

Female Fertility Following Chemotherapy for Breast Cancer: A Descriptive Study of 265 Cases Treated in Yaounde

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Abstract

Context: In Cameroon, breast cancer (BC) is usually diagnosed late in the disease course. About a third of women affected are aged less than 40 years. Chemotherapy (CT) could alter ovarian function and thereby compromise future fertility in these women. We therefore described the fertility of women following CT for BC in women treated at the Yaounde General Hospital (YGH). **Methods:** It was a retrospective, descriptive, cross-sectional study conducted over 8 months, from January to August 2017. We used the files of patients managed for BC from January 2011 to December 2015 in the medical oncology unit of the YGH. **Results:** We included 265 patients for the study following at least one year of CT. The mean age at the onset of CT was 35.9 ± 6.9 years. Most of the patients had fewer than 2 deliveries (68.3%). Intraductal carcinoma was the most frequent histological lesion (90.6%) and most often diagnosed in advanced stages (73.5%). As per CT, the FAC protocol was the most used (44.5%). The menstrual cycles of the patients were more regular prior to the onset of chemotherapy (89.4% vs. 58.9%), while the mean period of resumption of menstrual activity following cessation of chemotherapy was 6.3 ± 2.0 months. Chemotherapy-related amenorrhoea was observed in 29.1% of patients after 12 months of treatment. More than half of these women

(51.3%) complained of a drop in libido and 6.4% achieved pregnancy within 13 months following cessation of chemotherapy. **Conclusion:** Following chemotherapy for BC, menstrual cycle disorders are more frequent and this can affect the patients' reproductive potential. Fertility consultations should be integrated into the management plan of such patients.

Keywords

Chemotherapy, Fertility, Women of Childbearing Age, Breast Cancer, Yaounde

1. Introduction

Breast cancer is the first female cancer in Cameroon [1], with a significant number of young women amongst those affected [2] [3]. Many studies suggest the occurrence of more aggressive forms of breast cancer in young women [4] [5] [6]. The absence of screening in young people, associated to the low levels of knowledge on the condition is responsible for the late diagnosis of breast cancer [3] [7]. As a result, practitioners resort to more aggressive treatment protocols to ensure survival and/or remission.

In addition to its aesthetic and psychological complications, the management of breast cancer in women of childbearing age could decrease their fertility potential. Because of their young ages, advanced disease, and the aggressive nature of the tumours, chemotherapy constitutes the mainstay of conservative management plans. According to Rudra *et al.* in the United States, a higher proportion of women under 40 years of age require chemotherapy when compared to older women [8]. Chemotherapy is based on antimitotic regimens with well described effects on ovarian function. These drugs act through multiple mechanisms such as decreased blood flow to the ovaries, the destruction of the ovarian cortical vasculature with ensuing cortical fibrosis associated to the disappearance of primordial follicles [9] [10]. Chemotherapy accelerates physiological ovarian aging, and therefore significantly compromises the fertility of women.

Improvements in treatment options and a better codification of the management of breast cancers have significantly increased the survival of patients. There is a need to address the desire for childbearing in women after breast cancer treatment, because the recovery of ovarian function and fertility becomes an important goal for their post-treatment quality and hence the need to perform fertility assessments while managing young women for breast cancer [11].

In this study, we aimed to describe the characteristics of reproductive life as well as the fertility of women following treatment for breast cancer with chemotherapy. Alterations in ovarian function following chemotherapy, raise the need to resort to the increasingly available and accessible gamete conservation techniques.

2. Materials and Methods

We conducted a descriptive cross-sectional study of a population of women of

childbearing age, treated for breast cancer at the medical Oncology unit of the Yaoundé General Hospital over a period of 5 years from January 2011 to December 2015. The study took place from January 2017 to August 2017 (8 months). We collected the contact details of the patients followed up for breast cancer from the database of the medical oncology unit. Then, using these, we searched for and consulted their medical files at the hospital archives. The medical records granted us access to the patients' telephone numbers via which we contacted them. All those residing in Yaounde, and who granted their consent were invited to the service for an interview. The date and time were determined according to the availability of the patients. In some cases, and following patient authorisation we obtained the information by phone call. Similarly, for all patients living outside Yaoundé and wishing to participate in the study, the interview was carried out on the telephone. Data on diagnosis and chemotherapy protocols were collected from the patients' medical records. For the study, we selected women following a post-chemotherapy interval of at least 12 months.

We excluded from our study all patients with a known history of hysterectomy, chemotherapy, ovarian failure or those who had a recurrence of breast cancer or died before or during our study.

