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Research Article

# Reproductive and Psychological Issues in Non-Gynaecological Cancer Survivors of Mongolia

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**Received:** December 05, 2022; **Published:** December 26, 2022

## Abstract

**Introduction:** One of the long-term effects of chemotherapy in young adults who have had cancer is impaired fertility. Due to the infertility and fear of having cancer again may develop depression and anxiety.

**Objective:** To determine the psychological and reproductive status of women with non-gynecological cancer patients who underwent chemotherapy.

**Materials and Methods:** An observational, descriptive, cross-sectional study was conducted in patients who finished chemotherapy from 2017 to 2021 at Mongolian National Cancer center. Patients were asked for general demographic, reproductive history, menstrual cycle questionnaire, chemotherapy related questionnaire as well as WHO-QOL, HADS questionnaire. To assess the psychological issues healthy, normal menstrual cycled women were asked to give WHOQOL-BREF questionnaire, HADS questionnaire, as well. Women were asked to re-visit the hospital for the purpose of investigating ovarian function, and were subjected to physical examination, AMH measurement and ultrasound examination. Statistical analysis was done using SPSS26.

**Results:** The average chemotherapy cycle of the non-gynecological cancer patients were 9.91 ± 6.8 times. Gonadotoxic agents were used in 63.64%, low risk chemo-agents were used in 36.36%. The post chemotherapy ovarian median volume was 3.2 ± 3.1 cm on the right and 2.52 ± 1.9 cm on the left, which is relatively close to healthy women, but with a high standard deviation. The number of antral follicles were 1.23 ± 1.3, indicating a marked decrease in ovarian reserve. The average value of anti-Mullerian hormone in the studied women was 0.49 ± 0.59 ng/ml, and the level of anti-Mullerian hormone gradually decreased with increasing frequency of chemotherapy. There was no statistically significant difference between the frequency of chemotherapy and AMH, but there was an inverse relationship between the frequency of chemotherapy and AMH ($r = -0.1$ $p = 0.63$). The physical health and psychological health related QOL were significantly reduced in cancer survivors in comparison to healthy women, while no difference was found in social and environmental QOL. Moreover, the prevalence and severity of anxiety and depression is higher among cancer survivors compared to healthy women.

**Conclusion:** The decrease of ovarian function is related to type and frequency of chemotherapy cycles. Cancer survivors have severe anxiety and depression, suggesting the necessity of appropriate psychological support.

***Keywords:*** *Non-Gynecological Cancer Survivors; AMH; Infertility; HADS; WHO-QOL*

## Abbreviations

AMH: Antimullerian Hormone; HADS: Hospital Anxiety and Depression Scale; WHOQOL-BREF: World Health Organization Quality of Life Brief; QOL: Quality of Life

## Introduction

Cancer is one of the real public health issues in many countries and is the second leading cause of mortality in Mongolia [1]. In terms of the age in which cancer is diagnosed, children and young adults usually refer to the age of 30 years. Commonly occuring tumors among children and young adults include leukemia, brain tumors, lymphoma, neuroblastoma, and Wilms' tumor [2]. In high-income countries, 80% of childhood cancers are cured due to the better access to treatment. But in low- and middle-income countries, 15 - 45% of tumors are cured [3]. In Mongolia, as of 2019, 200.1 people per 100,000 populations diagnosed with cancer [4]. As of 2019, a total of 20,913 people with cancer are living in Mongolia, of which 318 women aged 18 - 30 were newly diagnosed with cancer during 2016 - 2020. Common cancers among young women of reproductive age include cervical, ovarian, thyroid, breast, and liver cancers [1]. All types of chemotherapy, radiation, hormonal drugs, and surgery can affect fertility. Infertility has been reported to be the most severe late consequence of cancer treatment [5] and the most stressful issue for cancer survivors [6]. The concept of post-treatment infertility can be a source of anxiety and emotional distress during disease management [7].

