Review

Breast Cancer Diagnosed During Pregnancy
Adapting Recent Advances in Breast Cancer Care for Pregnant Patients

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Breast cancer during pregnancy (BCP), although rare, is becoming more common and treatment should be as similar as possible to that for nonpregnant young patients with breast cancer. A group of specialists convened to review current guidelines and provide guidance on how recent advances in breast cancer diagnosis and treatment can be adapted for pregnant patients. The majority of patients with BCP will be considered for treatment during the pregnancy. Premature delivery should be avoided whenever possible. Most treatments, including sentinel lymph node biopsy, systemic therapy with taxanes, platinum agents, or dose-dense treatment can be safely given during pregnancy, after careful risk/benefit assessment for mother and child. Chemotherapy is contraindicated during the first trimester because of a higher risk of fetal malformations but is feasible in the second and third trimesters. Other treatments such as radiation therapy or anti–human epidermal growth receptor 2 treatment are in general not indicated during pregnancy but might be considered in some instances. Patient data should be collected in a systematic way whenever possible.

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Breast cancer diagnosed during pregnancy (BCP) is rare, but an increased awareness of treatment options has led to more intensive breast cancer treatment during pregnancy in recent years. The recommendations for diagnosis and treatment of BCP, first published in 2006 and updated in 2010, aimed to increase awareness that treatment during pregnancy is the first option,[1,2] adhering as closely as possible to the general recommendations for young nonpregnant women.

This article aims to provide guidance on BCP with a focus on novel data on BCP and recent advances in breast cancer therapy, including use of carboplatin, dose-dense chemotherapy, trastuzumab, neoadjuvant therapy, and sentinel lymph node biopsy (SLNB) as sole treatment, and how these can be adapted to the needs of pregnant patients (**Table 1**).

Methods

Members of the breast cancer guideline consortium of the German Cancer Society (DKG) (AGO Kommission Mamma; S.L., G.v.M., C.T.), the International Network on Infertility and Cancer in Pregnancy (INCIP) of the European Society of Gynecologic Oncology (S.L., K.v.C., P.B., F.A.), and other internationally renowned experts in the fields of breast cancer and placenta research (A.S., O.G., B.K., C.K., C.D., A.P., H.S., P.P., U.M.) reviewed the literature on BCP, with a focus on "when the general recommendation to treat as closely as possible to nonpregnant women cannot be followed." The aim was to provide a narrative review on this special patient cohort providing an update on current understanding of the disease, as well as diagnostic and treatment considerations. A meeting under the umbrella of the DKG and the UICC (Union Internationale Contre le Cancer), supported by DKG and the German Breast Group (GBG) Foundation, was held to discuss the draft recommendations.

Epidemiology

Breast cancer is one of the most common malignant neoplasms during pregnancy.[6,7] Overall, the incidence of BCP has been increasing during the last few decades (eFigure in the Supplement). Maternal age has been increasing in developed countries since the 1970s, and subsequently also in several developing countries.[8,9] The upward trend of breast cancer incidence and the postponing of childbearing have increased the numbers of BCP cases.[6,7,10,11] Approximately 1 in 5 breast cancers diagnosed in women aged 25 to 29 years is associated with a pregnancy, diagnosed either during pregnancy or during the first post-partum year. The reported occurrence of breast cancer diagnosed during pregnancy ranges from 2.4 to 7.3 per 100 000 pregnancies in population-based investigations.[6,7,10,11]

A Danish study found that 81% of pregnancies affected with breast cancer were terminated during the first trimester, whereas other reports found that only 19% of all BCPs were diagnosed in the

first trimester.[11,12] Delayed diagnosis is a likely explanation for the lower number of observed vs expected breast cancer cases.

