Letter to The Editor

Fertility Preservation in Iranian Cancer Patients: A Continuing Neglect

Gholamreza Toogeh, M.D.1, 2*, Mohammadreza Razzaghof, M.D.2, Fariba Zarrabi, M.Sc.2

1. Department of Internal Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2. Thrombosis Hemostasis Research Center, Tehran University of Medical Sciences, Tehran, Iran

It is not to be denied that one of the greatest breakthroughs of modern medicine is the day-to-day improvement in the diagnosis and treatment of cancer. Global statistics show a declining rate of mortality from cancer and rising rate of survival from this ominous disease (1). Mortality data over the past quarter-century is quite promising as it shows a decreasing mortality rate from all cancers combined by 1.5% per year since 1993 in men and by 0.8% per year since 1992 in women (2). It is most fortunate which all of the most common cancers in men (lung, colorectal, and prostate) and women (breast and colorectal) show this decreasing trend. Even lung cancer mortality in women has finally leveled off after several decades of increase. Despite such improvements in the survival rate of cancers, the incidence rate in Iran shows an increasing trend (3-5).

Iran, as a developing country, is undergoing an epidemiologic transition from communicable to non-communicable diseases (6). Breast cancer, the most common malignancy in women, has shown an increasing incidence in Iran in recent decades, especially in women of reproductive age (7, 8). The largest age group of Iranian women with breast cancer is among those 40-49 years of age. Although worldwide, breast cancer is uncommon in women less than 40 years of age, 23% of female breast cancer cases in Iran are under the age of 40 years (8). Thus, compared with the global average, the incidence of breast cancer in Iran is nearly one decade behind (9). A total of 42% of cervical cancer cases are diagnosed in women less than 45 years of age (10). In colorectal cancer, 42.9% of patients are younger than 50 years (11). Therefore, it appears that a considerable group of our cancer patients are or will be of reproductive or pre-pubertal age in the future.

Detrimental effects of cancer on fertility and mental health

It should be noted that cancer does not bequeath a valuable heritage to its survivors; rather, there are considerable prolonged physical and mental complications. One of the most important is the detrimental effect of cancer on fertility and reproduction in survivors. Fertility in patients with cancer can be impaired in one of two ways, either as a sequel of the cancer itself or an adverse effect of the treatment protocol in use such as radio-chemotherapy regimens or bone marrow transplantations (12). In Iran, the increasing incidence of cancer, improving trend in survival rates, and significant proportion of young patients with cancer attach considerable importance to this issue. Delaying childbearing for social and financial reasons causes even more women to endure fertility threats because of early-stage cancer diagnoses (13). Infertility that results from cancer or its treatment jeopardizes self-esteem, personal identity, sexuality, and self-image of cancer patients. It also causes feelings of emptiness and defeat, and a negative effect on families and marriages (14).

Available fertility preservation options

Fertility preservation options in male patients include sperm collection either by masturbation, electroejaculation, or testicular biopsy followed by cryopreservation of semen and testis tissue (15). In women, due to the non-replenishable number of ovarian follicles, fertility preservation is more complex and depends...
on patient age, urgency of the treatment, and the regimen and treatment dosages. These techniques include immature and mature oocyte cryopreservation, ovarian tissue cryopreservation, ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist, ovarian transposition, embryo cryopreservation, gonadal shielding, and conservative gynecologic surgery (16, 17). According to American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines on fertility preservation for cancer patients, established, highly recommended fertility preservation methods include sperm cryopreservation in males and embryo and oocyte cryopreservation in females. Patients should also be informed that other methods (i.e., testicular or ovarian tissue cryopreservation) are experimental. Hormone therapy to preserve fertility should not be recommended in males or females, as there is insufficient evidence of its effectiveness (18, 19).

Figure 1 summarizes the fertility preservation options for male and female patients. Of note, these fertility preservation methods are available, in various forms, in Iran (20-22).

