

MANAGEMENT OF BREAST CANCERS DURING PREGNANCY

*Recommandations du groupe français d'étude des cancers gynécologique et de la grossesse
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Roman Rouzier, Olivier Mir, Catherine Uzan, Suzette Delaloge, Emmanuel Barranger, Philippe Descamps, Jean-Pierre Lefranc, Lise Selleret.

ABSTRACT

The association of breast cancer and pregnancy, defined as breast cancer that occurs during pregnancy and up to 1 year after delivery is expected to increase as more women delay child-bearing over the age of 30. A better understanding of breast oncogenesis helps explain the dual epidemiological effect of pregnancy on the risk of breast cancer: firstly, the risk of breast cancer increases transiently after delivery, but then falls after 15 years. Breast cancer diagnosed during pregnancy is a stressful situation for the patient, her family as well as for the medical team. Although the different clinical breast examinations are not contraindicated, delay in diagnosis may often be noticed: a later stage of disease at diagnosis with nodal involvement in about 70 % of cases. The management of this clinical situation should conform as closely as possible to standardized approach for nonpregnant women. Most treatments indicated for the management of a localised breast cancer are not contraindicated, except breast radiotherapy. The termination of pregnancy is not justified by the diagnosis of cancer as it does not improve prognosis.

The management of breast cancer during the 2nd and 3rd trimesters of pregnancy should conform as closely as possible to standard protocols including surgery without sentinel node procedure as first-line treatment, and anthracycline-based chemotherapy which appears to be relatively safe for the mother and the foetus according to data currently available. The use of taxanes and targeted therapies is not recommended during pregnancy given the limited data available and the need for further study. Chemotherapy is not used and contraindicated during the first trimester. As result, treatment may be delayed if pregnancy is maintained. If breast-conserving surgery is a possible option, it should be performed immediately. The date of delivery depends on when cancer has been diagnosed and should be planned after the 35th week of gestation in most cases. It should be discussed with the oncologist and the obstetrician to minimize the risks of harm to mother and foetus. Radiotherapy and hormonal therapy should be delayed until after delivery.

INTRODUCTION

Cancer is the second leading cause of deaths in women aged 25-44¹, which makes the association of cancer and pregnancy, rare but not uncommon. Indeed, this disease affects between 1/1 000 and 1/6 000 pregnant women^{2, 3}. The association of breast cancer and pregnancy is expected to increase as more women delay child-bearing over the age of 30. Breast cancers remain the most commonly diagnosed cancers during pregnancy (Figure 1). Diagnosing breast cancer during pregnancy is a very stressful situation for the patient, her family as well as for the medical team. If termination of pregnancy has sometimes been considered, this option is not justified, firstly because it doesn't improve prognosis and also because most initial cancer treatments are not contraindicated according to available data. The possible risk of menopause after chemotherapy should also be discussed. Nonetheless, religious, social, medical and personal considerations may also influence the decision making process. Meticulous biological and staging evaluations are necessary for the optimal management of patients. This complex clinical situation requires a multidisciplinary approach in a cancer centre which should involve the patient and her partner. This team should decide when each treatment stage should be optimal⁴. The following guidelines first consider the context of pregnancy-associated breast cancers (PABC), the different treatment options available, and finally the management strategy depending on gestational age and stage of cancer.

DEFINITION, EPIDEMIOLOGY AND GENETICS

Definition

The association of breast cancer and pregnancy is defined as breast cancer that occurs during pregnancy and up to 1 year after delivery.

Epidemiology

The association of breast cancer and pregnancy is not uncommon, although few studies have considered the importance of the epidemiological aspect. Breast cancer is the first cancer associated with pregnancy. The incidence of pregnancy-associated breast cancer (PABC) is estimated to be about 1/3000 to 1/10000, which corresponds to 0,2%-3,8%⁵⁻⁷. In France, 350 to 750 cases are concerned each year. This incidence is lower in developing countries as the age of the mother at delivery is younger. 10% of women under the age of 40 who develop breast cancer are pregnant when it is diagnosed⁶. Saunders et al. considered that the association of breast cancer and pregnancy was a coincidence⁸. Indeed, if women aged 25-40 have 2 pregnancies, it corresponds to 10% of this time: this figure concurs almost exactly to breast cancers found in 11% of women under the age of 40. The mean age seems to be around 34. The number of PABC has been increasing in the last 30 years as the age of mother at delivery has also increased⁹. As a result, even though the incidence of malignant tumours does not increase because of the reproductive period, it increases with increasing age. It seems essential to create a specific registry for France, all the more so as the median age of women at delivery keeps on increasing. A closer follow up of pregnancies is required and may lead to diagnose cancers more frequently in pregnant patients.

Biological and epidemiological elements suggest there is a relation between pregnancy and the development of cancer. Lambe et al.¹⁰ conducted a case-control study of a nationwide cohort in Sweden linking the Cancer Registry and the Fertility Registry. The subjects were women from 1925 through 1960: 12, 666 patients with breast cancer were compared with 62, 121 control subjects. The authors used conditional logistic regression to estimate odds ratios for the development of breast cancer at different ages, according to maternal age at first delivery (as compared with nulliparous) and age at second delivery (as compared with uniparous). Uniparous women were at higher risks of developing breast cancer than nulliparous women for up to 15 years after childbirth and at lower risk thereafter. The excess risk was most important among women who were older at the time of their first delivery (odds ratio 5 years after delivery among women who were more than 35 at first delivery: 1, 26; 95% CI: 1,10 – 1,44). Women who had 2 pregnancies had a less striking increase in risk. The authors concluded that pregnancy has a dual effect on the risk of breast cancer: it increases transiently after childbirth but then falls after 15 years to a level below that of nulliparous women. In a population-based prospective study of 802 457 Norwegian women aged 20-56, Albrektsen et al.¹¹ observed a short term increase in risk of breast cancer after a full term delivery, with a maximum 3-4 years after delivery (IRR 1,99 ; 95 % CI 1,7–2,3). Similarly, it has been reported that women who have been exposed to fertility drugs seem to have a transient increase in the risk of having breast cancer in the first year of treatment¹².

