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Building a successful fertility preservation program at a major cancer center

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Over 150,000 reproductive age individuals face fertility-threatening cancer treatments each year. Improved detection and treatment of cancer in reproductive-age patients have greatly increased the long-term survival and made it possible for these individuals to consider their long-term quality-of-life after cancer including having biologic offspring. Various methods of fertility preservation (FP) are now available for both males and females. In order to maximize FP options available to patients facing imminent gonadotoxic therapies, it is crucial that women have quick access to FP care and that providers expedite FP strategies. The overarching goal of a clinical FP program is to help patients and their physicians consider the impact of treatment on future fertility and facilitate FP efforts in what is often a limited time period before cancer treatment begins.

Keywords: Cancer center, Fertility preservation, Program

INTRODUCTION

There has been a growing interest in fertility preservation (FP) over the past few years. This stems from improved cancer survival rates, increasing focus on quality of life throughout cancer treatments, continuing advances in assisted reproductive technologies (ART), as well as increased awareness about FP.

A comprehensive FP program has several missions. First and foremost, a FP program should provide patients with timely and comprehensive FP consultations. Second, it should offer a comprehensive range of appropriate FP treatments. Third, it should employ a multidisciplinary approach for these medically complicated patients. Fourth, it should provide long-term care for these cancer patients, who may have unique issues surrounding contraceptive needs, reproductive goals, and menopausal symptoms. Finally, it should serve as a resource of up-to-date FP information for healthcare providers.

Setting up a successful FP program is crucial to fulfilling these missions. Recently, several studies have determined the importance of patient-centered communication in FP [1]. Effective communication has been expressed as a goal for both compassionate and quality healthcare [2], and is even more important in this vulnerable patient population grappling with a new cancer diagnosis as well as fertility concerns. When developing a FP program, it is essential to utilize an interdisciplinary team, which can include oncologists, fertility specialists, embryologists, and mental health professionals. Also, procedural and institutional policies or regulations may be required to set up a clear plan for patient flow.

In this review, we discuss unique challenges in FP which should be considered before setting up a FP program, limitations of current FP programs, and key factors to build a successful FP program.

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UNIQUE CHALLENGES IN FP DICISION MAKING

There are several challenges inherent in decisions regarding FP. First, due to the time-sensitive nature of FP treatments, information-gathering and assimilation needs to happen rapidly. The most effective FP options (embryo, oocytes, and sperm banking) are those that are made available to cancer patients *before* treatment begins. In the American Society of Clinical Oncology (ASCO) guidelines, it was suggested that patients who are interested in FP should consider their options as soon as possible to maximize the likelihood of success [3]. The American Society of Reproductive Medicine (ASRM) guidelines also state that unless interested patients are properly referred before treatment, options for later reproduction may be lost [4]. However, there is often not enough time for decision making and completion of FP treatments before cancer treatments begin. For example, in breast cancer patients, it takes approximately 2 months between cancer diagnosis and the initiation of chemotherapy [5]. However, if neoadjuvant chemotherapy is planned, the interval between diagnosis and initiation of chemotherapy is usually only 1 month [5]. Moreover, although a FP treatment protocol takes approximately 2 weeks, initiation depends on the timing of the menstrual cycle and 14 days is likely insufficient time for FP treatment. Patients with hematologic cancers are often critically ill with coagulopathy or neutropenia which make immediate FP challenging.

Second, the complexity of the topics involved with FP adds challenges for patients to make fast and high-quality decisions. Poor FP knowledge and comprehension in patients prior to and after FP consultation has been reported [6,7]. Even the language used during an FP consultation is highly specialized, and can require comprehension of complex topics such as probabilities, embryology, and female anatomy and hormonal patterns. Discussion about FP options is more complex because each FP option (egg, embryo, and ovarian tissue cryopreservation) carries unique risks as well as varying probabilities of outcome. In addition, outcomes depend on various factors such as the dose and duration of cancer treatment, the age of the patient, the patient's baseline ovarian reserve when treatment begins, etc [8]. Finally, since these patients have just been told that they have cancer, they are often on the verge of information-overload, with the FP topic adding to their burden.

Third, FP treatments can be a significant financial burden for patients. Despite growing evidence of reproductive dysfunction resulting from cancer treatments, FP is not covered under most insurance plans in the US [9]. No states mandate coverage for FP for cancer patients prior to treatment. While some insurance does cover infertility treatments, patients at risk for iatrogenic infertility are different from patients treated for infertility (defined as the inability to conceive after 12 ovulatory months of unprotected sexual intercourse). Cancer patients may not have infertility at the time of diagnosis, but they need to undergo FP services prior to initiation of cancer treatments, which may increase the risk of becoming infertile in the future. For patients paying out-of-pocket for FP treatments, this can cost thousands of dollars, and often this charge must be paid before the FP treatments occur.

