Fertility preservation

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Abbreviations

AFC- Antral follicle count

AMH- Anti-Müllerian hormone

aPL- Antiphospholipid antibodies

APS- Antiphospholipid syndrome

ARFD- Age-related fertility decline

ART- Assisted reproduction techniques

ASCO- American society of clinical oncology

BC- Breast cancer

COH- Controlled ovarian hyperstimulation

COS- Controlled ovarian stimulation

DIE- Deep infiltrating endometriosis

E2- Estradiol

EOC- Elective oocyte cryopreservation

ESHRE- European society for human reproduction and endocrinology

FP- Fertility preservation

FSH- Follicle stimulating hormone

GnRH - Gonadotropin-releasing hormone

GnRHa- Gonadotropin-releasing hormone agonist

Gy- Gray

hCG- Human chronic gonadotropin

HER2- Human epidermal growth factor receptor 2

ICSI- Intracytoplasmic sperm injection

IVF- In vitro fertilization

LH- Luteinizing hormone

OC- Oocyte cryopreservation/ Ovarian cryopreservation

OHSS- Ovarian hyperstimulation syndrome

OMA- Ovarian endometrioma

OS- Ovarian stimulation

OTC- Ovarian tissue cryopreservation

POF- Primary ovarian failure

POI- Post-treatment ovarian insufficiency

POI- Premature ovarian insufficiency

SEF- Social egg freezing

SPE- Superficial peritoneal endometriosis

T-DM1- Ado-trastuzumab emtansine

TRA- Treatment related amenorrhea

Contents

Abstract

Title: Fertility preservation

Author: Daniel Barak

Fertility preservation describes the treatments and procedures performed in medicine to preserve or protect an individual's future capacity to bear biological children. Most of the time it includes the process of storing oocytes, embryos, or reproductive tissue for later conception.

Fertility preservation may be performed prior to fertility-altering treatment, such as chemotherapy, radiotherapy, hormonal therapy, HER2 therapy and immunotherapy or to people who want to postpone having children for social reasons until a later age, when fertility may have declined.

This comprehensive review explores the various reasons for fertility preservation and emphasizes the importance of considering fertility preservation options early. It covers fertility preservation technique types. The review discusses fertility preservation in the context of breast cancer, endometriosis, systemic lupus erythematosus and social freezing, offering valuable insights into this crucial aspect of reproductive health. It serves as a valuable resource in understanding the complex landscape of fertility preservation and its impact on family planning.

Key words: Fertility preservation, endometriosis, SLE, Social freezing, Breast cancer.

Sažetak

Naslov: Očuvanje plodnosti

Autor: Daniel Barak

Očuvanje plodnosti opisuje tretmane i postupke koji se izvode u medicini kako bi se očuvala ili zaštitila buduća sposobnost pojedinca da rađa biološku djecu. Većinu vremena uključuje proces pohranjivanja jajnih stanica, embrija ili reproduktivnog tkiva za kasnije začeće.

Očuvanje plodnosti može se provesti prije liječenja koje mijenja plodnost, kao što je kemoterapija, radioterapija, hormonska terapija, HER2 terapija i imunoterapija ili za osobe koje žele odgoditi rađanje djece iz društvenih razloga do kasnije dobi, kada je plodnost možda smanjena.

Ovaj opsežni pregled istražuje različite razloge za očuvanje plodnosti i naglašava važnost ranog razmatranja opcija za očuvanje plodnosti. Obuhvaća vrste tehnika očuvanja plodnosti. Recenzija govori o očuvanju plodnosti u kontekstu raka dojke, endometrioze, sistemskog eritemskog lupusa i socijalnog zamrzavanja, nudeći dragocjene uvide u ovaj ključni aspekt reproduktivnog zdravlja. Služi kao vrijedan izvor za razumijevanje složenog krajolika očuvanja plodnosti i njegovog utjecaja na planiranje obitelji.

Ključne riječi: očuvanje plodnosti, endometrioza, SLE, socijalno zamrzavanje, rak dojke.

Introduction

Fertility preservation is an extensive and fascinating field. It refers to the medical procedures and techniques used to protect or maintain a person's ability to have biological children in the future. Many women around the world have to deal with the need to preserve fertility due to various reasons. On the one hand, it could be due to a medical reason such as breast cancer, endometriosis, Systemic Lupus Erythematosus etc. On the other hand, it could be due to personal status and choices in their personal lives.

This thesis is a comprehensive review of the multifaceted field of fertility preservation. One of the reviews' central themes is oncofertility, which investigates the intersection of oncology and fertility preservation. It investigates the effects of systemic treatments for breast cancer on fertility, including chemotherapy, radiotherapy, hormonal therapy, HER2 therapy, and immunotherapy. The thesis focuses on the challenges and considerations that women diagnosed with breast cancer face, as well as the potential consequences for their reproductive health.
Furthermore, the review discusses fertility preservation options for women with SLE and endometriosis, which can have a significant impact on fertility. It discusses the effects of endometriosis surgery on ovarian reserve and emphasizes the importance of specific surgical techniques in order to minimize iatrogenic effects on ovarian reserve. In addition, surgical techniques that may help reduce ovarian damage in endometrioma surgery are indicated.

Finally, the review refers to the social freezing- 'putting fertility on hold'.
A significant component of modern fertility preservation techniques is social freezing, which gives women more autonomy over their reproductive schedules and the freedom to choose their family planning strategies. This whish could arise from various reasons, among them, the lack of a suitable partner for starting a family or a desire to develop professionally before starting a family.

In conclusion, this review on "Fertility Preservation" provides a thorough and insightful examination of the complexities and implications of fertility preservation.

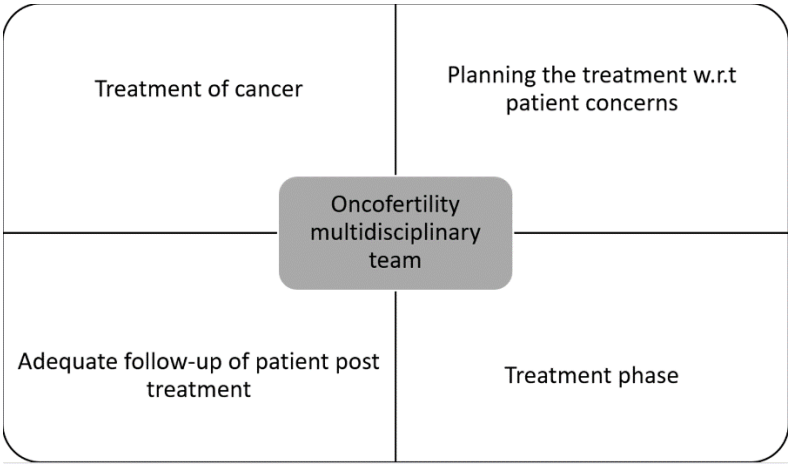
1. Oncofertility

Oncofertility is a medical field that combines oncology and reproductive endocrinology in order to maximize the reproductive potential of cancer patients and survivors.

The number of cancer survivors rising, the introduction of novel oncologic medications, the lengthening of treatment durations, and the advancement and improvement of reproductive treatments have all contributed to the developing field of oncofertility.(1)

Cancer treatments such as chemotherapy, radiation and surgery can reduce or eliminate a person's ability to conceive later in life. These treatments can cause ovarian damage in women, which can lead to genetically damaged oocytes (eggs), ovarian failure, early menopause or other reproductive issues.

