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Female fertility preservation: a clinical perspective

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Abstract

For patients with cancer, preserving the ability to start a family at a time of their choosing is especially important and may influence decisions pertaining to cancer treatment. For other women who have delayed childbearing for personal or professional reasons, fertility preservation offers the possibility of having a biological child regardless of age. Though these women may be interested in or benefit from fertility preservation, fertility preservation services remain underutilized. While embryo and oocyte cryopreservation remain the standard strategies for female fertility preservation recommended by the American Society of Reproductive Medicine, the American Society of Clinical Oncology and the European Society of Medical Oncology, other strategies (*e.g.* pharmacological protection of the ovaries and ovarian tissue cryopreservation) are the subject of increasing research. This review will present new data that have become available over the past few years pertaining to all available methods of fertility preservation.

Keywords

Fertility preservation; Drug therapy; Ovarian induction; Neoplasms

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This review will present new data that have become available over the past few years pertaining to all available methods of fertility preservation.

Social fertility preservation

With broader awareness of the age-related decline in female fertility, women who have delayed childbearing for personal or professional reasons are increasingly interested in fertility preservation techniques.[1-6] CDC data indicates that the rate of first birth in women aged 35-39 has increased 6-fold from 1973 to 2012.[7] Additionally, the average age of first birth has increased by 3.6 years between 1973 and 2006 and continues to rise.[7, 8] While there is data suggesting that the lack of a partner plays a large role in influencing social fertility preservation for women,[9] the recent advent of prominent tech companies offering to cover oocyte cryopreservation costs of their female employees may skew this trend for future social fertility preservation patients.[10] While social fertility preservation has been

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thought to promote reproductive autonomy for women, implicit corporate incentives to delay childbearing have brought public scrutiny to fertility preservation outside of medical necessity.[11, 12]

Though oocyte cryopreservation may allow women an opportunity to have biological children later in life, the American Society of Reproductive Medicine cautions: "Data on the safety, efficacy, cost-effectiveness, and emotional risks of elective oocyte cryopreservation are insufficient to recommend elective oocyte cryopreservation."[13] However, great strides continue to be made in improving the efficacy of oocyte cryopreservation following its change in classification from an experimental to viable method of fertility preservation in 2013.

Medical indications

The American Society of Clinical Oncology published its first guidelines on fertility preservation in 2006, in which it stated "As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years."[14] In line with this recommendation, the most common cancer treatments and their effects on fertility are reviewed here.

Cancer surgery

While not an option for many women of reproductive age, fertility sparing surgeries should be considered whenever possible in young patients with gynecologic cancers. Advances in the treatment of these cancers have resulted in the development of techniques that preserve reproductive organs without reducing survival rates.[15] Specifically, for some well-differentiated low-grade early-stage tumors, it is possible to conserve one or both ovaries or the uterus.

Radiation therapy

Radiation therapy used in the treatment of cancer has been shown to cause premature ovarian failure and infertility in female patients of reproductive age.[16] Though the effects of radiation on ovarian function are dose-dependent, the ovaries may be damaged from even scattered radiation.[15] Older women, with diminished ovarian reserve at baseline, have a higher risk of premature ovarian insufficiency after radiation therapy.[17] It has been suggested that a radiation dose of 2 gray to the ovaries is sufficient to result in a 50% reduction in ovarian reserve.[18]

Chemotherapy

As with radiation therapy, the effect of chemotherapy on ovarian reserve varies with the chemotherapeutic drug, the length of treatment, and the age of the patient.[19] For example, alkylating agents have been found to be especially gonadotoxic and many patients experience ovarian insufficiency after treatment with chemotherapeutics in this class.[20] Given the wide spectrum of effects on ovarian reserve, it is imperative that physicians understand the risk of specific agents when counseling patients. In terms of age, pre-pubertal

patients are less susceptible to damage by chemotherapeutic agents while older women are more susceptible to premature ovarian insufficiency.[21]

Established methods of female fertility preservation

Ovarian stimulation for embryo or mature oocyte cryopreservation remains the most likely strategy to result in subsequent pregnancy. For patients pursuing fertility preservation for medical indications, these procedures should be offered primarily assuming the patient's condition does not preclude safely carrying out controlled ovarian stimulation or oocyte retrieval.[4] Previously, concerns regarding having adequate time to undergo ovarian stimulation and oocyte retrieval precluded many cancer patients from pursuing fertility preservation. However, new data indicate that while it is ideal to stimulate ovaries within three days of the start of the menstrual cycle, random stimulation can be successful as well.[22]

Embryo cryopreservation

Embryo cryopreservation is an established technology that provides good success rates depending on the number and quality of stored embryos. Since sperm is required for oocyte fertilization, this method is limited to patients who have a committed male partner or who are prepared to use donor sperm.[4] This method of fertility preservation is further limited to females who are postpubertal.

