

Research Article

Pregnancy Associated Breast Cancer: Clinicopathological profile and Management in the Department of Gynecology - Obstetrics II of the HASSAN II Teaching Hospital of Fez (Morocco)

Solène Nyingone¹, Alpha Boubacar Conte^{1*}, Fatima Zohra Fdili Alaoui¹, Sofia Jayi¹, Jihad Jamor¹, Bineta Jho Diagne², Hikmat Chaara¹, Moulay Abdelilah Melhouf¹

¹Department of Gynecology-Obstetrics II, Hassan II Teaching Hospital, Sidi Mohamed Ben Abdellah University, Fez, Morocco

²Laboratory of Epidemiology and Community Health, Sidi Mohamed Ben Abdellah University, Fez, Morocco

***Corresponding author:** Alpha Boubacar Conte, Department of Gynecology-Obstetrics II, Hassan II Teaching Hospital, Sidi Mohamed Ben Abdellah University, Fez, Morocco; E-mail: abcconte33@yahoo.com

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Abstract

Background: Breast cancer represents in our department the most frequent cancer among gyneco mammary cancers. Its association with pregnancy rarely observed is reported to be the most common form of cancer diagnosed during pregnancy. Pregnancy-associated breast cancer (PABC) refers to breast cancer (BC) diagnosed during pregnancy, lactation, or in the postpartum period. We made this study in order to describe the clinicopathological profil of PABC and the management in our context.

Methodology: This is a retrospective study on 14 patients with Pregnancy-associated breast cancer managed in the service of Gynecology - Obstetrics II of the Hassan II teaching hospital in Fez (Morocco). We defined Pregnancy-associated breast cancer as any breast cancer discovered during an active pregnancy or during the 12 months following the pregnancy.

Results: The average age was 34,64years old. The most represented age group was that of 30 to 39 years old. 11 patients (78,6%) were pregnant and 3 (21,4%) were in postpartum period. Most of the patients (8/14: 57,1%) presented for breast nodule discovered by self-palpation Clinically, most of the tumors was at the stage of T3N1MX and T2N1MX. The breast ultrasound was in favor of lesions classified ACR5 in 57,1% of cases versus ACR4 in 42,9% of cases. Non-specific type invasive carcinoma was the most frequent histologic type (11/14 either 78,6% of cases). The majority of patients (78,6%) had an intermediate invasive grade of SBR (grade II). The frequent immunohistochemical type of the invasive carcinomas was Luminal B (57,1%). Chemotherapy was performed in 100% of cases. Among those in pregnancy 6 was neo-adjuvant (42,9%) and 8 was adjuvant (57,1%) at the median term of 24 weeks of gestation with extremes of 14 and 38 weeks of gestation. No patient was treated with herceptin during pregnancy. Adjuvant hormone therapy has been introduced in 6 patients' treatment (42,9%). Radiotherapy was performed in all cases and no patient received radiotherapy during pregnancy. We recorded a death rate of 21,5%.

Conclusion: The diagnosis PABC during pregnancy requires a good sense approach to management with careful consideration given at all stages to the needs of the mother and risks to the fetus. Pregnancy might prevent the approach of optimal treatment as the cancer might prevent the good evolution of the pregnancy.

Keywords: Breast cancer; Pregnancy; Postpartum

Introduction: Breast cancer represents in our department the most frequent cancer among gyneco mammary cancers. Its association with pregnancy rarely observed is reported to be the most common form of cancer diagnosed during pregnancy and occurs in 1 to 4 cases per 10,000 pregnancies [1-3] and it is expected to become even more common, since these days women often delay childbearing to their 30s and 40s when breast cancer rates tend to increase [4].

Pregnancy-associated breast cancer (PABC) refers to breast cancer (BC) diagnosed during pregnancy, lactation, or in the postpartum period [5]. The postpartum period is variably defined in the literature, ranging from 1 to 5 years after a pregnancy [6]. Breast cancer associated with pregnancy presents the clinician with particular challenges. The diagnosis may be delayed and difficult owing to the physiological changes within the breast and limitations on investigations. Moreover, once a diagnosis has been confirmed and staging completed, options for treatment will be influenced by the need to give optimal treatment to the mother whilst minimizing risks to the fetus [7]. We made this study in order to describe the clinicopathological profile of PABC and the management in our context.