Genetics

Cancers induced by a deleterious BRCA1 or BRCA2 mutation occurs at a younger age than sporadic cancers. As a result, some PABC may logically have something to do with such mutations. A population-based study from Sweden suggested that BRCA1 mutation carriers were at significantly higher risk of developing PABC : odds ratio [OR] 3,9; 95% CI: 1,4 –10,8) than BRCA2 mutation carriers (OR 1,9; 95% CI: 0,5–7,0) ¹³. In a multicentre case-control study conducted in Japan, the frequency of a family history of breast cancer was 3 times higher in women with PABC than in other patients with breast cancer not associated with pregnancy ¹⁴. These data lead to recommend genetic counselling for all patients with PABC.

If multiparity, young age at first childbirth and breast-feeding are associated with a reduced risk of breast cancer in the general population, the situation could be different in mutation carriers: indeed, BRCA1 regulates normal cell differentiation. Mammary epithelial cells divide and differentiate during pregnancy; these factors may probably influence the risk of breast cancer in BRCA1/2 mutation carriers in a different way than in non carriers. Andrieu et al. conducted a retrospective study of 1601 patients who were part of the international BRCA1/2 carrier cohort study¹⁵. Information was obtained from a questionnaire. During the study, 853 patients had breast cancer. The results were analyzed using a weighted cohort approach. In this cohort, there was no significant difference in the risk of breast cancer between nulliparous and multiparous women. Among parous patients, an increasing number of full-term pregnancies was associated with a significant decrease in the risk of breast cancer (p=0,008): the risk was reduced by 14% (95% confidence interval (95% CI): 6%-22%) for each pregnancy. This association was the same for BRCA1 and BRCA2 mutation carriers and was restricted to women aged 40 or older. In BRCA2 mutation carriers, first childbirth over the age of 20 was associated with an increased risk of cancer : between 20 and 24 years old, hazard ratio [HR] = 2,33 [95% CI = 0,93 à 5,83]; 25-29 years old, HR = 2,68 [95% CI = 1,02 à 7,07]; \geq 30 years old, HR = 1,97 [95% CI = 0,67 à 5,81]). In BRCA1 patients, first childbirth over the age of 30 was associated with a reduced risk of breast cancer as compared with first childbirth before the age of 20 (HR = 0,58 [95% CI = 0,36 à 0,94]). Neither induced abortions, miscarriages or breast-feeding were significantly associated with a high risk of breast cancer.

As a result, patients with breast cancer associated with pregnancy may have genetic predispositions. Genetic counselling should be recommended. Nonetheless, it is hard to define if pregnancies have long term protective effects against cancer in mutation carriers.

A BIOLOGICAL MODEL

As the risk of breast cancer transiently increases within 3 or 4 years following full-term pregnancy, a model of oncogenesis has to be considered¹⁶. During pregnancy, the number of mammary epithelial cells increases massively, which seems partly due to the expansion of stem or proliferating intermediate cell population. This proliferation of epithelial cells is accompanied by an increase in angiogenesis and of the number of stromal cells as well as changes in the extracellular matrix. HLA-G whose expression is correlated to maternal immune tolerance may favour the escape of tumour cells from immune surveillance¹⁷. Pregnancy and mammary involution following pregnancy may alter the stem cell niche and basement membrane. After lactation and involution, the number of mammary epithelial cells including stem cells, is decreased together with breast density due to the degradation of the extracellular matrix. If pregnancy occurs in a woman whose mammary epithelium already contains a stem cell that has a genetic alteration causing cancer, or if such event occurs during pregnancy, the number of these cells can consequently increase, potentially allowing an additional genetic alteration and clonal selection due to the increase in population size. During involution, proteolysis leading to the degradation of the extracellular matrix may lead to the destruction of the basement membrane and promote the progression, invasion and spreading of metastases.

This biological model helps understand why pregnancy has a dual effect on the risk of breast cancer: firstly, the risk of breast cancer increases transiently after delivery, but then falls after 15 years. Pregnancy increases the short term risk of breast cancer because of the stimulation of the growth of epithelial cells that have gone through the first stages of malignant transformation. After delivery, it confers protection by inducing the differentiation of mammary stem cells which have the potential for neoplastic change.

DIAGNOSIS

The clinical diagnosis of breast cancer is difficult during pregnancy or breast feeding firstly because of the physiological changes occurring in the breast (increased breast density, hypervascularity, engorgement) and also because it is rarely considered by the physician or even by the patient herself¹⁸.

Any suspicious signs including a painless lump, a cutaneous lesion or a unique duct bleeding or discharge which may occur infrequently should lead to the diagnosis of breast cancer. In retrospective case series, a painless mass is a complaint made by 82 to 95% of women presenting with breast cancer^{19, 20}. Clark reported that bilateral tumours occurred in 4,6 % of cases, and multifocal tumours have also been frequently reported²¹. However, the incidence of inflammatory tumours is not higher (1, 5 à 4%). Finally, axillary lymphadenopathies which may often be taken for accessory mammary glands, may lead to the diagnosis of breast cancer²². The diagnostic delay varies from 2 to 15 months. As a result, the risk of advanced-stage disease is 2.5 higher in PABC patients (40% of PABC) as compared to nonpregnant patients²³.

All women should be encouraged to practise breast self-examination during pregnancy and lactation as 90% breast cancers are diagnosed this way.²⁴ Breast ultrasound should be the first-line imaging procedure for the diagnosis of PABC. It can be performed during all trimesters of pregnancy without risks for the mother and fetus. If cancer is diagnosed, the use of a bilateral one-view mammography to rule out microcalcifications should be discussed. The density of mammary glands in pregnant women reduces the sensitivity of mammography^{23, 26}. Mammography (digital if possible) does not seem to be less sensitive or specific during lactation^{27, 28}. Mammography should be performed with adequate abdominal shielding. Consequently, it is not contraindicated in pregnant or lactating women, but, contrarily to nonpregnant patients, it should not be used as first-line imaging procedure. If a multifocal tumour is suspected during conventional imaging procedure, MRI can be considered before choosing neoadjuvant chemotherapy or surgery. However, it should not be systematically recommended. According to the recommendations of the European Society of Urogenital Radiology, MRI with gadolinium injection can be considered. No effect has been recorded after the administration of gadolinium-based contrast media during pregnancy²⁵.

