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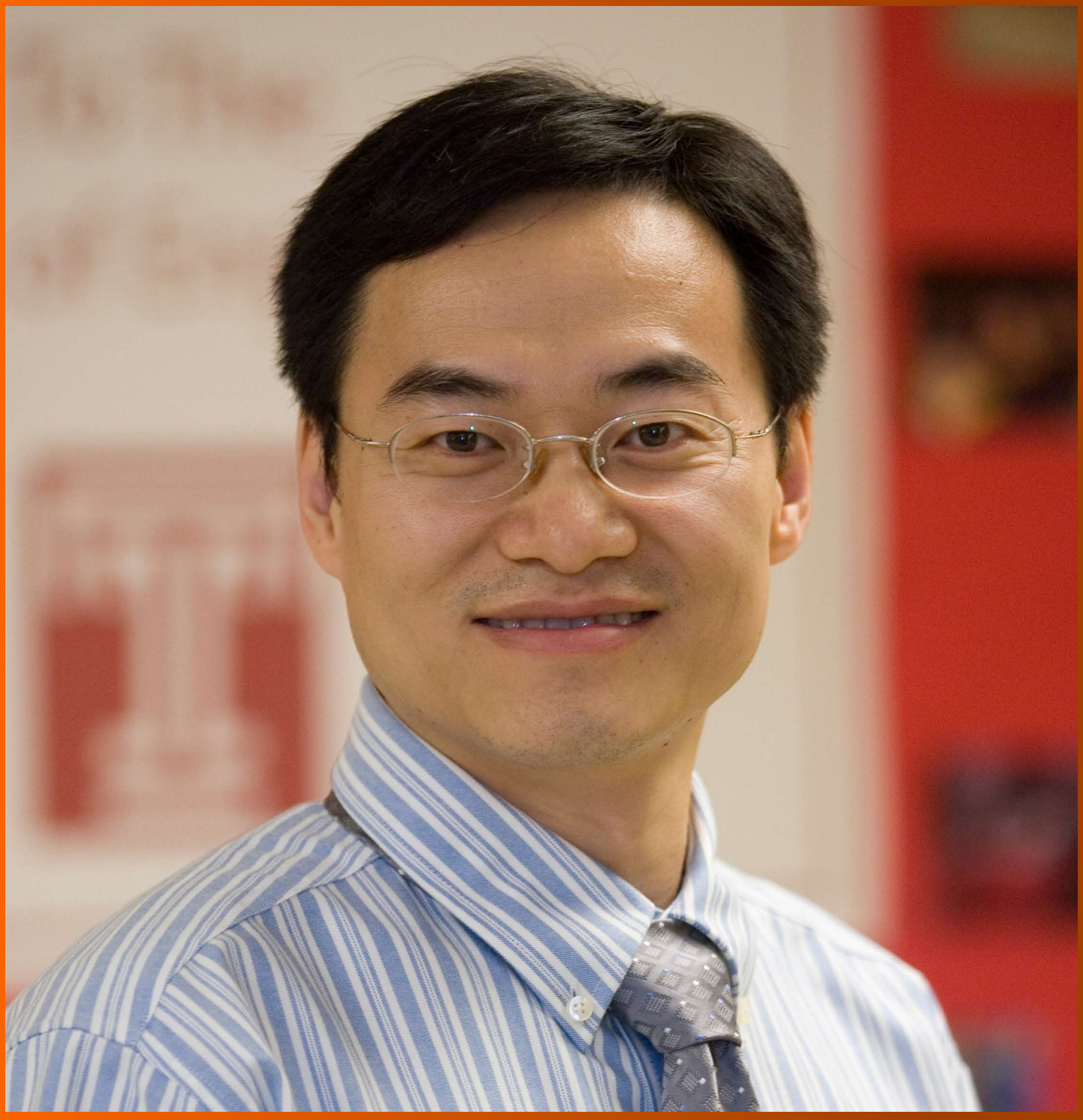