The term "oncofertility" describes the urgent and unfulfilled needs of cancer patients who may benefit from life-saving but potentially harmful therapies. A critical first step in educating cancer patients about the potential for treatment-induced premature ovarian failure and infertility, depending on the recommended anticancer therapies, is oncofertility counseling. This involves presenting various options to maintain ovarian function and fertility and debating the benefits and drawbacks of each. (2)



(3)

Figure 1

2. Impact of systemic treatments for breast cancer on fertility

2.1. Chemotherapy

Ovarian toxicity is a serious side effect of cancer treatment in young female patients. Chemotherapy and irradiation have been shown to be toxic to the ovaries, increasing the risk of early menopause, ovarian endocrine abnormalities, infertility, and premature ovarian failure (POF) in women.(3)

One of the most significant forms of treatment for breast cancer has been cytotoxic chemotherapy, which typically targets cells that are actively dividing, such as gonadal cells. The three most significant medications that are frequently used to treat breast cancer and have an impact on fertility are taxanes, doxorubicin, and cyclophosphamide.(2)

Chemotherapy risks vary depending on the patient's age (younger patients have a lower risk of ovarian failure), the chemotherapeutic drug used (alkylating chemicals pose the greatest risk), and the length of treatment.(3)
Chemotherapy is linked to a decrease in anti-Müllerian hormone (AMH) levels and an increase in follicle-stimulating hormone (FSH) levels in women, indicating a decline in ovarian reserve and potential fertility impairment. Reduced estrogen levels, which cause menopausal symptoms (such as hot flashes, vaginal dryness, or mood swings), is also common.(1)

The most hazardous cytotoxic chemotherapy drug in terms of the potential for treatment-related amenorrhea (TRA) and premature ovarian insufficiency (POI) is cyclophosphamide, an alkylating agent.
Compared to patients who did not receive cyclophosphamide treatment, those who did have a greater than twofold increased risk of developing TRA. Gonadal dysfunction is also brought on by the anthracycline doxorubicin and taxanes like paclitaxel and docetaxel, although the risks are not as great as those associated with cyclophosphamide. These medications are frequently given in combination or in sequential order in clinical practice. (2)

2.2. Radiotherapy

Radiation is especially harmful to oocytes. Acute ovarian failure and early menopause have been linked to hypothalamic, pituitary and pelvic radiation, either alone or in combination with alkylating drugs. Radiation exposure of 20-30 Gray (Gy) or 15 Gy total body radiation can cause a decline in ovarian function. Less than 6 Gy for adult females, less than 10 Gy for postpubertal females and less than 15 Gy for prepubertal females are associated with a significant risk of infertility in the pelvis or the entire abdomen.

At the prepubertal stage, the gonads are particularly sensitive to radiation; less than 2 Gy of radiation would destroy half of the immature oocytes and 25-50 Gy would cause infertility in one-third of young women and nearly all women over 40 years of age.

However, the quantity and quality of the oocytes play a significant role in the success of fertilization and embryo development. Oocyte preservation is therefore critical, whether done before or during cancer treatment. (3) The degree of radiation-induced impairment is determined by the radiation dose, the location of the ovaries in relation to the radiation field, the fractionation schedule and the patient's age at the time of treatment. (4)

All female reproductive organs are vulnerable to direct radiation damage if they are in the radiation field, but they can also be damaged by scattered radiation, even when shielding is present.(3)

2.3. Hormonal therapy

Tamoxifen is frequently used to suppress hormones in premenopausal patients with hormone receptor-positive breast cancers for a period of five to ten years. Tamoxifen treatment was associated with a markedly elevated risk of TRA; however, the majority of the side effects appear to be reversible. In the ASTRRA study, menstruation was restored in 69% of patients overall and 91% of patients under 35 who recovered from TRA after receiving tamoxifen with or without Goserelin over a five-year period. The majority of these patients also had their serum levels of estradiol (E2) and follicle stimulating hormone (FSH) restored (98% and 74%, respectively). Furthermore, there was no difference in the recovery of AMH levels between patients who underwent endocrine therapy and those who did not.(2)

2.4. Anti-human epidermal growth factor receptor 2 (HER2) therapy

Anti-HER2 medications such as trastuzumab, pertuzumab, lapatinib, ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan are used to treat HER2 positive breast cancer. Analyzing data from the ATTEMPT trial, which compared T-DM1 with trastuzumab plus paclitaxel, revealed that patients who received T-DM1 had a significantly lower 18-month rate of TRA. This suggests that anti-HER2 monotherapy has safer gonadal toxicity profiles than cytotoxic chemotherapy combinations. Additionally, dual inhibition of anti-HER2 therapy by combination or sequential treatment did not result in an increased incidence of TRA compared to anti-HER2 monotherapy in the additional analysis in the ALTTO trial. According to one study, patients receiving chemotherapy and trastuzumab experienced a better recovery of AMH levels than those receiving chemotherapy alone. HER2 was highly expressed in the ovarian blood vessels during the preclinical phase of the study, leading to the hypothesis that inhibiting HER2 may have shielded the gonadal organs from the possible gonadal toxicity mechanism of cytotoxic chemotherapy. When anti-HER2 medications are used together, the risk of TRA is comparatively low.(2)

2.5. Immunotherapy

In clinical practice, immune checkpoint inhibitors are used to treat breast cancer in the neoadjuvant and metastatic settings. Immunocheckpoint inhibitors may induce thyroiditis, adrenalitis and hypophysitis, all of which may impair fertilization through disrupted hypothalamic-pituitary-ovarian axis hormonal regulation. However, data regarding the direct impact of immune checkpoint inhibitors on POI are limited. In these situations, appropriate hormone replacement would be required to preserve fertility. Multidisciplinary care involving endocrinology and reproductive medicine specialists is required.(2)

3. Fertility preservation in women with breast cancer

Every year, nearly 1.5 million women under the age of 45 in the world are diagnosed with breast cancer. Age, sex, family history, an unhealthy lifestyle, gene mutations or even hormone replacement therapy are all risk factors for developing breast cancer. Many of these women will be advised to have adjuvant chemotherapy to reduce the risk of death or tumor recurrence. (5)

Depending on the kind, quantity and frequency of anticancer medications used during cancer treatment, gonadotoxic therapy may result in premature ovarian insufficiency and a reduction in reproductive function.(2)

These tumors typically develop from ductal hyper-proliferation and can progress to benign or aggressive metastatic carcinomas. It is worth noting that young patients are more likely to develop more aggressive carcinomas.(5)

To achieve optimal fertility preservation, cancer patients who are of reproductive age must be informed about the side effects of gonadotoxic medicines and the available fertility options prior to treatment.(2) Fertility and pregnancy issues that may arise during

treatment add to a patient's emotional and psychological distress if they are diagnosed with breast cancer at a young age. Physicians should address these issues early and intervene quickly after diagnosis to improve treatment outcomes and long-term quality of life for these women. (5)

The creation of anticancer drugs has enhanced the effectiveness of cancer treatments, extending the life expectancy of cancer patients. As a result, in the treatment of patients with breast cancer, the quality of life of cancer survivors following oncologic therapy has gained importance. The prevalence of breast cancer in women who are fertile is rising. For these people, fertility-preserving medications and quality of life after cancer treatment are especially important. Individuals who underwent fertility-preserving treatments before receiving cancer treatment stated that these treatments improved their quality of life after the cancer treatment.(2)

Something of great interest is that after young patients are diagnosed with breast cancer, approximately 50% of them are interested in becoming pregnant right after completion of therapy. Unfortunately, breast cancer survivors have the lowest possibility for a subsequent pregnancy. This is due to the gonadotoxic therapeutic approach and the long period of treatment.(5)

Several factors must be considered when deciding on the best method of fertility preservation, including the patient's age, the severity of the disease, the cancer stage, the urgency of immediate treatment, marital status, future pregnancy desire and the maximum available interval between controlled ovarian stimulation (COS) and the start of cancer therapy.

There are currently several options for fertility preservation. The decision to cryopreserve an oocyte, embryo, or ovarian tissue, as well as the use of a gonadotropin-releasing hormone agonist (GnRHa) in addition to systemic therapy, should be made after careful consideration of each patient's situation, medical status, needs and goals.(2)

The advancement of assisted reproductive technologies (ART) has aided in the development of methods and strategies for preserving fertility in cancer patients. These

include pharmacological protection of the ovary against gonadotoxic compounds used in cancer treatment and when indicated, ovarian transposition, as well as cryopreservation of oocytes, embryos or ovarian tissue prior to the start of anti-cancer therapy. Some of these fertility preservation methods are also used in women with medical conditions other than cancer, as well as in women who want to preserve their fertility for social reasons.(4)

4. Fertility preservation in pediatric and adolescent oncology patients

Fertility preservation (FP) in pediatric and adolescent oncology patients is a complex balance of cancer treatment needs and reproductive desires that necessitates a multidisciplinary approach. Early referrals to FP specialists are essential, as is counseling on cryopreservation options. Given the gonadotoxic effects of cancer treatments, proper patient selection and risk assessment are critical for achieving optimal results. (6)

Adolescents prefer oocyte retrieval and cryopreservation due to a lack of designated partners. Follicle growth patterns vary in post-pubertal girls and higher doses of follicle-stimulating hormone may be required for adequate maturation. Urgency in cancer treatment frequently leads to the use of standard ovarian stimulation protocols, but there is limited evidence on fertility and pregnancy outcomes. Ethical concerns, such as hymen integrity and religious beliefs, influence parental consent for fertility preservation. Obtaining the adolescent's consent is critical for procedures that affect their future reproductive life, in accordance with medical ethics and pediatric recommendations. Fertility preservation procedures should be performed using a shared decision-making model involving parents and adolescents, as well as comprehensive informed consent.(6)

