, Platas A, Bargalló-Rocha JE, et al. Cáncer de mama en mujeres jóvenes: Experiencia en el Instituto Nacional de Cancerología. Rev Mex Mastol. 2015;5(1):12–7.
11. Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol. 2014;32(11):1151e6.
12. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118:17 10–7.
13. Villarreal-Garza C, Martinez-Cannon BA, Platas A, et al. Fertility concerns among breast cancer patients in Mexico. Breast. 2017;33:71–5.
14. Litton JK. Breast cancer and fertility. Curr Treat Options Oncol. 2012;13:137–45.
15. Paluch-Shimon S, Pagani O, Partridge AH, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast. 2017;35:203–17.
16. 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.
17. Lambertini M, Goldrat O, Barragan-Carrillo R, et al. Viable options for fertility preservation in breast cancer patients: a focus in Latin America. Rev Invest Clin. 2017;69:103–13.
18. Lambertini M, Goldrat O, Clatot F, et al. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Curr Opin Oncol. 2017;29:243–52.
19. Gründker C, Emons G. Role of gonadotropin-releasing hormone (GnRH) in ovarian cancer. Reprod Biol Endocrinol. 2003;1:65.
20. Chapman RM, Sutcliffe SB. Protection of ovarian function by oral contraceptives in women receiving chemotherapy for Hodgkin's disease. Blood. 1981;58:849–51.
21. Li M, Huang H, Liang Y, Tan J, Lin D. Effect of Zoladex administered before chemotherapy on menstruation of patients with breast cancer. Chin J Clin Oncol. 2008;35:905–7.
22. Sverrisdottir A, Nystedt M, Johansson H, Fornander T. Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. Breast Cancer Res Treat. 2009;117:561–7.
23. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011;29:2334–41.

24. Sun J, Ren Y, Li W. Effect of Zoladex administered before chemotherapy on menstruation of patients with breast cancer. China Disabil Med. 2011;19:15–6.. n.d
25. Munster PN, Moore AP, Ismail-Khan R, Cox CE, Lacevic M, Gross-King M, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. J Clin Oncol. 2012;30:533–8.
26. Elgindy EA, El-Haieg DO, Khorshid OM, Ismail EI, Abdelgawad M, Sallam HN, et al. Gonadatrophin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial. Obstet Gynecol. 2013;121:78–86.
27. Jiang FY, Zhang QQ, Zeng J. Protective effect of GnRHa on chemotherapy Induced ovarian damage in breast cancer patients. Shandong Med J. 2013;53(8):16–8.
28. Karimi-Zarchi M, Forat-Yazdi M, Vafaeenasab MR, Nakhaie-Moghadam M, Miratashi-Yazdi A, Teimoori S, et al. Evaluation of the effect of GnRH agonist on menstrual reverse in breast cancer cases treated with cyclophosphamide. Eur J Gynaecol Oncol. 2014;35:59–61.
29. Song G, Gao H, Yuan Z. Effect of leuprolide acetate on ovarian function after cyclophosphamide-doxorubicin-based chemotherapy in premenopausal patients with breast cancer: results from a phase II randomized trial. Med Oncol. 2013;30:667.
30. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. JAMA. 2011;306:269–76.
31. Lambertini M, Boni L, Michelotti A, Gamucci T, Scotto T, Gori S, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. JAMA. 2015;314:2632–40.
32. Moore HCF, Unger JM, Phillips K-A, Boyle F, Hitre E, Porter D, et al. Final analysis of the prevention of early menopause study (POEMS)/SWOG intergroup S0230. JNCI J Natl Cancer Inst. 2019;111(2):djy185.
33. Leonard RCF, Adamson DJA, Bertelli G, Mansi J, Yellowlees A, Dunlop J, et al. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. Ann Oncol. 2017;28:1811–6.
34. Zhang Y, Ji Y, Li J, Lei L, Wu S, Zuo W, et al. Sequential versus simultaneous use of chemotherapy and gonadotropin-releasing hormone agonist (GnRHa) among estrogen receptor (ER)-positive premenopausal breast cancer patients: effects on ovarian function, disease-free survival, and overall survival. Breast Cancer Res Treat. 2018;168:679–86.
35. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. Fertil Steril. 2009;91:694–7.
36. Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim HA, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015;26:2408–19.
37. Bai F, Lu Y, Wu K, Chen Q, Ding L, Ge M, et al. Protecting effects of gonadotropin releasing hormone agonist on chemotherapy-induced ovarian damage in premenopausal breast cancer patients: a systematic review and meta-analysis. Breast Care. 2017;12:48–52.
38. Munhoz RR, Pereira AAL, Sasse AD, Hoff PM, Traina TA, Hudis CA, et al. Gonadotropin-releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early-stage breast cancer: a systematic review and metaanalysis. JAMA Oncol. 2016;2:65–73.
39. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol. 2018;36:1981–90.
40. Shen Y-W, Zhang X-M, Lv M, Chen L, Qin T-J, Wang F, et al. Utility of gonadotropinreleasing hormone agonists for prevention of chemotherapy-induced ovarian damage in premeno-

pausal women with breast cancer: a systematic review and meta-analysis. OncoTargets Ther. 2015;8:3349–59.
41. Yang B, Shi W, Yang J, Liu H, Zhao H, Li X, et al. Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials. Breast. 2013;22:150–7.
42. Wang C, Chen M, Fu F, Huang M. Gonadotropin-releasing hormone analog cotreatment for the preservation of ovarian function during gonadotoxic chemotherapy for breast cancer: a meta-analysis. PLoS One. 2013;8:e66360.
43. Silva C, Caramelo O, Almeida-Santos T, Ribeiro Rama AC. Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review and meta-analysis. Hum Reprod. 2016;31:2737–49.
44. Azim HA Jr, Davidson NE, Ruddy KJ. Challenges in treating premenopausal women with endocrine-sensitive breast cancer. Am Soc Clin Oncol Educ Book. 2016;35:23–32.
45. Lambertini M, Cinquini M, Moschetti I, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. Eur J Cancer. 2017;71:25e33.
46. Lambertini M, Di Maio M, Pagani O, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. The Breast. 2018;42:41–9.
47. Villarreal-Garza CM, Barragan-Carillo R, Bargallo-Rocha JE, et al. Physicians' knowledge and attitudes towards fertility preservation in Mexican young breast cancer patients. Cancer Res. 2018;78(4 Suppl). P6-11-09.
48. Biglia N, Torrisi R, D'Alonzo M, Codacci Pisanelli G, Rota S, Peccatori FA. Attitudes on fertility issues in breast cancer patients: an Italian survey. Gynecol Endocrinol. 2015;31(6):458e64.
49. Lambertini M, Fontana V, Massarotti C, et al. Prospective study to optimize care and improve knowledge on ovarian function and/or fertility preservation in young breast cancer patients: Results of the pilot phase of the PREgnancy and FERtility (PREFER) study. The Breast. 2018;41:51–6.
50. Snyder KA, Pearse W. Discussing fertility preservation options with patients with cancer. JAMA. 2011;306:202–3.
51. Duffy CM, Allen SM, Clark MA. Discussions regarding reproductive health for young women with breast cancer undergoing chemotherapy. J Clin Oncol. 2005;23:766–73.
52. Rashedi AS, De Roo SF, Ataman LM, et al. Survey of fertility preservation options available to patients with cancer around the globe. J Glob Oncol. 2018;4:1–16.
53. Cohen L, Hamer J, Helwig C, et al. Formal evaluation of PYNK: breast cancer program for young women-the patient perspective. Curr Oncol Tor Ont. 2016;23:e102–8.
54. Villarreal-Garza C, Castro-Sanchez A, Platas A, et al. "Joven & Fuerte": program for young women with breast cancer in Mexico—initial results. Rev Invest Clin. 2017;69:223–8.
55. Villarreal-Garza C, Platas A, Bargallo-Rocha JE, et al. Characterization of young Mexican patients with breast cancer who underwent oocyte/embryo preservation. The Breast. 2018;41:S9.