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MINIREVIEWS

Current state and controversies in fertility preservation in women with breast cancer

Enes Taylan, Kutluk H Oktay

Enes Taylan, Kutluk H Oktay, Innovation Institute for Fertility Preservation and In Vitro Fertilization, New York, NY 10019, United States

Enes Taylan, Kutluk H Oktay, Laboratory of Molecular Reproduction and Fertility Preservation, Department of Obstetrics and Gynecology, New York Medical College, Valhalla, NY 10595, United States

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Correspondence to: Kutluk H Oktay, MD, PhD, Laboratory of Molecular Reproduction and Fertility Preservation, Department of Obstetrics and Gynecology, New York Medical College, 40 Sunshine Cottage Rd, Valhalla, NY 10595, United States. koktay@fertilitypreservation.org
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Abstract

On average, over 25000 women are diagnosed with breast cancer under the age of 45 annually in the United States. Because an increasing number of young women delay childbearing to later life for various reasons, a growing population of women experience breast cancer before completing childbearing. In this context, preservation of fertility potential of breast cancer survivors has become an essential concept in modern cancer care. In this review, we will outline the currently available fertility preservation options for women with breast cancer of reproductive age, discuss the controversy behind hormonal suppression for gonadal protection against chemotherapy and highlight the importance of timely referral by cancer care providers.

Key words: Fertility preservation; Female breast cancer; Cryopreservation; Oocyte; Embryo; Ovarian suppression; Gonadotropin-releasing hormone agonist; Letrozole; Ovarian tissue cryopreservation

Core tip: Field of fertility preservation has experienced remarkable advances within the last 20 years. As a result, young cancer survivors have numerous options to maintain an important aspect of their quality of life, fertility. In this article we review the current state and controversies in fertility preservation. The article should be an important resource for professionals who take care of young women with breast cancer and other malignancies.

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INTRODUCTION

Breast cancer is the most common malignancy in women

and on average more than 25000 women are diagnosed with breast cancer before reaching the age of 45 years, each year in the United States[1]. Early diagnosis by virtue of significant advances in detection, and newly developed treatment strategies have remarkably improved the course of breast malignancies. According to the National Cancer Institute, 5-year-survival rate for the women under age 45 was estimated to be as high as 88%-98.5% in 2011[2].

While survivorship rates have dramatically increased in women with breast cancer, an important issue related to reproductive function has emerged. Most women with breast cancer are likely to undergo systemic adjuvant or neo-adjuvant chemotherapy with gonadotoxic side effects. As a consequence, preserving fertility potential has become an essential concept in the management of young cancer survivors. Fertility preservation has emerged from this concept as a new and dynamic discipline where oncology and reproductive medicine intersect.

In this review, we aimed to highlight the importance of fertility preservation as a part of routine care for breast cancer patients of childbearing age and outline the key fertility preservation options along with still experimental but promising therapeutic procedures.

COUNSELING FOR FERTILITY PRESERVATION

Because of the trend for having children in later reproductive ages, the number of women who experience breast cancer before completing childbearing is growing. Coupled with the increased survival rates and the growing healthy survivor population, fertility preservation has become an important component of cancer care and the maintenance of quality of life for survivors[3].

American Society of Clinical Oncology (ASCO) and American Society of Reproductive Medicine (ASRM) guidelines for fertility preservation in cancer patients strongly recommend that oncologist should inform their patients about the potential negative effects of chemotherapy on fertility before the initiation of the planned treatment and promptly refer patients to reproductive specialist to discuss the risk of ovarian damage and currently available fertility preservation options[4,5]. However, less than half of the oncologists in the United States always or often refer their cancer patients with fertility-related questions to fertility preservation specialist[6].

