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Comparison of Cryopreservation of Ovarian Tissue Versus Cryopreservation of Oocytes in Fertility Preservation

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Abstract

*This literature review aims to compare ovarian tissue cryopreservation (OTC) and oocyte cryopreservation (OC) as methods for fertility preservation. Electronic health science databases including PubMed, Clinical Key, ScienceDirect, and UpToDate were utilized. Seven articles met the inclusion criteria and were analyzed for this comprehensive review. This review indicates that both oocyte and ovarian tissue cryopreservation can effectively preserve fertility, however, ovarian tissue cryopreservation is deemed most effective for prepubertal girls at high risk of iatrogenic primary ovarian insufficiency (POI), or women who are unable to postpone gonadotoxic treatment. Ovarian tissue cryopreservation offers advantages that oocyte cryopreservation does not, such as multiple spontaneous pregnancies and resumption of ovarian function. Ovarian tissue cryopreservation also does not carry the risks associated with ovarian stimulation and delaying gonadotoxic treatment, unlike oocyte cryopreservation. Despite successful birth rates and low surgical risks associated with ovarian tissue cryopreservation, studies reveal a low utilization rate, with women often considering stored ovarian tissue as a “backup plan”. There is a need for further additional research on ovarian tissue cryopreservation, especially in the younger age groups, as there was limited participation in follow-up studies. Overall, the studies analyzed in this literature review support ovarian tissue cryopreservation as an effective method of fertility preservation but emphasize the importance of further investigation and follow-up studies.

Keywords: ovarian tissue cryopreservation, oocyte cryopreservation, cryopreservation techniques, ovarian tissue transplantation, fertility methods, cryopreservation safety

Introduction

*Premature ovarian insufficiency (POI) is defined as the early depletion of the ovarian reserve and is a leading cause of female infertility. Iatrogenic POI can occur in females following gonadotoxic treatments in women diagnosed with cancer or benign diseases requiring treatment. These treatments include chemotherapy, radiotherapy, and surgery (Cacciottola et al., 2022).

*Before recent innovations in fertility preservation, cancer survivors with POI could only achieve parenthood through adoption or donor gametes. Fortunately, now this can be achieved via oocyte cryopreservation (OC), embryo cryopreservation, and ovarian tissue cryopreservation (OTC). This literature review aims to compare OTC and OC.

*Cryopreservation of ovarian tissue can be performed in both pre- and post-pubertal females, and unlike oocyte cryopreservation, requires no ovarian stimulation. This results in avoidance of treatment delays and the risk of ovarian hyperstimulation syndrome. Ovarian tissue cryopreservation also does not require a male partner or sperm donor, and allows for a chance at natural conception, avoiding the financial burden of in vitro fertilization (IVF). Ovarian tissue cryopreservation is also the only method suitable for adolescents who have not reached reproductive maturity (Dhonnabhain et al., 2022).

Statement of the Problem

*Ovarian tissue cryopreservation (OTC) was previously labeled as an experimental fertility preservation procedure. This label was removed by the American Society for Reproductive Medicine in December 2019; however, the treatment is still considered experimental in many areas of the world. OTC is a unique option for women and adolescents with POI who cannot postpone gonadotoxic treatment. It can be performed during management of the disease and has low risk of complication. It is also the only option offered for pre-pubertal girls to preserve fertility before highly gonadotoxic treatments, as it does not require ovarian stimulation. OTC has growing success rates, and this literature review aims to compare OTC with OC.

Research Question

In women who require fertility preservation, does cryopreservation of ovarian tissue compared to oocyte cryopreservation result in higher rates of successful pregnancy and long-term preservation of fertility?

Literature Review

Efficacy of Oocyte Cryopreservation for Infertility

- Druckenmiller et al. (2016) performed a retrospective analysis of reproductive-age cancer patients' treatment cycles to demonstrate the viability of OC as a reproductive choice to patients undergoing gonadotoxic treatments.
- Cacciottola et al. (2022) reviewed therapeutic methods for both fertility preservation and hormone replacement therapy in young patients with iatrogenic POI and found that OTC has advantages over OC, such as multiple spontaneous pregnancies, resuming ovarian function thus replacing hormone replacement therapy, and alleviating postmenopausal symptoms.

Efficacy of Cryopreservation of Ovarian Tissue for Infertility

- Khattak et al. (2022) performed a systemic review and individual patient data meta-analysis of 735 women who have received fresh or frozen ovarian transplants to preserve reproductive and endocrine function. The study demonstrated a live birth rate of 28% for frozen transplants and 45% for fresh transplants, suggesting that it is possible to restore ovarian reproductive and endocrine function using fresh or frozen-thawed ovarian transplantation and should be offered as a routine fertility preservation method.
- Poirot et al. (2019) performed a retrospective study including 418 patients 15 years and younger who had gone through OTC before gonadotoxic treatment at a single medical center. However, no successful pregnancies have yet been achieved in this study population, and there was a very low utilization rate of the cryopreserved tissue (2.2%). It is necessary to obtain more follow-up studies in a few more years, especially due to the young age of many of the study population at the time of the study.