Our variables of interest were socio-demographic (age, age at onset of chemotherapy, level of education, marital status), clinical (clinical stage, histological type, therapeutic modalities, chemotherapy protocol used and the number of sessions) and the characteristics of reproductive life (parity, history of infertility, contraception, menstrual cycle's pattern before and after chemotherapy, delay of menstruation after chemotherapy, desire for pregnancy, libido, occurrence of pregnancy).

We defined post-chemotherapy amenorrhoea as the absence of menses following 12 months or more of treatment cessation, and oligomenorrhoea as too few menses or bleeds lasting less than 2 days. Regular menstrual cycles are cycles occurring every 21 - 35 days. Patients were staged for breast cancer as per the TNM classification.

Simplified AJCC TNM classification 2017	
Categories	Criteria
Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Ductal carcinoma
T1	Tumor \leq 20 mm in greatest dimension
T2	Tumor $>$ 20 mm but \leq 50 mm in greatest dimension
T3	Tumor $>$ 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules)
T4a	Extension to the chest wall

Continued

T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema of the skin
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma 0.2 mm
Nodes	
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastases
cN1	Metastases to movable ipsilateral axillary lymph node (s)
cN2	Metastases in ipsilateral axillary lymph nodes fixed or matted Or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
Metastases	
M0	No clinical or radiographic evidence of distant metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0

At the medical Oncology service of the Yaoundé General Hospital, chemotherapy is administered in cycles every 21 days. The most commonly used protocols were:

Protocols	Description
FAC50	5-fluorouracil 500 mg/m ² + Adriablastine 50 mg/m ² + Cytosan 500 mg/m ² (6 - 8 cycles)
AC60-Taxotere	Adriamycin 60 mg/m ² + Cyclophosphamide 600 mg/m ² + Taxotere 100 mg/m ² 4 cycles of AC60, followed by 4 cycles of Taxotere
AC60	Adriamycin 60 mg/m ² + Cyclophosphamide 600 mg/m ²
TAC	Taxol 135 mg/m ² (or 80 mg/m ² if weekly administration) + Adriamycin 50 mg/m ² + Cyclophosphamide 500 mg/m ²
FUN	5-fluorouracil 500 mg/m ² + Navelbine 25 - 30 mg/m ²

In the event of over expression of HER2, the weekly Taxotere or Navelbine regimens were proposed in association with Trastuzumab.

We analysed our data using SPSS 23.0 and Microsoft Excel 2010 software, and presented our results as means (+/-SD) for quantitative variables and frequency variables for qualitative variables.

3. Results

Between January 2011 and December 2015, 900 cases of breast cancer were managed at the Medical oncology unit of the Yaoundé General Hospital. From amongst these, 406 patients were selected after evaluating the information contained in the database of the Medical Oncology unit and the patient's medical records. The other files were those of patients who did not start chemotherapy. From the 406 patients, 141 patients were excluded amongst which: 31 deceased

patients, 100 who were still in chemotherapy for local or metastatic recurrence, 5 who had incomplete or absent records, 5 who had a history of hysterectomy before the diagnosis of breast cancer, and 1 who had a history of chemotherapy prior to the diagnosis of breast cancer. In the end, 265 patients were included for the study (**Figure 1**).

Sociodemographic characteristics

The average age of the patients at the time of the study was 39.2 ± 6.8 years, while the average age of patients at the onset of chemotherapy was 35.9 ± 6.6 years. Higher and secondary education levels were the most represented, representing 37% and 36.2% of cases respectively. Half of these were married (**Table 1**).

Clinical and histopathological characteristics

Table 2 represents clinical and histopathological characteristics. Pauciparous patients represented 68.3% (181/265) of the cases. Root canal carcinoma was the most diagnosed histological type (90.6%/240/265). The diagnosis was often made in advanced stages of the disease, *i.e.* T3 and T4 in proportions of 34.3% (96/265) and 39.2% (98/265) respectively.

Therapeutic variables

Table 3 represents the therapeutic aspects. The most common management plan for patients involved chemotherapy, surgery and radiotherapy in 70.6% (187/265) of cases. The FAC and AC60-Taxotere protocols were the most commonly used, in 44.5% (118/265) and 35.5% (94/265) of cases respectively.

Table 1. Patients socio demographic characteristics before CT (N = 265).

