HHS Public Access

Author manuscript

Cancer Metastasis Rev. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Cancer Metastasis Rev. 2015 December ; 34(4): 807–822. doi:10.1007/s10555-015-9600-2.

New advances in ovarian autotransplantation to restore fertility in cancer patients

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Abstract

Human ovary autotransplantation is a promising option for fertility preservation of young women and girls undergoing gonadotoxic treatments for cancer or some autoimmune diseases. Although experimental, it resulted in at least 42 healthy babies worldwide. According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic literature review was performed for all relevant full-text articles published in English from 1 January 2000 to 01 October 2015 in PubMed to explore the latest clinical and research advances of human ovary autotransplantation. Human ovary autotransplantation involves ovarian tissue extraction, freezing/thawing, and transplantation back into the same patient. Three major forms of human ovary autotransplantation exist including (a) transplantation of cortical ovarian tissue, (b) transplantation of whole ovary, and (c) transplantation of ovarian follicles (artificial ovary). According to the recent guidelines, human ovary autotransplantation is still considered experimental; however, it has unique advantages in comparison to other options of female fertility preservation. Human ovary autotransplantation (i) does not need prior ovarian stimulation, (ii) allows immediate initiation of cancer therapy, (iii) can restore both endocrine and reproductive ovarian functions, and (iv) may be the only fertility preservation option suitable for prepubertal girls or for young women with estrogen-sensitive malignancies. As any other fertility preservation option, human ovary autotransplantation has both advantages and disadvantages and may not be feasible for all cases. The major challenges facing this option are how to avoid the risk of reintroducing malignant cells and how to prolong the lifespan of ovarian transplant as well as how to improve artificial ovary results.

Keywords

Ovary autotransplantation; Female fertility preservation; Cancer; Cryopreservation; *In vitro* maturation; Oncofertility

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

1 Introduction

To preserve fertility of young women and girls especially those undergoing gonadotoxic treatments for cancer or some autoimmune diseases, several options are offered including embryo freezing, egg freezing, ovary autotransplantation, *in vitro* maturation (IVM), and ovarian protection [1-5].

According to the most recent female fertility preservation guidelines [6-21], human ovary autotransplantation is still considered experimental although it resulted in at least 42 healthy babies worldwide without any increased risk for miscarriage or congenital anomalies. Technically, human ovary autotransplantation involves ovarian tissue extraction, freezing/thawing, and transplantation back into the same patient. It is a promising option as it has several unique advantages in comparison to embryo freezing and egg freezing, the only two established options for female fertility preservation [22-27].

In this review, we explore the latest clinical and research advances of human ovary autotransplantation and investigate in detail its advantages and disadvantages as an option for female fertility preservation. We also suggest an updated model for integration of human ovary autotransplantation with the other options of female fertility preservation.

2 Methods

According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review of the literature was performed for all relevant full-text articles published in English from 1 January 2000 to 1 October 2015 in PubMed to explore the latest clinical and research advances of human ovary autotransplantation. Based on these inclusion criteria, the following electronic search strategy was performed in PubMed: (human ovary autotransplantation AND full text[sb] AND (“2000/01/01”[PDat]: “2015/10/01”[PDat]) AND English[lang]).

The full-text articles identified from the initial search underwent screening for titles and abstracts, then were checked for eligibility according to the inclusion criteria. Only the full-text articles that focus primarily on human ovary autotransplantation were included and fully reviewed. Data was extracted from the text, tables, graphs, and references of the included articles.

3 Results

A total of 163 full-text articles were identified from the initial search. After screening titles and abstracts, all 163 full-text articles were checked for eligibility according to the inclusion criteria. Only 147 full-text articles that focus primarily on human ovary autotransplantation were included and fully reviewed. PRISMA flow diagram of the systematic review process is illustrated in Fig. 1. Some significant articles were not identified from the initial search, but we reviewed them as well. Therefore, the final reference list was generated on the basis of originality and relevance to the broad scope of this review.

As an option for female fertility preservation, human ovary autotransplantation involves ovarian tissue extraction, freezing/thawing, and transplantation back into the same patient. Basically, there are three major types of human ovary autotransplantation including (a) transplantation of cortical ovarian tissue (orthotopic or heterotopic), (b) transplantation of a whole ovary, and (c) transplantation of ovarian follicles (artificial ovary) [22-27].

To date worldwide, the only forms of human ovary autotransplantation resulted in healthy live births are cortical ovarian tissue orthotopic transplantation (40 babies) and heterotopic transplantation (2 babies) although an accurate international registry is highly required (Tables 1, 2, and 3) [28-60].

In this section, we discuss in detail ovarian tissue extraction, ovarian tissue freezing/thawing as well as the three major types of human ovary autotransplantation.

3.1 Ovarian tissue extraction

Ovarian tissue is extracted surgically via laparoscopy, mini-laparotomy, or laparotomy. It should be indicated before initiation of gonadotoxic treatments for cancer or some autoimmune diseases. If feasible, it may be performed in the same setting with surgical ovarian transposition (oophoropexy) or surgical excision of primary pelvic and abdominal malignancies [22, 23, 61]. Ovarian tissue extraction is also indicated in some nonmalignant conditions such as benign ovarian tumors, severe or recurrent endometriosis, BRCA1 or BRCA2 mutation carriers, risk of premature ovarian failure, transgender operations, and bone marrow transplantation [22-26].

