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ORIGINAL ARTICLE

Assessment of Chemotherapy Induced Ovarian Failure Using Serum Anti-Mullerian Hormone in Premenopausal Breast Cancer Patients

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ABSTRACT

Background: Chemotherapy-induced amenorrhea (CIA) is a surrogate for ovarian failure, which is indicative of ovarian failure in young females taking chemotherapy. The CIA lacks sufficient reproducibility and reliability. Our aim is to assess the anti-Mullerian hormone (AMH) concentrations before and after chemotherapy (CTh) for premenopausal female patients with breast cancer and to correlate AMH values with menopausal status post-CTh.

Methods: This Prospective cohort study was conducted on 100 subjects at the Medical Oncology Department, Faculty of Medicine, Zagazig University. Pre-menopausal condition is characterized as two or more menstrual cycles in the 120 days before the start of CTh in females aged 18 to 45 years. The following data were obtained from the patient's sheets: patient history, clinical data, and AMH, estrogen, follicular stimulating hormone (FSH), and luteinizing hormone (LH) concentrations were assessed at baseline. Following blood tests were done after the end of the final cycle of CTh.

Results: Our study showed a statistically significant difference between baseline and post-chemotherapy hormonal biomarkers ($P < 0.05$). AMH levels were significantly decreased from(2.97 ± 1.94) to (0.47 ± 0.74) post-chemotherapy, and it is a sensitive prediction biomarker for ovarian failure induced by chemotherapy. There was a significant negative correlation between baseline AMH with BMI ($P<0.001$).

Conclusions: Serum AMH is a sensitive prediction biomarker of ovarian failure induced by chemotherapy, comparable with FSH, LH, and Estradiol levels.

Keywords: Chemotherapy, anti-Mullerian hormone, ovarian failure, breast cancer.

INTRODUCTION

Chemotherapy (CTh) may lead to premature menopause due to its direct harmful impacts on ovarian stroma and follicles. While inhibition of the ovary's activity may be beneficial in the management of some tumors, such as breast cancer (BC), it may induce undesirable effects such as infertility, cardiovascular disease, osteoporosis, and symptoms of menopause [1].

Therefore, women must receive clear information about the possibility of early menopause because of suggested CTh. Regretfully, there are currently no trustworthy methods to determine a woman receiving CTh's chance of experiencing early menopause [2].

Anti-Müllerian hormone (AMH) is generated by granulosa cells of primary, antral, and preantral follicles associated with the reserve of ovaries. It is effective in predicting the age of menopause in premenopausal cases with an accuracy of ±6 months [3]. The assessment ofAMH has been recognized as the most accurate biomarker of the quantity of small developing ovarian follicles, which indirectly represents primordial follicles number or the reserve of ovaries [4].

A significant body of proof has revealed that concentrations of AMH drop in women following CTh, with varying recoveries according to the treatment type [5]. Post-CTh AMH evaluation also predicts ovarian function recovery [3].

Breast cancer (BC) is the most prevalent cancer diagnosis among females [6]. Post-CTh ovarian function evaluation is not only crucial for directing therapeutic decisions concerning the optimal endocrine treatment in cases with hormone-receptor-positive (HR+) BC, but it is also essential to be able to guide individuals precisely on their chances for fertility and, by a greater awareness of the gonadotoxicity of various therapeutic regimens, guide women with greater precision of ovarian function outcome [7].

AMH is a well-established marker of ovarian function in cancer cases [8]. Many investigations have demonstrated the impact of various chemotherapy-based treatment regimens across a wide range of diseases, mostly in BC cases, as well as the utility of AMH in identifying premature ovarian insufficiency following therapeutic recovery. In addition, blood AMH concentrations before CThindicate ovarian recovery following the treatment.

This study aimed toassessCTh-induced ovarian failure (CIOF) using serum AMH in premenopausal breast cancer patients.

