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Review

Treatment of breast cancer during pregnancy: Regimen selection, pregnancy monitoring and more …

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ABSTRACT

Breast cancer is uncommonly diagnosed during pregnancy but when encountered, it poses several clinical conflicts. Managing patients with gestational breast cancer should not be associated with considerable risk of morbidity provided the choice of the right drug in the right time for the right patient. Due to its relative rarity, we lack a standardized approach to manage these patients. Previous reports have suggested that women can be offered treatment strategies similar to those offered in the "non-pregnant" setup. Nevertheless, generalizing treatment decisions is too hard and treatment of these cases should be tailored according to the clinical situation. In order to ensure proper counseling of these patients, there are several key points that need to be addressed. These include timing of chemotherapy administration, the scheduling of agents, and pregnancy monitoring. In this review, we provide some guidance on how to select the chemotherapy regimen and address the feasibility and safety of administering trastuzumab during pregnancy. We also discuss some practical points on monitoring these patients during the course of pregnancy.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer during pregnancy. Nearly 1 out of 3000 pregnancies is complicated with BC and approximately 10% of BC patients below the age of 40 develop the disease during pregnancy.[1] As BC incidence increases with age and due to the rising trend of delaying pregnancy to later in life,[2] this rare coincidence is expected to increase.[3] Breast surgery has been shown to be safe if performed during pregnancy.[4,5] On the other hand, there is a general agreement to postpone radiotherapy as well as tamoxifen after delivery; the latter particular being associated with high risk of fetal toxicity.[6–8] Hence, offering chemotherapy and targeted agents for pregnant women with BC remain the main clinical challenge.

In the meantime, we lack a standardized approach for treating BC patients diagnosed during pregnancy. Clinical decisions are mainly based on few small-sized cohorts (mostly retrospective), case-control studies and case reports. Given these limitations, oncologists should be aware of the principle clinical practice key points including treatment choice, scheduling, pregnancy monitoring and delivery planning to be able to manage these patients in an adequate manner.

Overview on the safety profile of common breast cancer regimens

The teratogenicity of drugs depends on several factors, including time of exposure, dose, protein binding and placental transfer.[9] There is no increased risk of teratogenicity during the first two weeks of gestation, in which spontaneous abortion is common. Between weeks 3–10 (i.e. weeks 5–12 of amenorrhea), the fetus is particularly vulnerable to the teratogenic effect of chemotherapy as organogenesis occurs during this period.[10] The use of chemotherapy during this period increases the risk of major malformations reaching up to 20%.[11–14] Given the considerable morbidity, if chemotherapy is planned during pregnancy, it should be started following the completion of the 12th week of gestation. Although the risks remain low, it is important to note that eyes, genitalia, haematopoietic system and central nervous system remain vulnerable to continued drug exposure, with the possibility of mild dysfunction during infancy and adulthood.[15]

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In breast cancer, indications for chemotherapy during pregnancy should not be different from those outside pregnancy.[8] In case of locally advanced hormone-receptor negative tumor, it is generally agreed that chemotherapy should be given. However, in patients presenting with operable, hormone-responsive disease, careful assessment should be made regarding the need for adjuvant chemotherapy during pregnancy.

Different chemotherapy regimens have been used for the treatment of gestational BC. Anthracyclines-based regimens are the most widely used is BC treatment and has been shown to be associated with favorable safety profile when administered during pregnancy.[16] Table 1 summarizes the results of important recently published studies.[17–20] Only two studies prospectively treated their patients. The first and largest study was reported by the group of MD Anderson in which patients were treated with FAC (5-florouracil, doxorubicin and cyclophosphamide).[18] The second was reported later by our group in which patients were treated with weekly epirubicin at a dose of 35 mg/m^2.[19] The other two studies retrospectively reported the results of patients exposed to different chemotherapy regimens; mainly anthracycline-based.[17,20] Despite the different regimens used across the four studies, they all showed that administering anthracycline-based regimens following the first trimester is not associated with detrimental effects on pregnancy. Similar results were presented recently by Loibl et al. on behalf of the German Breast Group (GBG).[21] In this large European registry project, 121 patients (51%) were treated with chemotherapy during pregnancy, 78% of whom were exposed to an anthracycline-based regimen. There was no differences encountered in terms of pre-term delivery, fetal weight and hemoglobin level between those treated during pregnancy and those who were not been treated.

