Drug Safety 1998 Feb; 18 (2): 135-142
0114-5916/98/0002-0135/$04.00/0

Treating Breast Cancer During Pregnancy

What Can be Taken Safely?

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Contents

Summary

The occurrence of breast cancer during pregnancy is a rare clinical situation. However, if it is diagnosed, a multidisciplinary approach involving an obstetrician, a medical oncologist and a surgeon is needed. In this situation, breast cancer should be treated according to the same principles applied in nonpregnant patients. Termination of pregnancy does not improve survival. Decisions regarding abortion should be based on the desires of the patient and on therapeutic necessities.

If required, surgery is always possible, but radiation therapy should be avoided because of the risk of fetal toxicity. Antineoplastic drug therapy, if indicated, is possible after the first trimester.

Breast cancer and cervical cancer are the 2 most commonly occurring cancers during pregnancy.[1] Pregnancy-associated breast cancers comprise not only those breast cancers arising during pregnancy, but also those that arise in the year after pregnancy. We will consider in this article only the first group of tumours: those arising during pregnancy itself. As the subclinical phase of the disease lasts for several years,[2] these cancers are presumed to have existed before the onset of the pregnancy.

Wallack and colleagues,[3] in a review of 32 papers, concluded that pregnancy associated with breast cancers accounts for 0.2 to 3.8% of all breast cancers. Alternatively, 1 breast cancer would be expected to arise in every 3000 to 10 000 pregnancies.[4] The frequency of concomitant breast cancer and preg-

nancy is at least 15% for patients who develop breast cancer before the age of 40 years.[3,5] The mean age of women who develop breast cancer during pregnancy is between 32 and 38 years,[3] although exceptional cases have been described for very young women (less than 20 years old).[6] The increased number of delayed pregnancies in women aged between 30 and 40 years may explain the higher frequency of the association in recent years.

1. Diagnosis

It must be emphasised that clinical breast examination of pregnant women is most important, and has to be done as soon as pregnancy is recognised in order to detect any suspicious mass. Indeed, clinical diagnosis will be increasingly difficult as the pregnancy progresses. Mammography is permitted during pregnancy; the abdomen can be protected by a lead apron. However, the interpretation of mammograms is more difficult because of the oedema and increased vascularity of the breast associated with pregnancy. Echography may be helpful in case of diagnostic difficulties with mammography.[7,8,9] A mammogram interpreted as 'normal' is not sufficient if there is a palpable lump, and more investigations have to be done. Max and Klamer[10] described 8 women with palpable breast lumps, 6 of whom were reported to have a 'negative' mammographic examination, but who in fact had histologically proven breast cancers.

Fine needle aspiration for cytology is an essential diagnostic tool that allows a cyst or galactocoele to be distinguished from a solid mass. Nevertheless, cytology during pregnancy is not as easily interpreted as that performed outside of pregnancy. The cytologist has to be informed that the woman is pregnant, and should be experienced in the diagnosis of these diseases. Indeed, false positive results are possible because of the hypercellularity of the mammary tissue and the more frequent occurrence of cytonuclear atypia.[11]

The usual benign lesions can occur during pregnancy, including adenofibroma, lipoma, papilloma, cysts and inflammatory phenomena. Lobular hyperplasia seems to be more frequent, while galactocoele, abscess and infarction of pre-existing adenofibroma have also been described.[12,13] Benign inflammatory mastitis or abscess must be distinguished from a cancerous inflammatory tumour. Inflammatory carcinoma of the breast is no more frequent during pregnancy than in nonpregnant women, contrary to what was previously believed.[14]

About 3% of breast cancers that arise during pregnancy are reported to be inflammatory breast cancers and, as yet, the specific outcome and prognosis of inflammatory breast cancer arising during pregnancy is unknown.[15,16] Nevertheless, a recent retrospective multicentre French study[17] described a 24% incidence of such inflammatory presentations. Each inflammatory breast lesion requires histological examination, so a biopsy must be performed. This is always possible, but it should be noted that increased vascularity necessitates meticulous haemostasis and also that breastmilk, acting as a culture medium, enhances the infectious risk.[18]