METHODS

Patients

This Prospective cohort study was conducted at the Medical Oncology Department, Faculty of Medicine, Zagazig University. Pre-menopausal condition is characterized as two or more menstrual cycles in the 120 days before the start of CTh in females aged 18 to 45 years.The ovaries' ability to produce estrogen drops dramatically and persistently after menopause, defined as the permanent cessation of menstruation. Menopause in our study of breast cancer patients was considered when the age was less than 60 years, and chemotherapy-induced amenorrhea was for ≥12 months with follicular stimulating hormone (FSH)and estradiol in the post-menopausal range on serial assessments.

Assuming the mean AMH was 1.67±0.44. vs. 1.9±0.37 in cases vs. control, the estimated sample was 100 subjects. Verbal and written informed consent were obtained from all participants after explaining the procedure and medical research. The research was conducted under the World Medical Association’s Code of Ethics (Helsinki Declaration) for human researchafter the approval of the Institutional Review Board (IRB).

Cases with the following criteria were included:premenopausal breast cancer patients, all patients were recruited after obtaining informed consent, and early-stage breast cancer on adjuvant chemotherapy. Cases with the following criteria were excluded: postmenopausal patients, pregnantpatientsreceiving GnRH Agonist treatment, and metastatic breast cancer patients.

Methods

The following data were obtained from the patient's sheets: age of patients, menstrual status, relevant family history, tumor grade and size, and stage. AMH, estrogen, FSH, and luteinizing hormone (LH) levels were measured at baseline. Following blood tests were done after the end of the final cycle of CTh. In the current study, most of the patients

(62%) received (4AC + 12 Taxol weakly), while15% received dose-dense (4AC+4Taxol), and 23% had (4AC alone). Twenty-one patients received Herceptin.

The AMH cut-off of 0.012 ng/mL predicts the postmenopausal status with a sensitivity of 24.2% and specificity of 30.5%.A woman of reproductive age will have normal AMH levels between 1.0 and 4.0 ng/mL. LH normal levels in the follicular phase of the menstrual cycle: 1.68-15 IU/mL. Midcycle peak: 21.9-56.6 IU/mL. Luteal phase: 0.61-16.3 IU/mL. Postmenopausal: 14.2-52.3 IU/mL.FSH normal levels before puberty: 0-4.0 mIU/mL (0-4.0 IU/L). During puberty: 0.3-10.0 mIU/mL (0.3-10.0 IU/L). Women still menstruating: 4.7-21.5 mIU/mL (4.5-21.5 IU/L). After menopause: 25.8-134.8 mIU/mL (25.8-134.8 IU/L).Estradiol normal levels are30-400 pg/mL for premenopausal women. 0-30 pg/mL for postmenopausal women.

Statistical Analysis

Jamovi project (2022) (Version 2.3) was utilized for data analysis. Quantitative variables used mean and standard deviation; qualitative variables were presented as numbers and percentages. For relation between quantitative variables of 2 groups, the Wilcoxon test Nonparametric test was used to compare outcomes between two dependent groups. For the relation between quantitative variables of more than 2 groups Kruskal–Wallis's test was used to compare two or more independent samples of equal or different sample sizes that are not normally distributed. For correlation between two quantitative variables Spearman's rank correlation test was used. Receiver operating characteristic (ROC) curve analysis assessed specificity and sensitivity. Area under the curve (AUC) was calculated and classified (9-10: Excellent, 8-9: good, 7-8: fair, 6-7: poor). P<0.05 is considered significant.

RESULTS

This prospective cohort study included 100 premenopausal breast cancer females. The demographic data of the included patients are shown in table (1). As the mean age among studied patients was 33.3 years ± 7.5SD, mean BMI of 21.8 kg/m2 ± 4.7 SD, 57% of patients were within normal ranges according to BMI, 18% were underweight, 16% were obese. A positive family history of breast cancer was identified in 19% of the patients.

