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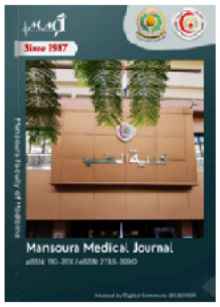

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Female Fertility Preservation: Current & Future Strategies

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Female Fertility Preservation: Current & Future Strategies

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Abstract

Recently, the spectacular progress in diagnosis, treatment, and prognosis of different malignancies has increased the demands on fertility preservation. Fertility impairment is considered one of the complications of radio/cytotoxic treatments in females who managed to overcome their cancer. This issue of fertility preservation also concerns those who are at risk of developing ovarian failure as well as healthy individuals who aim to overcome age-related fertility decline. Regarding female fertility preservation, there are various options that could be selected according to various factors, including the patient's age, type of the disease, as well as type and urgency of treatment. Among these options, embryo/oocyte cryopreservation as well as ovarian tissue cryopreservation and autotransplantation are the most reliable modalities for post- and pre- pubertal patients, respectively. Moreover, novel techniques such as the artificial ovary, isolation and cryopreservation of follicles and immature oocyte, potential pharmacological gonadoprotective agents, and stem cells transplantation have the potential to be used in the future. In this article, current and future female fertility preservation strategies are highlighted.

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Introduction

The preservation of female fertility is an important issue for young people at risk of becoming infertile due to diseases, treatments or simply ovarian dysfunction due to aging[1].

Infertility after cancer treatments is one of the major concerns for females with a history of cancer[2]. It is well recognized that chemotherapy and radiotherapy are greatly toxic to the ovaries, exposing pre-pubertal girls and women of childbearing age to an increased risk of premature ovarian insufficiency (POI) with subsequent infertility[2].

Advancements in the diagnosis and management of various cancers have dramatically improved the survival rates. However, such improvement has to be accompanied by a decrease in the adverse effects of treatments as well as an improvement in the quality of life of cancer survivors. Therefore, the development of fertility preservation techniques gives the patients appropriate choices before undergoing gonadotoxic treatments[1].

Furthermore, autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus as well as non-oncological hematological diseases such as aplastic anemia and thalassemia, besides various ovarian disorders, often necessitate treatments which can adversely affect future fertility[1].

There are various fertility preservation modalities that can be proposed depending on several factors including the nature of the pathology, the age of the patient, the required treatments, the urgency of such treatments, and whether there is a partner[3]. Some of these modalities have already shown their effectiveness and are now routinely used in assisted reproductive technology (ART) centers, while others still need further investigations[4].

Nowadays, the concept of fertility preservation has assumed greater importance. Therefore, this review will discuss the current and future female fertility preservation strategies and highlight their advantages and disadvantages.

Indications for female fertility preservation

Fertility preservation techniques can be offered to those who are at risk of infertility whatever the underlying etiology, whether malignancy, benign disorders, or social reasons[1].

Malignant diseases

One of the terrible long-term side effects of cancer treatments in females, whether chemotherapy or radiotherapy, is POI[2]. Chemotherapeutic drugs, particularly alkylating agents have shown to cause a high gonadal toxicity in females resulting in follicular loss, amenorrhea, and infertility[2]. Radiotherapy is not only capable of causing ovarian damage, but also can cause a decrease in uterine vascularity and volume, myometrial fibrosis, and endometrial injury[2].

Benign diseases

Benign conditions such as various hematological and autoimmune disorders may necessitate chemotherapy, radiation, and even bone marrow transplantation for their management, which can result in POI[1].

Bilateral benign ovarian tumors, recurrent ovarian torsion, and recurrent or severe ovarian endometriosis can also threaten future fertility[1]. Ovarian endometriomas are capable of inducing local intraovarian inflammation and can trigger follicular atresia with subsequent reduction in the ovarian reserve[5]. Furthermore, there is a rising

evidence that performing cystectomy on endometriomas causes considerable impairment in the ovarian reserve[5]. Other indications for fertility preservation include family history of POI and turner syndrome[3].

Social reasons

The age at which females are attempting their first pregnancy now has been steadily increasing, thus, age-related fertility decline or personal causes has evolved as an indication for elective fertility preservation[1].

Female fertility decreases significantly after the age of 35 years, thus, the term 'AGE banking' (oocyte banking for anticipated gamete exhaustion) has been anticipated to implicate preservation of the female childbearing potential in such cases[6].

The current strategies for female fertility preservation

Current techniques of fertility preservation include cryopreservation of embryos, oocytes or ovarian tissues, ovarian transposition, gonadal shielding, ovarian suppression, and conservative surgery[4](**Figure 1 & Table 1**).

