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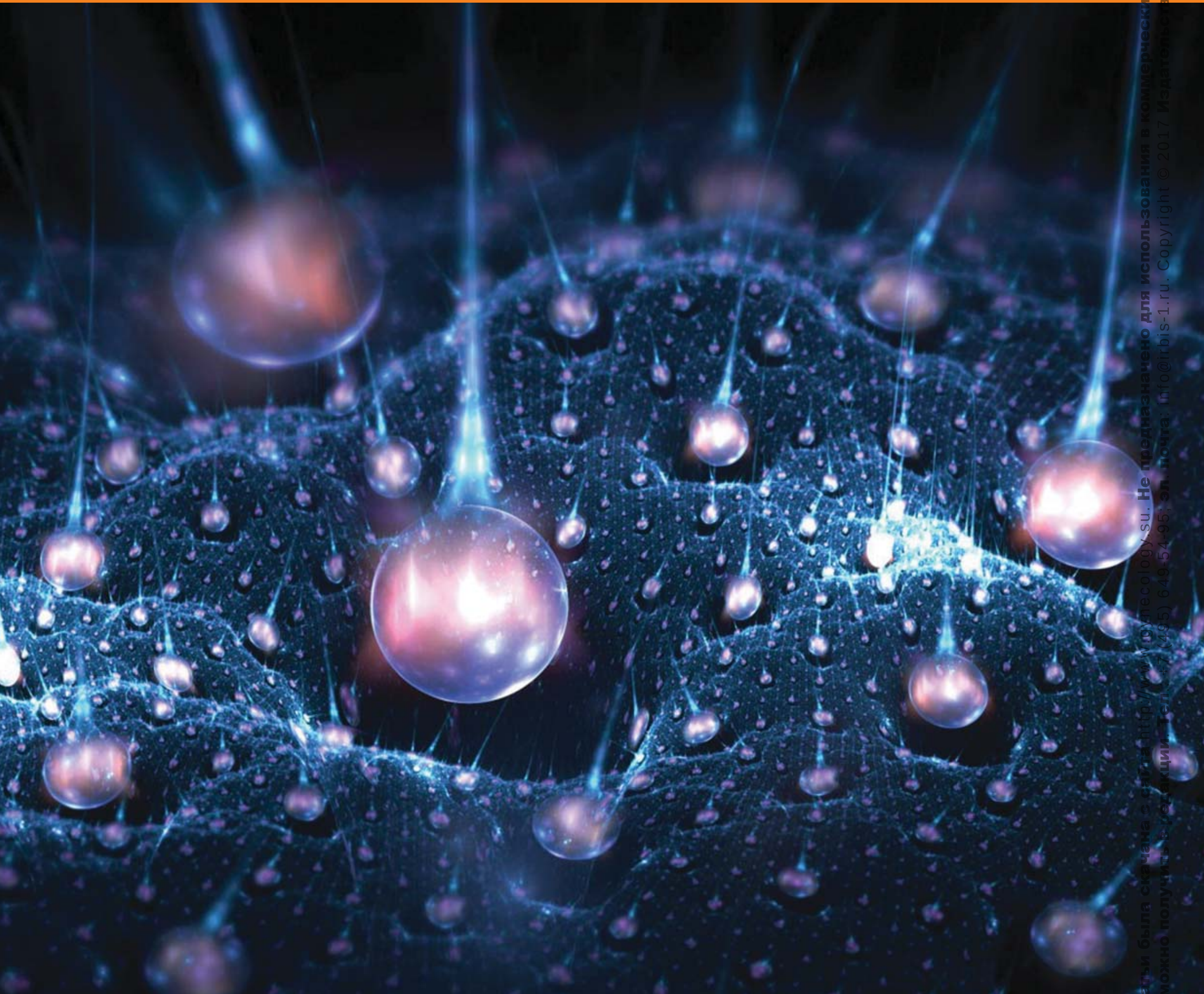

