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ORIGINAL STUDIES

The importance of physical activity in the rehabilitation program of female oncopediatric patients

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Abstract

Background. In the last 20 years, the survival rate in pediatric cancer patients has increased considerably, raising awareness about fertility and life quality. It is well known that physical activity plays an important role in cancer prevention and rehabilitation.

Aims. The current study aimed to raise awareness about oncofertility and poor fertility counselling, highlighting the need for improvement and whether or not physical activity should be introduced as a rehabilitation method in cancer patients.

Methods. Of 125 female patients, only 30 were included in the study after applying the inclusion criteria. The subjects received a questionnaire containing 14 questions about their fertility status, oncologic treatment, and rehabilitation counselling.

Results. The results showed that more than 86% of the subjects did not receive rehabilitation counselling, including fertility preservation methods and physical activity, and 80% could not conceive after cancer treatment. The results were statistically insignificant ($p>0.05$) because of the small number of subjects included in the study.

Conclusions. The lack of rehabilitation counselling leads to an increase in infertility and a decrease in life quality. Rehabilitation through physical activity should become a standard care option for these patients, improving mental and physical health.

Keywords: oncopediatry, fertility, rehabilitation, physical activity.

Introduction

Childhood cancer survivors in civilized countries represent about 80% of the children diagnosed and treated for cancer (Ward et al., 2019). Oncologic treatment is personalized according to the diagnostic and patient personal factors, being frequently multidimensional: chemotherapy, radiotherapy, targeted therapy, hormone therapy and surgery (Chow et al., 2016). Even so, cancer therapy is associated with short- and long-term side effects that may cause chronic and latent non-cancer disturbances and deteriorate life quality (Mina et al., 2017; Wittekind et al., 2021). For this reason, efforts are being made to limit the long-term effects of these treatments.

There is a global initiative to improve oncology care by rehabilitation of cancer survivors in order to enhance healthcare quality (Kessel et al., 2018; Wittekind et al., 2021). Rehabilitation of cancer treatment survivors remains an understudied area of rehabilitation science, and more research is needed in order to influence clinical practice. Multimodal rehabilitation should address a complex spectrum of interventions, such as physical exercises, nutritional, psychological, and risk factors prevention (Mina et al., 2017). Recently, many studies have shown that cancer rehabilitation through physical activity has a positive effect on the functional, physical, emotional, and mental side effects of cancer treatment survivors, improving their life quality (Hausmann et al., 2018). The current body of literature provides evidence in support of cancer rehabilitation programs in order to become a cornerstone of any cancer treatment plans (Tyrrell et al., 2014; Zaami et al., 2021).

In previous studies, exercise regimens as part of the rehabilitation program have been demonstrated to improve cancer patients' life quality during and after treatment (Yağlı et al., 2015; Tsianakas et al., 2017). Although important findings from studies were highlighted and discussed,

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supporting physical exercise is not a standard element of cancer therapy or rehabilitation. Cancer specialists and cancer support groups must educate patients about the advantages of physical exercise, particularly for symptoms such as tiredness, anxiety, depression, and a low sex drive that can influence the chance of a pregnancy, since prior research has shown the efficacy of such recommendations (Stout et al., 2017).

The physical and psychological distress associated with cancer treatments, as well as infertility, fatigue, pelvic floor symptoms, and functional impairment, are significant problems The increased number of patients who will remain infertile after treatment, significantly affects the life quality at the time of diagnosis and later in adulthood, and is not to be ignored (Font-Gonzalez et al., 2016).

Most children treated for cancer can expect healing with the preservation of reproductive function, but multiple treatment modalities can affect fertility. Numerous studies have evaluated the subsequent fertility problems of childhood cancer survivors (Romao & Lorenzo, 2017). In pediatric female patients with cancer diagnosed and treated when their reproduction function is not complete, fertility can be affected directly by involving reproductive organs or indirectly by inhibiting reproductive function (Penrose et al., 2013). Often female fertility can be affected either transiently or permanently by anti-cancer treatments. Actions to preserve fertility in pediatric cancer patients have become a matter of great interest due to the increased prognosis for multiple cancers (Smith et al., 2020). Despite this, the number of pregnancies obtained after the treatment of these patients with malignant lesions is lower than in the general population (Haggar et al., 2014). International guidelines recommend a discussion between a physician and their patients as early as possible. It is mandatory to acknowledge and document their risk of infertility due to illness and treatment, as well as their wish to have children after cancer treatment, and help by providing information on fertility conservation methods. In order to reduce or prevent such a risk, personalized fertility preservation/restoring strategies, have been developed, allowing successful pregnancies in oncopediatric survivors (Silvestris et al., 2020). As recommended by the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO), sperm cryopreservation and embryos/oocytes cryopreservation are standard strategies for maintaining fertility in male and female patients (Loren et al., 2013). Other methods (e.g. gonads pharmacological protection, gonadal tissue cryopreservation) are still considered experimental techniques (Peccatori et al., 2013). However, new data have recently emerged and have to be considered.

