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Breast cancer during pregnancy

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Introduction

Breast cancer associated with pregnancy is defined as breast cancer diagnosed during pregnancy, breastfeeding or during the first year postpartum.

The incidence of breast cancer during pregnancy ranges between 0.2% and 3.8% of all malignant breast tumors, but if only women of childbearing age (<45 years) are considered this prevalence reaches 7-14% [1, 2]. Although breast cancer is an uncommon condition in pregnant women, it is the most common malignancy associated with pregnancy after cervical carcinoma, with an estimated incidence of 1/3000 to 3/10000 pregnancies [2, 3]. There has been an increase in the incidence of breast cancer in women of childbearing age due to the delay in initiating pregnancies with respect to previous decades. The current average age of the pregnant woman with breast cancer is 36 years.

Classically, the prognosis in pregnant women has been thought to be worse than in non-pregnant women. However, currently, and based on case-control studies, the prognosis of pregnant women does not seem to differ from that of non-pregnant patients of the same age and stage of disease. It is possible that the worse prognosis initially attributed to pregnant women was due to a more advanced stage at diagnosis or a less standardized therapy [4].

Clinical experience of breast cancer in pregnant women is very limited due to its rarity, and therefore making therapeutic decisions can be complicated. Breast cancer in this group of women requires a change in the usual therapeutic approach, a modification of diagnostic methods, and often an adjustment of treatment sequences depending on gestational age [5]. It requires a multidisciplinary expert team as well as psychological and family support.

Tumor characteristics of breast cancer in pregnant women

Biological characteristics of breast cancers in pregnant women are similar to those in young non-pregnant women. However, these characteristics, as well as the greater aggressiveness, are determined by age rather than by pregnancy itself. The most frequent histological type of breast tumor in pregnant women is invasive ductal carcinoma with a high histological grade. It has been shown that breast tumors diagnosed during pregnancy are of greater size and have increased axillary involvement, lymphovascular invasion is common, as well as a lower incidence of hormonal receptor expression. The percentage of tumors expressing human epidermal growth factor receptor 2 (HER2) is inconsistent across studies, but appears to be higher in pregnant women with breast cancer [6, 7].

Diagnosis of breast cancer during pregnancy

A breast examination is recommended in all women at first pregnancy visit. Although over 80% of breast masses are benign in pregnancy, any breast node that persists beyond 2-4 weeks should be analyzed [8]. If breast masses or skin changes appear during pregnancy, pertinent studies should be performed to rule out malignancy.

Given the physiological changes of the mammary gland during pregnancy, the fear of using certain diagnostic procedures (mammography) may cause delays in diagnosis, which in many cases translates into a worse prognosis. If indicated, a mammogram can be performed using proper abdominal shielding, although it should be noted that the false negative rate is higher in pregnant women because of the physiological changes in the mammary gland. Breast ultrasound is important in differentiating solid and cystic lymph nodes and in assessing their morphology. Additionally, this method is very useful to evaluate breast masses in pregnant women in whom interpretation of mammography results is difficult due to the increased breast density. The routine use of magnetic resonance imaging is not recommended for the diagnosis of breast

nodules during pregnancy because the effectiveness of this technique has not been established in pregnant women and there are no safety data regarding the use of gadolinium in this population. Although fine-needle aspiration can be used to diagnose a breast mass in a pregnant patient, a core or excisional biopsy is required for a definitive diagnosis of invasive cancer. The potential for the development of a subsequent mammary fistula after core or excisional biopsy is overestimated, with very few reports in the literature [4].

Once breast cancer is diagnosed, assessment of metastatic spread should only include those studies needed for an effective treatment planning. Computerized tomography, magnetic resonance imaging and bone scintigraphy should be avoided during the first trimester of pregnancy. If metastatic disease is suspected, these studies may be performed from the second trimester on. On the contrary, mammography, chest X ray (using proper shielding) and ultrasounds may be used whenever they are required.

Prenatal follow-up assessment

Monitoring of pregnancy must be strict in patients with breast cancer. The accurate dating of gestation is fundamental to know the probable date of birth and, based on that, to assess the therapeutic options. A high-resolution ultrasound must be performed to assess the morphology of the fetus prior to treatment. Amniocentesis should be offered if there is an obstetric indication.