Data on the live birth rates from frozen embryos in cancer patients are limited. In a recent retrospective analysis, Cardozo *et al.* compared pregnancy rates in cancer patients who had a frozen embryo transfer with age and time-matched controls with tubal factor infertility. No difference was observed in cumulative pregnancy rate per transfer for cancer patients compared to controls, 37% *vs.* 43% respectively (P=0.49). Similarly, there was no difference in cumulative live birth rate per transfer, 30% *vs.* 32% respectively (P=0.85). Cancer patients had a higher likelihood of live birth resulting in twins (44% *vs.* 14%; P=0.035), which likely reflects the lack of underlying infertility in these patients.[23]

As alluded to above, there are several limitations of embryo cryopreservation. Since prepubertal patients cannot undergo the necessary ovarian stimulation, they cannot utilize this technique. The safety of ovarian stimulation should be carefully considered in women with estrogen-sensitive cancers, as the inevitable high estradiol levels may result in tumor progression.[19] From a logistical perspective, the use of partner or donor sperm may have implications on a patient's future reproductive autonomy; making this technique less appealing for those pursuing fertility preservation for lifestyle reasons. Similarly, complicated ethical and religious issues could arise surrounding the disposition of frozen embryos should the patient die or separate from her partner.[24] Lastly, since live birth rates from frozen embryos in cancer patients are limited, counseling is usually based on national and clinic-specific success rates using cryopreserved embryos, which may not be representative.

Mature oocyte cryopreservation

No longer considered experimental, mature oocyte cryopreservation involves stimulating the ovaries with gonadotropins and surgically retrieving mature oocytes.[13] Though ovarian stimulation is still required, unlike embryo cryopreservation, this technique does not require sperm and is therefore better suited to patients without a committed male partner and who do not wish to use donor sperm.[4] Recently it has even been suggested that oocyte preservation is a better option for all women to maintain reproductive autonomy.[19]

As with the embryo cryopreservation literature, data on pregnancy and live birth rates following oocyte cryopreservation in cancer patients are limited. Consequently, patient counseling should be based on success rates extrapolated from other populations, such as young oocyte donors.[13] In recent years, as cryopreservation and thawing techniques have improved, mature oocyte cryopreservation in young women without cancer has been associated with steadily improving pregnancy rates.[25, 26]

Multiple randomized controlled trials comparing fresh and vitrified/warmed oocytes have suggested that implantation and clinical pregnancy rates are similar. For example, in both 2008 and 2010, Cobo *et al.* reported an implantation rate of 40% and clinical pregnancy rate of 55% with vitrified oocytes, which was similar to that with fresh oocytes.[25, 27] In a similar study, Rienzi *et al.* found an implantation rate of 20% *versus* 21% and a pregnancy rate of 38% *versus* 45% vitrified *versus* fresh oocytes.[28]

If possible, oocyte retrieval should occur prior to starting cancer treatment. Though there are no human studies investigating oocyte and embryo quality following chemotherapy, chemotherapeutic agents are known to induce somatic and germ cell damage.[29] Despite the theoretical effects of cancer treatment, patients with a history of cancer do not have increase rates of congenital malformations, genetic abnormalities, or malignant neoplasms in their offspring.[30-32] Further, live birth rates from pregnancies in cancer survivors are similar to those of healthy siblings.[4] Therefore, if the patient's medical condition precludes oocyte retrieval prior to starting cancer treatment, future pregnancy is not contraindicated though the time period to delay childbearing remains unclear.