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BREAST CANCER AND PREGNANCY

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Summary

25 evidenced based clinical practice guidelines for fertility preservation in cancer patients exist. Breast Cancer in Pregnancy is a rare problem but the incidence is growing, because pregnancy will be delayed in elder age groups. Diagnosis of Breast Cancer is often delayed. If there is a mass, you have to do at first an ultrasound and than mammography if it is necessary. A tumor should be biopsied. Each kind of surgery is possible. Sentinel lymphnode dissection is controversial discussed. It is because of the blue dye, because this substance is not allowed during pregnancy. Technetium is allowed, but will be not accepted by the mother, because of fear of radiance. Radiation and hormonal treatment should be postponed after pregnancy. Chemotherapy can be done after 16 week of gestation. Delivery should not be in the first 3 weeks after chemotherapy, because the nadir of white blood cells should not be at the time of delivery to avoid infection. The fetal outcome is quite normal except weight, because of preterm delivery and growth retardation. Termination of pregnancy will not optimize the cancer prognosis. Pregnancy after breast cancer treatment is possible, perhaps with better prognosis, but that can be due to the healthy mother effect. Because the most recurrence are in the first two years, women should wait 2 years and cryopreservation of ovarian tissue, eggs or embryos before chemotherapy should be done.

Key words

Breast Cancer, pregnancy, tumor, chemotherapy, cryopreservation.

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РАК МОЛОЧНОЙ ЖЕЛЕЗЫ И БЕРЕМЕННОСТЬ

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Резюме

На сегодня имеются 25 подтвержденных клинической практикой рекомендаций по сохранению фертильности у больных раком. Рак молочной железы при беременности встречается нечасто, но с недавнего времени количество случаев возрастает, поскольку беременность все чаще наблюдается и в старших возрастных группах. Во многих случаях диагноз рака молочной железы запаздывает. Если пальпируется масса в молочной железе, женщина должна сначала сделать УЗИ и уже затем – маммографию, если это необходимо. При подозрении на опухоль – биопсия обязательна. Хирургические способы лечения весьма разнообразны. Возможность иссечения сторожевых лимфатических узлов неопределенна, поскольку используемый при этом синий краситель противопоказан беременным. Технеций разрешен к применению, однако будущие мамы не готовы пользоваться этим радиоактивным изотопом. Радиационное и гормональное лечение следует отложить до окончания беременности. Химиотерапию можно проводить после 16 недель гестации. Сроки лечения следует рассчитать так, чтобы роды не случились в течение первые 3 недели после химиотерапии. Причина в том, что вызванная химиотерапией лейкопения не должна совпадать со сроком родов, во избежание инфекций. Разрешение от беременности проходит нормально; вес новорожденного обычно снижен из-за преждевременных родов и задержки роста плода. Досрочное прекращение беременности не приводит к улучшению прогноза рака. Беременность после лечения рака молочной железы возможна, причем с лучшим исходом, но это может быть проявлением «эффекта здоровой матери». Поскольку большинство рецидивов рака приходится на первые два года после лечения, женщинам не рекомендуется беременеть в течение этих двух лет. До начала химиотерапии рекомендуется провести криоконсервацию ткани яичников, яйцеклеток или эмбрионов.

Ключевые слова

Рак молочной железы, беременность, опухоль, химиотерапия, криоконсервация.

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Introduction

Breast Cancer during pregnancy is also called gestational breast cancer or Pregnancy Associated Breast Cancer (PABC) and is defined as cancer during the whole pregnancy and the first year after. An other definition is gestational breast cancer during breast feeding too, equal the time duration of lactation.

Cancer is not only a physical problem, it includes psychological, economical and sociologic problems and it concerns not only the patients, it affects the whole family and also the doctors. Cancer during pregnancy is a rare event, but provides positions with special challenges. We have three problem-situations with cancer and pregnancy:

- Cancer during pregnancy;
- Pregnancy during cancer therapy;
- Pregnancy after cancer.