The tumors of grade 3 were 45%, followed by grade 2 (43%), then grade 4 (12%). Positive ER, PR, and HER2 were 75%, 55%, and 21%, respectively. Most patients (38%) had Ki67 from 10 to 20% (Table 2).

More than 60% of the studied patients received (4AC + 12 Taxol), while 15% received Dose-dense (4AC+4Taxol) and 23% had (4AC alone). Twenty-onepercent received Herceptin. Regarding post-chemotherapy menopausal symptoms, 77% had amenorrhea, 14% had irregular menses,and 9% had ongoing menses. Flushing was evident in 80% of patients, and headache in 60%. As regards post-chemotherapy complications; half of the studied patients had neuropathy, 26% were grade 1, 14% were grade 2 and 10%were grade 3. Neutropenia (10%),extravasation (3%), and cardiac toxicity (5%) also were side effects of CTH, but their incidence was not statistically significant (Table 3).

Table (4) showed a significant difference between baseline and post-CTh hormonal biomarkers (P <0.05), as the mean of estradiol levels significantly decreased from (126.79 ± 54.74) to (99.5 ±29.29) post-chemotherapy (P=0.002). In contrast, FSH and LH levels increased dramatically from 9.26 ±4.34 and 11.99 ± 12.4 up to 11.99 ± 12.4 and 13.16 ± 11.66, respectively(p<0.05). AMH levels reduced significantly from 2.97 ±1.94 to 0.47 ±0.74 post-chemotherapy (p<0.001). There was a significant negative association between baseline AMH and BMI (r=0.57, P<0.001). (Table 5)

A significant difference in estradiol levels among different menstrual patterns was determined, as it was the highest among patients with ongoing menses 133.5 ± 0.71 and the lowest 95.9 ± 27.7 among patients with amenorrhea (P=0.009). Similarly, AMH level was higher among patients with ongoing menses (2.5 ± 0.71) in comparison to patients with irregular menses (0.97 ± 0.15) and patients with amenorrhea (0.14 ±0.09) with a significant difference between the 3 groups (P=0.003). Concerning FSH level, it was lower among patients with ongoing menses in comparison to patients with amenorrhea, although this difference was not statistically significant (P>0.05). Also, LH levels were lower among patients with ongoing menses (11.2 ± 1.7) in comparison to patients with amenorrhea (14.22 ± 13.1), although this difference was not significant (P >0.05) (Table 6).

The ROC curve was conducted to discriminate between patients with and without menses; AMH had an AUC of 0.94 with sensitivity (94.3%) and specificity (90%), while estradiol had an AUC of 0.88 with sensitivity (88.6%) and specificity (85%) (Table7).

Table 1: Demographic and clinical data among studied patients

Variables	**Patients(n=100)**
Age (years) *Mean±SD* *(range)*	 33.3±7.5 (19 – 46)
BMI (kg/m^2) *Mean±SD* Underweight (<18.5) *N. (%)* Normal (18.5 – 24.9) *N. (%)* Overweight (25 – 29.9) *N. (%)* Obese (>30)	 21.8±4.7 18 (18%) 57 (57%) 9 (9%) 16 (16%)
Family history*N. (%)* Present Absent	 19 (19%) 81 (81%)

Table 2: Tumor pathology findings among studied patients

Variables		**Patients (n=100)** *N. (%)*
Tumor grade	Grade 1 Grade 2 Grade 3 Grade 4	0 (0%) 43 (43%) 45 (45%) 12 (12%)
Tumor stage	T1 T2 T3 T4	9 (9%) 49 (49%) 32 (32%) 10 (10%)
N-Stage	N0 N1 N2 N3	0 (0%) 33 (33%) 50 (50%) 17 (17%)

ER	Negative Positive	25 (25%) 75 (75%)
PR	Negative Positive	45 (45%) 55 (55%)
HER2	Negative Positive	79 (79%) 21 (21%)
Ki67	<10% 10 - 20% 20 – 30% 30 – 40% >40%	24 (24%) 38 (38%) 13 (13%) 17 (17%) 8 (8%)

