Review Article

Fertility Preservation in Surviving Women Following Cancer Treatment

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Abstract

For the afflicted female, Diminished Ovarian Reserve (DOR) has disastrous effects on her quality of life, fertility, fecundity, and general well-being. Gynecological operations and chemotherapy can also make DOR worse. By evaluating the gonadotoxicity and effectiveness of current chemotherapy regimens as well as the techniques used in gynecological procedures, the best regimen or technique can be chosen after a risk-benefit ratio study. This ought to be carried out in concert with methods for preserving fertility, such as cryopreservation, ovarian transposition and suppression, and medication. To meet the demand for oncofertility, novel strategies utilizing fertoprotective agents must be assessed. This guarantees the greatest protection of the follicular pool and the least amount of harm to the ovarian environment and function.

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Introduction

Women who have had appropriate therapy and follow-up even after suffering from hormone-sensitive cancers are considering getting pregnant, as the quality of life following treatment is increasing significantly due to the higher survival rates of female cancer patients. By attempting to avoid premature ovarian failure or even infertility, oncofertility improves the quality of life for cancer survivors. Until recently, the only methods available to preserve fertility for post-pubertal women and pubertal girls were ovarian transposition in women undergoing pelvic irradiation or embryo cryopreservation before gonadotoxic treatment using sperm donors in the latter case.[1, 2] These days, novel techniques including oocyte cryopreservation and harvesting are used.[3- 5] Because ovarian stimulation and subsequent oocyte cryopreservation may cause ovarian hyper-stimulation syndrome (OHSS), ovarian tissue cryopreservation is the sole alternative available to prepubescent girls.[6, 7]

Cryopreservation

One method that can be used on ovarian tissue, embryos, and gametes before starting chemotherapy is cryopreservation.[8] There are two ways to perform cryopreservation: vitrification and gradual freezing. Tissues are rapidly cooled during vitrification in order to avoid crystal formation.[7-10] The addition of cryoprotectants during vitrification increased cryopreservation despite the possibility of osmotic stress and cellular toxicity.[4, 11] Protocols vary depending on the reason for infertility, but typically two weeks of ovarian stimulation precede oocyte cryopreservation.[10] Using gonadotropins and a GnRH antagonist together to avoid OHSS is one method of regulated ovarian stimulation. Tamoxifen or letrozole can be administered to stop an increase in oestrogen levels in patients with endocrine-sensitive or oestrogen-producing tumors.[4, 10]

Comparing vitrification to slow-freezing after conception with fresh oocytes, success rates for oocyte cryopreservation have increased leading to higher clinical pregnancy rates (CPR) and live births.[10 -17]

In a similar vein, embryo cryopreservation, particularly when combined with vitrification, is a dependable, secure, and successful process.[12, 13] But because patients under 35 have the highest live-birth rates, there are ethical concerns , and the success varies with age.[16-18] Multiple strips of ovarian tissue are

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removed from the ovarian cortex of a single ovary during the standardized, invasive process of ovarian tissue cryopreservation.[18] The quantity of tissue removed is determined by the predicted risk of ovarian failure.[7, 19, 20] The chance of normal ovarian tissue activity returning is increased by ovarian tissue transplantation after malignancy.[2, 5, 15, 20] In general, the rates of complications are minimal, although malignant cells may re-implant themselves, particularly following hematologic malignancies.[6, 8, 17, 20] The danger of reintroducing cancer cells may be decreased by transplanting ovarian follicles rather than the complete ovary.[9,18, 20]

There are two types of transplantation: (1) orthotopic, which involves putting ovarian tissue into the medulla, the ovarian fossa, or the broad ligament intraperotonially, and (2) heterotopic, which involves putting ovarian tissue in the abdominal wall, the chest wall, or the forearm, outside the peritoneal cavity.[4, 20]

Since orthotopic transplantation offers a better environment for follicular growth than heterotopic transplantation, it is typically more successful than heterotopic transplantation, if the fallopian tubes are intact.[7, 8, 13, 20- 23] Transplantation is expected to guarantee ovarian function for four to seven years, assuming appropriate ovarian tissue preservation is done.[7, 21]

