REVIEW ARTICLE

Challenges in managing breast cancer during pregnancy

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ABSTRACT

Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring anytime during gestation, lactation or within one year after delivery. The optimal management of pregnant women with breast cancer is challenging and not well established; the main concern is the effect of the drugs on the developing fetus and long-term complications after in utero exposure to anti-cancer drugs. Surgical resection is the mainstay of treatment for early breast cancer diagnosed during pregnancy. Modified radical mastectomy is standard of care in first trimester, whereas breast-conserving surgery (lumpectomy with lymph node dissection) can be performed preferably in the second and third trimester. Of note, breast-conserving surgery is not contraindicated per se during the first trimester, but owing to the potential impact of delaying radiotherapy. Radiation therapy is not favored during pregnancy. Moreover, tamoxifen is contraindicated during pregnancy; the agent has been associated with birth defects in up to 20% of exposures. Chemotherapy is generally contraindicated during the first trimester because of the possible damage to organogenesis. Anthracyclines-based regimens are the most widely used is breast cancer treatment and were been shown to be associated with favourable safety profile when administered during pregnancy. As for taxanes, more limited data is available. The use of trastuzumab is contraindicated during pregnancy, given the apparent risk of oligo- and/or anhydramnios as well as the unknown long-term sequelae on the fetus. It is obvious that, diagnosis of breast cancer during pregnancy adds complexity to cancer treatment recommendations. In all cases, a multidisciplinary therapeutic approach among obstetricians, gynaecologists, surgical oncologists, radiation oncologists, medical oncologists, pediatricians and hematologists is clearly warranted.

KEY WORDS

Breast cancer; pregnancy; controversies; chemotherapy

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Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring anytime during gestation, lactation or within one year after delivery (1,2). Breast cancer is one of the most common tumor during pregnancy along with melanoma and cervical cancers and occurs in approximately one out of 3,000-10,000 pregnancies (3). Diagnosis of PABC is expected to become more frequent in the forthcoming years since there is an increasing trend for women to delay childbearing (4,5).

Significant controversy exists in the literature regarding the influence of pregnancy upon breast cancer prognosis. Some studies did not demonstrate any aggravating role (6-8), whereas other studies have reported that pregnancy itself may not represent a veritable poor prognostic factor for breast cancer, attributing any detrimental effects to the delayed diagnosis of tumours in pregnancy (9-13). On the other hand, some studies point to the opposite direction, indicating an independent, aggravating role of pregnancy (14-16). Of note, a recently published meta-analysis, including 30 studies, have shown that PABC is independently associated with poor survival particularly when diagnosed shortly post-partum (17).

In this context, it should be noted that diagnosis of breast cancer during pregnancy adds complexity to cancer treatment recommendations, taking into consideration that treatment

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strategies offered for pregnant women with breast cancer should not differ from their non-pregnant counterparts. Hence, the optimal management of pregnant women with breast cancer is challenging and not well established; the main concern is the effect of the drugs on the developing fetus and long-term complications after in utero exposure to anti-cancer drugs. This review, taking into consideration all available data, focuses on critical issues regarding the management of breast cancer during pregnancy, such as consultation of pregnant patients, surgical procedure, administration of chemotherapy regimens during pregnancy and lactation, radiation therapy, targeted treatment administration during pregnancy, etc.

Surgical procedure

Surgical resection is the mainstay of treatment for early breast cancer diagnosed during pregnancy (3,18). Modified radical mastectomy is standard of care in first trimester of pregnancy. Of note, breast-conserving surgery is not contraindicated per se during the first trimester, but owing to the potential impact of delaying radiotherapy; hence, mastectomy is considered in these cases. Breast-conserving surgery (lumpectomy with lymph node dissection) can be performed preferably in the second and third trimester because of the necessary ensuing radiotherapy that in any case must be delayed up until after delivery (3,18). The decision to proceed with breast-conservation or mastectomy should be based upon the clinical situation of each patient. In this context, it should be noted that surgery is a safe procedure and can be performed in all trimesters with minimal risk for the fetus; after the 12th week of gestation, in particular, the risk of abortion is minimal (19-23). Radical mastectomy may be followed by immediate breast reconstruction; however, there are no data on reconstructive breast surgery during pregnancy. Hence, reconstruction-if needed-should be better restricted to a prosthetic implant or preferably should be carried out post partum (24).