Table 3: Clinical data, post-chemotherapy menopausal symptoms, and neuropathy among studied patients

Variables		**Patients (n=100)***N. (%)*
Clinical data		
Type of chemotherapy	4AC (4AC +12 Taxol) (4AC+ 4Taxol) (DD)	23 (23%) 62 (62%) 15 (15%)
Target therapy	None Herceptin	79 (79%) 21(21%)
Post-chemotherapy menopausal symptoms		
Menstrual pattern Amenorrhea Irregular menses Ongoing menses		 77 (77%) 14 (14%) 9 (9%)
Flushing		80 (80%)
Headache		60 (60%)
Post-chemotherapy neuropathy		
Present	Grade 1	26 (26%)
	Grade 2	14 (14%)
	Grade 3	10 (10%)
Absent		50 (50%)

Table 4: Baseline and post-chemotherapy hormonal profile

	Hormonal profile		**P-value**
	Baseline	**Post-chemotherapy**	
Estradiol	126.79 ± 54.74 (51.8 – 308)	99.5 ±29.29 (50 - 150)	**0.002**
FSH	9.26 ±4.34 (2 – 20.5)	13.28 ±4.74 (6.1 – 21.5)	**<0.001**
LH	11.99 ± 12.4 (1 – 61.6)	13.16 ± 11.66 (5 – 61)	**0.03**
AMH	2.97 ±1.94 (1.2 – 8.9)	0.47 ±0.74 (0.04 – 3)	**<0.001**
Wilcoxn-rank test, P-value >0.05 Non-Significant; ≤ 0.05 Significant.			

Table 5: Correlation between baseline AMH with age and BMI

Variable	AMH	
	R	**P**
Age	-0.22	0.324
BMI	-0.95	**<0.001**

Table 6: Post-chemotherapy hormonal levels in relation to menstrual pattern

	Menstrual pattern			P-value
	Ongoing menses(n=9)	**Irregular menses(n=14)**	**Amenorrhea(n=77)**	
Estradiol	133.5 ± 0.71 (133 – 134)	97 ± 39.8 (51 – 120)	95.9 ± 27.7 (50 – 150)	**0.009**
FSH	10.1 ± 2.76 (8.1 – 12)	9.37 ± 3 (6.1 – 12)	14.35 ± 4.7 (7 – 21.5)	0.201
LH	11.2 ± 1.7 (10 – 12.4)	8.47 ± 3.72 (5 – 12.4)	14.22 ± 13.1 (5 – 61)	0.395
AMH	2.5 ± 0.71 (2 – 3)	0.97 ± 0.15 (0.8 – 1.1)	0.14 ±0.09 (0.04 – 0.4)	**0.003**

*Kruskal-Wallis's test, Non-Significant: P >0.05, Significant: P ≤0.05

Table 7: ROC analysis of Estradiol and AMH to discriminate between patients with and without menses

	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC
Estradiol	**99**	88.6%	85%	83.94%	90.48%	0.88
AMH	**1.1**	94.3%	90%	89.19%	94.74%	0.94

DISCUSSION

Around 20% of all new BC diagnoses occur before the age of 45 years. These people are prone to experiencing CTh-related ovarian impairment [9].

In examining infertility, AMH, estradiol, inhibin B, FSH, and LH have often been investigated as biomarkers of ovarian function in CTh-treated women [10].

In addition, it has been proposed that these biomarkers can predict ovarian function restoration in individuals planning for adjuvant endocrine treatment following CTh. Several investigations have found links between pre-CTh concentrations of these markers and the recovery of menstruation in BC cases [11].

