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Ovarian Function Preservation in Premenopausal Cancer Patients on Chemotherapy

*** Rana Mohamed Reda Mahmoud[1], Mostafa Mohamed Abdelhakiem[1], Mohamed Mofreh Mohamed Salem[2], Mohamed Awad Ebrahim[1]**

1Department of Medical Oncology, 2Department of Clinical Pathology,
Faculty of Medicine, Mansoura University, Egypt

***Corresponding author:** Rana Mohamed Reda Mahmoud, **Email: ranamohamedreda29@gmail.com, Tel:** +20 10 93192871

ABSTRACT

Background: Cancer therapies can negatively affect ovarian function, making fertility preservation a key concern for young patients. Gonadotropin-releasing hormone agonists (GnRHa) provide a non-surgical option for women who are unable to pursue or decline other fertility preservation techniques.

Objectives: This study aimed to evaluate the impact of using GnRHa alongside chemotherapy in breast cancer patients of childbearing age.

Patients and methods: This retrospective cohort study was conducted at the Oncology Center Mansoura University (OCMU). It included 30 patients with breast cancer. All participants underwent detailed medical history, physical examinations, and a range of laboratory and radiological investigations. Pathological assessments included evaluating ER, PR, Her-2neu status, Ki67, and FSH/E2 levels.

Results: Of the patients studied, 96% (26 of 27) regained regular menstruation, with 16 cases resuming menses within six months of chemotherapy. Three patients had unknown data due to hormonal pill use. One 45-year-old patient experienced amenorrhea with postmenopausal FSH and E2 levels. Two out of nine patients (22.2%) who tried to conceive achieved a full-term pregnancy. The 24 patients (80%) who did not conceive cited various reasons including being unmarried (16.6%), having completed their family (54.1%), local recurrence (12.5%), distant metastasis (4.1%), and actively seeking fertility (12.5%).

Conclusion: Using GnRHa with chemotherapy appears beneficial for fertility preservation, although efficacy varies with cancer type, treatment, and individual patient factors. This highlighted GnRHa's role in mitigating chemotherapy-induced ovarian toxicity, particularly in patients on high-infertility-risk regimens.

Keywords: Premenopausal cancer, Ovarian function, Chemotherapy, Gonadotropin-releasing hormone.

INTRODUCTION

The potential for treatment-induced gonadotoxicity is a significant concern for premenopausal women undergoing anticancer therapies [(1)]. The resulting premature ovarian insufficiency (POI) and infertility are a major concern to several patients, deeply affecting their family planning and psychological well-being. Therefore, clinical efforts to mitigate such adverse effects are crucial. The malignancies most frequently diagnosed in premenopausal women that are connected to a high risk of these side effects are breast, gynecological, and hematological cancers, which often necessitate the use of alkylating agents and other gonadotoxic chemotherapies [(2, 3)]. The risk of ovarian damage is a significant factor in the long-term survivorship of these patients.

Current clinical guidelines uniformly recommend that proper onco-fertility counseling be offered to all premenopausal women, irrespective of their specific disease type or stage. This counseling should be a multidisciplinary effort, involving oncologists, reproductive endocrinologists, and social workers, to provide comprehensive information. During these consultations, patients should be proactively informed about their specific risk of developing premature ovarian insufficiency (POI) from a proposed treatment regimen. They must also be educated on the available and time-sensitive strategies to counteract this significant side effect [(4)]. This empowers them to make informed decisions about their reproductive health.

The long-term effects of estrogen deficiency, resulting from an early loss of ovarian function, can profoundly impact the quality of life and overall health of these patients, which should not be underestimated. This deficiency can predispose individuals to various chronic health complications, including accelerated bone mineral density loss, an increased risk of cardiovascular disease, and potential cognitive or psychological sequelae. Consequently, it is imperative for clinicians engaged in cancer care to engage in a thorough and sensitive discussion of the POI risk as well as the importance of preserving ovarian function for long-term physical and mental well-being [(5)].

The cryopreservation of oocytes, embryos, or ovarian tissue represents a suite of established and standard strategies for fertility preservation in young women who are interested in future family planning [(6)]. Oocyte and embryo cryopreservation are widely utilized, often requiring a delay in chemotherapy initiation for ovarian stimulation. In contrast, ovarian tissue cryopreservation is a surgical procedure that can be performed without a significant delay in cancer treatment. These methods, while effective, often have associated costs and invasiveness that can influence patient choice.

