

**PREGNANCY
ASSOCIATED WITH
BREAST CANCER:
A REVIEW OF THE
LITERATURE**

Barbara Antonia Dups Talah

Pontificia Universidade Católica do Paraná,
Curitiba – PR.

Bruno Augusto Lopes

Hospital Universitário Clementino Fraga
Filho (HUCFF) - Universidade Federal do
Rio de Janeiro (UFRJ) - Rio de Janeiro/RJ

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Abstract: Goal: to expose the main concepts of Breast Cancer diagnosed during pregnancy, presenting its risk and protective factors, patient profile and diagnosis. **Literature Review:** Pregnancy-Associated Breast Cancer (CMAG) is a breast cancer disease that affects patients during the first year after pregnancy. CMAG reaches its peak close to the fourth decade of life. There are factors that can be both risk and protective, such as reproductive behavior. Women who conceived 3 years ago have a 2.66 times higher risk compared to those who gave birth 10 years ago, just as a first pregnancy at age 30 can reduce the risk by 25% for all CMAGs. Breastfeeding, unlike reproductive behavior, is restricted to protect the patient, reducing the risk by up to 4.3% every 12 months, adding 7% to this value per pregnancy. The most prevalent Pregnancy-Associated Breast Cancers are those with negative hormone receptors, therefore Triple Negative and HER-2 positive. Both have an advanced staging pattern, high Ki67 index and Invasive Ductal Carcinoma (IDC) histology. Within the CMAG histological classifications, CDI corresponds to 71-100% of cases. Clinical findings in the breast include thickening of the skin, secretion of purulent fluids or blood, inflammatory and lymphatic changes. Pregnancy-Associated Breast Cancer has tropism for vascular tissues and adjacent lymph nodes, causing 2.5 times more metastases than other tumors. **Conclusion:** There is a need to expand the field of research on Pregnancy-Associated Breast Cancer, given the magnitude of exponential growth presented by this pathology in recent decades. **Keywords:** Pregnancy, Neoplasms, Breast Cancer.

INTRODUCTION

Gestational Cancer is a rare phenomenon in medical practice (1). It is estimated at 1 case for every 1000 pregnant women per

year and around 1/3 of malignancies occur during this stage of a woman's life (2, 3, 4, 5, 6). Future expectations indicate the possibility of an increase in the cancer-pregnancy combination, mainly due to the increase in the birth rate at ages over 30 years old (1, 3). Faced with a complex and unusual situation like this, health professionals are challenged to deal with this situation that places the pregnant woman under an imminent high-risk classification (7, 8, 9).

The most common neoplasms during this period include breast and skin cancer, uterine cervix, ovarian and hematological neoplasms, respectively (7, 10, 11, 12). Some studies declare Melanoma as the main disease in this group, with an incidence between 0.05% and 0.1% (4, 5). However, other articles determine this role to Breast Carcinoma, whose name during pregnancy is Pregnancy-Associated Breast Cancer (CMAG) (2, 7, 9, 11, 13). The PANEL-Oncology reports 177,162 cases of Traditional Breast Cancer in women between January 2020 and July 2023 (14). It is estimated that the incidence of CMAG is equivalent to approximately 0.2 to 3.8% of this total (15).

Regardless of the classification or epidemiology of the oncological disease, the main concern is the high-risk pregnancy scenario (8, 9). Breast Cancer during pregnancy has an advanced metastatic potential due to its biological characteristics (15). 60% of pregnant women receive a late diagnosis of CMAG, this delay varies between 1 and 13 months in most cases (9, 13). Consequently, there is a 2.5 times greater risk of identifying the disease in advanced stages, which provides an unfavorable prognosis (8).

Individually, breast cancer, pregnancy and hospital admission are enough to generate complications, which is why they are alarming together (6). It is worth remembering that CMAG is not caused by pregnancy, it is just simultaneous events (9). The risks that CMAG

entails include premature birth of the baby, rupture of the amniotic membrane and venous thromboembolism, among other adversities (5, 6, 13). Therefore, it is essential that the multidisciplinary team is prepared to safely manage this situation, aiming for the integrity of the maternal and fetal organisms (8, 9, 10). The objective of this literature review is to expose the main concepts of Breast Cancer diagnosed during pregnancy, presenting its risk and protective factors, patient profile and diagnosis.