Treatment should be considered after obtaining histological results. Fine needle aspiration biopsy can be performed even though it is associated with risks of false-positive and false-negative results^{29, 30}. Indeed, some authors reported technical difficulties and sampling errors because of the frequency of lobular hyperplasia with a possible hypertrophy of the nucleolus and absence of size regularity³¹. The distribution of hyperproliferative cells of breast tissue may lead to false-positives. A core-needle biopsy is required as this technique can diagnose lesions with high sensitivity and specificity (90%). It should at least be performed under ultrasound guidance if a palpable mass is present, which may increase the sensitivity of the procedure. Stopping breastfeeding beforehand can reduce the risks of hematoma and milk fistula. Imaging procedures, core-needle or stereotactic biopsies are not contraindicated during pregnancy or breast feeding.

A complete assessment of PABC should include a chest X-ray (with abdominal lead shielding) and an abdominopelvic ultrasound. According to the European Association of Nuclear Medicine, a bone scan should be considered with regard to the potential benefits and risks to the mother and fetus. It exposes the fetus to only low doses (uterus dose: 0, 0063 mGy, dose for a fetus at 8 weeks gestation: 0, 0046 mGy, dose for a fetus at 18 weeks gestation: 0, 0026 mGy)

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[http://www.eanm.org/scientific_info/guidelines]). It can be performed after delivery and is only recommended during pregnancy to exclude a suspicion of bone metastases, which may alter the treatment.

PATHOLOGIC CHARACTERISTICS

Most PABC are invasive ductal carcinomas ³². Other histological forms have been diagnosed infrequently in pregnant and nonpregnant women. Histopathologic characteristics of PABC are reported in table 1. Most PABC are high grade and do not express hormone receptors. Amplification and/or overexpression of HER2 are present in almost 40% of cases. Pregnancy-associated breast cancers are generally highly invasive cancers.

The frequency of axillary node metastases seems higher in PABC. Figures reported in the literature vary from 47 % to 89 % ³³. The widespread use of neoadjuvant chemotherapy, responsible for axillary downstaging takes us back to former series to know the node involvement rate. In a series by Souadka ³⁴, an histologic lymph node involvement was found in 70 % of the 19 patients. Barrat reported that node metastases were found in 50 to 80 % cases vs 55 % in nonpregnant patients ³⁵. He noted that the prognosis was similar to that of nonpregnant patients in patients without node involvement, but was worse in patients who were pN⁺. In these historical series, pregnancy seemed to modify the prognosis as the frequency of node involvement and the seriousness of such situation were increased. In a more recent series by Petrek, node involvement rate reached 61 % in PABC versus 28 % in control patients who were not pregnant ^{9, 36}. During pregnancy, some specific conditions including lactating adenoma and gigantomastia do not generally pose any problems in terms of differential diagnosis.

SURGERY AND RADIOTHERAPY

Several specific questions should be discussed with the surgeon including the possibility of a breast-conserving surgery and consequently radiotherapy, as well as the sentinel lymph node biopsy.

Breast-conserving treatment

Pregnancy has long been considered an absolute contraindication to breast-conservation. It is no longer true although the following reservations have to be made. As a result of delayed diagnosis, pregnant women tend to have significantly more advanced disease than nonpregnant women. Mastectomy may be the preferred option in such context. Surgery is often more complex because of increased vascularity of the breast during pregnancy. A meticulous haemostasis is required⁹. In addition, as the median maternal age of women with PABC is 34 years, the decision to opt for a conservative treatment should be taken with regard to the high rate of local recurrences noted in this age group and the risk of multifocal disease. A thorough bilateral preoperative imaging is essential. The use of MRI has been discussed earlier. Only minimal oncoplastic surgery may be considered during pregnancy because of increased vascularity. Immediate breast reconstruction doesn't also make a lot of sense as it is difficult to achieve symmetry with the contralateral breast which continues to change as pregnancy advances.

Radiotherapy

Radiation can be safely used after delivery. However, it exposes the fetus to considerable risks during pregnancy. No anomaly was reported for embryo exposure to radiation doses of less than 300 mGy (0.3Gy). The American Academy of Paediatrics and the American College of Radiology do not recommend the termination of pregnancy if the fetus has been exposed to less than 5cgrays (0.05 Gy),^{43, 44} but most authors do not consider it if the fetus has been exposed to less than 0.1Gy.

The oldest data on the risks of malformations after radiation exposure come from findings in Hiroshima and Nagasaki. The prevalence of microcephalies and mental retardations described in exposed children has long been considered as a contraindication to breast radiation during pregnancy. However, recent findings should provide food for thought in the years to come.

Calculations of fetal doses from radiation exposure were revised in the 1990s. Breast or thoracic wall radiation exposes the fetus to only 0,1–0,3% of the total dose or 0,05–0,15 Gy for a regimen of 50 Gy³⁸. Towards the end of pregnancy, the fetus lies closer to the radiation field and can receive up to 2 Gy for the same protocol^{9, 38}. Van der Giessen et al. considered fetal dose exposure according to gestational age³⁹. For 6-25 MV x-rays, the maximal dose to the fetus ranges from 0, 03 Gy at 8 weeks gestation, 0, 20 Gy at 24 weeks, to 1, 43 Gy at 36 weeks. There are several case reports of normal children born after their mothers had received breast radiation therapy³⁹⁻⁴¹. The fetal doses ranged from 0,039 Gy to 0,18 Gy. The use of lead blocks reduced the dose the fetus was exposed to. Without using any lead blocks, the fetus would have been exposed to 0, 28 Gy. Breast and other radiation therapies (including brain radiation therapy) may be considered during pregnancy, but the dosimetry should be adapted accordingly by specialist teams.

These different theoretical data and descriptions may certainly challenge the dogma according to which « radiation cannot be performed during pregnancy ». However, as the duration of

neoadjuvant or adjuvant treatments tends to increase, breast radiation may most often be postponed until after delivery.

Major radiation-induced effects include fetal death during preimplantation (days 0-9 after conception) and malformations during organogenesis (between days 10–14 and 8 weeks). The incidence of malformations corresponds to 20 % of central nervous system anomalies for radiation exposure to 18 cgrays and to 100 % for radiation exposure to 200 cgrays. Exposing the fetus to radiation doses during the last stage of gestation (between 8 weeks until term) reduces the number of congenital malformations. After 30 weeks gestation, radiation-induced congenital malformations are uncommon. As a result, this information tends to assert that mammography can be safely performed during pregnancy and breast radiation therapy must be preferably postponed until after delivery. Only few studies have reported the long term effects of radiation therapy (even at low doses) on children exposed in utero as their mother were treated for breast cancer⁴⁵. Data reported above show that breast radiation is possible with appropriate lead shielding.