Three surgical possibilities of ovarian tissue extraction exist including partial, unilateral, or bilateral oophorectomy. If clinically reasonable, it is usually recommended to excise at least half of one ovary (partial oophorectomy), while the other ovary is left intact *in situ* to act as an ideal site for future orthotopic autotransplantation. The remaining ovary may also keep the potential for spontaneous resumption of endocrine and reproductive ovarian functions after gonadotoxic treatments. However, if severe ovarian damage is highly expected due to scheduled aggressive chemotherapy and radiotherapy, unilateral or bilateral oophorectomy can be performed as prophylaxis. In case future autotransplantation of a whole ovary is planned, excision of an ovary with a large part of its vascular pedicle is then a must [22-25]. Surgical excision of less than half of one ovary may put the whole procedure of ovarian tissue freezing and autotransplantation at risk for suboptimal histological and functional investigations of ovarian tissue before and after freezing and thereafter at risk for reintroducing malignant cells, transplanting nonviable ovarian tissue, or transplanting ovarian tissue with poor endocrine and reproductive functions [6-21].

Immediately after ovarian tissue extraction, the excised tissue is transported on ice to the local laboratory for further processing. If the local laboratory team is less experienced, the excised ovarian tissue could be shipped within 24 h under special transport conditions to centralized cryobanks for further processing by experts. After histological examination of a portion to exclude malignancy, most of the excised ovarian tissue is frozen for future autotransplantation. When possible, another portion (~20 %) of the excised ovarian tissue

may be processed as fresh for future transplantation of ovarian follicles (artificial ovary), IVM of oocytes or other research purposes [62, 63].

3.2 Ovarian tissue freezing

Ovarian follicles are the functional units of human ovary. Histologically, most of ovarian follicles are located within the ovarian cortex, and about 90 % of them are in the primor-dial stage. By freezing ovarian cortex, most of primordial follicles are preserved with favorable survival rate and uncompromised developmental potential due to their small size and low metabolic rate that make them resistant to cryoinjury [64-66]. Ovarian tissue freezing involves cryopreservation of cortical ovarian tissue or cryopreservation of a whole ovary either by slow freezing or by vitrification. To date, the standard method for ovarian tissue freezing is slow freezing; however, vitrification is also encouraged due to its promising results [67-71]. As a preparation for freezing, ovarian cortex should be dissected from medulla and further cut into ultra-thin strips (~10×5×1 mm each), slices (~4×2×1 mm each), or cubes (~2 mm^3 each). In case of cryopreservation of a whole ovary, a large part of its vascular pedicle must be present *in situ*. The ultra-thinness of ovarian cortical pieces or the presence of the vascular pedicle of a whole ovary is essential not only for proper perfusion of cryoprotectants but also for efficient revascularization after autotransplantation [22-25]. Some oocytes may expel spontaneously in the medium during dissection of the extracted ovarian tissue and then can be used for IVM [72-74] and subsequent *in vitro* fertilization (IVF), resulting recently in a reported live birth [75].

Slow freezing is the standard method for cryopreservation of cortical ovarian tissue or whole ovary. It involves exposure of cortical ovarian tissue or whole ovary to lower concentrations of cryoprotectants followed by slow cooling to −140 °C at low rates (~1 °C/min) via an automated freezing machine. It carries a very low risk for intracellular crystallization. However, it is a time-consuming method (within several hours) and usually needs a computerized freezing machine [64-71]. To date, several protocols for slow freezing/thawing have been described and at least 39 live births were reported worldwide after slow freezing/thawing of human cortical ovarian tissue (Tables 1 and 2) [28-57, 60].

Vitrification is a promising cryopreservation method as it has comparable outcomes to slow freezing. Vitrification involves exposure of cortical ovarian tissue or whole ovary to higher concentrations of cryoprotectants followed by ultra-rapid cooling to −196 °C at very fast rates (~20,000 °C/min) by direct plunging into liquid nitrogen. Vitrification is a cost-effective method as it is simple, time-saving (within few minutes), and it does not need an expensive freezing machine. Vitrification carries a very low risk for intracellular crystallization. However, it carries a risk for cellular toxicity and osmotic trauma due to higher concentrations of cryoprotectants as well as a risk for contamination due to direct exposure to liquid nitrogen [64-71]. To date, several protocols for vitrification/warming have been described, but only three live births were reported worldwide after vitrification/warming of human cortical ovarian tissue (Tables 1 and 2) [58, 59].

A group of histological and functional investigations of ovarian tissue should be performed before and after freezing to exclude the risk of reintroducing malignant cells, transplanting nonviable ovarian tissue, or transplanting ovarian tissue with poor endocrine and

reproductive functions. Examples of these investigations include histological examination, transmission electron microscopy, immunohistochemistry, terminal deoxynucleotidyl transferase-mediated biotinylated deoxyuridine triphosphate nick end-labeling (TUNEL) assay, polymerase chain reaction (PCR), estradiol and progesterone production *in vitro*, and xenografting [76-83]. After freezing, the ovarian tissue is stored in liquid nitrogen at −196 °C for up to 10 years. When the patient becomes cancer-free, her frozen ovarian tissue can be thawed and transplanted back to her (autotransplantation) in order to resume the endocrine and reproductive ovarian functions [6-21, 84].

3.3 Orthotopic autotransplantation of ovarian tissue

Orthotopic autotransplantation of ovarian tissue refers to transplantation of frozen-thawed cortical ovarian tissue back to the same patient into pelvic sites such as the remaining ovary, ovarian fossa, or broad ligament. It aims to resume both endocrine and reproductive ovarian functions. Usually, at least half of one ovary is excised via laparoscopy or mini-laparotomy. After dissection from medulla, ovarian cortex is further cut into ultra-thin pieces for cryopreservation via slow freezing as standard or via vitrification as a promising alternative. When autotransplantation is decided, avascular grafting of the frozen-thawed cortical ovarian tissue pieces is performed into the remaining ovary, ovarian fossa, or broad ligament via laparoscopy or mini-laparotomy [85-90].