Methodology: This is a descriptive retrospective study on 14 patients with Pregnancy-associated breast cancer managed in the service of Gynecology - Obstetrics II of the Hassan II teaching hospital in Fez between January 2017

to December 2019 and followed up later in the oncology department of the said hospital. It concerns a series of 14 cases presenting the association of breast cancer with pregnancy.

And we defined Pregnancy-associated breast cancer as any breast cancer discovered during an active pregnancy or during the 12 months following the pregnancy.

The selection criteria for these cases were the discovery of breast cancer during an active pregnancy or during the 12 months following it.

The exclusion criteria were the discovery of breast cancer after an abortion or after an aborted pregnancy.

For each patient included, the following parameters were studied: Demographic information recorded included age at diagnosis, strong family history of breast cancer (defined as having a first-degree relative with a breast cancer diagnosis). Pathologic details collected included the method of presentation, the onset during pregnancy or postpartum, the gestational age during pregnancy, the number of month during the postpartum, clinical stage, imagery classification, presence or not of secondary spread at the imagery, surgery type, grade and histology of the tumor, presence of lymphovascular invasion (LVI), phenotype group, treatment, the outcome of the pregnancy, the term of delivery and the type of delivery, the final evolution of the patients whether favorable (complete remission) or unfavorable (occurrence of metastasis or death during the treatment). The tumors phenotype group were classified into 4 groups according to the recommendations St. Gallen Internationals of 2013 [8]: luminal A: ER + and PgR + and HER2 negative and Ki67 weak; luminal B: either ER + and HER2 negative and Ki67 high or PgR negative /weakly positive, RE +, HER2 positive; HER2: ER and PgR negatives and HER2 positive; Triple negative: ER-, PgR-, HER2- The data were entered and analyzed using SPSS.20 software. The results were expressed in number, average, extremes and percentage.

Results

During the period covered by our study, 14 patients were diagnosed with pregnancy-associated breast cancer (PABC). The average age was 34,64 years old with the extremes of 28–43 years old. The most represented age group was that of 30 to 39 years old. Primiparous were most affected followed by pauciparous and multiparous with a respective rates of 50%, 28,6% and 21,4%. No specific risk factor was recorded from any patient story. Most of the patients (8/14: 57,1%) presented for breast nodule discovered by self-palpation with skin modification, 02 of them (14,3%) had a bloody nipple discharge plus a palpable nodule and 4 of them (28,6%) had a nodule associated with breast pain. Among the 14 patients of our study, 11 (78,6%) were pregnant and 3 (21,4%) were in postpartum period. Among those in pregnancy 5 (35,7%) were in the third trimester, 4 (28,6%) in the second trimester and 2 (14,3%) in the first trimester. In the postpartum period, the cancer was diagnosed at the 6th month for 2 patient and at the 9th month for 1 patient. Clinically, most of the tumors was at the stage of T3N1MX and T2N1MX (**table1**). The breast ultrasound was in favor of lesions classified ACR5 in 57,1% of cases versus ACR4 in 42,9 % of cases. Non-

specific type invasive carcinoma was the most frequent histologic type (11/14 either 78,6% of cases). The other types were 01 invasive micropapillary carcinoma, 01 moderately differentiated invasive carcinoma and 01 squamous cell metaplastic carcinoma, representing each of them 7,1% of cases. 57,1% of our patients had Lymphovascular invasion (LVI) at the time of diagnosis and none of them had metastasis at the same time. The majority of patients (78,6%) had an intermediate invasive grade of SBR (grade II) against 21,4% with the high invasive grade of SBR (grade III). The immunohistochemical distribution of the invasive carcinomas was as follow: Luminal B (57,1%), triple negative (21,4%), luminal A (14,3%) and HER2 (7,1%). The treatment was made of neoadjuvant chemotherapy or adjuvant chemotherapy associating surgery, and / or hormonotherapy and finally completed by radiotherapy.

Chemotherapy was performed in 14 patients (100%), 11 during pregnancy and 3 during the post-partum period. Among those in pregnancy 6 was neo-adjuvant (42,9%) and 8 was adjuvant (57,1%) at the median term of 24 weeks of gestation with extrems of 14 and 38 weeks of gestation. No patient was treated with herceptin during pregnancy. After childbirth, the only one patient HER positive received treatment based on herceptin. Adjuvant hormone therapy has been introduced in 6 patients treatment (42,9%), all of them from the pregnancy group after delivery. Radiotherapy treatment was performed in all cases). No patient received radiotherapy during pregnancy.