Fourth, FP treatment requires a multidisciplinary medical team and inter-professional approach. An inter-professional healthcare approach is a process by which two or more professionals collaborate to provide integrated and cohesive patient-care to address the needs of their population [10]. Interprofessionality involves continuous interaction, open communication, knowledge sharing, understanding of professional roles and common health goals. Diverse expertise is required to discuss and undertake FP options in young cancer patients facing fertility-threatening therapy, including providers such as a fertility specialist, oncologist, urologist, pathologist, genetic counselor, mental-health professionals, social worker, financial counselor, etc. To provide timely FP options, it is essential to coordinate diverse expertise in terms of time, space and medical treatments which is usually challenging and requires institutional support to achieve.

LIMITATIONS OF CURRENT FP PROGRAM

1. Low referral rate

There are several studies querying oncologists about referral to fertility specialist. A nationwide survey of oncologists found that even though 95% oncologists report that they routinely discuss fertility consequences of cancer treatments, over half (61.1%) rarely or never refer patients to FP consultation with a fertility specialist [11]. In the same study, 30% of oncologists responded that they rarely consider a woman's desire for future fertility when planning treatment [11]. In a retrospective cohort study, only 20.6% of cancer patients who were eligible for FP consultation received it [12]. Another study evaluating pediatric oncologists' attitude toward FP reports that while they acknowledge the importance of addressing FP, less than half reported referring male patients and only 12% reported referring female patients to a fertility specialist prior to treatment [13].

The reasons why many physicians are reluctant to endorse FP even with national guideline recommendations in place include lack of physicians' knowledge about fertility, their perception that FP may not be a priority for certain patients

(parous patients, older women, etc), and physicians' lack of adequate FP referral information [14]. Oncologists' attitude toward FP is significant in patients' decision making as these vulnerable patients are strongly influenced by the messages they receive from their oncology team [15]. Another obstacle of referral to fertility specialist is the oncologists' focus on initial cancer treatments. While prompt and appropriate treatments are essential, oncologists may focus most of their attention on these vital immediate issues, and minimal focus on future complications, such as infertility [14]. However, the ability to have biological children in the future is extremely important to a vast majority of cancer patients [16]. It is important for these patients to be aware of the risk of infertility and to be able to make the choice to pursue or forego FP independently on the basis of information provided by health care providers.

2. Low treatment rate

Aside from the low referral rate to fertility specialists, low treatment rate (egg or embryo banking) is a significant issue of current FP programs. Low treatment rate may be an inevitable consequence of all of the challenges to FP mentioned above, such as the narrow time window for FP prior to cancer treatment, no available insurance coverage for FP treatment and low referral rate to FP consultation. In a recent study investigating reproductive age breast cancer patients, it was reported that only 58% of patients who pursued FP consultation received FP treatments (egg, embryo or ovarian tissue cryopreservation) [17]. Considering the low referral rate to FP consultation mentioned above, the absolute number of patients who pursue FP treatments is quite small. Specifically, age, income, cancer stage and pursuing neoadjuvant chemotherapy were significantly associated with pursuing FP treatment [5]. Interestingly, women who received neoadjuvant chemotherapy were significantly less likely to pursue FP treatments. This finding is significant because cancer treatment plans may be modifiable and the survival gain of neoadjuvant chemotherapy in early stage breast cancer has not been validated [18]. This reinforces the importance of inter-professional collaboration to coordinate medical and FP treatments to appropriately maximize a patient's opportunity for future fertility.

Financial barriers are a crucial inhibiting factor of FP treatments. As mentioned above, FP is may not be covered under insurance plans and *in vitro* fertilisation (IVF) can be expensive. Some financial support programs for FP treatments might be helpful. Patients may consider applying for a financial assistance programs such as Fertile Hope's Sharing Hope Program or Walgreen's Heart Beat program. Also, some fertility centers in the US have a discounted package price for cancer patients undergoing FP treatments.

3. Lack of communication with patients and among disciplines

Several factors are involved in making a high-quality medical decision including acquisition of information and evaluation of one's personal values or attitudes [19,20]. A thorough understanding of the disease and treatment options is essential to make high-quality decisions [21]. In addition, a patient's participation in decision-making with her healthcare provider has been shown to lead to more favorable patient outcomes [22,23]. Importantly, all these steps are based on the efficient communication between patients and healthcare providers. However, there are several unique factors that may hinder conversations between patients and healthcare providers regarding FP options.