Ovarian shielding

As mentioned earlier, the effects of radiation on ovarian function are dose-dependent and the ovaries may be damaged from even scattered radiation.[15] Shielding to reduce radiation to the ovaries, when possible, is the standard medical procedure currently offered to patients.[16] Though shielding does not protect the ovaries completely, significant dose reductions have also been noted.[33]

Ovarian transposition

Another method for protecting the ovaries from radiation damage is ovarian transposition. Ovarian transposition involves moving the ovaries out of the radiation field, either at the time of initial oncologic surgery or as a separate procedure.[34, 35] In patients undergoing pelvic radiation, the ovaries are mobilized by cutting the utero-ovarian ligaments and anchored as high as possible above the pelvic brim — either on the anterior abdominal wall

or in the paracolic gutter.[19] This procedure can be performed either laparoscopically or by laparotomy. While it is estimated that this will help about half of the patients maintain some menstrual function and fertility, it does not fully protect the ovaries.[14]

The risks of ovarian transposition include: increased ovarian cyst formation, postoperative adhesions, chronic pelvic pain, migration of the ovaries back to their native position, and premature ovarian insufficiency. There is also a 1% risk of metastatic disease existing in the ovaries.[36] Since this procedure does not prevent ovarian damage by cytotoxic drugs, it should be performed in patients who require chemotherapy in addition to radiation therapy. Lastly, ovarian transposition may preclude future transvaginal oocyte retrieval if in vitro fertilization is required. Transabdominal retrieval may be accomplished in some patients.[37]

Experimental methods of female fertility preservation

According to the American Society of Reproductive Medicine,[4] the American Society of Clinical Oncology,[5] and the European Society of Medical Oncology,[6] the following approaches should still be considered investigational:

Ovarian tissue cryopreservation

In comparison to a single cycle of mature oocyte cryopreservation, the cryopreservation of ovarian cortical tissue presents an efficient and high-yield method of potentially preserving thousands of ovarian follicles through a single procedure.[4] This technique also offers the unique opportunity to preserve fertility for prepubertal girls, who are unable to pursue ovarian stimulation and IVF due to ethical concerns and physiological limitations, and patients that cannot afford to delay cancer treatments to undergo ovarian stimulation and oocyte retrieval.[38, 39] Through ovarian tissue cryopreservation, a sample of ovarian cortical tissue is obtained by laparoscopy or laparotomy, dissected into small fragments, and subsequently cryopreserved using a slow-cool technique or vitrification.[39] Live births have been recorded following transplantation of cryopreserved ovarian tissue in adult patients as well as a recent live birth from a patient that experienced ovarian failure following treatment for sickle-cell anemia at 14 years of age.[40]

While this procedure includes patients who would not qualify for fertility preservation, there are a variety of concerns that may ultimately detract its implementation. Although ovarian tissue cryopreservation would theoretically allow pre-pubertal females the unique opportunity of pursuing fertility preservation, ovarian function post-transplantation functions for only a limited time period.[41] Unless this procedure improves to the point of delaying the onset of ovarian failure, the risk of permanently disrupting endocrine function before reaching adulthood may present a much greater threat to the quality of a young patient’s life than potentially preserving future fertility. There is also a concern about reintroducing cancerous cells, especially from systemic cancers such as leukemia.[42] Considering the limited time of ovarian function following transplantation of ovarian tissue, this procedure is best suited for carefully-selected patients or those who cannot delay beginning cancer treatment.[43]

In vitro *maturation of immature oocytes*

Researchers have been working recently to improve methods of *in vitro* maturation (IVM) of immature oocytes. In this technique immature oocytes are retrieved either intraoperatively from ovarian tissue or doing an ultrasound guided oocyte retrieval. Once the eggs are retrieved, they can then be matured *in vitro*, and cryopreserved.[44] This course of treatment offers a novel method of retrieving oocytes while avoiding ovarian hyperstimulation, as well as avoiding ovarian hyperstimulation syndrome (OHSS) in healthy patients.[44, 45] Young cancer patients that are unsuitable candidates for ovarian stimulation or unprepared to decide on the creation of an embryo may be candidates for this experimental treatment.[46] The first healthy birth using IVM was reported in a 2014 case study where a patient presented with stage IIIC ovarian cancer and underwent surgery at which time immature oocytes were retrieved *ex vivo* after an oophorectomy.[47] Another study reported a healthy live birth involving extracorporeal oocyte aspiration followed by IVM and 5 years of embryo cryopreservation from a patient that had previously presented with a stage IA borderline mucinous cystadenoma.[48] Another study reported that estrogen-suppressed *in vitro* maturation (ES-IVM), a procedure that decreases FSH stimulation and cycle monitoring, displayed an efficiency similar to natural cycle and low-stimulation IVM while reducing costs and risks.[49] Although this study was not done in cancer patients, a similar technique could be used in the cancer population.

