Fertility after Cancer

Subjects: Obstetrics & Gynaecology

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Approximately one million new cases of cancer are diagnosed in women of reproductive age every year. In the last few decades, advances in early diagnosis and treatment have improved the survival rate. However, the adverse effects of anticancer therapy on the ovaries and uterus have a significant impact on future fertility and may affect the quality of life of cancer survivors. Impaired fertility in cancer survivors is a growing issue that is complicated by an increasing number of women delaying childbearing.

Keywords: infertility ; gynecologic cancers ; fertility sparing treatments ; ovarian damage

1. Introduction

The incidence of any type of cancer in 15–39 year old women is 52.3 rate per 100,000 [1].

In Italy, 3% of cancer cases are diagnosed in women under the age of 40. The most common types of cancer in women under 40 are breast cancer, thyroid cancer, melanoma, cervical cancer, endometrial cancer, ovarian cancer, leukemia/lymphomas, and colorectal cancer [2].

Breast cancer (BC) is the most common cancer in women under 49 (40% of all cancer cases). Despite the increased incidence of BC with age, approximately 7–10% of women diagnosed with BC are under 40 [3]. The incidence trend in Italy is slightly increasing (0.3% per year), whereas mortality continues to decline (−0.8% per year). The 5-year survival rate in young women (15–44 years) is 91% [4].

Thyroid cancer is common between the ages of 0–49 years (15% of all cancer cases). The most important prognostic factor is represented by the following histotype: the 20-year survival rate is 98–99% for papillary carcinomas and 80–90% for follicular ones (together they constitute 90% of thyroid cancer with papillary/follicular ratio 10:1), whereas it drops to 50–75% at 10 years for medullary carcinomas [5].

Melanoma is the third most frequent cancer in women aged between 18 and 39 years, with an increasing incidence trend (3.1% per year) [6].

Cervical cancer is the second for incidence in women. Its incidence increases with age up to 45 years with a peak between 45–55 years. The incidence rate is rising in developing countries but is decreasing in high resource countries [7].

Endometrial cancer has a very low incidence in reproductive age. Only 20% of endometrial cancers affect premenopausal women, and of these, no more than 5–8% affect women under 40 [8].

As for ovarian cancer, 80–90% occurs amongst women between the ages of 20 and 65 years old, and 90% of malignant tumors are diagnosed in women over the age of 40. A total of 5–10% of ovarian cancers are of intermediate malignancy (borderline) and approximately 30% of them affect women under 40. However, the diagnosis of epithelial ovarian cancer in women of reproductive age has become more frequent with increasing gynecological physical checkups [2].

Colorectal cancer's (CRC) incidence is increasing in women of reproductive age. Fortunately, the 5-year survival rate from CRC is improving, with a survival rate of 65% [9].

Considering pediatric cancer patients, a recent study of over 3500 young women who survived childhood cancer such as leukemia, central nervous system cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumor, shows a significantly higher risk of infertility than in the control group (RR: 1.48) [10][11]. There are still limited modalities available to preserve prepubertal fertility. Ovarian tissue reimplantation is the only fertility preservation technique that can be used to preserve prepubertal fertility, whereas mature oocyte cryopreservation is the

main technique used for fertility preservation in post-menarche adolescents. However, a growing awareness and competence on the subject is beginning to emerge, especially amongst oncology pediatricians in Northern Europe [12][13].

In the United States, the 5-year overall survival rate for all invasive cancers between ages 15–39 is about 82.5% [14]. Despite the increased incidence of cancer cases, advances in early diagnosis and treatment have increased the survival rate [15].