Orthotopic autotransplantation of frozen-thawed cortical ovarian tissue has several advantages including the following: (1) It requires no prior ovarian stimulation nor delay in cancer treatment; (2) it provides normal environment for follicle and oocyte development; (3) it allows spontaneous pregnancy, otherwise further ovarian stimulation, ovum pickup, and IVF can be performed; and (4) it may reduce the risk of reintroducing malignant cells due to avascular grafting [22-27, 85-90]. However, orthotopic autotransplantation of frozen-thawed cortical ovarian tissue has also some disadvantages including the following: (1) It carries the risk of reintroducing malignant cells especially in case of ovarian malignancies or in malignancies that may metastasize in ovaries; (2) it may increase post-grafting ischemia and follicle atresia due to avascular grafting; and (3) although it allows spontaneous pregnancy, spontaneous pregnancy may occur due to ovulation from the remaining ovary and not from the orthotopically grafted cortical ovarian tissue [22-27, 85-91]. To reduce the risk of reintroducing malignant cells, histological examination, immunohistochemistry, polymerase chain reaction, and long-term xenografting of ovarian tissue portion can be performed [77-83]. To reduce the window of post-grafting ischemia that may be responsible for atresia of ~70 % of follicles, angiogenic and antiapoptotic factors, gonadotropins, antioxidants, and mesenchymal stem cells (MSCs) can be used to enhance neovascularization and to prolong the lifespan of ovarian transplant [92-97].

With a great variability observed, ovarian function after orthotopic autotransplantation of frozen-thawed cortical ovarian tissue may resume 2–9 months post-operatively and it may last for up to 7 years. To date, this technique has resulted in at least 40 healthy babies worldwide; most of them were due to spontaneous pregnancies without the need for IVF (Tables 1 and 2) [28-59]. Although an accurate international registry is highly required, it is roughly estimated that the live birth rate per cortical ovarian tissue transplant is ~30 % [56].

In contrast, orthotopic transplantation of fresh and frozen-thawed cortical ovarian tissue was successful between monozygotic twin sisters and resulted in healthy babies [53-56].

Orthotopic autotransplantation of frozen-thawed cortical ovarian tissue is indicated as a fertility preservation option for young women (<40 years old), and girls scheduled to receive gonadotoxic treatments for cancer or some autoimmune diseases. It may be the only fertility preservation option suitable for prepubertal girls or for young women with estrogen-sensitive malignancies where ovarian stimulation and embryo or egg freezing are contraindicated [22]. Recently, the first live birth after orthotopic autotransplantation of cortical ovarian tissue cryopreserved during childhood has been reported [34].

According to several studies, systematic reviews and meta-analyses assessing the risk of reintroducing malignant cells, orthotopic autotransplantation of frozen-thawed cortical ovarian tissue should be contraindicated in ovarian carcinomas and malignancies that may metastasize in ovaries such as leukemia (high risk), gastrointestinal cancer (moderate risk), breast cancer, lymphoma, gynecological malignancies, and sarcoma of the bone and connective tissue (low risk). The risk of metastasizing into the ovaries is related not only to the type but also to the stage of the primary cancer at the time of ovarian tissue extraction [98-100]. In such cases, IVM or ovarian follicle transplantation (artificial ovary) may be offered as alternatives [101-103]. It is also not recommended to perform orthotopic autotransplantation of frozen-thawed cortical ovarian tissue in relatively old patients (>40 years old) or in patients with poor ovarian reserve [22].

For decades in animal research, orthotopic autotransplantation of frozen-thawed cortical ovarian tissue was successful and resulted in healthy offsprings in large mammals as sheep [104, 105].

3.4 Heterotopic autotransplantation of ovarian tissue

Heterotopic autotransplantation of ovarian tissue refers to transplantation of frozen-thawed cortical ovarian tissue back to the same patient into extrapelvic sites such as the subcutaneous space of abdominal wall or forearm. It aims to resume both endocrine and reproductive ovarian functions. Usually, at least half of one ovary is excised via laparoscopy or mini-laparotomy. After dissection from medulla, ovarian cortex is further cut into ultra-thin pieces for cryopreservation via slow freezing as standard or via vitrification as a promising alternative. When autotransplantation is decided, avascular grafting of the frozen-thawed cortical ovarian tissue pieces is performed into the subcutaneous space of abdominal wall or forearm [85-90].

Heterotopic autotransplantation of frozen-thawed cortical ovarian tissue has several advantages including the following: (1) It requires no prior ovarian stimulation nor delay in cancer treatment, (2) it is surgically easier and considered as a good alternative to orthotopic autotransplantation in case of severe pelvic adhesions or poor pelvic vasculature, (3) it allows easy monitoring of the grafted ovarian tissue, and (4) it may reduce the risk of reintroducing malignant cells due to avascular grafting [22-27, 85-90]. However, heterotopic autotransplantation of frozen-thawed cortical ovarian tissue has also some disadvantages including the following: (1) It carries the risk of reintroducing malignant cells especially in

the case of ovarian malignancies or in malignancies that may metastasize in ovaries; (2) it may increase post-grafting ischemia and follicle atresia due to avascular grafting; (3) it provides abnormal environment for follicle and oocyte development; (4) it does not allow spontaneous pregnancy; therefore, subsequent ovarian stimulation, ovum pickup, and IVF must be performed [22-27, 85-90].

To reduce the risk of reintroducing malignant cells and the window of post-grafting ischemia, same measures as described in orthotopic autotransplantation can be applied [77-83, 92-97].

With a great variability observed, ovarian function after heterotopic autotransplantation of frozen-thawed cortical ovarian tissue may resume 2–9 months post-operatively and it may last for up to 7 years. To date, this technique has resulted in the first two babies worldwide (Tables 1 and 2) [60]; in addition, it resulted in a four-cell embryo [106], a biochemical pregnancy [107], and a clinical pregnancy [108].

Heterotopic autotransplantation of frozen-thawed cortical ovarian tissue is indicated as an alternative to orthotopic autotransplantation in case of severe pelvic adhesions or poor pelvic vasculature due to previous intensive pelvic irradiation. It has also the same contraindications as described in orthotopic autotransplantation [22, 98-100].