However, there has been limited reporting on quantifiable biomarkers in this cohort after treatment. Biomarker values obtained after CTh could indicate alterations to ovarian function that differ from biomarker values assessed before any local or systemic therapy at the time of diagnosis. Biomarkers upon diagnosis represent the case's intrinsic follicle reservoir, whereas post-CTh values may define the exact follicle reserve following gonadotoxic treatment [12].

This study aimed to evaluate CIOF using serum AMH in premenopausal cancer cases.The current study showed mean age among studied patients was 33.3 years ± 7.5SD, a mean BMI of 21.8 kg/m2 ± 4.7 SD, 57% of patients were within normal ranges according to BMI, 18% were underweight, 16% were obese. A positive family history of breast cancer was identified in 19% of the studied patients. A significant negative relationship existed between baseline AMH and BMI (r=0.57, P<0.001). Park et al. [13]reported as body mass index (BMI) increased, AMH concentrations dropped; those who were overweight had substantially lower AMH levels than those who were underweight or normal. Research suggests that a higher body mass index (BMI) is associated with a decrease in folliculogenesis and lends credence to the idea that obesity can affect the follicular environment. Obese people may have different AMH concentrations because insulin resistance affects granulosa cells.

Potential lipotoxic effects on granulosa cells are also worth considering [14].Since adipokines like leptin and adiponectin participate in reproduction through the hypothalamic-pituitary-ovarian axis, it is plausible that they modulate ovarian function. Park et al. [13]

The granulosa cells of the ovaries also contain leptin and adiponectin receptors [15].Another theory is that people who are overweight may have altered metabolism, storage, and clearance of AMH[14].Although these findings point to an effect of obesity on AMH levels, it is not yet known whether this is because of changes in granulosa cell malfunction, follicular physiology, or follicle number.

Kim et al. [16] showed that at enrollment, cases had a mean age of 40.8±3.8 years, 29% of cases were diagnosed with advanced disease, 47.5% of cases tested positive for nodes, 51.2% of cases had 4 cycles of cyclophosphamide and doxorubicin, and 15.8% of cases got six rounds of combined doxorubicin and docetaxel without cyclophosphamide.

Regarding age, Romito et al. [5] study they demonstrated a varied CTh effect for each age range. Older women showed a lower decline than younger women. The reduced baseline AMH values in older cases most likely explain this impact. Serum concentrations of AMH progressively fall with time, even in healthy women (5.6% annually). Pre-treatment counseling for these cases is essential to advise them of the probable fertility decline. Clinicians should tell women with pregnancy desires about fertility-preserving options that could be adopted before beginning BC therapy [17].

Several research investigations have reported the relationship between chemotherapy-induced amenorrhea (CIA) and improved prognosis irrespective of HR status and cases with HR+ malignancies exclusively [18]. Previous reports revealed a survival improvement independent of the HR status [19].

In the current study, most of the studied patients (62%) received (4 AC + 12 Taxolweakly) while 15% received dose-dense (4AC+4 Taxol), and 23% had (4AC) alone. Twenty-onepercent received Herceptin, 77% of the studied patients had amenorrhea, 14% had irregular menses,and 9% had ongoing menses. Flushing was evident in 80% of patients, and headache in 60% of the studied patients.

The incidences of CIA and CIOF matched reported information, giving rates of 53% to 89% with poly-CTh [18,20]. Variations between CIOF and CIA are because cessation of menses may not always reflect real ovarian impairment since levels of estrogen might stay in a premenopausal range even after >1 year on CIA [21].