Annane et al. reported a series of 16 patients treated for breast cancer during pregnancy⁴². Among these patients, 10 were treated with conservative surgery (although 3 of them decided to end their pregnancy). No local recurrences with differed radiotherapy after delivery were observed after a median follow-up time of 87 months. No congenital anomalies or growth delays were noted for the 7 patients who had decided to continue their pregnancy.

As a result, even if breast conserving surgery may be performed during pregnancy, breast radiation should be postponed until after delivery.

Sentinel node procedure

There is only limited data on the safety of sentinel node procedure in pregnant patients.

Keleher et al.⁴⁶ and Gentilini et al.⁴⁷ studied fetal radiation exposure through the use of sentinel lymph node biopsy. The doses were low and consequently well below the doses reported in the recommendations.

Recently, Mondi et al. reported a series of 9 pregnant patients who underwent sentinel node procedure.⁴⁸ There were no deleterious effects on the growth of the fetuses.

In 2005, the American Society of Clinical Oncology convened an expert panel to provide recommendations on the use of sentinel lymph node biopsy⁴⁹. Considering the limited data available, the sentinel node procedure is not recommended during pregnancy. Most French medical teams do not consider such a procedure, especially because of the high prevalence of nodal involvement in the different series of patients with PABC: even if the procedure is technically possible, this prevalence confirms that pregnant patients should not currently undergo a sentinel node biopsy. However, the Sentinel Lymph Node procedure could be punctually considered during pregnancy following multidisciplinary decision-making to treat very small tumours or extended *in situ* carcinomas.

THE USE OF CHEMOTHERAPY DURING PREGNANCY

There is a paucity of information on the use of chemotherapy during pregnancy and its long-term effects. Patients should be clearly informed about these limits before making a decision concerning treatment strategy and the development of pregnancy. Cytotoxic chemotherapy causes genetic damage in exposed somatic cells including chromosomal breaks, translocations, deletions, gene mutations, aneuploidies and cell cycle disruptions^{50,51}. Cell culture and animal data regarding the carcinogenic, teratogenic and mutagenic effects of chemotherapy on embryonic and placenta cells are not reassuring.

Pharmacokinetics

Most cytotoxic agents have a molecular weight of less than 600 KDa, and cross the placenta and reach the embryonic circulation, unless they are extensively bound to plasma proteins⁵².

Plasma volume increases by approximately 50%, resulting in a larger dilutional space for water-soluble drugs.⁵³ The albumin concentration decreases while other plasma protein concentrations increase, partly due to high estrogen levels.

Many cytotoxic agents are bound to plasma proteins. Such changes (i.e. plasma volume and plasma concentrations) affect drug distribution and, thus, drug plasma concentration is likely to be greatest for drugs that are highly bound to proteins. An increased distribution volume will decrease the greatest concentration of the drug following bolus IV administration, and the half-life will also be longer unless drug metabolism or excretion is increased. As a result, concentration-time relationship may be modified; as the toxicity and effectiveness of cytotoxic drugs depend on this relation, it is particularly important.⁵⁶

Although the amniotic fluid is not usually compared to a pharmacological third space, it could be true for methotrexate whose distribution in a third space (ascites, pleural effusion) delays its elimination (« reservoir » effect) and increases its toxicity.

In addition, hepatic oxidation is more rapid during pregnancy, mainly because there is an increase in hepatic blood flow.⁵⁷ Renal plasma flow, glomerular filtration rate and creatinine clearance also increase.

Such changes lead to an increased clearance of drugs. No pharmacokinetic studies are available to determine whether dosages used in nonpregnant women are appropriate during pregnancy. Predictable pharmacokinetic variations owing to the physiological changes associated with pregnancy may lead to assume they are too slight. However, given the lack of clinical pharmacological data available, it must be assumed that drug dosages currently used in pregnancy are the ones recommended in nonpregnant patients.

All drugs cross the placenta and reach the fetus. Some of them moving more easily across the placenta to the fetus tend to be low-molecular-weight, highly-lipid-soluble, nonionized, and weakly bound to plasma proteins.

The expression of Pgp and MRP is also a determining factor for transplacental passage of xenobiotics⁵⁸ and considerably varies between patients.

Many cytotoxic drugs meet those criteria, and as a consequence, can theoretically cross the placenta and penetrate the fetal circulation. As a result, they have the same pharmacokinetic principles as before crossing the placenta, and are admitted in a system with a different maturity, especially concerning P450 cytochromes.⁵⁹

However, the immature fetal liver can metabolize a large number of drugs by oxidation, and fetal kidney may help in drug elimination. If drugs are excreted into the amniotic fluid, they may be ingested by the fetus and reabsorbed from the digestive tract, and thereby potentially increasing any deleterious effects of drugs, such as antimetabolites that are excreted in active form.

Moreover, some agents such as nitrogen mustards are bound to tissues, with virtually no active drug or metabolites excreted.

However, the placenta is also a route for drug elimination and is the main passage for the excretion of fetal waste. Despite two contradictory observations concerning adriamycin,⁶⁰⁻¹ there is a lack of knowledge on the transplacental passage of antineoplastic agents in humans.

At birth, the ability of the newborn to metabolize and excrete drugs is not well developed. Therefore, chemotherapy administered shortly before delivery may be particularly hazardous because of delayed metabolism and excretion when placental excretion can no longer occur.

Since data on the transplacental passage of cytotoxic agents in humans are lacking, analogies can be made between placental barrier (PB) and blood-brain barrier (BBB). BBB and PB respectively represent an obstacle to the delivery of toxic drugs present in the systemic circulation to the brain and the fetus. Each barrier is composed of a protective capillary network consisting of tight junctions between endothelial cells.

Drugs which cross BBB and PB have the same general features and are low-molecular-weight, highly-lipid-soluble (determined by octanol/water ratio), nonionized to physiological pH and weakly bound to plasma proteins.^{56,62-3} This leads to point out which cytotoxic agents cross the BBB and to compare their teratogenic effect to those which don't cross it.