Oncopediatric patients' fertility depends on several factors, including patient age, type and dose of therapy, and the anatomical area targeted by the therapy (Howell & Shalet, 1998). Therefore, when advising on fertility preservation, it is important to consider all these factors (Wasilewski-Masker et al., 2014). There is still no consensus on the selection of patients who would benefit from the preservation of fertility. Some are in favour of the fact that all patients should benefit from this due to the impossibility of detecting patients who will recover with minimal treatment and those who will have recurrences requiring additional gonadotoxic treatment (Romao & Lorenzo, 2017).

Chemotherapeutic agents affect both the reproductive and endocrine function of the ovary (van de Loo et al., 2019). Iatrogenic ovarian failure induced by cancer therapy may have a dramatic impact on the patient's life quality too because the reduced hormone bioavailability causes premature menopause with unpleasant vasomotor symptoms, sleep and genitourinary disorders, and cardiovascular diseases and osteoporosis (Silvestris et al., 2020). The risk of premature ovarian failure increases with age and varies with the regimen, duration, and cumulative dose of chemotherapy. Of the women who are treated with methotrexate, cyclophosphamide, or 5-fluorouracil, about 60-80% will develop premature ovarian failure (Meirow et al., 1999). A significant number of women who regained ovarian function after chemotherapy had an increased risk of early menopause even many years after stopping treatment. Besides the direct gonadotoxic effect, chemotherapy and radiotherapy also have an indirect effect on fertility by causing long-time side effects such as fatigue and low libido, influencing the quality of life of cancer survivors (Silvestris et al., 2020).

Hypothesis

The purpose of the current study was to identify the infertility risk factors in an oncopediatric female patient survivors group and the potential benefits of a rehabilitation plan that includes physical activity.

Material and methods

Research protocol

a) Period and place of the research

This project was approved by the Ethics Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, România. The study was performed in the Oncology Institute "Ion Chiricuţă" in Cluj-Napoca, România, in May 2022.

b) Subjects and groups

Participants (n=125) were identified from the patients diagnosed and treated at the Oncology Institute in Cluj-Napoca between 2008-2020. Eligibility criteria were: female sex, treated childhood cancer and aged over 20 years at the time of the study, informed consent to participate in the study, and contact data available. The exclusion criteria were: females survivors of pediatric cancer treatment aged under 20 years at the time of the study, oncologic treatment over 18 years of age, women with more than one cancer, endocrinopathies or other chronic diseases that may influence patients' fertility, lack of the informed consent or contact data.

c) Applied tests

After the inclusion criteria have been applied, only 30 patients have been enrolled in the study. By using semistructured interviews, demographic, medical and rehabilitation information were collected via a 14 items questionnaire. The demographic variables collected

included age and rural or urban settlement. Medical variables included cancer type and stage, date of diagnosis, type of treatments, disease status, fertility status and the presence or absence of cancer rehabilitation counselling at the beginning of the study. Fertility after cancer therapy was assessed based on the presence or absence of menstrual cycles, the number of abortions, the number of births, the type of birth (cesarean or vaginal) and the number of children obtained after treatment. Rehabilitation data included information about patients' rehabilitation counselling before and after the cancer treatment.

d) Statistical processing

Data were checked for normal distribution by using the Shapiro-Wilk test and for homogeneity of variance by Brown-Forsythe test. Then data were presented as mean ± standard deviation (SD) unless indicated otherwise. To compare group differences, the $\chi 2$ test was used for categorical variables and ANOVA analysis of variance with Tukey's post hoc test for continuous variables with normal distribution. Pearson's correlation and stepwise multiple linear regression were used to identify associations between different variables. For all analyses, p value<0.05 was considered significant. Microsoft Excel, MedCalc V158 and Hi square test were used to perform statistical analysis.

Results

The analysis of the patients' settlement revealed that half of the patients come from urban areas and the other half come from rural areas. Patients in rural areas had a higher percentage of pregnancies obtained after oncological treatment (26.7%), compared to those in urban areas (13.3%) (Table I).

An assessment of the age at the onset of the disease, the age at first pregnancy and the current age was also performed. It was found that the oncopediatric female survivor group's average age of the diagnosis was 15 years, the current age average was 24 years, and that most patients had their first pregnancy at around the age of 22 years (Table II).