This study detected a significant difference between baseline and post-CTh hormonal biomarkers ($P < 0.05$), as the mean of estradiol levels significantly decreased from (126.79 ± 54.74) to (99.5 ±29.29) post-chemotherapy ($P=0.002$). In contrast, FSH and LH levels increased dramatically from 9.26 ±4.34 and 11.99 ± 12.4 up to 11.99 ± 12.4 and 13.16 ± 11.66, respectively($p<0.05$). AMH levels reduced significantly from 2.97 ±1.94 to 0.47 ±0.74 post-chemotherapy ($p<0.001$). Additionally, there was a statistically significant difference in estradiol concentrations among different menstrual patterns, as it was the highest among patients with ongoing menses (133.5 ± 0.71) and the lowest (95.9 ± 27.7) among patients with amenorrhea ($P=0.009$). Similarly, AMH level was higher among patients with ongoing menses (2.5 ± 0.71) in comparison to patients with irregular menses (0.97 ± 0.15) and patients with amenorrhea (0.14 ±0.09) with a significant difference between the 3 groups ($P=0.003$). As regards FSH level, it was lower among patients with ongoing menses (10.1 ± 2.76) in comparison to patients with amenorrhea (14.35 ± 4.7), although this difference was not significant ($P>0.05$). Also, LH levels were lower among patients with ongoing menses (11.2 ± 1.7) in comparison to patients with amenorrhea (14.22 ± 13.1), although this difference was not significant ($P >0.05$).

According to Jacobson et al. [22] and Vriens et al. [23], it is generally documented that age influences the prediction of premature ovarian insufficiency (POI). Still, according to Torino et al. [24], the significance of biochemical

indicators has been uncertain. Krekow et al. [25] showed that women with ovarian recovery did not reveal differences in FSH levels. Chai et al. [26] have previously proposed that high-sensitivity AMH tests could be useful in this context. Anderson et al. [27] conducted a more extensive analysis utilizing a larger independent cohort of women to investigate the usefulness of post-CTh AMH as a predictor of subsequent POI. Despite considering a threshold value for FSH in the categorization of POI, AMH exceeded FSH.

In this study, the ROC curve was conducted to discriminate between patients with and without menses; AMH gave AUC 0.94 with sensitivity (94.3%) and specificity (90%), while estradiol AUC was 0.88 with sensitivity (88.6%) and specificity (85%).

Analysis of AMH as a POI diagnostic marker 24 months after diagnosis revealed much higher accuracy than in an earlier study in cases receiving treatment for BC when AMH was assessed employing a reduced sensitivity test [28].

The menstrual and hormonal alterations of menopause have been thoroughly studied in normal cases, but that classification notably excludes individuals treated with CTh [29]. The choice of hormonal drug after CTh is determined by menopausal condition.

Kim et al. [16] reported that age dichotomized at 40 years exhibited 30.8% sensitivity, 87.5% specificity, and 38.3% accuracy (P=0.420) in predicting menstruation improvement. Estradiol exhibited an 11.55% sensitivity, specificity, and 100% positive predictive value but with 23.3% accuracy (P=0.585). AMH demonstrated 92.3% sensitivity, 50.0% specificity, 92.3% positive predictive value, and 86.7% accuracy. Regarding predicting ovarian function recovery, AMH outperformed age and estradiol (P=0.008).

Inconsistent with our research, Henry et al. [30] showed that in 59 individuals treated with AI, post-CTh AMH was ineffective for predicting ovarian function restoration. However, we assumed that the major contributor to this discrepancy in results was low, undetectable levels of AMH induced by the inclusion of older cases in the previously described study because concentrations of AMH naturally fall with the aging condition [31].

In contrast, recent investigations utilizing high-sensitivity tests effectively established the predictive value of AMH concentration. In the Chai et al. [26] study, AMH concentrations assessed two years after diagnosis demonstrated 96% sensitivity in predicting menstrual recovery for the next three years. Additionally, Anderson et al. [27] reported that AMH levels at the end of CT revealed 84% sensitivity in predicting early ovarian insufficiency at 2 years. Our recommendation is a long-term evaluation of ovarian function recovery using (AMH) as a sensitive biomarker in addition to (Estradiol, FSH, and LH). Furlanetto et al. [32] showed that CIOF following therapy was linked to improved disease-free survival, particularly in individuals aged <30 years or with HR+ disease. CIA was related to better outcomes. Each 10-unit rise in FSH levels was correlated with a steady increase in disease-free survival.

