Zielińska Martyna, Zarankiewicz Natalia, Kosz Katarzyna, Kuchnicka Aleksandra, Aleksandrowicz Jakub, Książek Katarzyna, Mojsym Korybska Sylwia. Sexuality and fertility of young women suffering from breast cancer. Journal of Education, Health and Sport. 2019;9(4.S):175-185. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3358747
http://ojs.ukw.edu.pl/index.php/johs/article/view/7207
https://pbn.nauka.gov.pl/sedno-webapp/works/920356

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.07.2019. Revised: 25.07.2019. Accepted: 02.08.2019.

Sexuality and fertility of young women suffering from breast cancer

Martyna Zielińska[1], Natalia Zarankiewicz[1], Katarzyna Kosz[1], Aleksandra Kuchnicka[1], Jakub Aleksandrowicz[1], Katarzyna Książek[2] Sylwia Mojsym Korybska[3]

1. Students' Scientific Association of Chair and Department of Public Health, Medical University of Lublin
2. Chair and Department of Developmental Dentistry, Medical University of Lublin
3. Chair and Department of Public Health, Medical University of Lublin

Abstract

Breast cancer (BC) is the most common malignant tumor among women in the world. In Poland, it is the most commonly diagnosed cancer in women between the age of 25 and 44. The course of the disease in young women is more aggressive. As a result more aggressive anti-cancer therapies are used. BC treatment is associated with the occurrence of numerous adverse effects and long-term complications. Among them, sexuality and fertility disorders deserve special attention in the group of young patients.

The aim of this study is to review on the occurrence of sexual dysfunction and fertility disorders among young patients suffering from BC. The impact of BC treatment on the occurrence of these disorders has been analyzed. This review emphasizes also possible methods of sexual dysfunction and potential options of fertility protection which may be used in women who want to get pregnant after the end of the treatment.

This review is based on available data from medical publications and guidelines from 1987 to 2019, addressing issues of sexuality and fertility in young patients with breast cancer.
Young patients suffering from BC experience a variety of sexuality and fertility disorders. Sexual dysfunction includes among others: reduced libido, dyspareunia and difficulty in reaching an orgasm. The reason of the deterioration of the quality of sexual life is complex. Among the emotional factors, the most important role is played by changes in appearance, such as hair loss or breast amputation. Organic causes include dryness or loss of vaginal elasticity. The risk of fertility disorders is primarily associated with the use of cytotoxic drugs, causing premature ovarian failure and inducing amenorrhea. Chemotherapeutic agents with the highest risk of gonadotoxicity are alkylating drugs. Oncofertility is a branch of medicine combining oncology and reproductive medicine. Fertility protection of women who desire bearing a child after treatment is possible thanks to various methods of preservation. These include cryopreservation of embryos and oocytes, ovarian suppression with the use of GnRH analogs, ovarian transposition, freezing and transplantation of ovarian tissue. The most recommended method is embryo cryopreservation at present. Available data suggest no increased risk of cancer recurrence due to pregnancy in women after BC treatment.

Key words: breast cancer, young patients, sexuality, fertility, oncofertility

Introduction

Breast cancer (BC) is the most common malignancy among women in the world. According to the latest report of the World Health Organization (WHO) from 2018, there is 2,1 million newly diagnosed cases of breast cancer each year worldwide. Breast cancer is not only the most commonly diagnosed female cancer (24,2%), but also the leading cause of cancer death (15%) in women.[1] In Poland, there were 18615 new cases of BC in 2016. Almost 7 thousands (6943) patients suffering from BC died in Poland in 2016.[2]

BC in young women remains rare, because it affects only 4-6% of women under the age of 40. Nevertheless, it is the most common cancer among younger patients.[3] The National Cancer Registry states that in 2016 in Poland, there were 3563 (19%) new cases of BC among patients aged less than 50. 549 (7,9%) of all patients who died of BC in Poland in 2016, were below the age of 50.[2]

