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Review article

Oncofertility: Treatment options from bench to bedside

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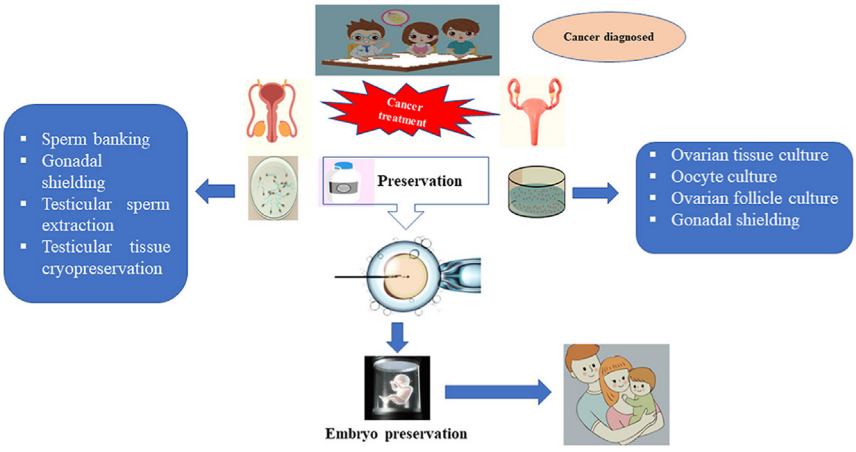
HIGHLIGHTS

- Chemotherapy, radiotherapy, and surgery may lead to premature female ovarian insufficiency or male germ cell loss.
- All patients diagnosed with a malignant tumor must undergo a consultation for fertility protection and its preservation.
- The knowledge, methods, and options for fertility preservation and conservation are discussed herein.
- Oncologists, surgeons, pediatricians, and hematologists need to have knowledge of fertility guards.

GRAPHICAL ABSTRACT



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ABSTRACT

In recent years, there has been continuous improvement in the treatment and diagnosis of cancer, which has led to a significant improvement in the survival rate of cancer patients. Treatments that include chemotherapy, radiotherapy, surgery, or combined therapy have several side effects that may lead to premature ovarian insufficiency in females or substantial male germ cell loss. Reproductive biologists recommend that all patients who are diagnosed with a malignant tumor must undergo a consultation for fertility protection and preservation. In this review, we discuss the background knowledge, methods, and options for fertility preservation and how these new strategies help oncologists, surgeons, pediatricians, and hematologists, conserve fertility and be aware of the concepts, methods, and importance of fertility guards. This review may aid in the advancement of novel personalized methods for fertility preservation according to patients' conditions.

Introduction

Oncofertility is the maintenance of fertility during cancer treatment and encompasses oncology and reproductive biology. The incidence of cancer diagnosis at a younger age has rapidly increased in the recent past,[1] and the survival rates of these cancer patients have also increased owing to lifesaving advancements in cancer treatment. Unfortunately, young cancer survivors are unaware that this advanced lifesaving

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treatment can adversely affect fertility. In addition to cancer, reproductive functions are at risk in many non-malignant disease conditions and their treatments.[2] Cancer can affect any age group and is a disease that does not discriminate against individuals based on age, race, or sex. According to the Indian Council of Medical Research (ICMR), approximately 1.15 million new cancer patients are registered annually in India. The ICMR and National Centre for Disease Informatics and Research (NCDIR) predict that by 2025, the number of cancer cases will rise to approximately 1.56 million.[3] This represents an increase of approximately 12% compared with the current figures. A total of 9.81% of males and 9.42% of females of a young age are at risk of developing cancer. The survival rate of young adults is increasing annually. Globally, the cure rate for childhood cancer has reached 75%.[4]

Advances in cancer treatment include surgery, chemotherapy, and radiotherapy, which have proven to be lifesaving; however, they result in gonadal toxicity. These treatments can harm normal fertility by causing deterioration of the hypothalamic-pituitary-gonadal (HPG) axis; cytotoxic, anatomical, and functional deficits; and emotional and sexual dysfunction.[5] Recent technological advances in reproductive techniques have enabled many patients with untreatable infertility to have children. These techniques are used by clinicians to achieve conception in patients following cancer treatment, with highly successful outcomes.[6]

