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Ovarian Tissue Cryopreservation versus Other Fertility Techniques for Chemoradiation Induced Premature Ovarian Insufficiency in Women: A Systematic Review and Future Directions

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Background

Recent advances in cancer therapy have led to increased cure rates and survival with high emphasis on quality of life. Chemoradiation therapy are well known to result in premature ovarian insufficiency (POI) and thus loss of fertility in women. Alkylating agents induce follicular atresia. Most data on oncofertility intervention recommendations comes from patients with solid tumors. Currently, ovarian tissue cryopreservation (OTC) is still categorized as experimental in the US though it is the only viable option for pre-pubertal patients and those that cannot delay chemotherapy initiation. Many retrospective, prospective studies, and case reports of fertility preservation methods among cancer patients are available, but with varying definitions of optimum fertility. From a patient perspective, live birth rate is the most important endpoint. There is minimal comparison of fertility preservation techniques to each other so far.

Methods

Electronic searches on peer-reviewed databases

Oocyte Cryopreservation | ***Embryo Cryopreservation*** | ***Ovarian Tissue Cryopreservation***

Study eligibility criteria:
Randomized and nonrandomized control trials
Prospective and Retrospective Cohort Studies with defined successful outcomes and failures
Case Studies, Case Series
Questionnaires

Data extraction:
regarding patient exposures (chemotherapy, radiation etc.), doses, fertility preservation methods, average time to conception, live births

Study Appraisal: Non-randomized clinical trials including case-control and cohort studies evaluated for risk bias through Newcastle-Ottawa Scale methodical assessment.

Results and Analysis

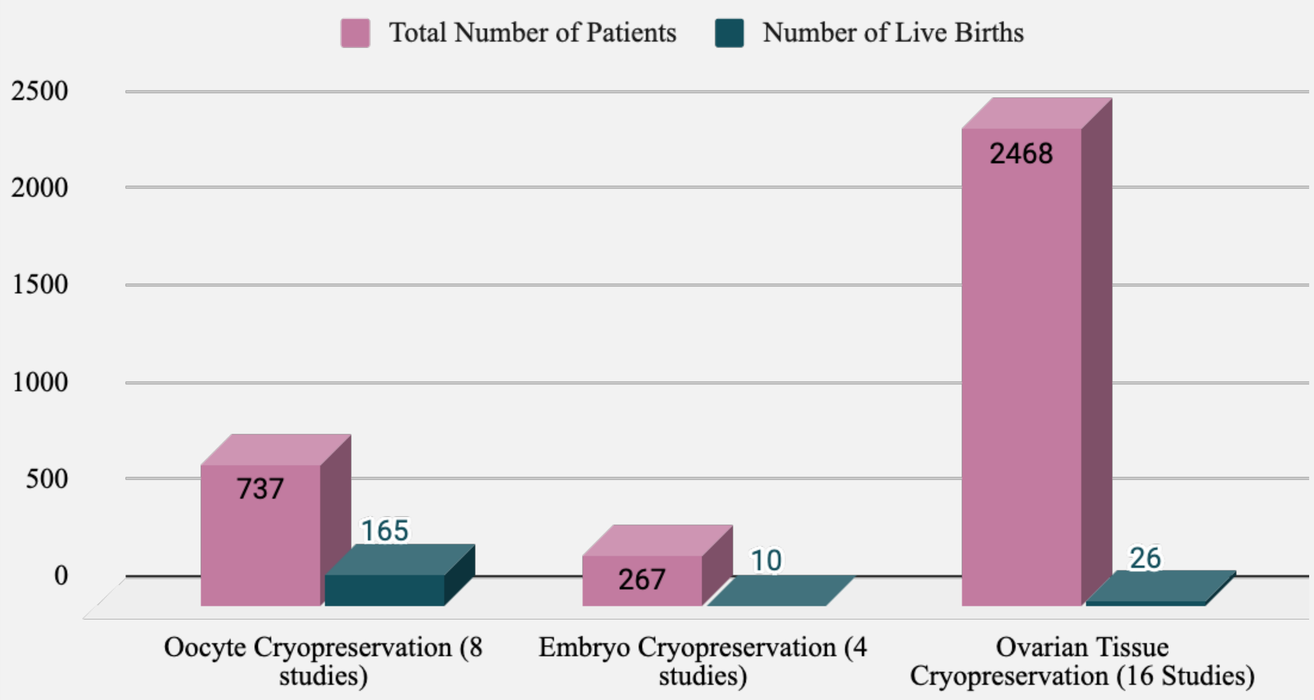

Figure 1: Number of Live Births Compared to total number of patients undergoing different Fertility Preservation Efforts

	Sample Study Size	Number of Patients	Average Age at Procedure	Patients Undergoing Cryopreservation
Mean	289	174	31.27	92.13
Median	126	54.5	30	26
Mode	NA	NA	NA	NA
Range	1253	851	11.5	424
Total	2312	1392	NA	737

Table 1: Oocyte Tissue Cryopreservation Data Analysis

	Sample Study Size	Number of Patients	Average Age at Procedure	Patients Undergoing Cryopreservation
Mean	349.75	232.25	33.63	66.75
Median	72	38	34.55	23
Mode	NA	NA	NA	NA
Range	1253	851	10.6	219
Total	1399	929	134.5	267

Table 2: Embryo Cryopreservation Data Analysis

	Sample Study Size	Number of Patients	Average Age at Procedure	Patients Undergoing Cryopreservation
Mean	229.56	194.75	23.05	154.25
Median	28	24	25	20
Mode	1	1	23	1
Range	1607	1607	25.1	1607
Total	3673	3116	NA	2468

Table 3: Ovarian Tissue Cryopreservation Data Analysis

Successful outcomes excluding live births/successful pregnancy:

- *High Follicle Viability post-Ovarian Tissue Transplantation*
- *Successful follicle growth and embryo development*
- *Fully restored ovarian function*
- *Spontaneous pregnancies after fertility treatment*
- *Serum Anti-Mullerian Hormone levels*

Discussion

The toxic effects of chemotherapy have been long established. Alkylating agents are implicated in infertility. Oocyte and embryo cryopreservation are well established, but drawbacks include required controlled ovarian stimulation, which requires prior hormonal therapy. Oocyte and embryo cryopreservation is also suitable for older adolescents that are post-pubertal, but not for patients who have not commenced menses. Moral implications exist as well for the mentioned fertility preservation techniques. Harvesting ovarian tissue can be done with minimal invasion, and can be applied to pre and post pubertal female cancer patients without the requirement of hormonal therapy. Ovarian function is allowed to resume on its own, allowing female patients to undergo menses, spontaneous pregnancy.

Conclusion

Previous publications illustrate the potential success of this intervention, especially in pre pubertal female patients. Future research priorities include:

a) Comparative trials in various methods of fertility preservation
b) Risk of fertility loss in HSCT patients is rare, prospective studies in this population are rare and thus critically needed.
c) Novel strategies to prevent or treat chemoradiation induced ovarian insufficiency including primordial follicle maturation techniques, regenerative medicine, and bioengineered ovaries should be tested in clinical trials.

References