DOI: https://doi.org/10.17816/aog629469

Fertility potential in patients with ovarian cancer

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ABSTRACT

Malignant neoplasms of the reproductive system are the most common form of oncological morbidity in women, accounting for over 30% of all cancer cases. Most antineoplastic agents act by inducing DNA damage in highly proliferating cancer cells, resulting in oocyte death. Ovarian toxicity is the most common side effect of cancer treatment in young women. Both chemotherapy and radiotherapy have been shown to be toxic to the ovaries, increasing the risk of premature ovarian failure, early menopause, endocrine disorders, and infertility. Patients who have undergone cancer treatment have severe follicular atresia, even if they have a regular menstrual cycle.

Currently, the most effective methods of preserving fertility in cancer patients include cryopreservation of oocytes and embryos after ovarian hyperstimulation. Other fertility preservation methods include ovarian tissue cryopreservation, follicle or embryo maturation *in vitro*, ovarian transposition, ovarian suppression, and adjuvant therapy.

Despite promising fertility prospects, iatrogenic infertility is one of the most undesirable adverse effects of cancer therapy for young women. Timely referral to a gynecologist prior to chemotherapy or radiation therapy is key to successful fertility preservation. Women should be aware of the available opportunities of assisted reproductive technologies, along with potential risks and failures with regard to their age, stage of disease, and treatment method. At this stage, it is necessary to develop well-defined and effective algorithms for oncologists, obstetrician-gynecologists, fertility specialists, and embryologists.

Keywords: literature review; oncofertility; ovarian cancer; breast cancer; iatrogenic infertility; premature ovarian failure; ovarian tissue cryopreservation; oocytes and embryo cryopreservation.

To cite this article:
Dobrohotova YuE, Matevosyan TA, Il'ina Ilu, Narimanova MR. Fertility potential in patients with ovarian cancer. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):385–394. DOI: https://doi.org/10.17816/aog629469

Received: 26.03.2024 **Accepted:** 17.06.2024 **Published online:** 12.12.2024

DOI: https://doi.org/10.17816/aog629469

Возможности фертильности при диагнозе «рак яичников»

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АННОТАЦИЯ

Злокачественные опухоли репродуктивной системы являются наиболее частыми в структуре онкологической заболеваемости женщин, их суммарная доля превышает 30%. Большинство используемых в практике онкологов противоопухолевых лекарственных средств действует путём индуцирования повреждения ДНК в сильно пролиферирующих раковых клетках, что приводит к гибели ооцитов. Токсичность для яичников является основным побочным эффектом терапии рака у молодых женщин. Доказано, что как химио-, так и радиотерапия токсичны для яичников и повышают риск преждевременной недостаточности яичников, ранней менопаузы, эндокринных нарушений и бесплодия. У пациенток, перенёсших противоопухолевое лечение, даже при наличии регулярных менструаций, будет выраженная атрезия фолликулов.

В настоящее время наиболее эффективными методами реализации репродуктивной функции для онкологических больных являются криоконсервация яйцеклеток и эмбрионов после гиперстимуляции яичников. К другим методам сохранения фертильности относятся криоконсервация тканей яичников, созревание фолликулов или яйцеклеток *in vitro*, транспозиция яичников, подавление функции яичников и адъювантная терапия.

Несмотря на многообещающие перспективы сохранения фертильности, ятрогенное бесплодие — один из самых нежелательных побочных эффектов противоопухолевой терапии, с которым может столкнуться молодая женщина. Своевременное направление пациента к гинекологу, до начала химиотерапии и лучевой терапии, является важным ключевым фактором успеха стратегий сохранения женской фертильности. Женщина должна быть осведомлена о современных возможностях вспомогательных репродуктивных технологий, о возможных рисках и неудачах, с учётом её возраста, стадии заболевания и метода лечения. На данном этапе необходимо разработать чёткие и эффективные алгоритмы действий для врачей-онкологов, акушеров-гинекологов, репродуктологов и эмбриологов.

Ключевые слова: обзор литературы; онкофертильность; рак яичников; рак молочной железы; ятрогенное бесплодие; преждевременная недостаточность яичников; криоконсервация тканей яичников; криоконсервация яйцеклеток и эмбрионов.

