

# Amenorrhea, fertility preservation, and counseling among young women treated with anthracyclines and taxanes for early-stage breast cancer, a retrospective study

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## Abstract

Chemotherapy may cause ovarian toxicity and infertility. Cancer patients are usually overwhelmed, and focus exclusively on cancer diagnosis and may not pay attention to fertility-related issues. In this paper we look at the rate of amenorrhea and fertility counseling among such young patients.

Premenopausal women with early-stage breast cancer treated with adjuvant or neoadjuvant chemotherapy were recruited. Amenorrhea was defined as absence of menstruation for  $\geq 12$  months after the completion of chemotherapy.

A total of 94 patients met the eligibility criteria and were included in this analysis. Median age at diagnosis was 35.7 (range, 22–44) years. Seventy-nine (85.9%) respondents were counseled about amenorrhea and 37 (40.2%) were considering having children. Long-term amenorrhea was reported by 51 (54.3%) patients. The addition of taxanes to anthracyclines, in 2 different regimens, increased the risk of amenorrhea to 69.2% and 66.7% compared to 38.9% with anthracycline-alone,  $P < .0001$ . Longer duration of chemotherapy ( $\geq 24$  weeks) might also be associated with higher rate of amenorrhea (67.7%) compared to 43.4% in those who had shorter duration ( $< 24$  weeks),  $P = .031$ .

The addition of taxanes to anthracycline-based chemotherapy increased the risk of amenorrhea. However, shorter duration of chemotherapy, even with taxanes, may lower such risk. Our study highlights the importance of fertility counseling to improve fertility preservation rates. Given the importance of taxanes, shorter regimens are associated with lower amenorrhea rates and should be preferred over longer ones.

**Abbreviations:** AC = adriamycin and cyclophosphamide, CMF = cyclophosphamide, methotrexate and 5-fluorouracil, FEC = 5-fluorouracil, epirubicin and cyclophosphamide, GnRH-a = gonadotropin-releasing hormone agonists, POF = premature ovarian failure.

**Keywords:** breast cancer, chemotherapy, gonadotropin-releasing hormone agonists, pregnancy, premature ovarian failure, premenopausal

## 1. Introduction

Breast cancer continues to be the most common cancer among females worldwide<sup>[1,2]</sup> and so in Jordan.<sup>[3]</sup> Of the more than

6000 new cancer cases diagnosed annually among Jordanians, 20% are breast cancer and almost half of them are premenopausal at time of diagnosis. Additionally, more than 15.0%, compared to less than 7.0% in western societies,<sup>[4]</sup> are below the age of 40 years at time of breast cancer diagnosis.<sup>[3]</sup>

The value of adjuvant chemotherapy in breast cancer, especially in younger patients, is undebatable. Published studies had shown that adjuvant chemotherapy prolonged both disease-free and overall survivals.<sup>[5]</sup> However, it is also known that chemotherapy may lead to premature ovarian failure (POF), amenorrhea, and impaired fertility in this young age group. Early menopause may also result in higher risk of osteoporosis,<sup>[6]</sup> cardiovascular diseases,<sup>[7]</sup> genitourinary dysfunctions, vasomotor symptoms like hot flashes,<sup>[8]</sup> and psychological disturbances.<sup>[9]</sup>

Previous published studies had reported variable rates of POF with cytotoxic chemotherapy. Much of the published literature focused on regimens incorporated anthracyclines and cyclophosphamide like adriamycin and cyclophosphamide (AC) and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) or the old cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen. In 1 study, the use of either CMF or cyclophosphamide, epirubicin and 5-fluorouracil, alone or with endocrine therapy in young women with breast cancer, increased the risk of premature menopause from less than 5% to more than 40%.<sup>[10]</sup>