Prior studies have highlighted socioeconomic disparities in referral patterns for FP consultation [12,24]. FP treatments can be costly; economic and social resources likely play a role in determining which groups are able to consider fertility after cancer treatments. Ideally, all interested patients, regardless of socioeconomic status, would have access to high quality information about FP. Unfortunately, due to insurance coverage and costly FP options, some patients may not be able to consider all treatment options. Given that there is inequality in referral patterns for FP consultation, some patients are not even given the opportunity for exposure to the field. One study showed that oncologists reported that they would be less likely to refer men for sperm banking who were human immunodeficiency virus (HIV)+ or openly homosexual [25]. Low access to FP was reported in women who identified with a sexual orientation other than heterosexual, despite having no differences in childbearing desires compared with women identifying as heterosexual [24].

Given the extreme time pressure about FP, prior exposure to the general topics regarding FP can be integral to enhance the communication between healthcare providers and patients. A study showed that previous exposure to FP information (high-quality websites, such as Fertile Hope, etc) prior to formal FP consultation is associated with better comprehension about FP treatment options, ideally resulting in a more productive conversation with a fertility specialist [6].

KEY TO A SUCCESSFUL FP PROGRAM

1. Strong connection between oncologists and fertility specialists

A strong connection between the oncology team and the fertility specialist is required for a comprehensive FP program. Oncologists' support for FP treatment is important in several

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aspects. First, FP process begins with oncologists addressing the possibility of infertility with patients who face fertility-threatening therapies before or during their reproductive years. In a recent study, a higher referral rate was shown in breast cancer patients compared to patients with other cancers [12], and it was speculated that a strong collaboration between breast oncologists and fertility specialists in that institution might contribute the higher referral rate. Second, it is well known that the primary physician's support and opinion have a significant influence on patient's decision making [26]. Finally, since FP always occurs in conjunction with primary cancer treatments, open communication between the fertility specialist and oncology team is crucial, especially if modifications are needed for the treatment plans. For example, a recent report demonstrated a lower FP utilization rate in a center where neoadjuvant chemotherapy has a broader use under research protocols compared to other centers [5]. In this case, a trade-off existed between pursuing FP treatments versus experimental neoadjuvant chemotherapy which would not permit the time necessary for FP. Ideally, if survival is equivalent between two treatment plans, a patient's desire for FP should be strongly considered and supported by her oncology team.

There may be several ways to increase oncologists' support for FP treatments. Improved FP education among the oncology team (via Grand Rounds, informal educational sessions, distribution of FP educational materials and resources providers and patients, etc.) could help allow oncologists to be more involved and make them aware of new developments in FP. At the institutional level, establishing policies that encourage patient education about FP as a required part of the consultation and treatment consent process could improve patients' awareness about FP. For example electronic medical records could flash an alert for all newly diagnosed reproductive-aged cancer patients to discuss and offer FP consultation.

2. Building a FP team

Early identification of key medical contacts facilitates the navigation of patients across specialties within the tight timelines necessary for FP in cancer patients. It is important that FP services and practices are clearly identified in order to facilitate referrals of newly diagnosed cancer patients by the oncology team members. For most FP programs based on multidisciplinary team work, FP consultations can occur within 24–72 hours of referral.

Most often, the medical FP team is initially assembled by a reproductive endocrinologist or an oncologist. An experienced anesthesia team may play a central role in evaluating patients for surgical FP procedures. On occasion, FP patients pose complex medical scenarios that require advanced anesthesia planning. The pathologist is a crucial contact for discussing disposition of ovarian and testicular tissue obtained for banking. Laboratory personnel who are highly experienced in clinical tissue banking are key members of FP team to freeze cells or tissues. Genetic counselors can help patients determine heritable conditions that patients may transmit to their offspring. Finally, mental health professionals can help patients and their families with counseling needs. They can discuss various ethical and legal issues to set a realistic expectation of FP treatment and provide emotional support which are usually beyond the scope of fertility specialists and oncologists.

Establishing an FP patient navigator position can significantly reduce the barriers between patients and specialists [4]. They play a role to shepherd patients and to ensure that patients do not get lost between the complex specialties. Within the multidisciplinary team setting, the FP patient navigator bridges institutional and disciplinary boundaries so that cancer patients are able to receive timely information regarding FP options. Also they serve as the primary contact for patients and clinicians. This function of the patient navigator makes it possible for patients to make well-informed decisions prior to the beginning of cancer treatment.