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In the context of ovarian function preservation, the only recommended medical treatment involves the administration of a gonadotropin-releasing hormone agonist (GnRHa) during the chemotherapy cycle. This strategy was developed as a less invasive option to potentially reduce the risk of gonadotoxicity, with the goal of protecting the ovarian reserve and preventing the negative consequences of POI in premenopausal women receiving cytotoxic therapy [7]. The proposed mechanism is that GnRHa induces a hypogonadotropic state, which places the ovaries in a quiescent, pre-pubertal-like state, making them less susceptible to chemotherapy-induced damage.

As recently demonstrated in the prospective PREFER study, there is a notable disparity in the uptake of these strategies. While less than 20% of young women diagnosed with breast cancer before the age of 40 years decided to undergo invasive cryopreservation strategies for fertility preservation, a considerably higher proportion—more than 90% of them—accepted the less invasive use of GnRHa during their chemotherapy regimen [8]. This finding highlights the practical and logistical barriers that influence patient decisions regarding fertility preservation.

Gonadotropin-releasing hormone agonists are medications utilized to downregulate both gonadotropin and sex hormone levels. They are commonly employed to reduce sex hormone levels in the treatment of hormone-sensitive cancers such as breast and prostate cancers **[9]**. With a higher receptor affinity and reduced susceptibility to enzymatic degradation, GnRH agonists are significantly more potent than the natural GnRH molecule because of their higher receptor affinity and resistance to enzymatic breakdown.

These agents work by first binding to GnRH receptors on pituitary cells, causing a temporary surge in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). However, within about a week of continuous use, the GnRH receptors become desensitized and downregulated. This leads to a significant and prolonged decrease in the pituitary's production of both LH and FSH [10].

The therapeutic role of GnRH analogues for ovarian preservation remains a highly debated topic in the scientific literature, characterized by conflicting evidence and heterogeneous data. The persistent debate regarding chemotherapy-induced ovarian function loss is in part due to the lack of a standardized definition of premature ovarian failure. This is often complicated by a reliance on the resumption of menses as a primary and potentially inadequate indicator of ovarian function. Additional contributing factors to these conflicting findings include variations in study populations, diverse chemotherapy regimens, and insufficient long-term follow-up data on reproductive outcomes and live birth rates [11].

This study aimed to evaluate role of using gonadotropin releasing hormone agonists concurrent with chemotherapy in female patients in child bearing period.

PATIENT AND METHODS

Study Design: This is a retrospective study carried out at Oncology Center Mansoura University (OCMU) on adult female Egyptian patients with breast cancer. Data were collected from registered patients fulfilling the protocol eligibility criteria.

Eligibility criteria: The current study included female patients at childbearing period with pathological proven cancer with curable intent and had regular menses.

Exclusion criteria: Cases with Oophorectomy, metastatic breast cancer, postmenopausal female patient and double malignancy.

Study procedures: All patients were subjected to detailed history taking including age, menopausal status, family history; symptoms of metastatic disease e.g., bone aches. Physical examination was conducted to assess breast mass, cervical lymph nodes, axillary lymph nodes and liver. Routine laboratory investigations also was performed, which included CBC, chemistry profile (SGPT, SGOT, serum bilirubin, serum albumin, serum creatinine and alkaline phosphatase), Tumor markers (CEA & CA15-3) and serology (HCV, HBV & HIV), Radiological investigations included bilateral sono-mamography, CT chest, abdomen and pelvis, PET/CT. Bone scan were conducted. Pathological evaluation included assessment of ER, PR, Her-2neustatus and Ki67 on pathology specimen and FSH/E2 level.

Sample size calculation: After revision of system in period from 2018 to 2022, average of premenopausal cancer patients 30 per year, 20% of them had incomplete data on system so sample size was 30.

Endpoints: Return of menses.

Ethical consideration: The study protocol was approved by The Institutional Review Board (IRB) of Mansoura University prior to its commencement. Subsequent approval was also secured from the administrative body of the hospital where the research was conducted. Throughout all phases of the study, the confidentiality and personal privacy of all participants were stringently respected, and the collected data were not utilized for any purpose beyond the scope of this investigation. The entire study was executed in strict adherence to the ethical principles outlined in the Declaration of Helsinki. All participants signed informed consents.