Among alkylating agents, Busulfan crosses the BBB, as well as cyclophosphamide (its concentration in the cerebrospinal fluid (CSF) reaches 1/10 of its plasma concentration). The diffusion of procarbazine in CSF is rapid although it is water-soluble.⁶⁴⁻⁶

Anthracycline drugs do not cross the BBB, and can be given with minimal risks in the second and third trimesters.⁶⁷

Among antimetabolites, 5-FU crosses the BBB although it is water-soluble,⁶⁸ and is found in CSF after bolus IV administration or continuous infusion.⁶⁴⁻⁹

Methotrexate is not fat-soluble, and strongly bound to plasma proteins, mostly ionized to physiological pH, and penetrates the CSF with difficulty.⁷⁰

Of the 6 patients receiving single chemotherapy associated with a malformation and reported in the literature, 5 patients were administered a drug which crossed the BBB (Aracytine, Busulfan, Cyclophosphamide, Chlorambucil, 5-FU) and 1 patient was administered a drug which did not cross the BBB (vinblastine). Of the 23 patients receiving recognized treatments associated with malformations, only this case of single chemotherapy using vinblastine did not contain any drugs crossing the BBB.⁷¹

These results suggest that crossing BBB could predict PB crossing, but a pharmacokinetic study on amniotic, fetal (blood cord) and maternal concentrations needs to be conducted in order to confirm this non absolute correlation.

More information concerning the impact of some cytotoxic agents administered during pregnancy is available on the website of the French *Centre de Renseignements sur les Agents Tératogènes* (CRAT): <http://www.lecrat.org/>

Pharmacotoxicity

The impact of chemotherapy on the developing fetus seems to depend on multiple factors including types, durations and doses of cytotoxic agents administered as well as gestational age.

During the first 2–4 weeks from conception, cell differentiation and organogenesis are minimal. As a result, cytotoxicity of chemotherapy results in a spontaneous abortion or normal development of the fetus (an “all or nothing” phenomenon). Later in the first trimester, chemotherapy may interfere with organogenesis with an estimated teratogenic risk of 10% for single chemotherapy

and 20% for combination chemotherapy^{50, 53}. During the second and third trimesters, organogenesis is complete with the exception of the central nervous system and gonads. Data are provided from clinical cases and patients often receive combination chemotherapy, which makes difficult the interpretation of the deleterious effects resulting from such a procedure. Complications of chemotherapy are limited and consist of intra-uterine growth retardation, still birth, preterm delivery and maternal and fetal transitory myelosuppression. The risk of malformations is limited and is similar to that in the general population (2-3%). Sterility, central nervous system maturation defect or diminished IQ may be seen later^{50, 54}. It is also important to insist on the risk of premature menopause in 1/3 of patients, especially when it is administered to patients over the age of 30.

Doxorubicin, cyclophosphamide and 5-fluorouracil are the most documented drugs for the treatment of breast cancers. Berry et al. and Ring et al. conducted the two largest series published in the literature.⁷²⁻³ They both reported only 24 patients treated for breast cancer when they were pregnant. In the series by Berry et al., patients received a median number of 4 cycles of chemotherapy during pregnancy.⁷² Despite one pre-eclampsia and two preterm deliveries without any causes found, none of the complications was related to chemotherapy. The median gestational age at delivery was 38 weeks. Apgar scores, birthweights and immediate postpartum health were normal for all of the children. Only one child developed transient leukopenia and two children developed alopecia. In the series by Ring et al. 17 women received adjuvant chemotherapy and 7 women received neoadjuvant chemotherapy.⁷³ They were treated with anthracycline-based chemotherapies. The median gestational age at delivery was 37 weeks. No significant maternal or fetal complication was reported. In these studies carried out in North America and in England, Adriamycin was the anthracycline agent administered with 50mg/m² doses. In France, Epirubicin 100 mg/m² per cycle dose should be preferably used. In the absence of known deleterious effects and dose toxicity of Epirubicin as compared to Adriamycin, the use of Epirubicin 100mg/m² dose may be recommended.⁷⁴ A pharmacokinetic study is absolutely warranted. To date, no cases of fetal, infant or adolescent cardiotoxicity have been reported after anthracycline-based chemotherapy was administered after the first trimester. Little information is available on the use of epirubicin which is more lipophilic and whose transplacental transfer is more important. More recently, the administration of taxanes and platinum salts in women with breast cancer or genital cancer was reported. Platinum salts were involved in auditory disorders and cerebral or cardiac malformations.⁷⁵⁻⁷⁷ It is important to know if the routine use of taxanes in pregnant patients is safe for the fetus as it has become essential for the adjuvant treatment of breast cancers with node involvement. Only several case-reports are currently available on the use of taxanes for the treatment of breast or ovarian cancers during pregnancy. To date, of the 9 reported patients treated with paclitaxel, few details on the maternal toxicity are available.⁷⁸ One case receiving paclitaxel was described and developed anhydramnios. No malformation was reported and the children seemed healthy with a median follow-up of 16 months (3-36 months). Six patients treated with docetaxel were reported: one child developed hydrocephalia before treatment with docetaxel was reported. All children (including the baby with hydrocephalia) were healthy with a median follow-up of 18 months (9-28 months). Six patients treated with Navelbine were reported. No maternal or fetal toxicity was reported and the children seemed healthy with a median follow-up of 23 months (6-35 months).

Data on the possible delayed effects of exposure to chemotherapy in utero are reassuring. The largest series reported no impact on the physical, neurological and psychological development of

a cohort of 84 children between 6 to 29 years old exposed in utero. Children also showed normal learning abilities as compared to control subjects.⁷⁹

Little is known about the development of cancer, integrity of germinal cells and reproduction outcomes in children exposed to chemotherapy in utero. Nevertheless, there is no evidence that the risks of cancer and infertility may be different as those in the general population.

Given the limited data available on the use of targeted therapies during pregnancy, the first clinical cases lead to recommend not using them. Breast cancers associated with pregnancy are found to have a higher level of HER 2 amplification than cancers not associated with pregnancy.⁸⁰ These tumours may thus be treated with trastuzumab (Herceptin®). However, trastuzumab crosses the placental barrier and the expression of HER2 is important in embryonic tissues. Of the 6 published studies on the use of trastuzumab during pregnancy, 3 cases of anhydramnios were reported.⁷⁸ In one case, anhydramnios was found reversible at trastuzumab withdrawal. No fetal malformation was reported and the children seemed healthy with a median follow up of 6 months (2- 18 months). One case of lapatinib-administration was reported: no side effect was reported. Given the lack of information available and considering one case of anhydramnios was reported, it is recommended to avoid using these targeted therapies during pregnancy. The benefits of trastuzumab-based therapy and its synergistic interactions with taxanes should be considered in women with HER2-positive breast cancer developing early in pregnancy with the necessity of postponing targeted therapy if pregnancy is maintained.

