

# Pregnancy-Associated Breast Cancer – Special Features in Diagnosis and Treatment

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## Key Words

Breast cancer · Pregnancy · Overall survival · Distant metastasis · Relapse · Prognosis · Chemotherapy · Endocrine treatment

## Summary

For obvious psychological reasons it is difficult to associate pregnancy – a life-giving period of our existence – with life-threatening malignancies. Symptoms pointing to malignancy are often ignored by both patients and physicians, and this, together with the greater difficulty of diagnostic imaging, probably results in the proven delay in the detection of breast cancers during pregnancy. The diagnosis and treatment of breast cancer are becoming more and more important, as the fulfillment of the desire to have children is increasingly postponed until a later age associated with a higher risk of carcinoma, and improved cure rates of solid tumors no longer exclude subsequent pregnancies. The following article summarizes the special features of the diagnosis and primary therapy of pregnancy-associated breast cancer with particular consideration of cytostatic therapy.

## Schlüsselwörter

Mammakarzinom · Schwangerschaft · Gesamtüberleben · Fernmetastasen · Rezidiv · Prognose · Chemotherapie · Endokrine Therapie

## Zusammenfassung

Schwangerschaft als lebensspendende Phase unseres Daseins und lebensbedrohende Malignome sind schon aus naheliegenden psychologischen Gründen nur schwer miteinander in Zusammenhang zu bringen. Symptome, die auf ein Malignom hindeuten, werden nicht selten von Patientin und Arzt ignoriert, woraus neben der erschwerten bildgebenden Diagnostik vermutlich die nachweisliche Verzögerung im Nachweis von Mammakarzinomen während der Schwangerschaft resultiert. Die Diagnostik und Therapie des Mammakarzinoms gewinnt zunehmend an Bedeutung, da die späte Realisierung des Kinderwunschs die Schwangerschaft zunehmend in ein Lebensalter mit höherem Karzinomrisiko rückt und höhere Heilungsraten von soliden Tumoren eine nachfolgende Schwangerschaft nicht mehr grundsätzlich ausschließen. Der folgende Artikel fasst die Besonderheiten von Diagnostik und Primärtherapie des schwangerschaftsassozierten Mammakarzinoms unter besonderer Berücksichtigung der zytostatischen Therapie zusammen.

## Introduction

For obvious psychological reasons it is difficult to associate pregnancy – a life-giving period of our existence – with life-threatening malignancies. Symptoms pointing to malignancy are often ignored by both patients and physicians, and this, to-

gether with the greater difficulty of diagnostic imaging, probably results in the proven delay in the detection of breast cancers during pregnancy [1–4]. The diagnosis and treatment of breast cancer are becoming more and more important, as the fulfillment of the desire to have children is increasingly postponed until a later age associated with a higher risk of carci-

noma, and improved cure rates of solid tumors no longer exclude subsequent pregnancies [5–9]. Various ethical aspects considering potential conflicts between optimizing maternal prognosis and prolonging pregnancy will have to become part of an informed consent between physicians and patients. This dialogue, however, has to be based on the profound knowledge of the state of the art in the treatment of pregnancy-associated breast cancer. The following article summarizes the special features of the diagnosis and primary therapy of pregnancy-associated breast cancer with particular consideration of cytostatic therapy.

## Epidemiology and Prognosis

Pregnancy-associated breast cancer is defined as breast cancer occurring during pregnancy or up to 1 year postpartum [10]. The incidence is increasing particularly in women having children in the last third of the fertile period of their lives. With an incidence of 1 in 3,000 to 1 in 10,000 pregnancies, pregnancy-associated breast cancer is the most common solid tumor during pregnancy after cervical carcinoma [11, 12]. The prognosis of pregnancy-associated breast cancer is identical with that of similar tumor stages outside of pregnancy, with an overall survival rate of 57% 5 years after the initial diagnosis [13]. However, pregnancy-associated breast cancer is often diagnosed in the more advanced stages of the disease, which might be due to delayed discovery as well as a more aggressive tumor biology.

