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Ovarian Tissue Preservation as a Method of Fertility Preservation

By

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Introduction / Background

While the majority of malignancies are diagnosed in the elderly population, 10% of malignancies are diagnosed in young patients before they have had the opportunity to have children and start a family. While incidence of cancer in a younger population is increasing, long term survival is also increasing.¹ However, cancer treatments, such as chemotherapy and radiotherapy, often have a gonadotoxic effect on the ovaries of both prepubescent girls and women of childbearing age, leading to infertility. Premature ovarian failure (POF) occurs in anywhere from 20% to 80% of cancer patients, depending on the treatment provided, dosages, and the patients age.¹ Because of the increasing survival rate of young women diagnosed with cancer, fertility preservation has been an increasingly important goal of treatment in oncology.

There are multiple methods of fertility preservation that are common in cancer patients. One method that is frequently used is oocyte or embryo cryopreservation. In this process, a woman's ovaries are stimulated so that multiple oocytes can be extracted. The oocytes can then be fertilized and frozen as embryos or frozen without fertilization. The procedure is commonly performed and considered to be a safe and effective method of preserving fertility.² However, there is a newer, more experimental method of fertility preservation known as ovarian tissue cryopreservation. In this procedure, either tissue from one ovary or one whole ovary is removed surgically, typically via a laparoscopic approach. This tissue is then frozen and stored for reimplantation in the pelvis after gonadotoxic treatment has been completed.² This procedure is still considered experimental and has not become a routinely used method of fertility preservation.^{2,3} This leads to the question: Among females with premature ovarian failure secondary to chemotherapy, how does ovarian tissue cryotherapy as a method of fertility preservation compare to oocyte cryopreservation, as measured by percentage of patients with

successful pregnancies after the procedure and return of ovarian function as determined by FSH level.

Discussion

Oocyte cryopreservation advantages and disadvantages

Both oocyte cryopreservation and ovarian tissue cryopreservation have their advantages and disadvantages. Oocyte cryopreservation is a frequently utilized procedure and multiple studies have shown that it is a very effective method of fertility preservation. One study reported that a cohort of women who underwent oocyte cryopreservation and later had their eggs thawed, fertilized, and implanted had an ongoing and delivered pregnancy rate of 57%.⁴

One advantage that oocyte cryopreservation has over ovarian tissue cryopreservation is that it is significantly less invasive. Oocyte harvesting for cryopreservation involves a needle inserted through the vaginal wall. When the patient is interested in pursuing pregnancy, the egg is then fertilized and inserted into the uterus through the cervix.² Ovarian tissue cryopreservation, however, involves one surgery to harvest the tissue, and another surgery to implant the tissue into the pelvis.²

Oocyte cryopreservation also has its downsides, particularly in patients who are looking to preserve fertility prior to treatment for malignancies. One major downside is that it can cause a delay in treatment for cancer patients. Follicles need to be stimulated in order to produce sufficient oocytes for harvesting, and that process takes time.¹ This delay in cancer treatment, can be unacceptable in patients with aggressive malignancies that require immediate gonadotoxic treatment. Oocyte cryopreservation also cannot be used in prepubescent girls, meaning that ovarian tissue cryopreservation is the only fertility preservation treatment for girls diagnosed with cancer prior to menarche.¹ Finally, if the cancer treatment results in ovarian failure, oocyte

cryopreservation cannot preserve ovarian function in patients who experience premature ovarian failure secondary to gonadotoxic treatment.⁵ This premature ovarian failure can lead to a long-term need for hormone supplementation, especially in young women.

Ovarian tissue cryopreservation advantages and disadvantages

There are some advantages that ovarian tissue cryopreservation has over oocyte cryopreservation. One advantage is that there is significantly less delay in cancer treatment because the ovaries do not need to be stimulated prior to the procedure.⁵ This allows for fertility preservation without complicating the cancer treatment. One study showed that out of 92 cancer patients who underwent surgery for preservation of ovarian tissue, only two experienced a delay in their cancer treatment, secondary to minor surgical complications.⁶ Ovarian tissue cryopreservation is also the only option for fertility preservation in prepubescent girls, as their ovaries cannot be stimulated prior to menarche.² Finally, ovarian tissue cryopreservation is the only option for patients who are looking for return of normal ovarian function and menstruation following gonadotoxic treatment. The goal of reimplantation of the frozen ovarian tissue is to allow the tissue to function as it did prior to removal. With this, normal hormonal regulation should return if the procedure is successful.