On the other hand, taxanes are increasingly used in managing patients with early and advanced BC nowadays.[22] Taxanes are substrates of the P-glycoprotein (Pgp), which is highly expressed on the maternal compartment of the placenta.[23] The Pgp protects the fetus against xenobiotics and might therefore reduce the transplacental transfer of taxanes. Moreover, they are metabolized by cytochrome P-450, which is increased by 50%–100% during the third trimester of pregnancy,[24] possibly resulting in a shorter half-life and a higher clearance of taxanes that could result in reduced toxicity profile during pregnancy. A recent systematic review of literature by Mir et al. identified twenty-seven BC patients treated with a taxane (either paclitaxel or docetaxel) during pregnancy.[25] All of them had favorable pregnancy course and outcome.

CMF (cyclophosphamide, methotrexate, and fluorouracil) is another regimen that has been widely used in the past and has been described in pregnant BC patients. Methotrexate is used for induction of abortion and has been associated with major malformations particularly after first trimester exposure.[26] However, normal outcomes were reported following second and third trimester exposures.[17] Nevertheless, given the reduced benefit of CMF compared to anthracycline-containing regimens and its potential teratogenicity, it is widely agreed to avoid this regimen during pregnancy.

Regimen selection

In the adjuvant setting, different anthracycline-based regimens are described with no clear consensus to use one rather than the other. However, it is suggested that both escalated-dose epirubicin and anthracycline-taxane regimens are most effective in terms of disease-free survival and overall survival.[27]

During pregnancy, dosages should not differ from those used outside pregnancy, even if few pharmacokinetic and pharmacodynamic data are available during pregnancy. The GBG suggests that treatment strategies offered for pregnant women with BC should not differ from their non-pregnant counterparts.[8,21] This recommendation is based on retrospective collection of outcomes of pregnant BC patients treated with different standard regimens during pregnancy. The main caveat of this approach is being based on retrospective data collection from different centers across different counties. This limits capturing the challenges faced during monitoring these patients particularly when grade III/IV adverse events are encountered. Also, it disregards that pregnancy is a particular situation that arguably requires a customized treatment approach, at least from an oncological perspective.[28] We have lately described the safety and efficacy of weekly epirubicin (35 mg/m^2) in the treatment of 20 women with gestational BC (mostly in the adjuvant setting).[19] Weekly fractionation results in low peak plasma concentration of the drug leading to low maternal toxicity and possible low placental transfer of the drug. Pharmacokinetic studies done on some of the patients enrolled in our trial showed that epirubicin levels are almost undetectable in the fetal circulation (M. Zucchetti; personal communication, December 2009). In addition, weekly application allows close monitoring of the pregnancy, which reassures both the patient and the treating physician. The regimen showed adequate clinical activity and was very well tolerated with no patients developing grade III or IV toxicities.

Table 1
Characteristics and results of the main studies using chemotherapy during pregnancy.

	Ring et al. [17]	Hahn et al. [18]	Peccatori et al. [19]	Cardonick et al. [20]
Data Collection	Retrospective, multi-centric	Prospective, mono-centric	Retrospective, mono-centric	Prospective and retrospective, multi-centric
Number of patients	24	57	20	104
Median gestational age (weeks) at starting chemo (range)	20 (15–33)	23 (11–34)	19 (16–30)	20
Chemotherapy regimen	AC, EC, CMF	FAC	Weekly epirubicin 35 mg/m^2	AC, EC, FAC, FEC, FAC-P; AC-P; AC-D; V
Median number of cycles (range)	4 (1–6)	4 (1–6)	12 (4–16)	4
Median gestational age (weeks) at delivery (range)	37 (30–40)	37 (29–42)	35 (28–40)	36 (34–39)
Pre-term delivery	0[a]	2 (4%)	1 (5%)	8 (8%)
Congenital anomalies [b]	1 (4%)	3 (5%)	1 (5)	4 (3.8%)
Maternal outcome at ~ 40 months	63%	70%	70%	Analysis for patients who received chemotherapy in this study was not performed
DFS	67%	77%	85%	
OS				