Prognosis

Breast cancer during pregnancy generally presents in more advanced stages when compared with that in nonpregnant women, potentially resulting in an overall worse outcome.[13] Several previous studies have addressed this issue, but because of small sample size, results were inconsistent.[14,15] The largest cohort study included 313 patients and, controlling for stage, prognostic factors, and adjuvant treatment, survival was similar for patients with BCP vs nonpregnant patients with breast cancer.[16] In contrast to breast cancer diagnosed during the first year after delivery, the diagnosis of breast cancer during pregnancy does not seem to be an independent poor prognostic factor, provided that standard treatment is administered. Despite possible pharmacokinetic changes, survival rates did not differ between patients who received chemotherapy during pregnancy vs after delivery.[12]

Diagnosis

Imaging Diagnostics

The general recommendations have not changed since 2010. Breast imaging and staging require separate consideration. Breast ultrasound and mammography can be safely and effectively performed during pregnancy.[17,18] Bilateral mammography is recommended in all women with a confirmed or highly suspicious malignant lesion. The radiation dose is less than 3 mGy (to convert to rad, multiply by 100 000), which corresponds to approximately 7 weeks of exposure to background radiation.[19] The estimated dose to the uterus and fetus is less than 0.03 μGy.[20] Nevertheless, many patients and physicians are concerned about radiation safety and this should be discussed with the patient. "In general, maternal and fetal radiation exposure and dose are affected by gestational age, anatomic site, modality, and technique."[19(p778)] The threshold for negative effects of radiation on the fetus is approximately 100 mGy, with uncertainty at doses between 50 and 100 mGy.[21] Contrast-enhanced magnetic resonance imaging (MRI) is not recommended during pregnancy. The use of iodinated and gadolinium-based contrast agents during pregnancy is insufficiently explored. The imaging and/or staging procedures should be conducted only in advanced stages in which they might alter the treatment. Unnecessary and less accurate staging procedures should be avoided, as in nonpregnant patients with breast cancer. Whole-body MRI has not been studied sufficiently in breast cancer in general. Although pharmacologic agents used for diagnostic nuclear medicine and positron-emission tomography probably do not result in radiation exposure exceeding 50 mGy, their use is not recommended during pregnancy.[22] All palpable masses require imaging and imaging-guided biopsy without delay.

Pathologic Analysis

Histopathologic diagnosis based on core biopsy of the suspicious lesion is the gold standard for BCP. The pathologist needs to be informed about the pregnancy. Overall, the histological features of BCP tumors do not differ from those in young nonpregnant women with breast cancer.[12] Almost all are ductal invasive, mainly hormone receptor negative and undifferentiated. In general, tumor mutations do not differ between pregnant and nonpregnant young women, although small series showed significant differences in gene expression analyses.[23] No definite conclusions for general practice can be drawn so far from these analyses. The main challenge for future research is the selection of an appropriate control cohort. Matching cohorts by treatment and/or histologic subtype, as well as by age, is required.

At a Glance

- The treatment of breast cancer during pregnancy should resemble the treatment of breast cancer in nonpregnant young women to the greatest possible extent.
- Diagnosis by core biopsy and selection of surgical options is similar to those in nonpregnant women; sentinel node mapping with blue dye only and flap reconstructions should be avoided. Radiotherapy should be postponed until after delivery.
- Avoid preterm delivery.
- Chemotherapy should be delayed until after the first trimester. Standard adjuvant/neoadjuvant anthracycline, cyclophosphamide, and taxane combinations should be used. Dose-dense but not intensified dose-dense (higher dose over shorter interval) therapy can be given, but special attention needs to be paid.
- Dose should be determined according to actual weight; limited clinical data do not show inferior efficacy of treatment during pregnancy in spite of concerns raised by pharmacokinetic data.

