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REVIEW ARTICLE

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Breast cancer in young women

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ABSTRACT

Caring for young breast cancer patients is a challenge for different medical specialists. An introduction of more effective agents results in improved outcomes. At the same time, the quality of life after cancer becomes more important. The problems of young women who develop breast cancer differ from those that apply for older patients. It applies especially to fertility impairment due to systemic therapy. In recent years, new guidelines for the treatment and management of young breast cancer patients in certain specific situations have been developed. The article presents the comprehensive approach to care for young breast cancer patients. The current principles of treatment, recommended by scientific societies, were discussed. The following specific clinical issues were addressed: fertility after chemotherapy, the methods of fertility preservation, pregnancy and breastfeeding after breast cancer, breast cancer in pregnant women, and contraception.

Key words: contraception, chemotherapy, pregnancy, fertility, breast cancer

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Introduction

Breast cancer is the most frequent cancer in women in Poland — in 2012 the number of new cases reached 17,000. It represents the second-most frequent cause of cancer deaths in women — 5574 deaths from breast cancer were registered in 2012. Eighty per cent of cases are breast cancers in women of age of 50 years or more [1]. In recent decades a continuously increasing incidence of this cancer has been observed, with an increasing number of cases in premenopausal women. Young women represent a specific group of patients with breast cancer. This is because of the differences resulting from diverse tumour biology, specific treatment strategies, and unique problems of this group of patients.

The European School of Oncology (ESO) and European Society of Breast Specialists (EUSOMA) have recently published a consensus regarding the treatment of young women with breast cancer [2]. Then European Society for Medical Oncology (ESMO) elaborated the guidelines regarding the issue of pregnancy and fertility in cancer patients [3]. However, the American Society of Clinical Oncology (ASCO) prepared recommendations on indications and methods of fertility preservation in this group of patients [4]. Some issues regarding the care of young women with breast cancer have been mentioned in the recently published consensus of St. Gallen 2015 [5].

In the article the aforementioned recommendations are discussed, and the issues regarding the treatment of young women with breast cancer based on the results of latest clinical trials in this group are presented.

Epidemiology and risk factors

According to conventional definitions, young women with breast cancer are those who were diagnosed at or before 40 years, and very young patients are women with a diagnosis of breast cancer at age of 35 or below [2, 6]. The percentage of young patients with breast cancer is similar in different countries and represents 5–6% of all breast cancer cases [7, 8]. However, the trend of continuously increasing incidence is observed. At the end

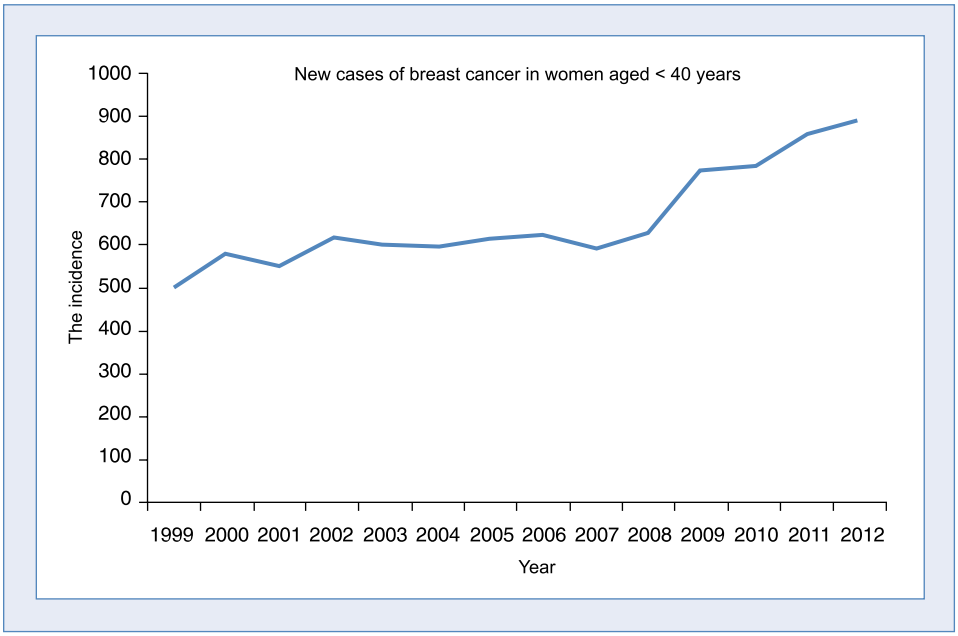

Figure 1. The incidence of breast cancer in young women in Poland in 1990–2012

of the twentieth century there were about 500 new cases of breast cancer in young women diagnosed in Poland, while in 2012 there were nearly 900 new cases (Fig. 1), which is almost equal to the number of all new cases of testicular cancer or gallbladder cancer [1].

The risk factors for breast cancer are similar to risk factors for general populations and include early first menstruation, late first delivery, lack of breast feeding, low progeny, family history of breast cancer and/or ovarian cancer, and use of oral contraception [9–11]. Genetic changes significantly more frequently predispose to breast cancer in young women. There are many more *BRCA1/2* mutations in young patients with breast cancer. In a clinical trial conducted in the United States in 89 consecutive young patients undergoing breast conservation treatment, genetic tests for *BRCA1* and *BRCA2* were performed. The mutations were found in 9% of patients [12]. This result found reflection in the recommendations referring to tests for assessment of *BRCA* status. The Polish Society of Clinical Oncology (PTOK, Polskie Towarzystwo Onkologii Klinicznej) recommends performing genetic testing in every woman who develops breast cancer before age 40 [13]. It should be emphasised that standard screening can detect only the most frequent mutations as well as large genome rearrangements (aberrations), so there is still a risk of not detecting rare mutations. The similar recommendations for *BRCA* status testing were elaborated by the ESO along with the EUSOMA and National Comprehensive Cancer Network (NCCN); nowadays it is recommended to perform tests in women under 45 years old [2, 14]. The problem of BRCA mutations in young patients is discussed later in the article.

The data regarding an influence of body mass index (BMI) of young women on the risk of breast cancer development are ambiguous. There were publications indicating the lack of correlation between high BMI and breast cancer risk, as well papers suggesting the protective influence of high BMI (in contrast to postmenopausal women) [15, 16]. The issue requires further investigation.

The diagnosis and biology of breast cancer in young patients

The diagnosis of breast cancer in young patients is often delayed, for a number of reasons. The screening program is addressed to older women (50–69 years old) due to higher incidence of breast cancer in this population. Also among young women, in cases of the appearance of suspicious lesions in breast it is often not recognised as a cancer risk, which delays the medical consultation and the undertaking of necessary activities [17]. The diagnosis of breast cancer in young patients is usually established when evidence suggestive of cancer symptoms appears (palpable painless tumour in breast). Breasts in premenopausal women consist of dense glandular tissue that makes the detection by mammography of early lesions difficult or even impossible. This is why an ultrasound examination is performed as well as mammography. Moreover, magnetic resonance imaging (MRI) of the breast can be considered in selected cases, especially if a genetic background of the disease is suspected. However, MRI is not recommended as a standard diagnostic procedure in young

women because it does not influence the results of the treatment (percentage of local recurrences and distant metastases) [2, 18].

Breast cancer in young women has a more aggressive course than in older patients. This is a result of its detection in more advanced stage secondary to delayed diagnosis, as well as more aggressive biology of breast cancer subtypes more frequently recognised in this group of patients — triple negative — or with over-expression of human epidermal growth factor receptor 2 (HER2) [9, 20]. In a prospective study (POSH, Prospective Study of Outcomes in Sporadic and Hereditary Breast) conducted in Great Britain on 2956 women aged ≤ 40, 24% of breast cancers presented HER2 over-expression and 19.9% of cases were triple negative [21]. Additionally, the histological grade of breast cancers in young women is often high (G3) [20]. These factors imply worse results of treatment [22].

