Appendix 1. Background and Special Considerations

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INTRODUCTION

In the context of early onset breast cancer (EOBC), defined as breast cancer before age 46, this review evaluated the literature related to special considerations that might affect the management of EOBC. The literature review was guided by the following question:

What special considerations are present in the management of EOBC, such as pregnancy-associated breast cancer (PABC) or the use of oncofertility in the setting of EOBC?

P – Patient, Problem, or Population. I – Intervention. C – Comparison, Control, or Comparator. O – Outcome(s) (PICO)

P: All women between ages 18 and 45, specifically women with disparities, to include high-risk groups other than white Americans (ie, African Americans, immigrants, unauthorized immigrants, Hispanics, Asians, rural women, women with low-education, women with low socioeconomic status, women with public insurance or no insurance, veterans, or incarcerated women)

I: Early screening and diagnosis; alternative therapies

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The authors provided this information as a supplement to their article.

C: Low-risk women, women at high risk who did not have screening, women with oncofertility or fertility-sparing counseling, chemoprevention and surgical prevention, women undergoing genetic screening compared with those who are not

O: Stage of disease at diagnosis, women undergoing fertility-sparing procedures, women undergoing surgical prevention or chemoprevention

METHODS

Literature Review

Using the PICO criteria, a search was conducted for English-language articles, specifically systematic reviews, meta-analyses, cohort studies, case–control studies, and randomized controlled trials. Also reviewed were major society or health services guidelines, including those from the National Comprehensive Cancer Network, U.S. Preventive Services Task Force, American College of Obstetrician Gynecologists (ACOG), American Cancer Society (ACS), American Society of Breast Surgeons, Society of Surgical Oncology, National Cancer Institute, American Society for Clinical Oncology (ASCO), Oncofertility Consortium, American Society of Reproductive Medicine (ASRM), and Society for Maternal–Fetal Medicine. The review also included international guidelines, such as those of the Royal College of Obstetricians and Gynaecologists (RCOG), the National Institute of Health and Care Excellence, European School of Oncology and European Society of Medical Oncology, European Society of Breast Cancer Specialists, and Canadian Contraception Consensus group.

Articles were excluded from the review if they were not available in English, were case series or reports, or focused on communication of risk-related treatment modalities after diagnosis.

RESULTS AND DISCUSSION

Epidemiology: Demographics, Survival, Patterns

Breast cancer is the most common form of cancer in women and represents the second leading cause of cancer death in women.[1] Based on breast cancer data from 2018 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, there were 266,120 new cancer diagnoses in the United States that year, representing 15% of all new cancer cases. In the same time period, there were 40,920 deaths.[2] Table 1 shows breast cancer incidence rates by age and race from 2012-2016 SEER data and Table 2 shows breast cancer mortality rates by age and race from 2012-2016 SEER data.

The SEER database had data specifically for EOBC cases in the 2011–2015 timeframe. Women between the ages of 20 and 45 made up 10.5% of new cancer cases during that time. A review of race showed that black women had the highest death rate at 38.7/100,000. While 5- year relative survival rates were largely similar across age groups, women below the age of 45 had among the lowest, second only to women age 75 and older.[3]

Table 1. Breast Cancer Incidence Rates by Age at Diagnosis, 2012-2016 By Race and Ethnicity

	All Races (includes Hispanic)	American Indian / Alaska Native (includes Hispanic)	Asian / Pacific Islander (includes Hispanic)	Black (includes Hispanic)	Hispanic (any race)	Non-Hispanic White	White (includes Hispanic)
Age at Diagnosis (years)	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people
15-19	0.2	—	—	—	—	—	0.1
20-24	1.6	—	1.1	2.1	1.4	1.7	1.6
25-29	9.9	—	8.5	11.7	8.3	10.0	9.7
30-34	29.0	19.3	26.2	32.5	24.0	29.9	28.4
35-39	63.6	42.5	58.8	68.6	50.7	67.4	63.0
40-44	128.4	63.1	124.5	125.4	101.2	138.6	129.3
45-49	194.7	96.2	189.2	183.0	148.7	210.4	197.0
50-54	233.6	133.3	207.9	232.3	183.6	247.5	236.1
55-59	266.8	174.4	223.4	275.6	214.8	279.5	269.9
60-64	340.6	246.6	270.4	336.0	270.8	360.1	348.1
65-69	424.5	279.9	312.5	393.6	332.7	454.0	439.5
70-74	464.6	321.3	311.7	428.0	333.6	504.6	484.1
75-79	457.1	291.5	259.0	426.2	319.0	503.5	481.6
80-84	414.1	255.4	231.8	387.6	283.5	452.0	434.0
85+	331.9	235.6	188.9	342.9	234.1	350.3	340.1