Variables	Number (n)	Frequency (%)
Profession		
housewife	70	26.4
civil servant	65	24.5
Trader	57	21.5
Private sector	53	20.0
Student	20	7.4
Educational status		
Higher	98	37.0
Secondary	96	36.2
Primary	68	25.7
Nil	3	1.1
Marital Status		
Married	135	51.0
Celibate	29	10.9
Free union	87	32.8
Divorced	6	2.3
Widow	8	3.0

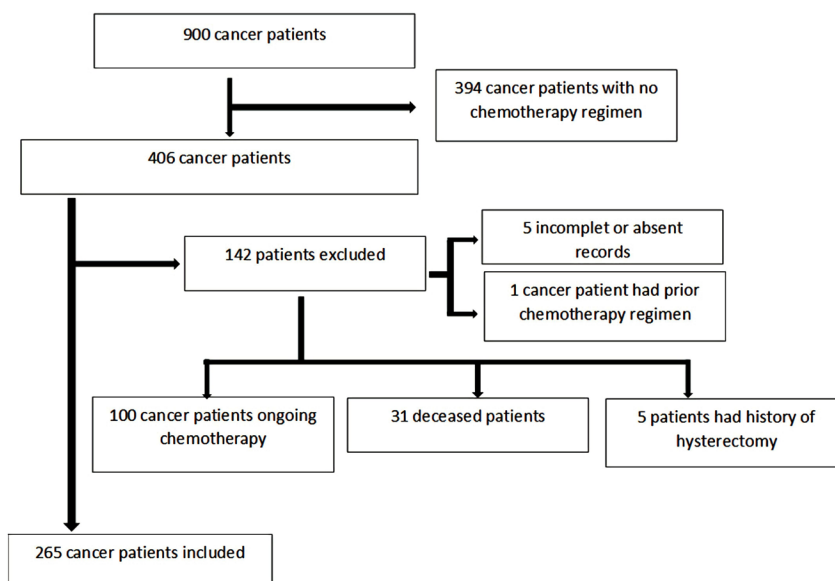


Figure 1. Flow chart of the screening process.

Table 2. Clinical and histopathological characteristics before CT (N = 265).

Variables	Number (n)	Frequency (%)
Age (years) at chemotherapy onset		
<30	28	10.6
30 - 39	126	47.5
≥40	111	41.9
Parity		
Nulliparous	27	10.2
Pauciparous	181	68.3
Multiparous	57	21.5
Menstrual cycle		
Regular	237	89.4
Irregular	28	10.6
Histological types		
Ductal carcinoma	240	90.6
Lobular carcinoma	18	6.8
Sarcoma	3	1.1
Paget's disease	1	0.4
Papillar carcinoma	1	0.4
Mixte carcinoma	2	0.8
Clinical stage of the disease		
T1	18	6.8
T2	30	11.3
T3	91	34.3
T4	104	39.2
TX	22	8.3

Table 3. Patient distribution by treatment modalities (N = 265).

Variables	Number (n)	Frequency (%)
Management plan adopted		
SCR	187	70.6
SCT	1	0.4
SCRT	7	2.6
SCRH	49	18.5
SC	15	5.7
S	6	2.3
Chemotherapy protocol applied		
AC60-Taxotere	94	35.5
FAC	118	44.5
AC60-Taxotere—Adriamycin	2	0.8
AC60	41	15.5
FAC-FUN	3	1.1
AC60-Taxotere—Herceptin	7	2.6

S: Surgery; SC: Surgery-Chemotherapy; SCHH: Surgery-Chemotherapy-Radiotherapy-Hormonotherapy; SCRT: Surgery-Chemotherapy-Radiotherapy-Targeted therapy; SCT: Surgery-Chemotherapy-Targeted therapy; SCR: Surgery-Chemotherapy-Radiotherapy.

Reproductive life variables

Table 4 and **Table 5** represent the reproductive life characteristics of our participants. Amongst the patients included, 11.7% (31/265) claimed to have infertility prior to breast cancer diagnosis. Regarding 188 patients who experienced a return of menses, the average period of return was 6.3 \pm 2.0 months, with extremes ranging from 1 to 11 months. The proportion of patients with an irregular cycle increased after chemotherapy from 10.6% (28/265) prior to 41.2% (109/265) after chemotherapy (**Table 5**). Seventy-seven patients (29.1%; 77/265) had chemotherapy-induced amenorrhea (**Table 5**), and most of them were above 40 years (90.1%; 70/77). Furthermore, 98/265 (37.0%) menstruated anew after 6 months. Patients reported a decrease in libido in 51.3% (136/265) of the cases and 13.2% (35/265) of them no longer had sexual intercourse after chemotherapy.