If the patient is going to receive chemotherapy, fetal growth assessment should be carried out using serial ultrasounds every 3-4 weeks prior to each chemotherapy cycle, as well as a fetal biophysical profile from week 28 to term and an assessment of the amniotic fluid, because its volume can decrease reversibly with the use some drugs [9]. An umbilical artery doppler study is also recommended to assess the status of the placenta and the fetal middle cerebral artery to rule out fetal anemia [9]. In patients

treated with potentially cardiotoxic drugs such as anthracyclines, it is advisable to carry out serial fetal echocardiography studies during treatment and in the neonatal period.

The expected date of delivery must be accurately known. It is recommended that gestation continues to week 37, but with advances in neonatal medicine today it is sometimes possible for babies to survive only 30 weeks of gestation. Delivery should be done vaginally because of its lower morbidity and mortality compared with caesarean section, particularly if chemotherapy is planned to be continued after delivery [4].

Maternal myelosuppression secondary to chemotherapy should be avoided and controlled during labor and the perinatal period to minimize the risk of infection and bleeding. Furthermore, chemotherapy administered close to delivery may lead to accumulation of drugs on the fetus or newborn, thereby increasing exposure and toxicity. Therefore, chemotherapy should not be given after the 35th week of gestation if delivery is to be spontaneous. Chemotherapy should be avoided during the last 2-3 weeks before delivery to minimize the risk of maternal and fetal neutropenia, although some authors recommend no less than 4 weeks [4]. After delivery, chemotherapy should be delayed by one or two weeks and breastfeeding should be discontinued. Although placental metastases are rare, the placenta should be sent for histological examination [4].

Treatment of breast cancer during pregnancy

If the psychological impact following a diagnosis of breast cancer is high, this is even greater if the diagnosis is compounded by a pregnancy. A diagnosis of pregnancy can affect the treatment and therefore the prognosis of the disease. The therapeutic approach to breast cancer during pregnancy requires the participation of a multidisciplinary team, which will choose the most appropriate treatment according to tumor stage. Based on the treatment required, and after informing of the potential risks

to the fetus, the patient and her family will decide whether to continue or terminate pregnancy. Until the decision is taken, the physician should provide all the necessary support to the patient.

For decades it was thought that pregnancy could worsen disease prognosis, and therefore in many cases women were advised to terminate pregnancy. Nevertheless, data from several retrospective studies have shown that the survival of pregnant patients with breast cancer is not increased by termination of the pregnancy, even if the cancer has spread [10-12]. It may be reasonable to discuss termination of pregnancy in women with advanced or metastatic disease, or in very early pregnancies because of the teratogenic risk of chemotherapy during the first trimester [12]. Breast cancer treatments include surgery, chemotherapy, radiotherapy and endocrine therapy.

Surgery in the pregnant woman with breast cancer

Surgery can be performed safely during all trimesters of pregnancy with minimal fetal risk. Mastectomy is a good choice when radiotherapy can not be delayed until after delivery. Breast-conserving surgery, when used, is more commonly performed at the end of the second trimester and during the third trimester, and radiotherapy is delivered postpartum [13].

The role of sentinel node mapping is controversial in pregnant patients because of concerns about the possible teratogenic effects of blue dye and the reliability of lymphatic mapping in the pregnant breast. Although some have used radioactive colloid alone in this subgroup of patients, sensitivity of lymphatic mapping is reduced when a single modality is used [14].

Cytotoxic therapy in the pregnant woman with breast cancer

The therapeutic approach may vary depending on the length of gestation. The effect of polychemotherapy during the first trimester of pregnancy involves a risk of

malformations that can reach 25%, whereas when only one drug is used the probability is 17%. This incidence of teratogenesis is much higher than in the general population (3%) [15, 16].

Chemotherapy can be administered from the second trimester onwards with some modifications to minimize harm to the fetus. There are enough safety data to suggest that there is no risk of fetal malformation when chemotherapy is administered during the second and third trimester [10, 17].