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Data from National Cancer Institute. SEER*Explorer: breast cancer SEER incidence rates by age at diagnosis, 2012-2016 by Race/Ethnicity. Available at: https://seer.cancer.gov/explorer/application.php?site=55&data_type=1&graph_type=3&compareBy=race&chk_sex_3=3&chk_race_1=1&chk_race_5=5&chk_race_4=4&chk_race_3=3&chk_race_6=6&chk_race_8=8&chk_race_2=2&chk_data_type_1=1&advopt_precision=1&showDataFor=sex_3_and_data_type_1. Retrieved February 13, 2020.

Table 2. Breast Cancer Mortality Rates by Age at Diagnosis, 2012-2016 by Race and Ethnicity

	All Races (includes Hispanic)	American Indian / Alaska Native (includes Hispanic)	Asian / Pacific Islander (includes Hispanic)	Black (includes Hispanic)	Hispanic (any race)	Non-Hispanic White	White (includes Hispanic)
Age at Death (years)	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people	Rate per 100,000 people
15-19	—	—	—	—	—	—	—
20-24	0.1	—	—	—	—	0.1	0.1
25-29	0.7	—	0.5	1.4	0.6	0.6	0.6
30-34	2.8	—	1.3	5.0	2.1	2.6	2.5
35-39	6.6	4.8	4.3	10.8	5.2	6.1	6.0
40-44	12.3	6.2	8.1	20.9	9.6	11.4	11.2
45-49	19.5	12.6	12.9	32.3	14.6	18.3	17.9
50-54	28.6	16.5	18.6	46.0	21.0	27.2	26.6
55-59	38.5	22.1	26.9	58.7	28.4	37.0	36.3

60-64	49.1	33.3	29.8	68.9	35.0	48.8	47.8
65-69	61.4	49.3	31.4	82.6	41.9	62.3	60.7
70-74	75.6	54.8	37.4	92.2	47.7	78.2	75.9
75-79	94.0	74.4	44.5	113.4	61.4	97.2	94.6
80-84	116.8	87.9	50.5	137.9	76.0	121.1	118.0
85+	173.7	121.8	76.1	195.5	113.8	179.6	175.9

Data from National Cancer Institute. SEER*Explorer: breast cancer SEER incidence rates by age at diagnosis, 2012-2016 by Race/Ethnicity. Available at: https://seer.cancer.gov/explorer/application.php?site=55&data_type=2&graph_type=3&compareBy=race&chk_sex_3=3&chk_race_1=1&chk_race_5=5&chk_race_4=4&chk_race_3=3&chk_race_6=6&chk_race_8=8&chk_race_2=2&advopt_precision=1&showDataFor=sex_3. Retrieved February 13, 2020.

In one study, women younger than 40 demonstrated poorer survival in early stage disease (I and II) compared with women older than 40.[4] Mortality was lower in women under 40 with advanced (stage IV) disease. This variation relates to tumors in younger women having more aggressive and biologically unfavorable characteristics of tumor subtypes, and younger women being generally in better health than women over 40 with advanced disease.[4] While mortality trends have improved in all women, young black women continue to have higher mortality rates compared with other young women with breast cancer, irrespective of stage or hormone receptors. Additionally, young black women were found to have slower reduction of annual hazard of death than their counterparts of other races, demonstrating potentially less progress in treatment.

Poorer prognosis in black women is thought to be multifactorial. In addition to having more-aggressive tumors, this population appears to have more risks related to access barriers, social determinants, and other factors.[5] Additionally, higher-stage, de novo metastatic breast cancer in young women is increasing for all types of women: non-whites, non-Hispanic blacks, Hispanics, Asian Pacific Islanders. However, and fortunately, unstaged disease tends to be decreasing. In a study by DeSantis et al, when stage was imputed for unstaged disease, non-Hispanic black women continued to trend higher, indicating continued increases in metastatic breast cancer in this population.[6]