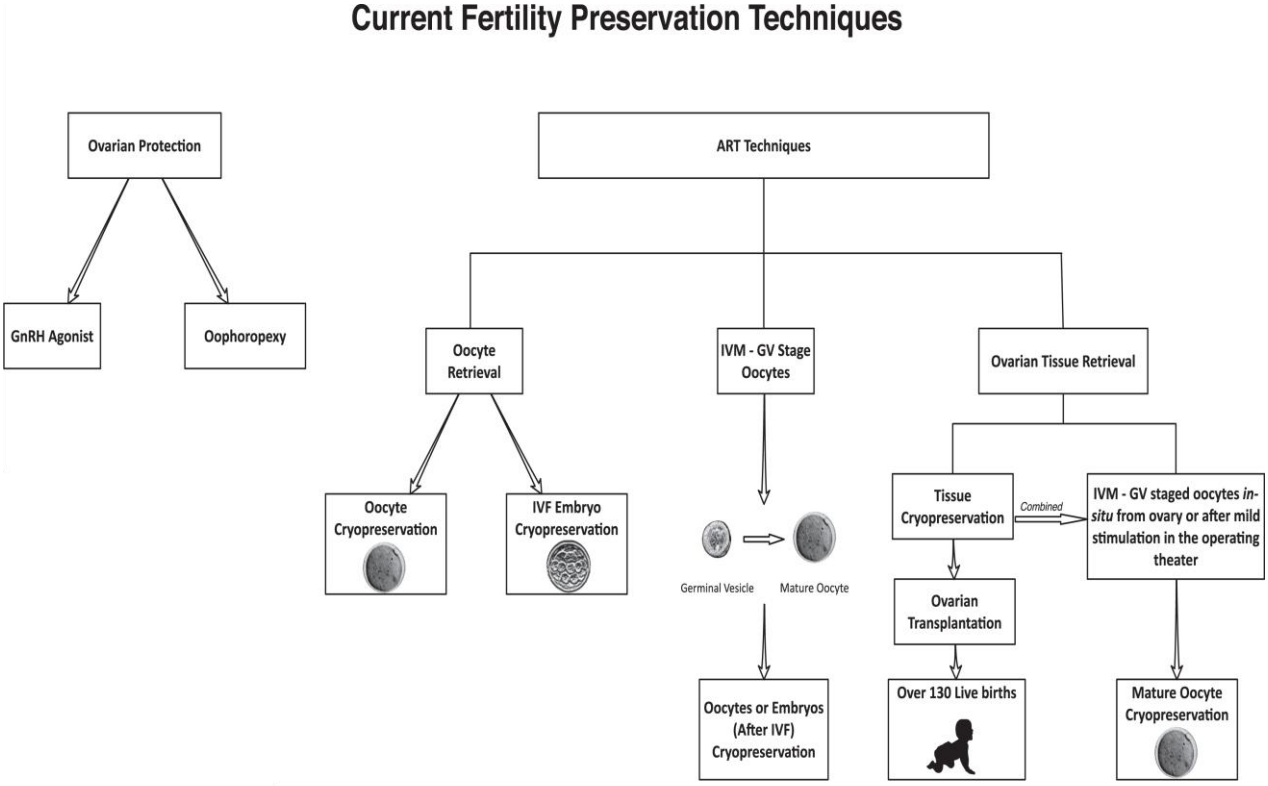

Figure 1. Diagram showing the current female fertility preservation modalities[3]. ART, assisted reproductive technology; GnRH, gonadotrophin-releasing hormone; GV, germinal vesicle; IVF, in vitro fertilization; IVM, in vitro maturation.

Table 1. Advantages and disadvantages of different female fertility preservation modalities[4].

Fertility preservation modality	Advantages	Disadvantages
Gonadotropin-releasing hormone agonists co-administration during cancer treatments	**1.** Some medical benefits	**1.** Controversial efficacy **2.** Potential side effects
Ovarian transposition	**1.** Relatively simple and rapid laparoscopic procedure	**1.** Only beneficial in patients undergoing pelvic radiotherapy
Embryo cryopreservation	**1.** Well established **2.** No risk of reimplantation of malignant cells	**1.** Only practicable in post-pubertal females with a male partner **2.** Requires time for controlled ovarian hyperstimulation **3.** Does not restore ovarian function
Oocyte cryopreservation	**1.** Well established **2.** Practicable in single females **3.** No risk of reimplantation of malignant cells	**1.** Only practicable in post-pubertal females **2.** Requires time for controlled ovarian hyperstimulation **3.** Does not restore ovarian function
Ovarian tissue cryopreservation and grafting	**1.** Practicable in pre-pubertal girls **2.** Do not delay cancer therapies **3.** Restore ovarian function	**1.** Age limitation (<35 years) **2.** Invasive surgical procedure

Embryo and oocyte cryopreservation

Embryo and oocyte cryopreservation are the most well-established and accepted strategies for female fertility preservation[4]. However, both necessitate the female to undergo at least one cycle of controlled ovarian hyperstimulation (COH) in order to proceed to oocyte retrieval, therefore, they can only be offered to post- pubertal females with enough time to undergo ovarian stimulation[4]. These procedures are not practicable in patients who need to begin gonadotoxic therapy urgently, as it takes 10-15 days for COH to trigger multiple follicular growth and oocytes retrieval[4].

One of the advantages of these techniques is that they carry no risk of reimplantation of malignant cells when performed in patients with malignancy[7]. It is obvious that these modalities provide the chance of achieving pregnancy, but do not restore the ovarian function[4].

Embryo cryopreservation requires a male partner, which brings all the legal and ethical concerns regarding the fate of the embryos if the patient died or she and her partner separated[8]. In contrast, oocyte cryopreservation can be undertaken by single women and conserves a woman's chance to procreate with a chosen partner in the future[8]. Oocyte cryopreservation **(Figure 2B)** can also be the perfect choice for those who have ethical or religious objections to embryo cryopreservation[8].