Oocyte cryopreservation (OC) is preferred for post-pubertal adolescents without partners, but cultural and religious considerations influence decision-making. Ovarian tissue cryopreservation (OTC) is an alternative to ovarian cryopreservation (OC) for

adolescents who have medical or time constraints. Ovarian tissue transplantation can restore endocrine function and increase the live birth rate in female cancer survivors by 26-41%. However, caution is advised due to the possibility of reintroducing malignant cells. OTC has been thought to be relatively safe for certain solid tumors, but a case series reported ovarian transplantation for leukemia after a thorough oncologic safety assessment. Furthermore, a study found that the majority of patients who banked ovarian tissue stopped doing so for various reasons, the most common of which was pregnancy.(6)

From all of the above we can understand the complexity involved in the procedure of fertility preservation in pediatric and adolescent cancer patients, emphasizing the importance of a multidisciplinary approach. Emerging technologies hold promise for restoring endocrine function and facilitating live births, but caution is advised due to concerns about the reintroduction of malignant cells. Future research should concentrate on long-term outcomes, psychological impact, ethical considerations, and accessibility of fertility preservation methods, with the goal of creating a more patient-centered and universally accessible approach.(6)

5. Fertility preservation types

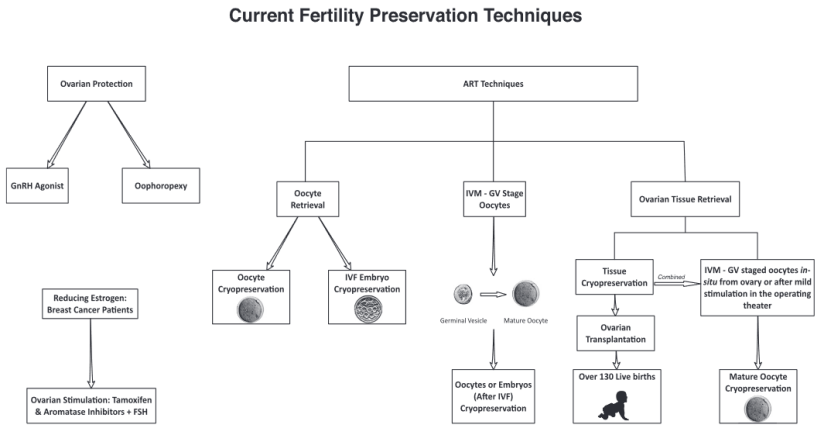
In breast cancer patients undergoing oncological treatment, fertility preservation is a critical issue. Given the physical and psychological stress that patients are under, fertility counseling is an absolute necessity.

Cryopreservation of mature oocytes is currently the most common method of fertility preservation. Other options, such as ovarian tissue preservation and gonadal protection during chemotherapy, have also been shown to be effective.(7)

Fertility preservation options are becoming increasingly important as cancer treatments improve and survival rates rise. Fortunately, there are several treatment options available to help you maximize your future fertility potential.

Fertility preservation in cancer patients is becoming a requirement rather than a choice as part of the overall treatment process. The American Society of Clinical Oncology (ASCO) also recommends that patients be referred to a fertility clinic before starting cancer treatment. As the number of young breast cancer patients grows year after year, it is critical for healthcare professionals caring for breast cancer patients to be well-versed in the subject.(2)

Breast cancer (BC) is the most common type of cancer in women worldwide. Significant evidence suggests that BC in young women is often more aggressive and has a worse prognosis than in older women. Given the growing trend of postponing childbearing, many patients of reproductive age have not met this need at the time of diagnosis, making treatment-associated infertility one of the most serious issues. As a result, fertility preservation (FP) should be considered prior to beginning any gonadotoxic therapies. Discussing the potential impact of anticancer therapies on ovarian function and fertility, as recommended by international guidelines, should be part of the multidisciplinary management of BC in young women, allowing both patients and clinicians to assess and manage fertility issues as early as possible.(8)



(4)

Figure 2

5.1. Oocyte Cryopreservation

Initially, slow freezing and rapid thawing techniques were used, but their success rates were low due to technical barriers such as ice crystal formation and disruption of the microfilament structural stability. (9)

Oocyte cryopreservation (OC) is a technique for freezing and long-term storage of woman's eggs for later use at subzero temperatures.

Oocytes can be cryopreserved using either a controlled freezing (slow freezing) or an ultrarapid freezing (vitrification) process. Initially, slow freezing and rapid thawing techniques were used, but their success rates were low due to technical barriers such as ice crystal formation and disruption of the microfilament structural stability. Extracellular ice formation drives cellular dehydration during equilibrium cooling or slow freezing. The first live birth from frozen oocytes was reported in 1986, using the slow freezing technique.

Cryoprotectants (CPAs) are substances that prevent the formation of ice crystals, thereby reducing cryodamage. Various permeating (e.g., glycerol, dimethyl sulfoxide or DMSO, 1,2 propanediol, PROH,) and nonpermeating (e.g., glucose, sucrose, fructose, trehalose) CPAs can be used during cryopreservation. Cells are exposed to a low concentration of CPA while gradually cooling.

Cryopreservation of oocytes has evolved over time. Its success is determined by a variety of factors, including the patient's age at the time of freezing, the indication, the total number of oocytes frozen, and the method of cryopreservation used. The most important factor is the age at freezing. Although there is no specific advice, 'the younger the better'.(10)

The development of oocyte vitrification, which uses ultra-rapid cooling methods, has proven to be a faster technique with better results. Vitrification could reduce damage to the internal structures of the oocyte, allowing the zona pellucida to harden more easily. Vitrification has significantly increased live birth rates, with a higher live birth rate reported for women under the age of 35 (live birth rate 50% vs. 22.9% in women over

the age of 36).(11) Since then, technological advancements have improved oocyte survival and reproductive outcomes, with fresh and cryopreserved oocytes showing comparable rates of implantation, pregnancy, miscarriage and live birth. As a result, oocyte vitrification has allowed women to preserve their reproductive potential by cryopreserving oocytes before they degrade in quantity and quality, a process known as EOC (elective oocyte cryopreservation). The most common reason for women to consider EOC has consistently been a lack of a partner, with less common but rising reasons being career or education-related.(9)

Apart from cancer patients, it has also been promoted as a mode of fertility insurance to overcome the age-related decline in fertility as well as post-surgical decline following endometriosis surgery.

Oocyte cryopreservation is an alternative method to embryo cryopreservation for women who do not have a partner or do not want to use donor sperm, as well as in countries where embryo cryopreservation is illegal. This technique, like embryo cryopreservation, necessitates controlled OS and oocyte retrieval and thus has the same drawbacks. (11)

The procedure of oocyte cryopreservation does not guarantee a future pregnancy; its success is ultimately dependent on the number of mature oocytes vitrified. It has been suggested that when considering the likelihood of a live birth, the number of oocytes to cryopreserve is determined by the patient's age—women under 38 years should aim to cryopreserve 15-20 oocytes, and women 38-40 years should aim to cryopreserve 25-30 oocytes, numbers that may be too large to achieve based solely on patient age. In another study, in women who had frozen their gametes for non-medical reasons, vitrification of 15 mature oocytes was associated with an 85% chance of live birth in women ≤ 35 years, while for women ≥ 36 years with a total of 11 mature vitrified oocytes, CLBR plateaued at 35.6%. In a more recent study, Hong suggests that if a patient is willing to undergo FP, at least 10-15 oocytes should be cryopreserved in order to increase the chances of a future pregnancy.(12)

Most centers recommend freezing before the age of 35, if possible, because maternal age at freezing has a significant impact on the likelihood of later successful embryo formation and pregnancy. (13)

Benefits of Oocyte Cryopreservation

Oocyte cryopreservation is becoming more popular around the world. Because of its simplicity and feasibility, it is the preferred method of fertility preservation in oncofertility. Furthermore, it gives women reproductive autonomy, allowing them to organize their personal and professional lives and overcome the age-related decline in fertility. Donor egg banking increases the number of donor eggs available, reduces costs, eliminates the need for synchronization between donor and recipient cycles, shortens the time to pregnancy and allows for quarantine of eggs for infectious disease screening. It prevents the waste of extra oocytes in cases where embryo freezing is not possible.(10)

Risks of Oocyte Cryopreservation

Oocyte cryopreservation subjects women to the risks of COS and surgical egg retrieval. To achieve fertilization with a vitrified egg, ICSI is required. Planned OC may provide women delaying motherhood for personal reasons with a false sense of security, as fertility declines with age. With open vitrification methods, there is also a theoretical risk of infectious disease transmission. However, it has yet to be observed.(10)

5.2. Embryo cryopreservation

Embryo cryopreservation is the most established fertility preservation method for BC patients who have male partners or for women who use donor sperm, but it raises several ethical and legal concerns, including prohibition in some countries, posthumous reproduction and divorce. This procedure incorporates ovarian stimulation (OS), oocyte retrieval, and in vitro fertilization (IVF). The success of this method is highly dependent on the number of stored oocytes or embryos as well as the age of the patient. OS with

gonadotropins is required to obtain more than one oocyte per cycle, which is critical for successful IVF, especially since most BC patients only have one opportunity to undergo IVF before beginning gonadotoxic treatment. (11)