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Very few studies addressed this issue among breast cancer patients treated with taxanes which is incorporated with almost all adjuvant or neoadjuvant breast cancer chemotherapy regimens.<sup>[11,12]</sup> In 1 study, researchers from the Memorial Sloan Kettering Cancer Center reported their experience on 166 premenopausal women aged 40 years or younger (median age: 36 years), all were treated with adjuvant anthracycline and taxane-based chemotherapy for early-stage breast cancer. Twenty-five (15%) patients developed POF and long-term amenorrhea. Women who experienced amenorrhea were found to be significantly older than those who did not ( $P < .01$ ).<sup>[13]</sup>

Despite its significant impact on their quality of life, counseling about POF and infertility associated with chemotherapy is not routinely practiced. A recent study from Germany that recruited 1191 young women with locoregional primary breast cancer, treated between 2006 and 2014 looked at patient-reported outcomes on issues that included fertility concerns. The mean age at diagnosis was 40 years. Only half of all patients had been informed about the risk of infertility following chemotherapy. However, counseling at a specialized fertility center was offered to only 13% and only 2% underwent fertility preservation procedures.<sup>[14]</sup> Given this low compliance rate, we put together a bundle of regulations to enhance our counseling and fertility preservation rates. Fertility counseling, both for males and females, was a key performance quality indicator; data on which is regularly collected and reported by our quality office. Additionally, fertility preservation is addressed while discussing the medical management of our young breast cancer patients during our twice-weekly multidisciplinary clinic breast cancer meetings. A fertility-preservation clinic run by an experience gynecologist was also established.

In this paper we look at the rate of amenorrhea and fertility counseling among young females diagnosed with breast cancer and treated with anthracycline with or without taxanes in a developing country like ours.

## 2. Methods

Premenopausal women with early-stage breast carcinoma aged 44 years or younger treated and followed at our center for at least 12 months after the completion of all chemotherapy were identified. Eligible patients were required to have invasive breast carcinoma treated with anthracycline and/or taxane-based adjuvant chemotherapy. Patients progressed during the first 12 months were excluded. Additionally, patients underwent surgical or medical ovarian ablation using gonadotropin-releasing hormone (GnRH) agonists ( $n = 79$ ) were also excluded. Patients could have received endocrine therapy as indicated by the hormone receptor status of their tumors.

Long-term amenorrhea was defined as absence of menstruation for 12 months after the completion of all chemotherapy. Follow-up evaluations were performed at 3-month intervals during the first year and every 4 months during the second and third year then every 6 months intervals thereafter. Information regarding menstrual status was obtained from patients during their follow up and/or a review of the medical records. A self-reported questionnaire was given for patients enrolled. Patients who agreed to participate signed a consent form consistent with our institutional review board guidelines.

The 2 primary study outcomes were the rate of fertility counseling, provided by the treating physician or medical team before initiation of chemotherapy, and the rate of POF. These

outcomes were obtained from patients' study questionnaires and medical record review. In addition to a series of sociodemographic questions, patients were required to respond to a group of questions related to menstrual cycle before and after chemotherapy, it also contains questions related to marital status at time of cancer diagnosis, prior marriage, prior kids and number, and their desire to have future ones.

Patients were also asked a series of "yes" or "no" questions regarding whether the treating medical team members, had discussed the risk of POF and potential infertility, and whether recommendations for ova preservation were made.

Study was reviewed by the institutional ethics committee and consents were waived.

## 3. Results

Between January 2014 and December 2017, a total of 94 patients met the eligibility criteria and were included in this analysis. The median age at diagnosis was 35.7 (range, 22–44) years. Majority (67, 71.3%) of the patients were married and most had a relatively low-income. Patient characteristics and pathological features of the tumor are detailed in Table 1. As illustrated, 56 (59.6%) patients had node-positive tumors while almost a third had human epidermal growth factor receptor-2-positive disease.