It should be stressed that providing timely and accurate information for women of reproductive age with breast cancer is critical for the preservation of future fertility chances before complete loss of the limited and irreplaceable ovarian reserve due to chemotherapy. We have previously shown that early referral of breast cancer patients, especially before breast surgery results in larger number of oocytes and embryos being cryopreserved and less time to the initiation of chemotherapy[7].

IMPACT OF CANCER TREATMENT ON OVARIAN RESERVE

Modern chemotherapeutic agents that are in use for breast cancer treatment can have a spectrum of ovarian toxicity, depending on the class of the agent, age of the patient, and the cumulative dose[8]. We have shown that the most gonadotoxic agents are those that mainly target oocyte genome causing DNA double strand breaks (DBSs)[9]. Under normal circumstances, DNA repair mechanisms are capable of maintaining genomic integrity, however, at the level of severe DNA damage due to genotoxic agents, those repair mechanisms remain insufficient. The severe DNA damage consequently leads to apoptotic death[9]. Ovarian reserve is made up of about 1 million primordial follicle oocytes at birth, and this number is reduced to approximately 500000 at the onset of puberty. These numbers are reduced to about 25000 at age 37 and nearly exhausted at menopause. Because primordial follicles cannot be regenerated, any chemotherapeutic agent that induces DNA breaks in primordial follicle oocyte will result in apoptotic death and cause irreversible reduction in ovarian reserve[9].

Among all gonadotoxic agents, those belong to the alkylating category such as cyclophosphamide, are the most gonadotoxic agents[10]. Because alkylating agents are non cell-cycle specific chemical compounds and hence can target and damage resting primordial follicles that constitute ovarian reserve[9,10].

The risk of chemotherapy-induced ovarian damage has been investigated in numerous clinical studies. Unfortunately, menstruation was used as the surrogate for ovarian function and fertility in the majority of the past studies[11]. However, return of menses is a poor surrogate for reproductive potential, and ovarian reserve might be severely diminished despite the resumption of regular menses[12,13]. In this context, it is reported that after treatment with CMF protocol (cyclophosphamide/methotrexate/5-fluorouracil) 20%-70% of women younger than age 40 experienced amenorrhea[14]. Comparing CMF protocol to the AC protocol (doxorubicin/cyclophosphamide), significantly lower rates of amenorrhea (69% *vs* 34%, respectively) have been reported with the AC protocol[15]. This finding is most likely related to a lower cumulative dose of cyclophosphamide reached with AC regimen. When a taxane administered in combination with AC (AC-T), it did not significantly increase the risk of amenorrhea compared with standard AC regimen[16]. Tables 1 and 2 summarize chemotherapeutic agents that are commonly used in breast cancer treatment and their potential impact on ovarian function[15-19].

Patient age at the time of chemotherapy inversely correlates with the likelihood of post-chemotherapy amenorrhea. In women with breast cancer, while the incidence of chemotherapy-induced amenorrhea was

Table 1 The risk of infertility and mechanism of damage associated with chemotherapeutic agents that are commonly used in breast cancer treatment

Chemotherapeutic agent	Class	Mechanism of action	Cell cycle effect	Risk of infertility
Cyclophosphamide	Alkylating agent	DNA cross-link formation and double strand breaks that result in inhibition of DNA function and synthesis leading to cellular apoptosis	Cell cycle non-specific	High risk
Doxorubicin Epirubicin	Anthracyclines	Inhibition of DNA synthesis and function due to inactivation of DNA topoisomerase II, free oxygen radical formation and induction of DNA double-strand breaks	Cell cycle non-specific	Medium risk
Carboplatin	Platinum analog	Inhibition of DNA synthesis and function *via* intra- and interstrand DNA cross-link formation by covalent binding to genome	Cell cycle non-specific	Medium risk
Paclitaxel Docetaxel	Taxanes	Inhibition of mitotic division by binding to microtubules with enhancement of tubulin polymerization	M phase	Low risk
Methotrexate	Antimetabolites	Inhibition de novo purine nucleotide synthesis by inactivation of dihydrofolate reductase	S phase	Low risk
5-fluorouracil		Inhibition of DNA synthesis and function via inactivation of Thymidylate synthase and alteration in RNA processing	S phase	Low risk
Trastuzumab	Monoclonal antibodies	Blockage of Human epidermal growth factor receptor 2 subdomain IV, antibody dependent cellular toxicity	NA	Low or no risk
Pertuzumab		Blockage of Human epidermal growth factor receptor 2 subdomain II, antibody dependent cellular toxicity		