Alternative and safer protocols for OS using aromatase inhibitors and tamoxifen with gonadotropins have been developed to reduce the risk of short-term exposure to very high estrogen levels in BC patients. For women with HR-positive BC, stimulation protocols with gonadotropins are the preferred option for OS in fertility preservation cycles because they are safer, more effective than tamoxifen protocols and are associated with a higher number of retrieved and fertilized oocytes. The use of these protocols resulted in an overall live birth rate of 45% per embryo transfer, which is comparable to those seen in a non-cancer population undergoing IVF for infertility.(11)

Random-start method represents a significant milestone in the field of fertility preservation technology, as it allows for the preservation of fertility in cancer patients without any delay in cancer therapy. The primary objective of the random-start method is cryopreservation, and hence, the challenge of utero–ovarian synchronization and preparation for embryo transfer, which is a potential pitfall of this approach, is not a concern for cancer patients. Although the random-start method exhibits a tendency toward a slightly elevated total dose of gonadotropin and a prolonged stimulation period during the cycle, no discernible distinction in the total quantity of retrieved oocytes and mature oocytes was observed between the two approaches.(5)

Random-start OS protocols for emergency fertility preservation begin in the late follicular or luteal phase of the menstrual cycle and allow OS to begin at any time during the cycle. With comparable numbers of retrieved oocytes, mature oocyte yield, and fertilization rates, random-start protocols have been shown to be efficient for fertility preservation. There is no need to wait for the onset of the next menstrual cycle when using these protocols because they reduce the waiting period for egg retrieval to about 2 weeks, allowing for an earlier start of oncologic treatment. Double OS protocols are being developed to allow for double stimulation in both the follicular and luteal phases of the same menstrual cycle in order to increase the number of obtained oocytes and, as a

result, the birth rate, without delaying cancer treatment. These protocols may be appropriate for patients with advanced maternal age and decreased ovarian reserve, but more research is needed. (11)

The urgency of fertility preservation in women undergoing cancer therapy often makes it difficult to initiate induction early in the follicular phase. However, recent developments in the physiology of human reproduction have led to the discovery of the multiple wave theory, which states that the recruitment of a group of follicles is performed multiple times throughout a single menstrual cycle. This has enabled the initiation of ovarian stimulation at any time during the menstrual cycle.(5)

5.3. Cryopreservation of immature oocytes

For BC patients, cryopreservation of immature oocytes or oocytes matured in vitro is a promising experimental fertility preservation option. This method is menstrual cycle independent and does not require OS, though a short OS lasting 3-5 days can be performed, resulting in a shorter period from BC diagnosis to cancer treatment initiation. Immature oocytes can be cryopreserved after in vitro maturation or cryopreserved at the immature stage and matured in vitro after thawing after retrieval. In vitro maturation (IVM) prior to cryopreservation is said to be a better option than post-thaw maturation because it results in higher maturation and survival rates.(11)

Understanding the mechanisms of oocyte maturation is critical for producing viable oocytes. Oocyte maturation has both nuclear and cytoplasmic components, with nuclear maturation spanning meiosis stages from Prophase-I to the formation of a mature metaphase II (MII) oocyte. The MII oocyte is inactive and awaits fertilization. Cytoplasmic maturation, which occurs concurrently with nuclear maturation in the oocyte, involves metabolic and structural changes that support fertilization and embryo development. The synchronization of nuclear and cytoplasmic maturation is critical for successful fertilization and healthy embryo development.(14)

Hormonal signals, interactions with somatic cells and transcription factors all control oocyte maturation in *vivo*. High levels of intracellular cAMP support the oocyte's meiotic arrest, and communication between the oocyte and cumulus cells is critical for regulating oocyte maturation. Following the LH surge, oocyte maturation begins via cascade signaling pathways and physiological changes in the pre-ovulatory follicles. The LH surge causes Graafian follicle enlargement, and factors such as GDF-9, BMP-15, and BMP-6 play important roles in this process. These coordinated molecular signals ensure that oocytes mature properly within the follicle.(14)

In *vitro* oocyte maturation, or IVM, lacks the natural signaling mechanisms found in vivo, resulting in spontaneous meiotic maturation of immature oocytes. This causes a premature breakdown of critical communication between the oocyte and cumulus cells, resulting in the loss of valuable metabolites. The conventional approach is to culture immature COCs until they reach metaphase II, but clinical human IVM programs frequently use in vivo gonadotropin stimulation to improve oocyte quality and quantity.(14)

IVM of human immature oocytes has benefits for fertility preservation, OHSS risk and economic constraints in IVF treatment. It also helps to advance infertility treatments and improve embryo development. Collaboration among experts is critical for refining techniques and developing standardized protocols for efficient and effective IVM programs, making it a valuable alternative for individuals who cannot undergo COH and increasingly relevant in routine clinical practice.(14)

5.4. Ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) is a fertility preservation method in which the ovarian cortex, which contains a large number of primordial follicles, is surgically removed and cryopreserved. After oncologic treatment, the ovarian tissue can be thawed and transplanted back into the patient, either to orthotopic (into the pelvic cavity; on the atrophic ovary, pelvic peritoneum) or heterotopic (outside of the pelvis; subcutaneous regions such as the forearm, abdominal wall) sites.(11)

OTC involves laparoscopic resection of ovarian tissue, either from the ovarian cortex containing primordial follicles or the entire ovary, followed by cryopreservation. The concept was initially proposed to reduce the risk of secondary premature ovarian insufficiency (POI) in women undergoing gonadotoxic chemotherapy, as well as to preserve fertility in pre- and peripubertal girls for whom OC is not an option. Following the success of OTC as a well-established method of fertility preservation in cancer patients, it has evolved into a technique for women undergoing treatment with a high or intermediate risk of POI due to benign diseases. This includes autoimmune, haematological or medical illnesses treated with cytotoxic agents, bilateral ovarian tumours, and severe recurrent ovarian endometriosis.(9)

Ovarian Tissue Cryopreservation (OTC) has several advantages, including the ability to perform it at any point in the menstrual cycle, the absence of ovarian stimulation, the absence of delays in cancer treatment and the absence of the need for a male partner/sperm donor. It causes the storage of numerous primordial follicles and the restoration of endocrine function. OTC is especially beneficial for breast cancer patients who require immediate gonadotoxic therapy but do not have time for traditional egg or embryo cryopreservation.

Ischemia after transplantation can result in significant follicular loss. The procedure has demonstrated promising live birth and pregnancy rates, with suggestions that combining oocyte vitrification and OTC could improve live birth rates even further.

Concerns about safety revolve around the potential reimplantation of malignant cells, particularly in patients with hematologic malignancies. Ovarian tissue examination is critical in cancer patients undergoing OTC to rule out malignant involvement. When transferring malignant cells is risky, ovarian follicles can be isolated, matured in vitro, fertilized, and transferred to the patient.

Another option is to create an artificial ovary by encapsulating isolated follicles in a scaffold, which allows them to grow and develop in an ovarian-like environment before being grafted to the patient. This method could be improved further by using robotic surgery and protective agents such as AS101 or sphingosine-1-phosphate (S1P).

Success is heavily reliant on ovarian reserve, which declines with age. Age under 35, a realistic 5-year survival chance, and at least a 50% risk of premature ovarian insufficiency are all recommended OTC selection criteria. (11)

Thawed or warmed tissue is transplanted into the broad ligament, remaining ovary, or ovarian fossae. Most patients' ovarian function is restored within 4-5 months of reimplantation, with over 90% experiencing restored function for 4-5 years. Age, previous chemotherapy exposure, graft size, cryopreservation method, follicle distribution and post-transplantation ischemia are all factors that influence the restoration of endocrine function following transplantation and graft longevity.
The procedure is considered successful when both menstruation and follicular growth are observed. A recent meta-analysis found that ovarian endocrine function was restored in 85.2% of women who received transplanted tissue. (9) (11)

The failure to restore ovarian function has been attributed to an insufficient amount of cryopreserved ovarian tissue or the procedure being performed at an advanced age. The average duration of ovarian function has been found to be 5 years, but normal graft function can be maintained for up to 10 years. Furthermore, both fresh and frozen grafts produced comparable ovarian function after two years of follow-up.(9)

To reduce the risk of post-implantation graft hypoxia, various methods have been described, including encapsulating the ovarian tissue with the isoform of vascular endothelial growth factor 165 within a collagen matrix. This has been shown to result in earlier revascularization and improved graft angiogenesis within the first three days after implantation. Anti-apoptotic agents like Sphingosine-1-phosphate (S1P), an endogenous phospholipid messenger, speed up ovarian graft revascularization to 2-3 days and increase microvascular density. This reduces tissue hypoxia and follicular cell apoptosis, increasing the overall success of the transplant. Plasma levels of S1P are significantly higher in younger women and synthesis has been shown to be directly associated with estrogen levels. As a result, if elective OTC (EOTC) is performed in young, healthy women, better outcomes and longer graft longevity may be observed when compared to women who have undergone the procedure for medical pathology.(9)

Another cause of follicular demise is the cryopreservation process itself, which promotes uncontrolled follicular activation of primordial follicles, also known as follicular burnout. In mouse studies, administration of recombinant anti-Müllerian hormone inhibited the initiation of primordial follicle recruitment, preventing ovarian reserve depletion and subsequent follicular burnout.(9)

Table I Advantages and disadvantages of elective oocyte cryopreservation versus elective ovarian tissue cryopreservation.

