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Fertility Preservation in Female Cancer Patients: Our Center Experiences

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ABSTRACT

Reproductive options are one of the most important issues to cancer survivors, and it is related to quality of life. Although most of young patients are interested in parenthood in future but significantly pretreatment access of patients to fertility preservation (FP) services is low, because of low referral rate and disparity. Data were retrospectively analyzed from 77 cancer patients who were referred to vali-e-asr reproductive center between March 2013 and February 2015. Their ovarian reserve was estimated with AMH test, Antral follicular count and FSH (if they were referred in first days of menstrual cycle). Embryo or oocyte cryopreservation was used based on participants' marriage status. Of 77(mean age 30, range: 16-45) patients 29(37.2%) were declined fertility preservation and the cost was the most frequent prohibitive cause. 10(12.9%) were excluded of fertility preservation services. Of 38 patients who were recruited for fertility preservation, 28(60.5%) were married, the mean number of embryos cryopreserved were 3.9. and the mean number of oocytes cryopreserved for 10 single participant in this group was 5.7. Our results demonstrate that oncologists have essential role in improving the provision of fertility preservation services. There are different available FP options that they can be use individualize. By assessing patients' prohibitive factor and making an attempt to diminish them such as cost of FP services, we can improve their quality of life.

Key words: Fertility Preservation, Female Cancer Patients, Oncofertility

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INTRODUCTION

Treatment of cancer with either systemic chemotherapy or radiotherapy affecting the spinal or pelvic area can result gonadal damage and fertility impairment [1]. It seems that a perception of reproductive issues, rather than to the fertility status is related to the depression, anxiety and quality of life. Interventions on female fertility status improved their quality of life, decisional regret, and decisional conflict [2]. The majority of cancer patients want to know the impact of cancer therapy on fertility [3]. Early referring the patients to specialist can help patients make better about fertility preservation [4]. But referral rates are low and referral disparities are reported. Approximately 70-75% of young cancer patients are interested in childbearing in future, but significantly the access of patients to fertility preservation techniques prior to treatment are lower [5]. The pivotal role of oncologists in the provision of fertility preservation services is undeniable. They are not only gate keepers, knowledge brokers, and referral initiators of fertility preservation consultation, but also they are catalysts in supporting cancer patients making important fertility preservation decision in conjunction with a fertility specialist consult [6]. Oncologists should consider fertility preservation approaches as early as possible during treatment planning, to preserve the full range of options and it is important for oncologists to have fundamental

information of fertility preservation techniques that are currently available as well as feasibility of these interventions for each individual [7, 8]. Fertility preserving options for female cancer patients include: oocyte cryopreservation, ovarian tissue cryopreservation and auto transplantation(cortical or whole), embryo transplantation, shielding and transposition of the ovaries during radiation. Ovarian suppressor agents [8-11]. safety of controlled ovarian stimulation has been analyzed in some kinds of tumors, and it has shown that the survival rate was not different between patients who pursued ovarian stimulation treatment, or not [12, 13]. Our options for fertility preservation in vali-e-asr infertility center are embryo and oocyte cryopreservation. We are going to present our oncofertility experiences, as a tertiary referral university hospital.

MATERIALS AND METHODS

Data were retrospectively analyzed from all cancer patients referred to the infertility center of vali-e-asr hospital (as a tertiary referral university hospital) between March 2013 and February2015.this study was approved by ethic committee of Tehran university of medical sciences as a research project by number 21140. All participants were signed a written informed consent at the first visit. Patients were counseled and evaluated by reproductive gynecologist. Their ovarian reserve were estimated with antral follicle count, and AMH (anti-mullerian hormone) and FSH test before treatment .Patientsat reproductive age and in whom ovarian reserve was reasonable and fertility preservation was indicated, were consulted for ovarian stimulation strategies.

All referred patients were postpubertal. Some of them had received chemotherapy or radiotherapy before referring. a consultation with oncologist was proposed as ovarian stimulation not being contraindicated. The breast cancer patients with hormone receptor-positive tumor received letrozole during ovarian stimulation. Conventional controlled ovarian stimulation or random start controlled ovarian stimulation was chosen based on their menstrual cycle day.

Participants were divided into 2 groups based on their marriage status, oocytes were cryopreserved for single patients and embryos were cryopreserved for married ones. Patients information including age, type of cancer, date of first visit, marriage status, type of treatments had received till referring time, hormonal test results if available, fertility preservation desire, cause of refusing or excluding fertility preservation , type of ovarian stimulation protocol , and outcome were collected in a database.

RESULTS

Seventy seven patients were referred to our infertility center between March 2013 and February 2015. The mean age was 30 years (range, 16-45 years). Of the 77 patients, 13 (16.8%) had received chemotherapy, and 6 (7.7%) had done radiotherapy, before referring.