BRCA Testing

Family history taking is a prerequisite, and genetic counseling should be offered according to national guidelines, which differ substantially between countries. *BRCA* testing will become treatment relevant. The majority of BCPs are triple-negative breast cancer (TNBC); in young patients with TNBC, the probability of detecting a germline *BRCA* mutation is approximately 20%.[24]

Local Treatment

Surgical Treatment

In general, the surgical approach is the same as for nonpregnant patients. Mastectomy is not recommended solely on the basis of pregnancy and possible consequent delay of the radiotherapy (RT). The general recommendations are detailed in a recent publication.[25] Immediate breast reconstruction after mastectomy is an essential component in the treatment of patients with breast cancer, particularly those who receive a diagnosis at a young age. On the basis of a single published experience, tissue expander insertion appears to ensure a short operation time and does not seem to be associated with considerable morbidity to the patient or the fetus. Hence, this surgical technique could be considered in the multidisciplinary treatment of women who receive a diagnosis of breast cancer during pregnancy.[26]

SLNB

Recommendations from the American Society of Clinical Oncology still state that pregnant patients should not undergo SLNB, based on cohort studies and/or informal consensus.[27] However, it has been

Table 1. Updated Recommendations for Breast Cancer Diagnosis and Treatment in Pregnant and Nonpregnant Women Incorporating Recent Advances

Intervention	Nonpregnant Women	Remarks for Pregnant Women
Diagnostic		
Ultrasound	NA	The preferred technique
Mammography	Techniques with lower exposure	Bilateral mammography recommended in case of BC
MRI and PET	Not generally recommended	Not recommended during pregnancy
Targeted Treatment		
Endocrine treatment	$GnRH^+$ aromatase inhibitors or tamoxifen	Not indicated
Trastuzumab and pertuzumab	Pertuzumab in addition to trastuzumab for neoadjuvant-treated patients	Risk/benefit analysis needs to be discussed, as early start of trastuzumab improves survival. However, fetal toxicity and oligohydramnios and anhydramnios need to be considered. No data for pertuzumab
Chemotherapy		
Anthracyclines	NA	Transplacental transport, although low, is higher vs taxanes. PK unchanged vs nonpregnant women
Taxanes	Paclitaxel and docetaxel are used mainly in sequential regimen. Weekly paclitaxel is the preferred taxane regimen	Transplacental transport very low. Small-series PK seems to be lower in pregnant vs nonpregnant women, but dose according to actual body weight and use dose for nonpregnant women. Prefer paclitaxel to docetaxel
Nab-paclitaxel	Higher pathological complete response rate in 1 study vs paclitaxel but no long-term data	No data during pregnancy, not indicated
Carboplatin	May be considered for neoadjuvant therapy in TNBC with or without germline *BRCA* mutation	May be considered for neoadjuvant therapy in TNBC with or without germline *BRCA* mutation
Fluorouracil	Does not demonstrate added value in nonpregnant women	Fluorouracil-containing regimen not indicated during pregnancy
Preferred Regimen Standard		
Epirubicin or doxorubicin with cyclophosphamide q3w followed by paclitaxel weekly	Taxane based: epirubicin-cyclophosphamide q3w followed by paclitaxel weekly is one of the most widely used regimens; long-term follow-up recently confirmed activity (reverse sequence is possible)	Taxane based: epirubicin with cyclophosphamide q3w followed by paclitaxel weekly (reverse sequence is possible—decision might be based on gestational age)
Epirubicin or doxorubicin with cyclophosphamide q3w followed by docetaxel q3w	An almost equally effective regimen—greater myelotoxicity, less sensory neuropathy	An option decision based on adverse effects and experience
Docetaxel-doxorubicin-cyclophosphamide	As effective as cyclophosphamide-doxorubicin-docetaxel, less frequently used because of higher toxicity	Not recommended during pregnancy because better evaluated and less toxic regimen available
Dose-Dense Regimen		
Epirubicin or doxorubicin with cyclophosphamide q2w followed by weekly paclitaxel[3,4]	Each is a standard regimen and an alternative to epirubicin or doxorubicin with cyclophosphamide q3w followed by paclitaxel weekly	Can be considered as an option in patients with higher risk BCP; G-CSF obligatory
Epirubicin or doxorubicin with cyclophosphamide q3w followed by paclitaxel q2w[3]		No data in BCP
Cyclophosphamide-doxorubicin with paclitaxel q2w followed by cyclophosphamide-doxorubicin-paclitaxel q2w[3,4]		Cyclophosphamide-doxorubicin q2w followed by paclitaxel q2w seems to be an alternative in patients with BCP[5]
Dose-Dense and Intensified Dose-Dense Regimens		
CT epirubicin-paclitaxel-cyclophosphamide q2w	Dose-dense and intensified dose-dense CT can be considered in certain high-risk patients	Intensified dose-dense CT is not recommended: high risk for febrile neutropenia and anemia with need for transfusion
Surgery		
Breast-conserving surgery or mastectomy	NA	Indication as in nonpregnant women
Sentinel lymph node biopsy	This is 1 standard procedure for a certain group of women. It is standard diagnostic procedure for women with cN0 disease.	Greater evidence to support use during pregnancy—use to be discussed in pregnant women. Radioactive tracer preferred. Use adapted 1-d protocol
Immediate breast reconstruction	NA	One series during pregnancy reported insertion of an expander as an option. Further breast reconstruction, eg, a flap is not a standard option during pregnancy—breast size differs between pregnant and nonpregnant status