Table 2 Common adjuvant chemotherapy regimens for breast cancer and their impact of fertility

Chemotherapy regimen	Risk of amenorrhea or infertility	
	Age ⩽ 35 yr	Age >35 yr
CMF	4%-40%	80%-100%
CEF	47%	80%-100%
CAF	No data	30%
AC	13.90%	68.20%
AC-T	9%-13%	65%-67%
AC-TH	0-14%	56%-67%

A: Doxorubicin; C: Cyclophosphamide; E: Epirubicin; F: 5-Fluorouracil; H: Trastuzumab; M: Methotrexate; T: Paclitaxel.

reported as 15%-40% under the age of 30, this incidence dramatically increases to 49%-100% for women older than 40 years of age[20]. The reason for this age-related difference is the fact that younger women have a larger ovarian reserve. Our previous studies indicated that on average, gonadotoxic chemotherapy regimens result in the loss of approximately 10 years worth of ovarian reserve[21]. Though both younger and older women would lose follicles, gonadotoxic chemotherapy is more likely to push older women over the threshold for menopause as they have lower reserve to begin with. However, regardless of age, females of all ages, including children, are expected to experience early menopause after exposure to gonadotoxic chemotherapy agents. Therefore fertility preservation and completion of family building as early as possible, is critical regardless of the age at chemotherapy exposure in most instances[22].

GONADOTROPIN-RELEASING HORMONE ANALOGS AND OVARIAN PROTECTION

There has been an ongoing controversy regarding the role of ovarian suppression in cancer patients using gonadotropin-releasing hormone (GnRH) analogs in order to protect ovaries from chemotherapy-induced damage[23].

The biggest concern regarding the effectiveness of ovarian suppression is that primordial follicles that constitute the ovarian reserve are quiescent and do not express gonadotropin or GnRH receptors[24,25]. Thus, any change in gonadotropin or GnRH serum levels has no plausible direct or indirect effect on primordial follicles (Figure 1). Furthermore, we have shown that gonadotoxic agents induce primordial follicle death *via* inducing DNA double strand breaks in oocytes in a non-cell cycle dependent fashion, hence there is no mechanism for ovarian suppression by GnRHa to prevent chemotherapy-induced DNA damage[9,26]. It should be recognized that GnRHa induces a hormonal state similar to prepubertal stage, and if ovarian suppression were to be protective, children of prepubertal age would be resistant to gonadotoxic effects of chemotherapy, which is shown to be not to be the case[27].

While some studies in women with breast cancer, which used menstruation as a marker, suggested some benefit in restoration of menstruation post-chemotherapy, these studies were marred by numerous weaknesses[28-30]. These include the utility of self-reported menstrual status, a highly unreliable surrogate for fertility, lack of placebo control (instead of GnRHa) or blinding, and lack of correction for the difference in desire to conceive between study and control groups[31].