Fertility and Pregnancy Counseling of Breast Cancer Patients with Germline *BRCA* Mutations

12

Margherita Condorelli and Matteo Lambertini

Introduction

Irrespective of their family history, approximately 12% of breast cancer cases diagnosed in women under the age of 40 are hereditary tumors secondary to the presence of germline deleterious mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2* [1, 2]. Due to the significant cumulative lifetime risk of developing not only breast tumors but also ovarian cancer and other malignancies [3], carrying a germline deleterious *BRCA* mutation has a major impact on patients' management in terms of prevention, diagnosis, and treatment. Notably, among these clinical implications, the indication to undergo risk-reducing salpingo-oophorectomy at a young age (before the age of 40–45 years) has a direct negative impact on patients' fertility and family planning [4].

According to current guidelines, all young women diagnosed with breast cancer under the age of 40 should be offered genetic counseling before starting treatment and tested at least for the *BRCA1* and *BRCA2* genes [5]. In addition, based on the recent widespread use of rapid multigene panel sequencing technologies in germline risk assessment [6], it is expected that a growing number of breast cancer patients will be aware of their *BRCA* status or the potential presence of germline deleterious mutations in other susceptibility cancer genes at the time of oncofertility

M. Condorelli
Fertility Clinic, CUB-Hôpital Erasme and Research Laboratory on Human Reproduction, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

M. Lambertini (✉)
Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy
e-mail: matteo.lambertini@unige.it

H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_12

counseling. Therefore, an increased awareness and attention should be paid to fertility and pregnancy-related issues in young women with *BRCA*-mutated breast cancer as well as in patients with other hereditary cancer syndromes.

Based on both the unique features and needs of these patients, as well as the limited evidence on the performance of fertility preservation strategies and on the safety of having a pregnancy following the end of anticancer treatments, oncofertility counseling is particularly complex in young women with newly diagnosed *BRCA*-mutated breast cancer [7]. This chapter aims to review the available evidence on the impact of carrying a germline deleterious *BRCA* mutation on the reproductive potential of these women as well as to discuss how to optimally manage the oncofertility counseling of young *BRCA*-mutated breast cancer patients facing fertility and pregnancy-related issues.

Impact of Carrying a *BRCA* Mutation on Ovarian Reserve and Fertility

In the last decade, there has been a growing concern about the potential negative consequences of carrying a *BRCA* mutation on female ovarian reserve and fertility [8].

Experimental studies have shown that the *BRCA*1 gene is expressed in human germ cells and blastocysts with a possible involvement in gametogenesis and embryogenesis [9, 10]. A lower ovarian reserve was observed in mice harboring a *BRCA*1 mutation [11]. Similarly, *BRCA*2-mutated mice were characterized by fewer oocytes that could complete meiosis and by a high frequency of nuclear abnormalities [12, 13].

In addition, DNA double-strand breaks (DSBs) repair pathway appears to have also a crucial role in ovarian aging by defending the ovaries from genotoxic stress [11, 14–16]. When the DSBs repair pathway is impaired, for example, as a consequence of mutations in the *BRCA* genes, an accelerated loss of ovarian reserve can occur due to the accumulation of DSBs in the oocytes [11].

However, despite the strong biological rationale supported by experimental data, translating this evidence into patients' counseling remains difficult considering the conflicting clinical findings available on this regard. Several studies have investigated fertility clinical outcomes (parity, age at menopause, infertility) and biological parameters (anti-Mullerian hormone [AMH] levels, follicular density, and DNA damage) in healthy women carrying germline deleterious *BRCA* mutations [7, 17–20]. The majority of these studies did not show a significant difference between *BRCA* carriers and non-carriers on reproductive outcomes. However, some studies showed that menopause appeared to occur at an earlier age for women carrying a *BRCA* mutation; in addition, a tendency for presenting lower AMH, reduced follicular density, and increased DSBs was also observed in these women, mainly in those carrying a *BRCA1* mutation. These

clinical findings are in line with preclinical evidence supporting the crucial role of DNA DSB in follicular depletion and ovarian aging as well as comprehensive genetic analyses showing the association between several genes involved in DNA repair (including *BRCA*) and age at natural menopause [21, 22]. However, these data derive from studies conducted in healthy women carrying germline deleterious *BRCA* mutations and cannot be directly applied to the breast cancer setting.

Ovarian Reserve, Treatment-Induced Gonadotoxicity, and Fertility in *BRCA*-Mutated Breast Cancer Patients

To date, limited clinical data exist on the impact of carrying germline deleterious *BRCA* mutations on ovarian function and fertility in the breast cancer setting. Specifically, few studies investigated the potential impact of these mutations on baseline reproductive potential, treatment-induced gonadotoxicity, and performance of fertility preservation strategies.

Ovarian Reserve in *BRCA*-Mutated Breast Cancer Patients

Limited data exist on the ovarian reserve of newly diagnosed *BRCA*-mutated breast cancer patients (Table 12.1) [11, 20, 23–25].

A case-control study investigated the age at menopause in treated breast cancer patients [23]. Mean age at menopause was 45.3 years for *BRCA*-mutated patients and 48.2 years for non-mutated patients ($p = 0.0277$) [23]. Four studies evaluated AMH levels in *BRCA*-mutated breast cancer patients before starting anticancer treatments [11, 20, 24, 25]. In the study by Titus et al. including 84 breast cancer patients, significantly lower mean AMH levels in those with a *BRCA* mutation were observed as compared to non-carriers ($p < 0.001$) [11]. At the subgroup analysis, this was mainly observed for *BRCA1*-mutated patients and not for those with a *BRCA2* mutation [11]. In a retrospective analysis conducted within two prospective studies, AMH was measured before starting anticancer treatments in 85 breast cancer patients who had access to fertility preservation procedures [24]. A nonsignificant trend for reduced AMH levels was observed in *BRCA*-mutated breast cancer patients ($p = 0.109$) with no distinction between those carrying a *BRCA1* or *BRCA2* mutation [24]. However, in two more recent and larger retrospective biomarker studies, AMH levels at diagnosis were comparable between *BRCA*-mutated and non-mutated breast cancer patients [20, 25].