Furthermore, in the last four decades, there has been a rising trend of delaying childbearing [16]. Hence, there is an increasing number of couples referred to Reproductive Medicine Centers for infertility problems after one partner has been treated for cancer. In these cases, the main cause of reduced fertility derives from the gonadotoxic effects of chemo/radiotherapy treatment [17]. As far as young women are concerned, there are two main concerns: the possible harmful effects of previous anticancer treatments on a future pregnancy, and the consequences pregnancy may have on the patient, particularly in the case of endocrine-sensitive neoplasms, even if to this day, there is no evidence of such possible adverse effects [18][19][20][21][22][23]. All reproductive-aged cancer patients must therefore be adequately informed of the risk of fertility loss/reduction as a consequence of anticancer treatments, and at the same time the strategies available to reduce this risk.

2. Influence of Cancer on Ovarian Function

If the cancer “per se” may induce alterations of ovarian functions, these should be investigated.

Several studies have examined the fertility of women with cancer before chemo/radiotherapy and show mixed results. Different studies found a negative interference of cancer on ovarian function even before starting cancer treatment [24][25]. Pal et al. were the first that found an adverse effect of the tumor on ovarian function [26]. An observational study described how women with hormone-dependent cancer have a poorer response to controlled ovarian stimulation, with fewer oocytes retrieved than those with non-hormone-dependent cancer [27].

Alvarez and Ramanathan found significantly fewer oocytes in breast cancer patients than in patients with hematological cancer [28]. In a retrospective cohort study that included 155 women, Volodarsky-Perel et al. showed that women with grade G3 and stage III-IV breast cancer had significantly fewer numbers of mature oocytes than patients with grade G1-2 and at stage I-II of the disease. Also, the number of cryopreserved embryos was lower in women with grade G3. The same researchers demonstrated that patients with high-grade cancer have fewer oocytes and embryos retrieved than those with low-grade cancer [29].

Similarly, Decanter et al. found fewer oocytes in women with cancer than in the age-matched control group [30]. Moria et al. showed that breast cancer patients had fewer retrieved oocytes than the control group [31].

However, most of the studies have not demonstrated relevant differences in ovarian reserve and oocytes retrieved between women with cancer and the healthy group. Almog et al., in their study with 81 women, stated that the ovarian function was not affected by the type of cancer [32][33][34][35][36].

These observations are thought to be linked to the systemic effect of cancer, causing higher catabolic status, increased stress hormones levels, and impaired function of the granulosa cells. Furthermore, invasive cancer infiltrates and destroys the surrounding tissue causing immune system reactions involving distant organs [37][38]. This systemic response conditions folliculogenesis, follicular cell proliferation, and oocyte maturation through the release of metalloproteases and growth factors [39][40].

Due to the close relationship between cancer and BRCA1 and 2 mutations, it is important to evaluate whether the cancer itself or the BRCA mutations underlie the reduced ovarian reserve in these women [41][42]. Porcu et al. demonstrated that BRCA 1 patients have a higher risk of premature ovarian failure compared to non-BRCA-mutated women with breast cancer and the healthy controls. BRCA1 groups have lower AMH levels and a significantly lower rate of mature oocytes. This effect seems to be independent of the probable interference of cancer. Therefore, the ovarian response after ovarian stimulation may be influenced by the presence of cancer [43].

More studies are needed to understand if there is a negative effect of cancer on ovarian function even before cancer treatment is started and if the type of cancer influences the ovarian response.

3. Effects of Cancer Treatment on Female Reproductive Function

The adverse effects of cancer treatment on female reproductive function are an increasing problem that affects the quality of life in survivors of childhood, adolescent, and young adult cancer.

The three principal anti-cancer treatments are surgery, radiotherapy, and chemotherapy.

In most cases, primary ovarian or uterine cancers are surgically removed together with these organs, leading to sterility. For these women, using donated eggs or surrogacy are the only chance to have a child [44].

Chemotherapy and radiotherapy may damage the reproductive system by destroying the hypothalamic–pituitary axis, the uterus, or the primordial and growing follicles within the ovaries.

The effects of chemotherapy and radiotherapy on the ovaries and uterus have a significant impact on the future fertility of childhood cancer patients as well as women up to the age of menopause.