A world-famous cyclist, Lance Armstrong, was diagnosed with metastatic cancer at the age of 25 and he vitrificated his sperm. After recovering from cancer, he had three children using his conserved sperm.[7] Many patients with cancer are not informed about the fertility implications of cancer treatment by their healthcare providers. Although many patients with cancer and their families are interested in preserving fertility, there is a need to bridge the gap in our understanding of the underlying biology, clinical techniques, and patient and provider awareness, especially among teenagers diagnosed with cancer. In males, the primary issue in fertility preservation is their lack of knowledge about the consequences of fertility-related cancer diagnosis.[8] Whereas in females, fertility preservation is difficult because their germ cells are limited in number, are in different maturity phases, and need to be retrieved surgically. Advanced knowledge of ovarian function, development of methods for mature follicles, and *in vitro* oocyte development are needed to help women diagnosed with cancer maintain their future fertility.[9]

The term oncofertility was coined by Prof. T. Woodruff in 2007, founder and director of the Oncofertility Consortium, University of Northwestern Chicago, Illinois, United States. Oncofertility is an interdisciplinary field comprising the development of methods to restore reproductive function and expand fertility options for young patients with cancer. Advancements in both reproductive and oncology disciplines are needed to solve fertility-related issues and create awareness to cope with the social, ethical, and legal issues that arise with the development of new reproductive interventions.[10] Researchers and clinicians should work together to solve such problems, and funding sources should support researchers and investigators engaged in this area.[11] The Oncofertility Consortium was founded to carry out research in the interdisciplinary areas of oncofertility, such as oncology, reproductive medicine, and the public. The Oncofertility Consortium represents a new approach to previously intractable problems by integrating the bench (basic and social research sciences), bedside (clinicians and clinical researchers), and community (humanities, law, and education).[12]

Concept of oncofertility

The history of oncofertility dates back to 1971 when US President Richard Nixon signed the National Cancer Act. This act marked the start of the 'war on cancer' and provided the necessary funding for a new National Cancer Institute (NCI), which would focus on the etiology, diagnosis, and treatment of the disease. The resources provided by the NCI are responsible for the earlier and better diagnosis of cancer, which has resulted in an increased number of cancer survivors.[13] When the NCI was formed, reproductive scientists were developing several new technologies to assist infertile women. The birth of Louise Brown in 1978, the first baby born using *in vitro* fertilization (IVF) preceded 3 decades of steady advances in reproductive intervention. Currently, IVF is routinely performed, which uses eggs matured *in vivo* with hormonal treatments, and freezes the embryos for implantation at a later stage.[14] Oocyte vitrification (an ultra-rapid freezing process that prevents ice-crystal formation) and cryopreservation technologies are continuously improving, and the number of babies born from the fertilization of frozen mature eggs has increased. Ideally, the development of cancer care and the advancement of reproductive knowledge should occur concurrently and provide fertility options for young patients with cancer. However, this is still hindered by the challenge of combining the separate specialties of oncology and reproductive medicine.[15] Cancer care has changed dramatically in the last 20 years with earlier diagnostics, the emergence of targeted cancer therapies, methods to reduce radiation doses and fields, and localized surgical procedures. With these advancements, cancer patients can now survive with their disease and what was once a fatal diagnosis is now a chronic illness, resulting in a curable disease. As the number of cancer survivors increases, the preservation of fertility in women, men, and children becomes critically important for patients and their families. Oncofertility also involves reproductive issues after cancer treatment, such as family planning, complex contraception, hormonal management throughout survivorship, and surrogacy.[16]

Dilemma of treatment, possible solutions, and future direction for oncofertility

In oncofertility, the dilemma of treatment includes deciding the medical care while respecting cultural factors. In adolescent patients with cancer, there may be communication barriers between physicians, the patient's guardians, and the patients themselves. The removal of such barriers through enhanced awareness and comprehensive communication may be effective. Therefore, it is important to include patients in conversations and listen to their perspectives.[17]

Future directions for the field of oncofertility

- Determine optimal cryopreservation and thaw techniques for reproductive tissues and gametes.
- Advance *in vitro* follicle maturation for primates.
- Improve integration of cancer survivors' psychosocial needs into the fertility preservation treatment plan.
- Improve communication regarding fertility issues between the healthcare provider and the patient.
- Develop broad-based multi-center studies for the progression and betterment of oncofertility services.

Guidelines relating to oncofertility

The following are the recommended guidelines from the American Society of Clinical Oncology (ASCO) Clinical Practice.