Genetic consulting

As mentioned previously, every young woman with breast cancer should be offered a consultation in a genetic outpatient clinic for adequate tests to be performed. *BRCA1* and *BRCA2* mutational status assessment is the most frequently performed screening test. During expanded diagnostics the mutations of *CHEK2*, *NSB1* as well as *TP53* are searched for. The information regarding the detection of mutations is of great importance for women and their close families. During the consultation a genetic specialist discusses the test results and gives precise recommendations for subsequent procedures to be followed. In the case of detection mutations in *BRCA1/2*, women should be recommended to participate in a medical care program. One should consider the potential psychological effect of this situation on mental wellbeing, especially in young women. According to guidelines, *BRCA1/2* mutation carriers should undergo prophylactic adnexectomy before age 40, which means the next surgery procedure in the course of treatment in cases of early breast cancer [13, 14]. Additionally, the prophylactic mastectomy should be taken into consideration, which is in accordance with recommendations of the PTOK, ESMO, and NCCN [13, 14, 23, 24]. If the patient refuses to undergo prophylactic surgery, she should be ensured access to breast imaging (mammography and MRI alternately every six months) as well as gynaecological imaging (trans-vaginal ultrasound examination with CA125 evaluation every six months). The risk of cancer in this population is high and the clinical stage of the disease advanced, despite the performance of screening tests (especially in ovarian cancer).

The patient should be referred for genetic consultation as soon as possible in the course of treatment because the result of genetic testing may influence the treatment [2]. It has been proven that in the case of breast cancer in *BRCA1* mutation carriers, the ovariectomy is the factor that prolongs the overall survival (OS) [HR (hazard ratio) = 0.30; 95% CI (confidence interval): 0.12–0.75; p = 0.01] [25]. The surgical procedure significantly decreases the risk of death from ovarian cancer, fallopian tube cancer, and cancer of the peritoneum in *BRCA1/2* carriers (HR = 0.20: 95% CI: 0.13–0.30; p < 0.001) [26, 27].

In case of detection of mutations in *CHEK2*, *NSB1*, or *TP53* women should also be offered participation in medical care and supervision programs.

Treatment of localised breast cancer

The treatment rules for young women with breast cancer are generally similar to those that apply to older patients. However, there are some differences that mainly regard hormone therapy.

Surgery

The methods of surgery in young women do not differ from these used in older patients with breast cancer. In every case, if possible, the procedure of breast conserving should be discussed with the patient. In young women the final aesthetic result is very important as it influences the appearance and sexuality. If there are indications for mastectomy, skin-sparing mastectomy and nipple-sparing mastectomy with immediate reconstruction should be considered [2].

The percentage of local recurrences in young women who undergo breast-conserving treatment is higher when compared with the mastectomy group. However, the method of surgery does not influence the OS in these patients, which has been confirmed by a meta-analysis in 22,000 young women with breast cancer, published in 2015 [28, 29]. Nonetheless, breast-conserving treatment is the preferred method of treatment [2].

Similarly to older patients, in the case of unsuspected axillary lymph nodes the procedure of sentinel node is recommended. There is no evidence that sentinel node biopsy leads to worse results of treatment in young patients [30]. However, the numbers of young patients recruited to clinical trials, when comparing the axillary lymphadenectomy to sentinel node biopsy in case of non-enlarged lymph nodes, were low, which also reflects the incidence of breast cancer in women under 40.

Recently the results of some relevant clinical trials regarding the strategy of treatment in case of sentinel nodes positive for metastatic lesions have been published. Z0011 was one such trial, which failed to confirm the benefits of axillary lymphadenectomy in patients who

underwent breast conserving treatment in case of unsuspected lymph nodes (cN0) and detection of metastatic lesions in 1–2 of the axillary lymph nodes [31]. During the analysis of these results one should remember that the trial had a non-inferiority design. Originally there was an assumption to recruit 1900 patients, but finally 891 patients were enrolled. Additionally, there was the significant imbalance between groups in terms of the incidence of micro-metastatic and macro-metastatic lesions in sentinel lymph nodes (micro-metastases were detected more frequently in patients referred for observation: 45% vs. 38%). The median age in the group was 56 years (24–92 years); the authors did not provide the percentage of women under the age of 40.

In the International Breast Cancer Study Group (IBCSG) 23-01 trial the role of axillary lymphadenectomy in case of detection of micro-metastatic lesions in sentinel lymph nodes of breast cancer patients was evaluated [cT1-2 cN0; in 92% of patients the tumour was < 3 cm; in 95% of cases there was one micro-metastatic lesion; median age 54 years (26–81 years), 44% of premenopausal patients] [32]. The results of the treatment were comparable in both groups. It has been documented that the axillary lymphadenectomy can be omitted, especially in patients with small tumours revealing high expression of steroid receptors with one micro-metastatic lesion in sentinel lymph nodes, who underwent the breast conserving surgery and tangential field radiation therapy of whole breast with subsequent systemic treatment.

In the ARAMOS trial comparing axillary lymphadenectomy to the irradiation of an axillary fossa in breast cancer patients (cT1-2 cN0) after a breast conserving surgery or mastectomy with macro- or micro-metastatic lesions or isolated cancer cells in the sentinel node, the young women were not enrolled [33].

It should be stressed during the analysis of the results of the aforementioned trials that in one-third of patients with metastases in sentinel lymph nodes (micro-metastatic, macro-metastatic lesions or an isolated cancer cells) other metastatic lesions have been detected in patients who underwent axillary lymphadenectomy [31, 33].

Breast reconstructions

Reconstructive surgery of the breast is extremely important in young women due to their quality of life and the final cosmetic result. Optimally, such procedures should be well planned before the surgery of the breast cancer. The progress in oncoplastic surgery allows the choice of the optimal surgery technique for the unique clinical situation — for example, implant insertion or free skin patch with vascular anastomosis.

Adjuvant radiation therapy

After breast conserving surgery for invasive breast cancer adjuvant radiation therapy of whole breast field is required in a standard total dose of 50 Gy delivered in fractions of 2 Gy or by strategy of mild hypo-fractionation to total dose of 40–45 Gy in fractions of 2.25–2.7 Gy. Additionally, the standard boost of 10 Gy is administered on the post-operative bed. As mentioned earlier, young age is a factor increasing the risk of local recurrence after breast conserving surgery, especially in the post-operative bed [34]. For that reason, in young women with additional unfavourable risk factors for local recurrence the individual decision to increase the boost dose to 16 Gy on the post-tumoural bed may be considered [35, 36].

It has been also shown that the risk for local recurrence in young women who have undergone mastectomy is higher when compared to the population of older patients. The rate of local post mastectomy recurrences in women in age < 35 years reached 12.5% in one of the clinical trials [37]. Recently the results of analysis regarding the role of adjuvant radiation therapy in women after mastectomy in age ≤ 35 years have been published [38]. This strategy proved its efficacy by statistically meaningful reduction of risk for loco-regional recurrence (HR = 0.54; 95% CI: 0.2–0.996). However, post-operative radiation therapy does not affect either the rate of recurrences or OS.

According to the St. Gallen 2015 consensus there are indications for adjuvant radiation therapy as follows [5]:

— in the case of breast-conserving surgery with no metastatic lesions in the lymph nodes detected (pN0) it is only the breast that should be irradiated; in case of documented metastatic lesions in lymph nodes (pN+) the field of the radiation therapy should also comprise the regional lymph nodes;
— after mastectomy if:
  - the tumour size is ≥ 5 cm;
  - there are metastatic lesions detected in four or more lymph nodes;
  - there are metastatic lesions detected in 1–3 lymph nodes in patients with breast cancer with unfavourable phenotype;
  - there is a macro-metastatic lesion in the sentinel node and no axillary lymphadenectomy is planned.

The treatment in case of the metastatic lesions in sentinel lymph nodes may vary — from omitting the axillary lymphadenectomy with subsequent tangential radiation therapy of the breast and the two levels of lymph nodes in the axillary fossa to the need for the resection of axillary lymph nodes.

Peri-operative chemotherapy

Adjuvant chemotherapy

According to St. Gallen 2015 recommendations the decision of adjuvant chemotherapy should not be based on the age of the patient as the only risk factor [5]. For that reason, the decision regarding chemotherapy should be based on the same strategy as in the general population of patients with breast cancer.