Special Considerations for Women with EOBC

Survivorship in women with EOBC is a critical component to initial evaluation and treatment, as well as ongoing care. Chemotherapy is often and variably responsible for inducing amenorrhea (chemo-induced amenorrhea [CIA]), menopause, or true ovarian failure, resulting in consequences such as infertility or subfertility, bone loss, and increased cardiac risk, as well as menopausal symptoms that can have significant impact on quality of life. The management of these conditions is complicated by limitations on treatment options. Additionally, survivorship involves management of posttreatment complications such as lymphedema, frozen shoulder, reconstruction, and other conditions, similar to sequalae that patients incur regardless of age of diagnosis. Specifically, age at diagnosis, hormone receptor status, and treatment regimen are important considerations in managing ongoing care for women affected by EOBC. Recently, the National Comprehensive Cancer Network and others have published comprehensive guidelines for survivorship.[7] Moreover, ASCO provides a comprehensive set of survivorship

recommendations specific to conditions.[8] In addition, the ACS and ASCO produced a collaborative, comprehensive set of survivorship guidelines after systematic review in 2015.[9]

Although not specific for women affected by EOBC, ACOG provides additional resources for care of gynecologic issues in women with breast cancer, many of which are applicable for those women with EOBC who are symptomatic as a result of their treatments. The recommendations include nonhormonal interventions for symptomatic patients who are precluded from using hormone replacement because of the deleterious effects it may have on recurrence and overall survival rates. The ACOG recommendations included use of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, as well as gabapentin, for vasomotor symptoms, use of lubricants and topical estrogens for vaginal dryness and dyspareunia, management of bone loss, considerations for safety of pregnancy after breast cancer, and preservation of fertility.[10] More recently, the North American Menopause Society and the International Society on Women's Sexual Health coauthored recommendations regarding the treatment of menopausal genitourinary syndrome in women with breast cancer. Although these recommendations are not specific for women with EOBC, the recommendations offers guidance to providers who treat this population.[11]

Emerging longitudinal information regarding sexual health specific for women with EOBC younger than age 40 demonstrate that sexual dysfunction is very common. While it improves for many patients over time, it worsens for others, further affirming the need to include ongoing attention to sexual function when evaluating survivorship.[12] Evaluation of women's sexual functioning after breast cancer diagnosis

revealed that younger women prefer to discuss sexual function issues face-to-face with their provider and were more likely to use online materials.[13]

Acknowledgement and treatment for cognitive decline in women with EOBC may also be a significant concern for survivorship and quality of life. Although the data are conflicting, the almost ubiquitous treatment with chemotherapy and ongoing endocrine therapy in women with EOBC leads to real and perceived cognitive declines that must be managed.[14]

In addition, and as addressed in survivorship guidelines, the need for ongoing primary preventive care services for women with EOBC is critical; appropriate care must be delivered. Attention to cardiovascular disease as a specific risk in this population related to chemotherapeutic agents, immune modulators, endocrine therapies, and radiation therapy, as well as the need to modify risk factors commonly shared for both cardiovascular disease and breast cancer, should be addressed as part of survivorship. The ABCDE model (A: awareness of risks of heart disease, aspirin; B: blood pressure; C: cholesterol, cigarette/tobacco cessation; D: diet and weight management, dose of chemotherapy or radiation, diabetes mellitus prevention/treatment; E: exercise, echocardiogram) has been suggested as tool to help reinforce the need for behavior modification and enhanced cardiac surveillance for survivors of breast cancer.[15]

Importantly, given the aggressiveness of tumors in the EOBC population, advanced and metastatic disease is more common, and survivorship is not always possible. The need to understand the application of palliative care services and their content more broadly in young women with EOBC

requires further study. Recently the Shady Pink Elephant end-of-life educational series was tested in a subset of young women with metastatic breast cancer to determined their attitudes and knowledge around end-of-life concerns. The intervention was positively received and demonstrated increased knowledge in this population, although it should be investigated on a larger scale.[16]

Contraception

Contraception is an important consideration for women with EOBC. Given the variability in posttreatment ovarian function, contraception should be addressed for sexually active women (or women considering sexual activity) who are at risk for pregnancy. While evidence-based recommendations exist, it appears that contraceptive counseling is inconsistent. A study from Switzerland demonstrated that 58% of contraceptive-eligible patients in a cohort were using ineffective (ie, World Health Organization [WHO] class III or IV) contraceptive methods, with an unintended pregnancy rate of 3.5%.[17] In a U.S. study of a cohort derived from the Fertility Information Research Study, analysis of 295 survivors (91 breast cancer survivors) found they were less likely to use effective WHO class I or II contraceptive methods than the general population (34% vs 53%). Only 56% of cancer survivors reported receiving family planning services (counseling, prescription, or procedure). In this study, breast cancer survivors were less likely to be using WHO class I or II contraceptive agents than more effective WHO class III and IV methods (WHO Medical Eligibility Criteria classifies contraception on a scale from Tier 1, most effective, to Tier 4, least effective). Furthermore, the importance of overtly addressing contraception was demonstrated by the fact that receipt of family planning services

increased use of tiers I-II (more effective) contraceptive measures twofold, as well as emergency contraception fivefold among patients who did have access to family planning services.[18]