Taken together, although results are conflicting, a potential negative impact of carrying a *BRCA* mutation on the ovarian reserve of newly diagnosed breast cancer patients even before starting anticancer treatments cannot be excluded. However, numbers remain too small to be conclusive.

Table 12.1 Ovarian reserve and age at menopause in *BRCA*-mutated breast cancer patients

Author	Type of study	*BRCA*+/ *BRCA*−	Ovarian reserve/age at menopause	Results (carriers vs. non-carriers)	Overall result
Rzepka-Górska et al. 2006 [23]	Case-control study	39/80	Age at menopause (mean) years	45.3 vs. 48.2; $p = 0.0277$	Difference favoring non-carriers over *BRCA1* carriers (no *BRCA2* included)
Titus et al. 2013 [11]	Cross-sectional study	24/60	AMH level (mean) ng/mL *BRCA1* vs. controls *BRCA2* vs. controls	1.22 vs. 2.23; $p < 0.001$ 1.12 vs. 2.23; $p < 0.001$ 1.39 vs. 2.23; $p < 0.127$	AMH levels favoring non-carriers over *BRCA1* carriers (no difference in *BRCA2*)
Lambertini et al. 2018 [24]	Retrospective analysis of two prospective studies	25/60	AMH levels (median) μg/L	1.8 vs. 2.6; $p = 0.109$	Nonsignificant trend in AMH levels favoring non-carriers over *BRCA* carriers
Gunnala et al. 2019 [20]	Retrospective cohort study	38/53	AMH level (mean) ng/ml AFC (mean)	2.6 vs. 2.4 adjusted $p = 1.0$ 15.2 vs. 13.9 adjusted $p = 1.0$	No difference
Lambertini et al. 2019 [25]	Retrospective biomarker analysis	35/113	AMH level (median), μg/L	1.94 vs. 1.66; $p = 0.53$	No difference

AMH anti-Mullerian hormone, *AFC* antral follicle count

Treatment-Induced Gonadotoxicity in *BRCA*-Mutated Breast Cancer Patients

DNA damage-induced follicle death is one of the main mechanisms of anticancer treatment-induced premature ovarian insufficiency (POI). Therefore, *BRCA*-mutated breast cancer patients may be particularly sensitive to the gonadotoxicity of anticancer therapies. However, counseling patients in this specific setting is particularly challenging due to the limited data available (Table 12.2) [26].

A large retrospective study investigated this issue by surveying 1954 young premenopausal *BRCA*-mutated breast cancer patients of whom 1426 received chemotherapy [27]. Treatment-induced POI was defined as ≥2 years of amenorrhea following chemotherapy without subsequent resumption of menstrual function. Main risk factors for the development of treatment-induced POI were increased age at diagnosis (7.2% in women ≤30 years, 33% in those between 31 and 44 years and 79% for patients ≥45 years; $p < 0.001$) and tamoxifen use (52% vs. 19%; $p < 0.001$).

Table 12.2 Gonadotoxicity of chemotherapy in *BRCA*-mutated breast cancer patients

Author	Type of study	*BRCA*+/*BRCA*−	Chemotherapy-induced gonadotoxicity	Results (carriers vs. non-carriers)	Overall result
Valentini et al. 2013 [27]	Observational study (survey)	1426/100	Chemotherapy-induced amenorrhea, %	25.6 vs. 49; $p = 0.18$	No difference
Lambertini et al. (2019) [25]	Retrospective biomarker analysis	35/113	Posttreatment AMH – 1 year after treatment, μg/L – 3 years after treatment, μg/L	0.09 vs. 0.06; $p = 0.39$ 0.25 vs. 0.16 $p = 0.43$	No difference

AMH anti-Mullerian hormone

Of note, *BRCA*2-mutated breast cancer patients had a higher risk of POI than those carrying a *BRCA*1 mutation (46.8% vs. 32.7%; $p < 0.001$); this finding was confirmed also when the analysis was restricted to the patients who did not undergo tamoxifen (36.6% vs. 27.8%; $p = 0.04$). By comparing the 1426 *BRCA*-mutated breast cancer patients exposed to chemotherapy to 100 treated non-carriers, no significant difference in treatment-induced POI rates was observed between the two groups (35.6% and 49%, respectively; $p = 0.18$). Similarly, no difference was described in the *BRCA1* and *BRCA2* subgroups (respectively $p = 0.10$ and $p = 0.50$) [27]. Among study limitations, it should be considered that POI was assessed retrospectively with a questionnaire based on menstrual function; in addition, type and dose of chemotherapy administered in the different groups of patients was not reported, number of controls was limited, and their baseline characteristics were not detailed.

Considering that amenorrhea is not the best indicator to define the gonadotoxicity of anticancer therapies [28], AMH has been proposed as better marker of treatment-induced gonadal damage [29]. A monocentric retrospective biomarker study investigated treatment-induced gonadal damage in this setting by assessing AMH in 148 early breast cancer patients diagnosed at ≤40 years of whom 35 had a deleterious germline *BRCA* mutation. All patients received anthracycline- and cyclophosphamide-based (neo)adjuvant chemotherapy followed by a taxane in the majority of the cases. When comparing between patients with or without *BRCA* mutations, AMH values after one year dropped significantly in all women without difference between the two groups (0.09 and 0.06 μg/L, respectively; $p = 0.39$). Recovery at 3 years was also similar between the *BRCA*-mutated and negative cohorts (0.25 and 0.16 μg/L; $p = 0.43$) [25].

Taken together, both studies that investigated treatment-induced POI in *BRCA*-mutated breast cancer patients showed similar conclusions: the presence of a deleterious germline *BRCA* mutation did not appear to worsen the gonadotoxicity of chemotherapy. Nevertheless, it should be highlighted that new treatment strategies including platinum agents [5, 30] and PARP-inhibitors [31] are being implemented in the management of *BRCA*-mutated breast cancer patients. Considering

that these agents act mainly by damaging the DNA, they may be particularly gonadotoxic in *BRCA*-mutated breast cancer patients considering their deficient DNA repair system. Therefore, the gonadotoxicity of these treatments needs to be urgently investigated in order to improve the oncofertility counseling of these patients.

Performance of Fertility Preservation Strategies in *BRCA*-Mutated Breast Cancer Patients

Carrying a germline deleterious *BRCA* mutation represents one of the important parameters (together with age of the patients, availability of a partner, and time available before starting chemotherapy) to be considered in counseling breast cancer patients on the three available fertility preservation strategies (Table 12.3).