- Discuss fertility preservation in all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk as a result of therapy.
- Refer patients who express interest in fertility preservation (and those who are ambivalent) to reproductive specialists.
- Address fertility preservation as early as possible before treatment starts.
- Fertility preservation should be documented in the medical record.
- Answer basic questions about whether fertility preservation may have an impact on successful cancer treatment.
- Refer patients to psychosocial providers.
- Encourage patients to participate in clinical studies.

Adult males

- Present sperm cryopreservation (sperm banking) as the only established fertility preservation method.
- Do not recommend hormonal therapy in men; it is not successful in preserving fertility.
- Inform patients that other methods such as testicular tissue cryopreservation, which does not require sexual maturity for future reimplantation or grafting of human testicular tissue, are experimental.
- Advising men with a potentially higher risk of genetic damage to sperm collected after chemotherapy initiation.

Adult females

- Present both embryo and oocyte cryopreservation as established fertility preservation methods.
- Discuss the option of ovarian transposition (oophoropexy) when pelvic radiation therapy is performed as a cancer treatment.
- Inform patients of conservative gynecologic surgery and radiation therapy options.
- Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method and that these agents should not be used to preserve fertility.
- Inform patients that other methods (e.g., ovarian tissue cryopreservation, which does not require sexual maturity for future transplantation) are still experimental.

Children

- Use established methods of fertility preservation (semen cryopreservation and oocyte cryopreservation) for post-pubertal minor children with patient consent, if appropriate, and parental or guardian consent.
- Present information on additional methods that are available for children but are still investigational.
- Refer to experimental protocols when available.[18]

Fertility preservation options

Males

Sperm cryopreservation, sperm retrieval surgery, testicular tissue preservation, and drug intervention are the most used methods for preserving fertility. Fertility preservation prior to the initiation of cancer treatment is required and is supported by the ASCO guidelines.[19] Cryopreservation of ejaculated sperm is a safe, non-invasive, and preferred method, with a success rate of approximately 90%. However, owing to a lack of patient and healthcare provider awareness, very few men provide sperm for cryopreservation before undergoing cancer treatment. The inconsistency in the awareness of the issue and recommendations given by a fertility specialist is the biggest obstacle in preserving fertility in male patients with cancer.[20] Therefore, informative education programs and awareness campaigns are two ways in which the Oncofertility Consortium supports men facing fertility issues. Puberty initiation plays a crucial role in successful sperm cryopreservation. Prepubertal individuals cannot produce or ejaculate sperm; hence, they are not suitable candidates for sperm cryopreservation. After cryopreservation, sperm can remain frozen for decades, with the longest period being 28 years, and cryopreserved sperm subsequently leads to live births.[21]

A recent survey of patients demonstrated that when patients were given options to cryopreserve their sperm, 50% of them decided to bank the sperm. Another study reported that 70% of cancer patients sought paternity after chemotherapy, and approximately 80% of the patients suggested cryopreservation to their known ones. In contrast to this compelling data, more than 50% of surveyed oncologists do not discuss sperm cryopreservation routinely, despite over 90% confessing sperm cryopreservation should be offered to almost every patient for their future planning.[22] A recent study confirmed that only 29% of cancer patients are eligible for fertility preservation when proper counseling is provided, and 11% undergo referral for sperm banking. Those with a lower median income, Medicaid insurance, or older age are less likely to be provided fertility preservation counseling, as it is cost-intensive, and older patients often lose interest in becoming parents or are already parents.[23] Other commonly cited reasons for not undergoing sperm banking include lack of knowledge, lack of interest, sexual orientation, anxiety, embarrassment, religious background, and most importantly, cost, many of which can be alleviated through the implementation of a formalized oncofertility program focusing on making it cost-effective and providing comprehensive counseling and scientific awareness.[24]

However, there are several patients diagnosed with cancer, mostly prepubertal boys, or those who cannot provide a semen sample. Attempts have been made to preserve the fertility of these patients by vitrifying the testicular tissue. By surgically removing and cryopreserving testicular tissue, survivors can undergo various transplantation methods to collect mature spermatozoa for IVF.[25] Immature testicular tissue was transplanted during testicular grafting. In contrast, spermatogenesis can be initiated by an infusion of spermatogonial stem cells (SSC) isolated from the testicular tissue. The ability to develop spermatocytes from stem cells to spermatids *in vitro* would offer young cancer patients an imperative fertility-sparing option; however, this would not be an easy method, as difficulties remain in carrying out *in vitro* maturation of sperm in clinical practice.[26] For males, the following factors should be considered during gamete or tissue preservation.