AC: doxorubicin, cyclophosphamide; EC: epirubicin, cyclophosphamide; FAC: 5-florouracil, doxorubicin, cyclophosphamide; FEC: 5-florouracil, epirubicin, cyclophosphamide; P: paclitaxel; D: docetaxel; N: vinorelbine; DFS: disease free survival; OS: overall survival.

[a] One spontaneous abortion.

[b] Only one major anomaly (Down Syndrome).

However, outside pregnancy, this regimen is not routinely used in the adjuvant setting and it has been criticized by some for being possibly suboptimal. Nevertheless, it is important to note that treatment during pregnancy does not comprise the whole adjuvant treatment period and reverting to more standardized regimens can be done following delivery. Also the differences between the different anthracycline-based regimens is at best modest in terms of effect on overall survival and is mainly attributed to the dose of anthracycline, which is very well preserved with a weekly epirubicin dose of 35 mg/m2. Finally, adding cyclophosphamide on weekly basis as well could be always a possibility if the treating physician is concerned regarding not administering an alkylating agent. As for taxanes, if required in the adjuvant setting, available data in pregnancy are rather reassuring.[25] But acknowledging the limited amount of evidence, they could be offered in sequence to anthracyclines following delivery.

In the advanced/metastatic setting, anthracyclines and anthracycline-based regimens remain the best choice as well.[8,16] For patients who are not good candidates for anthracycline-based regimens (e.g. previously exposed in the adjuvant setting), single agent taxane (paclitaxel or docetaxel) would be a preferred option.[16] Weekly administration of paclitaxel has been shown to be associated with higher efficacy and better tolerability compared to the 3-weekly schedule.[29,30] Given the potential advantages of weekly application of chemotherapy highlighted earlier, weekly paclitaxel appears to be an appealing option in this setting.

Data on other chemotherapeutic agents used in the metastatic setting remain very scarce. Table 2 summarizes an overview on the use of different systemic anti-cancer agents in metastatic BC. Vinca-alkaloids were shown to be safe when given during pregnancy for women with hematological malignancies.[31] But data in breast cancer is limited to very few case reports. A systematic review on the use of platinum salts suggested that carboplatin is associated with lower toxicity when given during pregnancy compared to cisplatin.[32] However, the number of carboplatin-treated cases was lower than those treated with cisplatin. As for capecitabine, we are not aware of any report that described its use in pregnant BC patients.

Women with bone metastases are frequently considered for bisphosphonates to decrease the risk of skeletal adverse events.[33] During pregnancy, pre-clinical models have shown an increase risk of fetal skeletal anomalies secondary to in-utero exposure to bisphosphonates.[34] Also, these drugs can result in hypocalcemia which could affect uterine contraction. However, clinical evidence mainly in the setting of osteoporosis did not witness any detrimental effects on the course or outcome of pregnancy even when administered during the first trimester.[35,36] Nevertheless, given the paucity of clinical data and worrying pre-clinical evidence, it is better to administer it following delivery whenever possible.

Trastuzumab in pregnancy

Trastuzumab is a humanized, IgG monoclonal antibody that targets the HER2 oncogene. The addition of trastuzumab to chemotherapy has shown to improve survival of BC patients with tumors over-expressing HER2, both in the adjuvant as well as in the metastatic setting.[37] The safety profile of trastuzumab during pregnancy is unclear. Current clinical evidence relies on 15 published case-reports only.[38] Of interest, 8/15 cases (53%) experienced a reduction in the amniotic fluid volume (oligohydramnios or anhydramnios), which is known to significantly increase the risk of premature delivery, foetal morbidity and mortality. This resulted in 4 neonatal deaths secondary to premature delivery which was complicated by respiratory and renal failure. Alterations in the amniotic fluid volume are most likely attributed to the effect of trastuzumab on the foetal kidney, where HER2 is highly expressed.[39]