For patients who are to undergo in vitro fertilization (IVF), COH is classically initiated at the start of the follicular phase of the menstrual cycle[9]. However, for those seeking fertility preservation prior to undergoing gonadotoxic treatments, the initiation of their therapy is usually time sensitive, making a 4-6 week delay unacceptable[9]. For such patients, 'random start' protocol is hence applied, which involves initiating COH at any point in the menstrual cycle[10]. By Utilizing such protocol, patients take 2-3 weeks to complete the procedure, which is suitable for oncologic patients[10]. Noticeably, this protocol is shown to be as efficient as the conventional start protocols[10].

Ovarian tissue cryopreservation and autotransplantation

For pre-pubertal girls and women who cannot postpone the initiation of their anticancer treatment, cryopreservation of ovarian tissue with subsequent autotransplantation (**Figure 2A**) is a choice for preserving their fertility as it does not

necessitate COH and hence not significantly postpone treatment[7].

However, there are certain strict selection criteria that have to be applied. These include: the age being <35 years (when the ovarian reserve is still relatively high), a realistic chance of survival for 5 years, and at least a 50% risk of developing POI[11].

A great advantage of such technique is that it restores not only pregnancy chances, but also the ovarian function, and hence spontaneous pregnancy can occur[7]. Furthermore, this modality, when performed in pre-pubertal girls, can induce their puberty[7].

Unfortunately, such method presents age restriction because of the paucity of ovarian primordial follicles after the age of 35 years[11]. Moreover, one of the greatest concerns with ovarian tissue autotransplantation is the risk of malignant cells reimplantation, especially in the background of hematological malignancies[7].

Ovarian tissue can be reimplanted inside the pelvic cavity (orthotopic reimplantation) or outside the pelvic cavity (heterotopic reimplantation) such as the forearm and abdominal wall muscles[12]. Orthotopic implantation indicates grafting the thawed ovarian fragments whether on the exposed ovarian medulla, if at least one ovary is present **(Figure 3)**, or in a specially created peritoneal window if both ovaries are absent[12](**Figure 4**). Heterotopic ovarian tissue transplantation might be preferred in patients with severe pelvic adhesions or anatomic distortion due to radiotherapy, which might lead to ischemic injury of the implanted graft due to impairing its vascularization[7,12]. However, results regarding pregnancy rates are much poorer[12].