Guidelines are available that provide recommendations for contraception for women with current or past history of breast cancer. The U.S. Medical Eligibility Criteria favor the copper T386 intrauterine device (IUD) for women with current and past breast cancer ; for past or no evidence of current disease, a levonorgestrel (LNG) IUD or other hormonal contraceptives can be considered (Category 3: theoretical or proven risks usually outweigh the advantages, but should be discussed with and administered in conjunction with the oncologist.)[19] The Canadian Contraceptive Consensus and the Society of Family Planning (SFP) endorse use of the LNG IUD in women with breast cancer who are taking tamoxifen without increasing their risk.[20,21] This endorsement is based on results from a metanalysis of three randomized controlled trials of the LNG IUD in breast cancer survivors on tamoxifen that demonstrated no increased risk of recurrence.[22]

The SFP also included the following guidelines regarding contraception in cancer:[21]

- Emergency contraceptive pills may be used by women at risk of breast cancer or breast cancer recurrence who decline emergency placement of a copper T380A IUD.
- Combination estrogen/progestin contraceptive therapy should not be used in women with a history of chest wall irradiation.

It appears that the recommendation to withhold estrogen/progestin contraceptive therapy in women treated with chest wall irradiation is based on a substantially increased risk of breast cancer in this

population because of prior irradiation. This recommendation appears to be based on expert recommendation and may warrant further investigation.

Contraception in other high-risk groups, such as BRCA carriers, was addressed in the Canadian Contraception Consensus, which states: "The use of [combined oral contraceptives] in BRCA1/2 carriers is controversial but appears to be associated with a decreased risk of ovarian cancer and no increase in the risk of breast cancer."[23] This statement is included in the ACOG Practice Bulletin, Hereditary Breast and Ovarian Cancer Syndrome, which represents a collaboration of ACOG and the Society for Gynecologic Oncology. The Practice Bulletin reports a 30–50% reduction in ovarian cancer while providing effective contraception.[24] These conclusions have been further affirmed in a prospective cohort study demonstrating no increased risk of breast cancer among carriers of BRCA 1 or BRCA2 who use oral contraception.[25] No information was encountered that specifically addressed contraception for women who had triple-negative EOBC. However, a copper IUD is likely the best choice, given the recommendations of the SFP and the U.S. Medical Eligibility Criteria.

Pregnancy

Pregnancy during and after diagnosis of breast cancer has been of concern related to both the hyperhormonal status of women (increased estrogen and progesterone) during pregnancy and interruption of endocrine therapy postpregnancy, which might theoretically lead to higher recurrence rates and increased mortality. Pregnancy-associated breast cancer is typically diagnosed during pregnancy or within 1 year of pregnancy. Several studies have demonstrated no increased risk of

recurrence or mortality with PABC or pregnancy after a diagnosis. Pregnancy after diagnosis of estrogen receptor (ER)-positive breast cancer does not worsen prognosis when compared with age-matched controls in a retrospective cohort study.[26] In a longer-term follow-up (7.2 years) of pregnancy after EOBC, no difference was seen in overall survival when compared with matched controls. However, overall survival was greater in ER-negative patients. This study found no difference when the following factors were controlled: abortion, breastfeeding, time to conception, and adjuvant therapy.[27] Furthermore, when considering timing, pregnancy occurring at least 10 months after breast cancer diagnosis was not found to be harmful and may even contribute to survivorship.[28]

It has been noted that PABCs are becoming more frequent. In PABC specifically, pregnancy does not appear to increase risk of breast cancer, and treatment may safely be administered in the second and third trimesters. Fetal risk of anomalies are significant if treatment begins in the first trimester, however.[29] The RCOG offers specific guidelines addressing pregnancy and breast cancer, which state the following:[30]

- Pregnancy does not worsen diagnosis for women diagnosed in pregnancy.
- Pregnancy-associated breast cancers occur in younger women who have higher risk of metastasis and ER-negative tumors that are associated with inferior prognosis independent of a concomitant or subsequent pregnancy.
- While the recommendation is to avoid first-trimester chemotherapy, anthracycline treatments are considered safe in the second and third trimesters. Less information is available on taxanes.