- Baseline fertility.
- Age at the time of treatment.
- Type of cancer and treatment(s).
- The amount of treatment.
- The length (duration) of treatment.
- The amount of time that has passed since treatment.
- Other personal health factors.
- Hormonal status.
- Condition of the testis.

Females

Due to advancements in treatment, the survival rates of patients with malignancies have increased tremendously, and issues associated with this, such as fertility preservation and restoration, have also gained much attention, specifically for young cancer survivors. There are considerably different challenges faced by female fertility compared to male fertility.[27] To the best of our knowledge, few well-established practices and several debatable experimental options are available to preserve female fertility. Embryo freezing and egg freezing are established practices.[28] The available options include ovarian protection techniques such as gonadotropin-releasing hormone (GnRH) analogs, surgical ovarian transposition (oophoropexy), hormonal suppression, gonadal shielding, and fractionated radiotherapy. Experimental options include ovarian tissue freezing and further auto-transplantation, oocyte *in vitro* maturation (IVM), artificial ovaries, stem cells, and neoadjuvant cytoprotective pharmacotherapy.[11] Each of these techniques may have some advantages and disadvantages and may not be suitable for every patient. Hormonal stimulation and collection of mature oocytes for performing IVF and cryopreservation are one of the preservative techniques for the cancer-diagnosed patient. Embryo freezing is one of the most used techniques. Despite this, embryo banking before cancer treatment has raised a variety of issues that should be considered in the decision-making process. Initially, this procedure may require several weeks, which would further delay treatment. Second, a sperm donor is

required at the time, and if the relationship status of the sperm donor with the patient changes, several legal issues could be raised regarding embryo acceptance.[29]

Embryo freezing has been the gold standard for female fertility preservation for decades and involves cryopreservation of *in vitro* fertilized oocytes by slow freezing or vitrification, which is preferred due to a healthier post-thaw survival rate. Embryo freezing requires earlier ovarian stimulation and maturation of oocytes and sperm for IVF. Therefore, it is not an appropriate technique for prepubertal girls because of the inactive hypothalamic-pituitary-ovarian (HPO) axis.[30]

Estrogen-sensitive cancers such as breast and endometrial cancers are not eligible for embryo freezing because conventional ovarian stimulation may result in high estrogen levels. In such cases, a substitute ovarian stimulation protocol that includes either tamoxifen (a selective estrogen receptor modulator) or letrozole (an aromatase inhibitor) may be used.[31] In addition, conventional ovarian stimulation may take several weeks, and even in some cases, it may result in complications of ovarian hyperstimulation syndrome, which is not suitable for women with highly aggressive malignancies that require immediate anticancer treatment. For example, in the case of leukemia, random-start ovarian stimulation for emergency fertility preservation may be an option. In a few cases, successful ovarian stimulation and subsequent embryo or egg freezing have been performed to preserve fertility in young women with hematological malignancies. The ideal storage time for frozen embryos, eggs, and sperm is almost 10 years; however, longer storage may be possible depending on modifications in local and national laws in several countries. In healthy women, the live birth rate for each frozen embryo transfer is approximately 30%. In females with cancer, the live birth rate per frozen embryo transfer is generally reduced; however, there is no increased risk of congenital abnormalities.[32]

Egg freezing has not been considered an experimental cryopreservation technique for female fertility preservation since the American Society for Reproductive Medicine (ASRM) declaration in 2012 but is still in practice in lower-income countries. Egg freezing requires early ovarian stimulation and mature oocyte retrieval without the need for sperm or IVF. Hence, it is not suitable for prepubertal girls but can be applied in the case of single women for embryo freezing.[33] Similar to embryo freezing, ovarian stimulation is required for egg freezing, to retrieve mature oocytes and therefore has the same disadvantages mentioned previously. In healthy women, the live birth rate per frozen oocyte is approximately 6%, owing to advances in vitrification protocols and egg donation programs. Several births after oocyte vitrification have been reported in women with cancer. Until sufficient data becomes available, the success of conventional egg freezing should be extrapolated with caution to patients with cancer during oncofertility counseling.[34]