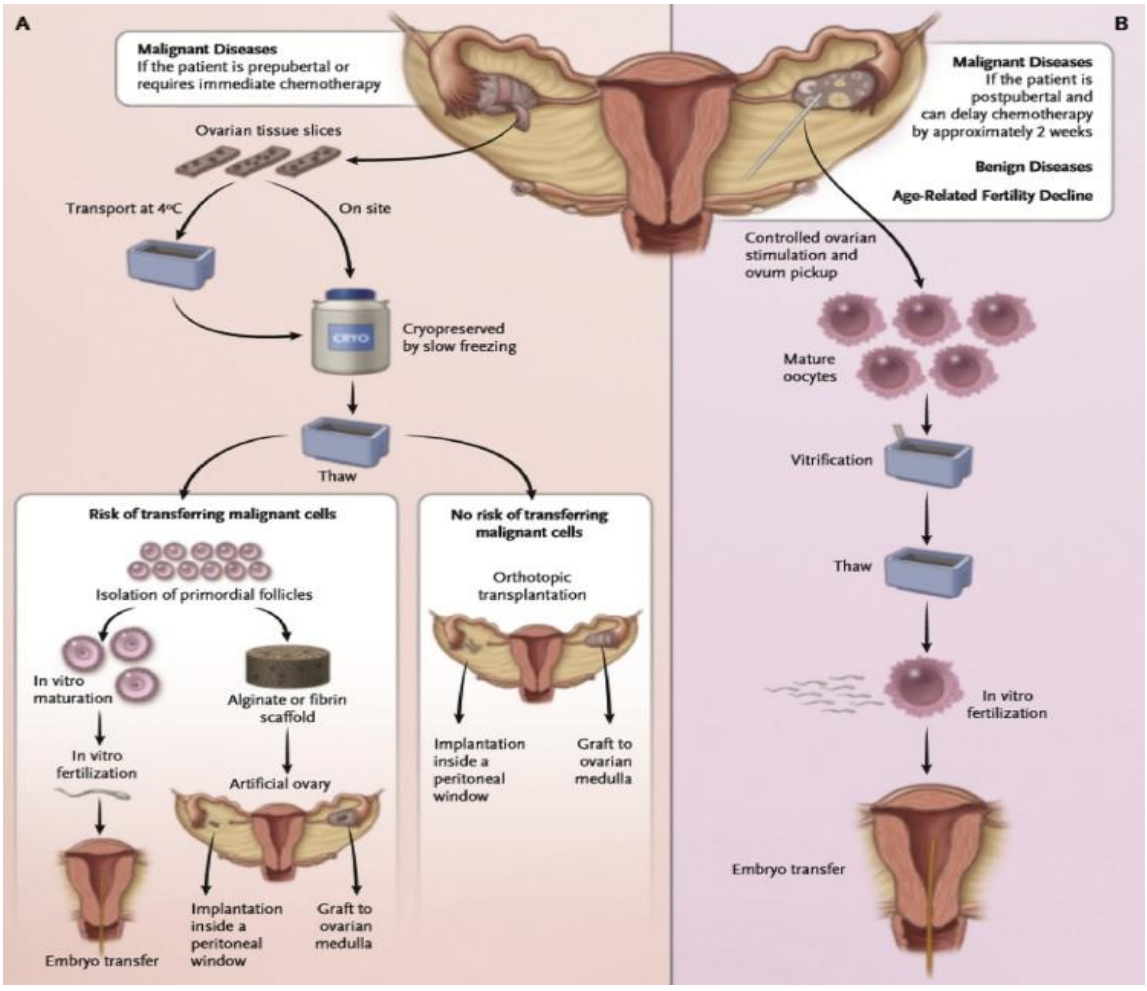

Figure 2. Schematic presentation of ovarian tissue cryopreservation (A) and mature oocytes cryopreservation (B)[7].

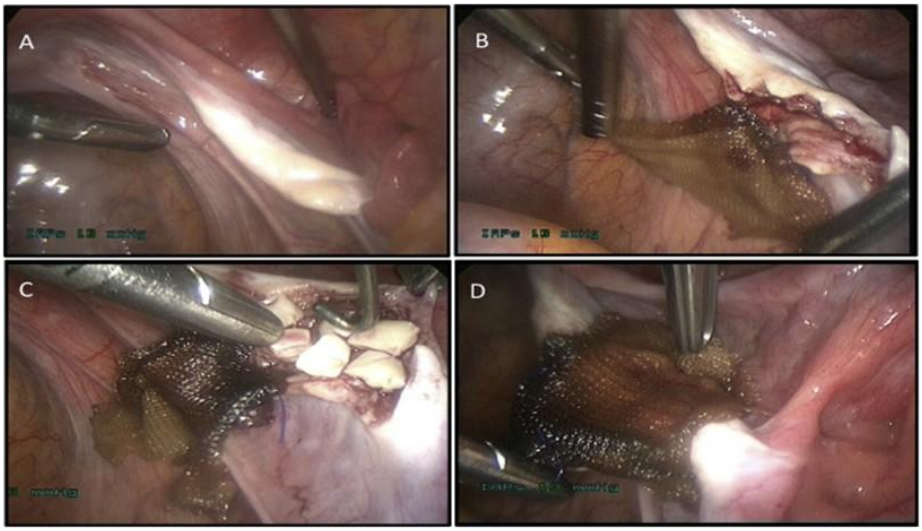

Figure 3. Laparoscopic image showing orthotopic ovarian tissue transplantation on the ovarian medulla[7].
A large piece of ovarian cortex is removed to gain access to the medulla and its vascular network (**A–B**). The ovarian fragments are placed on the medulla and covered with Interceed® and fibrin glue (**C–D).**

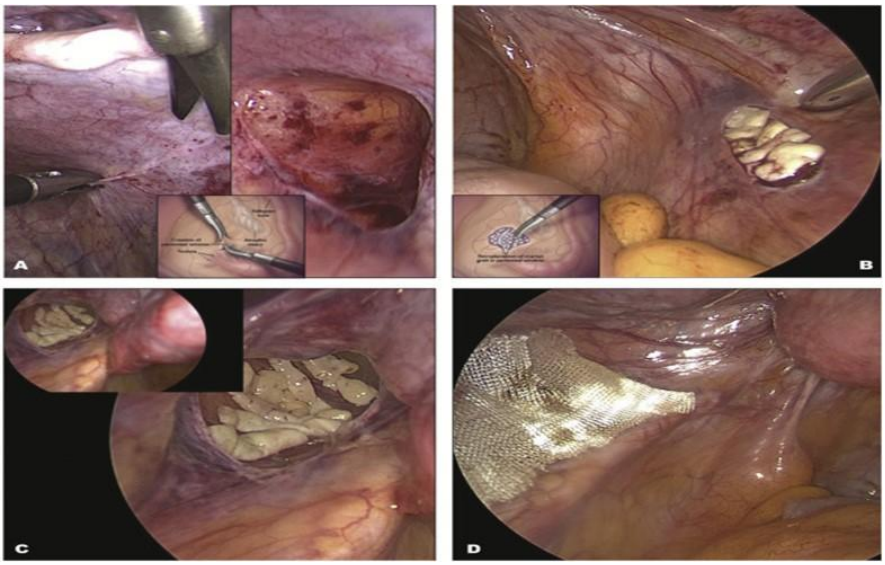

Figure 4. Laparoscopic image showing orthotopic ovarian tissue transplantation in a peritoneal window[7].
The incision for the peritoneal window is made on the anterior leaf of the broad ligament in an area where a vascular network is visible (retroperitoneal vessels) (**A**). The fragments are placed inside the window and subsequently covered with Interceed® and fibrin glue (**B–D**).