3.1. Ovarian Damage

Cancer therapy can involve the administration of a wide variety of therapeutic protocols [45].

The American Society of Clinical Oncology published a useful classification of cancer treatments based on their level of gonadotoxicity and their consequent risk of permanent amenorrhea [46].

The level of gonadotoxicity depends on chemotherapeutic classes, dose, method of administration (oral versus intravenous), and combination of drugs; moreover, the toxicity changes with the type of disease, the woman's age at the time of treatment, and the woman's pre-treatment fertility.

"Highly gonadotoxic treatments" cause permanent amenorrhea in at least an 80% of cases; the most common of them are, for example, chemotherapy used to treat breast cancer in women over 40 (combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin), external beam radiation to a field that includes the ovaries, or myeloablative conditioning for hematopoietic stem cell transplantation with high-dose alkylating agents (cyclophosphamide/busulfan) in combination with total body irradiation [46][47]. Different studies have reported that the risk of gonadal insufficiency after stem cell transplantation is related to a woman's age; the risk of infertility is 65–95% in adult women, higher than in prepubertal girls (around 50%) because of higher ovarian reserve [48][49].

Treatments classified as "intermediate gonadotoxicity" involve a 40–60% risk of amenorrhoea. These include adjuvant chemotherapy for breast cancer in women aged 30–39 (combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin) and escalated (second-line) chemotherapy used for Hodgkin's lymphoma [27].

"Low" gonadotoxic cancer treatments, with a risk of amenorrhea < 20%, include first-line treatment for Hodgkin's lymphoma (ABVD therapy) and treatment for acute lymphoblastic and myeloid leukemia [44].

Treatments considered "very low risk" or "no risk" are antimetabolites (such as methotrexate, cytarabine) and vinca alkaloids (vincristine, vinblastine), which do not cause damage to human follicles [44][47].

3.1.1. Impact of Chemotherapy

Many studies have investigated the type of damage of each chemotherapeutic agent on different cell types of the ovary.

These findings have reported that ovarian damage can occur via several mechanisms [50].

Apoptotic death of primordial follicle and growing follicles are caused by direct DNA damage (via DNA double-strand breaks and inter-strand crosslinking) [47][51].

Direct damage to the ovarian stroma causes fibrosis and hyalinisation of small blood vessels, resulting in ischemia and necrosis due to a reduction in ovarian blood volume and consequently indirect damage to follicles growth [47][52].

Indirect damage to primordial follicles is due to increased follicle activation. Meirow's group explained this mechanism of enhanced follicular demise owing to accelerated folliculogenesis by proposing the "burnout theory" [53][54]. In particular, the destruction of growing follicles and thus the local reduction in AMH concentrations causes an upregulation in the PI3K/PTEN/Akt signaling pathway.

3.1.2. Impact of Radiotherapy

Radiation therapy is one treatment modality for various types of malignancies, but unfortunately, exposure to ionizing radiation can lead to acute and long-term damage.

The effects of radiation to the abdominopelvic region depends on the dose intensity, fractionation, field of irradiation, and the age of the patient [44][55][56]. Women in the prepubertal period have ovaries relatively more resistant to gonadotoxicity [57].

The radiosensitivity of oocytes is high and differs according to their growth phase. In particular, dividing granular cells appear to be the main target of radiation-related gonadotoxicity.

Radiotherapy-induced ovarian injury also involves the stroma with vascular damage, leading to tissue atrophy and fibrosis [58].

The underlying mechanism induced by radiotherapy is both direct and indirect. The radiation induces a direct ionization of the cellular macromolecules, such as gonadal DNA causing multiple lesions within the helical turns of the DNA, which is referred to as “direct” damage. Radiotherapy also leads to the generation of reactive oxygen species (ROS) in cells, increasing oxidative stress and diminishing antioxidant defense mechanisms.

This imbalance may play a role in the etiology of radiotherapy-induced gonadotoxicity, which is defined as “indirect” damage [59].