Как цитировать:

Доброхотова Ю.Э., Матевосян Т.А., Ильина И.Ю., Нариманова М.Р. Возможности фертильности при диагнозе «рак яичников» // Архив акушерства и гинекологии им. В.Ф. Снегирёва. 2024. Т. 11, № 4. С. 385–394. DOI: https://doi.org/10.17816/aog629469

Рукопись получена: 26.03.2024 **Рукопись одобрена:** 17.06.2024 **Опубликована online:** 12.12.2024

DOI: https://doi.org/10.17816/aog629469

卵巢癌诊断下的生育可能性

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摘要

女性肿瘤发病率结构中，生殖系统恶性肿瘤的占比超过30%，是最常见的类型之一。目前临床广泛使用的抗肿瘤药物通过诱导高增殖性癌细胞的DNA损伤发挥疗效，但同时也导致卵母细胞的死亡。卵巢毒性是年轻女性癌症治疗中的主要副作用之一。研究表明，无论是化疗还是放疗，都对卵巢组织造成显著毒性，极大地增加了卵巢功能早衰、早绝经、内分泌紊乱和不孕的风险。即便患者在治疗后仍保持规律月经，其卵泡数量的减少依然显著。

目前，最有效的生育功能保存方法是通过卵巢超刺激后进行卵子和胚胎的冷冻保存。其他潜在的生育保存方法包括卵巢组织冷冻保存、体外卵泡或卵母细胞成熟、卵巢移位术、卵巢功能抑制及辅助治疗等。

尽管生育保存方法前景广阔，但医源性不孕仍是年轻女性接受抗肿瘤治疗后最不愿面对的副作用之一。在化疗和放疗开始前及时将患者转诊至妇科医生，是确保女性生育功能保存策略成功的关键因素。女性患者应充分了解现代辅助生殖技术的潜力、可能的风险及失败概率，并综合考虑自身的年龄、疾病分期及治疗计划做出明智的决策。在当前阶段，需为肿瘤科医生、产科医生、妇科医生、生殖专家和胚胎学家制定明确且高效的临床操作规范。

关键词：文献综述；肿瘤生育力；卵巢癌；乳腺癌；医源性不孕；卵巢功能早衰；卵巢组织冷冻保存；卵子和胚胎冷冻保存。

引用本文:

Dobrohotova YuE, Matevosyan TA, Il'ina Ilu, Narimanova MR. 卵巢癌诊断下的生育可能性. *V.F. Snegirev Archives of Obstetrics and Gynecology*. 2024;11(4):385–394. DOI: https://doi.org/10.17816/aog629469

收到: 26.03.2024 **接受:** 17.06.2024 **发布日期:** 12.12.2024

BACKGROUND

Hematologic malignancies such as Hodgkin's and non-Hodgkin's lymphomas, as well as breast cancer and gynecologic cancers such as pelvic cancer, are the most common cancers in women. The prevalence of these diseases has increased by 4.4% compared to 2020. At the end of 2021, 3,940,529 patients (3,973,295 in 2020; 3,928,338 in 2019) were being followed up in cancer hospitals, and 2,262,078 patients, or 57.4% (56.6% in 2020) of all cancer patients being followed up, had been followed up for at least 5 years [1].

The global and Russian oncology communities report that the cancer survival rates have increased significantly over the past 20 years due to improvement of cancer treatment, diagnosis, prevention, and awareness not only among healthcare professionals but also among patients [1].

Modern medical advances provide patients with great opportunities to achieve remission after cancer treatment and rehabilitation. However, many patients may face infertility due to the disease or its treatment [2]. In 2006, Teresa K. Woodruff launched a new interdisciplinary initiative in Michigan, USA, by founding the Oncofertility Consortium. A team of oncologists, fertility specialists, biologists, and other specialists decided to consider the preservation of reproductive material in cancer patients [3]. Despite rapid advances in reproductive medicine research, the issue of oncofertility is still relevant and not fully explored [4].

