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# Breast Cancer and Pregnancy: Epidemiology and Prognosis

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## ABSTRACT

***Objectives:*** *To describe the epidemiological, therapeutic and prognostic aspects of pregnancy-associated breast cancer.*

***Patients and Method:*** *This was a one-year prospective study from 1 January to 31 December 2020 at the Joliot Curie Institute of the Aristide le Dantec Hospital, including all patients with histologically confirmed breast cancer during pregnancy or at 1 year postpartum during the study period.*

***Results:*** *Of 850 cases of breast cancer, 13 (1.5%) were associated with pregnancy, with an average age of 32 years. All our patients were diagnosed at an advanced stage, 46.2% at stage IIIB and 38% at stage IV. Invasive ductal carcinoma accounted for 92% of cases, with 84% SBRIII. They underwent primary chemotherapy with anthracyclines and taxanes and mastectomy. All pregnancies resulted in full-term delivery with an average birth weight of 3000 g, except for one case of late abortion and intrauterine growth retardation. Maternal prognosis was poor, with a 38% mortality rate.*

***Conclusion:*** *Breast cancer is the most common cancer in pregnant women. This study showed that it is diagnosed at an advanced stage, resulting in a poor prognosis with a 38% mortality rate at one year follow-up.*

**Keywords**
Breast cancer, Pregnancy, Advanced stage, Treatment, Prognosis.

## Introduction

Breast cancer is a major public health problem. It is the most common cancer in women worldwide, with 2.3 million cases in 2020, and 88% of related deaths occur in sub-Saharan Africa [1]. It is the cancer most frequently encountered during pregnancy, with an incidence of 1 in 3,000 pregnancies, and accounts for 0.4% of breast cancers diagnosed in women aged between 16 and 49 [2,3].

Pregnancy-associated breast cancer (PABC) is defined as the occurrence of breast cancer during pregnancy or in the year following childbirth. Although rare, over the last decade there has been an increase in its incidence, probably linked to the later age of first pregnancy [4]. It is estimated that 7-14% of breast cancers that occur before the age of 45 coincide with pregnancy or breastfeeding. The association of bilateral breast cancer and pregnancy remains exceptional [5]. The concomitant occurrence of these two clinical entities poses various diagnostic, therapeutic and prognostic problems [6]. Diagnosis is often delayed due to physiological changes in the mammary gland, but also because mammography is less sensitive. Pregnancy is therefore considered an independent risk factor for breast cancer, with a 1.8-fold increase in the risk 5 years after the last birth [7].

Its management is multidisciplinary and represents a major challenge for doctors, who have to take account of a dual issue, i.e. the need to optimise both the maternal and foetal prognoses [4]. Based on ESMO (European Society of Medical Oncology) recommendations, treatment follows that of non-pregnant women, taking into account gestational age at diagnosis and term. The first choices are anthracycline-based compounds [3,4,8].

The prognosis is poorer than in women who are not pregnant, which may be mainly due to late diagnosis and limited treatment options [6]. Moreover, emotionally, this situation is dramatic, because the cancerous disease, which has a gloomy reputation, occurs in a woman who is expecting a happy event [4,9]. Our aim is to study the diagnostic and therapeutic features of this association, as well as the outcome of the pregnancy and the mother's future.

## Patients and Methods

### Eligibility criteria

This is a prospective descriptive study covering a one-year period from 1 January to 31 December 2020 at the Joliot Curie Institute of the Aristide le Dantec Hospital. Patients meeting the following criteria were included in the study: (1) histological confirmation, (2) pregnant or within 1 year of partum, (3) consulting during the year 2020. All patients with suspected breast cancer with or without pregnancy without histological evidence were excluded.

### Study Design

During our study period, 850 cases of breast cancer were reported. Of these, 13 were associated with pregnancy, with a prevalence of 1.5% (Figure 1). The initial clinical assessment consisted of a case history, a systematic medical examination, routine blood tests and a brain computed tomography (CT) scan supplemented by a chest X-ray and abdominopelvic ultrasound for extension. TNM stage was defined according to UICC 2017.