Statistical analysis

All data were analyzed using **SPSS© for Windows release 21**. Statistical significance was set at a two-tailed p-value of < 0.05. For qualitative variables, descriptive statistics were calculated using frequency distributions, reporting the number of cases and percentages.

For quantitative variables, central tendency and dispersion were described using the mean and standard deviation for normally distributed data, and the median and range for non-parametric data.

The Chi-square test was used to determine the association between categorical variables. When the test's assumptions were not met, Fisher's exact test was used instead. The independent-samples t-test was employed to compare the means of two distinct groups. Correlations between variables were assessed using Pearson's correlation coefficient for parametric data and Kendall's Tau non-parametric correlation coefficient for non-parametric data. Survival and progression-free survival were analyzed leveraging the Kaplan-Meier Product-Limit Estimator, with the Log-Rank Test deployed to compare survival curves across various groups.

RESULTS

This investigation was designed as a cohort study of breast cancer patients. All participants in this cohort received GnRHa concurrently with their systemic chemotherapy regimen. The inclusion criteria for the study dictated that all cases presented with an ECOG performance status of 0 and had a documented history of regular menses prior to the initiation of chemotherapy.

A) Patient characteristics:

Table (1) showed patient characteristics in the breast cohort (30 females). The median age was 36 years (range 28-45). Most patients were married (86.7%) versus unmarried (13.3%). BMI distribution was balanced across categories: Normal weight (6.7%), overweight (26.7%), and obese (66.7%). Reproductive history showed multigravida predominance (90.0%), followed by nulligravida (3.3%) and primigravida (6.7%), with similar parity patterns (multiparous 86.7%, nulliparous 3.3%, primiparous 10%). Current contraceptive use was reported by 86.7% of patients.

Comorbidities were rare, with 6.6% were hypertensive and 3.3% were diabetic patients. This cohort demonstrated the following distribution: HER2-enriched subtype (n=17/30, 56.7%), and TNBC (n=13/30, 43.3%). Lt side breast cancer was diagnosed in 60% of patients, while Rt side in 40%.

Table (1): Patient characteristics among breast group

Variable		N (%)
Age	Median age	36 (28-45)
Marital Status	Married	26(86.7%)
	Unmarried	4(13.3)
BMI Classification	Normal	2(6.7%)
	Overweight	8(26.7%)
	Obese	20(66.7%)
Early Menarche	Absent	17(56.7%)
	Present	13(43.3%)
Early Menopause	Absent	27(90.0%)
	Present	3(10.0%)
Gravidity	Nulligravida	1(3.3%)
	Primigravida	2(6.7%)
	Multigravida	27(90.0%)
Parity	Nulliparous	1(3.3%)
	Primiparous	3(10.0%)
	Multiparous	26(86.7%)
Contraception	Absent	4(13.3%)
	Present	26(86.7%)

B) Treatment patterns and clinical outcomes of breast cancer cases: Table (2) showed that 93.3% of patients received anthracycline-based chemotherapy, while a smaller proportion received non-anthracycline chemotherapy (6.7%). Novel therapies were employed in 100% of Her2 enriched cases, primarily involving Trustuzumab in preoperative and adjuvant setting by 64.7%, and Trustuzumab- Pertuzumab by 35.2%. One patient (n=1/13, 7.6%) received immune checkpoint inhibition with pembrolizumab. Breast conserving surgery was performed to 63.2% (n=19/30), while MRM was performed to 36.8% (n=11/30). Radiotherapy was delivered to 100% of patients (n=30/30), with no instances of ovarian irradiation. Overall, a pathological complete response (CR) was achieved in 35.7% of patients (n=10/30).

Table (2): Chemotherapy and response status among breast group

Variable		N (%)
Chemotherapy	Non-Anthracycline	2(6.7%)
	Anthracycline	28(93.3%)
Response status	pCR	10(35.7%)

C) Menstrual function and fertility outcomes: Regarding menstrual function recovery, 96% of patients resumed regular menstrual cycles (n=26/27), while 3.3% experienced amenorrhea with maintaining postmenopausal levels of follicle-stimulating hormone (FSH) and estradiol (E2) (n=4/59). Three cases were on adjuvant target therapy Trustuzumab-Pertuzumab at time of data analysis (n=3/30, 10%). Among those who regained menses, 65.5% resumed menstruation within 6 months (n=16/26), whereas 34.5% experienced a delayed return beyond 6 months (n=10/26). In terms of symptoms of premature ovarian failure (POF), 73.3% of patients reported no symptoms (n=22/30), while 26.7% experienced at least one symptom (n=8/30).

