

## Current State of Fertility Preservation in Cancer Patients—What is Established and What is Still Controversial?

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### Abstract

Fertility Preservation is an essential part of cancer care when treating young females and men. While semen cryopreservation is a straightforward approach for postpubertal men and there is the option of experimental testicular tissue freezing for prepubertal boys, the options for females are more tumultuous. The last 17 years brought us established approaches such the embryo and oocyte cryopreservation and the ovarian cryopreservation is ready to join the list. However, there still is no proven medical fertility preservation method and the controversy around the utility of GnRHa continues.

### Keywords

Fertility preservation, cancer, quality of life, oocyte and embryo cryopreservation, ovarian tissue cryopreservation, GnRHa

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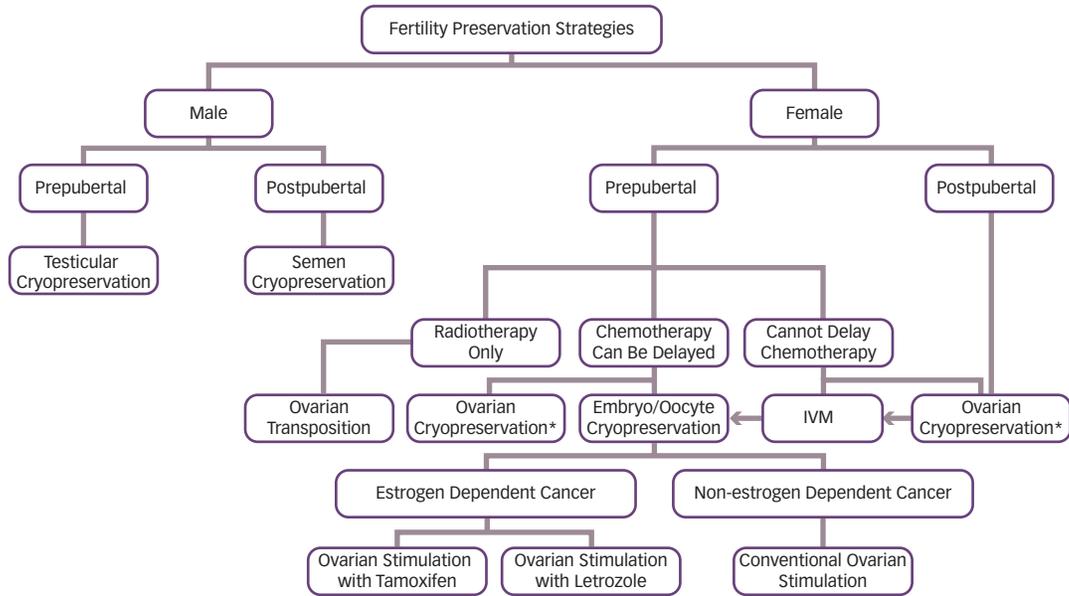
It has been estimated that approximately 1% of all females may be exposed to some form of gonadotoxic cancer treatment by the age of 45.<sup>1</sup> Given the quality of life consequences of cancer-treatment-induced infertility and ovarian failure, fertility preservation becomes an essential component of cancer care. The fertility preservation field has shown significant evolution within the past 17 years but it is not without its controversies. While embryo and oocyte cryopreservation are considered established techniques, various discussions continue around ovarian cryopreservation as well as the utility of Gonadotropin Releasing Hormone Agonists (GnRHa).

To us, ovarian cryopreservation followed by transplantation is the easier one to address first. The question revolves around whether it should still be considered experimental. Recent reports including some of ours put the number of live births over 60, with more than a third of women having at least one child after an ovarian transplant.<sup>2,3</sup> Ovarian cryopreservation has several advantages over gamete freezing techniques, as after transplantation, normal ovarian endocrine function can be restored and fertility can be achieved without assisted reproduction techniques. There is no need for ovarian stimulation or a significant delay before chemotherapy as tissue is harvested via a brief outpatient laparoscopic procedure. We have shown the safety of ovarian tissue harvesting in cancer patients,<sup>4</sup> even in those with multiple medical issues.

Why then, is ovarian tissue freezing still considered experimental? Among the several reasons that have been cited are the relative brevity of experience, lack of randomized studies—especially on the risk of reseeding cancer cells, and the unpredictable duration of ovarian function after a transplant. We performed the first case of autologous ovarian transplantation with cryopreserved tissue in 1999,<sup>5</sup> which successfully restored ovarian endocrine function in a surgically menopausal young woman. There is now 17 years of experience with this procedure. Animal as well as cadaveric studies suggest by and large that micrometastasis to the ovaries is not a real concern especially for the cancer types for which ovarian tissue freezing is commonly performed. And finally, with the advent of new transplant techniques, like the one we recently reported,<sup>2</sup> ovarian function becomes more predictable after transplants. Given this profile, ovarian cryopreservation stands as a valid method of fertility preservation. This is especially true when the patient is a child and hence cannot be a candidate for egg freezing, or when there is insufficient time or contraindication for ovarian stimulation.