Other toxicities to consider are increased frequency of miscarriage, possibility of low birth weight, and hematologic toxicity in the fetus [18, 19]. Changes that occur during pregnancy, such as the generation of a third space (fetal-placental amniotic fluid), increased volume distribution, and changes in the metabolism and elimination of drugs, may determine different toxicity patterns that may also indirectly affect the fetus. There is also a risk of long-term toxicities on chemotherapy, but information on this issue is scarce [20].

Clinical experience of pregnant women undergoing chemotherapy for breast cancer has resulted in allowing the administration anthracycline-based regimens from the second trimester onwards with some security [21]. With other active drugs, such as taxanes, vinorelbine or trastuzumab the experience is more limited [22]. Docetaxel, paclitaxel and vinorelbine have been used without serious toxicity to the fetus being detected [22].

For the moment, targeted therapies such as trastuzumab seem less safe because they are associated with anhydramnios [23]. To date, there is no experience with lapatinib or with bevacizumab. Use of bisphosphonates should also be avoided due to safety issues.

In the future, the development of prospective databases will provide additional information, especially in regard to possible long-term sequelae secondary to antitumor therapies.

Radiotherapy and endocrine therapy in the pregnant woman with breast cancer

Radiotherapy and endocrine therapy are not indicated during pregnancy due to the high risk of teratogenicity, and should be delayed until after delivery [24-26].

Risk of breast cancer during pregnancy in carriers of *BRCA*

In women with a family history of breast cancer without mutational study, pregnancy does not confer an increased risk of breast cancer. However, some studies have noted a significant increase in breast cancer incidence in the two years following pregnancy in *BRCA2* mutation carriers [27]. Because these data have not been confirmed in other studies [28], currently a known carrier of a *BRCA* mutation can not be advised against becoming pregnant, but it is our responsibility to inform these women of the available results.

Conclusions

- Breast cancer during pregnancy is occurring with increasing frequency because more women are delaying pregnancy into their thirtieth and fortieth decades.
- The prognosis in pregnant women is classically thought to be worse than in non-pregnant woman, which is probably mainly due to variable factors such as delayed diagnosis, rather than the actual pregnancy itself. Data indicate that the prognosis of pregnant women does not appear to differ from that of non-pregnant patients of the same age and stage of disease.
- Techniques to diagnose breast cancer in a pregnant woman are similar to those used in non-pregnant women (mammography, ultrasound, biopsy), with comparable efficiency. Studies to assess metastatic spread, such as computerized tomography or magnetic resonance imaging, should be limited to

those strictly necessary, and recommended only in cases of suspected metastasis.

- Monitoring of pregnancy must be strict in patients with breast cancer.
- The probable date of birth needs to be known to assess therapeutic options.
- The therapeutic approach to a pregnant woman with breast cancer requires the collaboration of a multidisciplinary team. The treatment of the cancer needs to be carefully planned, with consideration given to the potential risks to the developing fetus. Therapeutic abortion is rarely indicated except in women with advanced or metastatic disease or very early in pregnancy (first trimester), because of the potential teratogenic effects of chemotherapy.
- Although breast-conserving surgery has evolved as the major treatment in breast cancer, in pregnant women is recommended only in the final of the second trimester and third trimester because the radiotherapy has to be delayed after delivery.
- Radiotherapy and endocrine therapy should not be applied during pregnancy and should be delayed until after delivery.
- Pregnant women with breast cancer can be treated with anthracycline-based chemotherapy during the second and third trimesters of pregnancy with minimal risk to the fetus. There is less experience with other chemotherapy agents such as taxanes and vinorelbine, but to date no malformations have been described secondary to their use. For now, the use of bisphosphonates or biological therapies (trastuzumab, bevacizumab, lapatinib) can not be recommended.