Abbreviations: BC, breast cancer; BCP, breast cancer during pregnancy; cN0, baseline node negative; CT, chemotherapy; G-CSF, granulocyte colony-stimulating factor; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging; NA, not applicable; PET, positron-emission tomography; PK, pharmacokinetics; q2w, once every 2 weeks; q3w, once every 3 weeks; TNBC, triple-negative breast cancer.

shown that this procedure can be safely performed during pregnancy.[28,29] Sentinel lymph node biopsy involves locoregional administration of relatively low injected radioactivity doses, with rapid clearance of the negligible radioactivity in the body, as well as substantial and stable uptake at the injection site—which is shortly thereafter removed by surgical means. Considering the radiopharmaceuticals and the amounts of activity typically used for SLNB in optimized protocols, the doses absorbed by the fetus are mostly less than 20 μGy for 10 to 20 MBq (approximately 1 μGy/MBq [to convert becquerels to curies, 1 Bq ≈ 2.7×10^{-11} Ci]), as assessed by experimental results and Medical Internal Radiation Dose Committee models.[30,31]

From a maternal oncologic point of view, SLNB appears to be accurate and safe, with only 1 unsuccessful mapping and 1 recurrence among 97 patients with BCP.[32,33] Pregnant patients with breast cancer should be offered SLNB rather than axillary clearance whenever it is indicated according to general practice in nonpregnant patients. It is advisable to inject colloid in the morning (1-day protocol) to minimize radiation exposure. Blue dye as a sole procedure is not recommended outside pregnancy and is therefore not an option in BCP, because of the low (1%) but potentially harmful underlying risk of an anaphylactic maternal reaction.[34,35] In a small series of 25 women with SLNB during pregnancy, 7 received blue dye for mapping.[33]

Radiation Therapy

Radiation therapy during pregnancy is rarely indicated in BCP. In general, it is recommended to postpone RT until after delivery.[36] The available information on long-term consequences of in utero exposure to RT is limited.[37] The 2 factors that have to be considered when RT during pregnancy is indicated are the dose to the fetus and the risk that radiation exposure causes adverse effects to the fetus. It is important to relate the latter to the magnitude of spontaneously occurring abnormalities. Deterministic (teratogenic) effects must be discriminated from stochastic (carcinogenic) effects. The former are dose dependent and occur only above a certain threshold, while the severity of the latter is independent of the dose, although the probability is dose dependent and without a threshold.

In early pregnancy (when it may not have been diagnosed), irradiation will generally lead to spontaneous abortion, whereas from the third week onward malformations can occur. Radiation exposure may influence the development of the central nervous system, possibly inducing neuropsychological and behavioral dysfunction. The main stochastic effect is the induction of childhood cancer and leukemia. At low doses, the incidence of childhood cancer and leukemia (0.2%-0.3% for ages 0-15 years) does not seem to be increased. Following a dose of 10 mGy, the relative risk increases to 1.4, still resulting in a low absolute excess risk.[38] Another stochastic effect is the induction of germline mutations to the oocytes; however, there is no evidence of negative effects in humans (eTable in the Supplement).