Internationally, for example, the American Society of Clinical Oncology and the American Society of Reproductive Medicine recommend that women with cancer be presented with the possibility of preserving reproduction at the very beginning [8]. United Kingdom recommendations also include this type of advice [9]. Chemotherapy agents reduce ovarian reserve by causing oocyte destruction, direct damage to primordial follicles, accelerated primordial follicle activation, follicular atresia, stromal tissue damage, vascular damage, and inflammation [10]. Adverse drug reaction for ovaries, depending on the drug group.

Markers are used to determine the effect of cancer drugs on the ovaries. These include amenorrhea, early serum follicle-stimulating hormone (FSH) and estradiol (E2) levels, ultrasound antral follicle count (AFC) and serum anti-Müllerian hormone (AMH). It is convenient to use the vaginal probe to evaluate the ovaries with ultrasound. Determining the extent of ovarian dysfunction following cancer chemotherapy may provide an important role for further development of care in this area, in Mongolia.

## Aim of the Study

We aimed to investigate the effects of chemotherapy on ovarian function in non-reproductive tumors among women.

## Materials and Methods

### Study setting and design

This is an observational cross-sectional study and since there are few cases of cancer in young adults in Mongolia, we tried to enroll all the patients aging 18 - 35, who underwent chemotherapy during 2017 - 2021, at the Mongolian National Cancer Center (Figure 1). The main cancers were breast cancer and digestive organ cancer among young adults. In addition to these tumors, head and neck, lung, prostate, and soft tissue tumors were diagnosed. Alkylating agents and platinum-based drugs were highly gonadotoxic and anti-metabolites, vinca-alkaloids, anthracycline antibiotics were grouped as low risk chemotherapy.

### Source and study population

The study was conducted on a voluntary, informed consent basis. Questionnaire included demographic, reproductive, and chemotherapy data were collected from 30 cancer survivors. Quality of life was assessed using WHOQOL-BREF questionnaire (https://www.who.int/tools/whoqol/whoqol-bref) and the psychological status was assessed using HADS questionnaire (Figure 1).

However, only 22 women in a stable condition who could visit at the hospital were included in the study to check ovarian dysfunction. Physical condition, gynecological, ultrasound evaluation was performed during the examination.

### Data processing and analysis

Research indicators were graphically represented and tabulated using Microsoft Office softwares, and statistically analyzed by using SPSS 21 software. To analyze the relationship between chemotherapy and amenorrea, we use the Chi-square test. To compare the questionnaire results between groups the one-way ANOVA test was used.

## Results

### General information and ultrasound result

Totally 30 patients agreed to provide the questionnaire, and only 22 patients were able to visit the clinic to have the examination (Figure 1). The average age of the surveyed women was 32.09 ± 2.8, and the majority of them were married, 90.91% (20) (Table 1). Because Mongolian women marry early, the average number of pregnancies was 3 ± 1. The average number of births was 2 ± 1, the average age at first pregnancy was 21.32 ± 7.1, and the average age at last pregnancy was 25.77 ± 8.8.

The mean cycle days of mensraution before chemotherapy were 28 ± 1.5 days, and the mean menstrual days were 4.59 ± 1.4. Amenorrhea occurred in 10 (45.45%) women after chemotherapy, and in 12 (55.55%) women were still menstruating after chemotherapy, however the menstrual cycle changed to 31 ± 4.4 days, and the average menstrual period changed to 1.91 ± 1.2 days. The mean uterine size of the cancer survivors was 5.3 x 3.8 cm, and the endometrial thickness was 4.4 mm. The ovarian volume was 3.2 ± 3.1 cm on the right and 2.52 ± 1.9 cm on the left, which is relatively close to healthy women, but with a high standard deviation. The number of antralfollicles was 1.23 ± 1.3, which means that the ovarian reserve is clearly reduced.