Multiple studies have been done to determine the rate at which ovarian function actually returns. In one study, all 13 patients who had ovarian tissue reimplanted experienced return of normal ovarian function for a period of at least five years after the procedure, as determined by a decline in levels of follicle stimulating hormone (FSH) following the procedure.⁵ Another study showed that after three ovarian tissue autotransplants were performed, one transplant stopped functioning after nine years and the other two were still functioning after a 7 year period of time based on FSH levels⁷.

In a larger study, 52 of 56 women had restoration of ovarian function following ovarian tissue autotransplantation,⁸ and in one final study, 12 women who underwent the procedure had ovarian function return between eight and 26 weeks, with a lifespan of ovarian function lasting between 6 months and still functioning after 54 months.⁹ Looking at all this data together, it is clear that autotransplantation of cryopreserved ovarian tissue provides a robust return of ovarian function in almost all patients. This allows for an improved quality of life in cancer patients following treatment due to return of normal menstruation and hormonal regulation, as well as preventing the need for hormone replacement therapy in the younger patients. No other method of fertility preservation allows for return of ovarian function following gonadotoxic treatment.

Studies have also revealed that ovarian tissue cryopreservation is effective in allowing patients to become pregnant after reimplantation. In one smaller study ten of the 13 patients who underwent reimplantation of cryopreserved ovarian tissue became spontaneously pregnant at least once, resulting in 13 healthy babies and a 77% live birth rate.² Another study showed that three of eight patients that had their ovarian tissue reimplanted had become pregnant, although the study did not have any information on the outcomes of the pregnancies.¹ In yet another study, seven of 21 patients delivered healthy babies, resulting in a 33% live birth rate.¹⁰ Finally, one last study revealed that out of 60 patients who underwent autotransplantation of cryopreserved ovarian tissue, 11 patients have conceived and 6 had delivered 12 healthy babies, with two of the pregnancies ongoing at the time the study was published.⁸ These studies seem to confirm the efficacy of the procedure in returning fertility. However, the small sample size in most studies and the low overall return rate for reimplantation of cryopreserved ovarian tissue can make determining the true efficacy of ovarian tissue cryopreservation difficult.

Ovarian tissue cryopreservation has also been shown to be a very safe procedure. One study showed that in 309 cases of ovarian tissue cryopreservation procedure, the procedure only resulted in minor complications, mainly bleeding.³ In another study of 545 patients who underwent ovarian tissue cryopreservation, only one patient had a major complication (intra-abdominal hemorrhage).¹⁰ Not only is the procedure safe, but the patient satisfaction is very high. One study showed that 96% of patients were satisfied with the procedure, as determined by survey sent to patients who had undergone the procedure.¹⁰

However, one major concern with the procedure in cancer patients is the small but real risk of reintroducing cancerous cells in the cryopreserved ovarian tissue after remission of the cancer. One study showed that ovarian metastases are most common in patients with leukemia, but less common in patients with most other cancers.¹¹ Ovarian metastasis is also not seen at all in patients with breast cancer and lymphoma.¹¹ In cancer patients considering ovarian tissue cryopreservation, it is important to consider the type of cancer the patient has and the risk of ovarian metastasis prior to recommending the procedure. It is also important to educate the patient of the risk of reintroduction of the cancer prior to the procedure, especially in cancers that have a high risk of ovarian metastasis.

Conclusion

Ovarian tissue cryopreservation is an exciting and effective method of fertility preservation in patients with premature ovarian failure secondary to cancer treatment. However, it may not be the right choice for healthy women trying to prolong fertility. The ideal patient to undergo ovarian tissue cryopreservation is a prepubescent or young woman recently diagnosed with breast cancer or lymphoma and interested in ensuring their ovarian function returns and they are able to preserve fertility prior to gonadotoxic therapies. The procedure is still considered

experimental, but has been shown to be effective and safe in the right patient population. The procedure seems to be very effective based on the studies, but the poor rate of return for reimplantation of ovarian tissue and small sample size in most of the studies make it difficult to evaluate the true efficacy of ovarian tissue cryopreservation. 56 to 59 patients still haven't utilized tissue in one study, with reasons ranging from still being in cancer treatment, social and personal reasons, or the patient passed away from cancer.⁷ However, the patient satisfaction with the procedure is high, and the chance to preserve ovarian function and fertility has the opportunity to significantly improve patient lives following cancer treatment and remission. Some future areas to investigate include performing larger studies to show the efficacy of the treatment. It would also be interesting to investigate usefulness as treatment for patients with other causes of premature ovarian failure, such as Turner syndrome.

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