During pregnancy we have the fetus as a person which is affected by the cancer itself and by the therapy too. Therefore we have a conflict of interests between the disease of the mother and the well being of the fetus.

Breast Cancer during Pregnancy

The incidence of breast cancer during pregnancy is with 1 to 3000 pregnant women low, but considering the female world's population, it must be an high amount of affected women. Because of delaying child birth in older age groups in the last 40 years in the first world [1], the number of breast cancers during pregnancy is increasing. The mean maternal age is 33 years [2]. Most of them are diagnosed not during pregnancy but during the first post partum year.

The German Society of Senology and the University of Texas MD Anderson Center register all breast cancers during pregnancy [3], which are reported to them.

Diagnosis

The first step of diagnoses in pregnancy is often a palpable mass in the breast. If a breast mass is still palpable after 4 weeks, it should be clarified. But keep in mind that a delay of one month can increase the risk at lymphnode involvement for 1-2% [4]. The patient herself, or more often a nurse/ midwife/ doctor finds it. The first step should be an ultrasound because that can be done at every time during pregnancy and lactation. Ultrasound is very accurate [5]. If the ultrasound is suspicious, a mammography should be done. The sensitivity of mammography is between 78-87% [6].

In pregnancy a mammography can be done if the abdomen is protected by a lead apron. The dosage to the fetus is 0,004 Gy. The mammography during pregnancy and lactation is not so sensitive than without pregnancy because of the higher density of the breasts. The reduced sensitivity is due to increased water content, higher density and losscontrasting fat.

During pregnancy, after week 18th, the use of magnetic resonance imaging (MRI) is safe too. The MRI has the advantage that you can identify multifocal and multilocular breast cancer additionally.

Every suspicious mass should be biopsied. Core needle biopsy should be performed with 7-18 gauge needle. Using a fine needle biopsies you obtain a better differenciation between in situ carcinoma and invasive carcinoma and you can determine the kind of pathology of the tumor, the grading and the receptor status.

Most of the tumors are diagnosed in the first or second trimester. In Austria it is diagnosed early, because breast examination is a standard procedure at the first visit in pregnancy (till week 16th, normally between 6 and 8 week of gestation they come for a first check) according to the rules of the so called mother-child-passport.

In the literature [7] a phenomen for identifying breast cancer is described which is called the milk-rejection sign of breast cancer, if a newborn refuse one breast, you should do a mammography of this breast.

Pathology

Histopathologic features are similarily found in young non pregnant women [6]. The dominant histology is invasive ductal carcinoma (>80%). The majority is high grad, (40-95%). Lymphovascular invasion is common (60%) and the hormone receptor status differs in the literature from 30-70% [6,8].

Staging in Pregnancy

Everyone with breast cancer should be evaluated for distant metastasis. Pulmonary X-Ray is possible when the abdomen is covered. Ultrasound of the liver is also possible during pregnancy. CT of thorax and abdomen should not be done because of too high radiation exposure. Bone scan is not possible during pregnancy. MRI without contrast should be used for bone metastases or brain metastases [9,10].

Clinic

The standard procedures for monitoring the pregnancy and for cancer treatment should be done. The monitoring of pregnancy should be focused on fetal growth retardation by chemotherapy and red and white blood count, because of cytotoxicity of chemotherapy. Erythropoetin and GCSF can be used in pregnancy. Antiemetic drugs, like andrasetron or lorazepam are allowed. Before and after each chemotherapy cycle an ultrasound has to be done.

Termination of pregnancy does not improve the maternal outcome and is a social and ethical problem [11]. But the possible complications have to be discussed with the parents, at least with the mother. There is a discussion that patients with poor prognosis trend more to termination than women with good prognosis.