The majority of patients had a desire for pregnancy after chemotherapy (71.3%; 189/265) and this desire was especially expressed in the [30 - 40] year age group (**Figure 2**). The crude pregnancy rate 13 months after the end of chemotherapy was 6.4% (17/265) while the pregnancy rate was 22.4% (17/76) if we take into account women who expressed a desire for pregnancy. Most women who had a pregnancy had a desire to conceive (11.8%, 9/76) compared to the others (4.2%, 8/189) (**Table 6**) and all age groups before 40 years were concerned (**Table 7**).

Table 4. Reproductive life data of patients after chemotherapy (N = 265).

Variables	Number (n)	Frequency (%)
Menstrual cycle characteristics		
regular	156	58.9
oligomenorrhoea	32	12.1
amenorrhoea after 12 months	77	29.1
Onset of menses after end of chemotherapy*		
within 3 months	14	5.3
within 6 months	98	37.0
within 9 months	180	67.9
within 12 months	188	70.9
Libido levels		
Preserved	122	46.0
lowered	136	51.3
no response	7	2.6
Weekly coital activity (day)		
no sexual intercourse	35	13.2
1	109	41.1
2	96	36.2
3 and more	25	9.4
Pregnancy desire		
Yes	76	28.7
No	189	71.3
Pregnancy occurrence by age		
<30	8	3.0
30 - 39	8	3.0
>40	1	0.4

*cumulative number of women.

Table 5. Menstrual cycle characteristics after chemotherapy by age range (N = 265).

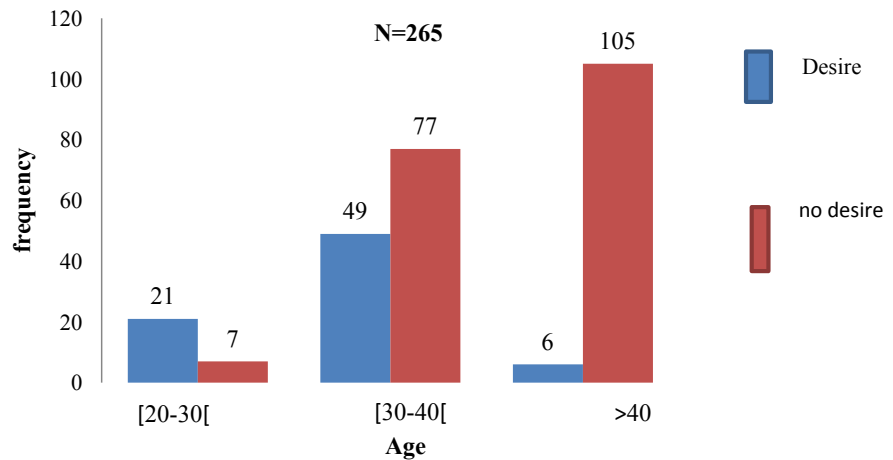
Menstrual cycle	20 - 29	30 - 39	≥40	Total
Normal	28 (17.9)	105 (67.3)	23 (14.7)	156 (58.9)
Oligomenorrhoea	0	14 (43.8)	18 (56.2)	32 (12.1)
Amenorrhoea	0	7 (9.1)	70 (90.9)	77 (29)

Table 6. Distribution of pregnancy occurrence by age.

Variables	[20 - 30]]30 - 40]]40 - 49]	Total
Pregnancy	8 (28.6)	8 (6.3)	1 (0.9)	17 (6.4)
No pregnancy	20 (71.4)	118 (93.7)	110 (99.1)	248 (94.6)
Total	28 (100)	126 (100)	111 (100)	265 (100)

Table 7. Distribution of pregnancy occurrence according to pregnancy desire.

Variables	Pregnancy desire	No pregnancy desire	Total
Pregnancy	9 (11.8)	8 (4.2)	17 (6.4)
No pregnancy	67 (89.2)	181 (95.8)	248 (94.6)
Total	76 (100)	189 (100)	265 (100)

**Figure 2.** Distribution of pregnancy desire by age range (N = 265).

4. Discussion

The occurrence of amenorrhea following chemotherapy reveals its toxicity to the ovaries. Several authors have echoed this in many studies [10] [11] [12] [13] [14]. The possibility of premature ovarian failure caused by chemotherapy, is potentially invalidating for women of childbearing age treated for breast cancer. According to Kemfang *et al.* (2011) [3] about 30% of breast cancers diagnosed in Cameroon affect women under 40 years of age. Most of the women in our study population who desired pregnancy (28.1%) were between 31 and 40 years of age.