Of the patients included in the study, most were diagnosed with head and neck tumours (36.7%) (Table III). Of these, only 9.1% were able to obtain a pregnancy after cancer treatment, with infertility among them being 90.9% (Table IV). The best fertility was shown in bone tumours (50%), followed by ovarian tumours (40%). Patients with abdominal and hematological tumours have a lower percentage of pregnancies, 25% and 12.5% respectively (Table IV).

Regarding the correlation between the received oncological treatment and the possibility of obtaining a pregnancy, the results of the study were not relevant ($p>0.05$). Chemotherapy was associated with a fertility rate of 21.1%, radiotherapy with a fertility rate of 14.3%, and surgery with a fertility rate of 22.2% (Table IV)

Another focus of the study was the rehabilitation counselling for fertility before cancer therapy and the importance of fertility preservation (Table V). The questionnaire regarding rehabilitation counselling collected data about receiving or not counselling information, about receiving fertility counselling before starting cancer treatment, and about the importance of preserving fertility; 86.70% of patients did not receive any rehabilitation counselling on fertility, and 96.70% of them considered the issue of fertility preservation in cancer patients to be important.

Table I
Demographic analysis of fertility.

	Births + abortions yes/no		
	yes	**no**	**Total**
Rural	4 (26.7%)	11 (73.3%)	15
Urban	2 (13.3%)	13 (86.7%)	15
	6 (20%)	24 (80%)	30

Table II
Mean age at first pregnancy.

	Current age	**Age at the onset of the disease**	**Age of first pregnancy**
min	19	7	18
max	31	17	29
mean	24±3.003	15±2.266	22±3.09

Table III
Oncologic treatment and cancer localization.

	Abdomen	**Head and neck**	**Hematology**	**Bone**	**Ovary**	**Total**
+ surgery	3 (60%)	2 (40%)				5
+ CT	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)	7
+ CT + surgery					4 (100%)	4
+ RT		6 (100%)				6
+ RT + CT		2 (25%)	6 (75%)			8
	4 (13.3%)	11 (36.7%)	8 (26.7%)	2 (6.7%)	5 (16.7%)	30

CT - chemotherapy; RT - radiotherapy.

Table IV
Types of oncologic treatment and first pregnancy.

		Births + abortions yes/no		
		yes	**no**	**Total**
RT	yes	2 (14.3%)	12 (85.7%)	14
	no	4 (25%)	12 (75%)	16
CT	yes	4 (21.1%)	15 (78.9%)	19
	no	2 (18.2%)	9 (81.8%)	11
Surgery	yes	2 (22.2%)	7 (77.8%)	9
	no	4 (19%)	17 (81%)	21
OT	+ surgery	1 (20%)	4 (80%)	5
	+ CT	2 (28.6%)	5 (71.4%)	7
	+ CT + surgery	1 (25%)	3 (75%)	4
	+ RT	1 (16.7%)	5 (83.3%)	6
	+ RT + CT	1 (12.5%)	7 (87.5%)	8
Localisation	Abdomen	1 (25%)	3 (75%)	4
	Head and neck	1 (9.1%)	10 (90.9%)	11
	Hematology	1 (12.5%)	7 (87.5%)	8
	Bone	1 (50%)	1 (50%)	2
	Ovary	2 (40%)	3 (60%)	5

OT - oncologic treatment; CT - chemotherapy; RT - radiotherapy

Table V
Fertility preservation counselling.

Have you received fertility preservation counseling?	**Total**	**%**
yes	4	13.30
no	26	86.70
Do you think the topic of fertility preservation in oncologic patients is important?	**Total**	**%**
yes	29	96.70
no	1	3.30
Total	30	100.00

Discussion

Data from the literature have indicated that there is a significant correlation between the age at which the cancer treatment started and the degree of fertility (Thomson et al., 2002). In those studies, fertility as a whole was analyzed, and in our study, we evaluated fertility based on the age of the first pregnancy, and therefore our results do not follow those from the mentioned study.

The demographic analysis of patient settlements revealed that in rural areas the patients' fertility was better than in urban settlements. In the urban settlement, there is a high population density and size, and the people are occupied in non-agricultural industries, and there are more risk factors, like pollution, unhealthy diet, low physical activity and high stress. This combination may be an explanation for the lower fertility in urban areas (Palomba et al., 2018). Another explanation for the low fertility rate in urban areas may be the spread of contraceptive treatments and the increased level of education with higher life standards requirements, which are inversely proportional to the first pregnancy's age.