Surgical Treatment

Surgery is safe at any stage of pregnancy. But before the 12th week the complication of abortion must be considered, not only depending to operation. Every kind of breast surgery, e. g. breast conserving surgery, is possible during the whole pregnancy. Breast conserving surgery can be done in the same manner as in non pregnant patients. But what is important: be sure that you have removed all with free margins of at least 2 mm. Our opinion is to have a free margin of 3-5 mm for good local control in pregnancy, because radiation has to be postponed. Mastectomy has to be done, if there is more than one tumor in the breast, or the tumor size is unfavorable to breast size, or if there is a large DCIS (ductal carcinoma in situ).

Left lateral position is necessary to avoid Vena Cava Syndrome especially after the 20th week of gestation, during the whole time of anaesthesia. Keep in mind that thromboprophylaxis with low molecular weight heparin has to be given for longer time. In every case, especially of total mastectomy you should avoid severe bleeding, which can result in hypotension and hypoxia for the fetus. You should avoid to give blood transfusions, to protect the immune system. The drains have to stay 1 or 2 days longer as usual.

The role of the sentinel node biopsy in early stage breast cancer in pregnancy has not been evaluated sufficiently. There is also the possibility that the lymphatic

passway has maybe changed in the pregnant breast. Lymphozurin used for identification of the sentinel lymph node is a category C drug and should not be used in pregnancy [9]. Recent studies show, that radiocoloid agents such as technecium-99m, has low radioactivity and should not be considered as a contraindication, but it should be only used in scientific randomized studies. Therefore a total lymph node dissection is favourable.

Complication of surgery in pregnancy are the same as in non pregnant women: Seroma / Haematoma, occure in 76%. Therefore you should remove the drains not too early. Wound infections should be avoided by use of antibiotics prophylactive. Swelling and lymphedema, with sometimes severe pains are reported in the literature between 12-56% [12].

Reconstruction Surgery of the breast should be done later after pregnancy as well as the complete cancer therapy, because that needs long time and a big blood loss is common.

In case of large tumors or infiltrating skin or chest wall neoadjuvant chemotherapy has to be discussed and to be assumed, that it has good results like in non pregnant women.

Chemotherapy

Systemic chemotherapy may be necessary for the treatment as in non pregnant women. The benefits for the mother must be compared with the potential longterm harm to the fetus from inutero exposal to chemotherapy agents. Dosage of chemotherapy has to be modified during pregnancy because of weight gain of the mother [13]. Delay in chemotherapy leads to an increase of metastatic disease of 5 to 10%.

In pregnancy there is an increase in blood volume, renal clearance and decrease of albumin leads to an increase of unbound active drug concentration, and therefore you have to be in consideration that pregnancy influences drug pharmacokinetics [14].

A study of chemotherapy with doxorubicin, cyclophosphamide (AC) or in combination of fluorouracil (FAC) showed no stillbirth, miscarriage or perinatal death [10]. The use of taxanes seems to be safe by limited data [15].

The overall risk for congenital malformation is reported with 2-3%. The incidence of major congenital malformations after using cytotoxic drugs is also about 3%, but in the first trimester it ranges from 10-20%. The risk of malformation decreases in the second and third trimester to 1-4% [16].

Side effects of chemotherapy on mother side are: hair loss, nausea, vomiting, neurotoxicity, cognitive impairment, chronic fatigue, neutropenia, anemia, mucositis, cardiotoxicity, diarrhea, obstipation.

Targeted Therapy

Tumortherapy has changed from empires to molecular targeted therapy. The molecular targets are on the surface of cells, intracellular or in the matrix, e.g. against the angiogenese.

Today very convenient is the use of trastuzumab against HER 2. The problem is that we don't have much information about the use in pregnancy. In animals there was no adverse effect to the fetus. In humans we could see fetal growth retardation and fetal kidney insufficiency [17]. So it is better to avoid a Her 2 therapy. (Outside pregnancy, women should use contraceptive methods for at least 7 month after trastuzumab therapy). Breast feeding is not allowed with trastuzumab, because it is unclear whether is it secreted in the milk.