| | Parameters | Mean ± St D |
|---|---|---|
| Demographic | Age | 32.09 ± 2.8 |
| | Marital status | |
| | Married | 90.91% (20) |
| | Unmarried | 9.09% (2) |
| Reproductive | Age at menarche | 13.6 ± 1.04 |
| | Pregnancy | 3 ± 1 |
| | Birth | 2 ± 1 |
| | Age at first pregnancy | 21.32 ± 7.1 |
| | Age at last pregnacy | 25.77 ± 8.8 |
| Menstrual cycle | Duration of menstrual cycle before chemotherapy | 28 ± 1.5 |
| | Duration of menstrual cycle after chemotherapy | 31 ± 4.4* |
| | Duration of menstraution before chemotherapy | 4.59 ± 1.4 |
| | Duration of menstruation after chemotherapy | 3.5 ± 1.8* |
| Ultrasound results | Uterine width | 3.8 ± 0.8 |
| | Uterine length | 5.3 ± 1.4 |
| | Thickness of endometrium | 0.44 ± 0.23 |
| | Volume of right ovary | 3.2 ± 3.1 |
| | Volume of left ovary | 2.52 ± 1.9 |
| | Antralfollicle number | 1.23 ± 1.3 |

***Table 1:*** *Demographic and reproductive characteristics of survivors.*

**P < 0.05, Chi-square analysis comparing the menstrual cycle.*

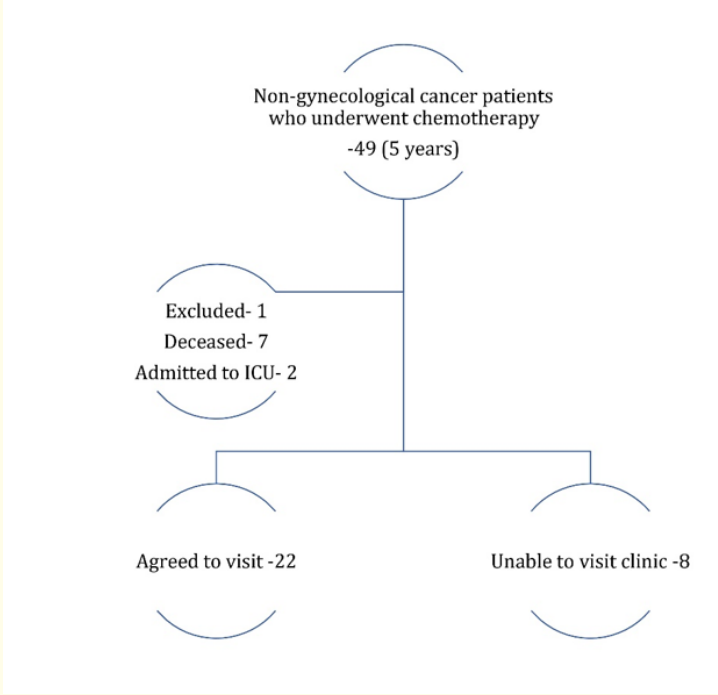


***Figure 1:*** *Participants.*

The average frequency of chemotherapy was 9.91 ± 6.8 for the women who participated in the study, and the maximum was 28 and the least was 3 cycle. Highly gonadotoxic agents were used in 63.64% (14), and 36.36% (8) received low-risk chemotherapy. Furthermore, 22.73% (5) were treated with a single drug, 40.91% (9) were treated with a combination of 2 drugs, and 36.36% (8) were treated with a combination of 3 drugs.

The mean frequency of chemotherapy in the women with amenorrhea was 11.3 ± 17, and 8.75 ± 6.5 in women without amenorrhea. Frequency of chemotherapy was not correlated with amenorrhea. The number of women with amenorrhea who received high-risk infertility chemotherapy was 6, compared to 4 women without amenorrhea. The number of women with amenorrhea who received chemotherapy with low risk of infertility was 8, compared to 4 women without amenorrhea. Chemicals with a high risk of infertility appear to be more likely to cause amenorrhea.