However, there have been debates about this method of preserving fertility in relation to chromosomal abnormalities, because data indicates that cryopreservation may result in changes to cell membranes, DNA integrity, and aneuploidies.[21] The prevalence of chromosome abnormalities and aneuploidy did not increase in vitrified embryos that were cryopreserved.[22, 23] This might also be used to embryos created from cryopreserved oocytes, in which the rate of euploidy is the same as that of blastocysts created from fresh oocytes despite impaired blastulation.[24] Accordingly, vitrification has been identified as the safest cryopreservation method.[21, 22, 25] Various nations have varied laws pertaining to cryopreservation.[11]

Ovarian suppression

The first drugs employed in ovo-protection for chemotherapy were gonadotropin releasing hormone (GnRH) agonists/analogues.[4, 5, 26] These drugs suppress the hypothalamic-pituitary-ovarian (HPO) axis, which lowers the ovary's vulnerability to and shields it from the toxicity of chemotherapy. Since GnRH agonists generate a pre-pubertal state, their method of action is not biologically plausible for the protection of ovarian function. If, however, ovarian suppression was protective, children would not be susceptible to the gonadotoxic effects of chemotherapy. Furthermore, several anti-cancer medications do not shield DNA double strand that breaks from the ovarian suppression brought on by GnRH agonists.[6, 26, 27]

As such, the effects of these agents on fertility are debatable and variable.[7-9, 27] Certain researchers maintain that there is no impact on the rate of pregnancy[10], while other researchers assert that these drugs have a positive effect on both ovarian function and the rate of pregnancy.[11, 27] Therefore, GnRH agonists may offer ovarian function a small degree of protection, particularly in women under 40 years of age.[10, 11, 26, 27]

Ovarian transposition

Often referred to as oophoropexy, ovarian transposition surgery involves laparoscopically removing the ovaries from the radiation area by generally attaching them to the anterolateral abdominal wall before starting pelvic irradiation.[12, 13, 28] In 85% of patients under 40 with a history of normal ovarian reserve, oophorexy performed prior to radiotherapy results in ovarian preservation and reduces ovarian radiation exposure by 5–10%.[14- 16, 28]

Pharmacologic protection

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S-1-P) inhibits the ceramide-induced apoptotic pathway, notably the sphingomyelin pathway, hence reducing follicular apoptosis. In human ovarian tissue xenografted in mice, S-1-P enhances vascular supply, density, and angiogenesis. Additionally, it eliminates or greatly reduces apoptosis induced by doxorubicin and cisplatin.[17, 18, 29 - 33] It follows that using it in ovarian transplantation will shorten the time it takes for the graft to re-oxygenate and avoid follicular loss.[17, 19, 29 - 33] When S-1-P is used on sheep ovaries for cryopreservation, it can quickly boost primordial follicle densities, enhance their quality, and promote tissue survival.[20, 21, 32, 33] S-1-P has a cytoprotective effect on human granulosa cells exposed to cyclophosphamide via activating the Akt signaling pathway.[22, 23, 32, 33]

Owing to its extremely short half-life, S-1-P can be injected directly into the ovary beginning 24 hours before chemotherapy. It is administered and continued for 72 hours after chemotherapy administration.[24-26, 33-37] S-1-P's apoptotic block may inhibit physiologic apoptosis, such as in DNA-damaged oocytes, which is one of the agent's two main concerns, the other being that it is uncertain whether it interacts with other chemotherapeutic treatments.[34]

Imatinib

Imatinib is not only a tyrosine-kinase inhibitor utilized in cancer treatment; it is also a c-Abl kinase inhibitor that, when taken in conjunction with cisplatin.[26, 34] it suppresses the activation of apoptotic pathways through TAp[63], but not in conjunction with other chemotherapeutic drugs such as doxorubicin.[33, 38] Imatinib may cause follicular apoptosis itself; hence there is conflicting evidence that it protects mice against cisplatin-induced primordial follicle death.[39] Its gonadotoxicity is yet unknown and more research are needed.[40]

Anti-mullerian hormone

Anti-Mullerian hormone (AMH) administered at supraphysiological dosages inhibits the activation of primordial follicles brought on by chemotherapy, hence preventing basic ovarian insufficiency.[28-31] Concomitant chemotherapy and AMH injection in mice provides contraception without altering the ovarian reserve or changing the HPO axis.[41] Because AMH is an endogenous hormone, there is reduced chance of negative effects while using it, which makes it advantageous.[26, 40, 41]

AS101

Administered orally and intravenously, AS101 is an immunomodulator, tellurium-based chemical, and antioxidant.[26, 34, 42]

In ovaries exposed to cyclophosphamide, AS101 maintains fertility and ovarian reserve in several ways. It prevents large follicle death by directly inhibiting the PI3K/PTEN/Akt signaling pathway, improves DNA repair processes in oocytes, and sustains the negative feedback inhibition on follicular activation by releasing AMH.[43, 44] As101 may also cause integrin inhibition, which in turn causes the PI3K/PTEN/Akt pathway to be down regulated.[26, 34, 44] AS101 does not interact with anticancer drugs and preserves the genetic integrity of the oocytes.

Granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF) delays the onset of ovarian insufficiency in mice receiving gonadotoxic chemotherapy by protecting the vasculature.[45, 46] This is primarily achieved by increasing the density of microvessels. G-CSF injection prevents both ischaemia and ischaemia / reperfusion damage which results in elevated AMH levels and increased counts of all follicle types.[47, 48] However, clinical trials involving humans are still required to confirm such outcomes.

Melatonin

When taken concurrently with chemotherapy, melatonin is believed to mitigate the damage to the ovaries caused by the drug, preserving the follicles. Melatonin preserves follicular dormancy and stops follicle loss in mice by blocking the phosphorylation of PTEN/AKT/FOXO3a pathway components produced by cisplatin.42 Because melatonin suppresses the generation of hydroxyl radicals, which cause mitochondrial damage, its antioxidant properties can also be employed to protect the ovary from radiation-induced damage.[49] Endogenous ovarian melatonin is not fertoprotective even if it is present.[50] Thus, more research is still needed to determine the exact mechanism by which melatonin shields the ovary from gonadotoxic injury.[50]

Novel strategies

In-vitro growth and maturation of follicles

There is a known risk associated with ovarian tissue transplantation that the patient may get reintroduced malignant cells. This is addressed to by a unique approach in which immature follicles are extracted and cultured in-vitro in alginate hydrogels until they reach maturity.[4, 50, 51]

The multistage process of follicle formation makes this treatment difficult. Only non-growing ovarian follicles have been produced in humans. If the technique proves effective in humans, girls of all ages may under take it, but more research is needed.[51]

Germ cells from pluripotent stem cells

Due to numerous technical and moral concerns, including the xenotransplantation of human stem cells, in-vitro germ cell production is still being studied in rats rather than being applied to humans.[4–7, 51, 52] Stem cells, induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESC) are the sources of germ cells. Although human embryonic stem cells could not yet be differentiated into oocytes, research is being done on the production of autologous oocytes from human induced pluripotent stem cells.[52]

Oocyte stem cells (OSC) induce the development of early follicular structures and oocytes in humans and mice, respectively.[51] Human OSCs are rare, albeit.[7,51]

Uterine transplantation

Women who have lost their uterus function undergo uterine transplantation.[4, 51] Although this treatment primarily benefits women who are born without a uterus, it may also benefit cancer patients.[51] Uterine donors may be living or deceased as long as the organs have reached their full potential.[53] After that, the recipient receives the transplanted uterus and is treated with immunosuppressive medications including tacrolimus, azathioprine, and corticosteroids in an effort to reduce or reverse organ rejection.[53, 54] It is notable that this is the most recent reports of human uterine transplants in scientific literature. The first live birth was reported in 2014 in Sweden from a 35-year-old woman who had undergone IVF after uterine transplantation.54 Since this is a novel technique, a more thorough examination of the related ethical and technical challenges is necessary.[4, 54]

Artificial ovary

Primordial follicles are encapsulated in an artificial ovary scaffold, which is often made of a 3D biodegradable material,[7, 52, 54] such as alginate, collagen, fibrin, plasma clot, decellularized ovarian extracellular matrix, or synthetic polymer such polyethylene glycol.[51, 52, 54] After being removed from the patient and placed onto the scaffold, primordial pre-antral follicles are cryopreserved. This removes the possibility of cancerous cells spreading.[7, 54, 55] Although the number of follicles recovered using this method is limited, nearly all of them are viable.[56]

Conclusion

The most popular approach for preserving fertility is still cryopreservation, with vitrification being the method of choice, because it is comparatively safe and effective. Along with ferto-protective drugs, other fertility preservation tactics that pose additional difficulties, are contentious, or are constrained by contradictions in the literature, necessitating a more thorough investigation to support the data that is already available.

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