Hormonal Treatment

Hormonal treatment is contraindicated during pregnancy, but can be given after birth, in case of the hormone receptorstatus is positive.Tamoxifen in pregnancy leads to vaginal bleeding, miscarriage, congenital malformations like Goldenhar's Syndrome and fetal death [18,19].

Tamoxifen is not allowed during breast feeding too.

Aromatase inhibitors are not used in general in premenopausale women.

Radiation Therapy

Radiation therapy is not possible during pregnancy and should be delayed, because of the risk of radiation to the fetus even if the abdomen is shielded. The dosage to the fetus would be 0,04-0,2 GY and that is to high. The exposure to radiation of the left breast of the mother is dangerous for the heart too, because of physiologic changes in the structure of the heart during pregnancy. You have time enough to postpone, because in non pregnant women you radiate after chemotherapy too (at least after 6 month of initiation of therapy). The most frequent complication of radiotherapy is burning of the skin of the breast and arm edema with severe pains, if you radiate the axilla.

Monitoring of Pregnancy

Mother and fetus can be monitored with prenatal standard care but it should be done in a centre for high risk pregnancies. Cardiotocography can be used during surgery to avoid fetal hypoxa and can be useful for documentation. Before starting chemotherapy ultrasound of the fetus must be performed, looking for growth retardation and malformation.

Evaluation of fetal growth should be performed before and after every cycle of chemotherapy. Cardiotokogram and Doppler ultrasound, if available has to be done after 25th week of gestation (or the week of gestation, when surviving of the child can be assumed).

A normal blood count is extremely important. If there is any problem with red or white blood count you can give erythropoetin or GCSF (filgastrim or lenograstim respectively).

In case of abnormal findings more stringent monitoring of the fetus or even preterm delivery might be necessary. But keep in mind that you need 3 weeks after the last chemotherapy before delivery to avoid the nadir of white blood cells.

Pregnancy-related complications such as preeclampsia, gestational diabetes mellitus and preterm labour should be treated based on standard recommendations in nonpregnant women.

Timing of Delivery

Labour can be induced or caesarean section performed when the maturation of the fetus is sufficient. If it is necessary and fetal lung maturity is essential, you can applicate corticoids for fetal lung maturation up to 37th week of gestation. Timing of delivery can be optimized in relation to the treatment of breast cancer. If chemotherapy is planed to continue after delivery, vaginal delivery may be less likely because it delays the initiation of chemotherapy. Patient's personal preferences and previous obstetric history should be considered. Delivery should occur approx 3 weeks after the last dose of antrazycline-based chemotherapy (no CHT after 35 week, because of the risk of spontaneous delivery in the neutropenic period with the danger of anaemia or infection).

If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities.

Very interesting is the recent study of Ardalan et al. (2016) reporting a decreased incidence of breast cancer in a 5 year period after delivery in a group delivered beyond 40 week of gestation in comparison to a group, who delivered between 37 and 40 weeks (OR:0,33). The explanation is that mammary cells have more time to obtain complete differentiation and maturation.

Fetal Outcome

At first there are no reports about metastases of breast cancer in the fetus or newborn, but Pavlidis N. et al. (2008) described 14 cases of breast cancer metastases in the placenta.

The long term implications for the child can show that there is low adverse impact on development of the children exposed to antracycline based chemotherapy in utero [9,13].

In an observational study [22] 447 patients with gestational breast cancer were registered, birth weight was affected by chemotherapy after adjustment for gestational age (p=0,018). 10% of the infants had side-effects, malformation or newborn complications.That was more frequent in 16% of newborn before 37 week in opposite to 5%, delivered later (p=0,0002).

In a Belgian study [23] the outcome of 129 children of mothers with cancer, diagnosed during pregnancy, was analysed. 96 of them were exposed to chemotherapy. The only difference to a matched control group, was the incidence of 62% of premature birth. There was no significant difference in weight, cognitive, cardiac or general development of children in early childhood born to mother with cancer in comparison to mother without cancer. A comment was written to this study by Vandenbroucke T. (2016) about some basic methodologic flaws.

