

Obstetrics & Gynecology:

November 2008 - Volume 112 - Issue 5 - pp 1160-1172

doi: 10.1097/AOG.0b013e31818bba31

Clinical Expert Series

Preservation of Female Fertility: An Essential Progress

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Abstract

Chemotherapy and radiation treatment for malignancies or other conditions such as hematologic and autoimmune disorders, have resulted in improved survival rates but may lead to sterility. Women who postpone conception until late reproductive years are also at increased risk to become infertile. The purpose of our review is to evaluate advances and techniques for fertility preservation. We performed a literature search using the keywords *fertility preservation*, *vitrification*, *oocytes*, *embryo*, *ovarian cryopreservation*, and *ovarian suspension* and conducted the search in MEDLINE, EMBASE, and the Cochrane Database of systematic reviews. The results show that today, it is possible to cryopreserve oocytes, embryos, or ovarian tissue. The most commonly used technique remains embryo cryopreservation. Another improvement is the development of vitrification or rapid freezing technique. For women undergoing local pelvic radiation, one should consider ovarian suspension. Medical professionals, patients, and their families should be aware that in some conditions, the reproductive function can be preserved. Although one cannot guarantee future fertility, a realistic hope for women at risk of having premature ovarian failure can now be offered.

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Creator: Green Journal

Created: 1/23/2009

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"Preservation of Female Fertility: An Essential Progress"

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November 2008 - Volume 112 - Issue 5

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1. Gonadotoxic chemotherapy is the most common cancer treatment encountered in young females aged 16 to 35 years. This exposure has the most limited fertility-sparing options. Most of these patients are not able to travel to advanced centers for specialized treatment. Therefore, isn't pretreatment with GnRHa the most practical option for these patients despite the statement by the American Society of Oncology? This can be administered by essentially all gynecologists and oncologists.

Response from Dr. Togas Tulandi:

There is a lack of evidence that GnRHa is effective in protecting the gonads against the gonadotoxicity of chemotherapy. Indeed, nonrandomized studies have demonstrated that the rate of resumption of menses in women treated with GnRHa is higher than in those untreated. However, in a randomized study of 18 women and 30 men with Hodgkin's disease treated with chemotherapy, Waxman et al found that GnRHa was ineffective. It seems the effects of GnRHa are suboptimal. Ideally, these patients are referred to have fertility preservation procedures or participate in a randomized trial. Otherwise, due to the possible beneficial effect of GnRHa, one could consider treating those women with GnRHa. They should be made aware about the limitation and side effects of the treatment.

2. Should the indications for fertility preservation be expanded to include advanced endometriosis even before undergoing major surgery, patients with chronic pelvic pain facing definitive surgery, and patients with diminished ovarian reserve? Also, this group could include those patients with autoimmune disorders and Fragile X syndrome as they are at high risk of early menopause. Oocyte freezing should be ideal for these candidates.

Response from Dr. Togas Tulandi:

Ideally, all women with the conditions mentioned above should be offered fertility preservation. The methods could be oocyte or ovarian tissue cryopreservation. It is hoped that in the future one could grow the primordial follicles in-vitro to a mature stage, providing unlimited number of oocytes from the ovarian tissue.

3. Is it ethically appropriate to allow a pregnancy after endocrine-responsive cancers are treated, such as endometrial, ovarian, and breast? Are the long-term risks of pregnancy in these circumstances really known? What is the role for a gestational carrier in such cases? You did not mention this option in your paper.

Response from Dr. Togas Tulandi:

Fertility preservation in women with genital cancer is a relatively new field. There are still many unanswered questions; for example, should we offer fertility preservation to women who already have one child, should we allow genital cancer survivors to conceive? In any event, fertility preserving surgery for stage I ovarian cancer is promising. In a report of 52 patients, 24 attempted to conceive. Subsequently, 17 patients conceived and delivered healthy babies. The estimated 5-year survival rate is 98%. The number of cases reported in the literature is still small. The answer whether physicians should allow a pregnancy in survivors of estrogen neoplasia is unknown. Until then one should consider it investigational. The use of a gestational carrier is a viable option. However, one should also take into account many factors including the patients' survival rate, and the quality of life.

4. The oocyte freezing option has been limited to those females without a partner and those not wanting donor sperm. Would it not be more inclusive to also consider oocyte freezing as an option along with embryo freezing even in those females with partners, particularly as the success rate with oocyte vitrification continues to increase? Oocyte freezing avoids the concerns related to stored embryos especially if the stresses of cancer treatment cause the couple to no longer desire a pregnancy together and/or the cancer treatment does not go as well as hoped.

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Response from Dr. Togas Tulandi:

The most common and successful technique is embryo cryopreservation. However, since the objective is to preserve fertility, all types of fertility preservation methods should be considered and offered to the patients.

5. There have been some reports of IVM being associated with spindle abnormalities. Since IVM is one of the primary treatment options, please comment on this issue.

Response from Dr. Togas Tulandi:

In a mouse model, compared to slow frozen oocytes, vitrified oocytes were more likely to maintain normal meiotic spindles and chromosome alignment (70.1% vs. 86.9%). However, the incidence of aneuploidy was similar (8.7% vs. 9.30%). It appears that the method of freezing plays a more important role in relation to spindle abnormalities than IVM technique. In fact, cryopreservation of oocytes at the germinal vesicle stage avoids spindle depolymerization decreasing the risk of polyploidy and aneuploidies.

6. Letrozole is mentioned several times as a treatment option. Have the recent negative comments about its use for ovulation induction altered your thoughts about the choice of this agent?

Response from Dr. Togas Tulandi:

The question about fetal safety of letrozole was raised in an abstract presentation in 2005; however, this unpublished study contains many flaws. Two subsequent reports with a large number of patients disproved this notion (Tulandi et al 2006 and Forman et al 2007). The concern that letrozole use for ovulation induction could be teratogenic is unfounded (Tulandi et al 2006; Forman et al 2007).