In animal research, heterotopic autotransplantation of frozen-thawed cortical ovarian tissue was successful and resulted in healthy offsprings in large mammals as monkey [109].

3.5 Autotransplantation of whole ovary

Autotransplantation of whole ovary refers to transplantation of frozen-thawed whole ovary with its vascular pedicle back to the same patient. It aims to resume both endocrine and reproductive ovarian functions as well as to overcome post-grafting ischemia and follicle atresia. One whole ovary is excised with a large part of its vascular pedicle (≥5 cm of the infundibulopelvic ligament) via laparoscopy or mini-laparotomy. The whole ovary must then undergo immediate cryoperfusion and cryopreservation via slow freezing as standard or via vitrification as a promising alternative. When autotransplantation is decided, vascular grafting and anastomosis of frozen-thawed whole ovary back to the same patient is performed via mini-laparotomy or laparotomy [110-118].

Autotransplantation of frozen-thawed whole ovary has several advantages including the following: (1) It requires no prior ovarian stimulation nor delay in cancer treatment; (2) it provides normal environment for follicle and oocyte development; (3) it allows spontaneous pregnancy, otherwise further ovarian stimulation, ovum pickup, and IVF can be performed; (4) it should reduce post-grafting ischemia and follicle atresia due to vascular grafting [110-118]. However, autotransplantation of frozen-thawed whole ovary has also some disadvantages including the following: (1) It has a higher risk of cryoinjury during freezing due to inadequate diffusion of cryoprotectants throughout the entire ovary, nonhomogenous cooling rate between the core and the periphery of the ovary, or cryoinjury of ovarian vasculature; (2) it has a higher risk of reintroducing malignant cells especially in case of ovarian malignancies or in malignancies that may metastasize in ovaries; (3) there is a

surgical difficulty of vascular anastomosis due to the small size of ovarian artery (~0.5 mm in diameter), short ovarian vascular pedicle (~5 cm in length), discrepancy between the diameters of graft and recipient vessels, and possible failure of microvascular anastomosis; (4) it has a higher risk of post-operative vascular complications including anastomotic bleeding, pseudoaneurysm, stenosis, or microvascular thrombosis; (5) its vascular complications can severely affect the survival of the entire ovary leaving no other attempt for transplantation [110-118].

To reduce the risk of reintroducing malignant cells, same measures as described in orthotopic autotransplantation can be applied [77-83]. To reduce vascular complications, microvascular anastomosis should be performed by an expert to attempt different types of anastomosis when needed such as end-toend, end-to-side, or fishmouth modifications [113, 119]. In the case of damaged remaining ovary by previous gonadotoxic treatments, its vascular pedicle may be used for vascular anastomosis of the transplanted frozen-thawed ovary [120].

After transplantation of frozen-thawed whole ovary, resumption of ovarian function is questionable. To date, this technique has not resulted yet in any reported live births. However, it is important to mention that fresh whole ovary transplantation between a donor and a recipient was successful with one reported live birth [121].

Autotransplantation of frozen-thawed whole ovary is still in research settings as an option for female fertility preservation. It has also the same contraindications as described in orthotopic autotransplantation [22].

In animal research, autotransplantation of frozen-thawed whole or hemi ovary was successful in large mammals as sheep and resulted in healthy offsprings [122-125].

3.6 Transplantation of ovarian follicles (artificial ovary)

Transplantation of human ovarian follicles refers to reimplantation of isolated preantral ovarian follicles into a biodegradable artificial ovary made of a three-dimensional alginate matrigel matrix. It aims to resume reproductive ovarian function as well as to avoid the risk of reintroducing malignant cells. At least half of one ovary is excised via laparoscopy or mini-laparotomy. Isolation of preantral ovarian follicles from ovarian cortex can be performed mechanically and/or enzymatically before or after cortical ovarian tissue freezing via slow freezing or vitrification. However, isolation of preantral ovarian follicles from fresh ovarian cortex improves the results. After isolation, preantral ovarian follicles are reimplanted into a biodegradable artificial ovary made of a three-dimensional alginate matrigel matrix. To allow follicular development, the biodegradable artificial ovary containing preantral follicles may be either cultured *in vitro* or *in vivo* via xenotransplantation into nude mice or theoretically via autotransplantation into the same patient. After the preantral ovarian follicles reach antral stage, the oocytes can be isolated for further IVM and IVF [23, 126-131].

Transplantation of human ovarian follicles has several advantages including the following: (1) It requires no prior ovarian stimulation nor delay in cancer treatment and (2) it has no

risk of reintroducing malignant cells. However, transplantation of ovarian follicles has also some disadvantages including the following: (1) It allows limited follicle and oocyte development; (2) it requires further oocyte isolation, IVM, and IVF; (3) it may require xenotransplantation to mature human ovarian follicles and that is not allowed in clinical practice due to several safety and ethical reasons; (4) it does not resume the endocrine ovarian function of the patient [132-135].

To date, transplantation of human ovarian follicles has not resulted yet in any reported live births. However, development of isolated small preantral follicles into large preantral stage or early antral stage after *in vitro* culture or xenotransplantation was achieved [136-139].

Transplantation of human ovarian follicles is still in research settings as an option for female fertility preservation. It is a promising alternative to autotransplantation to avoid the risk of reintroducing malignant cells. Nevertheless, xenotransplantation to mature human ovarian follicles is not allowed in clinical practice due to safety and ethical reasons [22, 23].

In animal research, transplantation of ovarian follicles into three-dimensional *in vitro* culture was successful in large mammals as monkeys and resulted in antrum formation, steroid hormone production [140, 141], and mature oocytes [142, 143].