The management of the pregnancy was based on strict monitoring by ultrasound and the outcome was as follow: 1 medical interruption of pregnancy (9,1%), 1 miscarriage (9,1%), and 9 delivery (81,8%). Among the 9 delivery also, 5 was by caesarian section (55,6%) and 4 by natural delivery (44,4%). The caesarian section was programmed in all the cases to ensure the rest of the treatment mainly for radiotherapy sake. 03 of the patients who underwent caesarian section were in preterm at 35 weeks of pregnancy and received corticotherapy for pulmonary maturation of the fetus.

During the monitoring, we lost contact with 3 patients (21,5%). 08 patients (57%) had a favorable evolution and 03 other patients (21,5%) developed metastasis and passed away.

Table 1: Clinical stadification of tumors

Clinical stadification	Effective (N = 14)	Percentage
T2N0MX	2	14,3
T2N1MX	3	21,4
T3N0MX	1	7,1
T3N1MX	3	21,4
T4BN1MX	1	7,1
T4dN0MX	2	14,3
T4dN1MX	2	14,3

Discussion

Although breast cancer was known in ancient times, it was uncommon until the 19th century, when improvements in sanitation and control of deadly infectious diseases resulted in substantial increases in lifespan [9]. In our department PBAC is becoming a common situation with the increase number of breast cancer in our society.

The frequency in studies depends on the operational definition given by authors knowing that The postpartum period is variably defined in the literature, ranging from 1 to 5 years after a pregnancy [6]. The definition we retained in our study may relatively minimize the number of cases reported in our study. Using the same definition of PABC to us, Abraham Hernandez and al. [10] collected 35 cases of PABC out of 12000 cases of breast cancer from October 1990 to October 2010. Which was representing 0.29%. In another study made by César Sánchez and al [11] in a cohort of 1631 patients with breast cancer, the prevalence estimated of PABC was 1%.

The median age of diagnosis for our patients was 34,64 years. Which is almost similar to the result reported by some authors.

Because the main risk factor for the development of breast cancer is exposure to estrogen, it has been theorized that pregnancy can stimulate and aggravate the evolution of breast cancer [12] Risk factors for PABC are similar to those for age-adjusted breast cancer. Women with BRCA1 or BRCA2 mutations are at an increased risk for breast cancer at a young age, and this risk is speculated to rise even higher due to hormonal changes during pregnancy [13].

It is established that nulliparous women have a higher risk of developing breast cancer than multiparous women [14]. We noticed in our study that PABC occurred to primiparous more than multiparous. Breast cancer in pregnancy most often presents as a painless mass or thickening in the breast occasionally associated with discharge from the nipple [15].

In our study, most of the patients consulted for breast nodule discovered by self-palpation with skin modification followed by patients with a palpable nodule associated with breast pain. Physiological breast changes associated with pregnancy, including engorgement, hypertrophy, and nipple discharge obscure detection for patient and physician. Therefore, delay in diagnosis is common, leading to more advanced stages at diagnosis than in the general population. As a consequence, breast cancer in pregnancy is associated with more metastases, and subsequently poorer outcomes, than breast cancer in non-pregnant women [16].

Diagnostic examinations of the breast during pregnancy need to be done by a skilled clinician, because gestational changes alter the tissue structure. Breast ultrasonography is the first diagnostic instrument used by clinicians when a breast mass and the axillary area need to be assessed in a pregnant woman, since it is non-ionising and has high sensitivity and specificity [17]. Subsequently, when breast cancer in pregnancy is diagnosed, bilateral and multicentric disease can be ruled out with mammography [18,19].

MRI with contrast agents is possible during pregnancy, but should only be used when it will alter clinical decision making, and when ultrasonography is inadequate [20].

As reported in studies, we noticed that invasive ductal carcinoma was the histological type the most frequent in our study [11,21].

Previous studies have shown that patients with pregnancy-associated breast cancer commonly present with pathological lymph node involvement (56–67%) [10,11,22] This same notice is made in our study where more than 50% of patients had lymph node involvement. As observed in our study, J de Garnier and al reported that the immunohistochemical distribution of PABC in their population of study was dominated by luminal B following by luminal A, triple negative and finally by HER2 [21].

The treatment of our patients was made of neoadjuvant chemotherapy or adjuvant chemotherapy associating surgery, and / or hormonotherapy and finally completed by radiotherapy after delivery.