Despite that the majority of patients (11/15) were unintentionally exposed to trastuzumab during the first trimester, yet no congenital anomalies were encountered. A recent study have shown that transplacental transport of IgG is very low early in pregnancy and increases gradually starting the second trimester to reach a concentration similar to that of the mother by the end of gestation.[40] Acknowledging that it is too premature to draw solid conclusions based on the available pre-clinical and clinical evidence, however, unlike chemotherapy, the risk associated with trastuzumab does not appear to be associated with early 1st trimester exposure. In an attempt to provide more robust conclusions in this area, there are ongoing efforts to collect the pregnancy events within the large adjuvant trastuzumab trials to better characterise the risk associated with 1st trimester exposure to trastuzumab.

On the other hand, it seems that prolonged exposure to trastuzumab (more than one trimester) is the key risk factor behind the development of oligohydramnios.[39] Seven out of 8 patients who developed oligohydramnios were exposed to trastuzumab for more than one trimester. However, the risk appeared to be much lower (1/7 cases) in those exposed to trastuzumab for one trimester or less.

Fetal and pregnancy monitoring

It has been shown that administering chemotherapy during the second and third trimesters is associated with an increased risk of intrauterine growth restriction (IUGR) and low birth weight,[12,41] which are mainly attributed to premature delivery. However, it is arguable that women with low tumor burden (e.g. adjuvant breast cancer) are at a lower risk of developing these complications. Pregnant women with high tumor burden (e.g. lung cancer, acute leukemia) are possibly more prone to premature delivery given the aggressive nature of their disease as well as the chemotherapy required.[28]

Table 2
Overview on the use of different systemic anti-cancer agents in metastatic BC.

Drug [Ref]	Overview
Anthracyclines [10,16]	Best option if not contraindicated (previous exposure, cumulative cardiac toxicity)
Paclitaxel [25]	Second best option, weekly application appears attractive to facilitate close monitoring of pregnancy
Docetaxel [16,25]	Less data compared to paclitaxel. Less favored as it is associated with a high risk of neutropenia requiring GCSF, in which we lack sufficient evidence regarding its safety during pregnancy
Vinorelbine [16,31]	Sporadic case reports, all with normal outcome. Data in hematological malignancies with other vinca-alkaloids (vinblastine) is reassuring. Could be considered if anthracyclines or paclitaxel are not feasible
Platinum salts [32]	Carboplatin appears to be less toxic during pregnancy compared to cisplatin. Considering the shorter infusion rate, adjusted dosing schedule and favorable toxicity profile, it is more favored than cisplatin
Bisphosphonates [34,35,36]	Available data in osteoporosis appears safe; however, pre-clinical models are worrying. Better postponed until delivery
Trastuzumab [16,38,39]	High risk of oligohydramnios with prolonged exposure (i.e. more than 1 trimester). Better avoided until delivery. If urgently need, restrict to short courses with close monitoring of the amniotic fluid volume
Tamoxifen [7,8,16]	Should be avoided completely

In the previously described case-series of BC patients treated with chemotherapy during pregnancy, median gestational age at starting therapy ranged from 19 to 23 weeks. In these reports, the incidence of congenital malformations was comparable to that encountered in the normal population. It included 1 newborn with Down syndrome, 1 with polycystic kidney, 1 with bilateral ureteral reflux, 1 with clubfoot, 1 with hip subluxation, 1 with pyloric stenosis, 1 with asymptomatic pulmonary fistula, 1 with holoprosencephalo and 1 with talipes and hemangioma, for a total of 8/205 cases exposed to chemotherapy in-utero (3.8%)