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References

1. Ring AE, Smith IE, Ellis PA (2005) Breast cancer and pregnancy. *Ann Oncol* 16:(12):1855-60
2. Pavlidis NA (2002) Coexistence of pregnancy and malignancy. *Oncologist* 7:(4):279-87
3. Anderson JM (1979) Mammary cancers and pregnancy. *Br Med J* 1:(6171):1124-7
4. Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B, et al. (2006) Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer* 106:(2):237-46
5. Gentilini O, Masullo M, Rotmensz N, Peccatori F, Mazzarol G, Smeets A, et al. (2005) Breast cancer diagnosed during pregnancy and lactation: biological features and treatment options. *Eur J Surg Oncol* 31:(3):232-6
6. Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A (2003) Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. *Cancer* 98:(5):1055-60
7. Euler U, Knopf B, Tulusan AH (2004) Breast cancer in young women aged 35 or less. *ASCO Meeting Abstracts* 22:(14_suppl):754
8. Woo JC, Yu T, Hurd TC (2003) Breast cancer in pregnancy: a literature review. *Arch Surg* 138:(1):91-8; discussion 99
9. (2008) Protocolo de cáncer de mama y embarazo. Available via: www.sego.es
Accessed November 2008
10. Gwyn KM, Theriault RL (2000) Breast cancer during pregnancy. *Curr Treat Options Oncol* 1:(3):239-43
11. Trivers KF, Gammon MD, Abrahamson PE, Lund MJ, Flagg EW, Kaufman JS, et al. (2007) Association between reproductive factors and breast cancer survival in younger women. *Breast Cancer Res Treat* 103:(1):93-102

12. Clark RM, Chua T (1989) Breast cancer and pregnancy: the ultimate challenge. *Clin Oncol (R Coll Radiol)* 1:(1):11-8
13. Kuerer HM, Gwyn K, Ames FC, Theriault RL (2002) Conservative surgery and chemotherapy for breast carcinoma during pregnancy. *Surgery* 131:(1):108-10
14. Amersi F, Hansen NM (2006) The benefits and limitations of sentinel lymph node biopsy. *Curr Treat Options Oncol* 7:(2):141-51
15. Wiebe VJ, Sipila PE (1994) Pharmacology of antineoplastic agents in pregnancy. *Crit Rev Oncol Hematol* 16:(2):75-112
16. Doll DC, Ringenberg QS, Yarbrow JW (1989) Antineoplastic agents and pregnancy. *Semin Oncol* 16:(5):337-46
17. Keleher AJ, Theriault RL, Gwyn KM, Hunt KK, Stelling CB, Singletary SE, et al. (2002) Multidisciplinary management of breast cancer concurrent with pregnancy. *J Am Coll Surg* 194:(1):54-64
18. Kerr JR (2005) Neonatal effects of breast cancer chemotherapy administered during pregnancy. *Pharmacotherapy* 25:(3):438-41
19. Giacalone PL, Laffargue F, Benos P (1999) Chemotherapy for breast carcinoma during pregnancy: A French national survey. *Cancer* 86:(11):2266-72
20. Aviles A, Niz J (1988) Long-term follow-up of children born to mothers with acute leukemia during pregnancy. *Med Pediatr Oncol* 16:(1):3-6
21. Azim HA, Jr., Peccatori FA, Scarfone G, Acaia B, Rossi P, Cascio R, et al. (2008) Anthracyclines for gestational breast cancer: course and outcome of pregnancy. *Ann Oncol* 19:(8):1511-2
22. Mir O, Berveiller P, Ropert S, Goffinet F, Pons G, Treluyer JM, et al. (2008) Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol* 19:(4):607-13

23. Sekar R, Stone PR (2007) Trastuzumab use for metastatic breast cancer in pregnancy. *Obstet Gynecol* 110:(2 Pt 2):507-10
24. Marty M, Mignot L, Gisselbrecht G, Morvan F, Gorins A, Boiron M (1985) [Teratogenic and mutagenic risks of radiotherapy: when and how to prescribe contraception]. *Contracept Fertil Sex (Paris)* 13:(1 Suppl):181-6
25. Fenig E, Mishaeli M, Kalish Y, Lishner M (2001) Pregnancy and radiation. *Cancer Treat Rev* 27:(1):1-7
26. Isaacs RJ, Hunter W, Clark K (2001) Tamoxifen as systemic treatment of advanced breast cancer during pregnancy--case report and literature review. *Gynecol Oncol* 80:(3):405-8
27. Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, et al. (2005) Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. *Int J Cancer* 117:(6):988-91
28. Tryggvadottir L, Olafsdottir EJ, Gudlaugsdottir S, Thorlacius S, Jonasson JG, Tulinius H, et al. (2003) BRCA2 mutation carriers, reproductive factors and breast cancer risk. *Breast Cancer Res* 5:(5):R121-8