That brings us to the controversy regarding ovarian suppression with GnRHa to protect ovaries during chemotherapy. The recent randomized trial by Moore et al. suggested that Zoladex® (AstraZeneca, Macclesfield, UK) may preserve ovarian function during chemotherapy in women with

Figure 1. An overview of contemporary fertility preservation strategies in men and women with cancer



Fertility preservation is simplified in postpubertal males with the routine availability and success of semen cryopreservation. In prepubertal boys, testicular cryopreservation is an experimental procedure with no attempts at testicular transplantation have yet been reported. In females, there is no proven medical method of fertility preservation available. When ovarian involvement is ascertained and only radiation treatment is planned to pelvic or abdominal area, ovarian transposition can yield satisfactory results, though up to 50% may fail due to ovarian vessel kinking, scatter radiation and ovarian remigration. If a gonadotoxic chemotherapy regimen is planned and there is sufficient time, ovarian stimulation followed by embryo or oocyte freezing is typically offered in sexually mature individuals. Oocyte cryopreservation can also be performed in children as young as 13 years of age. When there is insufficient time for ovarian stimulation, or the individual is not sexually mature for ovarian stimulation, ovarian cryopreservation is an option with livebirth rates now exceeding 30% per patient. Another option for those who cannot delay chemotherapy and when there is insufficient time for ovarian stimulation is the retrieval of oocytes without ovarian stimulation and subsequent in vitro maturation (IVM) for oocyte or embryo cryopreservation. Immature oocytes can also be recovered from small antral follicles during ovarian tissue freezing for the purpose of IVM, both in prepubertal and postpubertal females. For women with estrogen sensitive cancer, particularly of the breast, tamoxifen, or letrozole can be used along with gonadotropin stimulation to minimize estrogen exposure.

estrogen receptor (ER)+ breast cancer.<sup>6</sup> We have already discussed the weaknesses of this and similar studies elsewhere.<sup>7-9</sup> It appears that the studies on the subject are split with some favoring GnRHa while others showing no benefit. We analyzed this contradiction in a recent report,<sup>8</sup> and found that the studies that utilized proper markers of ovarian reserve did not find any benefit for ovarian suppression. In fact, positive studies incorrectly utilized menstruation as a surrogate of fertility and did not report on the regularity of cycles. The most common manifestation of impending ovarian failure is irregular menstruation, not amenorrhea. None of the randomized studies used placebo or blinding, leaving the door open to possibly interpreting any menstrual bleeding as a sign of normalcy in the GnRHa treatment group. Likewise, if the subject and the researchers know that the patient did not receive GnRHa, they may have a more pessimistic take on irregular or scant menstruation. Many studies did not even control for tamoxifen use, which can also alter menstruation. Moreover no study, including those which suggested some benefit to menstruation, conclusively showed any benefit to fertility. In the study by Moore et al., when the pregnancy intent was considered, there was no difference in conception rates.<sup>7</sup>

In a recent meta-analysis that included 10 eligible trials in 907 women with the primary outcome defined as the proportion of women with resumed ovarian function at the longest follow-up after the end of chemotherapy, GnRHa co-treatment did not favor ovarian function resumption (68.4% in GnRHa versus 59.9% in chemotherapy-alone; risk ratio [RR] 1.12, 95% confidence interval [CI] 0.99–1.27).<sup>10</sup> The results were not affected by type of malignancy ( $p=0.31$ ), age ( $p=0.14$ ), and GnRHa type ( $p=0.44$ ). GnRHa was also not protective based on follicle stimulating hormone (FSH)

(mean difference  $-2.63$ , 95% CI  $-7.33$  to  $2.07$ ), antral follicle count (AFC) (mean difference  $1.66$ , 95% CI  $-0.69$  to  $4.01$ ), or anti-Mullerian-hormone (AMH) (mean difference  $0.31$ , 95% CI  $-0.41$  to  $1.03$ ). The spontaneous conception probability was also similar (RR  $1.63$ , 95% CI  $0.94$ – $2.82$ ).<sup>5</sup>

This should not come as a surprise because chemotherapy induces ovarian failure by causing double strand DNA breaks and apoptotic death in primordial follicles<sup>11</sup> which are not hormone sensitive.<sup>12</sup> Hence the idea that suppression of FSH and luteinizing hormone (LH) hormones by GnRHa would somehow protect primordial follicle oocytes does not have any scientific rationale. In our opinion, GnRHa should not be offered as an effective measure of fertility preservation; it has already been dropped for men.