Table 12.3 Available strategies for fertility preservation in young women with breast cancer and recommendations in *BRCA*-mutated patients (modified from Lambertini et al. [7])

Strategy	Indication in breast cancer patients	Specificities to be considered in *BRCA*-mutated breast cancer patients	Indication in *BRCA*-mutated breast cancer patients
Oocyte/embryo cryopreservation after COS	Yes (standard strategy if enough time available)	Potential access to preimplantation genetic diagnosis Possible poorer response to COS – No data on post-treatment pregnancies	Yes (standard strategy if enough time available)
Ovarian tissue cryopreservation	Yes (experimental, but to be used if – Prepubertal – Already treated with chemotherapy – Not enough time for COS)	High risk of ovarian cancer → risk-reducing salpingo-oophorectomy before the age of 40–45 years Limited data on the efficacy/safety of the procedure (only two pregnancies reported in *BRCA2*-mutated breast cancer patients after transplantation) Exclusively transplantation in the ovaries	Only in very young patients who cannot perform oocyte/embryo cryopreservation
Ovarian suppression with GnRHa during chemotherapy	Yes (standard and complementary to cryopreservation strategies for fertility preservation)	High risk of ovarian cancer → risk-reducing salpingo-oophorectomy before the age of 40-45 years Lack of data from randomized trials on the efficacy and safety of the procedure	Only in very young patients

GnRHa gonadotropin-releasing hormone agonists, *COS* controlled ovarian stimulation

Oocyte/Embryo Cryopreservation

Oocyte/embryo cryopreservation is the standard fertility preservation method in postpubertal patients including young women with breast cancer, provided that there is sufficient time for controlled ovarian stimulation (COS) [5, 32–34]. Although the available evidence in this setting is still limited, this procedure is considered effective and safe, including among patients with hormone receptor-positive breast cancer (for whom the addition of tamoxifen or letrozole as part of COS protocol can be considered) [33, 34].

Few data are available on the efficacy and safety of this technique for counseling *BRCA*-mutated breast cancer patients (Table 12.4) [7]. In these patients, four studies investigated the response to COS, with two of them showing reduced performance in women carrying a *BRCA* mutation [20, 24, 35, 36]. In 2015, Shapira et al. evaluated the performance of COS (with a protocol that included tamoxifen in 19% of the cases) in 20 *BRCA*-mutated and 36 *BRCA*-negative breast cancer patients [35]. The number of collected oocytes (11.50 vs. 11.69; $p = 0.92$) and of zygotes (8.4 vs. 7.19; $p = 0.57$) was similar between the two groups; similarly, no difference in

Table 12.4 Oocyte/embryo cryopreservation in *BRCA*-mutated breast cancer patients

Author	Type of study	*BRCA*+/*BRCA*−	ART performance	Results (carriers vs. non-carriers)	Overall result
Shapira et al. 2015 [35]	Retrospective cohort study	62[a]/62[a]	Oocytes yield (mean) No. Poor response rate[b], %	13.75 vs. 14.75; $p = 0.49$ 8.06 vs. 6.45; $p = 1.00$	No difference
Turan et al. 2018 [36]	Secondary analysis of a prospective database	21/97[c]	Oocytes yield (mean) Embryos obtained (mean)	16.4 vs. 11.0; $p = 0.015$ 8.2 vs. 5.1; $p = 0.013$	Difference favoring non-carriers/ unknown status over *BRCA* carriers
Lambertini et al. 2018 [24]	Retrospective analysis of two prospective studies	10/19	Oocytes yield (median) Cryopreserved oocytes (median) Poor response rate, %[b]	6.5 vs. 9; $p = 0.145$ 3.5 vs. 6; $p = 0.121$ 40.0 vs. 11.1; $p = 0.147$	Non-significant difference favoring non-carriers over *BRCA* carriers
Gunnala et al. 2019 [20]	Retrospective cohort study	38/53	Oocytes yield (mean) Mature/ cryopreserved oocytes (mean)	17.0 vs. 16.3 adjusted $p = 1$ 14.4 vs. 13.1 adjusted $p = 1$	No difference

[a]Included also women without prior history of breast cancer
[b]Defined as retrieval of ≤ 4 oocytes in women younger than 38 years
[c]12 unknown status and 85 negative patients
COS controlled ovarian stimulation, *ART* assisted reproductive technology

fertilization rates was observed (70.6% vs. 59.66%; $p = 0.11$) [35, 37]. In line with biological and preclinical evidence, other two studies conducted in 2018 in which all women received COS that included letrozole as part of the protocol showed lower performance in *BRCA*-mutated breast cancer patients [24, 36]. The first study compared the outcomes between 10 *BRCA*-mutated and 19 non-mutated breast cancer patients. *BRCA*-mutated patients tended to retrieve less oocytes (6.5 vs. 9; $p = 0.145$) and to have a higher poor response rate (40.0% vs. 11.1%; $p = 0.147$) [24]. In the second study, the 21 *BRCA*-mutated breast cancer patients produced fewer oocytes (16.4 vs. 11.0, $p = 0.015$) and embryos (8.2 vs. 5.1, $p = 0.013$) as compared to the other 97 who were *BRCA* negative or untested [36]. Nevertheless, a more recent retrospective study included 91 breast cancer patients (of whom 38 carried a *BRCA* mutation) undergoing oocyte cryopreservation for fertility preservation with an antagonist plus letrozole COS protocol. The mean number of oocytes yield (17.0 and 16.3, for *BRCA*-mutated and non-mutated patients, respectively) and the mean number of mature/cryopreserved oocytes (14.4 and 13.1, respectively) were comparable (adjusted $p = 1.0$) [20].

There are a few important differences among these four studies that should be considered to interpret their results: (1) patient population (American and European women in three studies [20, 24, 36], and Israeli patients in the other [35]); (2) use of different protocols for COS (homogenous antagonist protocol including letrozole in three studies [20, 24, 36], and different protocols [long agonist protocol in 53% and antagonist protocol in 47% of the cases] with the use of tamoxifen in 19% of patients in the other study [35]). Notably, data remain limited with only 91 *BRCA*-mutated breast cancer patients included in all studies combined.

In terms of safety, only one prospective study conducted in a single center has provided evidence so far on the feasibility of using COS in breast cancer patients before starting chemotherapy [38]. In this study, the outcomes of 120 breast cancer patients who received COS (with a protocol that included letrozole) were compared with those of 217 that did not receive any fertility preservation strategies and served as controls. COS patients tended to have smaller tumor as compared to those in the control group ($p = 0.02$). After approximately 5 years of mean follow-up, no difference in relapse-free survival between the two groups was found (hazard ratio [HR], 0.77; 95% confidence intervals [CI], 0.28–2.13; $p = 0.61$). Among patients who underwent a genetic test, 47 were mutated in the *BRCA1* and/or *BRCA2* genes of whom 26 underwent COS while 21 did not. Also among *BRCA*-mutated patients, no significant difference in relapse-free survival was observed ($p = 0.57$) [38].