In luminal tumours chemotherapy is indicated in cases of:

— high histology grade of cancer (G3);
— the detection of metastatic lesions in ≥ 4 lymph nodes;
— low expression levels of steroid receptors;
— high Ki-67 proliferation index;
— massive infiltration of the lymph vessels and blood vessels.

In luminal A tumours chemotherapy is indicated especially in cases of metastatic involvement with breast cancer of ≥ 4 lymph nodes [39]. The older regimens, like AC or CMF, should be used in such cases because there is no strong evidence for advantages of regimens containing anthracyclines and taxanes.

In luminal B tumours adjuvant chemotherapy is recommended in most cases. In so-called Oxford analysis the regimens containing anthracyclines and taxanes proved to be beneficial in this group of patients; however, in luminal B tumours and lower risk of recurrence regimens based only on anthracyclines can be considered.

In HER2-positive cancers targeted therapy is important. Chemotherapy with anthracyclines and taxanes along with the trastuzumab is the standard of care, and at the latest should be started simultaneously with the taxane. The use of paclitaxel monotherapy (12 infusions administered every week) in combination with trastuzumab administered during a one-year period in highly selected patients with small cancers (tumour < 2 cm, pN0) is a novel option that may be considered. It is based on the results of single-arm phase II trial [40]. NCCN recommendations allow the use of this regimen in small cancers in I clinical stage with low risk of recurrence [36]. Patients under 50 years old represented 1/3 of the women enrolled in the study.

In the group of patients with triple-negative breast cancer chemotherapy based on anthracyclines and taxanes remains the standard of care. In this group dose-dense chemotherapy regimens may be considered, e.g. in patients with luminal B tumours and high risk of recurrence. The European Society for Medical Oncology recommends dose-dense chemotherapy in tumours with high Ki-67 proliferation index [24]. Young patients with breast cancer are suitable candidates for dose-dense chemotherapy due to their usually good performance status and no co-morbidities.

Preoperational chemotherapy

Locally advanced breast cancer

The preoperational systemic treatment of young women consists of chemotherapy. To date no clinical trial has proven the safety of preoperative hormone therapy in premenopausal women. Targeted therapy should be a part of the preoperative treatment in HER2-positive tumours. According to the St. Gallen 2015 consensus it should be the combination of pertuzumab with trastuzumab because it is recommended in older populations of patients [5].

Primarily resectable breast cancer

There is growing evidence of clinical trial results published recently indicating the benefits of preoperative therapy in patients with resectable breast cancer. It concerns so-called triple-negative and HER2-positive breast cancer. These subtypes of breast cancer, which have already been mentioned, are more frequent in the population of young women. This strategy is extremely interesting because it allows the performance of breast conserving surgery [41].

Adjuvant hormone therapy

The method of adjuvant treatment that differs the most in young women is hormone therapy.

In 2014 the results of two phase III clinical trials were published: the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), both indicating the new possibility for hormone therapy [42, 43]. Both trials were conducted by IBCSG in premenopausal patients with localised breast cancer with expression of steroid receptors (positivity was defined as ER/PgR ≥ 10%). A total of 5738 of patients were enrolled. The TEXT trial compared the treatment with exemestane and ovarian suppression to tamoxifen with ovarian suppression. In the SOFT trial, in which two arms were similar to the TEXT trial, a third arm was added that was treated with tamoxifen. In both trials peri-operative chemotherapy was allowed. The GnRH agonist — triptorelin was used for ovarian suppression, and alternatively either bilateral adnexectomy or irradiation of the ovaries was performed. Hormone therapy including treatment with triptorelin was conducted for five years in each of the study arms. It should be emphasised that 25% of patients enrolled to both trials were women under 40.

In the SOFT trial analysis to assess the influence of ovarian suppression as an addition to tamoxifen was performed. The benefit of such intervention was not achieved in the whole patient population. The five-year disease-free survival (DFS) was 86.6% if ovarian sup-

pression was undertaken versus 84.7% in the tamoxifen arm. There was no statistically significant difference in OS either (after five years of follow-up it was 97% and 95%, respectively). However, there was an advantage of ovarian suppression in patients after chemotherapy, whose menopausal status had not changed (their serum estradiol concentration was the same when compared to premenopausal period) (the percentage of five-year survival in patients who underwent chemotherapy: in the tamoxifen + ovarian suppression arm 95% versus 91% in the tamoxifen arm; HR = 0.64; 95% CI: 0.42–0.96). The differences in five-year disease-free survival in patients whose serum estradiol concentration was at the premenopausal level should be noted — in the tamoxifen arm it was 78% and 83%, respectively, if tamoxifen was administered with ovarian suppression, while it was the highest and achieved 86% in the arm of exemestane with ovarian suppression.

Moreover, the ovarian suppression improved the results of treatment in young patients (< 35 years old). In this population the chemotherapy had been administered in 94% of women. In the group of very young patients the highest 5-years disease-free survival was observed in those subsequently treated with exemestane in combination with the ovarian suppression (83%), while in the arm of tamoxifen combined with ovarian suppression it reached 79% and in the tamoxifen monotherapy arm 68%, respectively.

The comparison of two combined groups of the SOFT and TEXT trials was made to evaluate the efficacy of the exemestane and tamoxifen used along with ovarian suppression. The five-year disease-free survival in women receiving exemestane reached 91% and in the tamoxifen group 87%, respectively (HR for disease recurrence, second breast cancer or death = 0.72; 95% CI: 0.55–0.8; p < 0.001). However, the overall survival was similar in both groups.

Adverse events of intensity grade ≥ 3 were observed in 24% of patients receiving tamoxifen versus 31% in patients with additional suppression of ovaries. Hot flushes, sweats, decreased libido, vaginal dryness, insomnia, mood alterations, side effects from muscle and bones, as well as hypertension, glucose intolerance (including diabetes mellitus), and osteoporosis were more frequent in the group of the women receiving ovarian suppression.

The rates of grade ≥ 3 adverse events were comparable in patients under the ovarian suppression receiving tamoxifen or exemestane. Osteoporosis was more frequently observed in patients treated with exemestane (13% vs. 6% in patients receiving tamoxifen with ovarian suppression). Moreover, the incidence of bone fractures, side effects from muscles and joints, vaginal dryness, decreased libido, and dyspareunia was higher in the exemestane group. On the other hand, thromboembolic events, flushes, sweats, and urine incontinence were observed more frequently in the tamoxifen group receiving also the ovarian suppression.

The high rate of patients who did complete the scheduled treatment with tamoxifen or exemestane (11–22%) should be noticed. There were similar rates of incompliance observed in the ovarian suppression.

The data published previously identified the problem with drug compliance during the treatment with tamoxifen especially in young women. In a trial assessing the population in Great Britain 51% of patients under the age of 40 did not complete the treatment scheduled for five years [44]. These results indicate the need for verification of patients' compliance — for example, monitoring of drug compliance during scheduled appointments.

At the beginning of 2015, after a median follow-up of 94 months, the final analysis results of the Austrian Breast and Colorectal Cancer Study Group Trial (ABCSG-12) were published [45]. The trial evaluated treatment with zoledronic acid (4 mg every six months for years years) in combination with adjuvant hormone therapy (goserelin + tamoxifen/anastrozole) in 1803 premenopausal women. The median age was 45 years, and about 20% of patients were under the age of 40. The results of this trial differ from analysis of the SOFT and TEXT trials — the OS was significantly worse in patients treated with a combination of anastrozole and goserelin (HR = 1.63; 95% CI: 1.05–2.52; p = 0.03) with no difference in DFS.

According to the St. Gallen 2015 consensus, in premenopausal women with low risk of recurrence of breast cancer hormone therapy with tamoxifen is indicated. However, ovarian suppression is additionally indicated in patients:

— in age ≤ 35 years;
— with oestrogen serum concentration after the adjuvant chemotherapy at the premenopausal level (in the SOFT trial the ovarian suppression has been introduced within eight months of chemotherapy completion, if the serum estradiol concentration had been at the premenopausal level, patients were allowed to be treated with hormone therapy [43]);
— with metastatic lesions documented in ≥ 4 axillary lymph nodes;
— moreover, it should be considered in patients with G3 tumours or unfavourable results of molecular testing (such tests like: Oncotype DX, MammaPrint, PAM-50 ROR score, EndoPredict, Breast Cancer Index may be used for assessment of individual risk for recurrence in the first five years after breast cancer diagnosis).