0f 77 patients, 29 (37.2%) were affected by ovarian tumor, 10 (12.8%) by uterine tumor, 5 (6.4%) by uterine cervical tumor , 9 (11.6%) by breast cancer , 12 (15.4%) by lymphoma , 10 (12.8%) by other kinds of tumor, including ; rhabdomyosarcoma (1) chondrosarcoma (1) neurofibromatosis plexiform (1) colon cancer(2) retroperitoneal shunoma (1) ,ependymomma (1), thalassemia major candidates for bone marrow transplantation (1) nasopharyngeal cancer (1), hemangiopericytoma (1).

Of 77 patients, 51 (66.2%) were married, 23(29.9%) were single and 2 (2.6%) were divorced. Of 51 married patients 28(55%) person were recruited for fertility preservation, and 12 (23.5%) person were refused for fertility preservation, and 11(21.5%) person were excluded from fertility preservation. Of 23 single patients 10 (43.4%) were recruited for fertility preservation, 13(56.5%) were not recruited for fertility preservation. Of 2 divorced patients one of them was not recruited for fertility preservation, and the other one was excluded from ovarian stimulation protocol. Twenty tree individuals of married patients had infertility history.

Ovarian stimulation group

Of 38 patients who were recruited for fertility preservation, four individuals had received chemotherapy before referring. Among these 4 patients one could have an embryo for cryopreservation. And one patient had done radiotherapy before referring, whose ovarian stimulation result was a 18mm follicle without mature oocyte after pick up Table 1A.

Table 1A: Treatment protocols

Controlled ovarian stimulation protocol	frequency	Percent %
GnRH agonist (long protocol)	2	5.3
GnRH antagonist (conventional protocol)	12	31.6
Random start GnRH antagonist	21	55.3
Letrozole plus HMG	3	7.9

Of 28 married patients, one preferred to have oocye for cryopreservation. The mean level of AMH (in 26 patient was available) was 2.3 ng/ml (range, 0.1-14.3). The mean number of retrieved oocytes was 5.6 (range, 0-23) 3 participants(7.9%) did not have response to ovarian stimulation. The mean number of cryopreserved oocytes was 5.7(range, 0-12) and the mean age of participants in this group was 27 (range, 18- 45). The mean number of cryopreserved embryo was 3.9 (range, 0-17) and the mean age of participants in this group was 29.1 (range, 18-45) The mean time of ovarian stimulation was 9.48 days (min 6 days and max 15 days) and the mean of used gonadotropins were 350 IU per cycle. No OHSS was occurred. Table 2A, Table 3A.

Table 2 A: the reasons why 29 patients were declined for fertility preservation

cost	7(24.1%)
Apprehension about delay cancer treatment	5(17.2%)
Abstain cancer treatment by patients' choice	3(10.3%)
Treatment urgency	3(10.3%)
Distance from home	1(3.4%)
Patients' choice	1(3.4%)
Childbearing desire completed	2(6.8%)
Expire before ovarian stimulation	1(3.4%)
Preferred ovarian tissue cryopreservation	2(6.8%)
Fear of ovarian stimulations' complications	1(3.4%)
Were not available for asking	3(10.3%)

Table 3 A: The reasons why 10 patients were not indicated for fertility cryopreservation techniques

Endometrial complex atypical hyperplasia was the reason of referring	2 (20%)
FSH count more than 50	2 (20%)
Don't need for additional gonadotoxic treatment	2 (20%)
Gonadotoxic treatment before referring	4 (40%)

DISCUSSION

Oncofertility is a new interdisciplinary field that incorporates gynecologic oncologist, reproductive medicine gynecologists, general oncologist, biologists, psychologists, endocrinologists, and primary care physician in a common objective to provide fertility preservation options for cancer patients [14]. The crucial key factor to build a successful fertility preservation program, is that women have quick access to fertility preservation care and that providers expedite its' services. And it is conditioned by a unique challenge in fertility decision making, and overcoming to limitation of current fertility program. Such as, low referral rate, low treatment rate, and lack of communication with patients and among disciplines [15]. Based on American Society of clinical Oncology guideline as part of education and informed consent before cancer therapy, all patients regarding potential threats to fertility as early as possible should be prepared to discuss fertility preservation options and/or referred to appropriate reproductive specialists [16]. cancer patients may not have infertility at the time of diagnosis, but they need to undergo fertility preservation services prior to initiation of cancer treatment. [17]In a online poll, that was sent to oncologists at cancer center in north Carolina, to survey their regarding knowledge and practice patterns concerning fertility preservation , found that although 82% have referred patients to reproductive specialists, more than half rarely refer. And, 30% rarely consider a woman desire for fertility when planning treatment. Most oncologists at academic centers discuss the risk of infertility with cancer patients; rarely refere them to reproductive specialists [18].