There is no formal recommendation on timing of pregnancy from any professional society. The literature review found that expert opinion on timing ranged from 6 months to 3 years. The Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer (POSITIVE) trial is a multicenter effort underway to help determine timing of pregnancy that is evaluating discontinuation of endocrine therapy after 18 months to allow for pregnancy.[31] The literature review found no consensus or recommendation on timing of planning for pregnancy in women with ER- or triple-negative cancers.

Oncofertility and Fertility Preservation in Women with EOBC

Ovarian stimulation for in vitro fertilization (IVF) has been questioned as a risk factor in the development of breast cancer. Although few data assess artificial reproductive techniques and risk of breast cancer, a recent publication from the Netherlands did not demonstrate an increased risk of breast cancer in a cohort (Omega) of women who underwent ovarian stimulation for IVF when compared with a rigorous control group of women who underwent fertility treatments not including IVF (3.0 vs 2.9%, P=0.85).[32] These findings corroborate the data for more than 1 million women previously studied by Serventanis et al.[33]

While it does not appear that IVF treatments lead to breast cancer, questions remain as to the effects these techniques might have on patients undergoing fertility preservation procedures. Fertility preservation is a significant concern and has been addressed as a key issue in cancer survivorship for more than a decade.[34] In the most recent ASCO guidelines, embryo cryopreservation and

cryopreservation of unfertilized oocytes are suggested options for women with cancer.[34] The ASCO guidelines recommend gonadotropin-releasing hormone (GnRH) as second-line therapy if embryo or oocyte cryopreservation are not options to preserve ovarian function during chemotherapy.[35] (This recommendation is also endorsed by the RCOG.[30]) The ASCO recommendations recognize that ovarian cortex harvesting has become better studied but caution that it continues to be experimental; they also indicate that limitations on ovarian cortex harvesting may be removed in the near future for young women with cancers (except leukemias).

The ASRM addresses fertility preservation in women undergoing gonadotoxic therapy or gonadectomy for cancer.[36] These guidelines specifically address concerns in patients with breast cancer in a subset of the recommendations. For patients with breast cancer, they recommend the use of aromatase inhibitors to suppress estrogen levels during controlled ovarian hyperstimulation (COH) and consideration of prenatal genetic diagnosis during assisted reproduction in patients who are BRCA 1 or BRCA 2 carriers. The guidelines note that it is not known whether COH increases breast cancer recurrence risk. Given that fertility is a complex discussion, ASRM's fertility preservation videos may be a useful tool for shared decision making. The Oncofertility Consortium also offers a collection of fertility preservation tools and decision aids and provides a review of the literature for oncologists and reproductive oncologists to use in counseling and treating patients. The Oncofertility Consortium website catalogues major recommendations and high-quality papers in fertility preservation.[37] Similarly, the ACS offers a host of resources and guides for fertility preservation in women with cancer.[38]

Some of the supporting evidence leading to the guidelines for fertility preservation for breast cancer patients includes letrozole utilization in COH, which lowers peak estrogen levels without affecting oocyte count and does not lead to poorer prognosis than controls. Use of a GnRH trigger is recommended for women with breast cancer undergoing COH, as it leads to faster decline in estradiol rates and reduces rates of ovarian hyperstimulation.[39]

While GnRH agonist is not considered first-line therapy for ovarian preservation, there are emerging data regarding its use. A recent meta-analysis determined that GnRH agonist provides some protection from premature ovarian failure in women undergoing gonadotoxic therapy (not specific to EOBC). However, the duration of protection is unknown, and further study was recommended.[40] These data were further corroborated by an additional meta-analysis that evaluated both ovarian insufficiency and posttreatment pregnancy rates. Essentially, the risk of premature ovarian insufficiency was more than halved when GnRH agonist was administered at the time of chemotherapy, and subsequent pregnancy rates doubled.[41]