Ovarian suppression should be continued for five years in combination with tamoxifen or exemestane. The combination with exemestane is indicated especially in the case of involvement of ≥ 4 lymph nodes;

Table 1. The risk of relevant ovarian dysfunction secondary to use of cytotoxic agents in patients with breast cancer (according to the American Society of Clinical Oncology)

The risk of ovary dysfunction	The cytotoxic agent/ the regimen of chemotherapy	Comments
High risk (> 70%)	Cyclophosphamide (total dose)	5 g/m^2 in women > 40 years old or 7.5 g/m^2 in women < 20 years old
Intermediate risk (30–70%)	Cyclophosphamide (total dose)	5 g/m^2 in women in age of 30–40 years
	AC	4 cycles of AC + paclitaxel or docetaxel in women < 40 years old
Low risk (< 30%)	Regimens containing cyclophosphamide: CMF, FEC, FAC	Women < 30 years old
Unknown risk	Trastuzumab	

AC — doxorubicin + cyclophosphamide; CMF — cyclophosphamide + methotrexate + 5-fluorouracil; FEC — 5-fluorouracil + epirubicin + cyclophosphamide; FAC — fluorouracil + doxorubicin + cyclophosphamide

such treatment can also be considered in patients with age ≤ 35 years, with unfavourable results of molecular testing, or if a high grade breast cancer (G3) is diagnosed.

Prolonged hormone therapy (lasting 10 years) should be considered in patients with metastatic involvement of axillary lymph nodes or with other unfavourable factors found in histology report. In such cases after 5 years of treatment tamoxifen or letrozol should be used (if the patient is post-menopausal).

In premenopausal women hormone therapy should not be used as a preoperative treatment [24].

Unique problems of young women

Fertility disorders

Systemic treatment decreases fertility in most patients. The ovarian function after systemic therapy for breast cancer depends on the age of the patient at the time of chemotherapy use, the type and total dose of cytotoxic agents, and tamoxifen use because of the long period of time during which it is administered (5–10 years) [46].

Women giving birth for the first time are nowadays older by several years when compared to former decades. According the reports of the Główny Urząd Statystyczny (National Statistical Office) there has been an increase in the number of children born from women in age of 30–34 years with a secondary increase in the median age of women giving birth (in 1990 — 26 years, in 2012 — 29 years). There is also an increase in the median age of women at the time of giving birth for the first time. In 2012 mothers aged ≥ 30 years represented 43% and aged ≥ 35 years — 14%, and in 1990 it was 27% and 10%, respectively [47]. The data points to the fact that nowadays more and more women at the time of diagnosis of breast cancer do not have progeny or have not completed their plans regarding maternity.

The next important factor that influence the ovarian function is the type of cytotoxic agents used and their doses (Table 1). There are two distinct mechanisms that may lead to ovary impairment /damage as a result of chemotherapy administration: direct enhancement of apoptosis in ovarian follicles and oocytes as well as damage in ovarian blood vessels [48, 49]. The alkylating agents, especially cyclophosphamide, as a part of many regimens of adjuvant chemotherapy administered in breast cancer, significantly restricts the ovarian reserve that is the pool of ovular cells [51]. It has been proven that the administration of cyclophosphamide in a total dose of 2.4–3 g/m^2 in 12–16 weeks (like it is in AC, FAC, FEC, TC, and TAC regimens) leads ovaries to "age" by about 10 years [50]. There have been attempts to administer the adjuvant chemotherapy regimens without cyclophosphamide in young women. There is an ongoing TRIUMPH trial that address this question. Just a few years ago the AT regimen containing doxorubicin and docetaxel was still administered most frequently as the pre-operative treatment. However, due to the lower toxicity of sequential chemotherapy and its comparable or even higher efficacy shown in some trials, the AT regimen is currently used less often [24, 41]. By contrast, women with *BRCA1/2* mutations are more exposed to earlier occurrence of menopause [51]. Chemotherapy even accelerates this process.

Adjuvant hormone therapy also affects fertility. Its duration of 5–10 years is of great importance [46]. Prolonged hormone therapy is usually recommended in cases of higher risk of recurrence of breast cancer and previous use of chemotherapy. These two factors significantly decrease the chance for progeny.

The measurement of AMH (anti-Müller hormone) serum concentration which is unchanged during the menstrual cycle is the acknowledged method of assess-

ment of the ovarian reserve (the number of ovular cells in ovaries) [3, 52]. The hormone belongs to the superfamily of transforming growth factors beta (TGF-β) and is produced by primary, secondary, and early antral ovarian follicles. The baseline AMH concentration may be helpful in the assessment of the ovarian reserve and in making the decision regarding the methods of fertility preservation. The lower baseline concentration of AMH correlates with a lower chance for maintenance of the ovarian function after chemotherapy [53]. Physiologically the AMH serum concentration decreases beyond the age of 25 years and usually becomes undetectable at age 50–51 years, which correlates with the menopause [54].

Disturbances of the menstrual cycle often occur in the course of chemotherapy. It should be noted that the ovarian reserve/fertility cannot be assessed based on either arrest of menstruation or serum concentration of FSH, estradiol, and inhibin [55].

The interest of young women in fertility

The issue of potential fertility disorders is very important to young women, especially to those who have not completed their plans regarding maternity. There has been great progress in the treatment of the breast cancer in recent decades. Anticancer agents that are more and more effective have been discovered. This has prompted the growing importance of quality of life after completion of oncology treatment.

There have been clinical trials assessing the interest of young women with breast cancer in fertility issues. One of them enrolled 389 women up to 35 years old, who had been recently diagnosed with breast cancer. Patients answered questions in a questionnaire. 59% of the respondents declared their will to have progeny in the future and a further 41% did not give such a declaration, including 1/3 negatively answering the question being concerned for recurrence of breast cancer. A higher level of acceptance of risk of infertility was seen in women already having offspring [56, 58].

In another large prospective trial medical counselling regarding questions of fertility was assessed in a population of 620 young women (median age 37 years). The issue of systemic treatment in the context of its potential influence on fertility was discussed before the start of the treatment with 68% of responding patients and 51% of them were being concerned about the possibility of infertility as a consequence of the treatment. These concerns influenced the treatment in some cases — the patient decided to refuse the chemotherapy (1% of patients) or hormone therapy (3%) or decided to change the modality of the treatment being administered (different chemotherapy regimen — 2%, hormone therapy shorter than 5 years — 11%) [57].

In another clinical trial a questionnaire was answered after surgery. The answers of 657 women (median age at the time of diagnosis was 33 years; the average age at the time of questionnaire completion was 36 years) were analysed. 73% of the women were concerned about the influence of the treatment on increased risk of infertility. The issue was of greatest importance in women who declared the will of having more progeny, those who had not yet delivered, those who had only one child, and in those who had had problems becoming pregnant. Because of the aforementioned concerns about fertility disorders, 29% of women changed their decision regarding the treatment modality, and 72% of the patients discussed issues regarding fertility with their physician [58].

Patient referrals to a fertility specialist

Young women should be informed about the side effects of systemic therapy, including potential fertility disorders. According to ASCO and ESMO guidelines young women before the start of the treatment should be referred for consultation regarding fertility and the disorders that may result from planned therapy as well as potential methods of fertility preservation. Such a discussion should take place as soon as possible after the decision regarding the systemic treatment has been made, to enable patient referral to a specialist in fertility preservation [3, 4].

The factors that are important from the perspective of young women were assessed in patients with newly diagnosed breast cancer and referred to a specialist focusing on fertility problems. In a Canadian trial only 27 patients answered the questions; however, the conclusions are relevant [59]. Young patients should be referred for consultation at the earliest possible time, optimally just after the surgeon makes the diagnosis. This allows enough time to perform procedures of fertility preservation according to patient's decision. Patients complained of time pressure if the consultation had been scheduled just before the initiation of the chemotherapy. Patients also pointed out insufficient knowledge regarding the potential influence of oncology treatment on fertility, which they had before the consultation with the fertility and procreation specialist. This caused a focus on the risk of potential disorders instead of possibilities to preserve fertility. They reported this conclusion as being very surprising and depressing. The women also pointed out that access to educational materials and brochures addressing the methods of fertility preservation and its efficacy before such a consultation would have been helpful. Patients reported that a discussion with an advisor after specialist consultation would have helped in making the decision regarding the introduction of procedures to preserve fertility.