Considering the limited and conflicting available data, larger multicenter research efforts are needed to better assess the efficacy and safety of performing COS for oocyte/embryo cryopreservation before starting chemotherapy in *BRCA*-mutated breast cancer patients. Importantly, in these women, oocyte/embryo cryopreservation allows the access to pre-implantation genetic diagnosis.

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is still considered an experimental technique; however, it may be proposed to selected patients including prepubertal girls, adult

women who are scheduled for urgent gonadotoxic treatments, patients who were previously exposed to chemotherapy or when COS is contraindicated [39].

In *BRCA*-mutated breast cancer patients, limited data are available on the efficacy and safety of ovarian tissue cryopreservation. Two live births have been reported so far in *BRCA2*-mutated breast cancer patients who underwent ovarian tissue transplantation after treatment [24, 40]. The first patient was diagnosed at the age of 36 years; prior to chemotherapy, one ovary was cryopreserved and fragments transplanted to the contralateral one after the end of treatment. She had a spontaneous pregnancy and, after delivery, the remaining ovary was removed [40]. The second patient was diagnosed at the age of 33 years; she cryopreserved fragments from both ovaries before treatment initiation. Fifty-five months following chemotherapy completion, these fragments were grafted to the remaining ovaries and 8 months later she had a spontaneous pregnancy and delivered a healthy baby [24].

In terms of safety, it should be highlighted that ovarian tissue cryopreservation is not an optimal strategy in *BRCA*-mutated breast cancer patients considering their significant cumulative lifetime risk of developing ovarian cancer and the subsequent indication to undergo risk-reducing salpingo-oophorectomy before the age of 40–45 years. Therefore, in this setting, ovarian tissue cryopreservation should be considered only in patients who cannot perform oocyte/embryo cryopreservation and are younger than 35 years at the time of diagnosis. However, in most of the cases, no information is available on *BRCA* status at the time of oncofertility counseling at breast cancer diagnosis. However, considering the important clinical implications, *BRCA* mutational status should be investigated before performing any transplantation procedure. In *BRCA*-mutated patients, the tissue should be transplanted exclusively to the remaining ovaries so that it can be safely removed at the time of risk-reducing salpingo-oophorectomy. However, it should be highlighted that it is an ethical question whether to transplant frozen ovarian tissue in *BRCA* carriers. In the Norwegian experience, a breast cancer patient that was subsequently diagnosed with *BRCA1* and *BRCA2* mutations was advised against ovarian tissue transplantation despite her pregnancy wish [41]. A promising approach to avoid transplantation is in vitro maturation of ovarian follicles [42]. Nevertheless, while research in animal models is improving, results in human setting are still disappointing [43].

Ovarian Suppression with Gonadotropin-Releasing Hormone Agonists (GnRHa)

The use of ovarian suppression with GnRHa during chemotherapy has recently become an available option for ovarian function preservation in breast cancer patients [5, 34, 44]. The most recent findings coming from the largest randomized trials (i.e., the PROMISE-GIM6, POEMS-SWOG S0230, and OPTION trials) [45–47] and meta-analyses [48–50] have supported the efficacy and safety of this strategy in reducing the risk of treatment-induced POI. Despite significantly more posttreatment pregnancies were observed in patients treated with GnRHa during chemotherapy [48–50], numbers remain overall small. Therefore, ovarian suppression with GnRHa during chemotherapy should not be considered an alternative to

cryopreservation strategies for fertility preservation [5, 34, 44]. Nevertheless, differently from prior strategies, ovarian suppression with GnRHa during chemotherapy is a widely accessible option at a relatively low cost. Therefore, it can be considered also when cryopreservation techniques are not available for logistic or cost-related reasons.

So far, none of the available randomized trials has reported efficacy or safety data with the use of this strategy in *BRCA*-mutated breast cancer patients. There is only a case series by Wong and colleagues in which 3 out of 4 *BRCA*-mutated breast cancer patients receiving GnRHa during chemotherapy resumed menstrual function following chemotherapy, before receiving risk-reducing salpingo-oophorectomy [51].

Despite the limited data in this patient population, it is reasonable to propose this strategy in *BRCA*-mutated breast cancer patients diagnosed before the recommended age of risk-reducing salpingo-oophorectomy.

Post-treatment Pregnancies in *BRCA*-Mutated Breast Cancer Survivors

Prognostic Effect of Having a Pregnancy

Despite a high proportion of young women with newly diagnosed breast cancer desire to have a pregnancy following anticancer treatments, only a minority of them succeed to conceive [45–47]. Besides the risk of treatment-induced POI, another important explanation for the low pregnancy rates in these patients is represented by the concerns of patients and providers related to the possible detrimental prognostic effect of having a pregnancy in breast cancer survivors [52, 53]. Indeed, these concerns appear to be particularly important when counseling *BRCA*-mutated breast cancer survivors. In a recent survey conducted among physicians who attended two dedicated breast cancer congresses, 30% of the respondents agreed or were neutral on the statement that a pregnancy in breast cancer survivors may increase the risk of recurrence; however, this percentage significantly increased to 46% ($p < 0.001$) when the same question was referred to the population of *BRCA*-mutated breast cancer patients [54].

Over the past years, although a growing amount of evidence has shown that pregnancy after breast cancer can be considered safe [55–57], very limited data exists to counsel *BRCA*-mutated survivors. A multicenter, retrospective cohort study included 128 *BRCA*-mutated breast cancer patients with a pregnancy (at the time of diagnosis in 75, and following prior history of breast cancer in 53) and 269 matched nonpregnant controls to investigate the prognostic effect of pregnancy in this setting [58]. No difference in breast cancer specific mortality was observed between pregnant cases and matched nonpregnant controls (adjusted HR, 0.76; 95% CI, 0.31–1.91; $p = 0.56$). Similar findings were also shown for the subgroup of patients with pregnancy following prior history of breast cancer (adjusted HR, 0.73; 95% CI, 0.21–2.68; $p = 0.64$) [58]. A more recent and larger study addressed specifically the safety of having a pregnancy in young *BRCA*-mutated patients with prior history of breast

cancer [59]. This international multicenter cohort study included 1252 *BRCA*-mutated patients, of whom 195 (16%) had at least one pregnancy after prior breast cancer. Pregnancy complications and congenital anomalies were described in 11.6% and 1.8% of the cases, respectively (i.e., lower than expected in the general population). After a median follow-up time of 8.3 years, pregnant patients showed a better disease-free survival than those without a subsequent pregnancy (HR 0.71; 95% CI 0.51–0.99; $p = 0.045$) with no difference in OS (HR 0.86; 95% CI 0.44–1.67; $p = 0.65$). At the subgroup analysis, the superior outcome was shown to be restricted to pregnant patients with a *BRCA1* mutation (p-interaction < 0.01) [59].