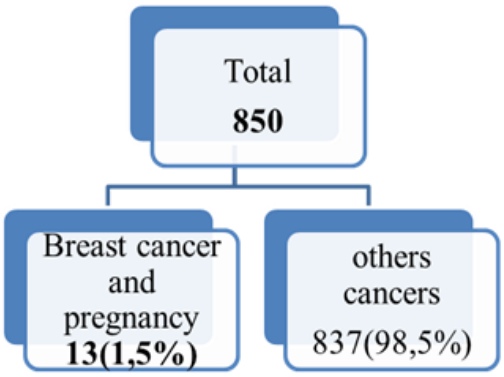


**Figure 1:** Statistics on cancers associated with pregnancy.

### Statistical Analysis

All data were entered and processed using SPSS 24.0 software. Qualitative variables were represented as proportion (%) and quantitative variables as frequency or mean (± standard deviation). Overall survival was calculated using the Kaplan-Meier method.

## Results

### General Characteristics of Patients

During the study period, 13 cases meeting the definition of pregnancy-associated breast cancer were collected out of a total of 850 breast cancer cases, representing a proportion of 1.5% (Figure 1). The mean age was 32 ±7 years, with extremes of 20 and 44 years. The 30-40 age group was the most represented, with 7 cases (53.8%) (Figure 2). The mean gestational age was 4.15 and the mean parity was 3.38. All had nodules ranging in size from 4 to 20 cm with an average of 12.14 cm (Table 1).

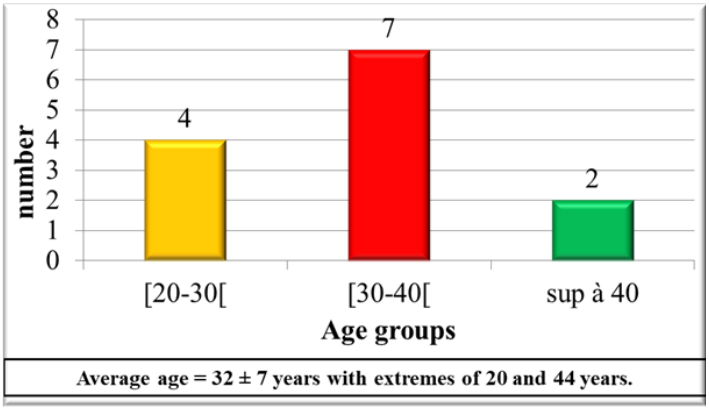


**Figure 2:** Breakdown of patients by age group.

**Table 1:** Distribution of patients by nodule size, gestational age and parity.

| Parameters | Nodule size (cm) | Age (year) | Gestité | Parity |
|---|---|---|---|---|
| Average | 12,15 | 32 | 4,15 | 3,38 |
| Median | 9,00 | 32 | 5,00 | 4,00 |
| Std. Deviation | 7,392 | 7 | 1,772 | 2,022 |
| Minimum | 3 | 20 | 1 | 0 |
| Maximum | 20 | 44 | 6 | 6 |

### Clinical Presentation

Eight of our patients (61.5%) were diagnosed during pregnancy and 5 (38.5%) post partum. The median gestational age at diagnosis was 21 SA (Table 2). All our patients were diagnosed at a very advanced TNM stage 2 (15.4%) at stage IIIA, 6 (46.2%) at stage IIIB, and 5 (38.4%) already had metastatic lesions at the time of diagnosis and lymph node involvement was noted in 100% of cases (Table 3). The histological type was mainly infiltrating ductal carcinoma NOS in 11 cases with histopronostic grade II and III in 5 and 6 cases respectively. Only one case (7%) of SBR II infiltrating lobular carcinoma was recorded (Table 4). Only one patient underwent immunohistochemistry (IHC) which was triple negative.