In addition to cytotoxic agents, hormonal therapy and other supportive medications are used for the treatment of breast cancer in nonpregnant patients.

The teratogenicity of tamoxifen has been proved in mice and it has been associated with at least 10 cases of fetal malformations in 50 pregnant women exposed²². The use of tamoxifen should be postponed until after delivery.

Supportive care

Analgesic drugs can be used. Biphosphonates cross the placental barrier and some studies revealed that their administration altered bone modelling in animals and had unfavourable effects on calcium metabolism in animals and humans.⁸¹⁻² As a result, the use of biphosphonates is not recommended during pregnancy. The use of antiemetic agents (ondansetron and metoclopramide) during pregnancy was validated by two international prospective trials which did not report any deleterious effects on the fetus.⁸³⁻⁴ Erythropoietin does not cross the placental barrier and its use for the treatment of some pregnant patients did not show any fetal harm.⁸⁵ Considering some reported cases, Granulocyte colony-stimulating factors (G-CSF) have been used safely⁸⁶ : if necessary, they may be used in case of febrile neutropenia.

Analgesic drugs or corticosteroids are not contraindicated. However, the use of NSAIDs is limited by the risks to the fetus.

MANAGEMENT OF BREAST CANCERS DURING PREGNANCY

An international expert meeting was recently conducted to provide guidelines on how to treat women with PABC. It requires a multidisciplinary approach: surgery may be performed during pregnancy and chemotherapy may only start after the first trimester has been completed.³² Treatment should conform as closely as possible to protocols for nonpregnant patients. Nonetheless, decisions and therapeutic sequences should be considered according to the gestational age, stage of disease and preferences of the patient (Figures 2 and 3).

Termination of pregnancy may be considered although former series showed that it didn't improve prognosis.^{21,87} Nonetheless, if cancer is diagnosed before 12 WG and surgery is not a possible option, the decision to continue pregnancy delays treatment. As a result, the consequences of this treatment delay should be clearly discussed with the patient.

Mastectomy with axillary lymph node dissection remains the standard treatment for breast cancer during pregnancy.^{32, 72-3, 88-9} Enlarged lumpectomy with axillary node dissection can be recommended only if radiotherapy is not delayed, although, in practice, it is postponed until after delivery. Sentinel lymph node procedure should not be recommended because even if radioactive tracers may be used,⁴⁸ blue dye mapping is not recommended (absence of marketing authorization) and this dual identification technique is the method used to obtain the best identification rate. Moreover, the high nodal involvement rate of patients with PABC leads to assert that these women should not undergo a sentinel lymph node biopsy.⁹⁰

Chemotherapy can start after the 1st trimester has been completed, at 14 weeks. A standardized protocol with anthracyclines (up to 100 mg/m² but 50 mg/m² in most studies) may be prescribed without any significant risks to the mother and fetus. However, two important elements should be considered:

- Anthracycline 50 mg/m² dose is not optimal, particularly in node-positive patients⁹¹
- Randomized trials showed that the combination of taxanes and anthracyclines increased survival rate in these patients.⁹²⁻³ However, given the limited data available, their use is not recommended as first line treatment.

No pharmacodynamic study on the use of cytotoxic drugs in pregnant women is available. Experts recommend³² to use the same cytotoxic doses as in nonpregnant patients with breast cancer. It may be recommended to use Epirubicin 100mg/m² per cycle dose.

The date of delivery should be planned according to the date when cancer was diagnosed. If diagnosis of PABC is made after 18 weeks, delivery should be planned after 35 weeks, and preferably beyond 37 weeks. It is recommended that delivery occurs 2 to 3 weeks after the last cycle of chemotherapy so as to minimize the risk of maternal and fetal neutropenia.⁹⁴ If PABC is diagnosed before 18 weeks, delivery should be induced after 35 weeks if possible (or even earlier if cancer was diagnosed earlier in pregnancy) so as to minimize complementary therapy delay (taxanes, radiotherapy). The administration of taxanes, platinum agents or Navelbine may be considered as a second treatment option, if anthracycline-based chemotherapy fails, and if patients have metastatic cancers. Hormonal or targeted therapies can't be considered during pregnancy or breast feeding. An observatory has to be developed to determine the short and long term effects and safety of the different treatments administered during pregnancy. The optimal use of cytotoxic drugs also requires further pharmacodynamic studies.

POST-PARTUM:

In most cases, timing of delivery should be planned. 3 weeks after the last cycle of chemotherapy, and depending on the obstetric conditions, the patient may have her labor induced or wait for the maturation of the fetus. Timing may be shorter if she is treated with weekly paclitaxel. Chemotherapy may start again at 10 days postpartum. There is no information to assert that syntocinon or bromocriptine is contraindicated in women with breast cancer as these molecules have an antiproliferative effect.⁹⁵⁻⁶

The contraceptive device to be recommended is the copper IUD which should be fitted approximately 6 weeks after delivery.

PROGNOSIS

Considering the limited number of information available in the literature, it is difficult to assert that the prognosis of women with PABC is worse than that of nonpregnant women. In a series, Bonnier et al.⁹⁷ reported a 5-year recurrent free survival rate of 69% in 154 patients with PABC versus 81% in 308 control subjects ($p<0, 05$). However, most studies have found no difference in prognosis, and the prognosis of women with PABC is believed to be similar to that in nonpregnant patients of the same age and stage of disease^{9,32,36}. The part linked to pregnancy seems very small and the amount of unfortunate elements may increase and alter prognosis: young age, high grade, absence of hormonal receptors, diagnosis delay and absence of standardized therapy. A strict follow up is essential although no specific recommendations related to PABC may be set up. An individual follow-up plan should be carried out during the interdisciplinary team meeting (ITM).