## Diagnosis

Making the diagnosis is rendered more difficult by the changed consistency and increased weight of the breast during pregnancy and lactation. Pregnancy delays the diagnosis of breast cancer by an average of 2–6 months [1–4]. A Norwegian study calculated that the diagnosis was delayed by 2.5 months during pregnancy and 6 months during the lactation period [4]. In a similar study by the M.D. Anderson Cancer Center, an average tumor size of pregnancy-associated breast cancer of 3.5 cm at the time of diagnosis was observed [10]. While mammography during pregnancy can be classified as a safe procedure with regard to the fetal radiation load of approximately 0.004 Gy [14], it often leads to false-negative results due to the altered radiodensity of the breast [2, 3]. Mammography plays a special role in imaging of undefined palpable lesions during pregnancy and lactation, but must be treated with particular care. For this reason, ultrasound examination of the breast is the method of choice for clarifying palpable abnormalities. It is capable of distinguishing between solid and cystic lesions with 97% certainty [2, 3]. In a Japanese study, ultrasound examination of the breast showed a sensitivity of 93% (n = 42) [2]. Magnetic resonance imaging is recom-

mended only in exceptional cases because of the transplacental action of the contrast agent, the potential heating of the fetus and the increased hypervascularity in pregnancy and lactation which limits the diagnostic value [14]. Screening for metastases with an increased radiation load (e.g. computed tomography, isotope bone scan) should be reserved for situations in which direct therapeutic consequences are derived from these investigations [15].

The diagnosis should be made primarily by punch biopsy for reasons that generally apply to breast cancer [16–18]. The risk of so-called ‘milk fistulas’ is generally low so that weaning is not obligatory. Due to the hypervascularity during and after pregnancy, the use of compression dressings to prevent hematomas is recommended [10]. The pathologist should always be informed of the patient’s gravid status in order to avoid incorrect diagnosis due to pregnancy-associated tissue changes.

## Histopathological Features

The great majority of pregnancy-associated breast cancers (75–90%) are of the invasive ductal type [1, 2, 19]. The tumor extent is in every respect more advanced than outside of pregnancy. Pregnancy-associated breast cancer is connected with generally bigger tumors and more frequent axillary lymph node metastases and distant metastases. Also, hemangiosis carcinomatosa is observed more often at presentation [2, 19–22]. Views differ on whether this phenomenon is a result of the delayed diagnosis or whether the disease dynamics are accelerated by pregnancy-associated factors such as altered vascularity, higher serum hormone levels or pregnancy-associated immunosuppression. Furthermore, the estrogen receptor status of pregnancy-associated breast cancer patients is negative much more often than that of age-matched control groups, which may be caused by down-regulation of the hormone receptor [1, 2, 13, 22–27]. More recent investigations have also shown that HER2/neu overexpression is encountered more often in pregnancy-associated breast cancer (58% of cases) [26].

## Surgery and Radiotherapy

In principle, the locoregional therapy of pregnancy-associated breast cancer is in accordance with the general guidelines for breast cancer therapy. Since there are no conclusive data on primary systemic therapy in pregnant patients, surgery is the primary treatment in most cases. Exceptions in the pregnant situation also include inflammatory or locally advanced carcinomas where primary surgery is not appropriate. The risk of abortion due to surgery involving general anesthesia is slightly increased (rate ratio 1.6–2). Breast-preserving surgery should be attempted and is associated with results similar to

those obtained with mastectomy [28, 29]. Because of the high incidence of axillary lymph node metastases (56–83%) [21], systematic axillary dissection is regarded as the gold standard. In recently published studies, measurements of activity after radionuclide labeling in the region of the breast and axilla yielded undetectable or very low radioactivity in the pelvis so that it appears unlikely that the fetus is at risk after sentinel node biopsy. However, because of the absence of clinical data, sentinel lymph node excision with radiotracer labeling should only be performed when strictly indicated [30, 31].

Radiation of the breast and/or chest wall is usually not performed during pregnancy because of the risk of malformation and radiotherapy-associated malignancies of the fetus. The risk increase of fetal malignancy is 6.57 cases/10,000/rad/y [32]. Since due to the usually advanced tumor stage, the risk of systemic recurrence predominates in the majority of patients, local radiotherapy is in most cases given only after the conclusion of systemic therapy and hence after the pregnancy. Lactation may be impaired after radiation of the breast [23].