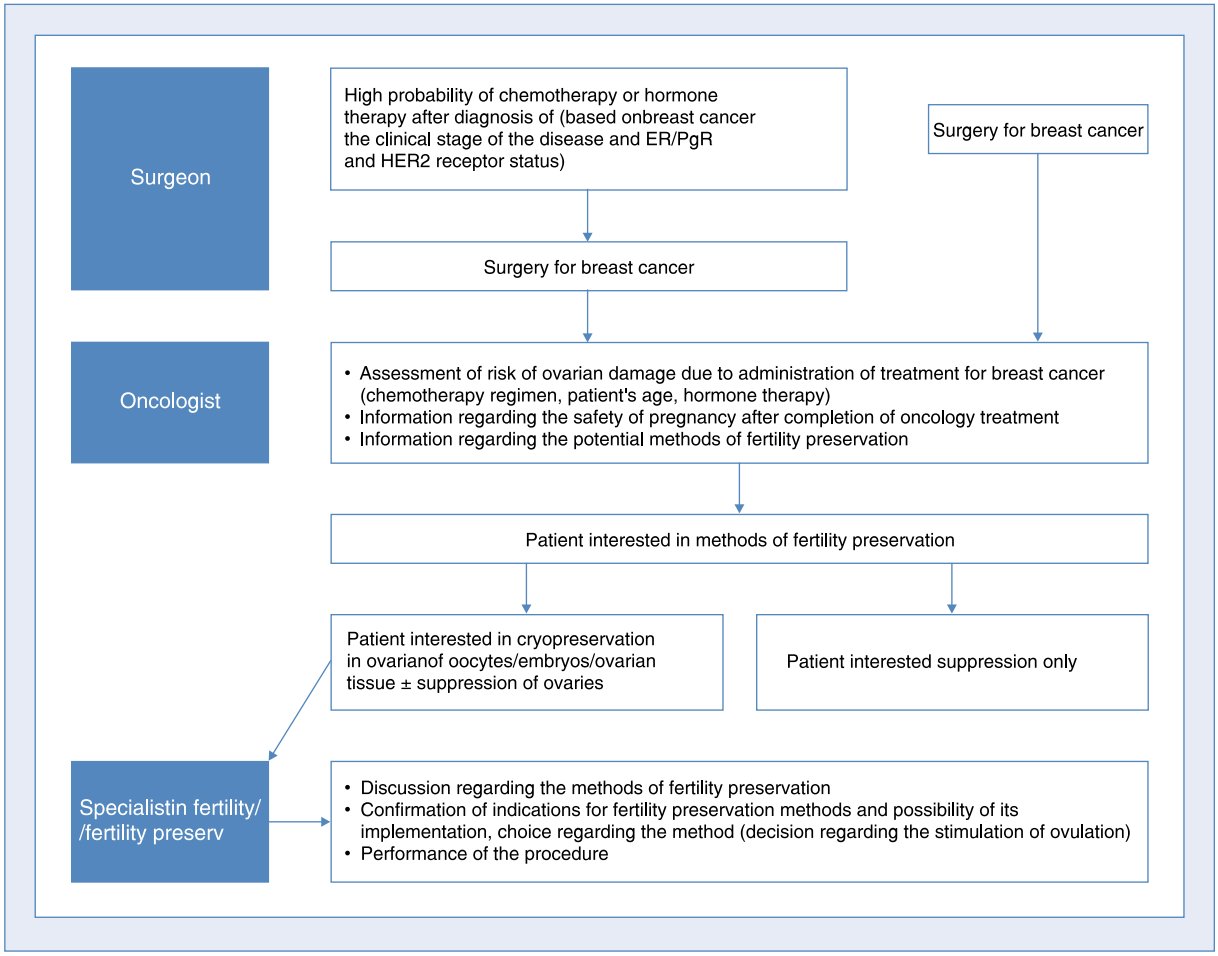

Figure 2. Proposed algorithm of referrals of young patients to consultation of specialist in procreation

An algorithm of referrals of young patients to specialists in procreation and fertility preservation is proposed in Figure 2.

Methods of fertility preservation

The data regarding the benefits and protective role of GnRH analogues on ovaries is conflicting. A meta-analysis of nine clinical trials has been published recently, and six of them referred to patients with breast cancer [60]. A reduction in the risk of premature ovarian function loss with use of GnRH analogues during chemotherapy has been shown [odds ratio (OR) = 0.43; 95% CI: 0.22–0.84; p = 0.013], especially in patients with breast cancer. However, it should be noted that the most frequently assessed parameter was menstruation arrest/termination, which, as previously mentioned, is not a reliable method for fertility assessment.

In 2015 the results of the Prevention of Early Menopause Study (POEMS) were published that changed the recommendations [61]. In this trial 218 premenopausal women with breast cancer without expression of steroid receptors treated after chemotherapy (various regimens) with or without goserelin (only during chemotherapy) were evaluated. There was a higher percentage of pregnancies in the goserelin arm (21% vs. 11%; p = 0.03) as well as better prognosis. Based on the results of this study, the St. Gallen 2015 experts definitely recommend ovary suppression in patients with breast cancer without the expression of hormone receptors to preserve ovarian function and fertility [5]. However, it should be emphasised that GnRH analogues are not registered in this indication.

The efficacy of GnRH analogues for protection of the ovaries is limited. The techniques of procreation support are more effective. A few years ago the cryopreservation of embryos or oocytes was the only recommended method of preservation of fertility. In 2013 the ESMO and ASCO published their recommendations [3, 4]. Both societies have recommended the aforementioned technique. Cryopreservation of the ovarian tissue was considered an experimental method at that time. According to the current St. Gallen 2015 guidelines, patients aged ≤ 40 years, who plan pregnancy in the future should be offered cryopreservation of ovarian tissue [5].

However, the methods discussed above have their limitations. 10–14 days of stimulation of the ovulation is obligatory to perform the cryopreservation of oocytes or embryos with subsequent oocytes collection [52]. There are concerns regarding stimulation of ovulation, especially in patients with hormone-dependent breast cancer. There are special techniques for ovulation stimuli developed with use of tamoxifen and letrozole, and the drugs are administered for the treatment of breast cancer to cope with the challenges and to restrict the increase of oestrogen concentration. To date, a great number of clinical trials have been conducted to address this issue. A project assessing the influence of ovary stimulation on the risk of breast cancer recurrence and its efficacy in terms of the number of collected oocytes was one of them. The best results have been achieved with use of letrozole with FSH — the lowest estradiol serum concentration with the highest number of mature oocytes collected. Moreover, the rates of recurrence were similar in the group with ovulation stimuli and the control arm [62]. In a larger trial with the use of the ovulation stimuli protocol with letrozole, the chemotherapy was usually initiated 12 days later when compared to the control arm. The percentage of patients with cancer recurrences did not differ [63]. The mentioned ovulation stimuli regimens with letrozole or tamoxifen are recommended by ESMO [3]. Promising data regarding the protocols of ovarian stimulation with letrozole has been published recently, which can be used in various phases of the menstrual cycle, which significantly shortens the time to initiation of chemotherapy [64].

If cryopreservation of the embryo has been chosen, extracorporeal fertilisation must be performed first, and partner or donor semen is needed.

There is no need for ovulation stimulation in the case of the ovarian tissue preservation. The procedure does not need any special preparation. When the oncology treatment is finished the fragments of preserved ovarian tissue are unfrozen and transplanted into the localisation of the remained ovaries (orthotopically) or to different localisation (heterotopically).

It should be emphasised that the methods of procreation support introduced before the systemic oncologic treatment present the most reliable strategy of fertility preservation; however, some patients may have objections of an ethical matter. GnRH analogues may only represent a helpful tool of ovarian protection (Table 2).