CONCLUSIONS

Breast cancer associated with pregnancy is a rare clinical situation, but its prevalence keeps on increasing. The clinical diagnosis may often be delayed and difficult. Breast cancers with node involvement seem to be more frequent in pregnant women than in nonpregnant patients. Additional examinations including ultrasound, mammography and biopsy can be considered without any risks for the fetus. The treatment should conform as closely as possible to protocols for nonpregnant patients. Nonetheless, decisions and therapeutic sequences should be considered according to the gestational age, stage of disease and preferences of the patient during a multidisciplinary meeting involving gynaecologists, obstetricians, radiologists, oncologists and paediatricians.

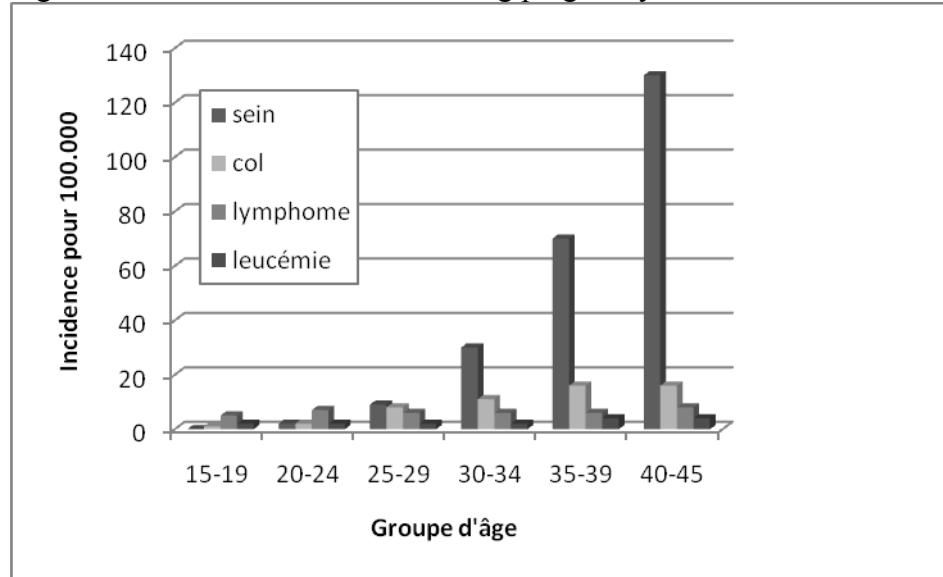
Breast-conserving surgery can be performed during pregnancy, but radiation therapy should be postponed until after delivery. Sentinel lymph node procedure is not recommended considering the only few cases reported so far. Hormonal or targeted therapy is not possible during pregnancy or breast feeding. FAC 50/FEC 100 chemotherapy can be prescribed after 14 weeks, if the tumour is not operable or not accessible for a conservative treatment, or in an adjuvant situation. The use of taxanes or targeted therapies is not recommended as routine treatment so far. The administration of taxanes, platinum agents or navelbine may be considered as a second treatment option, if anthracycline-based chemotherapy fails. The creation of a national pilot site as well as a specific registry may ultimately help in finding the optimal method to manage cancer during pregnancy.

It is absolutely essential that patients and her partners obtain honest and accurate information on the potential benefits and risks of the different treatment options before the final common decision making approved during the multidisciplinary meeting.

Table 1

Author	Year	Study design	No. subjects	Histology	Nuclear grade	ER	PR	Her-2
Ishida et al.	1992	Case-control	Cases : 72 (pregnant); 120 (lactating); 191 controls	No difference	Not examined	Fewer ER+ patients	Not examined	Not examined
Elledge et al.	1993	Case-control	15 cases (pregnant); 411 controls	Not examined	Not examined	No difference	No difference	58% +++ vs. 16% of controls
Elledge et al.(Tobon and Horowitz)	1993	Retrospective case series	14 cases	93% Invasive Ductal Carcinoma	Not examined	ER + : 50%	PR + : 36%	Not examined
Bonnier et al.	1997	Case-control	154 cases PABC; 308 controls	No difference	No difference	Fewer ER+ in pregnant women	Fewer PR+ in pregnant women	Not examined
Shousha	2000	Case-control	14 cases PABC; 13 controls	71% IDC vs 69% controls	80% poorly differentiated cancers vs 33% controls	50% positive vs. 91/9% controls	30% positive vs. 64% controls	44% +++ vs. 18% controls
Middleton et al.	2003	Prospective case series	39 cases (pregnant)	100% IDC	84% poorly differentiated cancers	ER +: 28%	PR +: 24%	28% +++
Reed et al.	2003	Retrospective case series	Cases:20 (pregnant) 102 (lactating)	82% IDC	95% G2-3	ER +: 34%	PR +: 28%	44% +++
Ring et al.	2005	Retrospective case series	24 patients	83% IDC	26% G2 74% G3	ER + : 58%	Not examined	42% +++

