

Treatment Outcomes of Carcinoma of the Breast in Pregnancy in Port Harcourt, Nigeria

Solomon N. Elenwo

Consultant General Surgeon, Breast Unit
Department of Surgery, University of Port Harcourt Teaching Hospital
and Senior Lecturer, University of Port Harcourt, Port Harcourt, Nigeria

Promise N. Wichendu

Department of Surgery, University of Port Harcourt Teaching Hospital
Port Harcourt, and Senior Lecturer
University of Port Harcourt, Port Harcourt, Nigeria

Rex Friday Ogoronte Alderton Ijah

Department of Surgery, Rivers State University Teaching Hospital
Port Harcourt, and Lecturer, PAMO University of Medical Sciences
Port Harcourt, Nigeria

ABSTRACT

Background: The belief that breast cancer during pregnancy is more aggressive than in non-pregnant women is still very common in our environment, even amongst medical personnel. Many clinicians still advise women with breast cancer during pregnancy to terminate the pregnancy on prognostic fears. Diagnosis of breast cancer during pregnancy is often delayed due to delayed presentation and some difficulties encountered with imaging during pregnancy. We present the outcomes of management as studied in this center. **Materials and Methods:** Information was collected from pregnant women who presented to the breast clinic over a 5-year period. The same treatment was given to all of them and the outcomes of treatment analyzed. **Results:** A total of 31 patients were seen during the period. The patients' age was between 28 years and 39 years, with a mean age of 32.5 years. Clinical staging showed that 20 patients (64.5%) were Manchester stage II, 9 (29%) stage III, 1 (3.2%) had stage I disease, while only one patient (3.2%) had stage IV disease. Majority of the patients in the study had acceptable outcomes for both the mothers and babies. **Conclusion:** Pregnancy does not increase the mortality of breast cancer, as some erroneously believe. Accurate timing of chemotherapy and radiotherapy results in no significant harm to the baby. Termination of a desired pregnancy should not be advised unless the woman so desires.

Keywords: Breast cancer, Pregnancy, Treatment, Outcome, Port Harcourt, Nigeria.

INTRODUCTION

Breast cancer in pregnancy is not very common, although with emerging information, it may not be considered rare,[1] occurring in one out of 3,000 pregnancies.[2] This is partly because early detection by the patient is hampered by the breast changes that occur during pregnancy. However, it still remains the most common cancer seen amongst pregnant women.[3-6] As

against earlier reports,[7-9] pregnancy does not increase the mortality from breast cancer.[10-12] Although some investigation and treatment modalities may need to be avoided during early pregnancy, this is done to avoid harm to the fetus and not to influence the treatment of the cancer. The decision to terminate a pregnancy because of breast cancer lies on the individual patient and should not be based on any medical advice. A researcher had posited, in a review of epidemiology of pregnancy-associated breast cancer, that age at first pregnancy, absence of breastfeeding and family history were foremost in evaluating a woman's risk for the disease.[13] Age standardized incidence of breast cancer in Africa is 37.9/100000, standardized rates in developed countries are three times higher than in developing countries.[14]

It has been stated that there are higher chances of finding breast cancer in coexistence with pregnancy among African women than their Caucasian counterparts since most African women with breast cancer are premenopausal.[15] In a study in Rwanda, out of the 117 patients with breast cancer recorded over a two-year period, 12 (10.3%) had pregnancy-associated breast cancer, with 6 surviving, 3 mortality, and 3 lost to follow-up.[16] Breast cancer in pregnancy has also been reported in Nigeria. A report from Nigerian Breast Cancer Study showed that family history of breast cancer and higher parity were associated with higher risk of pregnancy-associated breast cancer (and reduced risk of non-pregnancy-associated breast cancer), although the relationship was not statistically significant.[17] In a 12½ year study carried out in Zaria Northern Nigeria some 22 years ago, 14 women were reported to have breast cancer in pregnancy out the 95 younger women with breast cancer.[15] There are other reports of breast cancer in pregnancy in Northern Nigeria.[18, 19] Worthy of note is the occurrence of 31 cases of pregnancy-associated breast cancer out of a total of 1344 patients who had breast cancer in Zaria Nigeria, implying 2.3% of all breast cancer in that center.[19] There are also reports on breast cancer in pregnancy in Eastern Nigeria,[7] and the Western part of the country.

An earlier study carried out at the University of Port Harcourt Teaching Hospital over a thirteen-year period (1990 to 2002), had reported occurrence of 5 cases of breast cancer in pregnancy (intraductal carcinoma) with prognosis similar to non-pregnant women.[20] What has changed since the last 20 years of this report? This study therefore aims at determining the outcomes of treatments given to pregnant women with cancer of the breast in the University of Port Harcourt Teaching Hospital (UPTH) over a 5-year period.