Part of the difficulty in counseling for fertility preservation in this population—reflecting the need for universal counseling guidelines—relates to predictability of premature ovarian failure, often represented as CIA in this population. The rate of CIA or true ovarian failure is confusing as currently defined (ie, amenorrhea for a defined period, laboratory confirmation, or a combination) and varies from study to study. However CIA is defined, it is thought to be a factor of patient age (likely a surrogate for ovarian reserve) at the time of treatment as well as the treatment agent(s). In a recent metanalysis that included 23,673 patients from 74 studies, the rate of CIA was found to be 55% (95% confidence

interval [CI]: 50–60%) in all patients treated for EOBC. The rate of CIA increased by age, with estimates of 26% (95% CI: 12–43%) for women younger than 35, 39% (95% CI: 31–58%) for women 35–40, and 77% (95% CI: 71–83%) for women older than 40. Two risk factors associated with the occurrence of CIA were supported by strong evidence: age older than 40 and the use of tamoxifen (see Figure 1).[42] Providers should consider age and type of chemotherapy agents used in determining the risk of permanent ovarian failure, as delineated in Figure 1. For patients at low or intermediate risk for CIA, providers should offer contraceptive counseling to prevent unintended pregnancy caused by delayed return of ovarian function.

Figure 1. Metanalysis of risk of CIA by chemotherapy agent and age of diagnosis.

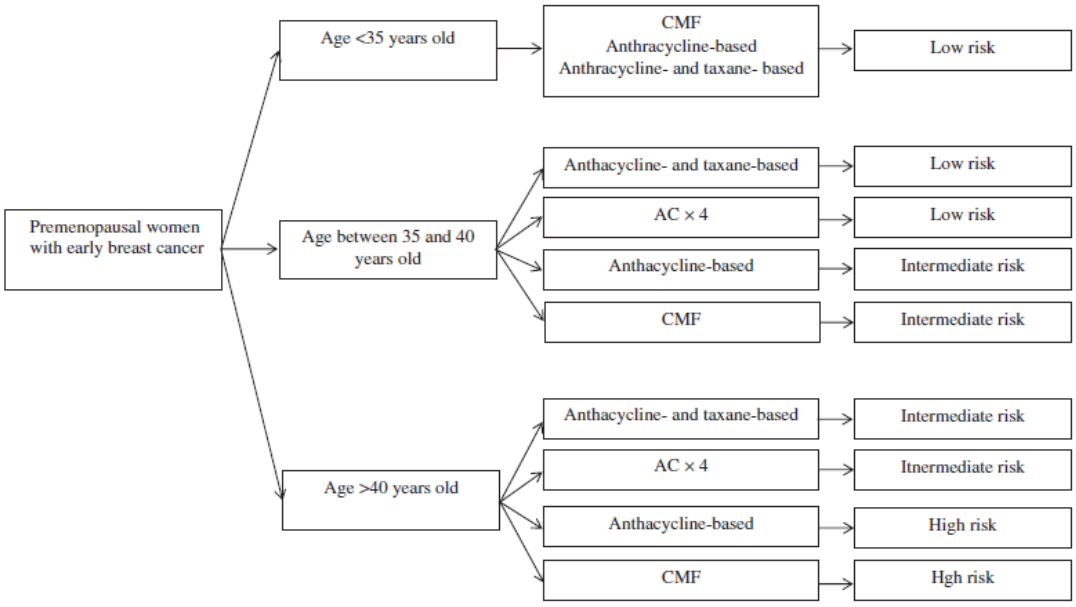

Figure 2. Flowchart of risk for chemotherapy-induced amenorrhea based on age and type of chemotherapy. AC: doxorubicin-cyclophosphamide.

Reprinted from Zavos A, Valachis A. Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. Acta Oncol 2016;55:664-70. https://www.tandfonline.com/doi/full/10.3109/0284186X.2016.1155738. Taylor & Francis Ltd, http://www.tandfonline.com

To elucidate medical provider attitudes towards fertility preservation, 91 medical oncologists (lead enrollers in clinical trials, most of whom work in National Cancer Institute-designated cancer centers) were surveyed regarding their willingness to enroll young breast cancer survivors in the POSITIVE trial. In addition, a needs assessment was performed in which providers were asked about fertility preservation counseling and practices. The majority of respondents (98%) reported that they counseled patients on

fertility preservation, and 79% stated that they refer to or consult with a fertility specialist or reproductive endocrinologist. The largest perceived barrier to counseling (47%) was related to cost and insurance issues. Time was not perceived as a barrier to counseling about fertility preservation.[43] With legislation mandating fertility preservation coverage in several states, the barrier of insurance coverage should lessen over time.