Ovarian suppression with GnRH agonists

The preservation of ovarian reserve by preventing iatrogenic loss using ovarian suppression is another novel approach to fertility preservation. Recent studies produced encouraging results for GnRH agonist treatment in avoiding premature menopause for breast cancer patients undergoing chemotherapy.[50-52] In a study by Del Mastro *et al.*, a year after the last cycle of chemotherapy it was shown that premature menopause was significantly lower in the women within the agonist group compared to the non-agonist group.[51, 52] Although more data is required, one study indicated that the administration of GnRH agonists with chemotherapy appeared to protect against ovarian failure.[50] Initial studies documenting the effect of GnRH agonists on preserving ovarian function are promising, however the precise mechanisms for these drugs are unknown and could benefit from additional research using traditional markers.[51, 53] Although there is still debate over its use as a standalone treatment, the use of GnRH agonists as a co-treatment to cryopreservation of oocytes, embryos, and ovarian tissue may improve fertility preservation.[54]

Male fertility preservation

Though a thorough discussion of male fertility preservation is beyond the scope of this review, a brief overview of both established and experimental techniques is offered below.

Established

Cryopreservation of a freshly ejaculated semen specimen is the preferred method of male fertility preservation. For patients who are unable to produce a specimen, or produce a specimen with azoospermia, a surgical approach for sperm extraction may be possible.[55] As is the case with women, gonadal shielding is recommended for men undergoing radiation

therapy. Though shielding does not protect the testicles completely, a significant reduction in radiation dose may be achieved.[56, 57]

Experimental

Research involving the harvesting of stem cells in the testes may offer a viable method of fertility preservation. Testicular tissue containing spermatogonial stem cells would be cryopreserved for transplantation back into the testes after the completion of gonadotoxic cancer treatments to restore proper function.[58] In comparison to cell suspension, human testicular tissue cryopreservation has a much higher post-thaw viability and the presence of supporting Sertoli cells may improve stem cell survivability.[59, 60] While this technique has been successfully performed in primates and rodents, a paucity of data within a clinical context underscores its status as experimental. The creation of spermatozoa from stem cells offers another theoretical option for male fertility preservation, however this treatment is years away from being introduced in human patients.[58] This technology would be especially useful for prepubertal boys that have not begun spermatogenesis and are thus unqualified for sperm banking.

Counseling

Improvement in cancer treatment has resulted in an increase in reproductively-aged, long-term survivors. Considering the long-term adverse effects of cancer treatment regimens on reproductive health, there is still an inadequate amount of fertility information available to newly-diagnosed cancer patients.[61] A prospective study indicated that patients who received sufficient reproductive health counseling prior to cancer therapy experienced reduced stress and anxiety levels throughout their cancer treatment.[62] While not as much data has been compiled outlining emotional issues, one article compiled a list of several important topics to be addressed in psychological counseling: “(1) preexisting psychological distress in patients undergoing treatment, (2) choice of fertility preservation strategy in the face of an uncertain relationship future, (3) decision making regarding use of third-party reproduction (e.g., sperm/egg donation, gestational surrogacy), (4) treatment expectations regarding pregnancy and miscarriage, (5) ethical issues related to treatment including the creation, cryopreservation, and disposition of embryos/oocytes, and (6) decision regret from patients who declined fertility preservation.”[63]

Limitations of existing literature

Unfortunately, fertility preservation methods are still applied relatively infrequently in the cancer population. As a result, knowledge about success and effects of different potential interventions is limited. Few large and/or randomized studies exist in the fertility preservation literature. The majority of the aforementioned data come from cohort studies, case series, small nonrandomized clinical trials, and case reports.[14]

Conclusions

Despite recent advances in the available techniques, fertility-preservation services remain underutilized.[4] While a cancer diagnosis 40 years ago was seen as a death sentence,

increasing rates in long-term survivorship have brought attention to addressing quality-of-life issues like the ability to create a family after cancer treatment and maintaining proper endocrine function. Additionally, fertility preservation may play a role in maintaining reproductive autonomy for women that choose to delay childbearing for professional or personal reasons.

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