Safety of Cryopreservation of Ovarian Tissue for Infertility

- Leflon et al. (2022) performed a retrospective observational study involving 87 women over the age of 18 to determine the gynecological and reproductive health outcomes in women who have undergone OTC before gonadotoxic chemotherapy or radiotherapy. The study demonstrated that 8% of women underwent ovarian tissue transplantation and six became pregnant and delivered at least once. There were no cancer reoccurrences in this study. The study revealed a high satisfaction rate, however a low utilization rate, even with a low surgical risk, low risk of cancer reoccurrence, and a successful birth rate.
- Dolmans et al. (2021) performed a case study review from five European centers' collective experience of transplanting ovarian tissue in 285 women. In this study, 26% successfully became pregnant and delivered one or two infants. Of the 221 women in this study with POI who underwent OTT, 88.7% had endocrine function resumption based on the return of menses. Comparing natural conception after OTC (40%) with IVF treatment after OTC (36%) showed comparable conception rates, although slightly higher in women who had natural, spontaneous conception. Also, the miscarriage rates were higher in women who underwent IVF (18%) than in women who had natural conception (10%). This study also revealed that chemotherapy without the use of alkylating agents before OTC does not alter the pregnancy success rate, indicating that women undergoing chemotherapy may still benefit from OTC and OTT. Twelve patients (4.2%) of 285 patients had a relapse following OTT, however, all relapses were due to the primary malignancy and not due to the graft, as the relapses were all near the primary location of the cancer.

Comparison of Oocyte Cryopreservation and Cryopreservation of Ovarian Tissue for Infertility

- Dhonnabháin et al. (2022) performed a systematic review to compare obstetric outcomes in patients undergoing cryopreservation of oocytes, embryos, or ovarian cortical tissue before gonadotoxic therapy. The study showed no significant difference in live birth rates among the three options: oocytes (25.8%), embryos (35.3%), and ovarian tissue (32.3%) ($p = .11$).
- Chung et al. (2021) performed a study comparing OC and OTC using a cost-effectiveness model. After undergoing OC, 1.56% of patients achieved a live birth, and 1.0% of patients achieved a live birth after OTC, with a p-value of <0.05 considered statistically significant differences. Results showed that the estimated cost for OC was \$16,588 and OTC was \$10,032. The results of this study showed that OC is more clinically successful but is much less cost-effective than OTC.

Discussion

*This literature review has examined and demonstrated that there is evidence that the utilization of ovarian tissue cryopreservation is a sufficient method of fertility preservation and should be offered as an option for women who wish to preserve fertility. Dolman et al. (2021) conducted a comprehensive review and suggests that both oocyte and ovarian tissue cryopreservation can be effective methods of fertility preservation. They highlight that the live birth rates are dependent on factors such as the amount of radiation received and chemotherapy exposure (Dolman et al., 2021). Druckenmiller et al. (2016) and Cacciottola et al. (2022) both support the effectiveness of oocyte cryopreservation as a method for post-pubertal fertility preservation in cancer patients. Furthermore, Cacciottola et al. (2022) highlights the importance of considering the patient's age and pubertal status when choosing between OC and OTC. Cacciottola et al. (2022) also supports OTC as an effective method of fertility preservation for prepubertal girls at high risk of iatrogenic POI or women who are unable to postpone or have already begun gonadotoxic treatment. OTC allows for multiple spontaneous pregnancies, an advantage to OC. OTC also has the advantage of resuming ovarian function, thus replacing hormone replacement therapy, and alleviating postmenopausal symptoms (Cacciottola et al., 2022).

*Dhonnabhain et al. (2022) presents a systematic review, indicating that oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation have similar clinical pregnancy and live birth rates. OTC also shows a lower miscarriage rate compared to embryo cryopreservation. They highlight that OTC does not carry the risks associated with ovarian stimulation and delaying gonadotoxic treatment, which can be a concern in OC (Dhonnabháin et al., 2022). Chung et al. (2021) compares oocyte cryopreservation and OTC, highlighting that oocyte cryopreservation may have better clinical success but is less cost-effective than OTC (Chung et al., 2021).

*Poirot et al. (2019) and Leflon et al. (2022) present data indicating a low utilization rate of cryopreserved ovarian tissue (2.2% and 8.0%). Many women in Leflon et al. (2022) study (50%) continued their ovarian tissue storage, however, viewing their stored ovarian tissue as a “backup plan”. Leflon et al. (2022) reported a higher natural pregnancy rate and high satisfaction among patients who underwent OTC. Thus, with the low usage rate, even with the low surgical risk, low risk of cancer reoccurrence, and successful birth rate, additional follow-up studies should be performed on women who underwent OTC, especially at a young age (Leflon et al., 2022; Poirot et al., 2019). A similar limitation in many of these studies is the limited participation of women returning for follow-up or utilizing their cryopreserved ovarian tissue, and additional follow-up studies may be beneficial. The studies analyzed in this literature review provide support for ovarian tissue cryopreservation as an efficacious and safe method of fertility preservation.

Applicability to Clinical Practice

The information provided in this literature review will be useful for medical providers who are needing to counsel women desiring fertility preservation on the various methods to choose from. Knowing the clinical outcomes, cost-effectiveness, and overall efficacy can significantly aid a patient in choosing the most appropriate fertility method for their individualized care. The information is also useful for women who find themselves in the position of needing or desiring fertility preservation and want to research and compare the available methods for themselves.

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