The treatment effects on fertility and reproductive function are poorly understood. Ovarian toxicity due to chemotherapy and radiation therapy is the most common side effect in young cancer patients. Anticancer treatments (chemotherapy and radiation therapy) have gonadotoxic side effects and are considered the most common causes of pathological and iatrogenic fertility loss in women [5, 6]. Both treatment options lead to premature ovarian failure, early menopause, ovarian endocrine disorders, and infertility [7, 8]. Therefore, the issue of gonadotoxicity prevention is still unresolved and attracts increasing attention from clinicians.

The primary objective of a physician is to save the patient's life. Only once a state of stable remission has been achieved, the options for preserving fertility and achieving reproductive function in this cohort of patients can be discussed.

EPIDEMIOLOGY

Breast cancer and gynecological cancers such as uterine cancer, cervical cancer, and ovarian cancer are the most common types of cancer in women, accounting for more than 40% of all cancers [4]. Ovarian cancer (OC) accounts for 1/5 of all malignant tumors in women. According to the International Agency for Research on Cancer, more than 165,000 new cases of ovarian cancer are reported worldwide each year, and more than 100,000 women die from ovarian cancer [1, 9].

The five-year survival rate is 90% in the early stages, decreasing in advanced stages (III–IV). The five-year survival rate is 15% in stage III and only 5% in stage IV [10].

Diagnosing OC in its early stages is obviously challenging due to the paucity of symptoms and the lack of specific signs. In addition, low cancer awareness among general practitioners and outpatient gynecologists results in late detection of OC.

RISK FACTORS FOR OVARIAN CANCER

OC is the most aggressive gynecological malignancy. A large international consortium reported the ovulation theory as one of the leading hypotheses for the development of serous, endometrioid, and clear cell ovarian tumors [11]. This theory holds monthly traumata of germinal epithelium over a long period of time due to ovulation responsible for the development of OC. These findings, together with the extensive evidence on reproductive factors that decrease the number of ovulatory years, such as parity and oral contraceptive use, are associated with a lower risk of OC [12], supporting the ovulation theory as a causal mechanism underlying ovarian carcinogenesis.

Genetic predisposition is demonstrated in patients with a family history of breast cancer and OC (mutations in the *BRCA1* and *BRCA2* genes) [13]. The average cumulative risk by the age of 70 years is 59.0% in *BRCA1* carriers and 16.5% in *BRCA2* carriers [14]. *KRAS* mutations are also associated with well-differentiated mucinous OC, with 11% of epithelial OC patients having *KRAS* mutations [15].

Epidemiologic studies have identified several hormonal risk factors for OC. These include early menarche [16], late onset of menopause, zero parity, no history of using combined oral contraceptives [16, 17], hormone replacement therapy, and polycystic ovary syndrome [18].

Hyperestrogenism is a significant risk factor for OC. Estrogen receptors α and β are expressed in normal ovarian cells. At high concentrations, estrogens are involved in early stages of malignant transformation [19]. Hyperandrogenism and obesity are also risk factors for OC [20, 21].

CHANGES IN OVARIAN RESERVE

Follicles at different stages of development can be found within the ovary of a woman of childbearing age. Folliculogenesis starts at week 12 of intrauterine development of a female fetus. The number of antral follicles in a girl is approximately 2 million at birth and 450–500 thousand at puberty. Biochemical pathways that regulate the activation of primary ovarian follicles include growth factors that act through signaling pathways, including the PI3K/AKT/mTOR pathway, which is active in oocytes and critically determines the size of the remaining pool of primary ovarian follicles [22].

Most follicles become atretic at some point during their growth phase, and the high rate of granulosa cell

proliferation in growing follicles makes them a sensitive target for many chemotherapeutic agents. It is important to consider that chemotherapy affects not only normal follicular development but also the ovarian stroma and vascular system, and this may have negative effects on a woman's health [23].