Through these pathways, radiotherapy can affect healthy normal tissues in the ovaries and can influence the length of a women’s fertile lifespan and the timing of menopause.

3.2. Uterine Damage

Recent trials have reported that anti-cancer treatments can cause permanent injury to the uterus and compromise its ability to allow and sustain a healthy pregnancy [60].

3.2.1. Impact of Chemotherapy

The percentage of pregnancies obtained through egg donation or using one’s own eggs before anticancer treatment is lower than in the control group. Even though patients underwent assisted reproductive technologies (ART), the implantation rate and clinical pregnancy rate (4.9% and 9.5%, respectively) were statistically significantly lower, underlining that cancer therapy-induced damage to the uterus may contribute to infertility [60][61].

A small number of studies have demonstrated that chemotherapy exposure during childhood (especially to alkylating agents) is associated with a smaller uterine size and volume [62][63].

Despite this indirect evidence of uterine damage induced by chemotherapy, there is a paucity of data regarding the specific pathological mechanism through which these drugs can act. Currently, the damage to endometrial epithelium, myometrium, uterine vasculature, and the endometrial stem cell niche can only be extrapolated from animal models or laboratory and clinical findings on the analogous cell line of other human tissue (for example intestinal stem cells, cardiomyocites, skeletal muscle) [60].

3.2.2. Impact of Radiotherapy

Radiation to the uterus can impair reproductive function. Evidence has reported that radiotherapy can cause microvascular injury with endothelial damage and myometrial fibrosis compromising uterine growth and distensibility. Radiation may also damage muscle fibers and decrease pelvic floor muscle function [47]; when the woman’s exposure happens before puberty, stunted uterine growth and fibrosis can only be partially rescued by hormone replacement therapy [37]. Critchley et al. reported a shorter uterine length and a rare uterine blood flow in patients who received radiation during childhood compared to women with a history of POF (Primary Ovarian Failure) without radiation exposure.

The radiation consequences on the uterus are greater in the case of exposure at a young age, leading to greater risks for future pregnancy. The radiation dose that poses the greatest risk of reproductive failure is >45 Gy in adults or >25 Gy in childhood [47].

4. Oncofertility

Approximately one million new cases of cancer are diagnosed in reproductive-aged women every year [60][64].

In the last few decades, life expectancy of these patients has increased thanks to anticancer treatments. The increased survival rate, combined with increased age for childbearing, has led to the occurrence of side effects such as fertility problems [65].

Diagnosis and treatment of tumors can often cause fertility problems in women. It has been estimated that 70–75% of cancer survivors are interested in parenthood and that 80% of them are affected by reduced fertility [66].

Despite patients' interest in parenthood, the percentage of patients who receive correct information varies from 51% to 95%, and the percentage of patients who access fertility preservation techniques is low [67][68].

Fertility loss can cause devastating emotional reactions in women impacting their plans for the future. Various studies demonstrate that discussing fertility preservation options can improve quality of life and can contribute to psychological health [69][70].

The creation of an oncofertility team around the patient would allow this conversation to happen at the appropriate time and would reduce fertility loss in cancer patients [71].

Oncologists should inform patients about impaired fertility risk and should provide information on strategies available to preserve it.

Fertility preservation strategies in females depend on age, type of treatment planned, diagnosis, presence of a partner, time available before starting treatment, and potential for cancer to metastasize to the ovaries [46].

After consultation with a hematologist, oncologist, and specialist in reproductive medicine, an adequate consult can be carried out to evaluate ovarian reserve and gonadotoxicity of the therapies and to propose an appropriate fertility preservation technique [64].