A wise balance between delivery anticipation with chemotherapy postponement or immediate administration of chemotherapy should be assessed for each case.[41] If there is a clear indication for chemotherapy (advanced/metastatic setting), it should not be delayed until fetal maturity for the potential detrimental effects on maternal outcome. In the adjuvant setting, it has been shown that early administration of chemotherapy within three weeks of surgery is associated with improved outcomes in patients with hormone-receptor negative tumors.[42] Also, data from a randomized study in stage I and II breast cancer patients showed that the delay of chemotherapy after radiotherapy, as compared with the opposite sequence, may increase the rate of distant metastases.[43] Data from Beadle et al. on patients who developed breast cancer during pregnancy, showed a trend toward improved survival for those patients who received any treatment (including chemotherapy) during pregnancy as compared with those who did not.[44] Accordingly, and given the apparent safety of different chemotherapeutics during pregnancy, the delay of chemotherapy until fetal maturity is not justified, unless delivery can be safely induced within 4–6 weeks from diagnosis.

If chemotherapy is initiated during pregnancy, strict fetal monitoring with morphometric ultrasound and umbilical artery doppler should be performed at regular intervals during gestational chemotherapy. As already discussed, chemotherapy should be delivered always after the first trimester. If chemotherapy is required during the first 12 weeks of amenorrhea, pregnancy termination should be considered.

Timing of delivery and neonatal issues

A pre-term birth is defined as delivery before the completion of week 37 of gestation.[45] Very early pre-term birth is gestational age at birth of less than 32 weeks while late pre-term birth is gestational age at birth of 32–36 weeks. In the general population, the rate of pre-term delivery is 12–13% in the United States and 5–9% in Europe.[46] It is considered the leading cause of infant mortality in industrialized countries and contributes significantly to neuro-cognitive, pulmonary and ophthalmologic morbidity.[47]

Despite that the risks are much lower for infants born at 32 through 36 gestational ages, the mortality and neonatal morbidity remain substantial.[47] Compared with infants born at term (at $\geq$ 37 gestational weeks), late pre-term infants have higher rates of temperature instability, respiratory distress, apnea, hypoglycemia, seizures, jaundice, feeding difficulties, periventricular leukomalacia, and re-hospitalizations. They are also associated with a higher risk of developing long-term effects, such as difficulties in motor skills, speaking, writing, mathematics, and behavior.[48] Furthermore, a study examining the relationship between gestational age at birth and outcomes in adulthood showed that the risks of medical and social disabilities in adulthood increase with decreasing gestational age at birth.[49]

In chemotherapy-exposed pregnancies, the rate of pre-term delivery is in the range of 10–13%.[41] In the majority of cases (80–90%), the indication for induction of labor is maternal cancer. However, on restricting those numbers to women with gestational BC, the incidence is lower ranging between 5 and 8%.[41] Table 1 shows the gestational age at delivery in BC patients treated with chemotherapy during pregnancy.

In planning the timing of delivery in pregnant BC patients, multiple factors related to chemotherapy administration should be taken into account (summarized in Table 3). To minimize the risk of maternal and fetal neutropenia and subsequent infection, delivery should be avoided during the maternal nadir. This is hard to control if 3-weekly regimens are used as the nadir period is usually long. This represents one more advantage for the weekly regimens as they are associated with lower myelotoxicity and shorter nadir periods.

Chemotherapy should not be given after 34–35 weeks of gestation as spontaneous delivery can occur before bone marrow recovery. The delay of delivery for 2–3 weeks after chemotherapy (depending on the regimen used) also allows for fetal drug excretion via the placenta. Chemotherapy administered shortly before delivery might not be eliminated from the fetus before delivery, and thus may persist in the newborn. This is especially true for pre-term babies, who have a limited ability to metabolize drugs due to liver and kidney immaturity.

For the well being of the fetus, all efforts should be made to delay delivery until week 35–37 of gestation. If chemotherapy is planned to be continued following delivery, the first dose should be given following adequate recovery. Vaginal delivery may be less likely to delay initiation of chemotherapy due to lower morbidity compared with cesarean section.[8] Although placental metastases in breast carcinoma are rare, the placenta should be histopathologically examined for metastases.[8,50] Breastfeeding during chemotherapy and hormonal therapy is contraindicated, as most of the agents used can be excreted in breast milk.