Use of amenorrhea as the sign of ovarian failure is also key weakness in trials of GnRHa for ovarian protection. Especially for breast cancer patients, chemotherapy often induces occult ovarian insufficiency that most frequently presents as irregular or even normal appearing periods rather than amenorrhea. When the serum anti-Müllerian Hormone (AMH), which is the most reliable quantitative

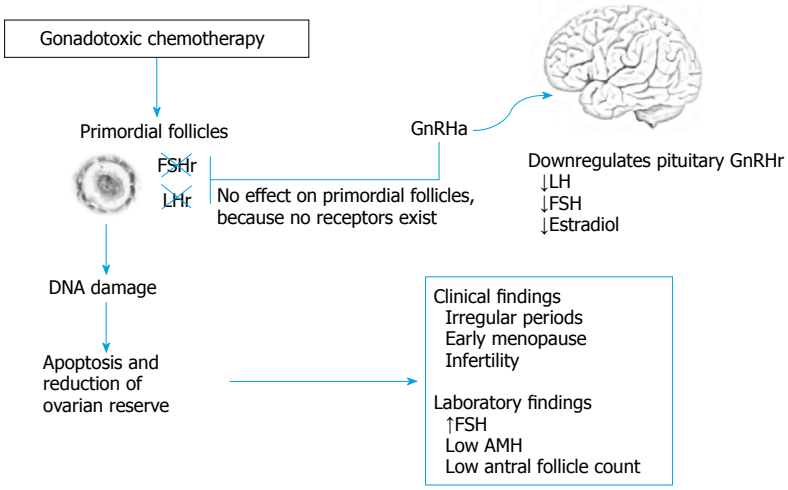

Figure 1 Impact of gonadotoxic chemotherapy and gonadotropin-releasing hormone analog on ovarian reserve and function. Gonadotoxic chemotherapy reduces ovarian reserve, which is made up of resting and hormone-insensitive primordial follicles, by induction of DNA damage and apoptotic death. GnRHa reduces pituitary GnRH production and, as a result, blocks the release of FSH and LH from the pituitary, which in turn results in the cessation of late-stage follicle development. Because primordial follicles do not have FSH, LH, or GnRH receptors, GnRHa cannot have a direct influence on ovarian reserve. AMH: Anti-Müllerian hormone; FSH: Follicle-stimulating hormone; FSHr: FSH receptor; LH: Luteinizing hormone; LHr: LH receptor; GnRH: Gonadotropin-releasing hormone; GnRHr: GnRH receptor. Oktay *et al*. *J Clin Oncol* 2016; **34**: 2563-2565, used with permission.

biomarker for ovarian reserve or appropriate criteria with serum FSH levels for defining ovarian failure was used, none of the studies showed fertility preservation benefit from GnRHa treatment[32-34].

Given the contradictory results and ovarian biological facts, the use of GnRHa for the prevention of ovaries from chemotherapy damage is still controversial and cannot be recommended as an effective method of fertility preservation.

OVARIAN RESERVE IN WOMEN WITH BRCA MUTATIONS

Most hereditary breast cancers are associated with germline mutations in *BRCA1* and *BRCA2* genes. BRCA genes are members of the ataxia-telangiectasia-mutated (ATM)-mediated DNA damage signaling pathway and are essential for DNA double-strand break (DSB) repair[35]. In addition to the increased risk for multiple malignancies, several clinical and experimental studies showed an association between BRCA mutations and diminished ovarian reserve[26,36-41]. While performing ovarian stimulation in women with breast cancer by using aromatase inhibitors for fertility preservation, we found significantly lower ovarian response rates in BRCA mutation carries particularly, among those with BRCA1 mutations[36]. In another important study, authors reported that unaffected women with BRCA mutation experience menopause 3-4 years earlier than healthy controls[38]. Recently, our laboratory showed that in BRCA1 mutant mice there is increased age-related accumulation of DNA double strand breaks in primordial follicle oocytes and the ovarian reserve is significantly lower. These BRCA1 mutant mice also showed reduced litter size and poor embryo development. These findings clearly indicate a biological connection between BRCA mutations, DNA repair and reproductive function. In the same study, we also showed that affected women with BRCA1 mutations had lower serum AMH levels compared to controls. Interestingly we did not find these differences in either BRCA2 mutant mice or affected women with BRCA mutations[26]. Confirming our findings in a prospective study, Philips *et al*[41] found 25% lower AMH concentrations on average in BRCA1 carriers compared to non-carriers. There was no significant association between the BRCA2 mutation status and the AMH levels.