Contraception in patients treated for breast cancer

The next important issue is contraception for young women with cancer. It is of great importance during therapy because allows the completion of the whole scheduled treatment. During the treatment for breast cancer teratogenic agents are frequently used, which is especially important in the first trimester of pregnancy. As mentioned earlier, the systemic treatment may disturb the menstrual cycle. Patients should be informed that menstruation arrest does not mean status of infertility and that the re-appearance of menstruation may not represent a status of fertility. It is recommended to continue contraception for about 3–6 months beyond the completion of anti-cancer systemic treatment [3].

Oral two-part contraception insignificantly increases the risk of breast cancer recurrence [65]. In 2015 the World Health Organisation (WHO) updated its recommendations regarding contraception [66]. The only recommended method of contraception is a copper intrauterine device. However, the risk of increased menorrhagia and anaemia should be taken into consideration, which may be a problem in patients undergoing chemotherapy. As for patients on tamoxifen, the intrauterine device may increase the hyperplasia of endometrium. There are more and more data including a meta-analysis published on 2014 [67] referring to the safety of intrauterine devices using levonorgestrel. The advantage of such devices is diminished menstruation bleeding. An intrauterine device with a reduced amount of the levonorgestrel may be an option [68]. However, the ESO and EUSOMA recommend contraception without hormones [2].

Pregnancy after treatment for breast cancer

It has been proven that the chance of maternity is significantly lower in patients who have completed treatment for breast cancer. The number of gestations adjusted for age is about 30% of the number of gestation in the general population [69].

Based on the results of clinical trials, it has been also shown that gestation in women who have undergone treatment for breast cancer does not increase the risk of either recurrence or death. The results of a meta-analysis of more then 14,000 premenopausal patients with breast cancer indicate even better prognosis in women who became pregnant after the oncological treatment [70].

There was also a clinical trial that assessed the correlation between long-term results and steroid receptor expression status. A total of 333 women who became pregnant after the completion of treatment for breast cancer were assessed and compared to 874 patients who had not delivered [71]. It was shown that the risk of recurrence of hormone-dependent breast cancer was the same in women who had not become pregnant after completion of the oncology treatment. The risk of disease recurrence did not depend on the steroid receptor status in women who had already completed their plans regarding maternity. Similarly, the time from the diagnosis of breast cancer (> 2 years vs. < 2 years) did not influence the risk of disease recurrence. Moreover,

Table 2. Methods of fertility preservation in young women with breast cancer

Method	Definition	Protection of the ovarian function	Comments
Cryopreservation of oocytes	Collection and cryopreservation of non-fertilised oocytes	No	• Stimulation of ovulation is necessary • Regimens of stimulation have been elaborated lately that allow its use in various menstruation phases, which shortens the time to initiation of the systemic treatment • The cost of the procedure restricts its use • Method recommended by St. Gallen 2015, ESMO and ASCO experts
Cryopreservation of embryos	Collection of oocytes, extracorporeal fertilisation, and cryopreservation of embryos	No	• Stimulation of ovulation is necessary • The regimens of stimulation have been elaborated lately that allow its use in various menstruation phases, which shortens the time to initiation of the systemic treatment • Partner or sperm donor required • The cost of the procedure restricts its use • Method recommended by ESMO and ASCO
Cryopreservation of ovarian tissue	Cryopreservation of ovarian tissue fragment and its implantation after the completion of oncology treatment	Probably yes	• Stimulation of ovulation is unnecessary • The cost of the procedure restricts its use • The risk related to collection of ovarian tissue along with cancer cells in case of advanced disease • Method recommended by St. Gallen 2015 experts
Ovarian suppression with GnRH analogues	GnRH analogues use during chemotherapy to protect the ovaries	The results of the POEMS trial indicate a protective effect in patients with ER/PgR-negative breast cancer	• Lack of evidence for protective effect in all premenopausal patients with breast cancer • To be used as additional method due to its limited efficacy • To be started 2–4 weeks before initiation of chemotherapy • No drugs registered to be use as ovarian protection • Method recommended by St. Gallen 2015 experts in patients with ER/PgR-negative breast cancer

ASCO — American Society of Clinical Oncology; ER — oestrogen receptor; ESMO — European Society for Clinical Oncology; PgR — progesterone receptor

abortion in woman who had the breast cancer in the past did not improve the results of the treatment. As in the aforementioned meta-analysis, there were higher overall survival rates in women who had become pregnant.

In 2015 the results of a clinical trial evaluating the influence of assisted reproductive technology (ART) on the prognosis of women previously treated for breast cancer were published. Data from 198 women including 25 who underwent ART was analysed [72]. The median follow-up since the diagnosis of breast cancer was almost nine years, and five years since the beginning of the gestation. No difference was found between groups in terms of risk of breast cancer recurrence or death.

It has been stated in ESMO recommendations that:

— gestation after completion of treatment for breast cancer is safe even in women who underwent treatment for hormone-dependent breast cancer;
— in case of gestation, its termination does not influence the mother's prognosis, and for that reason such procedure should be discouraged [3].

As mentioned before, young women quite often stop their adjuvant hormone therapy prematurely due to side effects. Taking this fact into consideration the POSITIVE clinical trial was designed with enrolment of patients with hormone-dependent breast cancer (age up to 42 years), who planned to get pregnant. After 18–30 months of hormone

therapy the patients were allowed to stop it and then to get pregnant, to give birth to a child/children, and then to restart the therapy. The safety of such a strategy was the primary end-point of the study. The trial is still ongoing; however, according to St. Gallen 2015 consensus, currently the strategy may be taken under consideration in young women with low risk of recurrence of breast cancer [5].

Breast-feeding after treatment for breast cancer

Large population trials have revealed that breast-feeding decreases the risk of breast cancer [73]. The data regarding this effect in women after treatment for breast cancer are limited; however, available literature indicate the safety of breast-feeding in this population [74].

In one study addressing breast-feeding after treatment for breast cancer the factors that triggered the women's decision of breast-feeding were distinguished. It was noted that women are often discouraged from breast-feeding by gynaecologists and oncologists. Breast-feeding did not influence the risk of disease recurrence or death [75].

Breast-feeding after mastectomy due to breast cancer as well as after breast conserving treatment is possible. In the second situation the amount of the mother's milk from the operated breast is reduced due to fibrosis of the gland secondary to performed radiation therapy. Additionally, there might be some problems to put the baby to the breast. Lactation counselling may be important in such cases [74].

Other problems of young women with breast cancer

There are several consequences of breast cancer that should be considered when taking care of young patients. These may be problems with job maintenance, professional aspirations, and social roles (of being a wife, mother for babies, housekeeper). The diagnosis of breast cancer often impels patients to change their priorities. The support from beloved persons, and sometimes from a psychologist or sexologist, is very important. Other young patients who have completed the treatment may be helpful by sharing their experience. Patients' organisations are very efficient in performing this function.

Self-acceptance in the context of changed appearance is extremely important for young women. Breast reconstructive surgery is crucial here. The chemotherapy may change the cognitive abilities ("chemobrain"). There are attention deficits, memory deficits, and concentration deficits in some patients, which may impede their everyday functioning.

As well as psychological problems secondary to oncology treatment there may be functional disorders in other systems that develop, and these are as follows:

- premature menopause — as a result of chemotherapy and hormone therapy administration and secondary ovarian dysfunction;
- vaginal dryness, dyspareunia — lubricant use is recommended;
- osteopaenia and osteoporosis — enhanced by the use of tamoxifen (in contrast to post-menopausal women [2, 76, 77], aromatase inhibitors and ovarian suppression — control densitometry should be performed every 12–24 months as well as calcium and vitamin D3 supplementation introduced along with encouragement for physical activity [78];
- cardiotoxicity — the risk of its development depends mostly on the total dose of administered anthracyclines, and for that reason it is very important to conduct the treatment based on safe doses, especially if adjuvant radiation therapy is also considered. Moreover, attention should be paid during the control visits to adequate prophylaxis of cardio-vascular diseases;
- obesity — the regular control of body weight and reminding the patient about physical activity is very important. Maintenance of the correct body weight may significantly prolong survival [79];
- subsequent cancers — cancer of the uterus may develop as a result of tamoxifen use (obligatory gynaecological controls during the therapy) and haematological cancers (especially the acute myeloblastic leukaemia and myelodysplastic syndrome after chemotherapy use).