Biology of BC in young women appears to be different in comparison to older patients. These variations may be a reason of more aggressive disease course. Differences include changes in the expression of key biomarkers, such as proliferation markers, HER2, estrogen receptors (ER) and progesterone receptors (PR).[4] At diagnosis in younger patients, lesions are larger and less mature, less frequently ER-positive and PR-positive, with more cases of HER2 overexpression.[3,5] In another study similar results were obtained. Women under the age of 40 at diagnosis more often experienced larger tumors, nodal involvement, immature and endocrine receptor-negative tumors.[4,6] The study of California Cancer Registry also showed higher expression of HER2 in patients below the age of 40.[7] Furthermore, younger patients have also poorer outcome in comparison to their older peers. Basal cancers are considered to have the worst prognosis of all subtypes of BC. Unfortunately, it is found in 34% of patients <40 years, compared to 17% in older women.[3,4,8]

Young women face more aggressive cancers and, consequently, they are treated with more aggressive courses of treatment.[9] BC treatment is based on the use of various methods. Early stage tumors, regardless of age, are treated with radical or conservative breast amputation followed by adjuvant radiation. Breast-conserving surgery is more desirable in young patients due to better cosmetic results. However, breast-conserving surgery entails a higher risk of local recurrence. Various studies have shown that younger age is an important risk factor for local recurrence after partial mastectomy.[10] One study demonstrated a 9 times higher risk of relapse in patients aged less than 35 after breast-conserving surgery compared to patients >60 years old.[11] Similar results were found in another study, which proved that the risk of local recurrence was 5 times higher in patients <40 years after partial mastectomy in comparison to older women. The effect of age on the risk of relapse was not seen with full mastectomy.[12] Systemic therapy is also exploited in BC treatment and contains both chemotherapy and hormonal therapy in endocrine receptor-positive tumors. The gold standard in hormonal treatment is currently the use of tamoxifen, possibly with ovarian function suppression.[3]

Complex and aggressive anti-cancer therapy is associated with the occurrence of many negative side effects. Some studies showed that patients under the age of 45 were more vulnerable and sensitive to negative effects of disease and treatment with the greatest impact on changes in quality of life.[13,14] Among the adverse effects, sexual and fertility disorders deserve special attention in young patients. The occurrence of sexual dysfunction and fertility disorders significantly reduces the quality of life of patients during and after the treatment of BC.

Sexuality of young patients with breast cancer

Sexuality is a very important element in maintaining a high quality of life in healthy young women as well as in BC patients. Sexual dysfunction is notified by 9-43% of the overall population.[15] Cancer treatment increases the risk of sexual dysfunction due to the many extensive side effects of the therapy. Several studies have investigated the incidence of sexual disorders among young breast cancer survivors (YBCSs). The conclusion of the study carried out by Alder et al.[16] was that 68% of women treated for BC reported problems with sexual functioning. Another study showed that among patients who were still during the therapy, 64% experienced sexual dysfunction. Furthermore, 45% of women after completed treatment have still complained about reduction in quality of sex life.[17]

The quality of sexual life of women depends on many factors: psychological, medical, sociocultural and interpersonal. A disorder in any of these spheres may have a negative impact on sexual functioning. Medical factors include: age, BC treatment modality and its side effects, menopausal status, drugs and fatigue. Psychological factors are: emotional well-being, body image, self-esteem, sense of feminity. The most important interpersonal factor is the quality of relationship with a partner, but also social support, communication, the importance of breast and sex and prior sexual life with a partner.[18]

The deterioration of the quality of sexual life is associated with many factors, which can be divided into two main groups: emotional and organic reasons. Among the emotional factors, the most important role is played by changes in the appearance. Breast amputation and postsurgical extensive scars, skin lesions and discolorations after radiation therapy, changes in body weight and chemotherapy-induced alopecia are serious problems for young patients. These physical changes can result in psychological disorders, such as lower self-esteem, loss of a sense of femininity, loss of self-confidence, development of anxiety or even depression.[9,19,20] What is important, the loss of hair during the chemotherapy is perceived by women as the most depressing side effect of treatment and even more traumatic than loss of a breast.[20] The most pertinent organic cause of sexual dysfunction in YBCSs is premature ovarian failure induced by BC therapy. Premature ovarian failure results in lowering the level of estrogens. This leads to the occurrence of genitourinary symptoms of menopause, atrophic vaginitis, dryness and loss of elasticity of the vagina or increased vestibular tenderness.[21]