For females, there are a few debatable options, including GnRH analogs, hormonal suppression, oophoropexy, and gonadal shielding. GnRH analogs are the most prescribed medications in the fields of gynecological endocrinology and reproductive medicine. Therefore, the role of GnRH analogs in the protection of ovaries before and during chemotherapy, predominantly for patients with hematological malignancies, is debatable.[35] Oophoropexy is the surgical transposition of ovaries from pelvic irradiation in cases of malignancies, along with pelvic diseases such as cervical carcinoma, vaginal carcinoma, and pelvic sarcoma. During oophoropexy, the ovaries are transposed either laterally near the pelvic wall or medially behind the uterus. Oophoropexy is performed via laparoscopy, mini-laparotomy, or robotic surgery. According to the ASCO guidelines, the success of oophoropexy in protecting the ovaries and preserving fertility is debatable and varies according to several factors, such as the dose, type, and site of pelvic irradiation, patient age, and whether chemotherapy is administered. Gonadal shielding is routinely used during pelvic irradiation to protect the ovaries, particularly in young patients. Similar to oophoropexy, gonadal shielding does not protect the ovaries from chemotherapy, resulting in gonad toxicity, and hence, has a limited role when chemotherapy is administered.[36] The following factors should be considered during fertility preservation in women.

- Condition of the ovary.
- Hormones, as are needed to help with egg release and further processing.
- A tumor or another issue may be present in the ovaries or uterus (womb), resulting in dysfunction.
- Damage to other parts of the reproductive system, which may prevent the release, fertilization, and implantation of eggs.

Challenging factors

Some of the challenging factors for cancer patients in preserving their fertility are.

- Lack of communication between fertility experts and oncologists.
- Lack of awareness.
- Few centers are available for cryopreservation.
- Costs and lack of insurance coverage.
- Cultural differences and religious concerns.
- Fear of delay in treatment.
- Fear of side effects on cancer treatment resulting from hormonal stimulation.
- Ethical and legal challenges after cancer, for example, the disposal of gametes.
- Misguided perceptions and certain complex societal and cultural attitudes.

Ethical Concerns Regarding Oncofertility and *in vitro* fertilization[37]

- Organs are not considered property and thus cannot be purchased or sold. There is a range of ethical issues related to oncofertility and IVF, such as:
- The quality of consent obtained from the parties.
- The motivation of the parents.
- Uses and implications of pre-implantation genetic diagnosis.
- Permissibility of sex selection (or the choice of embryos for other traits).
- Storage and fate of surplus embryos.

Future scope

The Oncofertility Consortium is an emerging branch that has rapidly grown over the past decades, and further improvements in this initiative are needed. Figure 1 details the process of oncofertility registration. A greater understanding of follicle maturation, the risk associated with younger cancer patients, and discovering several methods to conserve fertility options during times of serious anxiety regarding a cancer diagnosis. The principal aim was to identify methods to eliminate the risk of fertility in young patients with cancer. In addition to symptom management strategies, individual cancer-targeted drug development is required because different types of cancers cause different effects according to their origin and distribution. Additionally, other serious disease conditions, treatments, and therapies could hinder the fertility of young people. Therefore, awareness of fertility-related problems in patients with cancer is necessary.

For a cancer patient who is aged $\leq$14 years and who cannot freeze their sperm, the culture of SSC may be possible. However, the problem with this technique is the need to rebuild the microenvironment,