Metastatic breast cancer

The treatment of young patients with metastatic breast cancer is slightly different from the treatment of older women. There are some differences in this group of patients [80, 81]:

- tamoxifen hormone therapy with ovarian suppression/ablation is the preferred first-line treatment of patients with ER-positive, HER2-negative breast cancer. In the case of progression with the aforementioned treatment, aromatase inhibitor therapy should be considered with suppression (ablation) of the ovaries; the lack of recommendations for ovariectomy should be pointed out;
- no large prospective clinical trials addressing the efficacy of fulvestrant in this group of patients have been conducted so far, and for that reason this drug should not be used before menopause.

Young patient age is not a factor that should trigger the decisions regarding introduction of more aggressive therapy [2].

Breast cancer in pregnant women

The diagnostic roles for breast cancer in pregnant women are the same as those for the general population. After diagnosis the patient should be referred to a site experienced in the treatment of such cases. The decisions regarding therapy should be made by a multi-disciplinary team with specialists in gynaecology-obstetrics and neonatology.

Ultrasound is the preferred imaging method for staging. The radiation should be limited or the adequate abdomen protection should be used. The magnetic resonance imaging without gadolinium contrast can be used if the results of previously performed examinations are equivocal or if metastatic lesions in bones or brain are suspected. Neither computed tomography nor positron emission tomography is recommended during gestation [3].

The operational technique must be in accordance with rules for treatment of pregnant patients. The sentinel node procedure may be performed, but with one restriction: the radioisotope is recommended due to the risk of hypersensitivity reactions against methylene blue.

Radiation therapy can be performed after delivery. In non-pregnant women it takes usually six months from the surgery to initiation of radiation therapy due to administration of the adjuvant chemotherapy. In pregnant women radiation therapy is not an urgent procedure either. It is the treatment of pregnant women in the first trimester that is the biggest challenge because in this situation the surgery represents the only safe procedure. According to ESMO guidelines the radiation therapy can be postponed by more than six months; however, such a decision may increase the risk of local recurrence. The pros and cons should be considered in detail by a multi-disciplinary team, then the advantages and threats of various operational techniques and timing of the radiation therapy should be discussed with the patient [3].

The chemotherapy can be administered in the second trimester. It is recommended that the foetus' wellbeing is monitored on a regular basis because the gestation under chemotherapy is considered a gestation of high risk. The regimens: AC, FAC, FEC, and EC should be used as in non-pregnant women. Methotrexate should be definitely avoided due to its high teratogenic effect [82]. Weekly paclitaxel is preferred if there is a need for taxanes use. However, treatment with tamoxifen or trastuzumab is contraindicated during gestation (due to risk of congenital defects and oligohydramnios, respectively) [3].

Supportive treatment plays an important role in pregnant patients. There are no contra-indications for anti-emetics (including ondansetron and aprepitant); however, most of the safety data refers to metoclopramide. Steroids are recommended from the beginning of the second trimester. Prednisolone and hydrocortisone are preferred due to increased metabolism in the placenta and low penetration to the foetus. Granulocyte stimulating factors are allowed if indicated. Paracetamol is preferred as an analgesic, while non-steroidal anti-inflammatory drugs are permitted if required between the twelfth and thirty-second week of gestation [83].

The last cycle of chemotherapy should be administered three weeks before scheduled delivery to reduce the risk for anaemia and leukopenia. Attention should be paid to prevent premature deliveries (< 37 weeks of gestation) because it may increase the risk of cognitive and emotional disorders of the baby. Breast-feeding is not recommended during the oncology treatment due to the risk of the cytotoxic drug penetration to the mother's milk [3, 38]. However, the data regarding this issue is limited.

The available data indicates the lack of influence of chemotherapy administered in pregnancy on mental development of the child and the functioning of his/her heart. The literature regarding this issue provides data based on small numbers of children born from mothers who underwent chemotherapy, and short follow-up [84]. There is a need for further investigation of the potential effects of chemotherapy on the development of children.

Conclusions

The population of young patients with breast cancer grows every year. Although the treatment in this group is only slightly different from that used in the population of older women the problems met here significantly differ from problems in the older patients.

The treatment of young patients requires the cooperation of several specialists — as well as the oncologist, surgeon, and radiotherapist the engagement of a geneticist, endocrinologist and a gynaecologist and obstetrician in case of gestation. Dedicated teams are being formed in large oncology centres in the structures of so-called breast units, which significantly improves the quality of medical care in the specific group of young patients.

It is the responsibility of the physician to discuss with patients the currently recommended methods of therapy and to inform them about the potential adverse events of the treatment in terms of fertility disorders. There are effective and safe methods that allow preservation of fertility in patients treated for breast cancer. It has also been shown that having progeny after oncological treatment does not increase the risk of disease recurrence (Table 3).

The treatment of young women is often time consuming, emotionally engaging, and requires several discussions with the patient and between medical professionals. However, such efforts are not aimless because years later the patients are healthy but also fulfilled in their private and professional lives.

Table 3. Summary of recommendations regarding the treatment of young women with breast cancer

Genetic tests for *BRCA1/2* mutations should be performed in every young women with breast cancer
The treatment of young women should be conducted according to recommendations for the general population of patients with breast cancer with certain exceptions: • hormone therapy is not used as a standard pre-operative treatment • adjuvant hormone therapy based on the ovarian suppression (5 years) with tamoxifen/exemestane is recommended in patients with ER/PgR-positive breast cancer with higher risk of disease recurrence • hormone therapy with ovarian suppression is preferred in palliative treatment of patients with ER/PgR-positive breast cancer • no data available regarding the administration of fulvestrant
Contraception including intrauterine device should be recommended during the oncology treatment and 3–6 months after its completion
Systemic treatment is related to fertility disorders — patients should be referred for specialist consultation before treatment initiation — optimally just after the diagnosis of breast cancer
The fertility preservation methods in patients with breast cancer are safe
Pregnancy after treatment for the breast cancer does not increase the risk of disease recurrence or death
Breast feeding after treatment for breast cancer is possible and safe
During control visits attention should be paid to potential complications of oncology treatment: premature menopause, osteoporosis, cardiotoxicity, obesity, secondary cancers
In cases of diagnosis of breast cancer in pregnant women, treatment in a centre with adequate experience is required. The surgery is allowed, and the chemotherapy should be introduced not earlier than in the second trimester. Hormone therapy and trastuzumab are contraindicated in pregnant women. The radiation therapy should be introduced after delivery. Breast-feeding is not recommended during ongoing systemic treatment

