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Fertility preservation and cancer: Challenges for adolescent and young adult patients

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Abstract

Purpose of review—With increasing survival rates, fertility is an important quality of life concern for many young cancer patients. There is a critical need for improvements in clinical care to ensure patients are well informed about infertility risks and fertility preservation (FP) options and to support them in their reproductive decision-making prior to treatment.

Recent findings—A number of barriers prevent fertility from being adequately addressed in the clinical context. Providers' and patients' incomplete or inaccurate understanding of infertility risks exacerbate patients' reproductive concerns. For female patients in particular, making decisions about FP before treatment often leads to decision conflict, reducing the likelihood of making informed, values-based decisions, and post-treatment regret and distress. Recent empirically-based interventions to improve provider training around fertility issues and to support patient decision-making about FP show promise.

Summary—Providers should be knowledgeable about the infertility risks associated with cancer therapies and proactively address fertility with all patients who might one day wish to have a child. Comprehensive counseling should also include related issues such as contraceptive use and health implications of early menopause, regardless of desire for future children. Although the negative psychosocial impact of cancer-related infertility is now well accepted, limited work has been done to explore how to improve clinical management of fertility issues in the context of cancer care. Evidence-based interventions should be developed to address barriers and provide psychosocial and decision-making support to patients who are concerned about their fertility and interested in FP options.

Keywords

cancer; fertility; infertility; reproductive health; fertility preservation

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Introduction

Almost 80,000 children, adolescents, and young adults will be diagnosed with cancer each year (1, 2). Many will survive their diagnosis but over time will face a number of other challenges, including the potential loss of fertility. Fertility preservation (FP), however, could be an option for many of these patients. Although there is growing recognition of the importance of fertility in the context of cancer care, high rates of unmet information needs about infertility risks and FP options are still reported, and few patients actually pursue FP, despite wanting children in the future (3). Decisions regarding FP can be difficult and lack of informed decision-making may lead to future regret and distress (4, 5). This article will briefly describe the reproductive effects of cancer treatment and the FP and family-building options available to adolescent and young adult patients, discuss difficulties associated with FP decisions, outline key factors that influence clinical care, discuss empirically-based interventions developed to train clinicians and support patients in making fertility-related decisions, and explore the psychosocial effects of fertility problems among cancer survivors.

Reproductive Effects of Cancer Treatment

Multiple factors contribute to the risk of infertility after cancer treatment, including gonadal function prior to treatment, gonadal toxicity of chemotherapy, and the effects of surgery and radiation on reproductive structures. Radiation of the gonads and chemotherapy with alkylating agents pose the highest risk of infertility; platinum analogues, anthracyclines, and taxanes pose an intermediate risk (6, 7). It is challenging to quantify the precise risk of specific chemotherapeutic agents, as most are used in combination with other agents, doses vary based on the regimen, and there are an increasing number of new agents, including targeted and biologic therapies, with minimal long-term data on fertility outcomes.

Male patients receiving cancer treatment may develop impaired sperm production from depletion of the spermatogonial stem cell population or impaired sperm transport secondary to erectile or ejaculatory dysfunction (7, 8). Female patients receiving cancer treatment may undergo premature ovarian failure from depletion of ovarian follicles or may not be able to carry a pregnancy secondary to radiation-induced uterine fibrosis or hysterectomy (6, 8, 9). In addition, patients may develop disruption of the hypothalamic-pituitary-gonadal axis that regulates sperm production and oocyte maturation following cranial surgery or irradiation that involves the pituitary gland (8). Although estimates of risk have been established for some treatments (10, 11), it is impossible to predict with certainty how any one individual will be affected by their treatment.

Fertility Preservation Options

Advances in reproductive technology have given patients increasing options for preserving fertility potential. These include techniques to freeze gametes or gonadal tissue (cryopreservation) and strategies to reduce the gonadal toxicity of treatment. Fertility preservation will not be desired by or feasible for all patients, but for those who are interested, it should be completed before treatment begins as even a single treatment with gonadotoxic therapy can affect gamete quality and DNA integrity (12). Table 1 (13–19) and

Table 2 (8, 20–28) describe the FP options available for male and female patients, respectively.

For post-pubertal males, sperm banking is the optimal method of FP (16). Most patients obtain semen by masturbating at a licensed sperm bank. Patients are generally recommended to collect three specimens, with two to five days of abstinence before each (14). For males who cannot collect by masturbation, electroejaculation is an option; for those who have no sperm found in their semen, testicular sperm extraction is an option. For those undergoing radiation with potential testicular exposure, shielding may be an option.