The POSITIVE trial is an ongoing international prospective study that aims to investigate the safety of a temporary interruption of endocrine therapy for allowing pregnancy in breast cancer survivors with hormone receptor-positive disease [60]. Results from this study could give important information also for *BRCA*-mutated breast cancer patients, particularly for those with *BRCA2* mutations who are more likely to develop hormone receptor-positive tumors and, therefore, receive adjuvant endocrine therapy.

Prenatal Diagnosis (PND) and Pre-implantation Genetic Diagnosis (PGD)

For *BRCA*-mutated breast cancer patients interested in avoiding the 50% risk of transmitting the mutated gene to their children, two different techniques are available: PND in the case of spontaneous conception or PGD after in vitro fertilization [61].

In PND, a chorionic villi sampling is performed during the first trimester of pregnancy. Patients can choose to terminate the pregnancy if the fetus carries the mutation or has other identified pathologic conditions (e.g., trisomy 21). However, for most of the couples, pregnancy termination for hereditary breast and ovarian cancer risk appears to be unacceptable [62]. In a qualitative interview study, only one breast cancer survivors out of 25 participants decided to undergo PND [63]. However, once she underwent fetal ultrasound, it became inconceivable for her to terminate the pregnancy, regardless of genetic test result [63]. The choice to require PND is more often undertaken by older women, with higher level of education, with a prior breast or ovarian cancer history and when there is desire to conceive more rapidly and naturally [64].

In PGD, the mutation has to be characterized by a DNA analysis of the carrier and a first-degree relative who is also a carrier. The DNA of the partner is also being analyzed. Polymerase chain reaction (PCR) is used to perform the genetic diagnosis [65, 66]. After this first assessment, patients undergo COS and intracytoplasmic sperm injection (ICSI). On the third day of embryo development, one or two blastomeres are biopsied and analyzed with PCR. Unaffected embryos are left to develop to blastocyst stage for subsequent in utero transfer. In 2003, the European Society of Human Reproduction and Embryology has deemed PGD acceptable for late onset diseases such as hereditary breast and ovarian cancer [67]. The number of couples demanding PGD for *BRCA* mutations has been growing steadily over the

past years [19]. In the last decade, several authors have investigated through individual or group interviews as well as questionnaires the awareness and acceptability of PGD for couples carrying *BRCA* mutations [61, 62, 64, 65, 68]. A better knowledge of PGD was correlated with higher education level, younger age, being childless, and wishing to conceive rapidly; acceptability of the procedure was higher (79.5%) in couples with personal history of breast or ovarian cancer [64]. However, less than 40% of respondents would consider to undergo PGD for hereditary breast and ovarian cancer as compared to almost 60% who would choose it for other severe genetic disorders [64]. Main reasons for not considering to undergo PGD were physical and psychological burden, the relatively low pregnancy rate, a delay in childbearing, and the discarding of affected embryos that might not develop cancer [61–63, 69]. Overall, pregnancy clinical rates among *BRCA*-mutated patients are comparable to the outcome of PGD for autosomal dominant disorders (39.1% vs. 26.5% per embryo transfer, respectively) [70]. In a recent observational cohort study that evaluated the efficiency of the procedure, 145 PGD cycles were performed in 720 embryos [65]. The pregnancy rate was 23.9% per cycle started, and 26.5% in frozen cycles. Overall, 28 out of 31 singletons and 8 babies out of 10 twin pregnancies were born alive following the procedure. Two out of 3 patients who had PGD on embryos collected for fertility preservation before breast cancer therapy could deliver a healthy baby. In this study, two healthy *BRCA* carriers developed breast cancer shortly after treatment, although screening before COS was negative. The authors raised concerns about maternal safety of COS followed by IVF for PGD in healthy *BRCA* carriers [65]. Nevertheless, a large population-based study including 2,514 *BRCA1/2* mutation healthy carriers of whom 76 (3%) were exposed to COS found no increased risk of developing breast cancer for stimulated women (HR 0.79; 95% CI, 0.46–1.36) [71]. Although further evidence is needed, results from this study are reassuring for *BRCA*-mutated healthy carriers considering to undergo COS.

Conclusions and Future Perspective

Fertility and pregnancy-related issues are important concerns for young breast cancer patients. Carrying a germline deleterious *BRCA* mutation adds additional burden in this setting considering the limited data available to properly counsel these patients, the high risk of ovarian cancer with subsequent indication for risk-reducing salpingo-oophorectomy at a young age and the 50% risk of transmitting the mutation to their children. The growing number of young breast cancer patients currently tested for the *BRCA* genes and the increased use of multigene panel sequencing technologies will likely make more common the possibility to counsel patients carrying a germline deleterious *BRCA* mutation or affected by other hereditary breast cancer syndromes.

To date, while a growing body of knowledge has become available on the efficacy and safety of the different fertility preservation strategies as well as on the safety of having a pregnancy following breast cancer diagnosis and treatment, data

are scarce to properly and specifically counsel patients carrying a *BRCA* mutation. If available and allowed by national laws and regulations, oocyte donation and surrogacy represent other possible options for young women with breast cancer patients, including *BRCA*-mutated patients [72]. Nevertheless, in some circumstances, adoption remains the only possibility to enable cancer survivors to have a family; however, they may encounter barriers due to their medical history and these issues might be even greater for *BRCA*-mutated patients [73].

With the final goal to improve the oncofertility counseling of *BRCA*-mutated breast cancer patients, research efforts aiming to address the impact of carrying a *BRCA* mutation on their ovarian reserve, the gonadotoxicity of anticancer therapies including the more recently adopted agents, the performance of fertility preservation strategies as well as the safety of having a pregnancy following anticancer treatments should be considered research priorities. Large collaborative studies are needed to accrue adequate numbers that would allow deriving more solid evidence on the still existing gray zones in this field.

Acknowledgments Margherita Condorelli acknowledges the support from FNRS-Télévie for the conduction of her PhD at the Research Laboratory on Human Reproduction, CUB-Hôpital Erasme in Brussels (Belgium). Matteo Lambertini acknowledges the support from the European Society for Medical Oncology (ESMO) for a Translational Research Fellowship at the Institut Jules Bordet in Brussels (Belgium) during the writing of this book chapter.

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure: Margherita Condorelli declares no conflicts of interest. Matteo Lambertini served as a consultant for Teva and received speaker honoraria from Theramex and Takeda outside the submitted work.

References

1. Rosenberg SM, Ruddy KJ, Tamimi RM, Gelber S, Schapira L, Come S, et al. BRCA1 and BRCA2 mutation testing in young women with breast cancer. JAMA Oncol. 2016;2(6):730–6.
2. Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, Altman DG, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018;19(2):169–80.
3. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K-A, Mooij TM, Roos-Blom M-J, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317(23):2402–16.
4. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016;27(suppl 5):v103–10.
5. Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso M-J, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast. 2017;35:203–17.
6. Samimi G, Bernardini MQ, Brody LC, Caga-Anan CF, Campbell IG, Chenevix-Trench G, et al. Traceback: a proposed framework to increase identification and genetic counseling of BRCA1 and BRCA2 mutation carriers through family-based outreach. J Clin Oncol. 2017;35(20):2329–37.