References

1. Didkowska J, Wojciechowska U. Zachorowania i zgony na nowotwory złośliwe w Polsce. Krajowy Rejestr Nowotworów, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie. http://onkologia.org.pl/raporty/.
2. Partridge AH, Pagani O, Abulkhair O et al. First international consensus guidelines for breast cancer in young women (BCY1). Breast 2014; 3: 209–220.
3. 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): 160–170.
4. Loren AW, Mangu PB, Beck LN et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013; 19: 2500–2510.
5. Coates AS, Winer EP, Goldhirsch A 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 Ocol 2015; 8: 1533–1546.
6. Cardoso F, Loibl S, Pagani O et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012; 18: 3355–3377.
7. Samphao S, Wheeler AJ, Rafferty E et al. Diagnosis of breast cancer in women age 40 and younger: delays in diagnosis result from underuse of genetic testing and breast imaging. Am J Surg 2009; 4: 538–543.
8. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. Semin Oncol 2009; 3: 237–249.
9. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012; 11: 1141–1151.
10. Beaber EF, Malone KE, Tang MT et al. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiol. Biomarkers Prev 2014; 5: 755–764.
11. Clavel-Chapelon F, Gerber M. Reproductive factors and breast cancer risk. Do they differ according to age at diagnosis? Breast Cancer Res Treat 2002; 2: 107–115.
12. Golshan M, Miron A, Nixon AJ et al. The prevalence of germline BRCA1 and BRCA2 mutations in young women with breast cancer undergoing breast-conservation therapy. Am J Surg 2006; 1: 58–62.
13. Jassem J, Krzakowski M, Bobek-Billewicz B et al. Rak piersi. In: Krzakowski M, Warzocha K (ed.) Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych. Via Media, Gdańsk 2013: 211–263.
14. NCCN Guidelines. Genetic/Gamilial High-Risk Assessment: Breast and Ovarian. Wersja 2. 2015.
15. Xia X, Chen W, Li J et al. Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep 2014; 4: 7480.
16. Michels KB, Terry KL, Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. Arch Intern Med 2006; 21: 2395–2402.
17. Ruddy KJ, Gelber S, Tamimi RM et al. Breast cancer presentation and diagnostic delays in young women. Cancer 2014; 1: 20–25.
18. Houssami N, Turner R, Macaskill P et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. J Clin Oncol 2014; 5: 392–401.
19. Keegan TH, DeRouen MC, Press DJ, Kurian AW, Clarke CA. Occurrence of breast cancer subtypes in adolescent and young adult women. Breast Cancer Res 2012; 2: R55.
20. 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; 3: 1061–1066.
21. Copson E, Eccles B, Maishman T et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18–40 years at diagnosis: the POSH study. J Natl Cancer Inst 2013; 13: 978–988.
22. 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; 3: 341–347.
23. Balmana J, Diez O, Rubio IT, Cardoso F, Group EGW. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2011; Suppl 6: 31–34.
24. Senkus E, Kyriakides S, Ohno S i wsp. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol 2015; 26 (Suppl 5): 8–30.
25. Huzarski T, Byrski T, Gronwald J et al. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. J Clin Oncol 2013; 26: 3191–3196.

26. Finch AP, Lubinski J, Moller P et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2014; 15: 1547–1553.
27. Metcalfe K, Lynch HT, Foulkes WD et al. Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. JAMA Oncol 2015; 3: 306–313.
28. Mahmood U, Morris C, Neuner G et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiat Oncol Biol Phys 2012; 5: 1387–1393.
29. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (</= 40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy. Breast 2015; 3: 175–181.
30. Krag DN, Anderson SJ, Julian TB et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 10: 927–933.
31. Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 6: 569–575.
32. Galimberti V, Cole BF, Zurrida F et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013; 4: 297–305.
33. Donker M, Straver ME, van Tienhoven G et al. Comparison of the sentinel node procedure between patients with multifocal and unifocal breast cancer in the EORTC 10981-22023 AMAROS Trial: identification rate and nodal outcome. Eur J Cancer 2013; 9: 2093–2100.
34. Arvold ND, Taghian AG, Niemierko A et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol 2011; 29: 3885–3891.
35. Bartelink H, Maingon P, Poortmans P et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015; 1: 47–56.
36. NCCN Guidelines. Invasive Breast Cancer 2015. Wersja 3.
37. Beadle BM, Woodward WA, Tucker SL et al. Ten-year recurrence rates in young women with breast cancer by locoregional treatment approach. Int J Radiat Oncol Biol Phys 2009; 3: 734–744.
38. Quan ML, Osman F, McCready D et al. Postmastectomy radiation and recurrence patterns in breast cancer patients younger than age 35 years: a population-based cohort. Annals of Surgical Oncology 2014; 21: 395–400.
39. Hugh J, Hanson J, Cheang MC et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol 2009; 8: 1168–1176.
40. Tolaney SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015; 2: 134–141.
41. Rastogi P, Anderson SJ, Bear HD et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 5: 778–785.
42. Pagani O, Regan MM, Walley BA et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014; 2: 107–118.
43. Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015; 5: 436–446.
44. Huiart L, Dell'Aniello S, Suissa S. Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. Br J Cancer 2011; 10: 1558–1563.
45. Gnant M, Mlineritsch B, Stoeger H et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Ann Oncol 2015; 2: 313–320.
46. Peccatori FA, Pup LD, Salvagno F et al. Fertility Preservation Methods in Breast Cancer. Breast Care 2012; 3: 197–202.
47. Główny Urząd Statystyczny DBDiRP: Podstawowe informacje o rozwoju demograficznym Polski do 2013 roku. 2014.
48. Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. Cancer 2007; 10: 2222–2229.
49. 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; 6: 1626–1633.
50. Kim SS, Klemp J, Fabian C. Breast cancer and fertility preservation. Fertil Steril 2011; 5: 1535–1543.
51. Finch A, Valentini A, Greenblatt E et al. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril 2013; 6: 1724–1728.
52. Lambertini M, Anserini P, Levaggi A, Poggio F, Del Mastro L. Fertility counseling of young breast cancer patients. J Thorac Dis 2013; Suppl 1: 68–80.
53. 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; 16: 3404–3411.
54. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-mullerian hormone from conception to menopause. PloS One 2011; 7: e22024.
55. Committee on Gynecologic Practice. Committee opinion no. 618: Ovarian reserve testing. Obstet Gynecol 2015; 1: 268–273.
56. Senkus E, Gomez H, Dirix L et al. Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3-98. Psychooncology 2014; 2: 173–182.
57. 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; 11: 1151–1156.
58. Partridge AH, Gelber S, Peppercorn J et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004; 20: 4174–4183.
59. Hill KA, Nadler T, Mandel R et al. Experience of young women diagnosed with breast cancer who undergo fertility preservation consultation. Clin Breast Cancer 2012; 2: 127–132.
60. Del Mastro L, Ceppi M, Poggio F et al. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev 2014; 5: 675–683.
61. Moore HC, Unger JM, Phillips KA et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015; 10: 923–932.
62. 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; 19: 4347–4353.
63. 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; 16: 2630–2635.
64. Cakmak H, Rosen MP. Ovarian stimulation in cancer patients. Fertil Steril 2013; 6: 1476–1484.
65. Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer Res 2014; 15: 4078–4089.
66. WHO. Medical eligibility criteria wheel for contraceptive use. 2015.
67. 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; 10: 6419–6429.
68. Aiken AR, Trussell J. Recent advances in contraception. F1000Prime Rep 2014; 6: 113.
69. Stensheim H, Cvancarova M, Moller B, Fossa SD. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. Int J Cancer 2011; 5: 1225–1236.
70. 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; 12: 786–793.
71. 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; 1: 73–79.
72. Goldrat O, Kroman N, Peccatori FA et al. Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. Eur J Cancer 2015; 12: 1490–1496.
73. Scoccianti C, Key TJ, Anderson AS et al. European Code against Cancer 4th Edition: Breastfeeding and cancer. Cancer Epidemiol 2015, doi: 10.1016/j.canep.2015.03.
74. Azim HA Jr, Bellettini G, Gelber S, Peccatori FA. Breast-feeding after breast cancer: if you wish, madam. Breast Cancer Res Treat 2009; 1: 7–12.
75. Azim HA Jr, Bellettini G, Liptrott SJ et al. Breastfeeding in breast cancer survivors: pattern, behaviour and effect on breast cancer outcome. Breast 2010; 6: 527–531.
76. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry

in healthy premenopausal and postmenopausal women. J Clin Oncol 1996; 1: 78–84.
77. Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. J Clin Oncol 2006; 4: 675–680.
78. Jassem J, Duchnowska R, Kawecki A et al. Badania kontrolne po leczeniu w najczęstszych nowotworach litych u dorosłych. NOWOTWORY Journal of Oncology 2014; 5: 415–435.
79. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst. 2012; 11: 815–840.
80. Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014; 10: 1871–1888.
81. Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014; 5: 489–502.
82. Hyoun SC, Obican SG, Scialli AR. Teratogen update: methotrexate. Birth Defects Res. A Clin Mol Terat 2012; 4: 187–207.
83. Amant F, Van Calsteren K, Halaska MJ et al. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. Int J Gynecol Cancer 2009; Suppl 1: 1–12.
84. Amant F, Verheecke M, Ottevanger PB et al. Cancer during pregnancy: a case-control analysis of mental development and cardiac functioning of 38 children prenatally exposed to chemotherapy. Ann Oncol 2014; Suppl 5: 267PD_PR.