4 Discussion

Female fertility loss refers to the permanent inability of a woman to conceive due to complete depletion of her oocytes. The most common causes of fertility loss in women are aging and gonadotoxic treatments for cancer and some autoimmune diseases. Other less common causes of female fertility loss include bilateral oophorectomy, familial premature ovarian failure, gonadal agenesis, and some genetic disorders [1-5].

Each year worldwide, several million women are diagnosed with different types of cancer. According to GLOBOCAN study in 2012, the number of new cases of cancer in women was about 0.7 million in the USA, 1.7 million in Europe, and 6.6 million worldwide [144]. Approximately 10 % of women with cancer are diagnosed during their reproductive years, and nearly 80–90 % of them can survive due to advances in cancer diagnosis and treatment [145].

The most common cancers in young women (age <40) are breast (29 %), lung (13 %), colorectal (8 %), uterine and cervical (6 %) cancer, thyroid carcinoma (6 %), lymphoma (4 %), melanoma (4 %), leukemia (3 %), kidney (3 %), and pancreatic (3 %) cancer [145]. The most common cancers in female adolescents (age 15–19) are lymphoma (23 %), leukemia (12 %), thyroid (11 %), central nervous system malignancies (10 %), bone tumors (7 %), melanoma (6 %), and ovarian germ cell tumors (2 %) [146]. The most common cancers in prepubertal girls (age 0–14) are leukemia (31 %), central nervous system malignancies (21 %), lymphoma (10 %), neuroblastoma (7 %), Wilms tumor (5 %), bone tumors (4 %), rhabdomyosarcoma (3 %), and retinoblastoma (3 %) [146].

As a common side effect of cytotoxic cancer treatments, the probability of young female cancer survivors to conceive after chemotherapy and radiotherapy is markedly reduced by

~50 % with an increased risk of miscarriage, preterm labor, and low birth weight babies [147-149]. However, when ovaries are exposed to aggressive chemotherapy and radiotherapy, gonadotoxicity occurs leading to irreversible damage of ovarian follicles and oocytes, premature ovarian failure, and fertility loss in more than 80 % of cases [150, 151]. Alkylating chemotherapy such as cyclophosphamide, ifosfamide, and busulfan, in addition to ionizing radiotherapy to the pelvis and abdomen, and cranial or total body irradiation are the most aggressive cancer treatments to the ovaries and can lead to gonadotoxicity and subsequent fertility loss in almost all cases [152-154]. Several studies have assessed the risk of chemotherapy- and radiotherapy-induced gonadotoxicity and subsequent fertility loss for common cancers in females. The risk of gonadotoxicity and subsequent female fertility loss is significantly related to the type, dose, site, and fractionation of the chemotherapy and radiotherapy, the type and stage of cancer as well as to the age of the young women and girls at the beginning of treatment [147-154].

To preserve fertility of young women and girls undergoing gonadotoxic cancer treatments, several options can be offered including embryo freezing, egg freezing, ovary autotransplantation, IVM, and ovarian protection. However, each of those fertility preservation options has advantages and disadvantages and may not be feasible for all cases [1-5]. That is why many guidelines have been published concerning the possible options and strategies for female fertility preservation. Most of these guidelines were published by the American Society of Clinical Oncology (ASCO) [6, 7], American Society for Reproductive Medicine (ASRM) [8-10], European Society for Medical Oncology (ESMO) [11, 12], US Oncofertility Consortium [13, 14], International Society for Fertility Preservation (ISFP) [15-18], Fertility Preservation Network FertiPROTEKT [19], American Academy of Pediatrics (AAP) [20], and Association of Pediatric Hematology/Oncology Nurses (APHON) [21].

According to the most recent guidelines [6-21], human ovary autotransplantation is still considered an experimental option for female fertility preservation. Although experimental, ovarian autotransplantation is promising due to its unique advantages in comparison to embryo freezing and egg freezing, the only two established options for female fertility preservation. Distinctively, human ovary autotransplantation (i) does not need prior ovarian stimulation, (ii) allows immediate initiation of cancer therapy, (iii) can restore both endocrine and reproductive ovarian functions, and (iv) may be the only fertility preservation option suitable for prepubertal girls or for young women with estrogen-sensitive malignancies where ovarian stimulation and embryo or egg freezing are contraindicated (Table 3).

The major and serious challenges facing ovarian autotransplantation are how to avoid the risk of reintroducing malignant cells and how to prolong the lifespan of ovarian transplant as well as how to improve artificial ovary results [6-21]. That is why several medical and ethical concerns should be taken into account before offering this technique to cancer patients. Recently, the Edinburgh selection criteria have recommended that ovarian autotransplantation can be offered to young women, female adolescents, and prepubertal girls undergoing gonadotoxic cancer treatments only when there are a realistic chance of survival, a risk of fertility loss >50 %, no or low risk for reintroducing malignant cells,

negative serology for blood transmitted diseases, and informed consent by parents or legal guardians in case of a child patient [61]. Overall, ovarian autotransplantation should be contraindicated in ovarian carcinomas and malignancies that may metastasize in ovaries such as leukemia (high risk), gastrointestinal cancer (moderate risk), breast cancer, lymphoma, gynecological malignancies, and sarcoma of the bone and connective tissue (low risk) [98-100].

Technically, ovarian autotransplantation is a very sophisticated procedure that requires a highly skilled oncofertility team of oncologists, gynecologists, reproductive biologists, and transplantation surgeons. That is why it should be performed only at highly specialized centers, and it should be offered only to preserve fertility of young women (<40 years old) and girls undergoing gonadotoxic treatments for cancer or some autoimmune diseases and not to preserve fertility of patients with benign conditions nor the women who want to postpone their childbearing for nonmedical reasons [22, 155].