All patients had regular menses at time of diagnosis and before initiation of adjuvant chemotherapy. Treatment schedule and dosing are detailed in Table 2. Briefly, 4 cycles of AC (doxorubicin at a dose of 60 mg/m<sup>2</sup> plus cyclophosphamide at

**Table 1**

### Patients characteristics.

	Category	Number of patients*	Percentage
Educational level	High School or lower	29	30.9%
	Diploma	18	19.1%
	University Graduate	38	40.4%
	Post Graduate	9	9.6%
Income (USD)	<1400	64	71.9%
	1400–4000	21	23.6%
	>4000	4	4.5%
Nationality	Jordanian	90	95.7%
	Non-Jordanian	4	4.3%
Marital Status	Single	19	20.4%
	Married	67	71.3%
	Others	8	8.5%
Tumor Size (T)*	T1	26	28.6%
	T2	43	47.3%
	T3	21	23.1%
	T4	1	1.1%
Lymph nodes status (N)	Positive	56	59.6%
	Negative	36	38.3%
	Unknown	2	2.1%
TNM Stage*	I	14	16.9%
	II	45	54.2%
	III	24	28.9%
ER*	Positive	74	80.4%
	Negative	18	19.6%
PR*	Positive	75	81.5%
	Negative	17	18.5%
HER-2 Status*	Positive	30	32.6%
	Negative	61	66.3%

ER = estrogen receptor, HER-2 = human epidermal growth factor receptor-2, PR = progesterone receptor.

\* Total might be less than 94 as some patients did not respond to all questions or data not available.

**Table 2****Chemotherapy and anti-HER2 treatment.**

	Type of chemotherapy	Number	Percentage
Chemotherapy	AC × 4	18	19.1%
	AC every 3 wk for 4 cycles followed by Paclitaxel every 3 wk × 4, or AC every 3 wk for 4 cycles followed by weekly Paclitaxel × 12 wk	13	13.8%
	FEC every 3 wk for 3 cycles, followed by Docetaxel every 3 wk for 3 cycles	35	37.2%
	AC every 3 wk for 4 cycles followed by Docetaxel every 3 wk for 4 cycles (Neoadjuvant)	18	19.1%
	Others	10	10.6%
Anti-HER2 therapy	Trastuzumab	29	30.9%

AC=adriamycin and cyclophosphamide, FEC=5-fluorouracil, epirubicin and cyclophosphamide, HER2 = human epidermal growth factor receptor-2.

a dose of 600mg/m<sup>2</sup> delivered every 3-week. Docetaxel was given at 100mg/m<sup>2</sup> every 3 weeks while paclitaxel was given at a dose of 85mg/m<sup>2</sup> weekly for 12 weeks. Additionally, FEC (5-fluorouracil at 500mg/m<sup>2</sup>, epirubicin at 50mg/m<sup>2</sup>, and cyclophosphamide at 500mg/m<sup>2</sup>) was given every 3 weeks.

In the adjuvant setting, low-risk, node-negative patients were treated with AC regimen for 4 cycles, while high-risk node-negative patients and all node-positive patients were given anthracycline-based chemotherapy (AC for 4 cycles or FEC for 3 cycles) followed by a taxane (paclitaxel weekly for 12 weeks or docetaxel every 3 weeks for 3 cycles). In the neoadjuvant setting, all patients were treated on a unified program; 4 cycles of AC followed by 4 more cycles of docetaxel, all delivered every 3 weeks.

A total of 84 (89.4%) patients received anthracycline-based chemotherapy while 66 (70.2%) patients received additional taxanes. Seventy-eight (83.0%) were on hormonal therapy with tamoxifen, too.

Seventy-nine (85.9%) respondents were counseled by their oncologists about amenorrhea as a complication of chemotherapy and 37 (40.2%) were considering having children post treatment and 43 (46.7%) stated that they would use the service.

Fifty-one (54.3%) patients developed long-term amenorrhea. Patients who were treated with anthracycline based chemotherapy regimen in the form of AC without taxanes (n=18) had significantly lower rate of amenorrhea (38.9%) compared to a rate of 69.2% among those who received an additional 12 weeks of weekly paclitaxel (n=13), and 66.7% among those (n=18) who received an additional 4 cycles of docetaxel every 3 weeks,  $P < .0001$ . Amenorrhea was reported by 16 (45.7%) of 35 patients who received 3 cycles of FEC followed by 3 more cycles of docetaxel, all were given at 3-week intervals. Combined together, the rate of amenorrhea was significantly higher (56.1%) with taxanes-containing regimens compared to anthracycline-alone regimen (38.9%),  $P = .024$  (Table 3).