Our results indicated a higher percentage of births in patients from rural areas. In these settlements, there is a lower population density and size, and the people are engaged in agriculture. Increased fertility in rural areas could be explained by a healthier diet, unpolluted environment, and more physical activity (Kitchen et al., 2017) (free of stress and pollutants), suggesting that physical activity is important in cancer rehabilitation, as well as infertility preservation. Many studies have proven the importance of exercise therapy in chronic diseases (Buffart et al., 2017; Teich et al., 2019; Lin et al., 2016), and some types of cancer rehabilitation and fertility preservation (Tyrrell et al., 2014). As suggested by the American Cancer Society, National Comprehensive Cancer Network and American College of Sports Medicine recommendations, exercising is safe and helpful in increasing physical function, muscular endurance, and cancer-related tiredness, thus increasing the life quality in cancer survivors. Many national guidelines now recommend exercise prescription and other physical interventions in order to prevent and reduce long-term side effects and disability in oncology patients (Dennett & Elkins, 2020). The rehabilitation programs designed for cancer survivors considered personal preferences, and walking was the most preferred activity because it is easy, its intensity can be adapted to personal needs, and also allows conversation (Tsianakas et al., 2017). The difficulties of a cancer patient's health state, clinical history, and functional skills bring a range of variables that further complicate exercise recommendations. As a result, exercise prescription is often disregarded while planning cancer treatment and recovery from oncological treatments (Tyrrell et al., 2014).

The literature describes the location of the tumor as an important factor in obtaining a pregnancy after cancer treatment, as subdiaphragmatic or skull irradiation can lead to infertility (Lambertini et al., 2016). Radiation exposure has a gonadotoxic effect, which can induce long-term ovarian insufficiency and infertility. Because cranial irradiation can alter the hypothalamic-pituitary-gonadal axis, hormone secretion disturbances may occur. The uterus can be damaged by radiation treatment. Changes in uterine vascularization, as well as reduced uterine volume and flexibility, myometrial fibrosis and necrosis, and endometrial atrophy and insufficiency, are all caused by childhood radiation exposure. Radiation has a considerable influence on reproductive potential, hence fertility preservation procedures should be undertaken before and/or during anticancer treatments. Our results showed that the highest infertility is found among patients with head and neck tumors (90.9%). Long-term negative effects of radiation treatment on the reproductive organs might compromise pubertal development, hormone balance, and sexual function, thus lowering the quality of life (Marci et al., 2018).

In the study group, we found a low degree of counselling regarding the importance and usefulness of the rehabilitation program. This could contribute to the increased infertility rate because the patients from our study declared counselling would have high importance for their rehabilitation decision. There seems to be limited

alternatives and significant challenges in adopting fertility preservation measures promptly, in the interval between cancer diagnosis and therapy. Oncologists and fertility professionals are frequently unaccustomed of scheduling short visits before beginning cancer treatment for patients who need urgent care, the success of which is tied to rigorous time schedules and constraints. Research findings (Bentsen et al., 2021; Lambertini & Demeestere, 2018) reported that young cancer survivors are often uninformed about oncofertility options and assign this lack of knowledge to limited and non-standardized reproductive counselling methods, poor information dissemination, and insufficient support and guidance from healthcare providers in patients' decision-making processes. Such flaws might limit survivors' access to fertility preservation operations before the initiation of antineoplastic medication, causing disappointment and frustration. Towards that end, it is important to begin a productive discussion with both health professionals and institutions, as well as to facilitate communication and cooperation among specialists and cancer patients, in guiding them to the oncofertility facilities that are best suited to their particular requirements. Reliable and comprehensive counselling may also be beneficial to the patient's psychological health. Moreover, there are enough data suggesting that introduction of the physical activity in the rehabilitation plan of oncoperiatric female patients may improve fertility as well.

Although the current study does provide new and important information, a number of limitations should be considered. Because the number of the included patients was small, and the patients who were more interested in infertility accepted easier to participate, the generalization of the findings might be limited.

Conclusions

Based on the study results we concluded that:

1. Fertility in oncopediatric patient survivors is low.
2. The demographic analysis showed that the subgroup of patients from rural areas had a higher fertility rate than those in urban areas.
3. Regarding the localization of the tumour, head and neck tumours had the lowest fertility rates.
4. The high infertility rate risk in the female oncopediatric survivors seems to be associated with the lack of patient counselling regarding the rehabilitation methods for fertility preservation, including physical activity.
5. Regarding the life quality and rehabilitation after cancer treatment, it is well established that exercise is helping cancer patients to achieve better health and functional results, but further research is needed in order to conclude whether physical exercise is directly influencing the fertility of oncopediatric patients survivors. Although most national recommendations mention that cancer survivors achieve physical activity requirements, exercise prescription is complicated and involves consideration of a variety of factors to have a beneficial and safe impact on those who have been diagnosed with cancer.

Conflict of interests

There is no conflict of interests.

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