2. Evolution and Prognosis

The poor prognosis of breast cancer in pregnancy is generally thought to result from late diagnosis, and the consequent delays in initiating treatment.[5,15-17,19] It may also relate to the relatively young age of the patient, which in itself appears to be a pejorative factor.[20-22] In the French multicentre study of Giacalone and colleagues,[17] the overall 3-year survival was 57% for patients with breast cancer during pregnancy, compared with 74% for nonpregnant patients with breast cancer; this difference was no longer significant if metastatic and inflammatory tumours were excluded. However, the recent study of Schoultz et al.[23] suggests that when adjusted for age, the prognosis is similar. The French multicentre study[17] did not find that pregnancy was a bad prognostic factor in itself, but confirmed the detrimental influence of a young age at diagnosis.

3. Staging

Routinely, in nonpregnant patients, staging generally includes chest x-ray, liver echography or computed tomography (CT) scan, and bone radionuclide scan. However, the specific problem associated with pregnancy is the risk of teratogenicity from irradiation. The period from conception to the fourteenth day is the most sensitive to radiation, which greatly increases the risk of miscarriage.

Following atmospheric exposure to a dose of 1 to 9 cGys after the detonation of atomic bombs over Hiroshima and Nagasaki, the children of women who were 6 to 11 weeks' pregnant at the time experienced an 11% incidence of microcephaly and mental retardation.[24] An increased risk of leukaemias and solid cancers in patients whose mothers had undergone an abdominal x-ray during their pregnancy has also been described.[25,26]

Therefore, it is better to avoid abdominal and pelvic CT scans and bone radionuclide scans. Chest x-ray is permissible, as is magnetic resonance imaging,[27] if they are needed to determine the stage of the disease.

4. Therapeutic Tools

4.1 Surgery

Surgery is always possible during pregnancy. If necessary, a modified radical mastectomy is feasible. The surgical option has to be chosen using the same conditions as for patients outside pregnancy, so conservative surgery is allowed for small tumours; in these cases radiotherapy can be delayed until after delivery.[28]

4.2 Radiotherapy

Irradiation has to be avoided because of fetal risks (section 3). Irradiation during the 10 first days of pregnancy is thought to cause fetal death; during the period of organogenesis and the beginning of the fetal period, microcephaly, mental retardation, growth delay and bone malformations are possible. These anomalies have been described with more than 2 cGys irradiation.[29] Irradiation at a later stage of pregnancy can cause sterility and subsequent cancers in the child. The toxicity of radiotherapy depends on dose, energy, field size and distance between the fetus and the radiation volumes; however, gestational age is fundamental in determining the nature and severity of toxicity.[30]

If conservative treatment is indicated, that is in the case of small tumours (≤3cm), it is preferable to postpone irradiation until after delivery. Nevertheless, there are no published series concerning the outcome of such a strategy for pregnant women. Similarly, it seems appropriate to postpone irradiation if it is needed after mastectomy, for example, in the presence of axillary nodal involvement. If a post-mastectomy locoregional recurrence occurs during pregnancy, it is reasonable to discuss the possibility of antineoplastic drug therapy after surgical resection.

4.3 Antineoplastic Drug Therapy

The toxic effects of antineoplastic drug therapy depend on the gestational age, the administered dosages and the type of drug. Nevertheless, data are anecdotal and often incomplete. Antineoplastic drug therapy has proven efficacy in treating patients with breast cancer in adjuvant, neoadjuvant and metastatic settings, but it needs to be delivered as early as possible in order to be efficacious. Thus, the choice of the protocol has to balance the benefit to the mother with the risk to the fetus.

4.3.1 The Mother

The gravid state modifies classical pharmacological data: there is an increase in plasma volume with an increased dilution space for hydrosoluble drugs, decreased plasma albumin levels and increased levels of other plasma proteins, because of an increase in available estrogen. These alterations may explain significant modifications of parameters such as the area under the concentration-time curve. Moreover, amniotic fluid may function as a third pharmacological space, delaying elimination and therefore enhancing the toxicity of some drugs (e.g methotrexate).[31-33] At the very least, the alterations in hepatic metabolism, and the increases in renal plasma flow, glomerular filtration rate and

creatinine clearance can also modify the clearance of cytotoxic drugs.[34]