ANTITUMOR THERAPY AND GONADOTOXICITY

Most antitumor agents used in oncology practice act by inducing DNA damage in highly proliferating cancer cells, leading to oocyte death [24]. The first studies of the chemotherapy effects on women's reproductive function were published in the 1970s, with reports of amenorrhea, ovarian function suppression, and follicular destruction [25, 26]. In the early 1970s, the Department of Pediatrics and the Department of Pathology at Stanford School of Medicine published the first research papers on the effects of chemotherapeutic agents on female reproductive function, based on a case report of long-term treatment with cyclophosphamide in a young woman. Ovarian histology revealed an irreversible side effect of ovarian destruction. The pathologists discovered a complete absence of egg cells (follicles) in the ovaries, although it was known that the woman's karyotype was XX. Ovarian toxicity is a major side effect of cancer therapy in young women. Both chemotherapy and radiation therapy are shown to be toxic to the ovaries and increase the risk of premature ovarian insufficiency, early menopause, endocrine disorders, and infertility [7]. Antitumor therapy is associated with significant follicular atresia, even in women with regular periods. This may be explained by the effects of alkylating agents on DNA function during the active replication phase [7, 27].

Laboratory tests show high levels of follicle-stimulating hormone (FSH) and low levels of inhibin B, estradiol, and anti-Müllerian hormone (AMH), indicating follicular atresia and premature ovarian insufficiency. Pelvic ultrasound shows a decrease in ovarian volume, as well as a reduction in the number and size of follicles [28].

EFFECTS OF RADIATION THERAPY ON FERTILITY AND METHOD OF OVARIAN TRANSPLANTATION BEFORE RADIATION THERAPY

Ovarian transposition (oophoropexy) is a surgical procedure performed to reposition the ovaries out of the radiation field by separating one or both ovaries and fallopian tubes from the uterus. The appendages are sutured to the posterior wall of the abdominal peritoneum, away from the radiation field, using non-absorbable sutures. However, this technique is not always successful, and there is still a risk of ovarian migration back into the radiation field [29, 30].

ONCOFERTILITY OPTIONS FOR EGG PRESERVATION

Currently, egg and embryo cryopreservation after ovarian hyperstimulation is the most effective way to achieve reproductive function in cancer patients.

Other fertility preservation techniques include ovarian tissue cryopreservation, *in vitro* maturation of follicles or eggs, ovarian transposition, ovarian suppression, and adjuvant therapy [23].

EFFICIENCY OF EGG AND EMBRYO CRYOPRESERVATION

Egg and embryo cryopreservation is an important component of assisted reproductive technologies used in women with any cancer diagnosis. Depending on the disease stage and the treatment plan, some women may undergo ovarian stimulation followed by egg retrieval and cryopreservation. Standard hormone stimulation for egg retrieval and cryopreservation usually takes 12–14 days [31].

How to decide which technique to use? Egg cryopreservation is the most appropriate technique for women who do not have a male partner, as it does not require the collection of male biological material. When a patient wishes to use her cryopreserved eggs, they are thawed and fertilized, and the resulting embryos are implanted in the uterus. However, the pregnancy rate in this case is only 4–12%.

Women who have a partner should be offered cryopreservation of both an embryo and an egg. First, ovulation is stimulated in a controlled manner, and then the eggs are collected by puncture. In case of male factor infertility, intracytoplasmic sperm injection is used. Embryos are cryopreserved by vitrification at the 8-cell, morula, and blastocyst stages [31]. Vitrification is the ultra-rapid freezing of eggs, embryos, and ovarian tissue. Vitrification is a simpler and less expensive procedure than slow freezing. The American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology reported that the survival rate of eggs after vitrification and thawing is 90–97%, the fertilization rate is 71–79%, the implantation rate is 17–41%, and the clinical pregnancy rate per thawed egg is 4.5–12% [32]. These high rates explain why vitrification is the preferred cryopreservation technique for fertility preservation in women, including young cancer patients who wish to achieve their reproductive function. Side effects of embryo cryopreservation that may delay the initiation of treatment for the underlying disease include ovarian hyperstimulation syndrome after controlled ovulation induction, massive bleeding, or intraperitoneal infection after egg retrieval. It remains controversial whether controlled ovulation induction, which increases serum estradiol levels, is safe for patients with estrogen-sensitive cancers, including breast cancer. These patients are treated with a

controlled ovulation induction protocol in combination with an aromatase inhibitor such as letrozole to prevent an increase in serum estradiol levels [33]. The number of mature eggs and embryos obtained with controlled ovulation induction in combination with letrozole is comparable to that obtained using the protocol without letrozole. No increase in the risk of breast cancer recurrence within five years of diagnosis and implementation of the protocol was reported [33].