We suggest, by integrating ovarian autotransplantation with other options of female fertility preservation, the chance of preserving fertility can be comprehensively amplified (Fig. 2). If clinically feasible, ovarian autotransplantation can be proceeded by emergency or conventional ovarian stimulation and further embryo or egg freezing. After ovarian tissue extraction, *ex vivo* isolation of follicles and oocytes for artificial ovary and IVM can be attempted. In case one ovary is left *in situ*, ovarian protection techniques such as oophoropexy, GnRH analogs, and pelvic shielding should be considered [22-27, 156-160].

5 Conclusion

Although experimental, human ovary autotransplantation is a promising option for female fertility preservation. The major challenges facing this option are how to avoid the risk of reintroducing malignant cells and how to prolong the lifespan of ovarian transplant as well as how to improve artificial ovary results. Moreover, an international registry is absolutely required for better evaluation, improvement, and establishment of this procedure.

Acknowledgments

Funding Not applicable

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Key message (implications for practice)

Human ovary autotransplantation involves ovarian tissue extraction, freezing/thawing, and transplantation back into the same patient. Although experimental, it is a promising option for fertility preservation of young women and girls undergoing gonadotoxic treatments for cancer or some autoimmune diseases. To date, it resulted in at least 42 healthy babies worldwide. The major challenges facing this option are how to (i) avoid the risk of reintroducing malignant cells, (ii) prolong the lifespan of ovarian transplants, (iii) improve artificial ovary results, and (iv) establish an accurate international registry.

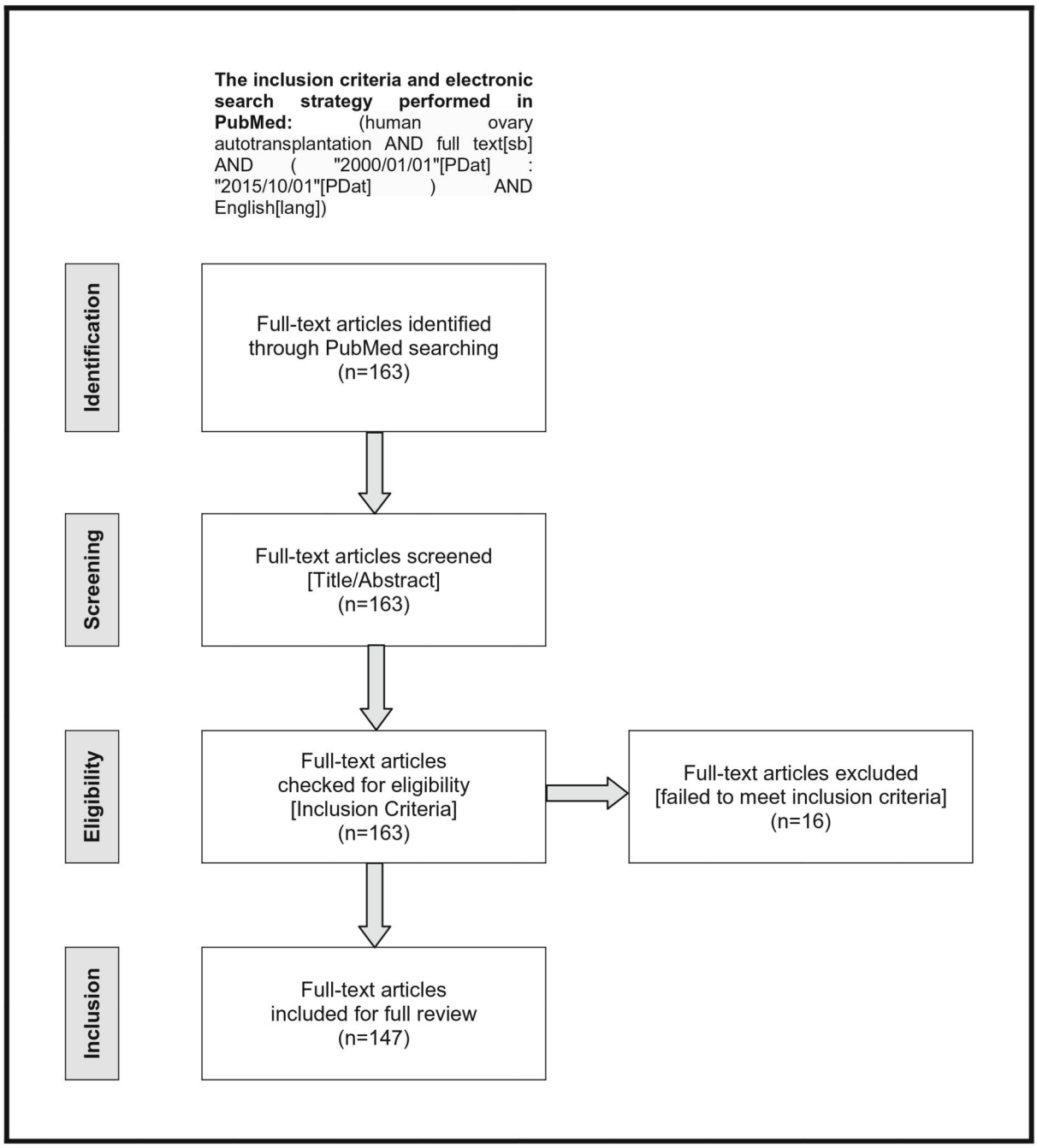

Fig. 1.
PRISMA four-phase flow diagram of identification, screening, eligibility, and inclusion steps