Given the accumulating evidence that the ovarian reserve may be lower in women with BRCA mutations, it is possible that these women are more prone to chemotherapy-induced loss of ovarian reserve and ovarian insufficiency. However this is yet to be shown in prospective clinical trials. Nevertheless, while counseling women with BRCA mutations on fertility preservation, the possibility of higher risk of chemo-induced infertility should not be omitted.

FERTILITY PRESERVATION OPTIONS FOR BREAST CANCER PATIENTS

Embryo cryopreservation after *in vitro* fertilization (IVF) is currently considered as an established fertility preservation option, which offers the best chance of livebirth for women with a partner or single women who elect to use donor sperm. Numerous studies have demonstrated up to 60% clinical pregnancy rates and around 34% livebirth rates after transfer of frozen-thawed embryos in infertility patients with mean age of 35.1 ± 4.03, which is comparable to fresh embryo transfer[42,43]. When preimplantation genetic screening utilized, the livebirth rates can increase up to 77% after transfer of euploid frozen-thawed embryos[44]. In women with breast cancer with the mean age of 35.8 ± 4.1, we have shown a livebirth rate of 45%, which appeared to be superior to those undergoing frozen embryo transfer for infertility[45].

Cryopreservation of mature or immature oocytes is another fertility preservation option for women without a partner and those not wishing to use donor sperm due to legal, ethical or religious considerations. Mature oocytes can be effectively cryopreserved using a vitrification method and the success rates of post-thaw fertilization and pregnancy rates have approached those with

Table 3 Fertility Preservation options for reproductive age women with breast cancer

Fertility preservation option	Current status	Advantages	Disadvantages
Embryo Cryopreservation	Established	Highest cumulative pregnancy rates	Requires about two weeks delay in the initiation of cancer treatment Requires hormonal stimulation for oocyte retrieval Requires *in vitro* fertilization with male partner or donor sperm
Oocyte Cryopreservation	Established	No need for male partner or sperm donor	Requires about two weeks delay in the initiation of cancer treatment Requires hormonal stimulation for oocyte retrieval
Ovarian Tissue Cryopreservation and Transplantation	Currently experimental, may change as success rates are rising	No need for hormonal stimulation No need to significantly delay in the initiation of chemotherapy No need for male partner or sperm donor	Requires outpatient laparoscopic surgery for ovarian tissue harvesting and subsequent transplantation

fresh oocytes in young patients, though success rates with frozen embryos may still be better[46,47]. Oocyte cryopreservation success rates vary depending on age, number of oocytes frozen and the freezing protocol. In a recent individual patient data meta-analysis we calculated these success rates[48] (An interactive online success rate estimator can be found online at http://fertilitypreservation.org/index.php/probability-calc).

Based on an individual patient meta-analysis encompassing thaw cycles with frozen oocytes, we have calculated the age-based success rates for oocyte cryopreservation. An interactive online egg freezing success rate estimator can be found at this link: http://fertilitypreservation.org/index.php/probability-calc, and can be useful in patient counseling.

Immature oocytes can be obtained from patients without undergoing ovarian stimulation due to dearth of time and also at the time of ovarian tissue harvesting for fertility preservation. After retrieval, immature oocyte may be cryopreserved before or after undergoing *in vitro* maturation (IVM) process[49]. Lee *et al*[50] suggested performing IVM for immature oocytes before cryopreservation rather than post-thaw as they observed significantly higher maturation and survival rates with that approach. Although IVM is still an experimental fertility preservation method and limited to a number of fertility centers, this method has recently resulted in live births[51].

Embryo and oocyte cryopreservation methods are widely used and currently considered as established methods of fertility preservation. However, typically 10-14 d of controlled ovarian stimulation is needed to obtain mature oocytes (Table 3).