Conclusion

Serum AMH is a sensitive prediction biomarker to ovarian failure induced by chemotherapy in comparison with FSH, LH, and Estradiol levels. This study recommended long-term evaluation of ovarian function recovery using (AMH) as a sensitive biomarker in addition to (Estradiol, FSH, LH). Further studies with large sample sizes produce significant results. Additional prospective randomized studies should be performed to confirm our results. Further assessment of the relation between obesity and ovarian dysfunction.

Conflict of interest

The authors declared that they have no conflicts of interest with respect to the authorship and/ or publication of this article.

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REFERENCES

1. **Martin HL, Ullah S, Abbas N, Scott‐Hoy A, Kichenadasse G, Karapetis CS, et al.** Predicting chemotherapy‐induced menopause using baseline and post‐chemotherapy anti‐Müllerian hormone levels: Results of a pilot study. *Cancer Rep* (Hoboken). 2021;4:e1342.
2. **Cioffi R, Mangili G, Sarais V, Cervini L, Longo**

V, Bergamini A, et al. Do stage and grade of malignancy impact fertility preservation in breast cancer patients? *J Gynecol Obstet Hum Reprod*. 2021; 50:102215.

3. **Anderson RA, Kelsey TW, Perdrix A, Olympios N, Duhamel O, Lambertini M, et al**. Diagnostic and predictive accuracy of anti-mullerian hormone for ovarian function after chemotherapy in premenopausal women with early breast cancer. *Breast Cancer Res Treat*. 2022; 192:273–82.
4. **Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, et al.** The physiology and clinical utility of anti-Mullerian hormone in women. *Hum Reprod* Update. 2014; 20:370–85.
5. **Romito A, Bove S, Romito I, Zace D, Raimondo I, Fragomeni SM, et al**. Ovarian Reserve after Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. *J Pers Med*. 2021; 11:704.
6. **Sharma R.** Breast cancer burden in Africa: evidence from GLOBOCAN 2018. *J Public Health* (Oxf). 2021; 43:763–71.
7. Anderson RA, Cui W. Improving analysis of ovarian function and female fertility in cancer survivors. *Fertil Steril*. 2022; 117:1057–8.
8. **Iwase A, Hasegawa Y, Tsukui Y, Kobayashi M, Hiraishi H, Nakazato T, et al.** Anti-Müllerian hormone beyond an ovarian reserve marker: the relationship with the physiology and pathology in the life-long follicle development. *Front Endocrinol* [Internet]. 2023 [cited 2024 Apr 9];14. Available from: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2023.1273966/full
9. **Pedersen RN, Esen BÖ, Mellemkjær L, Christiansen P, Ejlertsen B, Lash TL, et al**. The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis. *J Natl Cancer Inst*. 2022; 114:391–9.
10. **Li N, Rowley SM, Thompson ER, McInerny S, Devereux L, Amarasinghe KC, et al.** Evaluating the breast cancer predisposition role of rare variants in genes associated with low-penetrance breast cancer risk SNPs. *Breast Cancer Res*. 2018; 20:3.
11. **Xu H, Zhang M, Zhang H, Alpadi K, Wang L, Li R, et al.** Clinical Applications of Serum Anti-Müllerian Hormone Measurements in Both Males and Females: An Update. *Innovation*. 2021; 2:100091.
12. Silvestris E, Dellino M, Cafforio P, Paradiso AV, Cormio G, D'Oronzo S. Breast cancer: an update on treatment-related infertility. *J Cancer Res Clin Oncol*. 2020; 146:647–57.
13. **Park HT, Cho GJ, Ahn KH, Shin JH, Kim YT, Hur JY, et al.** Association of insulin resistance with anti-Mullerian hormone levels in women without polycystic ovary syndrome (PCOS). *Clin Endocrinol* (Oxf). 2010;72(1):26-31.