Reported POF-related symptoms included vaginal dryness, headaches, cardiovascular and neurological complaints, osteoporosis, mood instability, hot flashes, and decreased menstrual duration. Concerning fertility outcomes, 22.2% achieved pregnancy (n=2/9). Of those, 100% had full-term pregnancies. The 24 patients (80%) who did not conceive, the reasons included being unmarried (16.6%), having already completed their family (54.1%), experiencing local recurrence (12.5%), distant metastasis (4.1%) and actively seeking fertility (12.5%), as shown in table (3).

Table (3): Menstrual recovery and pregnancy among breast group

Variable		N (%)
Menstrual Function Recovery	Regular Menses	26(86.6%)
	unknown	3(10.0%)
	Amenorrhea	1(3.3%)
Return of Menses	≤ 6-months	16(65.5%)
	> 6-months	10(34.5%)
Pregnancy	No Pregnancy	25(96.1%)
	Pregnancy	2(22.2%)
Symptoms of Premature Ovarian Failure	Absent	22(73.3%)
	Present	8(26.7%)

DISCUSSION

Fertility preservation has increasingly become a critical consideration for younger patients undergoing cancer treatment. The primary concerns associated with chemotherapy in female cancer survivors include premature menopause and an elevated risk of subfertility [(12)]. Gonadotropin-releasing hormone agonists (GnRHa) bind effectively to the gonadotropin receptors in the pituitary, leading to a loss of these receptors, their downregulation, and desensitization within pituitary gonadotropic cells. As a result, the secretion of luteinizing hormone (LH) is suppressed, and the release of follicle-stimulating hormone (FSH) from the pituitary is inhibited. This cascade of events reduces estradiol synthesis in the ovaries, leading to lower circulating estrogen levels, which in turn inhibits the proliferation of hormone receptor-positive (HR+) tumors [(13)].

Although GnRHa has demonstrated effectiveness in preserving ovarian function, its role in fertility preservation remains inconclusive. Several studies argue that GnRHa should not be regarded as a substitute for established fertility preservation methods, such as oocyte cryopreservation [[14]]. Nonetheless, GnRHa may offer benefits for women who lack access to, decline, or are contraindicated for surgical fertility preservation options [(7)]. The administration of GnRHa injections concurrently with systemic treatment for breast cancer has been consistently shown to enhance fertility preservation outcomes. This therapeutic strategy is associated with an increased incidence of subsequent pregnancies and a decreased risk of premature ovarian insufficiency (POI). Conversely, the efficacy and utility of GnRHa in the treatment of other cancer types remain highly controversial within the clinical community. The current body of evidence is conflicting and limited, thus necessitating further rigorous clinical trials to comprehensively evaluate the benefits and risks of this approach in non-breast cancer malignancies [(15)].

The current study aimed to evaluate role of using GnRHa concurrent with chemotherapy in female patients in child bearing period with cancer of curable intent. This retrospective cohort study was conducted at Oncology Center Mansoura University (OCMU) through the period from (2018) to (2022), on 30 patients with breast cancer, all cases received Goserlin cotreatment with chemotherapy. The vast majority of cases regained regular menses (n=26/27, 96%), (n=16/26, 65.5%) of patients resumed menstruation within six months of chemotherapy, while the remaining (n=10/26, 34.5%) experienced delay after six months. One case (3.3%) had amenorrhea (failure to regain menses) with maintained postmenopausal level of FSH and E2, she was 45 years old. While, three (3/30, 10.0%) were on adjuvant target therapy Trustuzumab-Pertuzumab at time of data analysis. Spontaneous pregnancy documented for 22.2%, (n=2/9), with full term baby. The other cases who did not conceive (24 case, 80%) had the following data: 4.1% was single (n=1/24), 12.5% were divorced (n=3/24), 54.1% completed their family (n=13/24), 12.5% developed local recurrence (n=3/24), 4.1% developed metastasis (n=1/24), and 12.5% were seeking for fertility (n=3/24). These findings are Consistent with the findings of the randomized, controlled study by **Munster *et al.*** [(16)], which rigorously evaluated the use of the gonadotropin-releasing hormone (GnRH) analogue triptorelin to preserve ovarian function in women undergoing chemotherapy for early-stage breast cancer. It was reported that menstrual function was resumed in 88% of

patients (23 out of 26) within the GnRH analogue group. This recovery occurred after a median duration of 5.8 months, with a range extending from 1 to 19 months, following the completion of the cytotoxic treatment regimen. However, a notable finding was that despite the high rate of menstrual recovery, no pregnancies were reported among the patients in this specific study group, a result that highlights the complexities of translating ovarian function preservation into successful reproductive outcomes.