4.1. Fertility Preservation Options

Different fertility preservation strategies can be proposed (**Figure 1**):

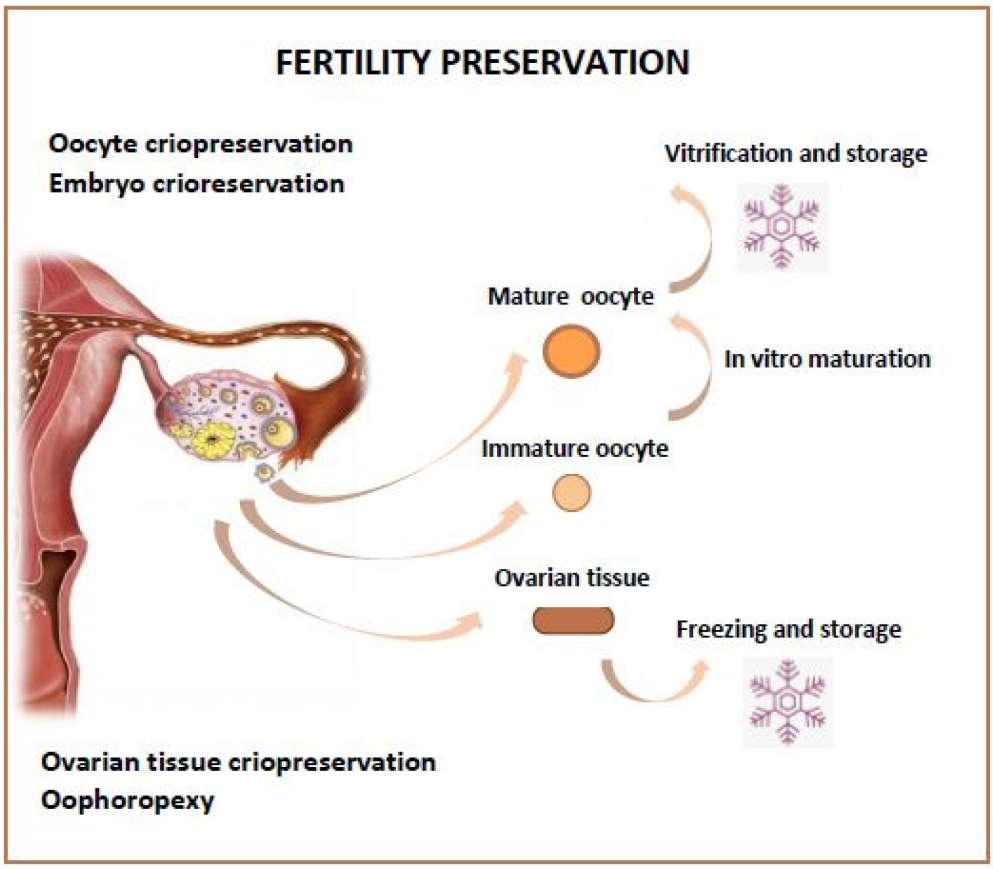

Figure 1. Fertility Preservation Options.

- Hormone Protection by Suppressing Ovaries
- Oophoropexy
- Embryo Storage, Oocyte Storage
- Ovarian Tissue Storage
- Fertility Sparing Surgery

4.1.1. GnRH-Analogues

In cancer patients who are candidates for chemotherapy, the use of GnRH analogues should be proposed but not considered as an alternative to cryopreservation [72].

GnRH analogues are used as chemoprotectors; used during chemotherapy they induce menopause, suppressing the ovarian cycle.

In 2018 and 2020, ASCO Guidelines and the European Society for Medical Oncology, respectively, recommended that GnRHa use should be offered to all cancer patients who desire to preserve fertility. [73]

In 2018, the British Fertility Society affirmed that GnRHa should be started immediately before chemotherapy and continued for the duration of therapy. [73]

GnRH analogues arrest ovarian cells in the G0 phase inducing cellular quiescence and making these cells less responsive to chemotherapy [74][75]; this treatment has shown effects in reducing primary ovarian insufficiency (POI) risk, increasing pregnancy rates, and having no negative effects on the cancer's outcome.

The use of GnRH analogues can be also proposed in patients with hormone receptor-positive disease with safety [76].