| Parameters | Participants | Amenorrhea | | P value |
|---|---|---|---|---|
| | | Yes | No | |
| Chemical drug combination | | | | |
| 1 drug combination | 22.73% (5) | 2 | 3 | 0.00 |
| 2 drugs combination | 40.91% (9) | 2 | 7 | 0.00 |
| 3 drugs combination | 36.36% (8) | 6 | 2 | 0.00 |
| Drug with high risk of infertility | 63.64% (14) | 6 | 4 | 0.00 |
| Drug with low risk of infertility | 36.36% (8) | 8 | 4 | 0.00 |
| Frequency of chemotherapy Mean ± St D | 9.91 ± 6.8 | 11.3 ± 17 | 8.75 ± 6.5 | 0.401 |

***Table 2:*** *Correlation between chemotherapy and amenorrhea.*

### AMH level post-chemotherapy

The average value of anti-Müllerian hormone in the studied women was 0.49 ± 0.59 ng/ml. There were inverse relationship between the frequency of chemotherapy and AMH (r = -0.1 p = 0.63; Figure 2A). As the frequency of chemotherapy increases, the level of antimüllerian hormone tends to decrease gradually (Figure 2B). Moreover, the median value gradually decreased with more chemical drug combinations (p = 0.52). There is a tendency to decrease AMH in women treated with high-risk chemotherapy compared to women treated with low-risk chemotherapy (P = 0.2; Figure 2C). There is no statistically significant difference between AMH level and menstrual status (Figure 2D), however the median of AMH is lower in amenorrheic group.

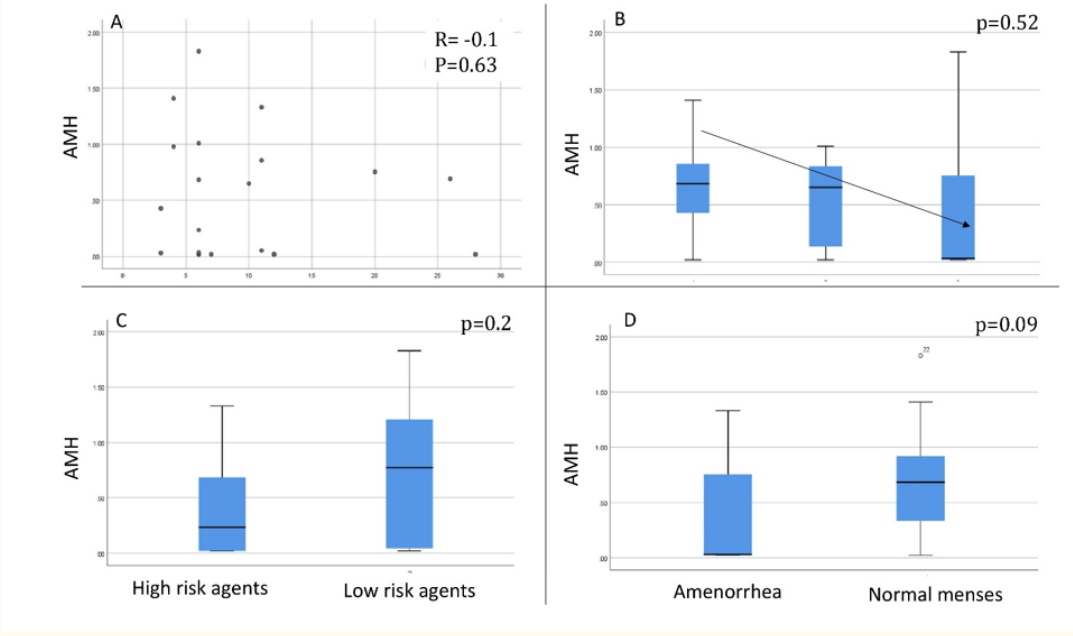


***Figure 2:*** *AMH and chemotherapy.*

### The results of the questionnaire for assessing the quality of life and psychological status

WHOQOL-BREF questionnaire was used to assess the quality of life of cancer survivors. The physical health and psychological health status of women affected by non-gynecological cancer were significantly reduced compared to healthy young women, while there was no difference in social and environmental status (Table 3).