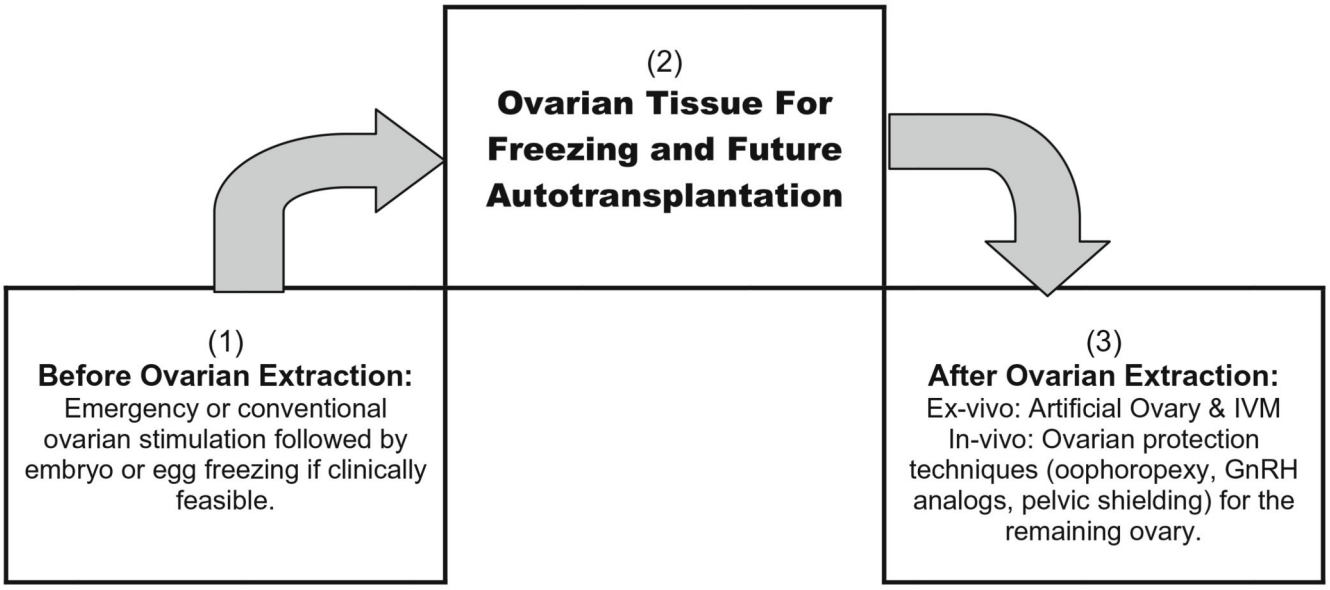

Fig. 2.
Integrating ovarian autotransplantation with other options of female fertility preservation

Table 1

Reported 42 live births after human ovary autotransplantation–updated and modified from [41] and [56]

Group	Reference	Human ovary	Freezing	Autotransplantation	Live births (*n*) total=42	Country
Andersen et al.	[28-31]	Cortical tissue	Slow freezing	Orthotropic	6	Denmark
Demeestere et al.	[32-34]	Cortical tissue	Slow freezing	Orthotropic	3	Belgium
Donnez and Dolmans et al.	[35-41]	Cortical tissue	Slow freezing	Orthotropic	6	Belgium
Meirow and Dor et al.	[42, 43]	Cortical tissue	Slow freezing	Orthotropic	3	Israel
Revel et al.	[44]	Cortical tissue	Slow freezing	Orthotropic	3	Israel
Burmeister et al.	[45]	Cortical tissue	Slow freezing	Orthotropic	1	Australia
Sánchez-Serrano et al.	[46]	Cortical tissue	Slow freezing	Orthotropic	2	Spain
García Rada	[47]	Cortical tissue	Slow freezing	Orthotropic	1	Spain
Piver et al.	[48, 49]	Cortical tissue	Slow freezing	Orthotropic	3	France
Revelli et al.	[50]	Cortical tissue	Slow freezing	Orthotropic	1	Italy
Dittrich et al.	[51, 52]	Cortical tissue	Slow freezing	Orthotropic	3	Germany
Silber et al.	[53-56]	Cortical tissue	Slow freezing	Orthotropic	4	USA
Rodriguez-Wallberg et al.	[57]	Cortical tissue	Slow freezing	Orthotropic	1	Sweden
Kawamura et al.	[58]	Cortical tissue	Vitrification	Orthotropic	1	Japan
Suzuki et al.	[59]	Cortical tissue	Vitrification	Orthotropic	2	Japan
Stern et al.	[60]	Cortical tissue	Slow freezing	Heterotopic	2	Australia

Table 2

Reported 42 live births after human ovary autotransplantation (simplified)

Cortical ovarian tissue	Orthotopic autotransplantation	Heterotopic autotransplantation
Slow freezing	37 [28-57]	2 [60]
Vitrification	3 [58, 59]	0
Total live births	40	2

Table 3

Human ovary allotransplantation (related references are cited within the original text)