METHODOLOGY

This is a Narrative Literature Review of 38 articles, during the period from July to August 2023. The databases used were Pubmed, Embase and Scielo. In addition, the American Cancer Society (ACS) breast cancer guideline and the information technology department of the single health system (DATASUS) were consulted in the PANEL - oncology section. The data extracted from DATASUS refers to the last 3 years according to the following inclusion criteria: women, malignant breast neoplasm, age range from 0 to +80 years and throughout the national territory. The languages covered were English, Portuguese and Danish. The descriptors used were “pregnancy”, “neoplasms” and “breast cancer”.

LITERATURE REVIEW

PATIENT PROFILE, RISK AND PROTECTION FACTORS

Pregnancy-Associated Breast Cancer (CMAG) is a breast cancer disease that affects patients during the first year after giving birth. CMAG reaches its peak close to the fourth decade of life, therefore, the patient profile includes women between 35 and 50 years old facing their first pregnancy (3, 7, 13, 16, 17). Only 20% of cases are diagnosed in individuals under 50 years of age. There is an annual increase of 0.06% in this rate, which is

responsible for 21.2% of deaths related to this disease (13). Furthermore, women in older age groups during their first pregnancy have an increased risk of developing CMAG over the next 5 years (18).

Half of cases in young women coincide with a family history and 30% are associated with genetic mutations (7,23). The main risk factors include exposure to thoracic radiotherapy during ages 10 and 30; previous diagnosis of invasive neoplasia after 35 years (increase in risk by an additional 1.7% for 5 years); family history (increases the risk by 20%); smoking, obesity and alcohol consumption (20, 21). There are factors that can be both risk and protective, such as reproductive behavior. Women who conceived 3 years ago have a 2.66 times higher risk compared to those who gave birth 10 years ago, just as a first pregnancy at age 30 can reduce the risk by 25% for all CMAGs (18, 22).

Breastfeeding, unlike reproductive behavior, is restricted to protect the patient, reducing the risk by up to 4.3% every 12 months, adding 7% to this value per pregnancy (18, 22, 23). The period of breastfeeding is directly proportional to protection, mothers who breastfeed for 1-2 years reduce rates by 32-49% (19). However, the breastfeeding rate varies according to the economic development of the region, being higher in developing countries, however with a tendency to reduce in Brazil since the 1970s (24, 25). Although breastfeeding is promising, the protection it offers is limited covering Triple-Negative Breast Cancer (TNBC) classes at 20% and BRCA1 at 22-55%. The exposure influence on BRCA2 and HER2 positive cases remains independent of breastfeeding habits (18, 23).

CMAG SUBTYPES

In clinical medicine, the most important subdivision is intrinsic, whose subtypes include TNBC, HER-2 positive, Luminal A

and B (26). The most prevalent Pregnancy-Associated Breast Cancers are those with negative hormone receptors, therefore Triple Negative and HER-2 positive (27). Both have an advanced staging pattern, high Ki67 index and Invasive Ductal Carcinoma (ICD) histology (26). Within the CMAG histological classifications, CDI corresponds to 71-100% of cases (16).

DIAGNOSIS AND STAGING

CMAG presents more aggressively than traditional breast cancer, due to accelerated cell proliferation in the face of high levels of estrogen, progesterone and growth factors (28, 29). Furthermore, during pregnancy, gene expression patterns in the breast are altered, generating a tendency towards invasion and biological aggressiveness (27, 29). Epithelial cells now have a large number of genes associated with cellular repair, oncogenes, cell proliferation genes and immune response activators. As a result, there are more non-silent mutations of the mucin genes, BRCA1 and CHECK2, known for their oncological potential (21, 29).

Clinical findings in the breast include thickening of the skin, secretion of purulent fluids or blood, inflammatory and lymphatic changes (27, 30). Prenatal care is essential for the efficient diagnosis of conditions such as CMAG, contributing to an increase in incidence and a favorable prognosis (7, 12, 31). It is worth remembering that the guidelines of the American Society of Clinical Oncology (ASCO) and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) organizations do not recommend self-examination, to the detriment of physical examination by a professional (32). Currently, non-invasive physical examinations for detection of aneuploidy suffer from unforeseen sensitization to neoplasms. A significant portion of women do not participate in

screening exams, leading to delays in diagnosis (7, 12, 33, 34). In Brazil, approximately 20% of women do not receive prenatal care (27). The risk of CMAG becoming metastatic increases by 0.9% for each month delay in diagnosis (29).