The delay of three weeks after maternal chemotherapy decreases but does not rule out completely the child's risk of bone marrow suppression at birth. Most of the reported neonatal complications are related to anticipated delivery and include breathing difficulties, and subarachnoid hemorrhage.[17–20,41] Acknowledging the limited

Table 3
Chemotherapy in pregnant breast cancer patients: Clinical practice issues.

Timing of chemotherapy	Type of chemotherapy	Timing of delivery
• Chemotherapy should not be given before the 13th week of gestational age • Delay of chemotherapy until fetal maturity is not supported by data • Chemotherapy should not be given after the 34th-35th week of gestation.	• Anthracycline-containing regimens should be used. FAC/FEC, AC/EC or weekly epirubicin can be considered • In the adjuvant setting, sequential treatment with taxanes after delivery. Single agent taxanes can be used in the metastatic setting in patients not candidates for anthracycline-containing regimens. • Strict fetal monitoring during chemotherapy is warranted	• Delivery should be avoided in the first three weeks after last cycle of chemotherapy • A maximal effort should be made to delay delivery until at least 35–37 weeks of gestational age • In planning the timing of delivery, the well being of the fetus should be balanced against efficacy of BC treatment

FAC: 5-florouracil, doxorubicin, cyclophosphamide; FEC: 5-florouracil, epirubicin, cyclophosphamide; AC: doxorubicin, cyclophosphamide; EC: epirubicin, cyclophosphamide; BC: breast cancer.

amount of data, there is apparently no significant long-term effects on the children exposed to BC chemotherapy in-utero compared to the normal population. In a study involving 130 patients (104 received chemotherapy), Cardonick et al. performed long-term pediatric assessment for 93 babies at a mean age of 41.8 months.[20] Mean weight and height percentiles were 48% and 58% respectively. Medical issues included gastroesophageal reflux, pneumonia, corneal abrasion, IgA deficiency, otitis media, and speech delays in 2 cases exposed to chemotherapy in utero. In the same study, long-term medical issues affecting children not exposed to chemotherapy included speech delay in 1 case and neurofibromatosis in another. In our prospective study using weekly epirubicin, all newborns were normal at a median follow-up period of 2 years following delivery.[19] In the MD Anderson study, follow-up until school age was conducted for 18 of the newborns showing normal development as well.[18]

Conclusions

Diagnosis of BC during pregnancy is a relatively rare clinical situation, but when encountered it poses several clinical conflicts and thus administering chemotherapy and targeted agents remain a major challenge. We believe applying standard regimens is not always possible and we need to consider tailored approaches for these women.

Chemotherapy should not be administered before the 12th and after the 34th-35th weeks of gestation. Anthracycline-based regimens remain the treatment of choice in the early and advanced settings. Single agent taxane could serve as an alternative for those who are not good candidates for anthracyclines. The application of weekly regimens remains an attractive approach and worth consideration in these patients. Limited data on trastuzumab are worrying and this drug should be avoided during the course of pregnancy whenever possible. If deemed necessary, it should be restricted to only one trimester with very close monitoring to the amniotic fluid volume. All efforts should be made to delay delivery until at least 35–37 weeks of gestational age to reduce the risk of fetal morbidity associated with prematurity.

In the setting of gestational BC, treatment decisions will always relay on limited evidence and respecting patients' autonomy is such situations is of at most importance. Patients should be properly counseled and informed that decision-making will relay on relatively scarce data. Treatment decisions should be tailored according to each particular case taking into account intent of therapy, disease stage, tumor biology, gestational age at delivery and possible materno-fetal risks.

The development of prospective registry for patients with gestational BC would provide us with more robust conclusions on the maternal breast cancer outcome in addition to short and long-term outcome of the newborns. In this regard, there is an ongoing European registry project coordinated by the GBG in collaboration with the Breast International Group (BIG), which will hopefully refine our knowledge in this challenging disease.

Conflict of interest

None.

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