Alternative family planning options

These include oocyte donation, gestational carriers (surrogates), and adoption. For patients with ovarian factor of infertility, oocyte donation with subsequent IVF is an established modality for providing reproduction[13]. The oocyte from the donor is fertilized with the partner's sperm, and the resultant embryo is then transferred into the female's uterus[13]. Meanwhile, surrogacy is a fertility preservation modality which can be provided to women with uterine factor of infertility, or those with any contraindication for pregnancy in order to achieve motherhood by using embryos created by themselves or with the help of a donor to be transferred to the uterus of a gestational carrier[14]. Most notably, Islamic religion absolutely prohibits the use of third-party

reproductive assistance, such as gamete donation, surrogacy, and ovarian allotransplantation[15].

Minimizing the adverse effects of chemo & radio therapy on fertility

Shielding and ovarian transposition (Oophoropexy)

In pathologies treated by lower abdominal or pelvic irradiation only, patients could benefit from using a lead shield to protect their ovaries from the adverse effects of irradiation[16]. Moreover, ovarian transposition is a surgical procedure that can be performed before undergoing pelvic irradiation in order to place the ovaries away from the planned radiation field[17]. However, this approach is not always effective due to the radiation scatter[17]. Hence, during the procedure, it could be wise to take biopsies from the ovary for cryopreservation[17]. An additional limitation of such modality is the theoretical possibility of the presence of malignant cells in the ovaries, hence, it is necessary to provide counselling to patients regarding such risk and to exclude malignancies with a high risk of ovarian involvement from such modality[4]. Furthermore, ovarian failure might result from their migration back into the pelvis before completion of the radiotherapy course[17]. Thus, it is recommended that surgeons place metallic clips at the base of the ovary as a radio-opaque marker at the time of the operation in order to allow the oncologic radiologist to modify the field of radiation if needed[17].

Gonadotrophin-releasing hormone (GnRH) agonists

The use of GnRH agonists is a pharmacological method of ovarian protection during chemotherapy[18]. Anticipated mechanisms for their action include; the suppression of hypothalamic pituitary axis which leads to inhibition of the recruitment of preantral follicles and their development into antral follicles in order to lessen the decrease in the ovarian reserve[18]. Also, reduction of the ovarian perfusion which results in decreasing the concentrations of the chemotherapeutic agents reaching the ovaries[18]. Moreover, it has been reported that GnRH agonists may prevent chemotherapy-induced menorrhagia by abolishing the monthly menstrual flows[18].

Generally, the use of GnRH agonists as a mean of fertility preservation is still controversial and current guidelines do not support depending on such modality solely for fertility preservation[18].

Fertility sparing surgery in gynecologic cancers

Cervical cancer

There are several available fertility sparing surgeries for patients with cervical cancer[19]. Patients with stage 1A1 disease can be treated via loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC)[19]. While patients with tumor stage of 1A2 and small stage 1B1 (tumor size <2 cm), could be managed with simple or radical trachelectomy, respectively[19]. Alternatively, patients with stage IB disease could be treated with a combination of three courses of neoadjuvant platinum-based chemotherapy together with conservative surgery, which is considered an effective fertility-preserving option for such cases[20].

It should be noted that procedures of cervical excision are associated with a significant rise in the risk of obstetric complications such as preterm delivery and prematurity which is attributed to the loss of physiological function and anatomical support of the cervix[20].

Noticeably, for patients who are to undergo radiation therapy for cervical cancer, it is recommended using high-precision radiotherapy modalities such as magnetic resonance imaging (MRI)-guided brachytherapy, as an attempt to preserve the uterus and the ovaries from the radiation effect[20].

Endometrial cancer

Currently, there are limited uterine sparing approaches for fertile females with endometrial cancer. Options include hormonal therapy with progestins and/or hysteroscopic resection of the tumor[21]. Such approaches might be proposed to patients with well differentiated endometrial adenocarcinoma with no evidence of lymphovascular space invasion or myometrial invasion on imaging via transvaginal sonography or MRI[21]. It should be noticed that such patients have to be monitored with endometrial biopsy every 3 to 6 months for treatment response, putting into consideration that high-risk histological subtypes and higher stages of the disease are not applicable for such conservative treatment[21].

For early-stage endometrial cancer, studies have revealed that sparing the ovaries at the time of hysterectomy could be a safe option that does not increase the risk of tumor recurrence[21]. Since such patients are not capable of achieving spontaneous pregnancy, IVF with subsequent embryo transfer to a gestational carrier is an option that could be proposed[14]. In addition, uterine transplantation had resulted in live births and could be considered in selected cases to allow pregnancy[22].

Ovarian cancer

For reproductive age patients with early-stage ovarian cancer including the International Federation of Gynecology and Obstetrics (FIGO) stage IA & IB, and borderline ovarian tumors (BOTs), there are some available options for ovarian preservation. Amongst the options, unilateral salpingo-oophorectomy is a therapeutically safe choice for patients with unilateral BOT[23]. In addition, ovarian cystectomy could be preferred when both ovaries are involved and complete resection is achievable[23].

For early-stage (IA & IB) invasive epithelial ovarian cancer, utero-ovarian sparing surgery with complete peritoneal staging and pelvic/para-aortic lymphadenectomy has been shown to be a safe therapeutic option with successful pregnancy outcomes[24].

The future strategies for female fertility preservation

Future strategies (**Figure 5**) are based on the use of new pharmacological agents as well as the advances in ART, cryotechnologies, novel cell culture systems, bioengineering, and stem cells[3].