**Lack of knowledge: physicians versus patients**

It is a fact that women with cancers report great emotional distress and misgiving from unmet information about fertility preservation options besides cancer treatment (16, 23, 24). Ghorbani et al. (25) studied Iranian oncologists’ attitudes on fertility preservation. Only 46% of oncologists expressed awareness of fertility preservation techniques. Although the oncologists believed that radio-chemotherapy had a 30% damage rate on reproductive organs, 67% of them believed that fertility preservation should be offered to all patients. However, only 40% offered fertility preservation. Of note, only 15% of oncologists delayed treatment to refer patients to fertility preservation.

**Fig.1:** Fertility preservation options for both male and female with cancer.
centers. The most important reason why parents of children with cancer did not think of fertility preservation before cancer treatment was the lack of knowledge. Sadri-Ardekani et al. (26) studied on parental attitudes toward fertility preservation in 456 boys with cancer. They reported that parents of boys with cancer had limited knowledge about the risks of infertility due to cancer treatment. However, the majority desired some sort of fertility preservation once informed about these risks. More than one-third of parents wanted some sort of fertility preservation even if the chance of infertility was less than 20%.

In sum, the results of these studies highlight the fact that knowledge of both oncologists and patients about the necessity and importance of fertility preservation in Iran is inadequate. The increasing incidence of cancer, improving trend in survival rates, and significant proportion of young patients with cancer in Iran emphasize that this important issue, termed "oncofertility" by Dr. Teresa Woodruff in 2006 as new discipline (16), should be brought to the forefront in the health system policies of Iran. In order to achieve this, we make the following recommendations:

1. Ministry of Health and Medical Education organized and supervised educational programs, panels, and seminars should be held with the contribution of all related medical subspecialties including adult and pediatric oncologists, gynecologists, surgical oncologists, urologists, radiotherapists, and embryologists.

2. Regulations should be established by deputies of treatment in medical universities to oblige fertility counseling before the start of cancer treatment, in the same manner as routine laboratory tests and cardiology counseling.

3. National clinical guidelines should be developed for proper case selection and referral, and the choice of an appropriate fertility preservation technique. These guidelines should be developed by a committee of relevant specialist groups and supervised by the Treatment Deputy of the Ministry of Health and Medical Education.

4. Standard institutes specialized in the preparation and preservation of reproductive tissues that include sperm, ovule, fetus, and testis and ovary tissues should be endorsed, equipped and expanded under the supervision of the Ministry of Health and Medical Education.

5. Appropriate insurance and financial support should be provided for adequate coverage of costs, guaranteeing the integrity of tissues and compensation for probable damage.

Acknowledgements

The authors declare that they have no financial support and conflict of interests.

References

1. DeSantis CE, Siegel RL, Sauer AG, Miller KD, Fedewa SA, Alceraz KI, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. CA Cancer J Clin. 2016; 66(4): 290-308.

2. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghaffour A, et al. Cancer statistics, 2005. CA Cancer J Clin. 2005; 55(1): 10-30.

3. Mohagheghi MA, Mosavi-Jarrahi A, Malekzadeh R, Parkin M. Cancer incidence in tehran metropolis: the first report from the tehran population-based cancer registry:1998-2001, Arch Iran Med. 2009; 12(1): 15-23.

4. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajesadeghi N, Seddighi Z, et al. Cancer incidence and mortality in Iran. Ann Oncol. 2009; 20(3): 556-563.

5. Rafie manesh H, Rajaei-Behbahani N, Kiani Y, Hosseini S, Pouramandar Z, Mohammadian-Hafshejani A, et al. Incidence trend and epidemiology of common cancers in the center of Iran. Glob J Health Sci. 2015; 8(3): 146-155.

6. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five common cancers in Iran. Arch Iran Med. 2010; 13(2): 143-146.

7. Keramatinia A, Mousavi-Jarrahi SH, Hiteh M, Mosavi-Jarrahi A. Trends in incidence of breast cancer among women under 40 in Asia. Asian Pac J Cancer Prev. 2014; 15(3): 1387-1390.