Nevertheless, data are insufficient to precisely evaluate the quantitative consequences of these pharmacological variations and to determine the best chemotherapeutic regimens (in view of the therapeutic index) during pregnancy. So, conventional regimens are usually offered to pregnant patients.[35]

4.3.2 The Fetus

Many diverse, early or late toxic effects, both reversible and irreversible, may affect a child exposed to cytotoxic agents *in utero*. Data are fragmentary, and have been obtained from isolated cases described in the literature. Little is known about the transplacental passage of cytotoxic drugs and reports on this topic are highly inconsistent.[36,37] Therefore, reliable predictors of toxicity are not available. For example, Gaillard and colleagues[38] studied the transplacental passage of epirubicin in an *in vitro* model of perfused mature placenta, and found that 3.6% of the amount administered to the mother would cross the placenta. This suggests a minor potential for fetal toxicity of epirubicin.

First Trimester

Immediate toxic effects can be observed, such as *in utero* death, prematurity, hypotrophy, malformations and visceral abnormalities. The risks are clearly dependent on the timing of administration (gestational age) and the administered drugs. Treatment during the first week invokes the all-or-nothing law: miscarriage or a healthy fetus.[31] Thereafter, and until the end of the first trimester (culmination of organogenesis) cytotoxic treatment may cause malformations, the incidences of which are difficult to appreciate: rates of 7.5% (4/53),[39] 12.7% (9/71)[40] and 17% (24/139)[41] have been reported. These incidences may have included toxicity from other causes, such as radiation therapy (sections 3 and 4.2), to which a proportion of these malformations could be attributed,[42] and because of the high variability of teratogenic potential from one agent to another.

For instance, administration of antimetabolites (particularly methotrexate) during the first trimester is associated with a significant risk of miscarriage and malformations.[43] Alkylating agents such as nitrogen mustards and cyclophosphamide are considered to be highly teratogenic too. In a review, Doll and colleagues[31] found 6 cases of malformations in 50 children exposed to an alkylating agent *in utero* during the first trimester; in 4 cases, the mothers had also received radiation therapy.[31] Cyclophosphamide, if delivered during the first trimester, may cause various malformations (e.g. absence of ears, single coronary artery).[32] Nevertheless, numerous cases of healthy infants have been described after *in utero* exposure to cyclophosphamide during the first trimester.[44]

Two of the most widely employed groups of cytotoxic drugs for the treatment of women with breast cancer, the anthracyclines and the vinca alkaloids, seem to possess little teratogenic potential. In fact, no case of malformation has been described with anthracyclines or vinblastine. Both of the cases of malformations (cardiac and renal) reported in association with vincristine appeared in a context of polychemotherapy: vincristine plus procarbazine in one case, vincristine plus nitrogen mustard (the major teratogenic potential of which is well known in the other case).[45]

Overall, administration of cytotoxic agents during the first trimester of pregnancy is associated with a significantly higher frequency of malformations, often with decreased viability of the child.[46] Nevertheless, besides the timing of treatment, the nature of the agent, dosage, frequency of administration, duration of treatment, use of drug combinations (25% of malformations for polychemotherapy versus 6% for monochemotherapy, excluding methotrexate[39]) are also crucial parameters. When methotrexate is included in the series, fetal abnormalities associated with monotherapy appear in 17% of patients.

Second and Third Trimesters

No increase in risk of malformation seems to occur during treatments that take place in the second or third trimester.[31] However, as with therapy

during the first trimester, delays in fetal growth and functional development (especially neuropsychological), miscarriage, premature birth and functional alteration of organs can be observed.[31]

For pregnancy as a whole, Nicholson[39] reports that 40% of infants whose mother received antineoplastic therapy have a subnormal birthweight, while Zemlickis and colleagues[46] found a mean birthweight in such children that was statistically inferior to that of infants of women who were not treated with these agents (2.227kg versus 3.519kg). Sutcliffe[47] described 82 cases of miscarriages or medical abortion in 218 pregnancies associated with cytotoxic drug treatment. Schaison and colleagues[48] have reported 1 case of myocardial infarction after *in utero* exposure to doxorubicin in an infant that died at 8.5 months' gestation. Some cases of neonatal myelosuppression with haemorrhagic and infectious syndromes have been described.[49,50]

Use of all antineoplastic drugs seems possible during the second and the third trimester of pregnancy. We have treated 3 patients with locally advanced breast cancer with vinorelbine and fluorouracil at 24, 28 and 29 weeks' gestation, respectively, without evidence of fetal malformation.[51] One of the children presented with anaemia at day 21, but his mother had also been treated with an anthracycline-based regimen.