As far as sentinel lymph node biopsy (SLNB) in pregnant women is concerned, there are insufficient safety data to support this procedure during pregnancy owing to radiation concerns. However, a dosimetry study followed by a prospective trial on 12 pregnant breast cancer patients (25,26) supported the safety of SLNB, when performed with low-dose lymphoscintigraphy using 99m-Tc human serum albumin nanocolloids. In this study, eleven healthy babies were born with no malformation and with normal weight, whereas one newborn had a ventricular septal defect suspected before lymphoscintigraphy. Moreover, there was no evidence of axillary recurrence at a median follow-up of 32 months. By contrast, blue dye is associated with a risk of an anaphylactic maternal reaction, which would probably distress the fetus (27). Therefore, the use of blue dye should be avoided during pregnancy. Hence, SLNB with low-dose lymphoscintigraphy using 99m-Tc human serum albumin nanocolloids may be considered in selected cases and within centers with experience in carrying out this technique (28).

Radiation therapy

Radiation therapy is not favored during pregnancy owing to its teratogenic effects on the fetus; hence, there is a general agreement to postpone radiotherapy up until after delivery (3,18,24,29). In the first trimester (before the completion of organogenesis), radiotherapy may be related to fetal death, malformations, microcephaly, intrauterine growth retardation, mental retardation, and induction of childhood neoplasms and hematologic disorders (30,31). Adjuvant radiotherapy to the breast is never an "urgent" procedure; hence, postponing it could be better given the potential hazards of the fetus. Of note, the latter remains very low anyways during the first and second trimester with adequate shielding given that the uterus is far from the radiation field (31,32). However, in patients with brain metastases, radiotherapy to the brain is certainly given during pregnancy because there is an urgent clinical need with very low potential fetal adverse effects (31,32).

Hormonal treatment

According to current clinical recommendations, tamoxifen is contraindicated during pregnancy; the agent has been associated with birth defects in up to 20% of exposures, including Goldenhar's syndrome (33), ambiguous genitalia, vaginal bleeding, and spontaneous abortion (34-36). During pregnancy, tamoxifen and its metabolites interact with rapidly growing and developing embryonic or fetal tissues (37). Although several case reports describe tamoxifen exposure and healthy neonatal outcomes (38), there is a general agreement to postpone tamoxifen up until after delivery (29). In this context, it should be noted that aromatase inhibitors are not indicated in premenopausal women.

Chemotherapy administration

Chemotherapy plays a key role in improving the survival of patients with early stage breast cancer. The decision to administer chemotherapy in pregnant women with breast cancer should follow the same guidelines as applied to non-pregnant patients. Chemotherapy is generally contraindicated during the first trimester because of the possible damage to organogenesis, whereas several recent studies have shown that certain chemotherapy regimens can be relatively safely administered during the second and third trimester (39-41). Worthy of note, in the first trimester, the risk of congenital malformations ranges from 10-20%, whilst it drops to 1.3% in the third trimester of

pregnancy (39).

In this context, it should be noted that although pregnancy will alter the pharmacokinetics of cytotoxic drugs, there are currently no studies justifying a change in dosage. Hence, during pregnancy, dosages should not differ from those used outside pregnancy, even if few pharmacokinetic and pharmacodynamic data are available during pregnancy (24).