MATERIALS AND METHODS

A prospective study was carried out involving of all pregnant women with breast cancer seen at the breast unit of the University of Port Harcourt Teaching Hospital (UPTH) between March 2009 and March 2014. Port Harcourt, a cosmopolitan city and capital of Rivers State, was therefore the study area. Rivers State is one of the State in the southern part of Nigeria, having two teaching Hospitals (a newly established state teaching hospital, and a long-existing Federal teaching hospital). This federal teaching hospital – the UPTH – has a functional Breast Unit (Study Setting) in the Surgery Department of the Hospital that serves as a referral center for Port Harcourt and its environs.

Total population of pregnant women with breast cancer was used. Information (primary data) was obtained from the patients during routine history taking, physical examination and

investigations, and this included their age, presenting complaints, clinical diagnosis/staging and histopathology. The diagnostic and staging modalities employed included clinical examination, breast and abdominal ultrasonography, mammography and plain chest x-ray (with abdominal shielding). Skeletal survey was not done for fear of radiation. All patients had their specimen sent for histology and the fact that the patients were pregnant was communicated to the pathologists. Magnetic resonance imaging and immunohistochemistry were not done because they were not operational or available in our center during the study period. (Except four patients who came with immunohistochemistry results from outside which were all triple negative). All the patients had core needle biopsies for histology. Sentinel node biopsy was not done because all our patients had palpable nodes at presentation.

Treatment modalities given and outcomes were also recorded. The treatments offered included surgery and chemotherapy at 30 weeks gestation or above using the regime consisting of Cyclophosphamide, Epirubicin and 5-Fluoro-uracil (CEF). Radiotherapy was deferred to the post-partum period. They all underwent modified radical mastectomy. None of them received any form of hormonal or targeted therapy. Outcome was assessed by the length of disease-free interval during follow-up.

RESULTS

Table 1: age and pattern of breast cancer presentation in pregnancy

S/N	AGE (YEARS)	PRESENTATION	STAGE AT DIAGNOSIS (Manchester)	HISTOPATHOLOGY REPORT
1	31	Huge LBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2, Triple Negative
2	29	Fungating LBM at 29 Weeks	Stage IIIB	Invasive Breast Cancer, SBR3, Triple Negative
3	31	LBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR1, Triple Negative
4	28	LBL at 32 Weeks	Stage II	Invasive Breast Cancer, SBR1, Triple Negative
5	30	LBL at 25 Weeks	Stage II	Invasive Breast Cancer, SBR1, Triple Negative
6	29	RBL at 26 Weeks	Stage III	Invasive Breast Cancer, SBR3
7	32	Fungating RBM at 27 Weeks	Stage IV	Invasive Breast Cancer, SBR3
8	30	RBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2
9	29	LBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2
10	30	LBL at 25 Weeks	Stage II	Invasive Breast Cancer, SBR2
11	35	LBL at 27 Weeks	Stage IIIB	Invasive Breast Cancer, SBR2
12	34	RBL at 26 Weeks	Stage I	Invasive Breast Cancer
13	32	LBL at 27 Weeks	Stage II	Invasive Breast Cancer
14	36	LBL at 26 Weeks	Stage III	Invasive Breast Cancer, SBR3
15	30	LBL at 30 Weeks	Stage II	Invasive Breast Cancer, SBR2
16	36	RBL at 28 Weeks	Stage III	Invasive Breast Cancer, SBR3
17	32	RBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2
18	30	LBL at 24 Weeks	Stage II	Invasive Breast Cancer, SBR2
19	38	RBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2

20	34	LBL at 30 Weeks	Stage II	Invasive Breast Cancer, SBR2
21	34	LBL at 27 Weeks	Stage III	Invasive Breast Cancer, SBR2
22	30	RBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2
23	31	LBL at 28 Weeks	Stage II	Invasive Breast Cancer, SBR2
24	37	LBL at 24 Weeks	Stage III	Invasive Breast Cancer, SBR2
25	39	RBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2
26	35	LBL at 28 Weeks	Stage II	Invasive Breast Cancer, SBR2
27	34	LBL at 24 Weeks	Stage III	Invasive Breast Cancer, SBR2
28	36	LBL at 26 Weeks	Stage II	Invasive Breast Cancer, SBR2
29	32	LBL at 26 Weeks	Stage III	Invasive Breast Cancer, SBR2
30	34	LBL at 28 Weeks	Stage III	Invasive Breast Cancer
31	28	RBL at 26 Weeks	Stage II	Invasive Breast Carcer
SUMMARY	Mean = 32.5	Mean = 26.6 Weeks	Stage I=1 Stage II=20 Stage III=9 Stage IV=1	

(RBL = Right Breast Lump; RBM = Right Breast Mass; LBL = Left Breast Lump; LBM = Left Breast Mass)

A total of 31 patients were seen during the period. The patients' age was between 28years and 39years with a mean age of 32.5years. Nine of them (29%) had right-sided disease while 22 (71%) had their tumors on the left. All presented with painless lumps on the breast and had invasive ductal carcinomas. The age of pregnancy ranged between 24weeks and 32weeks with a mean gestational age at presentation of 26.6weeks. Clinical staging showed that 20 patients (64.5%) were Manchester stage II, 9 (29%) stage III, 1 (3.2%) had stage I disease, while only one patient (3.2%) had stage IV disease.