All the factors mentioned above have the negative impact on quality of sexual functioning and lead to development of sexual dysfunction. Young women suffering from BC experience several sexual disorders. A decrease in interest of sex becomes the first problem of deterioration of sex life. Patients complain about weakened libido. It is difficult for women to achieve

feelings of desire and sexual arousal. During the sexual intercourses, they can feel unable to relax and they can enjoy sex less than they did before the disease and the treatment. The common and major problem is also dyspareunia. Experiencing discomfort or even pain during sexual intercourses also discourages women from sexual activities. Another significant disturbance is incapacity to achieve orgasm. In the study conducted by Blouet et al.[19] orgasm was one of the most altered domains of sexuality in BC survivors. Other most altered domains in this study were desire and frequency of sexual activity. BC patients admit having sex less often than before the diagnosis. All of these disorders result in reduced satisfaction of sexual life in YBCSs.[9,19,20,22] Kedde et al.[22] have investigated also sexual behaviors and subjective sexual well-being of young women with breast cancer. Results of this study showed that young patients who were still undergoing BC treatment had a lower incidence of sexual fantasies, masturbated less frequently or did not masturbated at all and more often had no intimate contact with regular partner in the past 6 months in comparison to the Dutch population of healthy women. They experienced also more sexual stress, felt guilty about their sexual behavior and were less satisfied with the quality of their sexual life.

Sexuality is still commonly perceived as a taboo subject. Patients may be ashamed and afraid to address the problem of sexual dysfunction during the medical visit.[19] However, it is crucial to report sexual health issues. It is possible to provide an intervention, which can minimize sexual disorders. Pharmacotherapy of genitourinary symptoms of menopause is based on using vulvovaginal moisturizers, vaginal DHEA, low-dose vaginal estrogens and testosterone. Non-hormonal interventions remain a first-line choice, nonetheless, vaginal hormonal preparations are thought to be safe for BC patients. Therefore, vaginal hormonotherapy also can be used in some patients. The use of 4% aqueous lidocaine and vaginal dilatators may have a positive impact on increasing pleasure during sexual activity.[21] Besides, the quality of sexual life of YBCSs is significantly related to the quality of their relationships. Kinsinger et al. observed that women who were given more support from their intimate partners experienced fewer sexual difficulties.[23] Providing support for the couples and improving communication between partners is essential in order to maintain satisfactory sex life during and after BC treatment. Another method used with a view to improving intimate relationships among partners is sensate focusing or any other intimacy exercise.[21]

Fertility in breast cancer patients

Treatment of BC places young patients at a great risk of reduction in fertility or even infertility. A number of reasons can impact negatively on reproductive function in YBCSs. The major