Finally, the feasibility of ovarian stimulation in women with estrogen-sensitive cancer continues to improve. To minimize the estrogen exposure during ovarian stimulation for oocyte and embryo cryopreservation, we developed a concurrent aromatase inhibitor and gonadotropin treatment protocol.<sup>13</sup> In two recent studies, we showed that over 50% of women who preserved embryos with this method were able to have at least one child<sup>14</sup> and that long term cancer recurrence rates were not increased regardless of the BRCA status or whether the ovarian stimulation took place before or after surgery.<sup>15</sup> In addition, the flexibility of ovarian stimulation protocols have also increased with the introduction of random start stimulation protocols.<sup>16</sup> Studies have now shown that the efficiency of an oocyte retrieval is the same regardless of when the stimulation is started in relation to the onset of menstrual period.<sup>16</sup> As a result, an oocyte embryo cryopreservation treatment can be initiated immediately and completed in as little as a 2 weeks' time.

In conclusion, options for fertility preservation have significantly improved for cancer patients (Figure 1). Embryo, oocyte, and ovarian tissue cryopreservation are all proving to be effective strategies. However, there are no proven medical means of preserving fertility,

including the utility of GnRH analogs. Depending on the age of the patient, available time, cancer diagnosis, and desired outcomes, fertility preservation experts can tailor a strategy that best suits each woman with cancer. ■

1. Rodriguez-Wallberg KA, Oktay K, Fertility preservation during cancer treatment: Clinical guidelines, *Cancer Manag Res*, 2014;6:105–117.
2. Oktay K, Bedoschi G, Pacheco F, et al., First Pregnancies, Live birth and In Vitro Fertilization Outcomes After Transplantation of Frozen-Banked Ovarian Tissue with a Human Extracellular Matrix Scaffold using Robot-Assisted Minimally Invasive Surgery, *Am J Obstet Gynecol*, 2016;214:94.e1–9.
3. Jensen AK, Kristensen SG, Macklon KT, et al., Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark, *Hum Reprod*, 2015;30:2838–45.
4. Oktay K, Oktem O, Ovarian cryopreservation and transplantation for medical indications: Report of an ongoing experience, *Fertil Steril*, 2010;93:762–8.
5. Oktay K, Karlikaya G, Ovarian function after autologous transplantation of frozen-banked human ovarian tissue, *N Engl J Med*, 2000;342:1919.
6. Moore HC, Unger JM, Phillips KA, et al., Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy, *N Engl J Med*, 2015;372:923–32.
7. Oktay K, Rodriguez-Wallberg K, Munster P, Ovarian protection during adjuvant chemotherapy, *N Engl J Med*, 2015;372:2268–9.
8. Oktay K, Turan V, Failure of GnRHs to Preserve Fertility: An Appraisal Based on the Quality of Evidence, *JAMA Oncol*, 2015;1:1–2.
9. Rodriguez-Wallberg K, Turan V, Munster P, Oktay K, Can ovarian suppression with gonadotropin-releasing hormone analogs (GnRHs) preserve fertility in cancer patients?, *Ann Oncol*, 2015;27:257.
10. Elgindy E, Sibai H, Abdelghani A, Mostafa M, Protecting Ovaries During Chemotherapy Through Gonad Suppression: A Systematic Review and Meta-analysis, *Obstet Gynecol*, 2015;126:187–95.
11. Soleimani R, Heytens E, Darzynkiewicz Z, Oktay K, Mechanisms of chemotherapy-induced human ovarian aging: double strand DNA breaks and microvascular compromise, *Aging (Albany NY)*, 2011;3:782–93.
12. Oktay K, Briggs D, Gosden RG, Ontogeny of FSH receptor gene expression in isolated human ovarian follicles, *J Clin Endoc Metabol*, 1997;82:3748–51.
13. Oktay K, Buyuk E, Libertella N, et al., Fertility preservation in breast cancer patients: a prospective comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation, *J Clin Oncol*, 2005;23:4347–53.
14. Oktay K, Turan V, Bedoschi G, et al., Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer, *J Clin Oncol*, 2015;33:2424–9.
15. Kim JY, Turan V, Oktay K, Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer, *J Clin Endocrinol Metab*, 2016;jc20153878. [Epub ahead of print]
16. Sonmezer M, Turkuoglu I, Coskun U, Oktay K, Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles, *Fertil Steril*, 2011;95:2125.
17. Cakmak H, Katz A, Cedars MI, Rosen MP, Effective method for emergency fertility preservation: random-start controlled ovarian stimulation, *Fertil Steril*, 2013;100:1673–80.