Several studies have shown that the use of Goserelin has preserved fertility in a high percentage of patients affected by breast cancer [77][78].

The use of Goserelin reduces premature ovarian failure risk as well as prevalence of amenorrhoea and also improves disease-free survival and overall survival [79][80].

AMH can be used to evaluate the GnRHa protective effect on fertility [73].

4.1.2. Oophoropexy

Ovarian transposition (oophoropexy) consists of surgical removal of the ovaries from the irradiation site.

This strategy can be proposed to patients who are candidates for pelvic radiotherapy (children and pre-menopausal women who desire to preserve fertility and prevent early menopause), in cases of gynecological or hematological cancers, such as cervical cancer and Hodgkin's lymphomas, and in cases of medulloblastoma, urogenital rhabdomyosarcoma, pelvic sarcomas, Wilm's tumor, and rectal cancer [75][81][82].

Before the procedure, a pelvic MRI should be performed to ensure that the tumor does not involve the ovarian region.

Ovarian transposition can be performed by laparoscopy or laparotomy (in case of concomitant resection of the tumor). One or both ovaries are relocated, either medially (behind the uterus in the case of Hodgkin's Lymphoma), laterally, near the inguinal ring, in the paracolic gutters, or near the lower kidney pole (in the case of urogenital tumors, medulloblastoma, and rhabdomyosarcoma), or to any distant site.

At the end of the procedure, two metal clips should be applied to the transposed ovaries to make them visible on imaging.

Possible complications of oophoropexy are: torsion of the ovarian blood vessels, development of benign ovarian cysts, and subsequent chronic pain and ovarian and abdominal wall metastases at the trocar site [81][82][83].

Success rate of this treatment, in terms of preserved ovarian function, varies between 60% and 83% and several spontaneous pregnancies after this procedure are described. Nevertheless, some researchers claim that these patients could require assisted reproductive technologies because of increased distance between the ovary and the fallopian tube.

This increased distance compromises oocyte migration through the Fallopian tube and impairs fertility [82].

4.1.3. Embryo and Oocyte Cryopreservation

Embryo cryopreservation is one of the options to preserve fertility.

An oocyte and a sperm cell (obtained from a male partner or sperm donor) are needed to create an embryo [75].

Embryo cryopreservation is a good choice for patients with a stable relationship because of better pregnancy outcomes [84]. However, not all women have a stable relationship at the time of diagnosis; in this case, oocyte cryopreservation is a valid alternative, giving women an opportunity to procreate with a chosen partner in the future, without the need to fertilize the oocyte after retrieval [85][86].

Embryo and oocyte cryopreservation cause a two-week delay in chemotherapy initiation [71][87].

Ovaries are stimulated with daily injections of follicle-stimulating hormone and stimulation can be started at any point in the menstrual cycle.

Follicle growth is monitored by ultrasounds and blood tests (serum estradiol and progesterone levels). Ovulation is induced with an HCG injection when appropriate and oocytes are collected by transvaginal aspiration (with ultrasound guidance). The oocytes retrieved can be cryopreserved or fertilized in vitro to obtain embryos [46][88].

Oocyte and embryo cryopreservation, performed prior to anti-cancer therapies, are defined by the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) as the most appropriate procedures to ensure motherhood in cancer survivors [89].

Among reproductive-aged women, breast cancer is one of the most frequent. In some cases, this is a hormone-sensitive cancer because of the expression of estrogen receptors.

In patients with these tumors, exposure to high estrogen levels can be risky. In order to avoid this exposure, oocytes can be recovered from a natural cycle or from ovarian stimulation protocol with aromatase inhibitor or tamoxifen (chemoprotective agents that have ovulation-inducing properties) [74][90].

4.1.4. New Strategies

Among new strategies, immature oocytes retrieval is an experimental technique that involves cryopreservation of immature oocytes or matured in vitro.