SUMMARY

In summary, EOBC represents approximately 10% of all breast cancers. Women with EOBC have more aggressive tumors and worse prognoses when compared with women without EOBC. Black women are most affected and have worse outcomes that are considered multifactorial.

Survivorship is an imperative component of the care continuum for women with EOBC, as the majority of women with EOBC will not succumb to their disease. Effective contraception is often overlooked as part of the treatment regimen for patients with EOBC. This review concluded the following:

- Copper IUD is the recommended contraceptive method for women with EOBC.
- The LNG IUD for contraception is safe in concomitant use with tamoxifen.
- Emergency contraception can be provided to women after a diagnosis of EOBC. Copper-containing IUD is the preferred method, but progestin regimens can be used.
- A family planning consultation with a provider should be part of the treatment protocol for women with EOBC.

For fertility preservation, the following should be considered:

- Oocyte/embryo cryopreservation is considered first-line therapy.
- Ovarian tissue harvesting appears promising.
- Use of GnRH agonist should be an option when ovarian oocyte/embryo cryopreservation is not possible and should be considered to offer some protection to the ovary.
- Aromatase inhibitors and GnRH agonist triggers should be used when employing COH to lower estrogen levels.
- Prenatal genetic diagnosis should be considered in women with BRCA mutations undergoing IVF procedures after a diagnosis of breast cancer.

In relation to pregnancy, the following should be noted:

- Pregnancy is not considered to increase risk of breast cancer recurrence after EOBC.
- Gaps in knowledge exist regarding the timing of conception.
- When breast cancer is diagnosed in pregnancy, chemotherapy can be safely instituted in the second and third trimesters.

REFERENCES

1. Centers for Disease Control and Prevention. Breast cancer: black women have higher death rates from breast cancer than other women. Vital Signs. Atlanta, GA: CDC; 2012. Available at: https://www.cdc.gov/vitalsigns/BreastCancer/?s_cid=bb-vitalsigns-103. Retrieved October 21, 2019.

2. National Cancer Institute. Cancer stat fact: female breast cancer. Available at: https://seer.cancer.gov/statfacts/html/breast.html. Retrieved October 22, 2019.

3. U.S. Cancer Statistics Working Group. U.S. cancer statistics data visualizations tool, based on November 2018 submission data (1999-2016). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2019. Available at: https://gis.cdc.gov/Cancer/USCS/DataViz.html. Retrieved October 23, 2019.

4. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg 2009;208:341-7.

5. Ademuyiwa FO, Gao F, Hao L, Morgensztern D, Aft RL, Ma CX, et al. US breast cancer mortality trends in young women according to race. Cancer 2015;121:1469-76.

6. DeSantis CE, Ma J, Jemal A. Trends in stage at diagnosis for young breast cancer patients in the United States. Breast Cancer Res Treat 2019;173:743-7.

7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Survivorship. V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 29, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

8. American Society of Clinical Oncology. Prevention and survivorship. Available at: https://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/survivorship-compendium-0-accessed. Retrieved October 21, 2019.

9. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. CA Cancer J Clin 2016;66:43-73.

10. Management of gynecologic issues in women with breast cancer. Practice Bulletin No. 126. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:666-82.

11. Faubion SS, Larkin LC, Stuenkel CA, Bachmann GA, Chism LA, Kagan R, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause 2018;25:596-608.

12. von Hippel C, Rosenberg SM, Austin SB, Sprunck-Harrild K, Ruddy KJ, Schapira L, et al. Identifying distinct trajectories of change in young breast cancer survivors' sexual functioning. Psychooncology 2019;28:1033-40.

13. Stabile C, Goldfarb S, Baser RE, Goldfrank DJ, Abu-Rustum NR, Barakat RR, et al. Sexual health needs and educational intervention preferences for women with cancer. Breast Cancer Res Treat 2017;165:77-84.

14. Meattini I, Desideri I, Francolini G, Vannini A, Perna M, Garlatti P, et al. Systemic therapies and cognitive impairment for breast cancer: an overview of the current literature. Med Oncol 2017;34:74.

15. Montazeri K, Unitt C, Foody JM, Harris JR, Partridge AH, Moslehi J. ABCDE steps to prevent heart disease in breast cancer survivors. Circulation 2014;130:157.

16. Rowe J, Schapmire T. The shady pink elephant: end of life education for young women affected by breast cancer [preprint]. J Cancer Educ 2018; DOI: 10.1007/s13187-018-1446-1.