7. Lambertini M, Goldrat O, Toss A, Azim HA, Peccatori FA, Ignatiadis M, et al. Fertility and pregnancy issues in BRCA-mutated breast cancer patients. Cancer Treat Rev. 2017;59:61–70.
8. de la Noval BD. Potential implications on female fertility and reproductive lifespan in BRCA germline mutation women. Arch Gynecol Obstet. 2016;294(5):1099–103.
9. Giscard d'Estaing S, Perrin D, Lenoir GM, Guérin JF, Dante R. Upregulation of the BRCA1 gene in human germ cells and in preimplantation embryos. Fertil Steril. 2005;84(3):785–8.
10. Eakin CM, Maccoss MJ, Finney GL, Klevit RE. Estrogen receptor alpha is a putative substrate for the BRCA1 ubiquitin ligase. Proc Natl Acad Sci U S A. 2007;104(14):5794–9.
11. Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, et al. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. Sci Transl Med. 2013;5(172):172ra21.
12. Sharan SK, Pyle A, Coppola V, Babus J, Swaminathan S, Benedict J, et al. BRCA2 deficiency in mice leads to meiotic impairment and infertility. Development. 2004;131(1):131–42.
13. Weinberg-Shukron A, Rachmiel M, Renbaum P, Gulsuner S, Walsh T, Lobel O, et al. Essential role of BRCA2 in ovarian development and function. N Engl J Med. 2018;379(11):1042–9.
14. Govindaraj V, Keralapura Basavaraju R, Rao AJ. Changes in the expression of DNA double strand break repair genes in primordial follicles from immature and aged rats. Reprod Biomed Online. 2015;30(3):303–10.
15. Zhang D, Zhang X, Zeng M, Yuan J, Liu M, Yin Y, et al. Increased DNA damage and repair deficiency in granulosa cells are associated with ovarian aging in rhesus monkey. J Assist Reprod Genet. 2015;32(7):1069–78.
16. Govindaraj V, Krishnagiri H, Chauhan MS, Rao AJ. BRCA-1 gene expression and comparative proteomic profile of primordial follicles from young and adult buffalo (Bubalus bubalis) ovaries. Anim Biotechnol. 2017;28(2):94–103.
17. Lin W, Titus S, Moy F, Ginsburg ES, Oktay K. Ovarian aging in women with BRCA germline mutations. J Clin Endocrinol Metab. 2017;102(10):3839–47.
18. Giordano S, Garrett-Mayer E, Mittal N, Smith K, Shulman L, Passaglia C, et al. Association of BRCA1 mutations with impaired ovarian reserve: connection between infertility and breast/ovarian cancer risk. J Adolesc Young Adult Oncol. 2016;5(4):337.
19. Derks-Smeets IAP, van Tilborg TC, van Montfoort A, Smits L, Torrance HL, Meijer-Hoogeveen M, et al. BRCA1 mutation carriers have a lower number of mature oocytes after ovarian stimulation for IVF/PGD. J Assist Reprod Genet. 2017;34(11):1475–82.
20. Gunnala V, Fields J, Irani M, D'Angelo D, Xu K, Schattman G, et al. BRCA carriers have similar reproductive potential at baseline to noncarriers: comparisons in cancer and cancer-free cohorts undergoing fertility preservation. Fertil Steril. 2019;111(2):363–71.
21. Stolk L, Perry JRB, Chasman DI, He C, Mangino M, Sulem P, et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. Nat Genet. 2012;44(3):260–8.
22. Day FR, Ruth KS, Thompson DJ, Lunetta KL, Pervjakova N, Chasman DI, et al. Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. Nat Genet. 2015;47(11):1294–303.
23. Rzepka-Górska I, Tarnowski B, Chudecka-Głaz A, Górski B, Zielińska D, Tołoczko-Grabarek A. Premature menopause in patients with BRCA1 gene mutation. Breast Cancer Res Treat. 2006;100(1):59–63.
24. Lambertini M, Goldrat O, Ferreira AR, Dechene J, Azim HA, Desir J, et al. Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients. Ann Oncol. 2018;29(1):237–43.
25. Lambertini M, Olympios N, Lequesne J, Calbrix C, Fontanilles M, Loeb A, Leheurteur M, Demeestere I, Di Fiore F, Perdrix A, Clatot F. Impact of taxanes, endocrine therapy and deleterious germline BRCA mutations on anti-müllerian hormone levels in early breast cancer patients treated with anthracycline- and cyclophosphamide-based chemotherapy. Front Oncol. 2019;9:575. [Epub ahead of print]. https://doi.org/10.3389/fonc.2019.00575.
26. Paluch-Shimon S, Peccatori FA. BRCA 1 and 2 mutation status: the elephant in the room during oncofertility counseling for young breast cancer patients. Ann Oncol. 2018;29(1):26–8.

27. Valentini A, Finch A, Lubiński J, Byrski T, Ghadirian P, Kim-Sing C, et al. Chemotherapy-induced amenorrhea in patients with breast cancer with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2013;31(31):3914–9.
28. Partridge AH, Ruddy KJ, Gelber S, Schapira L, Abusief M, Meyer M, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril. 2010;94(2):638–44.
29. Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2015;103(3):e9–17.
30. Poggio F, Bruzzone M, Ceppi M, Pondé NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29(7):1497–508.
31. Poggio F, Bruzzone M, Ceppi M, Conte B, Martel S, Maurer C, et al. Single-agent PARP inhibitors for the treatment of patients with BRCA-mutated HER2-negative metastatic breast cancer: a systematic review and meta-analysis. ESMO Open. 2018;3(4):e000361.
32. Practice Committee of American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2013;100(5):1214–23.
33. Peccatori FA, Azim HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi160–70.
34. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(19):1994–2001.
35. Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, et al. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertil Steril. 2015;104(5):1162–7.
36. Turan V, Bedoschi G, Emirdar V, Moy F, Oktay K. Ovarian stimulation in patients with cancer: impact of letrozole and BRCA mutations on fertility preservation cycle outcomes. Reprod Sci. 2018;25(1):26–32.
37. Shapira M, Raanani H, Meirow D. IVF for fertility preservation in breast cancer patients—efficacy and safety issues. J Assist Reprod Genet. 2015;32(8):1171–8.
38. 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):1364–71.
39. Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA, Peccatori FA, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016;14:1.
40. 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):325–36.
41. Tanbo T, Greggains G, Storeng R, Busund B, Langebrekke A, Fedorcsak P. Autotransplantation of cryopreserved ovarian tissue after treatment for malignant disease: the first Norwegian results. Acta Obstet Gynecol Scand. 2015;94(9):937–41.
42. Telfer EE, McLaughlin M. In vitro development of ovarian follicles. Semin Reprod Med. 2011;29(1):15–23.
43. McLaughlin M, Albertini DF, Wallace WHB, Anderson RA, Telfer EE. Metaphase II oocytes from human unilaminar follicles grown in a multi-step culture system. Mol Hum Reprod. 2018;24(3):135–42.
44. Lambertini M, Cinquini M, Moschetti I, Peccatori FA, Anserini P, Valenzano Menada M, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: A GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. Eur J Cancer. 2017;71:25–33.
45. Lambertini M, Boni L, Michelotti A, Gamucci T, Scotto T, Gori S, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovar-