	Elective oocyte cryopreservation	Elective ovarian tissue cryopreservation
Advantages	• Biological offspring is feasible • Invasive surgery and general anaesthesia is not required • Oocytes retain their reproductive potential from the age they were cryopreserved, with improved outcomes observed in younger women • Similar outcomes between cryopreserved warmed oocytes and fresh IVF cycles • Procedure is cost-effective when cryopreservation is carried out at the optimal age • Successful pregnancy, livebirth and perinatal outcomes have been reported • Duration of cryopreserved oocytes does not affect the risk of aneuploidy or alter gene expression of the thawed oocytes • Procedure is associated with a low rate (%) of decision regret	• Biological offspring is feasible • Hundreds of primordial follicles can be cryopreserved at one time • Follicles within the ovarian tissue retain their reproductive potential from the age they were cryopreserved, with improved outcomes observed in younger women • Effective methods have been described to improve follicular survival rates • Successful outcomes have been reported regarding endocrine function, livebirth, pregnancy rates and perinatal outcomes • Spontaneous conception is possible • Several pregnancies can be achieved from the same graft • Women can use cryopreserved tissue later in life as a method of cHRT to prevent POI or early menopause, if not used for fertility preservation for ARFD
Disadvantages	• Offspring is not guaranteed • More than one cycle of COS may be required to retrieve adequate oocyte numbers to improve chances of successful livebirth • Ovarian stimulation increases the risk (albeit minimal) of thrombotic events and OHSS • Undergoing ovarian stimulation is associated with short and long-term psychological effects in infertile couples • Poor outcomes including total number of oocytes retrieved, pregnancy and livebirth rates are associated in women undergoing the procedure >35 years old • Oocytes may not end up being used, due to spontaneous conception, or through choice • A finite number of oocytes are retrieved and cryopreserved	• Offspring is not guaranteed • Multiple laparoscopies are indicated (resection and implantation of ovarian tissue) with associated surgical and anaesthetic risk • Long-term surgical risks such as adhesions, could impair the ability to achieve spontaneous pregnancy • Risks are associated with poor longevity of the graft when cryopreservation is performed at an advanced age or an inadequate volume of tissue is retrieved • Poor outcomes including pregnancy and livebirth rates are associated in women undergoing the procedure >40 years old • Tissue may not end up being used, due to spontaneous conception, or through choice • Risk of removing ovarian tissue may impact ovarian reserve and bring age of menopause earlier

ARFD, age-related fertility decline; COS, controlled ovarian stimulation; cHRT, cell tissue hormonal replacement therapy; OHSS, ovarian hyperstimulation syndrome; POI, premature ovarian insufficiency.

(9)

Table 1

5.5. Artificial ovaries

Artificial ovaries containing isolated follicles could be a game changer in restoring fertility without the risk of reseeding the cancer. In the early 1990s, researchers transplanted fresh and cryopreserved isolated murine ovarian follicles embedded in fibrin or plasma clots or collagen gels into sterile mice's ovaries, resulting in the birth of offspring. To isolate human primordial follicles, enzymes such as collagenase or Liberase must be digested. The fragile isolated follicles must be embedded in a 3D supporting matrix that degrades over time to allow folliculogenesis and blood vessel formation. As supporting matrices for implantation into immunodeficient mice, researchers used plasma clots, alginate hydrogels, and fibrin. Fibrin appears to be promising for use in human preantral follicles.(4)

5.6. Oophoropexy

Oophoropexy is a surgical procedure that involves surgically attaching a woman's ovary to the abdominal wall or pelvic sidewall.
Young patients undergoing pelvic irradiation may undergo oophoropexy to shield their ovaries or move them as far away from the radiation field as possible. Because of the risk of spontaneous ovarian relocation, the procedure should be performed close to the radiation treatment. Some degree of protection has been documented, but scattered radiation and changes in ovarian blood supply limit success to around 50%. The procedure may also make future oocyte retrieval more difficult, as well as promote some ovarian dysfunction and cyst development. There have been reports of spontaneous conception after oophoropexy. A combined approach of transposition of one ovary and tissue retrieval for cryopreservation from the other ovary may be considered in some cases.(4)

5.7. Ovarian suppression with gonadotropin releasing hormone agonists

Gonadotropin-releasing hormone agonists are used to reduce gonadotropin and sex hormone levels. They are commonly used in the treatment of hormone-sensitive cancers such as breast and prostate cancer to lower sex hormone levels. (5)

Another advantage of using a GnRH agonist is that it eliminates monthly menstrual bleedings during chemotherapy and may thus prevent chemotherapy-induced menorrhagia. GnRH agonist binds to GnRH receptors in the anterior pituitary, stimulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. Prolonged receptor activation causes desensitization and down-regulation of gonadotropin secretion. GnRH receptors are typically down-regulated after one week of therapy, along with a decrease in pituitary production of both LH and FSH. Several

GnRHa formulations, including leuprolide, goserelin, triptorelin, buserelin, and histrelin, are approved for parenteral administration and on the market. (4) (5)

GnRHa is thought to reduce vascularity in the ovary, reducing the perfusion and chemotherapy delivery, thus actually protect them from chemotherapeutic agents. Preventing increased recruitment of primordial follicles, and up-regulating antiapoptotic pathway. Although the development of unilaminar follicles is thought to be FSH independent, and they do not express gonadotropin receptors, GnRH agonists may inhibit the recruitment of primordial follicles.

GnRH agonists have been studied for their ovarian protection in patients with estrogen-receptor-positive breast cancer. According to one study, adding a GnRHa to chemotherapy resulted in a higher pregnancy rate and a lower ovarian failure rate than chemotherapy alone. The majority of other studies in similar patients reported a decrease in the rate of premature ovarian failure, though some found that GnRH agonists were ineffective unless tamoxifen was included in the treatment protocol. (4)

Because of its noninvasive nature, ease of administration and lack of requirement for assisted reproductive technologies or chemotherapy delay, the administration of GnRHa for fertility preservation in breast cancer patients is appealing. To reduce the initial flare effect, GnRHa should be given at least one week before chemotherapy.

The use of GnRHa for fertility preservation, on the other hand, is still considered experimental, with limited long-term data and the need for further research. While some studies indicate that GnRHa reduces the risk of premature ovarian failure and increases pregnancy rates, limitations include the use of ineffective surrogates for ovarian function, such as amenorrhea, and the lack of randomized controlled trials. Furthermore, there is no discernible increase in serious adverse effects when GnRHa is added to chemotherapy. Successful pregnancy is the best primary outcome for fertility preservation, and it can be assessed using ovarian reserve biomarkers such as antimüllerian hormone (AMH), inhibin B levels, or antral follicle count. Overall, GnRHa can be used instead of or in addition to established fertility preservation techniques when embryo or oocyte cryopreservation is not possible. (11)

6. BRCA mutations

Breast cancer treatment strategies are determined by a number of factors, including the subtypes, stage, and germline BRCA status of the cancer, as well as the age and menopausal status of the patients. Cytotoxic chemotherapy, hormone therapy, targeted therapy and immunotherapy are all used in systemic treatment. As a result, a variety of factors influence the risk of TRA and subsequent post-treatment ovarian insufficiency (POI) in breast cancer patients. (1)

Women who have BRCA1 and BRCA2 mutations have a higher lifetime risk of developing breast cancer, contralateral breast cancer, and ovarian cancer. According to a recent prospective study, the lifetime risk of BC for BRCA1 and BRCA2 carriers is around 70%, and the lifetime risk of ovarian cancer is 44% for BRCA1 and 17% for BRCA2 carriers. By the age of 40, the cumulative risk of developing BC is reported to be 24% for BRCA1 carriers and 13% for BRCA2 carriers, while the cumulative risk of developing ovarian cancer is 2% for BRCA1 carriers and 0% for BRCA2 carriers. Women who have a BRCA1/2 mutation should have bilateral salpingo-oophorectomy before the age of 35-40, after they have finished childbearing, to reduce their risk of developing ovarian cancer and BC.(11)

7. Ovarian stimulation

Ovarian stimulation process using hormone medications to produce multiple eggs.The most effective method for preserving fertility in women with breast cancer is cryopreservation of embryos or eggs. Oocyte retrieval, on the other hand, is preceded by ovarian stimulation via a hyper-estrogenic environment. Short-term estrogen exposure has raised concerns about the safety of traditional protocols, prompting the development of new ones aimed at counterbalancing estrogen exposure in women with breast cancer undergoing ovarian stimulation for fertility preservation. The addition of

the selective estrogen receptor (ER) modulator tamoxifen or the aromatase inhibitor letrozole to these alternative stimulation protocols has never been compared to standard ovarian stimulation in a randomized controlled trial (RCT).