### Cytostatic Therapy

Chemotherapy is indicated in the majority of patients with pregnancy-associated breast cancer. After the first trimester, anthracycline-containing chemotherapy is regarded as the treatment standard just as in non-pregnancy-associated breast cancer. In the only prospective study to be carried out on the use of FAC chemotherapy (5-fluorouracil, doxorubicin, cyclophosphamide) during pregnancy, no fetal anomalies were observed [23]. In general, in breast cancer treatment, anthracyclines are regarded as the drugs with the best benefit-risk relationship, while folate antagonists, such as methotrexate, are strictly contraindicated, as they are the main cause of fetal malformation [33]. The systemic use of cytostatic substances during pregnancy must be indicated particularly strictly, as it not only poses risks for the mother but also substantial hazards for the fetus. In principle, the benefits of chemotherapy during pregnancy for the mother must always be weighed against the resulting risks for the fetus, and this situation must be taken into account in the selection, dosage, number of cycles and administration of cytostatic agents [34].

Undoubtedly, the risk for the fetus is highest when chemotherapy is given during the first trimester of pregnancy – the period of gestation in which the dynamics of organogenesis make the embryonic organism particularly vulnerable to cytostatic substances. There is a significantly increased risk of abortion and fetal anomalies, which appears to be greatest between weeks 2 and 8 post-conception [35–37]. In a study by the National Cancer Institute (NCI), all but 2 of 52 chemotherapy-associated fetal anomalies had occurred following chemotherapy during the first trimester. As the risk of fetal malformation is 16% in the first trimester compared to 1.3% in the later stages of pregnancy [38], cytostatic therapy should

in principle be avoided during this time. After organogenesis is concluded, the hematopoietic system, the central nervous system, the eyes and the ears remain more at risk than other fetal organs [39]. Although the risk of malformation rapidly decreases in the second and third trimester, the risk of intrauterine growth retardation and premature delivery due to cytostatic treatment is increased [40]. However, observational studies have not found any learning disorders or hematological or immunological abnormalities in children up to early school age [41].

Anthracyclines exert their effect by incorporating the high-molecular-weight substance into the DNA. Most data during pregnancy have been obtained with doxorubicin. Fetal malformation occurred in more than 200 patients, but only when the cytostatic drug was used during the first trimester as opposed to later gestational periods [42–47]. As experiences with the use of epirubicin in pregnancy are much more limited (n = 13) [48, 49], doxorubicin should be the drug of choice, if an efficacy similar to that of epirubicin can be assumed, as is the case with breast cancer. However, the question remains whether fetal cardiotoxicity is a result of the transplacental action of the anthracyclines, which is observed dose-dependently in adults. In an echocardiographic study of fetuses between weeks 20 and 40 of pregnancy, no increase in cardiomyopathy was found when anthracycline-unloaded fetuses were compared to chemotherapy-loaded fetuses [50]. Because of the lack of long-term experience with this substance group, however, appropriate caution is required when considering the indication, as 4 cases of postnatally diagnosed cardiotoxicity have been reported after intrauterine anthracycline loading. Therefore, signs of postnatal heart failure should be particularly watched out for [51, 52].

Antimetabolites, such as the folate antagonist methotrexate, represent the most problematic group of cytostatics with regard to their use in pregnancy. They inhibit the cell metabolism by being incorporated as false substrates during DNA or RNA synthesis regardless of the cell cycle. Methotrexate in a dose of more than 10 mg/week causes malformations in the first trimester similar to those of the aminopterin syndrome: cranial dysostosis, disorders of bone maturation, hypertelorism, broad nasal saddle, micrognathia and ear deformities. Following administration of the antimetabolite 5-fluorouracil during pregnancy, a total of 53 cases were described with different outcome, ranging from unremarkable courses to intrauterine fetal death. Intrauterine growth retardation was observed in 11% of cases [53, 54]. The antimetabolites cytarabine and mercaptopurine are not used in gynecological oncology.