The staging remains the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) (2). The tumor is often diagnosed at stage II or III (11). 53-71% of CMAGs have positive nodes. These are bulky masses measuring 3.5 cm, while the other subtypes appear with an average of 2 cm (27). Pregnancy-Associated Breast Cancer has tropism for vascular tissues and adjacent lymph nodes, causing 2.5 times more metastases than other tumors (11, 27).

There are different imaging techniques to stage cancers, but it is important to adapt them during pregnancy, considering the safety of the fetus, metastatic risk and viability of the baby, respectively (11). Imaging exams can use two types of radiation: non-ionizing and ionizing (35). Ionizing radiation is avoided because it has the ability to penetrate tissues, adding teratogenicity to the embryo (10, 35). The imaging tests using this radiation are: Computed Tomography (CT), Mammography, Positron Emission Tomography (PET) and Radiography (X-ray) (35). Complications vary depending on the amount of radiation and gestational age of exposure (2, 10).

Mammography is a localized exam with low radiation, therefore it is safe as long as a lead vest is used in the abdominal region, which reduces the risk of malformations by 50% (7, 35). However, it is important to note that histological variation during pregnancy affects mammography sensitivity, which decreases as density and hypervascularity increase (11, 20, 29, 35). Mammography results classified as BI-RADS D have a 2.11 times higher risk compared to more dispersed fibro-glandular tissues filled with fat belonging to a BI-RADS

B (95% CI 1.84-2.42) (20).

Ultrasonography (US) is the first choice, it is a more accessible exam, which allows the immediate identification of benign lesions, such as cysts and galactoceles (2, 7). In total, it has 80.1% sensitivity and 88.4% specificity for malignancies (2). The appearance on US is a low echogenic mass with irregular edges attached to a liquid, which presents central necrosis or cystic degeneration, due to the blood demand for tumor growth (30). If accompanied by microcalcifications, it may indicate breast cancer, unlike macrocalcifications, which are physiological (36, 37, 38). Combined with mammography, it generates an increase of 15.5% in the MRI screening rate for ipsilateral cancer and 3.9% for contralateral cancer. This happens by providing cranio-caudal and medio-lateral oblique views in the extensive evaluation of the tumor, multifocality and bilateral disease (2).

Biopsy evaluation is always indicated regardless of the results of imaging tests, due to the possibility of physiological changes masking the neoplasia (30). The pathologist must be informed about the pregnancy in order to avoid false positives (7, 17). Histopathological examination of the breasts reveals the association with the genetic expression of HER-2 and Ki-67 (7, 8). The risk of recurrence is elevated for up to 2 years in hormone receptor-negative patients. While, for patients who are positive, the annual risk remains constant. Late relapses tend to have a more favorable prognosis compared to recent ones (32).

CONCLUSION

Pregnancy-Associated Breast Cancer is a high-risk condition, whose pathophysiological mechanisms are not yet fully understood by science. The incidence of this disease tends to rise increasingly as a result of the increase in pregnancies approaching the age of 40.

Triple Negative and HER-2 positive CMAG are the most prevalent, both tend to appear in advanced stages.

Women between 35 and 50 years old who are experiencing their first pregnancy are part of the profile of patients with this condition. Risk factors include components of the patient's past history, such as a previous diagnosis of invasive cancer after the age of 35 or exposure to thoracic radiotherapy for 10 to 30 years. In addition, classic risk elements such as family history, smoking, obesity and alcohol consumption are also included. While protective factors include breastfeeding and reproductive behavior.

Symptoms in the breast include thickening of the skin, secretion of purulent fluids or blood, inflammatory and lymphatic changes. Essential prenatal exams include ultrasound and mammography, preferably performed together to increase sensitivity and overcome the limitations of these exams. On biopsy, the majority of CMAGs are Infiltrative Ductal Carcinomas, often positive nodes of advanced stage II or III. In order to avoid diagnostic errors, it is essential to inform the pathologist about the patient's pregnancy condition due to the physiological changes that hide the pathological ones. Finally, there is a need to expand the field of research on Pregnancy-Associated Breast Cancer, given the magnitude of exponential growth presented by this pathology in recent decades.

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