The radiation dose received by the fetus depends on the distance between the RT field and the position of the fetus, so is dependent on gestational age, as well as the amount of leakage of irradiation outside the radiation field and the use of effective shielding, which can reduce the dose by 50% to 75%. During the first months of pregnancy, the uterus does not extend outside the true pelvis, and, provided that appropriate techniques and shielding are used, the dose to the fetus will be only 0.1% to 0.3% of the prescribed dose to the breast, resulting in a very low risk of inducing malformations.[37] Several cases with RT administered for BCP are reported, with low fetal doses and resulting in the delivery of healthy babies.[39] Therefore, RT might be considered in the first or early second trimester if the risk of delaying or omitting RT is believed to outweigh that of harming the fetus.

Systemic Therapy (Chemotherapy)

Chemotherapy is contraindicated during the first trimester of pregnancy because of a higher risk of inducing fetal malformations. The (US) National Toxicology Program monograph reports a prevalence of malformations of 14% if chemotherapy is given in the first trimester, declining to 3% if chemotherapy is applied later in gestation.[40] In comparison, the reported rate of major malformations in the general population is approximately 3% in the United States and 6.7% in a German registry.[41,42] Postponing chemotherapy treatment until after delivery might seem to be an option. However, data in nonpregnant young women indicate that delaying or postponing chemotherapy might increase the risk of relapse.[43] Therefore, it is recommended to treat women with BCP during the second and third trimester, following guidelines for nonpregnant young patients as closely as possible.[1,2] Some anticancer agents, such as trastuzumab, tamoxifen, and endocrine agents, should in general be avoided during pregnancy, given their potential fetal toxicity.[1,2] Individual decisions may be taken.

Anthracyclines, cyclophosphamide, and taxanes, the standard adjuvant or neoadjuvant combination recommended for nonpregnant patients, are recommended for treatment of BCP, after the first trimester.[44-46] One of the most widely used regimens, that is also used during pregnancy, is epirubicin hydrochloride–cyclophosphamide followed by weekly paclitaxel. The reverse sequence, starting with a taxane, is also possible.[47] Currently the data do not support the use of anthracycline- or taxane-free regimens because these are not considered to be standard in nonpregnant women. It was found that fluorouracil does not add any benefit to an anthracycline-taxane–based regimen[48] and is therefore no longer indicated for breast cancer therapy.

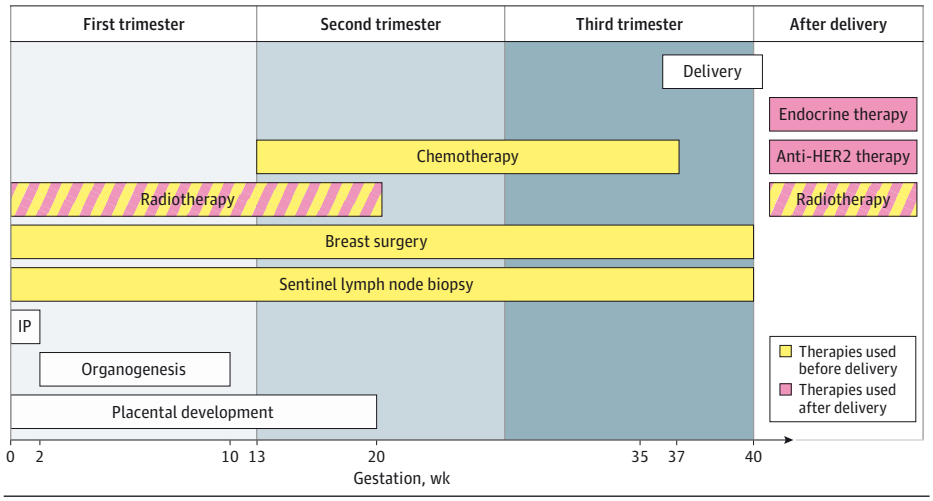
Platinum derivatives may have a role in the treatment of patients with TNBC.[49] Neoadjuvant trials demonstrated significantly higher pathological complete response rates by adding carboplatin, but data are immature for survival analyses. Therefore, carboplatin therapy may be considered during the second and third trimesters of pregnancy.[50,51] It is unclear which platinum molecule is most effective, but carboplatin may have less overall toxicity than cisplatin.[40]