Alkylating agents, in particular cyclophosphamide, are also an integral part of common chemotherapy schedules for the treatment of breast cancer. A range of malformations, such as limb, eye and ear deformities, have been observed following the use of cyclophosphamide during the first trimester [55–57]. From the second trimester, alkylating agents can apparently be used with much lower risks. Of 92 documented

**Table 1.** Valid chemotherapy regimens in pregnancy-associated breast cancer

| Regimen              | Agents   | Dosage/administration/interval  |
|----------------------|--|---|
| 4x EC                | epirubicin<br>cyclophosphamide                   | 90 mg/m <sup>2</sup> / i.v. / d1, q3w, 4 cycles<br>600 mg/m <sup>2</sup> / i.v. / d1, q3w, 4 cycles   |
| FEC120 (Levine)      | 5-fluorouracil<br>epirubicin<br>cyclophosphamide | 500 mg/m <sup>2</sup> / i.v. / d1+8, q4w, 6 cycles<br>60 mg/m <sup>2</sup> / i.v. / d1+8, q4w, 6 cycles<br>75 mg/m <sup>2</sup> / p.o. / d1–14, q4w, 6 cycles |
| FEC100 (Bonnetterre) | 5-fluorouracil<br>epirubicin<br>cyclophosphamide | 500 mg/m <sup>2</sup> / i.v. / d1, q3w<br>100 mg/m <sup>2</sup> / i.v. / d1, q3w<br>500 mg/m <sup>2</sup> / i.v. / d1, q3w                                    |

q3w: 3-weekly, q4w: 4-weekly, d: day.

cases, 2 fetuses died intrauterinely, in each case when the alkylating agent was combined with other cytostatics [58]. Intrauterine growth retardation was observed in 7% of cases [59]. The alkylating agents dacarbazine and busulfan are not used in gynecological oncology, and there are no conclusive results regarding ifosfamide. Chemotherapy regimens which have been extensively evaluated and have shown acceptable safety are summarized in table 1.

No or little data is available on newer agents which have proven increased efficacy in the treatment of breast cancer, such as paclitaxel, docetaxel, gemcitabine or capecitabine. Despite the vast experience with taxanes of almost 10 years, only 2 case reports are currently available on the use of taxanes in pregnant patients [60–62]. Considering the modest overall survival benefit of the novel agents in comparison to conventional chemotherapy, such as FEC (5-fluorouracil, epirubicin, cyclophosphamide), the authors recommend favoring cytostatic regimes which have been extensively evaluated.

The timing of chemotherapy during pregnancy should in principle be aimed at completing the final cycle at least 2–4 weeks before the (planned) birth, as both the maternal and the fetal chemotherapy-induced side effects can lead to a significant increase in intra- and postpartum complications. At the time of birth, myelosuppression in the mother should have passed the leukocyte nadir in order to minimize the risk of peripartum infection. Moreover, the organs of the neonate are not capable of sufficiently metabolizing cytostatics still present in the fetal body without the transplacental detoxification assistance of the mother [23, 63, 64].

### Endocrine Therapy

Adjuvant endocrine therapy with anti-estrogens during pregnancy is contraindicated for 2 reasons: on the one hand, a range of tamoxifen-associated fetal anomalies are found in the literature [65, 66], and on the other hand, there is currently no evidence that endocrine therapy during pregnancy leads

to an improved prognosis. This observation might be attributable to the fact that most pregnancy-associated breast cancers are hormone receptor-negative. Analogously, iatrogenic induction of menopause does not lead to an improved prognosis. In fact, in 2 studies, a worsening of the prognosis was observed in patients who had undergone oophorectomy [2, 20]. Termination of pregnancy does not lead to an improved prognosis either but may actually impair the prognosis, and it is not indicated from an oncological point of view [12, 67].

### Further Family Planning

Premenopausal breast cancer patients who want to have children frequently seek advice on further family planning after successful conclusion of the primary breast cancer treatment. Unfortunately, all available recommendations are without adequate evidence [10, 68]. So far, the originally anticipated increase in the risk of recurrence due to the endocrine changes during pregnancy has not been confirmed by any study [69]. However, the survival advantage postulated in a few studies of patients who became pregnant in the years following successful treatment of breast cancer is presumably based on a ‘healthy mother effect’ [10, 70]. Despite this fact, there is not data indicating that pregnancy after successful treatment of primary breast cancer compromises maternal prognosis. Consequently, fertility-preserving aspects should be considered when treatment is planned in premenopausal women. Gonadotropin-releasing hormone analogues are the only available medical protection against gonadotoxic chemotherapy. Assisted reproductive technology offers excellent results but requires a delay in implementing chemotherapy. Despite recent reports of embryo development after the transplantation of cryopreserved-thawed ovarian tissue, clinical experience is limited, and the technique remains experimental [71]. In summary, the decision for or against having children after the conclusion of primary breast cancer treatment should be guided by personal lifestyle choices rather than vague medical hypotheses [72].

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