A large study with median follow-up of 18.7 years of 84 children reported that there is no evidence of physical congenital abnormalities or any neurologic or psychological abnormalities. Children demonstrating normal learning and educational behaviour [25].

Prognosis of Cancer

In the literature the results differ extremely. Amant F. et al. (2013) and Litton J.K. et al. (2013) did not register a negative survival rate or progression. No significant differences were reported in progression (HR 1,30) or overall survival (HR1,19) in comparison to non pregnant women with breast cancer diagnosed during pregnancy [26,27].

A meta-analysis of 30 studies with 3,628 cases had a significant higher death rate HR 1,44 and more worse events in the group of cancer diagnosed postpartum (HR 1,84) than diagnosed during pregnancy [28].

Loibl S. et al. (2015) registered the disease free survival after starting chemotherapy during pregnancy was 70,6 month and 94,4 month in the group starting chemotherapy after pregnancy. That did not differ significantly. The reason could be that the patients with better prognosis got the chemotherapy later. This study was not a scientific paper; it was only an observational study [29].

Follow Up

Patients with gestational breast cancer should have the same follow up as non pregnant women. Half year after the end of therapy there should be done a mammography, and than each year. Local control by a doctor should be done all 3 month. More important than regular ultrasound of liver or X-Ray of the lungs or tumor markers is the dialog with the patient about problems of health, sexual life or psychologic problems.

Pregnancy during Breast Cancer Therapy

It is rather unlikely that women get pregnant during therapy, especially during chemotherapy. To avoid getting pregnant you should recommend contraception during therapy without hormons.

The best would be an intrauterine device with copper, silver or gold.

Using a condom is also possible, but it is not so safe like the intra uterine device.

Especially in the first trimester chemotherapy can damage the embryo.

Pregnancy after Breast Cancer

One important feeling for cancer survivors is to be healthy enough for getting pregnant [30]. Pregnancy after breast cancer is rare, but if people want a child (about 2%) the women cannot be stopped.

Three main problems have to be addressed:

1. Is there a higher risk for a recurrence?
2. Is there a higher risk for the fetus because of cytotoxicity of the chemotherapy?
3. Regarding sterility and fertility.

According to a study of Azim H.A. et al. (2011) pregnancy after breast cancer has a decreased risk for mortality RR 0,59. That can be based on the "healthy mother effect", meaning that only healthy, free of recurrence women get pregnant [31].

About 50% of patients get amenorrhoic after chemotherapy [32]. Ovarian function after chemotherapy is depending on age and ovarian function at the starting time of chemotherapy [33].

Amenorrhoea will be in 21-71% in women younger than 40 years and 40-100% in patients older than 40 years. Chemotherapy with anthracycline results in less amenorrhoea [34].

Fertility preserving options depend on age, partnership and physical status of the women and the time between diagnosis and starting of treatment, because it needs time especially for embryo freezing but it has the best results.

On the other side there is the possibility of freezing ovarian tissue, if there is no time or no partner at the moment. But it is now to early to speak about good results with this method.Reproductive function can be preserved, but no guarantee can be given [35].

If infertility remains it can lead to severe stress [36]. Therefore the topic of fertility has to be addressed by the doctors before starting cancer treatment.

Regulating Fertility: if you have done cryopresation of ovarian tissue, freezing ovaries or embryos, there should be artificial reproduction not before 2 years after end of therapy. Font-Gonzales et al. (2016) found [37], if cryopreservation is not done, there will be a discussion between the oncologist and gynaecologist about hormonal stimulation for artificial reproduction. Only 34% of patients with breast cancer in the past, report about a dialog with their doctors before starting therapy about fertility [38,39].

To test the ovarian reserve, the AMH (anti-Müllerian hormone) testing can give a good overview about fertility.

A social problem is who takes care of the newborn during further therapies [40]. Women with less 2 years between delivery and breast cancer had significantly increased risk for poorer survival rate than women with interval of more than 5 years [35].

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