cause of decreased fertility in reproductive age women is the prevalence of premature ovarian failure (POF). Unfortunately, POF is a common long-term complication of widely used cytotoxic therapies. The risk of following chemotherapy induced ovarian dysfunction depends on the patient age and on the type and dose of cytotoxic drug received during the therapy.[24,25] Chemotherapeutic agents act primary on primordial follicles and induce apoptosis in pregranulosa cells. These changes lead to the loss of oocytes and follicles.[10] The agent, which is considered to be the most gonadotoxic drug used in BC treatment, is cyclophosphamide. Cyclophosphamide and other alkylating agents cause the greatest harm to fertility because they affect not only actively diving cells but also non-active pregranulosa cells and oocytes.[26] Alkylating drugs reduce the reproductive lifespan due to reduction in primordial follicular reserve.[27] Platinum agents, anthracyclines and taxanes tend to be of moderate to low risk of developing fertility dysfunction.[28] Ovarian dysfunction caused by chemotherapy include temporary or permanent amenorrhoea. Amenorrhoea as an adverse effect of chemotherapy occurs in 40-68% of YBCSs.[10] Standard courses of radiation used in BC treatment does not cause significant ovarian toxicity.[29] Young women after breast cancer must also make a difficult decision about undergoing the procedures that inhibit ovarian function in order to reduce the risk of BC recurrence. For this purpose, ablative hormonotherapy (surgical, radiological or pharmacological) may be used.[9,28] Tamoxifen and aromatase inhibitors may be used in BC treatment additionally even for 10 years since diagnosis. This hormonal treatment is a contraindication to pregnancy.[28] The delay in pregnancy additionally reduces the chances of having a child after completing the treatment of breast cancer.[30]

Nowadays many women decide on delaying child bearing because of various reasons. In BC patients future fertility may be threatened because of the use of systemic therapies affecting ovarian function. Fortunately, fertility preservation is a promising option for those women who desire having a child after BC. It should be discussed with patients prior to initiating therapy.[21] It is reasoned to assume that fertility preservation is the priority for patients below the age of 40 who desire bearing a child.[10]

Preserving fertility in patients undergoing therapy that may impair reproductive potential is the main goal of oncofertility. Oncofertility is a new branch of medicine combining oncology and reproductive medicine. Oncofertility Poland is integrated into the Polish Society of Oncological Gynecology since 2015 and unites currently 12 centers from all over the country.[31,32]

At present, there are several potential options of fertility protection for young BC patients, including embryo cryopreservation, oocyte cryopreservation, cryopreservation of ovarian tissue, transplantation of ovarian tissue and ovarian suppression.[10,21,30,33,34] Embryo

cryopreservation is considered to be the most established and clinically available strategy. Achieving pregnancy due to this method is relatively effective and provides up to 35% chance of pregnancy.[10,30] One of the disadvantages is that it requires hormonal ovarian stimulation. The use of follicle-stimulating hormone (FSH) increases circulating estrogen level, which may worsen the prognosis of ER-positive BC cases. Substituting FSH with tamoxifen or aromatase inhibitors such as letrozole is safer option ensuring ovarian stimulation.[30,33,35] The necessity of delaying the onset of BC treatment for at least 2 weeks and the need of male partner or sperm donor are other drawbacks of this procedure.[30,34] Oocyte cryopreservation is an alternative method achieving similar reproductive results. This procedure is recommended especially for patients who do not have a male partner, do not want to use donor sperm or have religious or ideological objections to choose the method of embryo cryopreservation.[33] Cryopreserved ovarian tissue transplantation does not require sperm and hormonal stimulation. This method is still considered to be experimental, despite the fact that there have been already documented 40 pregnancies among patients after reimplantation of cryopreserved ovarian tissue.[10,33,34,36,37] The last method of preservating the ovarian function is ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists. This method may be considered only in BC patients with endocrine receptor-negative tumors.[33,38] The efficacy of ovarian suppression in fertility preservation is not confirmed and side effects of this method are unknown.[30]

Pregnancy following breast cancer treatment

Numerous studies have researched the safety of pregnancy after BC. Available data show no increased risk of relapse due to pregnancy, even in patients with hormone-positive malignancies.[21,33,39] Interestingly, patients who became pregnant in less than 2 years after the diagnosis had a longer disease-free survival compared to women who did not get pregnant. This fact suggests that pregnancy after breast cancer may even play a protective role and reduce the risk of death of 41%.[40] There are no confirmed recommendations for the timing of safe conception after completed breast cancer treatment. This time varies from 2 to 5 years. It is advisable to wait until adjuvant therapies are completed, especially in women at higher risk of relapse.[21] Furthermore, cytotoxic drugs used in BC therapy do not increase the risk of congenital abnormalities in children of YBCSs. Low birth weight and preterm deliveries were observed in 40% of pregnancies in the study of Mulvihill et al.[41] A high proportion of miscarriages (29%) was reported. Although, this is explained by ovarian dysfunction after chemotherapy and the older age of breast cancer survivors.[42]