A total of 31 patients had chemotherapy for more than 24 weeks, 21 (67.7%) had amenorrhea compared to 23 (43.4%) of 53 patients who had a shorter duration of chemotherapy,  $P = .031$  (Table 4). Only 7 (7.4%) patients were 30 years or younger at time of chemotherapy administration; 2 (28.6%) of them had amenorrhea compared to 49 (58.3%) of 84 patients above the age of 30 years,  $P = .127$ .

**Table 3****Rate of amenorrhea according to chemotherapy regimen.**

Type of chemotherapy	Total	No. of patients with amenorrhea	Percentage	P-value*
AC × 4	18	7	38.9%	
AC × 4 followed by weekly paclitaxel × 12 wk/AC every 3 wk for 4 cycles followed by paclitaxel every 3 wk × 4	13	9	69.2%	
FEC × 3 Followed by docetaxel every 3 wk × 3	35	16	45.7%	.024
AC × 4 followed by docetaxel × 4	18	12	66.7%	
Others	10	7	70.0%	
Total	94	51	54.3%	

AC=adriamycin and cyclophosphamide, FEC=5-fluorouracil, epirubicin and cyclophosphamide.

\* AC (anthracycline-alone) versus all others (anthracycline and taxanes).

**Table 4****Rate of amenorrhea according to duration of chemotherapy.**

Chemotherapy	Number	Amenorrhea	Percentage	P-value*
24 wk or less	53	23	43.4%	
• AC	18	7	38.9	
• FEC-docetaxel (6 cycles)	35	16	45.7	.031
More than 24 wk	31	21	67.7%	
• AC-paclitaxel weekly or every 3 wk	13	9	69.2	
• AC-docetaxel (8 cycles)	18	12	66.7	

AC=adriamycin and cyclophosphamide, FEC=5-fluorouracil, epirubicin and cyclophosphamide.

\* 24 wk or less versus >24 wk.

#### 4. Discussion

Population of Jordan is younger one; almost 38% of Jordanian females are younger than the age of 40.<sup>[14]</sup> This, among other factors, might explain the lower incidence of breast cancer in the country compared to western societies.

The use of chemotherapy to treat early stage breast cancer; both in the adjuvant and neoadjuvant settings, is widely practiced especially so among younger patients with high-risk pathological features. Chemotherapy, in this age group, may induce premature menopause with its associated poor fertility. Though fertility is considered one of the key aspects of quality of life for breast cancer survivors, it is usually poorly addressed at diagnosis, by both physicians and patients, alike! Given the nature of cancer as an illness, patients are usually overwhelmed with such diagnosis and their focus is usually on the cancer and how soon they will start active treatment. Many patients and families are usually under the impression that pursuing fertility preservation might delay their treatment, thus negatively affecting their cure rates. Additionally, patients may not be aware of their potential fertility loss, and such problem may not be communicated well by the treating physicians.<sup>[15]</sup> A survey study of young female cancer survivors reported that feeling too distressed or overwhelmed at the time of diagnosis, lack of knowledge about fertility preservation options, and concerns about cost were the main barriers to fertility preservation.<sup>[16]</sup>

The issue of fertility might not be in the mind of many treating oncologist whose focus is chemotherapy and its immediate complications. A cross-sectional survey developed to self-evaluate knowledge, attitude, and behavior regarding fertility preservation of over 800 Japanese breast cancer specialists. Survey items included questions regarding knowledge and attitude toward fertility issues, fertility-related practice and potential barriers for the discussion of fertility with patients. Responding physicians also answered few questions related to their socio-demographic background. Among the 400 respondent physicians, female and younger oncologists (age less than 50 years) and those working in a multidisciplinary environment had significantly higher probability of referring patients to reproductive specialists. Physicians who scored better in knowledge items and positive attitudes toward fertility preservation were also more likely to discuss potential fertility issues with cancer patients. Higher risk of tumor recurrence, lack of collaborating reproductive specialists, and time constraints in the clinic were among the main barriers identified.<sup>[17]</sup>