In the same line, the meta-analysis conducted by **Wong *et al.*** [17], which aimed to assess whether gonadotropin-releasing hormone analogue (GnRHa) cotreatment during chemotherapy for breast cancer preserves ovarian function. It was reported that the rate of spontaneous menstruation resumption was significantly higher in the GnRHa cotreatment group. This study's findings also led to the conclusion that the administration of a gonadotropin-releasing hormone agonist (GnRHa) concurrently with chemotherapy may be a beneficial strategy. This approach appears to be effective in preserving future fertility and protecting ovarian function in women undergoing treatment with gonadotoxic chemotherapeutic agents.

In the study by **Wong *et al.*** [17], it was reported that 104/125 (84%) resumed menstruation with a median time to menstrual recovery of 6 months (range: 1–43 months) after the last goserelin injection. Of the 125 assessable patients, nearly 57 (46%) expressed interest in becoming pregnant. Among those, 42 patients (74% of those interested) attempted pregnancy, and 66.6% successfully conceived spontaneously (n=28/42), and 4.7% used assisted fertility with donor eggs (n=2/42).

In a meta-analysis conducted by **Yuan *et al.*** [18], which aimed to evaluate the effects of gonadotropin-releasing hormone agonists (GnRHas) on various reproductive outcomes in premenopausal breast cancer patients undergoing gonadotoxic chemotherapy. It was reported that the combination of GnRHa and chemotherapy significantly increased pregnancy rates compared to chemotherapy administered as a monotherapy. Furthermore, this combined approach demonstrably reduced the overall incidence of premature ovarian failure (POF). Regarding the secondary endpoints, the GnRHa group exhibited significantly improved rates of menstrual recovery and a lower incidence of amenorrhea, a key indicator of ovarian function, in the 1-2 year follow-up period after the completion of chemotherapy.

In a corroborating meta-analysis, **Chen *et al.*** [19] aimed to comprehensively assess the efficacy and safety of GnRH analogues administered either before or concurrently with chemotherapy to prevent chemotherapy-induced ovarian damage in a diverse population of premenopausal women with both malignant and non-malignant conditions. Their pooled analysis revealed a marked difference in reproductive outcomes. The incidence of menstruation recovery or maintenance was found to be 74.5% (178 out of 239) in the GnRH agonist plus chemotherapy group, a substantially higher rate compared to the 50.0% (110 out of 221) observed in the control group. The analysis also showed that pregnancy rates in the case group were 9% (32 out of 356), which was higher than the 6.3% (22 out of 347) reported in the control group, suggesting a clinically meaningful benefit.

These findings are further substantiated by a substantial body of evidence from multiple independent clinical trials and meta-analyses. The collective data consistently demonstrate that premenopausal women who received ovarian function suppression via gonadotropin-releasing hormone agonists concurrently with chemotherapy were significantly less likely to experience ovarian failure. This protective effect was also associated with substantially higher rates of menstrual resumption when compared to a control cohort that did not receive such medical treatment [20]. The consistent nature of these results across various studies reinforces the clinical utility of GnRHa as a viable strategy for ovarian preservation in this vulnerable patient population.

CONCLUSION

The current study concluded that all patients received GnRH agonists during chemotherapy, demonstrated a high rate of menstrual recovery (96.2%) post-treatment, and 22.2% successfully achieved spontaneous pregnancy (n=2/9). This further supports the role of GnRH agonists in mitigating chemotherapy-induced ovarian toxicity, particularly in patients undergoing chemotherapy regimens that are commonly associated with a high risk of infertility. Overall, the use of gonadotropin-releasing hormone agonists administered concurrently with cytotoxic chemotherapy appeared to be a beneficial strategy for preserving fertility in a significant number of patients. While the evidence suggests a clear advantage, its specific efficacy is subject to considerable variability, which is dependent on a confluence of factors including the type of cancer, the specific treatment regimen employed, and individual patient characteristics such as age and baseline ovarian reserve. However further research with larger scales, and longer follow-up is necessary to fully validate our findings.

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