Conclusions

Aggressive breast cancer therapy results in the frequent occurrence of sexuality and fertility disorders in young patients. It is highly important to remember that maintaining high quality of sex life and protecting fertility are currently priorities for most patients under the age of 40. Oncofertility increases the chance of having a child by women after breast cancer treatment. And most importantly - current knowledge suggests that pregnancy after breast cancer is safe and does not increase the risk of relapse.

References

1. International Agency for Research on Cancer, World Health Organisation, *Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018*, 2018
2. http://onkologia.org.pl/raporty/
3. Radecka B., Litwiniuk M., *Breast cancer in young women*, "Ginekologia Polska" 2016, 87, 9: 659-663
4. Azim H.A., Partridge A.H., *Biology of breast cancer in young women*, "Breast Cancer Research" 2014, 16:427-435
5. Anders C.K., Fan Ch., Parker J.S., *Breast carcinomas arising at a youngage: unique biology or a surrogate for aggressive intrinsic subtypes?*, "J Clin Oncol." 2011, 29:18–20
6. Gnerlich J.L., Deshpande A.D., Jeffe D.B., Sweet A., White N., Margenthaler J.A., *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, 208:341–347
7. Keegan T.H., DeRouen M.C., Press D.J., Kurian A.W., Clarke C.A., *Occurrence of breast cancer subtypes in adolescent and young adult women*, "Breast Cancer Res" 2012, 14:R55
8. Azim H.A., Michiels S., Bedard P.L., Singhal S.K., Criscitiello C., Ignatiadis M., Haibe-Kains B., Piccart M.J., Sotiriou C., Loi S., *Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling*, "Clin Cancer Res" 2012, 18:1341–1351
9. Hungr C., Sanchez-Varela V., Bober S.L., *Self-image and sexuality issues among young women with breast cancer: practical recommendations*, "Revista de Investigacion Clinica" 2017, 69:114-122
10. Kasum M., Beketić-Oreškovićb L., Peddic P.F., Slavko O., Johnson R.H., *Fertility after breast cancer treatment*, "European Journal of Obstetrics & Gynecology and Reproductive Biology" 2014, 173:13-18
11. Voogd A.C., Nielsen M., Peterse J.L., *Difference on risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials*, "J Clin Oncol" 2001, 19:1688–97
12. Arriagada R., Le M.G., Contesso G., Guinebretiere J.M., Rochard F., Spielmann M., *Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer*, "Ann Oncol" 2002, 13:1404–1413

13. Préau M., Bouhnik A.D., Le Coroller Soriano A.G., Two years after cancer diagnosis, what is the relationship between health-related quality of life, coping strategies and spirituality?, "Psychol Health Med." 2013, 18:375–386

14. Baucom D.H., Porter L.S., Kirby J.S., Gremore T.M., Keefe F.J., *Psychosocial issues confronting young women with breast cancer*, "Breast Dis" 2005, 23:103–113

15. Habold D., Bondil P., *L'intervention sexologique en oncologie*, "Presse Med" 2014, 43:1120-1124

16. Alder J., Zanetti R., Wight E., Urech C., Fink N., Bitzer J., *Sexual dysfunction after premenopausal stage I and II breast cancer: do androgens play a role?*, "J Sex Med" 2008, 5(8):1898–906

17. Kedde H., Van de Wiel H.B.M., Weijmar Schultz W.C.M., Wijsen C., *Sexual dysfunction in young women with breast cancer*, "Support Care Cancer" 2012, 21:271–280

18. Jankowska M., *Sexual functioning in young women in the context of breast cancer treatment*, "Reports of practical oncology and radiotherapy" 2013, 18:193–200