14. Tal R, Seifer DB. Potential mechanisms for racial and ethnic differences in antimüllerian hormone and ovarian reserve. *Int J Endocrinol*. 2013; 2013:818912.
15. **Merhi Z, Buyuk E, Berger DS, Zapantis A, Israel DD, Chua S Jr, et al**. Leptin suppresses anti-Mullerian hormone gene expression through the JAK2/STAT3 pathway in luteinized granulosa cells of women undergoing IVF. *Hum Reprod*. 2013;28(6):1661-9.
16. **Kim H-A, Choi J, Park CS, Seong M-K, Hong S-E, Kim J-S, et al**. Post-chemotherapy serum anti-Müllerian hormone level predicts ovarian function recovery. *Endocr Connect*. 2018; 7:949–56.
17. **Api M.** Is ovarian reserve diminished after laparoscopic ovarian drilling? *Gynecol Endocrinol*. 2009; 25:159–65.
18. **Zhao J, Liu J, Chen K, Li S, Wang Y, Yang Y, et al.** What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis. *Breast Cancer Res Treat*. 2014; 145:113–28.
19. **Swain SM, Jeong J-H, Geyer CE, Costantino JP, Pajon ER, Fehrenbacher L, et al.** Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med*. 2010; 362:2053–65.
20. **Zavos A, Valachis A.** Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. *Acta Oncol*. 2016; 55:664–70.
21. **Braverman AS, Sawhney H, Tendler A, Patel N, Rao S, El-Tamer M, et al**. Serum estradiol above the postmenopausal level after chemotherapy-induced amenorrhea in breast cancer patients. *Clin Pract*. 2006; 3:609.
22. **Jacobson MH, Mertens AC, Spencer JB, Manatunga AK, Howards PP**. Menses resumption after cancer treatment-induced amenorrhea occurs early or not at all. *Fertil Steril*. 2016; 105:765-72.e4.
23. **Vriens IJH, De Bie AJR, Aarts MJB, de Boer M, van Hellemond IEG, Roijen JHE, et al.** The correlation of age with chemotherapy-induced ovarian function failure in breast cancer patients. *Oncotarget*. 2017;8:11372–9.
24. **Torino F, Barnabei A, De Vecchis L, Sini V, Schittulli F, Marchetti P, et al.** Chemotherapy-induced ovarian toxicity in patients affected by endocrine-responsive early breast cancer. *Crit Rev Oncol Hematol*.2014; 89:27–42.
25. **Krekow LK, Hellerstedt BA, Collea RP, Papish S, Diggikar SM, Resta R, et al**. Incidence and Predictive Factors for Recovery of Ovarian Function in Amenorrheic Women in Their 40s Treated with Letrozole. *J Clin Oncol*. 2016;34:1594–600.
26. **Chai J, Howie AF, Cameron DA, Anderson RA. A** highly-sensitive anti-Müllerian hormone assay improves analysis of ovarian function following chemotherapy for early breast cancer. *Eur J Cancer*. 2014; 50:2367–74.
27. **Anderson RA, Mansi J, Coleman RE, Adamson DJA, Leonard RCF.** The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early

breast cancer. *Eur J Cancer*. 2017; 87:58–64.

28. **Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al.** Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA*. 2011; 306:269–76.
29. **Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al.** Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol*. 2011; 29:2334–41.
30. **Henry NL, Xia R, Schott AF, McConnell D, Banerjee M, Hayes DF.** Prediction of postchemotherapy ovarian function using markers of ovarian reserve. *Oncologist*. 2014; 19:68–74.
31. **Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al.** Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients with Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. *J Clin Oncol*. 2018; 36:1981–90.
32. **Furlanetto J, Marmé F, Seiler S, Thode C, Untch M, Schmatloch S, et al**. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials. *Eur J Cancer*. 2021; 152:193-203

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