Potential new pharmacological gonadoprotective agents

As shown in **Figure (5)**, various pharmacological gonadoprotective agents have been investigated.

Sphingosine-1-phosphate (S1P) is an inhibitor of cell death[25]. It has been revealed that it interferes with doxorubicin-induced oocyte apoptosis[25].

Another potential gonadoprotective agent is imatinib, which is a tyrosine kinase enzyme inhibitor[26]. Its administration in combination with cisplatin has shown to preserve murine ovarian follicles[26].

Moreover, tamoxifen, a selective estrogen receptor modulator used in management of

estrogen-dependent tumors, has demonstrated promising results[27]. Studies revealed that tamoxifen administered to rats during chemotherapy had reduced follicular loss and decreased doxorubicin-induced oocyte destruction[27].

Furthermore, the immune modulator; AS101 inhibits the signalling pathway responsible for primordial follicle development and possesses anti-inflammatory and anti-apoptotic properties[28].

Also, it has been revealed that modifying the mode of administration of chemotherapeutic agent via encapsulating arsenic trioxide, used to treat against hematological malignancies, decreased ovarian damage in mice[29].

As regard gene therapy, it was found that mice deficient in the pro-apoptotic puma and noxa genes were protected from radiation-induced follicular atresia, suggesting that such therapy might play a role in follicular protection against irradiation[30].

Approaches to improve the life span and quality of grafted ovarian tissue

Early post transplantation hypoxia is still a concern due to its adverse effect on follicle survival. Therefore, improving vascularization of the grafted tissue is crucial in order to increase the survival rates of the follicles and improve the effectiveness of ovarian tissue transplantation[31](**Figure 5**).

Free-radical scavengers like melatonin and vitamin E as well as the component of the extracellular matrix; hyaluronan have antioxidant, anti-inflammatory, and anti-apoptotic effects[31]. Accordingly, host treatment with melatonin in combination with ovarian graft incubation with vascular endothelial growth factor (VEGF)-A, vitamin E, and hyaluronan-based biological glue has shown to enhance neovascularization and decrease apoptosis[31].

Additionally, it was revealed that the VEGF 111 isoform, which is resistant to proteolysis and has a relatively long plasma half-life, enhanced the angiogenesis of sheep ovarian cortical tissues transplanted to immunodeficient mice[32].

Moreover, incubation of human ovarian samples with basic fibroblast growth factor (bFGF) with subsequent implantation into immunodeficient mice has shown to enhance angiogenesis, increase granulosa cell proliferation and decrease apoptosis[33].

The artificial ovary

Over recent decades, tissue and organ bioengineering has offered promising solutions to otherwise unsolvable medical problems[34]. The artificial ovary is an extension of such efforts in the field of fertility preservation[34](**Figure 6**).

Researchers stated that the artificial ovary refers to "a temporary surrogate of the natural ovary in which isolated follicles, ovarian stromal cells and a combination of growth factors can be encapsulated together inside a biomaterial- based scaffold"[35]. Thus, it is suggested that the artificial ovary is able to play the two roles of the ovary; the exocrine function of female gamete production as well as the endocrine function of steroid hormone secretion[35].

The two major possible problems following any transplantation surgery are ischemic injury and immune rejection[34]. Since ovarian cells transplanted in the artificial ovary are of autologous origin, they do not induce serious immune reaction[36]. However, immune reaction against the scaffold is still a concern; hence, such

delivery biomaterials should be designed to minimize the immune response[36].

One of the solutions to alleviate ischemia and reperfusion injury is to use angiogenic biomaterial or co-transplantation of endothelial cells[36]. Additionally, treatment of the graft with vitamin E and VEGFs, as well as host treatment with vitamin E and melatonin was investigated in animal ovary transplantation studies and showed to improve graft outcomes[31].