19. Blouet A., Zinger M., Capitain O., Landry S., Bourgeois H., Seegers V.T., Pointreau Y., *Sexual quality of life evaluation after treatment among women with breast cancer under 35 years old*, "Support Care Cancer" 2019, 27:879–885

20. Ghizzani A., Bruni S., Luisi S., *The sex life of women surviving breast cancer*, "Gynecological Endocrinology" 2018, 34(10):821-825

21. Lopresti M., Rizack T., Dizon D.S., *Sexuality, fertility and pregnancy following breast cancer treatment*, "Gland Surg" 2018, 7(4):404-410

22. Kedde H., Van de Wiel H.B.M., Weijmar Schultz W.C.M., Wijsen C., *Subjective sexual well-being and sexual behavior in young women with breast cancer*, "Support Care Cancer" 2013, 21:1993–2005

23. Kinsinger S.W., Laurenceau J.P., Carver C.S., Antoni M.H., *Perceived partner support and psychosexual adjustment to breast cancer*, "Psychol Health" 2011, 26:1571-1588

24. Lee S.J., Schover L.R., Partridge A.H., Patrizio P., Wallace W.H., Hagerty K., Beck L.N., Brennan L.V., Oktay K., *American Society of Clinical Oncology recommendations on fertility preservation in cancer patients*, "J Clin Oncol" 2006, 24:2917–2931

25. Dabrosin C., *An overview of pregnancy and fertility issues in breast cancer patients*, "Annals of medicine" 2015, 47(8):673-678

26. Partridge A.H., Ruddy K.J., *Fertility and adjuvant treatment in young women with breast cancer*, "Breast" 2007, 16:175-181

27. De Pedro M., Otero B., Martin B., *Fertility preservation and breast cancer: a review*, "Ecancer Medical Science" 2015, 9:503
28. Ronn R., Holzer H., *Breast cancer and fertility: an update*, "Wolters Kluwer Health" 2015, 9(3):285-293
29. Gracia C.R., Chang J., Kondapalli L., *Ovarian tissue cryopreservation for fertility preservation in cancer patients: successful establishment and feasibility of a multidisciplinary collaboration*, "Journal of Assisted Reproduction and Genetics" 2012
30. Hickey M., Peate M., Saunders C.M., Friedlander M., *Breast cancer in young women and its impact on reproductive function*, "Human Reproduction Update" 2009, 15(3):323–339
31. http://oncofertility.pl/
32. http://oncofertility.pl/osrodki/
33. Zalecenia Grupy Roboczej ds. Zachowania Płodności u Chorych Onkologicznych i Chorych Hematologicznych oraz Innych Chorych Leczonych Terapiami Gonadotoksycznymi "ONCOFERTILITY" (GROF) Polskiego Towarzystwa Ginekologii Onkologicznej, 2017
34. Christinat A., Pagani O., *Fertility after breast cancer*, "Maturitas" 2012, 73:191– 196
35. Oktay K., Buyuk E., Libertella N., Akar M., Rosenwaks Z., *Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation*, "J Clin Oncol" 2005, 23:4347–53
36. Oktay K., Buyuk E., Veeck L., *Embryo development after heterotopic transplantation of cryopreserved ovarian tissue*, "Lancet" 2004, 363:837–840
37. Donnez J., Dolmans M.M., Pellicer A., *Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation*, "Fertil Steril" 2013, 99:1503–1513
38. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
39. Schover L.R., Kaaij M., Dorst E., Creutzberg C., Huyghe E., Kiserud C.E., *Sexual dysfunction and infertility as late effects of cancer treatment*, "EJC Supplements" 2014, 12:41-53
40. Azim H.A., Santoro L., Pavlidis N., *Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies,* "Eur J Cancer" 2011, 47:74-83
41. Mulvihill J.J., McKeen E.A., Rosner F., Zarrabi M.H., *Pregnancy outcome in cancer patients*, "Cancer" 1987, 60:1143–50
42. Blakely L.J., Buzdar A.U., Lozada J.A., *Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence,* "Cancer" 2004, 100:465–469