**Table 2:** Patient's condition at time of diagnosis.

| Parameters | N | % |
|---|---|---|
| During pregnancy | 8 | 61,5 |
| post partum | 5 | 38,5 |
| TOTAL | 13 | 100 |

**Table 3:** Distribution of patients according to TNM stage.

| STADIUM | N | % |
|---|---|---|
| IIIA | 2 | 15,4 |
| IIIB | 6 | 46,2 |
| IV | 5 | 38,4 |
| TOTAL | 13 | 100 |

**Table 3b:** Histological type and Scarff-Bloom and Richardson histopronostic grade.

| HISTOLOGICAL TYPES | N | % |
|---|---|---|
| CINOS SBR III | 6 | 46,2 |
| CINOS SBRII | 5 | 38,4 |
| CLI SBR II | 1 | 7,7 |
| FIBROCYSTIC MASTOPATHY | 1 | 7,7 |
| **Total** | **13** | **100** |

**Table 4:** Breakdown of patients by treatment received.

| TREATMENT | N | % |
|---|---|---|
| Chemotherapy | 12 | 92 |
| Mastectomy and Axillary Excision | 6 | 46 |
| Radiotherapy | 2 | 15,2 |
| Total | 13 | 100 |

### Treatment

All patients received neoadjuvant chemotherapy based on anthracyclines and/or taxanes either during pregnancy in the 2nd or 3rd trimester or in the post partum period, except for one patient who died the day before her session. Six of our patients (46%) had a CAM after chemotherapy and 15% were still undergoing chemotherapy at the end of the study. None of our patients received hormone therapy or targeted therapy.

### Patient follow-up

### Outcome of the Pregnancy and the Mother's Future

Regarding pregnancy outcome, all pregnancies resulted in delivery. Most of our patients gave birth by the basic route, i.e. 69%, with only one case of late abortion, i.e. 7%, which occurred after 3 courses of AC for a gestational term of 26 days' gestation. We obtained an average gestational age of 38.5 days with a maximum of 40 days. Apart from one case of growth retardation at 2100 g, all our patients have had a birth weight of over 3000 g. To date, all the children are doing well.

### The mother's future

The results were worrying: 5 of the 13 patients died, representing a mortality rate of 39%. Of these 5 deaths, 3 patients (60%) were diagnosed in the post-partum period and 2 (40%) during pregnancy. Despite a survival rate of 61%, 39% of patients did not survive**.**

## Discussion

### Epidemiological aspect

Breast cancers diagnosed during pregnancy or within a year of giving birth are considered to be pregnancy-associated breast cancers. It is the most common cancer encountered during pregnancy [1]. It represents 0.2% to 3.8% of all breast cancers compared with 1.5% found in our study [10,11]. This proportion remains low but is tending to increase due to the decline in the age at first pregnancy and the increase in the overall incidence of the number of pregnancies in the third and fourth decades [3,12]. Pregnancy-associated breast cancer occurs in relatively young patients, with an average age of around thirty [5,12,13]. This average age is similar to our own, which is 32 ± 7 years, with the majority between 30 and 40 (53.8%). The patient's age is the most important factor. According to the literature, ten per cent of women under 40 with breast cancer are pregnant at the time of diagnosis. The higher the age at the time of the first pregnancy, the greater the risk [11,14].

### Clinical Characteristics

The cornerstone of the diagnostic process is the triple test, which includes palpation, imaging and biopsy [15].

### Clinical Size of the Tumour

All our patients presented with T4 and T3 tumours with a mean of 12.1 cm and extremes of 3 cm and 20 cm. Our mean size obtained is greater than that obtained by Hadjji et al. [12]and Boudy et al. [13] This difference could be explained by the fact that their centre carries out a systematic clinical breast examination during the first pregnancy follow-up consultation, in accordance with the recommendations of the French National College of Gynaecologists and Obstetricians (CNGOF) and the French National Authority for Health (HAS). It is also due to the fact that this cancer appears in young women who are not routinely screened for small lesions [15].