Question 1 of the WHOQOL-BREF questionnaire is self-reported and assesses the wellness of life. The cancer survivors significantly lower than that of healthy women.

Compared with healthy women, the prevalence of anxiety and depression was significantly higher among cancer survivors, moreover the severity of anxiety and depression was higher in the cancer survivors.

## Discussion

Non-gynecological cancer survivors with young age have high risk of infertility and premature menopause. Current study is to evaluate the post chemotherapeutic patients' ovarian function and psychological issue. Main cancers of Mongolian young women are breast cancer and gastrointestinal cancers. Since anthracycline and taxane group chemotherapy are widely used in breast cancer, the people involved in our study used anthracycline, taxane, and alkylating drug group therapy. Thus, the loss of ovarian function is more common in women who have used alkylating agent group preparations, which is consistent with the findings of researchers from other countries [11].

| | Parameters | Mean ± Standard deviation | P value |
|---|---|---|---|
| WHO-QOL | **Physical Health** | | |
| | Cancer group | 49.5 ± 11.7 | 0.003 |
| | Healthy group | 58.9 ± 11.5 | |
| | **Psychological** | | |
| | Cancer group | 62.3 ± 11.9 | 0.003 |
| | Healthy group | 72.7 ± 13.6 | |
| | **Social** | | |
| | Cancer group | 62.5 ± 17.1 | 0.557 |
| | Healthy group | 68.8 ± 25.6 | |
| | **Environment** | | |
| | Cancer group | 59.2 ± 14.2 | 0.626 |
| | Healthy group | 57.5 ± 13.7 | |
| | **Wellness** | | |
| | Cancer group | 53.13 ± 16.6 | 0.001 |
| | Healthy group | 70.532 ± 0.7 | |
| Depression | Cancer group | 17.5 ± 7.8 | 0.01 |
| | Healthy group | 13.03 ± 6.3 | |
| Anxiety | Cancer group | 8.5 ± 5.0 | 0.00 |
| | Healthy group | 4.07 ± 2.4 | |

***Table 3:*** *Result of the life quality assessment questionnaire.*

Infertility occurs in children and young adults after chemotherapy [12]. The risk of amenorrhea after 70 - 80% and directly depends on the age of the woman. Ovarian reserve is a complex clinical phenomenon that depends on age, genetics, and environmental variables. After the age of 35, the ovarian reserves decrease rapidly and the quality of the eggs decreases, so the chances of pregnancy also decrease [13]. An AMH of less than 0.5 indicates low ovarian reserve, and this test has a sensitivity of 85% and a specificity of 82%. Internationally, the normal serum level of AMH for women under 35 years of age is 1.5 - 4 ng/ml. Moreover, vaginal ultrasound examination is one of the important methods to assess the ovarian reserve. Our patients had normal ovarian size, however low antral follicles, which is consistent with other studies [10].

The psychological issue and quality of life is important for cancer survivors. When cancer treatment is initiated, treatment-related toxicities and efficacy represent important determinants of patient quality of life [14]. Side effects of chemotherapy and prolonged hospital stays can significantly reduce an individual's quality of life and affect activities of daily living [15]. Although prolonging survival remains the primary goal of chemotherapy, palliation of symptoms and preservation of quality of life are important therapeutic concerns. Moreover, 17% and 9% of cancer survivors experience moderate to severe depression and anxiety. Many cancer patients have mental and emotional disorders that reduce their quality of life [16].

## Limitation of the Study

Our study limitation was the small study population due to the low incidence of the young cancer patients. However, this was the first study in Mongolia, indicating the need of psychological and reproductive care in cancer survivors.

## Conclusion

Non-gynecological cancer survivors of ovarian function significantly depend on the type of chemotherapy and the number of chemotherapeutic agent combinations. Careful consideration and appropriate psychological support are needed for young cancer survivors.

## Acknowledgements

We thank department of Mongolian National Cancer Center, Institute of Biomedical sciences, and MD clinic for their support.

## Conflict of Interest

No conflict of interest.

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**Volume 12 Issue 1 January 2023**