When there is insufficient time for ovarian stimulation, the only available strategy other than immature oocyte retrieval and IVM for women with breast cancer is ovarian tissue harvesting and cryopreservation for future transplantation. Since the first report of ovarian transplantation with cryopreserved tissue by our group, there have been more than 80 livebirths with over 30% of livebirth rate after ovarian transplantation[52,53]. Some have raised the concern of reintroducing malignant cells back into the body along with ovarian tissue. However, studies showed no evidence of malignant cells in cryopreserved ovarian tissues from non-metastatic breast cancer patients and those with bone and soft tissue tumors[54-56].

CONTROLLED OVARIAN STIMULATION PROTOCOLS

The major issue associated with the conventional ovarian stimulation protocols is elevated circulating estradiol levels due to the development of large number of follicle at once. Therefore, conventional stimulation protocols are considered unsafe in women with estrogen-sensitive breast cancer.

Although oocytes can be retrieved from ovaries without performing ovarian stimulation (natural cycle IVF), this strategy typically does not provide more than one oocyte per cycle and yield an embryo in only 60% of cycles[57]. On the other hand, use of tamoxifen alone for ovulation induction showed better results in mature oocyte and embryo yield compared to natural cycle IVF[58]. Tamoxifen may also be used in combination with low dose gonadotropins for IVF, resulting in increase multiple mature oocytes and embryos[59].

While reducing the circulating estrogen levels, aromatase inhibitors induce the secretion of endogenous FSH by releasing the hypothalamic-pituitary axis from estrogenic negative feedback[60]. We showed that letrozole in combination with gonadotropins can produce comparable outcomes to conventional IVF while providing significantly lower estradiol levels and decreased gonadotropin requirements[45]. We also showed that pregnancy outcomes after ovarian stimulation with letrozole protocol in premenopausal breast cancer patients before adjuvant chemotherapy were similar to a non-cancer population[60]. Moreover, after short and mid-term follow up letrozole-gonadotropin protocol was associated with disease free survival rates[61].

One of the concerns related with ovarian stimulation

before adjuvant or neo-adjuvant chemotherapy is the delay in the initiation of breast cancer treatment. However, studies have shown that initiation of chemotherapy can be delayed up to 12 wk after breast surgery without any adverse effect on survival and recurrence rates[62,63].

Another concern is that letrozole protocol is that it is a teratogenic agent if used during pregnancy. However, in the setting of fertility preservation, embryos are never exposed to letrozole as the fertilization takes place *in vitro* and the resultant embryos are cryopreserved for later use. Additionally, it has been reported that there was no difference in congenital malformation and chromosomal abnormality rates among children born after ovarian stimulation with clomiphene or letrozole for infertility[64].

PREGNANCY AFTER BREAST CANCER

Patients in the decision process for fertility preservation treatments frequently question the safety of pregnancy after completion of cancer treatment. Based on the current evidence, pregnancy after breast cancer is not associated with increased risk of adverse outcomes[65]. In general, patients are advised to delay pregnancy at least 2 years after diagnosis, as the risk of recurrence is highest in this time frame. In the case of ER-positive breast cancer, pregnancy is contraindicated during tamoxifen treatment because of teratogenicity. For breast cancer survivors who do not want to delay childbearing for the completion of tamoxifen treatment or for those with other medical contraindications, gestational surrogacy may be a suitable option to utilize their frozen eggs or embryos in the future[10,65].

CONCLUSION

Fertility preservation has become a crucial part of survivorship and an important aspect of comprehensive cancer care. Fortunately, there are several well-established treatment options including embryo and oocyte cryopreservation and safer ovarian stimulation protocols. Moreover, there are emerging experimental methods such as ovarian tissue cryopreservation and transplantation and IVM, which are showing promise. To maximize the utility of these available options and avoid significant delays in the initiation of chemotherapy, timely referral to fertility preservation counseling should be an integral part of the care of young women with breast cancer.

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