In 2018, the American Society of Clinical Oncology issued an updated guideline recommending that health care providers discuss fertility preservation with all patients of child-bearing age planned to undergo anticancer treatment that may affect their fertility.<sup>[18]</sup> Compliance with such guidelines continues to be a problem. In 1 retrospective study that included 303 women with breast cancer, aged 40 years or younger treated with chemotherapy and/or endocrine therapy, only 26% had fertility counseling with their physician; majority (89%) of them sought further fertility preservation options.<sup>[19]</sup> Our counseling rates; approaching 90%, are significantly higher than previously reported. Our multidisciplinary approach to breast cancer care which mandates a full discussion with all patients diagnosed with early-stage breast cancer and having “fertility counseling” as a key performance indicator, in addition to having a “fertility-preservation” clinic had probably improved our compliance rates.

Definitions of amenorrhea is so variable in previously published studies and that may explain the wide range of

reported POF and infertility rates especially after the use of taxanes. Some studies reported on rate of amenorrhea immediately after completion of chemotherapy<sup>[20]</sup> while others reported rates at 3, 6, or 12 months.<sup>[21]</sup> The impact of various definitions is illustrated by Padmanabhan et al, who reported the incidence of amenorrhea from the beginning of CMF chemotherapy at 3 months, 6 months, and 12 months later as 50%, 70%, and 80%, respectively.<sup>[22]</sup>

Our rates of amenorrhea, however, are relatively high. The sequential addition of taxanes to standard adjuvant anthracycline-based chemotherapy, resulted in statistically significant higher rates. The effect of duration of chemotherapy, in its own, is difficult to study in small studies like ours. Patients with longer duration of chemotherapy are those who were treated with taxanes thus extending the duration of chemotherapy. However, patients who had taxanes following anthracyclines for shorter duration (6 cycles) like the FEC-docetaxel regimen had lower rates of amenorrhea (45.7%) compared to those who had similar regimen but for 8 cycles; 69.2% with AC-paclitaxel and 66.7% with AC-docetaxel. Because the efficacy of many of the taxanes-containing chemotherapy regimens are almost equivalent, oncologist might consider giving the shorter regimen that is associated with less amenorrhea.

Patient-related factors, mainly age, may also contribute to the variable amenorrhea rates. In 1 study, Goldhirsch et al reported that 33% of women age younger than 40 years and 81% of women age older than 40 years become menopausal during adjuvant, classic CMF with oral cyclophosphamide for 6 months.<sup>[23]</sup>

The currently available options for fertility preservations and its associated cost are not encouraging, either. Ova or embryo cryopreservation may not be available within the same facility and lots of time, including our hospital, insurance coverage is not usually provided. In these situations, the use of GnRH agonists might be considered.<sup>[24]</sup> Several clinical trials and meta-analyses have shown that premenopausal women who received ovarian function suppression using GnRH agonists while on chemotherapy were less likely to have ovarian failure and had higher rates of menses resumption compared to patients who did not. Obviously, this should not be viewed as alternative unless it is clear that patients might not be able to have the more standard ova cryopreservation done.

The adoption of multidisciplinary approach and comprehensive programs including “fertility-preservation” clinics in addition to special training and educational sessions for healthcare providers are necessary to improve on fertility counseling and meet the expectations of such young breast cancer patients.

#### Author contributions

**Conception and design:** Hikmat Abdel-Razeq.

**Collection and assembly of data:** All authors.

**Data analysis and interpretation:** All authors.

**Manuscript writing:** All authors.

**Final approval of manuscript:** All authors.

**Agree to be accountable for all aspects of the work:** All authors.

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