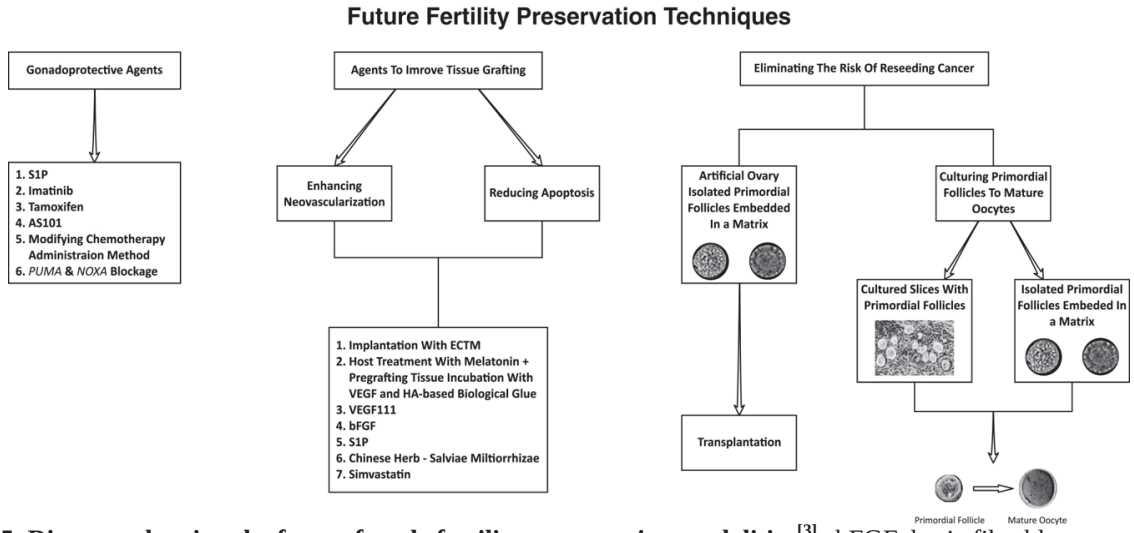

Figure 5. Diagram showing the future female fertility preservation modalities[3]. bFGF, basic fibroblast growth factor; ECTM, decellularized human extracellular matrix; HA, hyaluronan; S1P, sphingosine-1-phosphate; VEGF, vascular endothelial growth factor.

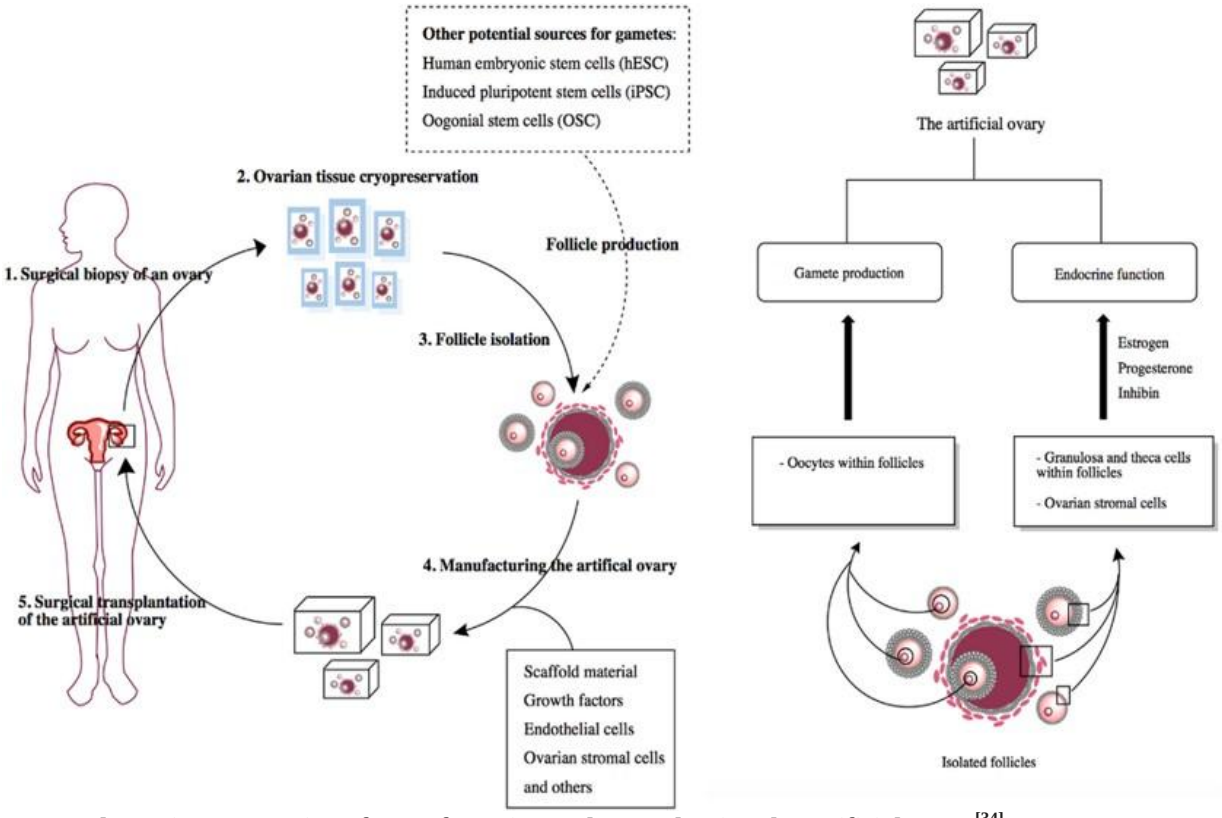

Figure 6. Schematic presentation of manufacturing and transplanting the artificial ovary[34].

In vitro maturation (IVM) of immature oocytes

This technique involves collection of immature oocytes from preantral and small antral ovarian follicles[37]. Those oocytes can be aspirated in vivo or collected ex vivo in combination with ovarian tissue cryopreservation. After that, they are incubated in a maturation medium, with final cryopreservation of mature oocytes or embryos produced via IVF[37](**Figure 2A**).

Noticeably, IVM can be applied in pre-pubertal girls, performed regardless of cycle phase, and can allow pregnancy with decreased risk of malignant cells reimplantation[37].

Uterine transplantation and ovarian tissue allotransplantation

Uterine transplantation is not only possible, but also a live birth has been born from a transplanted uterus[22]. This helps in achieving pregnancy for patients with an absolute uterine factor of infertility[9].

On the other hand, ovarian allotransplantation is emerging as a potential choice for patients with ovarian factor of infertility, especially those with repeated oocyte donation failure[13]. Indeed, this procedure has been performed between two sisters and led to the first published live birth after allografting ovarian tissue[38].