Inbar and Ron[28] reported a case of a 33-year-old pregnant woman diagnosed with breast cancer during the twentieth week of gestation who was treated with 4 courses of full-dose adjuvant antineoplastic therapy including doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks; the baby was born at 36.5 weeks' gestation without any abnormalities.

Willemse and colleagues[42] reported the birth of a healthy infant whose mother was treated with 2 cycles of doxorubicin, methotrexate and vincristine during the third trimester. After amniocentesis in the thirty-third week, the patient developed fever; a baby girl was delivered vaginally and had sepsis and mild respiratory distress; she recovered and was functioning normally 2 years after delivery.

Barni et al.[52] treated a 31-year-old woman with breast cancer, who was 28 weeks pregnant, with weekly intravenous doxorubucin therapy (20 mg/m^2 for 4 courses). The treatment was well tolerated by the woman and she gave birth to a 3.1kg baby with Apgar scores of 9 and 10, 1 and 5 minutes following delivery, respectively. The baby's blood count, chest x-ray and ECG were all normal.

Dreicer and Love[53] treated a pregnant patient with metastatic breast cancer from the second trimester to 3 weeks prior to caesarean delivery. She was treated on a 4-week cycle with oral cyclophosphamide 150 mg/m^2 on days 3 to 12, doxorubicin 50 mg/m^2 on day 2 and fluorouracil 300 mg/m^2/day continuously via an infusion pump from day 1 to 7 with escalating doses to a maximum of 500 mg/m^2/day. The patient received a total dose of 11 000mg cyclophosphamide, 193mg of doxorubicin and 19 775mg fluorouracil. A healthy newborn of estimated gestation 38 weeks was delivered by caesarean section. At 24 months, the child was in excellent health.

Meador and colleagues[54] collected 4 cases of newborns with normal peripheral blood count, despite the fact that their mothers, who had been treated with antineoplastic drug therapy for haematological abnormalities, had severe pancytopenia at the time of delivery.

Long Term Follow-Up

The late effects of antineoplastic drug therapy after *in utero* exposure are unclear. Follow-up of children is often short and reports concerning long term development are uncommon. This aspect of the care of women exposed to antineoplastic therapy during pregnancy needs to be addressed.

The growth of children who survive cancers that are treated during infancy is often disturbed, especially if cerebral irradiation was performed, probably because of hypothalamic-pituitary axis toxicity. Antineoplastic drug therapy may lead to a growth delay but, in the absence of radiotherapy, this effect is transient. Growth accelerates at the completion of the therapy.[55] Potential effects on

the child exposed *in utero* are theoretical and have not been reported in the offspring of women treated for breast cancer.

One case of a child with low intelligence quotient and multiple congenital anomalies after exposure from conception to daunorubicin, cytarabine and thioguanine was reported by Reynoso and colleagues.[50] Another study evaluated the growth and development of 43 children of mothers treated with antineoplastic drug therapy during pregnancy (19 during the first trimester); in all children, physical, neurological, psychological, haematological, immune function and cytogenetics were normal.[56]

Antineoplastic agents interfere with gonadal function, and adverse effects have been demonstrated in children exposed at a young age. However, little is known about exposure occurring *in utero*. Aviles and colleagues[57] reported a case of a woman treated with such drugs during pregnancy *in utero* who went on to deliver a normal child.