17. Guth U, Huang DJ, Bitzer J, Moffat R. Unintended pregnancy during the first year after breast cancer diagnosis. Eur J Contracept Reprod Health Care 2016;21:290-4.

18. Dominick SA, McLean MR, Whitcomb BW, Gorman JR, Mersereau JE, Bouknight JM, et al. Contraceptive practices among female cancer survivors of reproductive age. Obstet Gynecol 2015;126:498-507.

19. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep 2016;65(RR-3):1-104.

20. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. Canadian Contraception Consensus (part 3 of 4): chapter 8 - progestin-only contraception. J Obstet Gynaecol Can 2016;38:279-300.

21. Patel A, Schwarz EB. Cancer and contraception. SFP Guideline #20121. Contraception 2012;86:191-8.

22. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis. Int J Clin Exp Pathol 2014;7:6419-29.

23. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. No. 329-Canadian Contraception Consensus part 4 of 4 chapter 9: combined hormonal contraception. J Obstet Gynaecol Can 2017;39:229-268.e5.

24. Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110-26.

25. Schrijver LH, Olsson H, Phillips KA, Terry MB, Goldgar DE, Kast K, et al. Oral contraceptive use and breast cancer risk: retrospective and prospective analyses from a BRCA1 and BRCA2 mutation carrier cohort study. EMBRACE, GENEPSO, BCFR, HEBON, kConFab, and IBCCS [published erratum appears in JNCI Cancer Spectr 2018;2:pky041]. JNCI Cancer Spectr 2018;2:pky023.

26. Azim HA Jr, Kroman N, Paesmans M, Gelber S, Rotmensz N, Ameye L, 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.

27. 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;110:426-9.

28. Valachis A, Tsali L, Pesce LL, Polyzos NP, Dimitriadis C, Tsalis K, 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.

29. Martinez MT, Bermejo B, Hernando C, Gambardella V, Cejalvo JM, Lluch A. Breast cancer in pregnant patients: A review of the literature. Eur J Obstet Gynecol Reprod Biol 2018;230:222-7.

30. Royal College of Obstetricians and Gynaecologists. Pregnancy and breast cancer. Green–top Guideline No. 12. London, UK: RCOG; 2011. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_12.pdf. Retrieved October 22, 2019.

31. International Breast Cancer Study Group. Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer (POSITIVE). ClinicalTrials.gov identifier: NCT02308085. Bethesda, MD: National Library of Medicine; 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT02308085. Retrieved October 22, 2019.

32. van den Belt-Dusebout, A. W., Spaan M, Lambalk CB, Kortman M, Laven JS, van Santbrink EJ, et al. Ovarian stimulation for in vitro fertilization and long-term risk of breast cancer. JAMA 2016;316:300-12.

33. Sergentanis TN, Diamantaras AA, Perlepe C, Kanavidis P, Skalkidou A, Petridou ET. IVF and breast cancer: a systematic review and meta-analysis. Hum Reprod Update 2014;20:106-23.

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;36:1994-2001.

35. Munhoz RR, Pereira AA, 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 meta-analysis. JAMA Oncol 2016;2:65-73.

36. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. Fertil Steril 2013;100:1214-23.

37. Oncofertility Consortium. Oncofertility decision tool web portal. Available at: http://oncofertility.northwestern.edu/resources/oncofertility-decision-tool-web-portal. Retrieved October 23, 2019.

38. American Cancer Society. Preserving fertility in women with cancer. Atlanta, GA: ACS; 2017. Available at: https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/fertility-and-women-with-cancer/preserving-fertility-in-women.html. Retrieved October 21, 2019.

39. 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 2017;32:1033-45.

40. Hickman LC, Llarena NC, Valentine LN, Liu X, Falcone T. Preservation of gonadal function in women undergoing chemotherapy: a systematic review and meta-analysis of the potential role for gonadotropin-releasing hormone agonists. J Assist Reprod Genet 2018;35:571-81.

41. 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.

42. Zavos A, Valachis A. Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. Acta Oncol 2016;55:664-70.

43. Rosenberg SM, Gelber S, Gelber RD, Krop E, Korde LA, Pagani O, et al. Oncology physicians' perspectives on practices and barriers to fertility preservation and the feasibility of a prospective study of pregnancy after breast cancer. J Adolesc Young Adult Oncol 2017;6:429-34.