Stem cells transplantation

Stem cells transplantation showed promising results for POI cases as regard clinical, histopathological, and immunohistochemical outcomes[39].

Interestingly, there was a study on human subjects in which autologous iliac crest-derived bone marrow mesenchymal stem cells were injected into the ovaries of ten women with POI, in which two women regained menstruation and one achieved pregnancy with subsequent delivery of a mature living healthy female baby, named Zeinab[40](**Figure 7**). She is the first baby to be born to a POI mother treated with autologous stem cells transplantation[40].

Interestingly, researchers succeeded to isolate oogonial stem cells (OSCs) from human ovaries, which displayed the essential features of oocyte-generating germline stem cells[41]. This finding gives a strong impetus to investigate the use of patient-derived induced pluripotent stem cells (iPSCs), a type of pluripotent stem cells which can be generated from adult somatic cells such as skin fibroblasts and peripheral blood mononuclear cells via genetic reprogramming, to generate autologous primitive or pregranulosa cells that would be aggregated with OSCs to enable de-novo, ex-vivo generation of autologous human ovarian tissue[41](**Figure 8**).

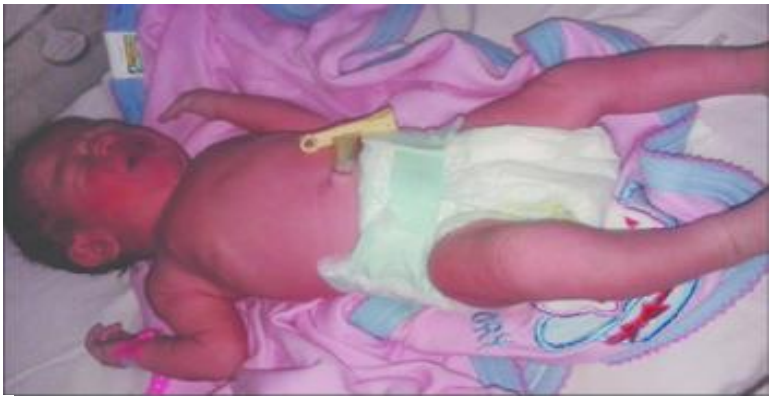

Figure 7. Zeinab's photo, the first baby to be born to a POI mother treated with autologous stem cells transplantation[40].

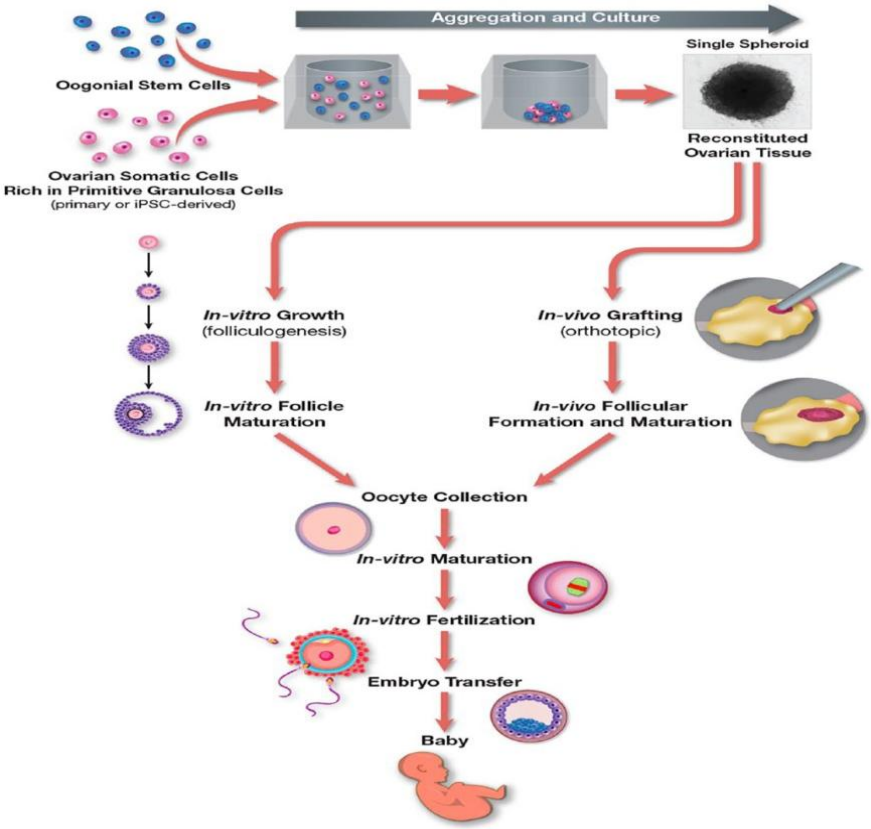

Figure 8. Working model for ex-vivo generation of autologous human ovarian tissue[41]. iPSCs; induced pluripotent stem cells.

Conclusion

The field of female fertility preservation has shown tremendous advances over the recent decades. Currently, embryo and oocyte cryopreservation remain the most effective and accepted modalities. However, in addition to the currently available modalities, there are numerous new ones that continue to hold promise to be used in the future. The artificial ovary, in vitro maturation of ovarian follicles and immature oocytes, and stem cell technologies are amongst these promising modalities that may be utilized in clinical practice in the near future.

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