A lot is said about the treatment of PABC. The goals of breast cancer treatment are the same for pregnant and non-pregnant women: to control the cancer locally and prevent systemic spread. Systemic treatment includes adjuvant or neoadjuvant chemotherapy regardless of patient's [23].

Therapeutic strategies are determined by tumour biology, tumour stage, gestational age, and the patient's and her family's wishes. Counselling is crucial because of the complexity of the issue. A multidisciplinary team with all involved specialties should assess the medical (obstetric, oncological, paediatric, and genetic), ethical, psychological, and religious issues. The proposed treatment should adhere to the standard for non-pregnant patients [24]. Once a diagnosis of breast cancer has been made, it is important not to delay treatment. If the patient is near term, it is reasonable to proceed with delivery prior to treatment. However, if the patient is remote from term, treatment must be initiated [25]. There has been no evidence to show that termination of pregnancy in the first or second trimester affects prognosis [26].

For patients with large tumors, neoadjuvant chemotherapy is chosen to identify a pathologic complete response, identify who will do well postoperatively, or to downstage a tumor and allow breast conservation, if desired. For patients diagnosed prior to 12 weeks when chemotherapy would not be an option, surgery should be performed, followed by adjuvant chemotherapy after 12 weeks of gestation. The treatment course may need to be altered due to pregnancy, ie, a patient diagnosed during the first trimester of pregnancy should undergo surgery only with chemotherapy delayed until the second trimester, even if the preference would have been to use neoadjuvant chemotherapy were she not pregnant [23].

Radiation for breast cancer is delayed until after delivery. Fetal radiation exposure would be unacceptably high at the standard dose of radiation for breast cancer. Fetal exposure can range from 3.9–15 rad during the first trimester, when the uterine fundus is farthest from the breast, to up to 200 rad toward the end of pregnancy. Considering the radiotherapy, there is a great concern about possible harms to the fetus and for this reason, radiotherapy is not routinely recommended during pregnancy and should be postponed until after childbirth whenever possible [27].

Considering also the high frequency of hormonal expression (positivity of estrogen receptor and progesterone receptor) in pregnancy-associated breast cancer, inquiries about the utilization of endocrine therapy in this scenario are pertinent. The physiological changes necessary for a healthy pregnancy and fetal development are mainly hormone mediated. Consequently, the utilization of drugs that block estrogen and progesterone production or action might interfere with those physiological processes. Of note, tamoxifen, the most utilized drug in the pre-menopausal context, is teratogenic in animals and has been associated with birth defects in children of women who inadvertently have utilized the medication during pregnancy. Hence, endocrine treatment is contraindicated [28, 29].

In general, PABC patients should be considered as high-risk obstetric patients, with routine fetal and maternal health checkup at least once every three weeks [30]. Fetal development should be assessed prior to the initiation of treatment. As discussed above, a time-interval of three weeks is recommended between last chemotherapy administration and delivery and preterm delivery should be avoided. Vaginal delivery is preferred since post-partum anti-neoplastic treatment can be resumed immediately after delivery, while at least a one-week interval is recommended after caesarean section.

After delivery, the placenta should be pathologically inspected as previous reports found placental metastases [31,32]. Breastfeeding during and a few weeks following chemotherapy administration is not recommended, and milk production should be inhibited to avoid accumulation of lipophilic anti-neoplastic agents in the milk [24].

Our study, far from being perfect, is limited by its retrospective nature which did not allow us to include certain variables allowing us to better describe the histological characteristics and better assess our different therapeutic attitudes but also the survival of different patients; it also remains limited by the small size of our sample.

Conclusion

The diagnosis PABC during pregnancy requires a good sense approach to management with careful consideration given at all stages to the needs of the mother and risks to the fetus. At all stages the management of the patient should be decided by a multidisciplinary team, incorporating not only breast surgeon, medical and clinical oncologists, but also obstetricians, neonatologists and specialist nursing staff in order to ensure the best possible outcome for both mother and infant. Pregnancy might prevent the approach of optimal treatment as the cancer might prevent the good evolution of the pregnancy. Due to the high rate of death in our study despite the small size of the

sample, further study is needed to determine the prognosis and the factor leading to the success or the failure of the management in our context of developing country.

Conflicts of interest: There are no any conflicts of interest between the authors of this present manuscript.

Contributions from the authors: All the authors participated to the present study.

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