Balkenende et al. in 2022 were the first to compare the efficacy of alternatives to traditional stimulation protocols, concluding that, despite a noticeable reduction in estradiol peak, alternative ovarian stimulation protocols containing tamoxifen or letrozole had no effect on the number of cumulus-oocyte complexes (COCs) retrieved at follicle aspiration. There was also no evidence of a difference in the number of oocytes or embryos banked or the number of canceled cycles. And the two antipode studies only mention that letrozole or tamoxifen may have a negative effect on fertilization and embryo quality during fertility preservation cycles. More research is required to confirm these findings.

The most commonly used protocol for stimulating patients with breast cancer is to administer letrozole 5 mg or 60 mg tamoxifen orally on days 2-3 of the cycle. After two days of letrozole treatment, a variable dose of recombinant FSH (rFSH) ranging from 150 to 300 IU/day is added. When the serum estradiol concentration exceeds 250 pg/mL or the follicles reach a diameter greater than 13 mm, GnRH antagonists are started to avoid an early peak of LH. Follicular growth is monitored until at least two follicles reach 20 mm in diameter, at which point ovulation is induced with GnRH agonists. The use of GnRH agonists was found to cause a faster and greater decline in estradiol levels than hCG trigger ovulation, without affecting the number of mature oocytes collected or the rate of fertilization. The extended version of this letrozole protocol, which also includes final rFSH and the induction of ovulation with GnRH agonists (triptorelin), has been used regardless of the molecular characteristics of breast cancer. (5)

8. Fertility preservation in women with endometriosis

8.1. Fertility preservation in endometriosis

Endometriosis is a chronic inflammatory disease that affects about 10% of reproductive-age women, with an even higher prevalence in infertile women. The presence of endometrial glands and stroma outside of the uterus, most commonly involving the pelvis, ovaries, and fallopian tubes, distinguishes it. Endometriosis can impair fertility through a variety of mechanisms, including anatomic distortion of the reproductive tract, decreased ovarian reserve, decreased oocyte and embryo quality and iatrogenic injury during surgery.(15)

Endometriosis is associated with decreased AMH levels, particularly in patients with ovarian endometriomas (OMA). The condition also affects antral follicle count (AFC), which can lead to accelerated ovarian aging and premature ovarian insufficiency (POI). Endometriosis also affects granulosa cell function and has genetic implications for follicle-stimulating hormone (FSH) receptor variants.

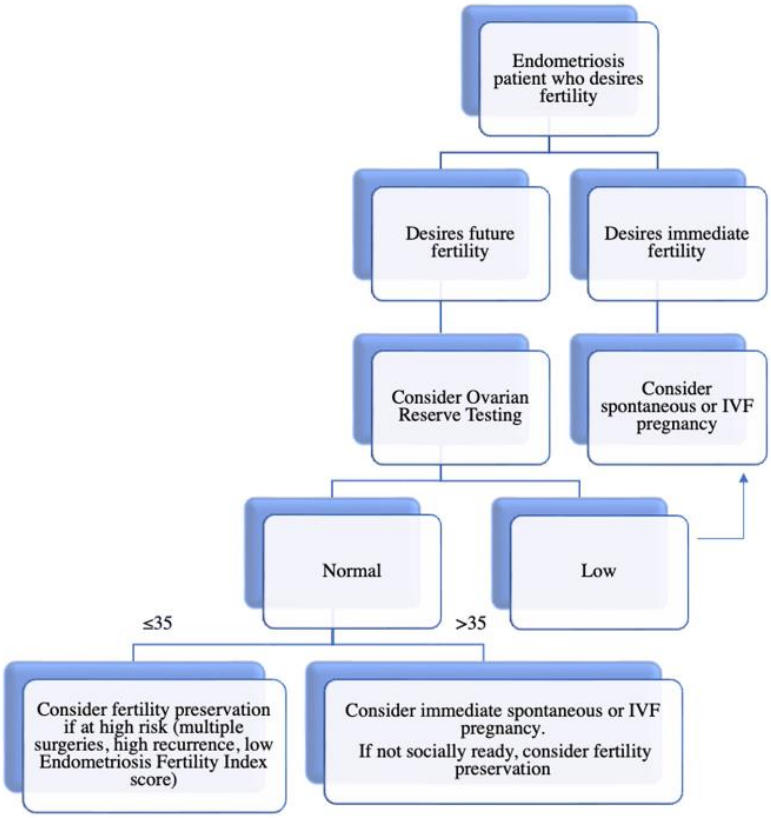
Ovarian endometriosis is associated with infertility due to the low AMH levels, peritoneal inflammation and the inadvertent removal of healthy ovarian tissue during surgery. Approximately half of endometriosis patients seeking fertility require advanced assisted reproduction techniques. Oocyte cryopreservation has emerged as a promising strategy for preserving fertility in these patients, particularly when discussed early in the diagnosis, ideally before the age of 35 and prior to surgical intervention. This is an excellent opportunity to discuss future fertility and the advantages of oocyte cryopreservation.(12)

Fertility preservation is difficult in endometriosis patients due to decreased ovarian reserve and oocyte/embryo quality. Ovarian endometriomas can impair ovarian reserve, resulting in lower AMH levels and oocyte yields. Studies suggesting various mechanisms of damage to the ovarian reserve, such as inadvertent removal of follicles, electrocoagulation damage, interruption of ovarian vascularization, and local inflammatory reactions.(12) The clinical impact on spontaneous conception and IVF

outcomes, however, is unknown. Endometriosis is linked to a decrease in mature oocyte retrieval and fertilization rates, as well as abnormal embryo development. Despite these obstacles, most studies show that endometriosis has little effect on IVF outcomes when compared to other causes of infertility. This emphasizes the importance of IVF and other fertility preservation methods for endometriosis patients seeking to maximize fertility.(15)

Cryopreservation of oocytes and embryos is effective, especially in young patients prior to surgical management. Studies show that non-surgical patients over the age of 35 have a higher ovarian response and live birth rate. However, due to limited evidence on efficacy, oocyte quality, and cost-effectiveness, widespread use in all endometriosis patients is premature. According to recent research, women over the age of 35 should vitrify at least 10-15 oocytes in order to achieve a cumulative live birth rate of 40-70% in 1-2 cycles. Due to age-related fertility decline, patients over the age of 35 should consider immediate pregnancy. (15)

Ovarian tissue cryopreservation (OTC) is used to preserve reproductive potential and is becoming more popular in the treatment of conditions such as endometriosis. There are two types of cryopreservation techniques: ovarian cortical tissue cryopreservation and whole ovary cryopreservation, each with different transplantation options. While there is evidence that OTC is effective for other conditions, there is limited evidence that it is effective in endometriosis patients. OTC has advantages such as timing flexibility, but it necessitates two surgical procedures.(15)



(15)

Figure 3

8.2. Impact of endometriosis surgeries on ovarian reserve

Endometriosis has a significant impact on fertility, with approximately 50% of patients requiring IVF for a live birth. The condition is classified into three types: superficial peritoneal endometriosis (SPE), ovarian endometrioma (OMA) and deep infiltrating endometriosis (DIE). Surgical removal of OMA has been linked to a decline in ovarian reserve, while fertility preservation through oocyte vitrification is suggested as a valid treatment option. The European Society for Human Reproduction and Endocrinology (ESHRE) advises women with extensive ovarian endometriosis to discuss the benefits and drawbacks of fertility preservation with their clinicians.(12)

Endometriosis patients should be counseled on reproductive planning and the risks of delayed childbearing due to both pathologic and iatrogenic causes of infertility.

Additionally, before beginning treatment, fertility preservation options should be considered.