The susceptibility of germ cells to the mutagenic effects of antineoplastic drug therapy is of concern, and suggests a risk for the lineage of patients treated during childhood. Nevertheless Mulvihill and colleagues[58] reported a very low incidence (0.3%) of cancers among 2308 descendants of childhood cancer survivors. This incidence was not significantly different from that of the healthy siblings' offspring (0.23%). Thus, although germ cells may be relatively insensitive to the mutagenic effects of antineoplastic drug therapy, this has not been demonstrated for germ cells of *in utero* treated children.[59]

One case of multiple congenital malformations has been reported in a child, with occurrence of a neuroblastoma at 14 years of age, and of a metastatic papillary thyroid carcinoma at 16 years of age. This boy was exposed, from conception, to monthly cyclophosphamide; his mother, who had acute lymphoid leukaemia, also received aminopterin sodium, which would be expected to produce congenital abnormalities such as cranial dysostosis,[41] just before conception. The woman previously received vincristine, mercaptopurine and prednisone for more than 8 years. Transplacental carcinogenesis has been suggested for this case.[50]

In summary, antimetabolites and alkylating agents must be avoided during the first trimester, especially methotrexate; anthracyclines and vinca alkaloids appear to be the least harmful of the antineoplastic agents during pregnancy.[45,51,52] On the other hand, during the second and the third trimesters use of all antineoplastic agents seems possible.

4.4 Hormonal Treatment

In the past, it was often proposed to systematically carry out medical abortions together with ovariectomy in women with breast cancer during pregnancy. In fact, abortion has no therapeutic effects[20,60,61] and no benefit has ever been associated with ovariectomy in terms of reduction in relapse rate and/or survival from cancer.[62,63]

It is no more logical to propose the use of tamoxifen, first, because of its poor efficacy before menopause – in this respect, it is worth noticing that tumours among these patients are often estrogen-receptor negative[20] – and second, because of its potential teratogenic risk. Cullins and colleagues[64] reported a case of treatment with tamoxifen during pregnancy. The child presented with Goldenhar's syndrome, which comprises abnormalities of the eyes, ears and vertebrae. Out of 50 women whose pregnancies were associated with tamoxifen, 19 had normal births, 8 had medical abortions, 13 were lost to follow-up and 10 had children with a fetal/neonatal disorder, of whom 2 had congenital craniofacial defects.

5. In Practice

The rule will be to treat the mother as thoroughly as possible, while respecting her pregnancy. There are 2 relatively straightforward situations.

1. The pregnancy is near to term and whatever the stage of the disease, usual treatment is possible. Immediate surgery is indicated for patients with operable disease, together with radiotherapy and

antineoplastic drug therapy, if necessary, after inducing labour.

2. The disease is quite limited, with a very good prognosis. Surgical treatment is always possible, and if radical, it is sufficient on its own; otherwise, radiotherapy must be delayed after delivery.

In contrast, an ideal therapeutic regimen cannot be applied without risk to the fetus when dealing with a woman with inoperable disease at the beginning of pregnancy, particularly with an inflammatory or metastatic breast carcinoma or with important nodal involvement requiring the rapid initiation of systemic antineoplastic drug therapy. In this case, medical abortion is the option of choice, with antineoplastic treatment starting without any delay.

During the second or the third trimester of pregnancy, if surgery alone is inadequate and the patient wishes to keep her child, it is possible to start antineoplastic drug therapy with antineoplastic agents such as doxorubicin, cyclophosphamide and, perhaps, vinorelbine.[28,51] A limited number of courses can be administered while waiting for the fetus to mature to a gestational age at which labour can be induced. It is better to do this than to let an aggressive tumour evolve without treatment, even for periods as short as 2 months.

6. Breastfeeding

There is no valid reason to contraindicate breastfeeding when it is desired and possible. It has never been shown that withholding breastfeeding improves the mother's prognosis. It is, however, preferable to stop breastfeeding: (i) before a surgical operation, in order to reduce the breast volume and mammary vascularisation and to reduce the risk of secondary infection associated with milk acting as a culture medium;[18] and (ii) during antineoplastic drug therapy, as the drugs are transferred to the breastmilk and can induce neonatal neutropenia.[47]

7. Risk of Fetal Metastasis

Fetal metastasis from a maternal breast tumour has never been reported. On the other hand, placental metastases[65] have been described; 50% of the cases were solely microscopic.

8. Conclusion

Breast cancer treatment during pregnancy requires the cooperation of a multidisciplinary team, in which obstetricians, oncologists and surgeons present their point of view in order to give the patient the best chance of cure, while trying to preserve the pregnancy if the mother so wishes.

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