Several studies have shown that dose-dense (same dose administered over a shorter interval) or intensified dose-dense (IDD) (higher dose over a shorter interval) treatment leads to better survival than conventionally dosed chemotherapy regimens, especially in high-risk patients.[52,53] Whereas dose-dense chemotherapy seems to be an acceptable option during pregnancy, IDD chemotherapy has not been studied systematically and only a small number of reports are available.[5] The high rate of grade 2 to 4 anemia (59%), with a need for transfusion in 28% of patients, and the high risk of febrile neutropenia (7% despite primary granulocyte

Table 2. General Rules for Safe Application of Chemotherapy During Pregnancy

Rule	Comment
Maintain dose intensity	Important to discuss timing of the chemotherapy start in relation to delivery
Use published standard protocols	Neither decrease nor increase the dose. Do not increase treatment intervals
Dose according to actual body weight	Important to avoid underdosing, which is a risk factor during pregnancy, due to physiologic variation in drug pharmacokinetics. We do not recommend dose adaptation in overweight nonpregnant women
Do not increase the dose	Some data show a lower area under the concentration-time curve and maximum serum concentration in women treated with taxanes during pregnancy vs nonpregnant women. On the basis of 11 cases without outcome data, dose increase cannot be recommended
Recommended to discontinue chemotherapy at approximately week 35 to 37 of gestation	To allow the bone marrow to recover and prevent hematologic toxicity to mother and child

Figure. Overview of Therapeutic Options During Pregnancy



Crucial phases: implantation (0-2 weeks), organogenesis (2-10 weeks), fetal phase (>10 weeks). Starting chemotherapy from week 13 to 14 instead of week 10 allows a "safety period." Radiotherapy if indicated and decided not to be postponed to after delivery can be applied during the first until early second trimester. Preferred option if possible is to apply after delivery. Endocrine therapy and anti–human epidermal growth factor receptor 2 (anti-HER2) treatment is to be given after delivery. IP indicates implantation.

colony-stimulating factor [G-CSF] prophylaxis), mandate a strict risk/benefit analysis and IDD therefore cannot generally be recommended in BCP.

General rules for administering chemotherapy to a pregnant patient with breast cancer are summarized in **Table 2**. The physiological variations in drug pharmacokinetics during pregnancy raise important concerns regarding optimal drug dosing in pregnant patients.[54] Physiologic alterations associated with pregnancy result in lower maximal concentrations of chemotherapy and a lower area under the concentration-time curve.[55] Most anticancer agents are empirically prescribed according to body surface area, resulting in large interpatient variability, even in patients who are not pregnant.

An increased activity of major enzymes involved in the metabolism of taxanes and anthracyclines (including cytochrome p450 isoforms such as CYP3A4 or CYP2C8) has been observed during the late trimesters of pregnancy, potentially resulting in decreased drug exposure.[56] Moreover, because albumin concentrations vary significantly during pregnancy and taxanes are highly protein bound, this may lead to significant changes in taxane pharmacokinetics.[54] Pharmacokinetic data comparing the use of anthracyclines and taxanes in pregnant vs nonpregnant patients demonstrated that taxane serum levels were significantly decreased during pregnancy, especially for paclitaxel.[57] Conversely, exposure to anthracyclines was not significantly modified by pregnancy.[54,55]

Whether doses should be increased in pregnancy remains uncertain, given that such increases could result in severe toxic effects, with potential harm for mother and neonate. Second, in overweight women, who also have altered pharmacokinetics, the dose will not be increased.[58] Third, it was shown that the chemotherapy is as active in pregnant as in nonpregnant women.[59] Thus, dosing based on body surface area, using the current patient weight (prior to every course), remains a standard, as well as using the same dose for pregnant as nonpregnant women.