While several mechanisms, including distorted pelvic anatomy, inflammatory mediated changes and decreased endometrial receptivity, have been implicated in the pathogenesis of endometriosis-related infertility, iatrogenic injury from surgical treatment is one of the most significant when considering fertility preservation.(15)

A 2014 Cochrane Review analyzing three randomized controlled trials discovered that laparoscopic treatment for stage I-II endometriosis was associated with an increase in live birth and clinical pregnancy rates when compared to diagnostic laparoscopy. While surgery may be beneficial for fertility in mild cases, data suggests that it may not be beneficial in advanced endometriosis patients.(15)

Consideration for fertility preservation is especially prudent in the case of endometriomas in a patient desiring future fertility because evidence overwhelmingly demonstrates the negative impact of surgery, including damage to the ovarian cortex with decrease in ovarian reserve. Significant reductions in AMH levels following endometrioma excision, particularly in women with bilateral endometriomas (up to 30% in unilateral versus up to 44% in bilateral endometriomas), support these findings.(15)

While some studies support the removal of endometriomas before natural conception, overall evidence does not support endometrioma surgery before IVF. Several reviews found that women who undergo endometrioma excision have similar IVF outcomes to those who do not have surgery. Therefore, endometriomas are not routinely removed before IVF. However, in cases where surgery may improve access for oocyte retrieval and prevent spillage of endometrioma contents, an individualized approach can be considered.(15)

There are no randomized controlled trials (RCTs) evaluating spontaneous conception and IVF outcomes in cases of DIE resection, and observational data is inconclusive. Expert consensus recommends IVF over surgery for women with DIE who want children, but a surgical approach may be favored for those experiencing infertility and pain. Repeat surgery does not improve fertility outcomes and IVF should be considered

before additional endometriosis surgery, unless pain management is a priority. Patients should be counseled on the risks and benefits of surgery, including its impact on future fertility and the possibility of ovarian reserve decline. Fertility preservation should be offered, particularly for those at risk of iatrogenic ovarian reserve injury. If surgery is chosen, efforts should be made to use techniques that minimize damage to the ovarian reserve.(15)

8.3. Surgical techniques to minimize iatrogenic effects on ovarian reserve

Cystectomy and ablation are surgical procedures used to reduce ovarian injury in endometriosis patients. Cystectomy is the standard procedure, but it causes more ovarian reserve injury than ablation. Ablation with plasma energy or a CO2 laser is less harmful. Cystectomy is currently the standard surgical approach for endometriomas. To protect the healthy cortex, the plane between the endometrioma and the ovarian cortex must first be identified. To avoid forceful tissue separation, controlled traction and counter traction should be used to peel the endometrioma from the cortex. If bleeding at the ovarian hilum occurs, electrosurgery should be used sparingly. Several studies show that suture or hemostatic sealants are superior to electrosurgery in terms of minimizing ovarian reserve injury. Despite several improved outcomes, such as pain resolution, spontaneous conception, and recurrence rates, cystectomy causes more injury to the ovarian reserve than ablative approaches.(15)

8.4. Reproductive counseling

Counseling and shared decision making are critical in the treatment of endometriosis and the preservation of fertility, especially before surgical intervention. Providers should be aware of the patient's treatment and fertility goals, as well as the limited evidence for routine fertility preservation in all endometriosis patients. However, there is promising evidence to recommend its use in young patients at high risk of diminished ovarian reserve. Patients should be counseled on the risks of IVF and/or surgery, as well as potential procedural risks in advanced disease. It is important to note that oocyte cryopreservation does not guarantee pregnancy, and the patient should be informed about the financial, psychological, and physical implications of fertility preservation.(15)

9. Infertility in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the most common form of lupus and is a multisystem autoimmune disease. Although the exact cause is unknown, hormonal and immunological characteristics, as well as genetic predisposition, are thought to be contributing factors. Disease presentation varies, but it is typically characterized by remission and relapse.

Fertility is a common concern for women with SLE. In addition to known indirect factors that influence a woman's ability to conceive, such as cytotoxic agents, other medications, advanced age and the disease's psychosocial effects, direct disease-related factors are thought to influence fertility. These include decreased ovarian reserve, irregular menstruation (as a result of disease activity), and the presence of antiphospholipid antibodies. The question of whether SLE has an intrinsic effect on fertility remains unanswered. (13)

SLE primarily affects women of childbearing age, making reproductive health concerns critical for rheumatologists who provide comprehensive care. Infertility as an aspect of SLE-related reproductive health is understudied, but of greater interest as assisted reproductive technology (ART) methods become increasingly sophisticated and more widely available. (13)

9.1. SLE and assisted reproductive technology

When fertility in women with SLE is impaired for any reason, ART may be required to achieve pregnancy. The safety of such elective procedures in SLE patients, particularly those with positive aPL or APS, is a major concern that necessitates guidance from both rheumatology and reproductive endocrinology and infertility (REI) specialists.

The procedures vary, but they typically include ovarian stimulation, oocyte retrieval, IVF, and the transfer of the fertilized embryo into the uterus. Oocytes can be frozen or fertilized after being retrieved—usually through transvaginal puncture following ovarian stimulation—by incubation with sperm or intra-cytoplasmic sperm injection. After fertilization and incubation, the embryo can be transferred into the woman's uterus at either the cleavage (2-3 days postretrieval) or blastocyst stage (5-6 days postretrieval). Blastocyst transfer has become more common in recent years; blastocysts can also be frozen and transferred later in a non-stimulated cycle.

Changes in protocol have reduced the risk and severity of ovarian hyperstimulation syndrome (OHSS), a condition in which cystic enlargement of the ovaries causes fluid shifts from the intravascular to the third space due to increased capillary permeability. Pre-implantation genetic testing of embryos prior to transfer can improve the likelihood that transferred euploid embryos result in successful implantation, clinical pregnancy, and live birth for some patients.

Ovarian stimulation is generally considered to be safe in patients with SLE if disease is clinically inactive and prophylactic anticoagulant medications are administered when

indicated. All SLE patients should be evaluated for disease activity, with ART postponed for those with moderate or severe disease activity.

While there are risks, such as SLE flare and thrombosis, complications are rare. IVF-induced thromboses have frequently occurred in the context of OHSS; however, the incidence and severity of OHSS have significantly decreased with current protocols that use GnRH-a rather than human chorionic gonadotropin to trigger final oocyte maturation.

Patients with SLE, particularly those without a long-term partner, may have medical and social reasons to seek oocyte cryopreservation. Many patients would benefit from cryopreserved oocytes in terms of pregnancy planning due to disease-related activity and age-related fertility decline. A woman taking pregnancy-incompatible medications like MMF or methotrexate (but not CYC) can continue her medication and safely freeze her eggs without fear of teratogenic effects, preserving her potential for biological offspring in the future when she no longer needs these medications.

Patients with SLE are advised to pursue pregnancy during periods of quiescent disease, which may result in postponed pregnancy plans and an older age with reduced fertility once disease quiescence is achieved. (13)

10. Infertility

Infertility is defined as a woman's inability to conceive after 12 months of unprotected sex. The term subfertility is sometimes used interchangeably with infertility or to describe any degree of reduced fertility. Infertility is common: in the United States, approximately 10%-15% of couples attempting to conceive experience infertility due to female and/or male factors; endocrine, anatomical, genetic, or behavioral changes; or for unknown reasons. A large multinational study of infertile couples conducted by WHO discovered that female factors were responsible in 37% of cases, male factors in 8% of cases, and male and female factors combined in 35% of cases.

Female infertility can be caused by abnormalities in the ovaries, uterus, fallopian tubes, or endocrine system. Tests for female infertility commonly include progesterone, thyroid function, prolactin, and ovarian reserve measurements. Ultrasound, sonohysterography, hysterosalpingography, hysteroscopy, and laparoscopy are imaging studies and procedures used to evaluate uterine anatomy, tubal patency, and the presence of endometriosis.

Ovarian reserve, which predicts fertility, is defined as the ovary's functional capacity (remaining oocyte quantity and quality). Oocyte quality refers to the likelihood that a fertilized oocyte will give birth to a live infant. Biochemical tests for ovarian reserve include follicle-stimulating hormone (FSH), estradiol, inhibin B, and anti-Müllerian hormone (AMH). Antral follicle count and ovarian volume are two ultrasonographic measurements. AFC and AMH levels are reported in studies that reflect ovarian reserve, including those involving SLE. Unlike FSH, AMH levels remain relatively stable throughout the menstrual cycle and are more sensitive and specific than other biochemical measures. Fertile women have values ranging from 1.0 to 3.5 ng/mL, while values below 1.0 ng/mL indicate reduced ovarian reserves. AMH testing is simpler to perform; multiple studies have found that AMH and AFC are equally effective in predicting ovarian reserve. OV is a less sensitive marker than AMH or AFC, with inter- and intracycle variability.(13)

11. Social freezing: “Putting Fertility on Hold”

Gender equality and improved women's rights have increased women's professional and educational opportunities, as well as their financial independence and empowerment. The age of first-time motherhood among women in the European Union (EU) has risen from 28.8 in 2013 to 29.3 in 2018, indicating a shift in reproductive aspirations. This deferral of childbearing years has serious reproductive consequences.