3. Design of FP consultation

FP consultation with a fertility specialist is a patients' main informational resource regarding fertility and FP options. In a recent survey study evaluating female cancer patients who pursued FP consultation, 100% of patients answered that FP consultation was the most helpful resource for information and 73% of patients made up their mind about treatment after the consultation [16]. Because, in most cases, only one FP appointment occurs because of time constraints, it is crucial that this single visit is as efficient as possible to allow for information gathering.

Utilization of a decision aid as a part of FP consultation can potentially help patients better understand the complex topics [27]. Patient decision aids are tools that help people become involved in decision making by making explicit the decision that needs to be made, providing information about the options and outcomes, and by clarifying personal values [28]. The efficacy of decision aids in medical decision making has been validated in various diseases including cancer [29]. Studies investigating breast cancer patients who pursued breast reconstruction surgery found that patients who used an interactive digital decision aid demonstrated greater factual knowledge, reduced anxiety, and increased postoperative satisfaction compared with patients given preoperative instruction using standard methods alone [29,30]. Pre- and

postconsultation exposure to informative resources such as brochures and websites about FP options may be helpful, too. Practically speaking, patients have to be informed how to access these resources and a patient navigator or members of the oncology team could assist in providing this information. Also, having a brief discussion with a patient navigator prior to FP consultation may help to make a complex FP topic more understandable and accessible. To allow patients to make a high-quality decision, it is essential to understand their decision-making process. Various factors such as social status, language barriers, financial concerns, and cultural background can be related to a patient's medical decision making. In a recent study, decision-making about FP treatment appears to be significantly impaired in patients grappling with financial concerns and when the opportunity to ask questions was not felt to be sufficient [16]. To minimize decisional conflict, it is essential to identify and discuss the unique factors that individual patients find challenging about FP. Having a follow-up visit or additional contact with a fertility specialist after the initial FP consultation was found to be significantly associated with lower decisional conflict [7]. Follow-up communication via phone or email may be ideal and realistic under the time pressure.

SPECIAL CONSIDERATION IN FP FOR PATIETNS WITH GYNECOLOGIC CANCERS

FP in patients with gynecologic cancers can be challenging—gynecologic cancers are heterogeneous, requiring a unique approach for each situation. For now, conservative management is the only FP option in patients with ovarian cancers [31-34], and borderline ovarian tumors [35,36]. In cervical cancer patients, simple or radical trachelectomy may be an option for FP in patients with early stage disease. Egg or embryo cryopreservation can be offered to some patients who will receive pelvic radiation therapy or chemotherapy. However, the oocyte retrieval procedure can be challenging because there is risk of bleeding and/or reseeding cancer cells if the aspiration needle traverses the tumor. FP options in endometrial cancer are currently limited to hormonal methods. Many studies reported favorable pregnancy outcome after hormonal treatment in endometrial cancer patients, however the total number of patients remains low [37-42]. Options such as ovarian tissue cryopreservation and IVF with *in vitro* maturation may be options, though they are considered experimental, with limited data about rates of future conception. As endometrial cancer is linked to obesity and anovulation, many women with the diagnosis may have primary or secondary infertility and would require assistance to conceive regardless [42]. However, the safety of pregnancy and ART after hormonal treatment, particularly in the case of a hormonally responsive tumor, is unclear.

Since there are no randomized clinical trials studying FP in gynecologic cancer patients, patients who desire FP should clearly understand that data regarding outcome are very limited, especially the feasibility and safety of FP techniques including commonly used FP techniques such as oocyte or embryo cryopreservation. One study found that the referral rate to a fertility specialist was the lowest in gynecologic cancer patients [12], perhaps because the gynecologist-oncologist is more comfortable in discussing FP than oncologists in other disciplines. However, these patients may benefit from a formal consultation with a fertility specialist to discuss other FP options and the difficulty and implications of getting pregnant after conservative cancer treatments. In many gynecologic cancer cases, final diagnosis and staging are often not made until after fertility-damaging surgery has occurred; thus earlier patient education and evaluation through FP consultation is important.

CONCLUSION

While more FP options now exist for reproductive-age cancer patients, access to these services continues to be limited. A tremendous number of individuals need to be involved to move a patient from cancer diagnosis to completion of FP in a short period of time. While caring for FP patients can be challenging, helping appropriate patients pursue FP options is important because it can give patients a sense of control over their reproductive options and hope for the future. For this reason, there has been a continuous movement to expand the FP program to all comprehensive cancer centers in US over the past few years.

CONFLICT OF INTEREST

JEM was a consultant at Ferring Pharmaceuticals in 2013. There are no competing interests to disclose from JK and KHK.

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