### TNM stage

All our patients were diagnosed at a very advanced TNM stage (stage IIIA, IIIB and IV), which corroborates the data in the literature according to which pregnant women are 2.5 times more likely than non-pregnant women to have advanced breast cancer at the time of diagnosis [6,12,13,15]. This can be explained by the fact that clinical diagnosis of breast cancer is difficult during pregnancy or breastfeeding due to anatomical changes in the breast (increase in size, hypervascularisation, engorgement), which make it difficult to diagnose, and that the diagnosis of cancer is rarely considered by either the practitioner or the patient [15]. Characteristically, it has been estimated that a one-month delay in diagnosis results in a 0.9% increase in the chances of lymph node metastasis [16]. This explains the finding that 5 (38.4%) were already metastatic at the time of diagnosis and 100% lymph node involvement. Cordoba et al. [6] also found that 5 (20%) of their patients were already metastatic at the time of diagnosis. With regard to lymph node involvement, results similar to ours were obtained by Reyes et al. [17] and Cordoba et al. [6]. Axillary involvement appears to be more frequent in pregnancy-associated breast cancer than in non-pregnancy-associated breast cancer. It has been calculated that the risk of lymph node metastases increases by 0.028% per day of delay in diagnosis [13,16].

In our series, the mean age at diagnosis was 20 weeks' amenorrhoea (20 SA), with extremes of 07 and 38 SA. Five patients were diagnosed in the post partum period, i.e. 38%, and the vast majority (62%) had an active pregnancy. No medical termination of pregnancy was performed. This result is similar to that of Hajji et al. and Cordoba et al. [6,12] who obtained a mean gestational age at diagnosis of 21 weeks' amenorrhoea.

### Histological Type and Scarff-Bloom and Richardson Histopronostic Grade

Pathological examination remains the gold standard for diagnosis. As in the case of non-pregnant patients, biopsy and pathological examination must be carried out in good time for BIRADS IV/V lesions with a strong clinical suspicion and an imaging examination, in order to guide the treatment plan [9]. The different histological types of breast cancer occur with the same frequency in pregnant women as in non-pregnant women [18]. In our series, 12/13 cases (93%) were invasive ductal carcinomas and only one case (7%) was invasive lobular carcinoma. This result confirms the data in the literature where invasive ductal carcinomas are the most common (70-90%), followed by invasive lobular carcinomas (10-20%) [10,12,16,19].

The Scarff Bloom and Richardson (SBR) histopronostic grading was high. Our tumours were aggressive with 84% being grade III and 26% grade II. We did not encounter any grade I tumours. These are aggressive tumours Garnier et al. [4] in his series found only 10% grade I and 62% grade III.

### Hormone Receptors

In our study, only one patient underwent HC immuno-histochemistry, which was triple negative. Hormone receptors are more frequently negative during pregnancy. For others, this is a characteristic of cancers in young women, with 50 to 70% of hormone receptors being negative [9].

### Genetic Risk

Cancers linked to a deleterious BRCA1 or BRCA2 mutation occur at an earlier age than sporadic cancers. In this case, the risk of developing CSAG is greater than in the general population with a family history of cancer [4,15,19]. None of our patients had undergone BRCA mutation testing, but 2 of them (16%) had a family history of first-degree breast cancer.

### Treatment

The management of malignant diseases in pregnant women is a challenge for obstetricians, oncologists and neonatologists alike. Based on the recommendations of the ESMO (European Society of Medical Oncology) [20] treatment follows that of non-pregnant women, combining chemotherapy, surgery, radiotherapy and even hormone therapy depending on the histological type, age stage and gestational age at diagnosis [2].

### Chemotherapy

In our series, all our patients received initial chemotherapy (neoadjuvant) either during pregnancy in the 2e or 3e trimesters or in the post partum period, except for one patient who died the day before her session. According to recommendations in the literature, they all received antracyclines and/or taxanes 10. Chemotherapy was administered from 14 weeks' gestation. The average time between the last day of chemotherapy and delivery was at least 2 weeks.

IN THE 1er trimester, chemotherapy is embryotoxic, with risks of malformations of up to 10 to 20%; risks of abortion or even death in utero see [4,20]. The same attitude was adopted in the study by Garnier et al. [4] in which all patients received chemotherapy, 59.4% as neoadjuvant and 39.6% as adjuvant. The same applies to Hadjji et al. [12].