These oocytes can be used for vitrification or to obtain embryos by ICSI with partner sperm. This strategy allows for a reduction in the time needed for preservation and avoids exposure to hyperestrogenism caused by stimulation [91].

Mature oocytes can be obtained by in vitro maturation of immature oocytes (IVM) or in vitro activation of dormant follicles (IVA) [89].

Achieving pregnancy is possible using oocytes maturated in vitro [92] but pregnancy rates are lower in patients who have used embryos obtained from immature oocytes or oocytes matured in vitro than those who have used embryos obtained from mature oocytes [91].

After treatment, patients should be informed about their ovarian function using different parameters (AMH, FSH, estradiol) in order to decide whether to use cryopreserved oocytes or to start a new cycle [92].

The discovery of ovarian stem cells in the ovarian cortex, first found in mammals and then also in women, opened new chances to preserve fertility.

Despite these findings, in vitro maturation of ovarian stem cells (OSC)s to oocyte-like cells (OLCs) still needs to be investigated for future clinical use in female cancer survivors [89].

4.1.5. Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation (OTC) is the only fertility preservation strategy available in prepubertal patients and those who cannot postpone treatment [87][93].

The entire ovary or part of this can be collected laparoscopically at any period of menstrual cycle. Obtained tissue is sliced and cryopreserved.

When patients are declared free from cancer with a good prognosis, the ovarian tissue is thawed, tested to assess the absence of cancer cells, and reimplanted orthotopically or heterotopically [94].

Although the use of this technique has shown good results in adult patients, ex vivo maturation of ovarian tissue taken in childhood and the subsequent auto-transplantation is still considered experimental [95].

One of the problems of ovarian tissue transplantation is that revascularization occurs after a few days from the time of the procedure. This causes tissue ischemia and a loss of more than 60% of the primordial follicles [74].

Local administration of antiapoptotic and angiogenic factors can improve the revascularization of ovarian tissue [96].

Another problem with ovarian tissue transplantation is the possibility of transferring cancer cells in patients. Even though the tissue is controlled before freezing and before transplantation, the risk of tumor cell transmission remains.

This risk increases in certain tumors, leukemia being a case in point [97][98].

Therefore, this treatment is only proposed to patients with a low risk of ovarian metastasis [75].

Tumor cell transmission can be reduced by transferring primordial follicles onto an artificial tissue to replace native organs [99].

Depending on the number of follicles in cryopreserved tissue, ovarian function resumes after transplantation for 4–5 years on average and in some cases up to 7 years [86][100].

The first pregnancy after this fertility preservation technique was obtained in 2004; pregnancy and live birth rates are growing exponentially over the years. [87][101].

Patients who have undergone this fertility preservation strategy often have undetectable AMH levels, but spontaneous pregnancies after orthotopic transplantation have been reported [73].

AMH level is not associated with the duration of ovarian graft function or the possibility to achieve pregnancy in these women [102].

4.2. Success Rates

Cryopreservation of embryos, oocytes, ovarian tissue, or fertility preservation does not guarantee achieving a pregnancy in the future [71].

Among survivors, pregnancy rates are about 40% lower than the general population [16].

Several studies have described success rates after fertility preservation techniques:

- Live birth rate (LBR) ranges from 20% to 45% in patients undergoing embryos-cryopreservation [103][104].
- Live birth rate varies from 20% to 50%, depending on age, in women undergoing oocytes cryopreservation [105][106][107].
- Live birth rate (LBR) ranges from 18.2% to 41.6% in patients undergoing ovarian tissue cryopreservation and reimplantation [101][106][108][109][110][111][112].
- Live birth rate (LBR) revolves around 8.9% in women undergoing in vitro maturation (IVM) [89].
- Live birth rate (LBR) revolves around 7% in patients undergoing in vitro activation (IVA) [89].
- Few studies have been carried out on pregnancy rates after oophoropexis. Despite this, pregnancies have been reported after this procedure by various researchers [82][113].

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