Human ovary autotransplantation	(A) Transplantation of cortical ovarian tissue		(B) Transplantation of whole ovary	(C) Transplantation of ovarian follicles (artificial ovary)
	Othrotopic	Heterotopic		
1. Definition	Transplantation of frozen-thawed cortical ovarian tissue back to the same patient into the remaining ovary, ovarian fossa, or broad ligament	Transplantation of frozen-thawed cortical ovarian tissue back to the same patient into the subcutaneous space of abdominal wall or forearm	Transplantation of frozen-thawed whole ovary with its vascular pedicle back to the same patient	Reimplantation of isolated preantral ovarian follicles into a biodegradable artificial ovary made of three-dimensional alginate matrigel matrix
2. Aim	To resume endocrine and reproductive ovarian functions	To resume endocrine and reproductive ovarian functions	**1** To resume endocrine and reproductive ovarian functions **2** To overcome post-graftingischemia and follicle atresia	**1** To resume reproductive ovarian function **2** To avoid the risk of reintroducing malignant cells
3. Ovarian Extraction	At least half of one ovary via laparoscopy or mini-laparotomy	At least half of one ovary via laparoscopy or mini-laparotomy	At least one whole ovary with its vascular pedicle via laparoscopy or mini-laparotomy	At least half of one ovary via laparoscopy or mini-laparotomy. Isolation of preantral ovarian follicles can be performed before or after ovarian tissue freezing
4. Freezing/thawing	Slow freezing is the standard. Vitrification is promising.	Slow freezing is the standard. Vitrification is promising.	Slow freezing is the standard. Vitrification is promising.	Slow freezing is the standard. Vitrification is promising.
5. Transplantation	Avascular grafting of frozen-thawed cortical ovarian tissue pieces into the remaining ovary, ovarian fossa, or broad ligament of the same patient	Avascular grafting of frozen-thawed cortical ovarian tissue pieces into the subcutaneous space of abdominal wall or forearm of the same patient	Vascular grafting of frozen-thawed whole ovary back to the same patient	Reimplantation of isolated preantral ovarian follicles into a biodegradable artificial ovary made of three-dimensional alginate matrigel matrix. The biodegradable artificial ovary containing follicles may be either cultured *in vitro* or *in vivo* (xenotransplantation or autotransplantation) to allow follicular development.
6. Advantages	**1** No ovarian stimulation, no delay in cancer therapy **2** Normal environment for follicle and oocyte development **3** Spontaneous pregnancy is possible **4** Avascular grafting reduces the risk of	**1** No ovarian stimulation, no delay in cancer therapy **2** Surgically easier and good alternative to orthotopic autotransplantation in case of severe pelvic adhesions or poor pelvic vasculature. **3** Easy monitoring of the grafted ovarian tissue	**1** No ovarian stimulation, no delay in cancer therapy **2** Normal environment for follicle and oocyte development **3** Spontaneous pregnancy is possible **4** Vascular grafting can reduce post-grafting	**1** No ovarian stimulation, no delay in cancer therapy **2** No risk of reintroducing malignant cells

Human ovary autotransplantation	(A) Transplantation of cortical ovarian tissue				(B) Transplantation of whole ovary		(C) Transplantation of ovarian follicles (artificial ovary)	
	Othrotopic		Heterotopic					
		reintroducing malignant cells	**4**	Avascular grafting reduces the risk of reintroducing malignant cells		ischemia and follicle atresia		
7. Disadvantages	**1**	Risk of reintroducing malignant cells	**1**	Risk of reintroducing malignant cells	**1**	Higher risk of cryoinjury	**1**	Limited follicle and oocyte development
	2	Avascular grafting may increase post-grafting ischemia and follicle atresia	**2**	Avascular grafting may increase post-grafting ischemia and follicle atresia	**2**	Higher risk of reintroducing malignant cells	**2**	Requires further oocyte isolation, *in vitro* maturation (IVM) and IVF
	3	Spontaneous pregnancy can occur due to ovulation from remaining ovary not due to the orthotopically grafted cortical ovarian tissue	**3**	Abnormal environment for follicle and oocyte development	**3**	Surgical difficulty of vascular anastomosis due to the small size of ovarian artery, short ovarian vascular pedicle, and possible failure of microvascular anastomosis	**3**	Xenotransplantation to mature human ovarian follicles is not allowed in clinical practice due to safety and ethical reasons.
			4	Spontaneous pregnancy is not possible. IVF is a must.	**4**	Higher risk of post-operative vascular complications including anastomotic bleeding, pseudoaneurysm, stenosis, or thrombosis	**4**	Does not resume the endocrine ovarian function of the patient
					5	Vascular complications can severely affect the survival of the entire ovary leaving no other attempt for transplantation.		
8. Outcome	**1**	Ovarian function may resume 2–9 months post-operatively, and it may last for up to 7 years.	**1**	Ovarian function may resume 2–9 months post-operatively, and it may last for up to 7 years.	**1**	Resumption of ovarian function is questionable.	**1**	Has not resulted yet in any reported live births.
	2	Resulted in at least 40 healthy babies worldwide Note: Orthotopic transplantation of fresh and frozen-thawed cortical ovarian tissue between monozygotic twin sisters was successful and	**2**	Resulted in two healthy babies worldwide; in addition, it resulted in a four-cell embryo, a biochemical pregnancy, and a clinical pregnancy.	**2**	Has not resulted yet in any reported live births Note: Fresh whole ovary transplantation between donor and recipient was successful with one reported live birth.	**2**	Possible development of isolated small preantral follicles into large preantral or early antral stage after *in vitro* culture or xenotransplantation

Human ovary autotransplantation	(A) Transplantation of cortical ovarian tissue		(B) Transplantation of whole ovary	(C) Transplantation of ovarian follicles (artificial ovary)
	Othrotopic	**Heterotopic**		
	resulted in healthy babies. resulted in healthy babies.			
9. Indications	Fertility preservation for young women (<40 years old) and girls scheduled to receive gonadotoxic treatments for cancer or some autoimmune diseases.	As an alternative to orthotopic autotransplantation in case of severe pelvic adhesions or poor pelvic vasculature due to previous intensive pelvic irradiation	Still in research settings as a fertility preservation option for young women and girls scheduled to receive gonadotoxic treatments for cancer or some autoimmune diseases	**1** Still in research settings as a fertility preservation option for young women and girls scheduled to receive gonadotoxic treatments for cancer or some autoimmune diseases **2** As an alternative to autotransplantation to avoid the risk of reintroducing malignant cells
10. Contraindications	**1** Ovarian carcinomas and malignancies that may metastasize in ovaries **2** Relatively old patients with poor ovarian reserve	**1** Ovarian carcinomas and malignancies that may metastasize in ovaries **2** Relatively old patients with poor ovarian reserve	**1** Ovarian carcinomas and malignancies that may metastasize in ovaries **2** Relatively old patients with poor ovarian reserve	Xenotransplantation to mature human ovarian follicles is not allowed in clinical practice due to safety and ethical reasons.
11. Animal research (large mammals)	Resulted in healthy offsprings in sheep	Resulted in healthy offsprings in monkeys	Resulted in healthy offsprings in sheep	Resulted in mature oocytes in monkeys