Anthracyclines-based regimens are the most widely used is breast cancer treatment and were been shown to be associated with favourable safety profile when administered during pregnancy (42). More specifically, the most commonly used regimens, in the adjuvant setting, include 5-fluorouracil combined with doxorubicin (5-FU-A) and epirubicin or doxorubicin in combination with cyclophosphamide (E or A-C). Of note, no clear differences could be attributed to the aforementioned different regimens regarding maternal toxicities, short or long term fetal outcome and pregnancy outcome. Moreover, in the neo-adjuvant and in the advanced/metastatic setting, anthracyclines and anthracycline-based regimens remain the best choice (42,43).

More limited data is available on taxanes. More specifically, they have recently been incorporated in the ESMO and NCCN guidelines (3,18), as being considered relatively safe to administer beyond the first gestational trimester; the risk of abortion or congenital anomalies increases when they are administered during the first trimester. Moreover, the Food and Drug Administration classify docetaxel and paclitaxel as a category D drug (i.e., able to be administered in pregnancy if necessary).

According to a recent systematic review, a completely healthy neonate was born with a normal Apgar score, appropriate fetal growth and acceptable weight in the majority of breast cancer patients with taxanes administration during pregnancy (44). Moreover, 27 out of 30 children (90%) were completely healthy at a median follow-up of 16 months; among the remaining cases, one child with recurrent otitis media, one child with IgA deficiency and mild constipation and another child with delayed speech were reported (44,45). However, it should be underlined that there is limited information concerning the long-term consequences for the offspring. Moreover, only *ex vivo* data are available on the transplacental transfer of taxanes in humans, whilst in a human placental perfusion model, the transplacental transfer rate of paclitaxel was found to be low (<5%) (46).

Hence, as for taxanes, if required in the adjuvant setting, limited data is available in pregnancy (44). Still, acknowledging the limited amount of evidence, taxanes could be offered in sequence to anthracyclines following delivery (29). Regarding the metastatic setting, it seems that single agent taxane (paclitaxel or docetaxel) may represent an appealing option, especially for patients who are not suitable candidates for anthracycline-based regimens (44,47).

Targeted therapy during pregnancy

Trastuzumab

According to ESMO and NCCN guidelines (3,18), the use of trastuzumab is contraindicated during pregnancy, given the apparent risk of oligo- and/or anhydramnios as well as the unknown long-term sequelae on the fetus (48). Notably, the Food and Drug Administration classify trastuzumab as a pregnancy category B drug. While studies in cynomolgus monkeys reported no harm to the fetus, they failed to reveal placental transfer of trastuzumab in monkeys [reviewed in (48)].

A recent meta-analysis has shown that trastuzumab administration emerges as relatively safe during the first trimester of pregnancy, whereas a high incidence of oligohydramnios and/or anhydramnios is observed when this agent is used beyond the first trimester (49). An intriguing observation of this meta-analysis is that all children exposed to trastuzumab exclusively during the first trimester of pregnancy were completely healthy and showed no evidence of congenital malformations (50-52). Indeed, the occurrence of oligohydramnios/or anhydramnios was confined to pregnancies exposed during the second or third trimesters (49). A study by Pentsuk *et al.* concurred with this meta-analysis (53), showing that fetal exposure to trastuzumab is very low during the first trimester, and increases during the second half of gestation, to reach a drug concentration at birth similar to that of the mother.

Hence, as concerns trastuzumab administration in the adjuvant setting during pregnancy, it should be noted that there is no cause for exposing the pregnant HER2- positive woman and the fetus to the potential hazard of the agent. Mounting evidence outside pregnancy confirm the efficacy of trastuzumab even after 6 months of adjuvant chemotherapy (54), suggesting that a monoclonal antibody could be safely administered after delivery. On the other hand, as far as metastatic HER2- positive breast cancer is concerned, trastuzumab should be avoided and chemotherapy could start from the second trimester. However, in selected cases, where the agent may be urgently needed, its administration is recommended for a short period with careful control of the amniotic fluid, fetal growth and kidney function; should signs of oligohydramnios be observed, the agent should immediately be discontinued (49).