8. Harirchi I, Karbakhsh M, Kashefi A, Mottahen AJ. Breast cancer in Iran: results of a multi-center study. Asian Pac J Cancer Prev. 2004; 5(1): 24-27.

9. Sadjadi A, Nouriae M, Ghorbani A, Alimohammadian M, Malekzadeh R. Epidemiology of breast cancer in the Islamic Republic of Iran: first results from a population-based cancer registry. East Mediterr Health J. 2009; 15(6): 1426-1431.

10. Karimi-Zarchi M, Mousavi A, Gilani MM, Barooti E, Mirrashahi-Yazdi A, Dehghani A. Conservative treatment in early cervical cancer. Int J Biomed Sci. 2013; 9(3): 123-128.

11. Azadeh S, Moghimi-Dehkordi B, Fatem SR, Pourhooseingholi MA, Ghiasi S, Zali MR. Colorectal cancer in Iran: an epidemiological study. Asian Pac J Cancer Prev. 2008; 9(1): 123-126.

12. Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA Jr, Peccatori FA, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016; 14: 1.

13. Maltaris T, Koelbi H, Seufert R, Kiesewetter F, Beckmann MW, Mueller A, et al. Gonadal damage and options for fertility preservation in female and male cancer survivors. Asian J Androl. 2006; 8(5): 515-533.

14. Tschudin S, Bitzer J. Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases. Hum Reprod Update. 2009; 15(5): 587-597.

15. Trost LW, Brannigan RE. Oncofertility and the male cancer
patient. Curr Treat Options Oncol. 2012; 13(2): 146-160.
16. Harp D, Chowdhury I. Oncofertility: an emerging branch of women’s health. Int J Cancer Res Prev. 2015; 8(2): 291.
17. Hormoz M, Akbarpour M, Hosseini Gohari L, Heidari M, Salehkhoo Sh, Jedi Tehrani M, et al. Common techniques for preserving fertility in girls and young women undergoing cancer treatment. J Reprod Infertil. 2011; 12(2): 85-92.
18. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013; 31(19): 2500-2510.
19. Peccatori FA, Azim HA Jr, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 Suppl 6: v160-170.
20. Karimi Zarchi M, Mousavi A, Gilani MM, Barooti E, Amini Rad O, Ghaemmaghami F. Fertility sparing treatments in young patients with gynaecologic cancers: iranian experience and literature review. Asian Pac J Cancer Prev. 2011; 12(8): 1887-1892.
21. Eftekhar M, Pourmasumi S, Karimi-Zarchi M. Preservation of ovarian function during chemotherapy and radiotherapy in young women with malignancies. Iran J Reprod Med. 2014; 12(6): 377-382.
22. Amirjannati N, Sadeghi M, Hosseini Jadda SH, Ranjbar F, Kamali K, Akhondi MA. Evaluation of semen quality in patients with malignancies referred for sperm banking before cancer treatment. Andrologia. 2011; 43(5): 317-320.
23. Canada AL, Schover LR. The psychosocial impact of interrupted childbearing in long-term female cancer survivors. Psychooncology. 2012; 21(2): 134-143.
24. Crawshaw MA, Sloper P. ‘Swimming against the tide’-the influence of fertility matters on the transition to adulthood or survivorship following adolescent cancer. Eur J Cancer Care (Engl). 2010; 19(5): 610-620.
25. Ghorbani B, Madahi P, Shirazi E, Ardekani HS, Kamali K. Iranian oncologists’ attitude towards fertility preservation in a sample group. J Reprod Infertil. 2011. 12(1): 33-36.
26. Sadri-Ardekani H, Akhondi MM, Vossough P, Maleki H, Sedighnejad S, Kamali K, et al. Parental attitudes toward fertility preservation in boys with cancer: context of different risk levels of infertility and success rates of fertility restoration. Fertil Steril. 2013; 99(3): 796-802.