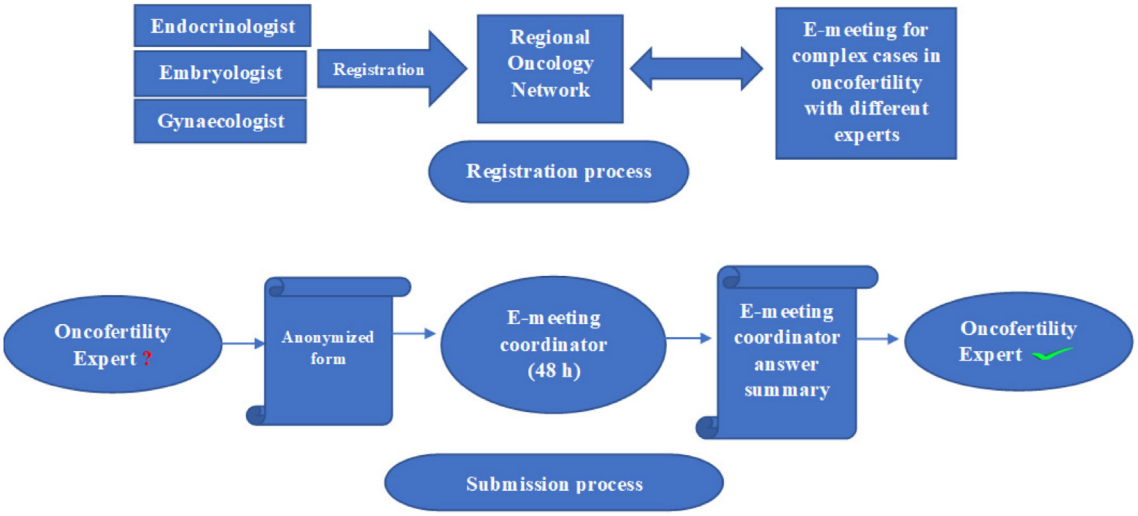

Figure 1. Registration and submission process for complex cases in oncofertility.

especially the SSC niche, for continuous development and differentiation into mature sperm cells. More research is needed to determine the proliferation rate of SSC and to sustain their functionality after testis replacement. Despite this fact, more progress is needed to achieve the production of mature sperm after the completion of spermatogenesis, which has the ability of fertilization and requires the formation of a microenvironment of testicular tissue in which immature testicular tissue can mature and SSCs can proliferate into mature sperm.

The mechanism underlying cancer treatment-induced ovarian impairment remains unclear. Animal experiments have demonstrated that chemotherapy accelerates follicle activation and the apoptosis of stromal and germ cells. Future experimental studies should include the co-immunohistological staining of apoptotic markers and follicle activation in ovarian tissues. In future studies, alternative mechanisms may be elucidated. Human studies are crucial for understanding the mechanisms of ovarian damage. For example, ovarian tissues should be surgically collected from patients who experience ovarian failure due to chemotherapy and these tissues should be further stained for apoptotic and follicular maturation markers. Furthermore, these results should be correlated with genetic profiles. Moreover, along with the genetic profile, serum follicle-stimulating hormone (FSH) and anti-Müllerian hormone (AMH) levels should be evaluated to determine any correlation between the genetic profile and other tests. Cancer treatments such as chemotherapy, radiation, and surgery may prevent a person's ability to have children later in life. Oncofertility research has focused on increasing fertility preservation options. With 10% of cancer patients younger than 40 years, this problem affects almost 135,000 individuals in the United States every year. With the increase in cancer survivorship, fertility preservation in women, men, and children has become a critical topic for patients and their families. The ability to preserve fertility prior to cancer treatment can provide hope to families at the time of diagnosis. Oncofertility also incorporates reproductive issues after cancer treatment, such as family planning, complex contraception, and hormonal management throughout survivorship, surrogacy, and adoption, and improves the lives of cancer patients.[38]

Study limitation

This review focuses only on options for fertility preservation for males and females undergoing cancer treatment. Although many techniques are being developed, further improvements in this field are required.

Conclusion

With advancements in cancer therapy, long-term survival rates have greatly improved. Hence, the protection and preservation of fertility in patients with malignant tumors has received increasing attention worldwide. In particular, the viability of frozen testicular tissue and SSC needs to be confirmed, and culture conditions need to be identified for the expansion of SSC. Several cancer survivors have children through testicular sperm cell extraction, but the success of this intervention after the treatment of childhood cancer has not yet been confirmed. These methods need to be further studied for confirmation of effectiveness and application in clinical practice. Cryopreservation of ovarian tissue can be combined with the removal of small antral follicles, which ultimately makes it possible to freeze ovarian tissue and isolate immature oocytes. Improved freezing techniques, making ovarian tissue transportation safe, will be implemented among women with benign diseases such as recurrent endometriosis and age-related fertility decay, with vitrification of oocytes emerging as the technique of choice for non-oncologic signs in the future.

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Authors contribution

Divya Gupta: conceptualization, formal analysis, writing–original draft, and writing–review and editing; Shubham Singh: conceptualization; validation, writing–original draft, and writing–review and editing; Sangeeta Shukla: data curation, and formal analysis; Sadhana Shrivastava: conceptualization, resources, supervision, and validation.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

None.

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