ian function, pregnancies, and disease-free survival: a randomized clinical trial. JAMA. 2015;314(24):2632–40.
46. Leonard RCF, Adamson DJA, Bertelli G, Mansi J, Yellowlees A, Dunlop J, et al. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. Ann Oncol. 2017;28(8):1811–6.
47. Moore HCF, Unger JM, Phillips K-A, Boyle F, Hitre E, Moseley A, et al. Final analysis of the prevention of early menopause study (POEMS)/SWOG intergroup S0230. J Natl Cancer Inst. 2019;111(2):210–3.
48. Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim HA, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015;26(12):2408–19.
49. Bai F, Lu Y, Wu K, Chen Q, Ding L, Ge M, et al. Protecting effects of gonadotropin-releasing hormone agonist on chemotherapy-induced ovarian damage in premenopausal breast cancer patients: a systematic review and meta-analysis. Breast Care (Basel). 2017;12(1):48–52.
50. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient–level data. J Clin Oncol. 2018;36(19):1981–90.
51. Wong M, O'Neill S, Walsh G, Smith IE. Goserelin with chemotherapy to preserve ovarian function in pre-menopausal women with early breast cancer: menstruation and pregnancy outcomes. Ann Oncol. 2013;24(1):133–8.
52. Biglia N, Torrisi R, D'Alonzo M, Codacci Pisanelli G, Rota S, Peccatori FA. Attitudes on fertility issues in breast cancer patients: an Italian survey. Gynecol Endocrinol. 2015;31(6):458–64.
53. Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, Del Mastro L, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast. 2018;42:41–9.
54. Lambertini M, Di Maio M, Poggio F, Pagani O, Curigliano G, Del Mastro L, et al. Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young BRCA-mutated breast cancer patients. Reprod Biomed Online. 2019;38(5):835–44.
55. Lambertini M, Martel S, Campbell C, Guillaume S, Hilbers FS, Schuehly U, et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Cancer. 2019;125(2):307–16.
56. Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J Natl Cancer Inst. 2018;110(4):426–9.
57. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016;160(2):347–60.
58. Valentini A, Lubinski J, Byrski T, Ghadirian P, Moller P, Lynch HT, et al. The impact of pregnancy on breast cancer survival in women who carry a BRCA1 or BRCA2 mutation. Breast Cancer Res Treat. 2013;142(1):177–85.
59. Lambertini M, Ameye L, Hamy AS, Zingarello A, Poorvu PD, Carrasco E, et al. Safety of pregnancy following breast cancer (BC) in patients (pts) carrying a BRCA mutation (mBRCA): results of an international cohort study. J Clin Oncol. 2019;37:15_suppl:abstract 11506.
60. Pagani O, Ruggeri M, Manunta S, Saunders C, Peccatori F, Cardoso F, et al. Pregnancy after breast cancer: Are young patients willing to participate in clinical studies? Breast. 2015;24(3):201–7.
61. Quinn GP, Vadaparampil ST, Tollin S, Miree CA, Murphy D, Bower B, et al. BRCA carriers' thoughts on risk management in relation to preimplantation genetic diagnosis and childbearing: when too many choices are just as difficult as none. Fertil Steril. 2010;94(6):2473–5.
62. Derks-Smeets IAP, Gietel-Habets JJG, Tibben A, Tjan-Heijnen VCG, Meijer-Hoogeveen M, Geraedts JPM, et al. Decision-making on preimplantation genetic diagnosis and prenatal

diagnosis: a challenge for couples with hereditary breast and ovarian cancer. Hum Reprod. 2014;29(5):1103–12.
63. Ormondroyd E, Donnelly L, Moynihan C, Savona C, Bancroft E, Evans DG, et al. Attitudes to reproductive genetic testing in women who had a positive BRCA test before having children: a qualitative analysis. Eur J Hum Genet. 2012;20(1):4–10.
64. Gietel-Habets JJG, de Die-Smulders CEM, Derks-Smeets IAP, Tibben A, Tjan-Heijnen VCG, van Golde R, et al. Awareness and attitude regarding reproductive options of persons carrying a BRCA mutation and their partners. Hum Reprod. 2017;32(3):588–97.
65. Derks-Smeets IAP, de Die-Smulders CEM, Mackens S, van Golde R, Paulussen AD, Dreesen J, et al. Hereditary breast and ovarian cancer and reproduction: an observational study on the suitability of preimplantation genetic diagnosis for both asymptomatic carriers and breast cancer survivors. Breast Cancer Res Treat. 2014;145(3):673–81.
66. Sagi M, Weinberg N, Eilat A, Aizenman E, Werner M, Girsh E, et al. Preimplantation genetic diagnosis for BRCA1/2—a novel clinical experience. Prenat Diagn. 2009;29(5):508–13.
67. Shenfield F, Pennings G, Devroey P, Sureau C, Tarlatzis B, Cohen J, et al. Taskforce 5: preimplantation genetic diagnosis. Hum Reprod. 2003;18(3):649–51.
68. Menon U, Harper J, Sharma A, Fraser L, Burnell M, ElMasry K, et al. Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. Hum Reprod. 2007;22(6):1573–7.
69. Rubin LR, Werner-Lin A, Sagi M, Cholst I, Stern R, Lilienthal D, et al. "The BRCA clock is ticking!": negotiating medical concerns and reproductive goals in preimplantation genetic diagnosis. Hum Fertil (Camb). 2014;17(3):159–64.
70. Daum H, Peretz T, Laufer N. BRCA mutations and reproduction. Fertil Steril. 2018;109(1):33–8.
71. Derks-Smeets IAP, Schrijver LH, de Die-Smulders CEM, Tjan-Heijnen VCG, van Golde RJT, Smits LJ, et al. Ovarian stimulation for IVF and risk of primary breast cancer in BRCA1/2 mutation carriers. Br J Cancer. 2018;01:357–63.
72. Luke B, Brown MB, Missmer SA, Spector LG, Leach RE, Williams M, et al. Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016;31(1):183–9.
73. Rosen A. Third-party reproduction and adoption in cancer patients. J Natl Cancer Inst Monogr. 2005;2005(34):91–3.