### Hormone Therapy

None of our patients received hormone therapy. Tamoxifen is contraindicated during pregnancy, and up to 20% of malformations have been described, including craniofacial anomalies, sexual ambiguity and Goldenhar syndrome in newborns exposed to tamoxifen during gestation [21-23].

### Surgery

In our study, surgery was performed as soon as feasible. 6 of our patients (46%) had MCA after neoadjuvant chemotherapy and 15% were still receiving chemotherapy at the end of the study. Surgery is always possible, even during pregnancy, but it is often more haemorrhagic than in the gynaecological period. The indications remain the same as outside pregnancy, with a reservation for the first trimester. Furthermore, surgery does not increase the risk of foetal malformation [21,24].

### The Radiotherapy

None of our patients underwent radiotherapy during pregnancy, and we carried out 2 parietal and lymph node chain irradiations in the post-partum period after an MCA and a total encephalon irradiation for secondary cerebral localisations. Gestational term is fundamental in determining the toxicity of radiotherapy. Depending on the term, there are significant risks of malformations, neurocarcinological risks of mental retardation, etc. [4]. For all these reasons, radiotherapy should be deferred until after delivery [2,6,10].

## III-Pronosis: OUTCOME OF PREGNANCY AND FUTURE OF THE MOTHER

### Result of Pregnancy

No termination of pregnancy was performed in our series. Termination of pregnancy has long been considered to improve prognosis [24]. However, recent studies have shown the opposite to be true [15,20]. It may only be proposed in the first trimester if pregnancy compromises the initiation of treatment. Its indication has decreased in recent years [21]. The spontaneous abortion rate is low, estimated at 7%, which is identical to that of the general population [26]. It is advisable to continue the pregnancy as close to term as possible [27].

In our series, we had an abortion rate similar to that found in the literature, i.e. 7% (1/13), which resulted in the expulsion of a macerated stillbirth after 3 courses of AC for a gestational term of 26 days' gestation. Similarly, the mean term obtained was a median of 38.5 SA with a maximum of 40 SA, a result similar to that of Boudy et al. [13] (37 SA). Apart from one case of growth retardation at 2100 g, all our patients had a birth weight of over 3000 g. To date, all the children are doing well. Similar results have been reported by several African authors [13,26].

### The mother's future

The overall prognosis of our patients remains poor after one year's follow-up, with 5 of the 13 patients dying, representing a mortality rate of 38%. Of these 5 deaths, 3 patients (60%) were diagnosed in the post-partum period and 2 (40%) during pregnancy. This high mortality rate is mainly due to the late diagnosis and advanced stage of the cancer. The prognosis for women treated for breast cancer during pregnancy is the same as outside pregnancy. It is the age and stage of the disease, together with its biological characteristics, that determine the prognosis. Murphy et al. [28] confirms that these prognostic data are identical to ours, but there are more metastatic forms. Azim et al. [29] conclude that the diagnosis is worse for patients who develop breast cancer during the post-partum period and not during pregnancy. No significant difference in survival was found between pregnant women with breast cancer and non-pregnant women with breast cancer, after adjustment for age and stage of disease. However, we know that due to pregnancy-related changes in the breast, breast cancer is often diagnosed at a more advanced stage in pregnant women than in non-pregnant women. Thus, breast cancer during pregnancy is associated with larger tumours and a higher incidence of lymph node involvement than breast cancer in non-pregnant women [4,30]. Termination of pregnancy would not improve prognosis, as pregnancy has no influence on the course of the disease [28,31].

## Conclusion

Breast cancer is the most common cancer in pregnant women. Its diagnosis is often delayed and made at an advanced stage. Additional examinations such as ultrasound, mammography and biopsies are possible. Management is multidisciplinary, involving oncologists, obstetricians and paediatricians. Therapeutic decisions are adapted to the gestational age, the stage of the disease and sometimes to the patient's choice, and maternal and foetal monitoring will be carried out. It is important to understand that terminating the pregnancy does not improve the prognosis, because it is not the pregnancy that alters the prognosis of breast cancer but the type of tumour at that age.

In the interests of good care, it would be important to create a network of expert centres to optimise the care and monitoring of mother and child in the short, medium and long term.


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