Table 2: treatment given and outcome of breast cancer in pregnancy

Patient's S/N	Surgery	Chemotherapy	Radiotherapy	Outcome
1	Modified Radical Mastectomy	CEF at 30 Weeks	Defaulted	Unsatisfactory
2	"	"	Deferred to Post-partum	Satisfactory
3	"	"	"	"
4	"	"	"	"
5	"	"	"	"
6	"	Defaulted	Defaulted	Unsatisfactory
7	"	CEF at 30 Weeks	Defaulted	Unsatisfactory
8	"	"	Deferred to post-partum	Satisfactory
9	"	"	"	"
10	"	"	"	"
11	"	"	"	"
12	"	"	"	"
13	"	"	"	"
14	"	"	Defaulted	Unsatisfactory
15	"	"	Deferred to Post-partum	Satisfactory
16	"	"	"	Unsatisfactory
17	"	"	"	Satisfactory
18	"	"	"	"

19	"	"	Defaulted	Unsatisfactory
20	"	"	Deferred to Post-partum	Satisfactory
21	"	"	"	"
22	"	"	"	"
23	"	"	"	"
24	"	Defaulted	"	Unsatisfactory
25	"	"	"	Satisfactory
26	"	CEF at 30 Weeks	Deferred to Post-partum	"
27	"	"	"	"
28	"	"	"	"
29	"	Defaulted	Defaulted	Unsatisfactory
30	"	"	Defaulted	"
31	"	CEF at 30 Weeks	Deferred to Post-partum	Satisfactory

(CEF = Cyclophosphamide, Epirubicin, and 5-Fluorouracil)

Table 2 shows the treatment modalities offered to patients and a summary of the outcome. All the patients had modified radical mastectomy. Twenty-six patients had chemotherapy at 30 weeks of gestation with no congenital birth defects, while 5 defaulted from chemotherapy. Seven patients defaulted from radiotherapy.

Table 3: outcome of patients follow-up

S/N	FOLLOW-UP PERIOD	NUMBER (n=31)	RECURRENCE	MORTALITY
1	> 5 Years	8	Nil	Nil
2	4 - 5 Years	7	Nil	Nil
3	3 - 4 Years	4	1	Nil
4	2 - 3 Years	2	Nil	Nil
5	1 - 2 Years	-	-	-
6	< 1 Year	1	Nil	Nil
7	Lost to Follow Up	9	-	-

Table 3 show the outcome of follow up for the 31 patients during the study period. Eight patients were followed up for 5 years with no recurrence and no mortality. Seven patients were followed up for 4 – 5 years without recurrence of mortality. One out of the 5 patients followed up for 3 – 4 years had recurrence without mortality. Nine patients were lost to follow up (29%).

DISCUSSION

There were thirty-one cases of breast cancer in pregnancy within a five-year period. This can be considered a rise in occurrence over the years when compared with only five cases reported in the same center over thirteen-year period from 1990 to 2002.[20] The mean age (32.5 years) at diagnosis of breast cancer in pregnancy in our study is similar to the mean age of 32.5 years for the four patients reported in a Ghanaian study.[21] However, the mean age at diagnosis is different / older than an earlier report in Port Harcourt calculated at 24.5 years. Also, the mean gestational age of 26.6 weeks seen in our study is different from the calculated mean gestational age of 13.5 for the Ghanaian study. Most patients presented with stage II disease followed by stage III. All had invasive ductal carcinoma. Majority of the patients in our study had left-sided breast tumors. This is similar to the findings in the Ghanaian study, as 3 out of the 4 patients

had left-sided tumors.[21] As in non-pregnant women, most breast cancers in pregnancy present as painless lumps in the breast. Bloody nipple discharge can be seen but this is said to be rare.[22] All our patients presented with painless lumps. Breast changes during pregnancy often delay the patients' ability to palpate any lumps in their breasts until later.[23] This is probably why only one patient in our study presented with stage I disease.