OVARIAN TISSUE CRYOPRESERVATION

Ovarian tissue cryopreservation remains an experimental but rapidly evolving technique. It has some significant advantages over egg and embryo cryopreservation. Ovarian tissue is obtained laparoscopically and the resulting material is divided into cortical strips containing a large number of primary follicles. The tissue is then cryopreserved as described above. An advantage of this technique is that ovarian tissue can be obtained from a patient of any age, whereas mature eggs required for embryo or egg cryopreservation can only be obtained from adults or postpubertal girls [34]. In addition, ovarian tissue cryopreservation can be performed within several days because it does not depend on ovulation stimulation. Ovarian tissue cryopreservation can be combined with embryo/egg cryopreservation. This combination procedure may increase the potential for fertility preservation. When cryopreserved ovarian tissue fragments need to be used, they are thawed and transplanted into either the pelvic cavity, the ovarian medulla, or the peritoneal window. The number of pregnancies after autotransplantation of cryopreserved ovarian tissue is increasing rapidly [35]. In 2017, nearly 100 children worldwide were reported to have been conceived after cryopreserved ovarian tissue transplantation [36]. The risk of the tissue re-infection with malignant cells, known as minimal residual disease, is the major concern with cryopreserved ovarian tissue transplantation for cancer diagnoses. This issue was addressed by scientists from the Laboratory of Reproductive Biology – Rigshospitalet (Copenhagen, Denmark). In 2012, a literature review was published describing the clinical outcomes of ovarian tissue transplantation from cancer patients into rodents. The results were compared before and after chemotherapy. The safety of the technique was determined for different cancer diagnoses. The researchers concluded that transplantation of frozen/thawed ovarian tissue may be associated with reintroduction of malignant cells [36].

IN VITRO OOCYTE MATURATION AND *IN VITRO* FOLLICLE GROWTH

When ovarian stimulation is impossible or contraindicated, ovarian tissue or egg cryopreservation, vitrification of embryos isolated from small antral follicles after *in vitro* maturation, may serve as an alternative technique [37].

Advances in research on *in vitro* maturation techniques indicate that early maturation or biphasic *in vitro* maturation strategies result in better outcomes [38]. Immature cumulus–oocyte complexes are insufficiently developed (e.g., from small antral follicles) and “maturate” in the presence of a meiosis inhibitor within 2–48 hours. *In vitro* follicle growth involves the collection of female ovarian tissue or individual immature follicles for *in vitro* culture and maturation [38, 39]. Once the eggs mature *in vitro*, they can be fertilized using traditional techniques, including intracytoplasmic sperm injection followed by insemination into the uterine cavity.

CONCLUSION

Despite the high potential for fertility preservation, iatrogenic infertility is one of the most undesirable side effects of cancer treatment in young women. In practice, cancer treatment faces many medical, economic, social, and legal barriers worldwide, especially in underdeveloped countries. To overcome these barriers, an oncologist should collaborate with a fertility specialist in the management of these patients. First of all, it is important to decide which medical goal takes priority in each case: saving a life or preserving reproductive function. Timely referral to a gynecologist prior to the initiation of chemotherapy and radiation therapy is a key success factor in female fertility preservation strategies. A woman should be informed about advances in assisted reproductive technologies, possible risks and failures, taking into account her age, disease stage, and treatment options. A healthcare professional should obtain voluntary informed consent indicating all possible outcomes. Clear and effective algorithms for oncologists, obstetricians/gynecologists, fertility specialists, and embryologists need to be developed at this stage.

ADDITIONAL INFO

Authors’ contributions. Yu.E. Dobrokhotova approved the final version of the manuscript; I.Yu. Il’ina developed the concept and approved the final version of the manuscript; M.R. Narimanova developed the concept and edited the text; T.A. Matevosyan prepared and edited the text. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

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