Moreover, unlike chemotherapy, trastuzumab does not induce amenorrhea (55), thus, an accidental pregnancy during its administration cannot be precluded if no adequate contraception is used. Of note, according to Azim *et al.* (56), patients who became pregnant after a trastuzumab-free interval of more than 3 months appeared to have normal pregnancy courses and outcomes. These data may be of particular significance to women who accidentally fall pregnant during trastuzumab administration but do not wish to terminate the pregnancy; in

this setting, trastuzumab should be discontinued and pregnancy be allowed to continue without urging an abortion. However, it should be stressed that no definite conclusion can be drawn given the limited number of observations; clinicians should always advise women to use active contraception while on trastuzumab therapy and to continue doing so for up to 6 months following completion of treatment (48,49,52).

Other biologics

There are insufficient data on lapatinib administration during pregnancy, but its pharmacological characteristics (massive transplacental transfer) would strongly caution against its use during pregnancy; hence, lapatinib cannot be recommended during pregnancy (3,18,24). Of note, there is only one report on lapatinib exposure in a woman during the first and second trimesters; the agent was discontinued and the delivery was uncomplicated with a healthy newborn (57).

Moreover, the use of bevacizumab during pregnancy cannot be recommended, given its mode of action and the lack of available data (3,18,24).

Supportive treatment

Antiemetics such as 5HT antagonists, steroids, or antihistamines are not contraindicated during pregnancy. Granulocyte-stimulating factors are considered as pregnancy category C; hence, they should be used during pregnancy by the clinical necessity (1). Concerning bisphosphonates, limited data is available for their use during pregnancy. More specifically, data on 51 pregnant women for different indications did not reveal any increase in maternal and/or fetal morbidity (58). However, given that bisphosphonates remain in mineralised bone for several years and that available data on pregnant patients are limited, it should be clearly stated that bisphosphonates should be used with caution and on personalized basis; if used, hypocalcaemia affecting the contractility of the uterus should be avoided (58,59).

Fetal and pregnancy monitoring

A multidisciplinary approach involving medical and surgical oncologists, high-risk obstetric care, genetic counsellors, pharmacists, radiation oncologists, and neonatologists is mandatory for the successful management of women with breast cancer during pregnancy (24). It is without doubt that strict fetal monitoring with morphometric ultrasound and umbilical artery Doppler should be performed at regular intervals during gestational chemotherapy (3,18,24).

The timing of delivery should be balanced according to the oncological treatment schedule and the maturation of the fetus; as in non-cancer patients, the aim of a full term delivery (>37 weeks' gestation) is important since prematurity affects the cognitive and emotional development of children (60-62). Moreover, it is recommended that patients should not receive any chemotherapeutic agents for at least 3 weeks prior to delivery so as to avoid problems associated with haematopoeitic suppression (bleeding, infection, anaemia) in the mother and baby, and to prevent drug accumulation in the fetus (24,43,63). The mode of delivery is determined based upon the obstetrical indication (24). Although metastases to the placenta is a rare event in breast cancer patients, the placenta should always be evaluated after delivery (64,65).

In the absence of safety data, breastfeeding in the first weeks after chemotherapy is not recommended (3,18,24). Of note, primary inhibition of milk production is needed because especially lipophylic agents such as taxanes can accumulate in the milk.

Conclusions

In this context, it should be noted that treating cancer during pregnancy represents a relatively uncommon situation. The available data are limited and consist mainly of case reports, case series, and retrospective registries; hence, in order to provide further information for this challenging clinical situation, improved collaboration between registries and cancer centers is more than warranted given the long-term implications for both the breast cancer patient and neonate.

Moreover, it should be stressed that in all cases, a multidisciplinary therapeutic approach among obstetricians, gynaecologists, surgical oncologists, radiation oncologists, medical oncologists and hematologists is clearly warranted; the optimal therapeutic strategy in a pregnant patient with breast cancer diagnosis should take into consideration the gestational age, stage of breast cancer, treatment options, the wishes of the patient, and a host of psychological, ethical, religious, and even legal considerations.

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