Cancer of the breast in pregnancy is usually associated with delayed diagnosis because of physiological changes in the breast and tend to present at a younger age.[24, 25] A one-month delay in diagnosis is said to lead to a 0.9% rise in the likelihood of nodal involvement.[26] Diagnosis of breast cancer in pregnancy is based mainly on history and physical examination, breast ultrasonography, mammography and histology. Ultrasonography is very sensitive,[27] since it can easily identify the nature of a breast lump, i.e. whether it is solid or cystic. With the abdomen properly shielded, mammography can safely be done during pregnancy with little risk to the fetus.[5] Plain chest x-ray can also be done with adequate shielding as a way of staging the disease. The best diagnostic tool is tissue biopsy¹³ which was done for all our patients.[28] Histological diagnosis is made slightly more difficult in pregnancy owing to the hyperproliferative changes that occur in the breasts during this period. Prior knowledge by the pathologist of the pregnancy is helpful. Most of the tumors are high-grade, hormone receptor negative, and show increased expression of the human epidermal growth factor receptor 2 (HER2).[29, 30] Most of the breast cancers in pregnancy are invasive ductal carcinomas,[31-33] and this is the case in all our patients.

Delaying treatment for breast cancer on account of pregnancy is unnecessary unless the baby is to be delivered within the next 2-4weeks.[34] Terminating a pregnancy after a diagnosis of breast cancer is a decision to be taken by the patient and her relations after being properly informed of the modalities of treatment and any risks. Treatment of these patients should, as much as possible, be similar to that in non-pregnant women. The goal is to control the disease and prevent or treat systemic metastasis. Breast surgery is safe during the three trimesters of pregnancy without any significant risk to the unborn baby.[35] Surgery was done for all our patients as soon as a histological diagnosis was made irrespective of the age of the pregnancy. The extent of surgery need not be modified because all types of surgery on the breast are said to be as safe in the pregnant women as in their non-pregnant counterparts.[27] Some studies, however, report increased risk of miscarriage and preterm birth following surgery during the first trimester but no increased risk of congenital abnormalities.[36, 37] Anesthetic agents are not known to be teratogenic.[38]

Five patients defaulted from chemotherapy while seven defaulted from radiotherapy. Chemotherapy should be considered if nodal involvement is confirmed (or presence of features suggesting increased risk of recurrence).[39] Almost all of our patients had stage II disease and above. Use of chemotherapy in the first trimester is associated with defects in 10-20% of fetuses.[40, 41] Chemotherapy is better avoided in early pregnancy for fear of fetal abnormalities or miscarriages.[42, 43] Commencing these drugs from the 14th week of gestation is recommended.[44] It is safe throughout the second and third trimesters.[45-49] All our patients had chemotherapy from the 30th week of gestation because most presented during the second trimester and it took some time to obtain histological diagnosis. No reduction in doses of chemotherapeutic agents is recommended in pregnancy in comparison with non-pregnant women.[50] Reports indicate that the most favoured combination for chemotherapy

in pregnancy is an anthracycline-based regime.[12, 23] This was used for all our patients. We avoided the use of taxanes because of their uncertain safety profile in pregnancy. Animal studies show that they may cause intra-uterine growth retardation and even fetal death.[51] None of our patients had need for targeted therapy. Even then, the use of trastuzumab in pregnancy is not recommended because of fetal abnormalities, particularly oligohydramnios.[52] There is also a general rule to avoid the use of tamoxifen during pregnancy because of its teratogenic effects.[28]

In order to limit the risk of complications all our patients were delivered within 2-3 weeks after the last dose of chemotherapy. Neutropenia in the mother and/or the fetus may result if delivery is delayed.[37] Radiotherapy was postponed till after delivery in our patients. It may, however, be done if it is to prevent imminent disabling metastases, e.g. spinal cord compression, where it can be done with adequate fetal shielding.[53, 54] In the third trimester, early delivery may be considered so as to commence a badly needed radiotherapy. All of the 15 patients who had a minimum of 4-year follow up were found to have no recurrence or no mortality. One out of the 5 patients followed up for 3 years was found to have recurrence. Nine patients were lost to follow up. The delay in presentation and diagnosis, high grade and increased expression of HER2 suggest a poor outcome compared to non-pregnant patients. In the past it was believed that breast cancer in pregnancy was associated with poor survival.[55, 56] More recent studies, however, show that the outcome of treatment of breast cancer in pregnancy is similar to that of non-pregnant women when matched for age and stage.[11, 25, 57] These studies are in line with our experience. Only one patient (4.5%) had an unsatisfactory outcome and no mortality was recorded during the study period.

CONCLUSION

Cancer of the breast occurring during pregnancy is not uncommon. Presentation and diagnosis may be delayed but the treatment should, as much as possible, be as aggressive as in non-pregnant women. Surgery is generally indicated irrespective of the gestational age. Chemotherapy should be avoided in the first trimester, while radiotherapy should generally be postponed till after delivery. The use of hormonal agents and targeted therapy is still controversial. The outcome of treatment is comparable to that in non-pregnant women, thus obviating the need for unnecessary termination of the pregnancy.

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