Whereas maternal drug exposure is a concern in terms of treatment efficacy, the transplacental transfer of anticancer agents is a critical issue for fetal safety. The placenta is the central organ for fetal-maternal exchange, in addition to its functions such as the protection of the fetus and preparing the maternal body for pregnancy and subsequent lactation.[60] Although the transplacental transfer of pharmaceuticals can be well analyzed using the perfused human ex vivo placenta, toxic effects of cancer therapy on the human placenta are poorly understood and data are limited.[61] One reason for this might be that most animal models fail to represent central features of human placentation, with even closely related species such as rhesus monkeys show diverging invasion patterns.[62]

Data on transplacental transfer rates indicate similar and reassuring data on anthracyclines and taxanes, although with marked interpatient variability, particularly with docetaxel.[13] As a consequence, from the fetal safety point of view, paclitaxel therapy should probably be preferred to docetaxel therapy in pregnant patients.[63] Significant transplacental transfer of carboplatin was demonstrated, but long-term data from the children remain limited.[40,64]

A significantly higher incidence of small-for-gestational-age neonates is observed when chemotherapy is given during pregnancy, indicating a potentially toxic influence on placental devel-

Table 3. Supportive Therapy for Chemotherapy During Pregnancy

Drug Class	Examples	Recommendation
Antiemetics		
5-HT3 antagonists	Ondansetron, palonosetron, granisetron, tropisetron, dolasetron	Ondansetron therapy during pregnancy not associated with significantly increased risk of adverse fetal outcomes. Other 5-HT3 antagonists are less well investigated. Granisetron does not appear to cross the placenta
Neurokinin 1 inhibitors	Aprepitant, fosaprepitant	No data available; single reports with no adverse outcome—can be given if necessary
Corticosteroids	Dexamethasone, betamethasone, methylprednisolone	Dexamethasone therapy contraindicated in first trimester (risk of cleft palate). Attention deficit disorder reported with dexamethasone and betamethasone use. Methylprednisolone is the preferred option
H1 antagonists		Seem to be safe
H2 antagonists	Ranitidine, cimetidine	No increased incidence of malformations with H2 blocker. Can be used to prevent allergic reaction
Proton pump inhibitors	Omeprazole, pantoprazole	Seems to have muscle-relaxant effects in vitro
Colony-Stimulating Factors		
G-CSF	Daily use (filgrastim, lenograstim) or long acting (pegfilgrastim, lipegfilgrastim)	Information about the use of G-CSF during pregnancy is limited. In a series of 34 children exposed to daily G-CSF therapy, no splenomegaly and no increased rate of opportunistic infections was reported

Abbreviations: H1, histamine H1 receptor; H2, histamine H2 receptor; G-CSF, granulocyte colony-stimulating factor; 5-HT3, 5-hydroxytryptamine.

opment leading to placental malfunction, eg, via incomplete trophoblast invasion into the uterus, resulting in a decreased transfer of nutrients to the fetus.[12,65] Organogenesis is completed at approximately the 10th week of gestation (and this is the reason why chemotherapy can be considered from that time point onward), but trophoblast invasion of the placenta is not completed until approximately week 20.[66] These observations explain why starting chemotherapy at week 14 might interfere with late stages of placental development (**Figure**).

Anti–Human Epidermal Growth Receptor 2 (Anti-HER2) Treatment

Trastuzumab is indicated as an integral part of primary treatment in women with HER2-positive breast cancer. Initiating trastuzumab therapy as early as possible, and in combination with the cytotoxic agents rather than in sequence, is associated with a better long-term outcome in nonpregnant patients.[67] In a recent review, the authors identified 18 reports in the literature of using trastuzumab during pregnancy and 19 newborns.[45] They described oligohydramnios and anhydramnios as the most frequent adverse effect (33%), which was in general self-limiting when trastuzumab therapy was discontinued. However, most of the pregnancies ended prematurely and 4 of the newborns died as a result of complications of prematurity (mainly respiratory failure). Although trastuzumab use is generally not recommended during pregnancy, it may be discussed in special high-risk situations.[45] Fetal and maternal risks and benefits need to be weighed, and informed decision making is crucial, if trastuzumab is considered for use during pregnancy. However, inadvertent fetal exposure to 1 to 2 cycles of trastuzumab therapy is no reason for termination of pregnancy. Treatment with pertuzumab in addition to trastuzumab and chemotherapy increases the pathological complete response rate in patients with HER2-positive breast cancer, but currently there are no data on use of pertuzumab during pregnancy.