Women have a smaller reproductive window than men do. Women's potential for conception gradually declines after the mid-thirties, reaching a lower level after 35 years. Because of a decrease in the quantity and quality of primordial follicles, which is linked to a decreased likelihood of oocyte fertilization, an increased risk of aberrant embryos and fetal loss, women's fertility declines yearly until menopause.(16)

Women who want to preserve their fertility and reduce the effects of age-related fertility decline (ARFD) can now undergo elective oocyte cryopreservation (EOC). While this allows women to extend their reproductive lives, it does not ensure future live births.(9)

For social or medical reasons, more and more women are undergoing tissue or oocyte cryopreservation in an effort to increase the likelihood of having genetic offspring. In advance of age-related fertility decline and ineffective fertility treatments at older ages, women can preserve their fertility through social egg freezing (SEF). With a much higher success rate, freezing a woman's eggs is best done before the age of 35, when the quantity and quality of eggs start to decrease.(16)

EOC is more socially acceptable, promotes gender equality in society and strengthens women's reproductive autonomy. Planned oocyte cryopreservation appears to be a preferred method of preventing age-related infertility, despite controversy. It may also give women the impression that they are more financially, socially, and psychologically stable before becoming mothers.(16)

The process of social freezing typically involves the following steps: ovarian stimulation, egg retrieval, freezing and storage.

There is controversy surrounding the terminology used. The majority of women prefer the term "elective egg freezing." "Social egg freezing" draws attention to the socially embedded nature of women's reproductive choices. The phrases "non-medical egg freezing" and "egg freezing for non-medical reasons" are frequently used. The term "AGE banking" (oocyte banking for anticipated gamete exhaustion) originated from the idea that cryopreserved oocytes should be viewed as a preventive medical intervention that shields women against age-related declines in fertility.(16)

Since 2012, a growing number of fertility clinics across the globe have started offering women who wish to preserve their reproductive potential over an extended period of time the option to elective oocyte cryopreservation. Following many years of study, we are beginning to understand why more and more women globally are freezing their eggs elective rather than medical reasons. The most frequent reason given by women for delaying having children is that they do not have a partner who is suitable for starting a family. Professional factors, such as finishing school, advancing in one's career, and workplace rigidity—women view getting pregnant before the age of 35 as having an impact on their career—are the second reason.(16)

For healthy women between the ages of 30 and 41, elective egg freezing is permitted as a preventive medical measure against age-related infertility issues. The social benefits of egg freezing are obvious: women can preserve their fertility while pursuing career goals, achieving financial security or finding a suitable partner. Furthermore, this technology gives women of all reproductive ages the chance to become parents to genetic offspring when they achieve financial security and have enough emotional and mature support. (13)(16)

Conclusion

A comprehensive and insightful examination of the multifaceted field of fertility preservation is provided in this review.

It delves into the intersection of oncology and fertility preservation, addressing the impact of systemic treatments for breast cancer on fertility. The field of oncofertility has expanded due to a variety of factors, including an increase in the number of cancer survivors, the development and improvement of reproductive treatments, the introduction of novel oncologic medications and the extension of treatment durations.

It discusses fertility preservation options for women with conditions such as endometriosis and systemic lupus erythematosus. It also highlights the rising trend of social freezing and its impact on family planning.

With all the progress in our world today, we should not underestimate the unique and individual approach to every woman’s needs, because every woman should be at the center and every woman must get her own personal and individual care.

After reviewing the described methods of fertility preservation, I have realized that it was only the tip of an iceberg. Because this review focuses only on a few selected reasons that can lead women to the need of fertility preservation. Namely, there are many more conditions for which fertility preservation should be taken into consideration such as other types of cancer, autoimmune diseases, blood diseases, genetic and hereditary diseases etc. that may harm women's fertility and therefore lead them to its preservation.

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References

1. Varlas VN, Borș RG, Crețoiu R, Bălescu I, Bacalbașa N, Cîrstoiu M. Fertility-sparing surgery: a hopeful strategy for young women with cancer. J Med Life. 2023 Jul;16(7):974–80.

2. Hong YH, Park C, Paik H, Lee KH, Lee JR, Han W, et al. Fertility Preservation in Young Women With Breast Cancer: A Review. J Breast Cancer. 2023 Jun;26(3):221–42.

3. Bewtra C, Acharya N. Preservation of Fertility in Cancer Patients: A Narrative Review. Cureus. 2023 Oct;15(10):e47910.

4. Fisch B, Abir R. Female fertility preservation: past, present and future. Reprod Camb Engl. 2018 Jul;156(1):F11–27.

5. Boutas I, Kontogeorgi A, Koufopoulos N, Dimas DT, Sitara K, Kalantaridou SN, et al. Breast Cancer and Fertility Preservation in Young Female Patients: A Systematic Review of the Literature. Clin Pract. 2023 Nov 13;13(6):1413–26.

6. Park SJ, Han JY, Kim SW, Kim H, Ku SY. Current Position of Oncofertility in Adolescent Female Cancer Patients: A Comparative Review on Society Guidelines. Vivo Athens Greece. 2024;38(1):48–57.

7. Moragón S, Di Liello R, Bermejo B, Hernando C, Olcina E, Chirivella I, et al. Fertility and breast cancer: A literature review of counseling, preservation options and outcomes. Crit Rev Oncol Hematol. 2021 Oct;166:103461.

8. Fleury A, Pirrello O, Maugard C, Mathelin C, Linck C. Breast cancer and ovarian tissue cryopreservation: Review of the literature. J Gynecol Obstet Hum Reprod. 2018 Oct;47(8):351–7.

9. Kasaven LS, Saso S, Getreu N, O'Neill H, Bracewell-Milnes T, Shakir F, et al. Age-related fertility decline: is there a role for elective ovarian tissue cryopreservation? Hum Reprod Oxf Engl. 2022 Aug 25;37(9):1970–9.

10. Pai HD, Baid R, Palshetkar NP, Pai A, Pai RD, Palshetkar R. Oocyte Cryopreservation - Current Scenario and Future Perspectives: A Narrative Review. J Hum Reprod Sci. 2021;14(4):340–9.

11. Vuković P, Kasum M, Raguž J, Lonjak N, Bilić Knežević S, Orešković I, et al. FERTILITY PRESERVATION IN YOUNG WOMEN WITH EARLY-STAGE BREAST CANCER. Acta Clin Croat. 2019 Mar;58(1):147–56.

12. Mifsud JM, Pellegrini L, Cozzolino M. Oocyte Cryopreservation in Women with Ovarian Endometriosis. J Clin Med. 2023 Oct 26;12(21):6767.

13. Stamm B, Barbhaiya M, Siegel C, Lieber S, Lockshin M, Sammaritano L. Infertility in systemic lupus erythematosus: what rheumatologists need to know in a new age of assisted reproductive technology. Lupus Sci Med. 2022 Dec;9(1):e000840.

14. Das M, Son WY. In vitro maturation (IVM) of human immature oocytes: is it still relevant? Reprod Biol Endocrinol RBE. 2023 Nov 22;21(1):110.

15. Rangi S, Hur C, Richards E, Falcone T. Fertility Preservation in Women with Endometriosis. J Clin Med. 2023 Jun 28;12(13):4331.

16. Varlas VN, Bors RG, Albu D, Penes ON, Nasui BA, Mehedintu C, et al. Social Freezing: Pressing Pause on Fertility. Int J Environ Res Public Health. 2021 Jul 30;18(15):8088.

Figure 1 - Bewtra C, Acharya N. Preservation of Fertility in Cancer Patients: A Narrative Review. Cureus. 2023 Oct;15(10):e47910.

Figure 2- Fisch B, Abir R. Female fertility preservation: past, present and future. Reprod Camb Engl. 2018 Jul;156(1):F11–27.

Figure 3- Rangi S, Hur C, Richards E, Falcone T. Fertility Preservation in Women with Endometriosis. J Clin Med. 2023 Jun 28;12(13):4331.

Table 1- Kasaven LS, Saso S, Getreu N, O'Neill H, Bracewell-Milnes T, Shakir F, et al. Age-related fertility decline: is there a role for elective ovarian tissue cryopreservation? Hum Reprod Oxf Engl. 2022 Aug 25;37(9):1970–9.