Despite their young age, the majority of our patients (73.5%) had locally advanced-stage disease (T3, T4) at the time of diagnosis, which is frequently the case in resource-limited countries [2] [3] [5] [7]. This is because patients generally seek medical attention late in the course of disease [1] [12], unlike in industrialized countries where the diagnosis is made earlier [13]. The late discovery of the disease is associated with poor survival rates [2], ultimately leading to aggressive treatments, especially in young women [14]. These treatments are likely to be more toxic to the ovaries.

In addition, young age is a poor prognostic factor [15] for breast cancer. The average age in our study population was 35.9 years.

Many authors have evaluated the toxicity of the chemotherapeutic agents used in the management of breast cancers, with evidence that treatment protocols affect ovarian function differently. The toxicity depends on the age of the patient, the agent used, including the dose and the protocol [16]. Cyclophosphamide-based protocols induce the highest rates of chemotherapy-induced ovarian

failure especially after 40 years [16] [17]. Long JP *et al.* [18] had found that although both CAF and DPT affected ovarian function, alterations with the CAF protocol was less pronounced. The FAC protocol (44.5%) was the most used in our study, a fact not consistent with recent literature, which increasingly recommends a sequence-based protocol with Anthracyclines and Taxanes, known to be less toxic to ovaries [19] [20]. The reason for this is that many chemotherapeutic agents remain unavailable in our setting, and their relatively high cost makes them inaccessible for the majority of these patients who have limited resources in the absence of a Universal health coverage scheme.

Age is a determining factor in the occurrence of menstrual disorders following chemotherapy. The average age of women in our study was young at 35.9 years. This is probably why only 41.1% of our patients had cycle disorders such as amenorrhoea or oligomenorrhoea after chemotherapy. In the study by Tiong *et al.* [21], 93.1% of women reported amenorrhea at the end of treatment and 77.9% reported same 12 months after chemotherapy in a female population in which the average age was 43.3 years. These authors also found that age was the most important risk factor for the occurrence of chemotherapy-induced amenorrhoea because the rate of amenorrhoea increased with increasing age. This finding was further corroborated by the work of Ben-Aharon *et al.* [22], which showed that women under 35 years of age recovered from alterations in chemotherapy-induced ovarian circulation faster than their older counterparts. Menstrual disorders are likely to occur in women who already have some degree of aging ovarian function [23] [24]. Amongst the women who complained of amenorrhea, 37% had a resumption of menstrual activity after 6 months. This rate was higher than those described in literature with different treatment protocols [21].

We observed 17 (6.4%) cases of spontaneous pregnancies 13 months after chemotherapy, and a 10.4% pregnancy rate among women under 40 years of age. Despite the return to normal of the menstrual cycle, young women survivors of chemotherapy will undergo varying degrees of altered ovarian function that will interfere with their fertility [25].

The pregnancy rate amongst women over 40 years of age was extremely low at 0.9% with Gerber B *et al.* [26] reporting a 3% spontaneous pregnancy rate amongst women over 40 years of age, suggesting a more severe alteration in fertility in women over 40 years of age, even if their menstrual cycle remains intact.

Literature findings estimate that 70% of patients under 45 years of age who are treated for breast cancer would desire a child after the end of their treatment [27], however we found a lower proportion in our study. This could be explained by the fact that most of our patients already had at least one child. In order to avoid the residual teratogenic risk of chemotherapy, a minimum of at least 1 year following the last course of chemotherapy is recommended (at least 3 months after stopping Tamoxifen) [28]. Unfortunately safety time is not often taken into consideration.

Our study presented some limits. First, we studied overall female fertility fol-

lowing chemotherapy regardless of the protocol used. Also, the size of our sample did not allow us to isolate the protocol favorable to fertility, or better still to identify the molecule most toxic to the ovaries. In addition, data obtained by telephone posed the risk of information bias. Finally, we evaluated the fertility of women and not that of the couple, with the risk of missing potential male partner infertility as the sole cause for childlessness.

5. Conclusion

Chemotherapy alters the fertility of women treated for breast cancer. Cycle disorders are more frequent after chemotherapy. The resumption of normal menstrual cycle activity does not guarantee future childbearing. The high proportions of patients wanting pregnancy after chemotherapy suggest the need to integrate fertility consultations into the management of breast cancer patients and to look out for factors associated with fertility potential following chemotherapy.

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Data Availability Statement

The data used to support the findings of this study are included within the article.

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Avoid the stilted expression, “One of us (R. B. G.) thanks...” Instead, try “R. B. G. thanks”. Do NOT put sponsor acknowledgements in the unnumbered footnote on the first page, but at here.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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