In this survey, our 3 years experience of oncofertility demonstrated that in spite of great improvements in fertility preservation services, the referral rate of female cancer patients in reproductive ages is low and in inappropriate time. Just as we mentioned, there were 13 individuals that referred after receiving chemotherapy and radiotherapy. And 2 persons were referred without correct indications. And no prepubertal patient was referred.

Today, there are different treatment options for fertility preservation in female cancer patients. We have chosen embryo cryopreservation in our reproductive center, unless they would be single that in these cases we use to oocyte cryopreserve for them. We prefer embryo cryopreservation because in other studies, oocyte cryopreservation achieved inferior results in the past, versus embryo freezing, due to the low rates of survival,

fertilization and development [19]. While the number of good-quality embryos in cancer patients seems to be lower than a normal population, because of similar cumulative live birth rate to that achieved with fresh embryos in non-cancer patient, the utilization rate of this method can be considered high [20]. However, oocyte cryopreservation instead of embryos is of considerable importance, and gives women reproductive autonomy. Because the use of male-partner sperm to create embryo introduce several ethical, moral, and legal concerns and this technique is not allowed in some countries such as Italy [21, 22]. Cryopreservation of ovarian tissue is a reasonable method for prepubescent girls and is suitable for cancer patients requiring immediate treatment who have not enough time for adequate harvest of mature oocyte before such treatment. However this method is experimental [23, 24]. We have used this technique for 2 of our patients.

Furthermore decision to recruit fertility preservation techniques is complex. In survey of 208 female cancer survivors, significantly higher prevalence of high decisional conflict was perceived in participants who were not referred for FP consultation, as well as participants who informed cost of FP services to be prohibitive. Other reasons for not pursuing FP were informed; lack of time, and distress related to more decision regret, and not having childbearing desire. And decisional conflict scale was lower for women who underwent FP treatment [25, 26]. We should make attempts to optimize care in order to attain a higher quality of FP decision [27]. This is consistent with our study, as mentioned the most prohibitive factor in our patients was the cost of fertility preservation services. With accentuation that Iran's Ministry of Health and Medical Education has to cancer patients and reproductive services, we hope that we could be able to support female cancer survivors. The other apprehension was time wasting and delaying cancer treatment. Fortunately, random-start controlled ovarian stimulation has been as effective as conventional type and would minimize delays and allow more cancer survivors to undergo FP. This protocol still delays cancer treatment for 2-3 weeks [28]. In our reproductive center, we use this protocol for cancer patients if indicated, time frame until the initiation of cancer treatment was at least 2 weeks [29]. Complications of ovarian stimulation in cancer patients are another concerned, which dissuaded one of our patients of FP.Indeed there are some concerning events at patients with neoplasm inherently have a hypercoagulable state like thromboembolism, that poses an increased morbidity and mortality. Also these patients may therefore be at even greater risk OHSS develops following COS. And if OHSS develops, cancer therapy may delay. Also growth of tumors in estrogen-sensitive cancers (like breast cancer and uterine cancer) may be induced by elevated serum estradiol levels as a result of ovarian stimulation. [30-32] the association between breast cancer and exogenous estrogen oblige us to use specific protocols to stimulate breast cancer patients include anti-estrogen agents such as letrozole [33]. Suchlike protocol in estrogen-receptor positive cancer patients in our reproductive center is taking on.

In a survey which compared 17-years IVF experiences outcomes of cancer patients who underwent oocyte retrieval and embryo/oocyte cryopreservation prior to gonadotoxic therapy to those of age and time-matched controls with tubal factor infertility, concluded that they were comparable [34]. However, known outcomes and complications of fertility preservation should be declare, and patient autonomy should be respected. It is more essential for adolescent patients. [35]. Patients who decline preservation techniques should receive ovarian protection agents like GnRH-agonist or combined oral contraceptives [22, 36].

CONCLUSION

Today fertility preservation against gonadotoxic treatments of cancers is an important issue for improving cancer survivors' quality of life. All women should be consulted about available options of fertility preservation and chance of parenthood in future. It is possible on the condition that a multidisciplinary approach network be organized and oncologists would be the initiation of this chain. A discussion on fertility options of reproductive-age and prepubertal cancer patients should be an inevitable part of pretreatment counseling process by oncologists. All cancer survivors with childbearing desire should be referred to reproductive specialistsand should access to fertility preservation services.

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Conflicts of Interest

The authors declare that they have no competing interests.

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