Supportive Treatment

The overall aim is to offer the best supportive therapy without adding further risk. In general, the majority of supportive regimens can be given safely during pregnancy (**Table 3**). According to international guidelines, women receiving an anthracycline-cyclophosphamide combination are at particularly high risk of nausea and vomiting. A 3-drug regimen including a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) inhibitor is recommended in nonpregnant patients.[68] 5-HT3 antagonists have been extensively studied for pregnancy-induced and spinal anesthesia–induced nausea and vomiting and were shown to be safe.[69] Use of NK1 inhibitors, without adverse effects, has been reported only in single cases of a BCP registry (S.L., unpublished data, 2015), but these agents cannot be recommended until more safety data become available. The recommendation on dexamethasone remains unchanged (Table 3).[70-72]

Although G-CSF support can reduce the occurrence of febrile neutropenia, its effectiveness and safety profile during pregnancy are not clearly confirmed. One retrospective analysis reported that the use of daily or long-acting G-CSF did not affect outcome in the newborn.[73] Because dose-dense chemotherapy absolutely requires the use of primary prophylaxis with G-CSF, this supportive treatment should not be withheld if a careful risk/benefit assessment indicates that this more aggressive form of chemotherapy is required.

Obstetrical Care

In utero exposure to chemotherapy has also been associated with a small increase in risk of preterm rupture of membranes (3% vs 0%) and preterm labor (6% vs 2%).[12] The largest and most recent studies report a mean gestational age at delivery of 36 to 37 weeks, indicating that a significant proportion of patients deliver (iatrogenically) preterm.[12,65] Reassuring data from older studies investigating

long-term outcome of children antenatally exposed to chemotherapy were recently confirmed using a standardized age-appropriate assessment to examine neurocognitive functioning, as well as in a subsequent case-control study.[74,75] Because prematurity has an important impact on neuropsychological outcome, this should be avoided whenever possible. Treatment during pregnancy may help to achieve a full-term pregnancy. Also, the cardiac outcome of children who received anthracyclines antenatally appears to be reassuring.[76]

The obstetrician should see the patient at least once every 3 weeks to perform an ultrasound assessment of the fetus, the amniotic fluid, and the flow in the umbilical artery, in addition to standard prenatal care. Prior to start of treatment, the status quo of the pregnancy should be documented and the estimated date of delivery confirmed. If the pregnancy is complicated, for example by gestational diabetes or hypertension, additional measures need to be implemented and shorter intervals might be necessary.

It is recommended to deliver as closely as possible to term, after close observation of mother and child. A 2- to 3-week interval between the last chemotherapy cycle and delivery is recommended, in order to allow the bone marrow to recover and prevent hematologic toxicity to mother and child.

Conclusions

Breast cancer should be treated during pregnancy following the general guidelines for young nonpregnant patients as closely as possible. The complex medical situation of BCP requires a multidisciplinary discussion. Major concerns are congenital malformations, effects on fetal growth, preterm delivery, and long-term toxic effects in the children.[12] An individual risk/benefit analysis, taking into account the mother and fetus, is crucial. Staging and treatment procedures need to be discussed, with the aim of reducing the toxic effects on the fetus from (accumulated) radiation exposure. A close collaboration with the obstetrician and perinatologist is warranted.

Evidence for current and future recommendations for BCP, taking into account the evolution of treatment for the care of our patients, can be generated only by large prospective cohort studies. Cases of BCP should be registered through the German Breast Group (http://www.germanbreastgroup.de) or through the registry of the INCIP (http://www.cancerinpregnancy.org). These international collaborations started 10 years ago and have provided the basis of current knowledge on BCP.

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