Figure 1 :Prevalence of tumours during pregnancy



Incidence for 100.000

Breast
Cervix
Lymphoma
Leukemia

Age groups

Figure 2

Less than 14 weeks of gestation at histologic diagnosis

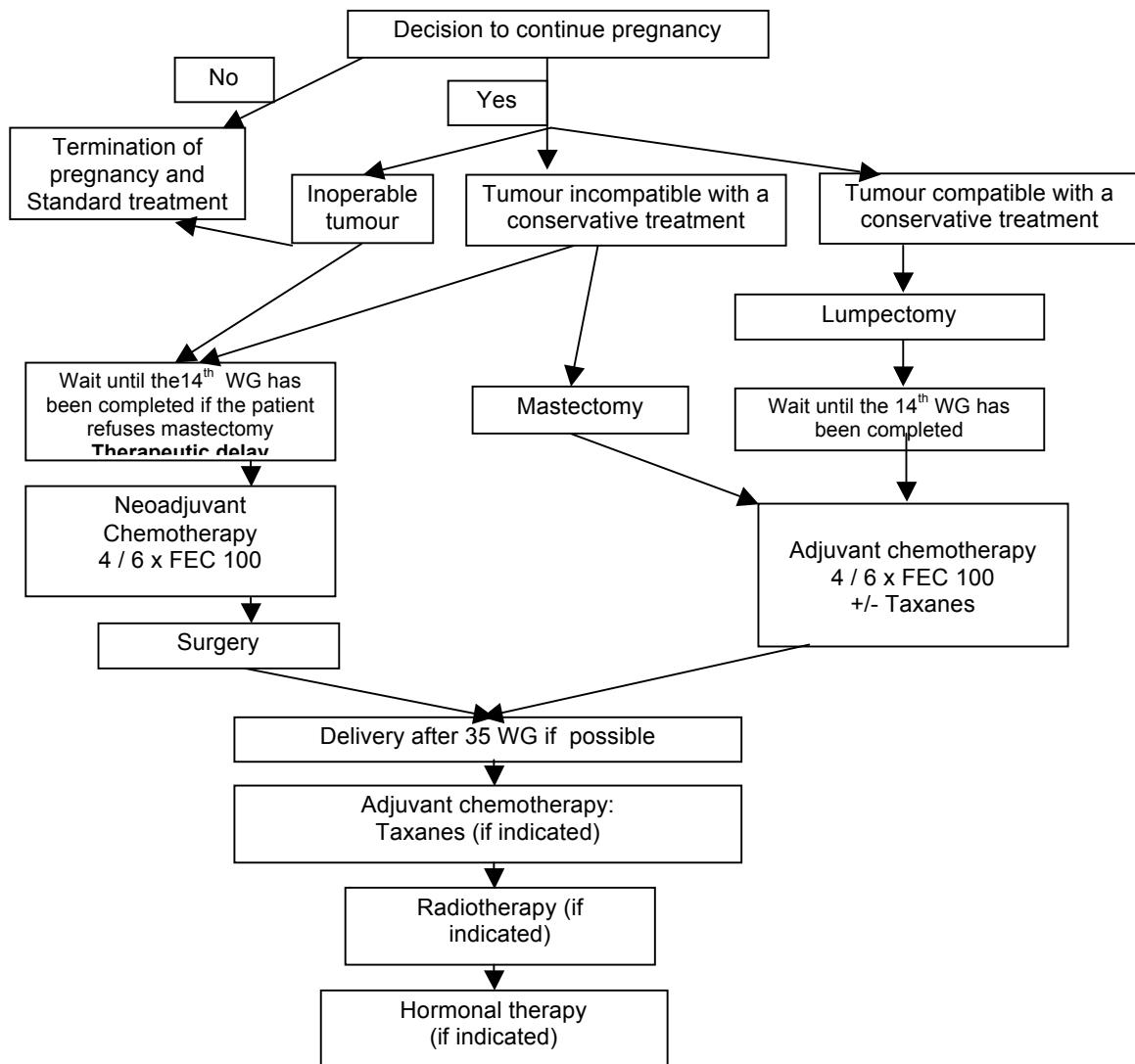
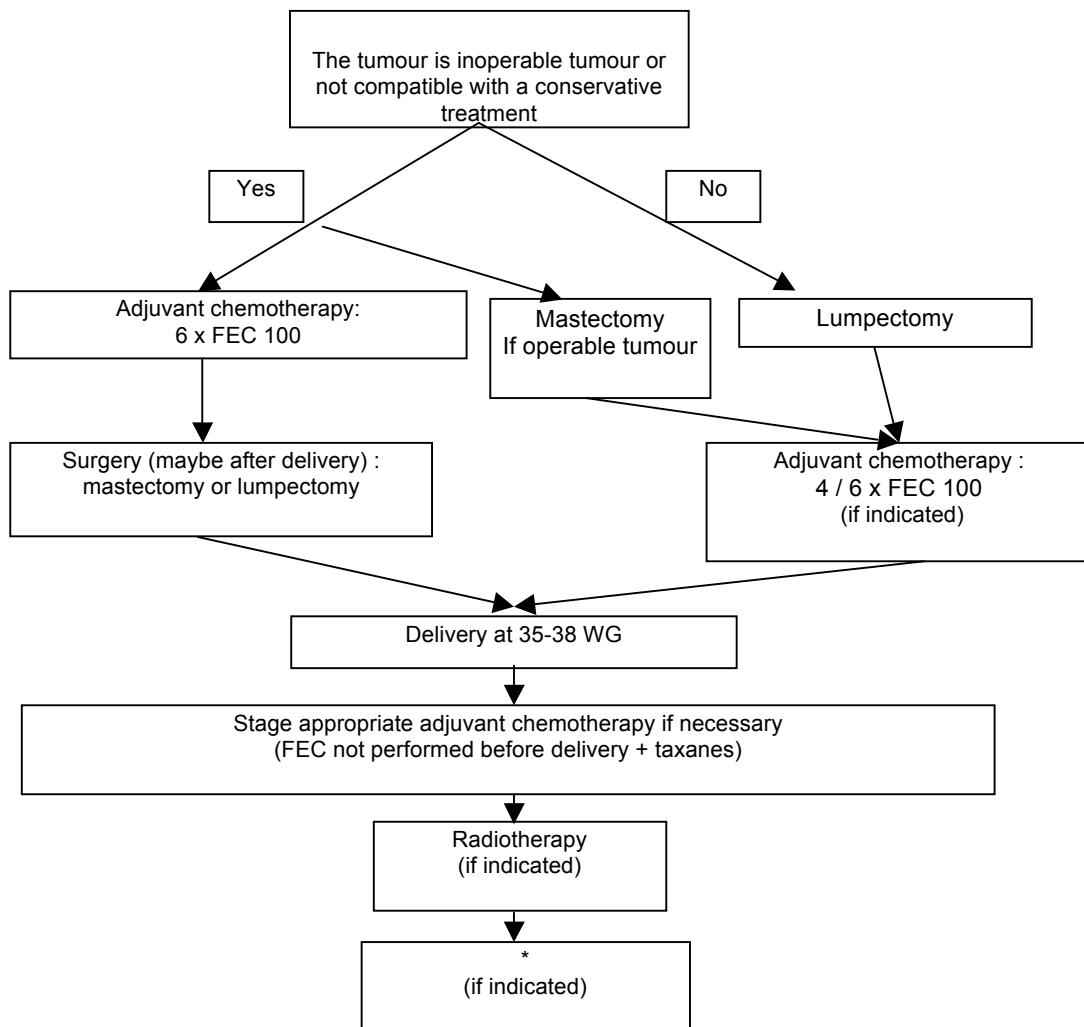


Figure 3

14-34 weeks of gestation at histologic diagnosis



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