For post-pubertal females, egg or embryo freezing is the optimal method of FP (12, 20, 21, 29). Patients self-administer hormone injections for about 10 days to stimulate follicle growth and then undergo transvaginal retrieval of mature eggs performed under anesthesia. Patients can freeze unfertilized eggs or have them fertilized with sperm in the laboratory (in vitro fertilization, IVF) and freeze the resulting embryos. Success rates are age-related, with younger women more likely to be successful than older women (20, 28). Egg freezing may be preferred by women without male partners who do not want to use donor sperm to create embryos, and for women who do not want to freeze embryos for religious or personal reasons. For females who cannot take the two to three weeks required to undergo egg or embryo freezing, ovarian tissue freezing may be available as an experimental option. Other FP options include ovarian transposition, ovarian suppression, and modifications in the cancer treatment plan.

Alternative Family-Building Options

As patients make decisions about FP, it is important for them to be aware of alternative ways to build a family if they are unable or choose not to pursue FP and have impaired fertility in the future. Table 3 describes these options, which include use of donor gametes or embryos, surrogacy, and adoption (30).

Addressing Fertility in Clinical Care

Clinical practice guidelines stipulate that all cancer patients of reproductive age (and parents/guardians of children and adolescents) be made aware of fertility risks and FP options prior to treatment (U.S. guidelines include the American Society of Clinical Oncology [ASCO] (29); National Comprehensive Cancer Network [NCCN] (31); American Academy of Pediatrics [AAP] (32); American College of Obstetricians and Gynecologists [ACOG] (33); European guidelines are available from the European Society for Medical Oncology [ESMO](34)). Initiating developmentally appropriate conversations and providing the opportunity for patients or parents to ask questions and access specialized fertility care is a critical aspect of treating adolescent and young adult cancers (35). Females, in particular, have reported a desire for tailored, personalized information during treatment planning (36).

Despite guidelines, patients, particularly females, consistently report not receiving adequate information prior to treatment or not understanding the information provided (37, 38). Incidentally, similar problems are also reported post-treatment as survivorship care plans often do not include comprehensive sexual and reproductive health counseling (39–41).

Young women who felt they received inadequate information reported anger and frustration, while feeling adequately informed was more likely to lead to satisfaction with decision-making about FP (42).

Although providers are increasingly addressing fertility with their patients (43), recent studies indicate improvements are still needed (44, 45), and both patient- and provider-reported frequency of fertility-related discussions vary greatly (43, 46, 47). In a review of the literature, patients' unmet fertility information needs ranged from 66% to 100%, and between 11% to 90% of patients rated the information they received as sufficient (43). Differences have been reported based on gender: among adolescent and young adult survivors attending support group conferences in the U.K. in both 2004 and 2011, most males remembered having had a discussion about fertility prior to treatment and generally being satisfied, whereas females were less likely to have remembered a discussion and more likely to be unsatisfied with discussions when they occurred (48). Armuand et al. also found that females reported more negative experiences related to patient-provider communication about fertility than males (49).

While physicians indicated greater comfort than nurses discussing fertility, the majority of oncology providers report a desire for further training and education (43, 47). A number of studies have documented barriers preventing optimal management of fertility issues in oncology settings. At the provider level, factors associated with reduced likelihood of fertility discussions include lack of knowledge and training, time constraints, insufficient resources, embarrassment, closeness in age to the patient, and issues being seen as irrelevant to the providers' specialty or clinical practice (43, 46, 47, 50, 51). Patient characteristics including age, female gender, (provider perception of) low income and insurance coverage, disease type, poor prognosis or poor health status, treatment gonadotoxicity and perceived infertility risk, nulliparity, and religious and cultural factors have also been associated with lowered rates of fertility discussions (3, 43, 46, 47, 50, 51). Situational barriers include parents being present, lack of communication among treatment team members, and urgency to start treatment (43, 46, 47, 50, 51).

Linkeviciute and colleagues reviewed worldwide differences in provider practices and factors influencing clinical decisions to discuss FP with their patients (52). Only providers from the U.S. and the U.K. discussed fertility with the majority of their patients; American providers were found to have more biased practices compared to British based on factors related to social issues, gender, and race. Fertility discussions and referrals for a fertility consultation occurred less frequently in other countries, despite consistency in patient reports that fertility consultations were an important part of their cancer treatment. A 2013 study from Japan reported a 42% referral rate of those eligible; and a 2010 study from Saudi Arabia reported 42% of oncologists reported routine discussions of fertility, while 39% never made referrals to a FP specialist. In general, however, female patients and racial minorities in the U.S. were vulnerable to not having fertility issues addressed. Similar factors were shown to contribute to provider practices, including disease type, patient prognosis, lack of knowledge, time constraints, and reluctance to delay treatment. A 2011 study from Iran surveyed 30 oncologists and found that 40% felt that patients needed to initiate the discussion themselves.

Decision Making about Fertility Preservation

Even for patients who are informed of fertility risks prior to treatment and have the option to consider FP, decision-making about FP can be difficult and wrought with uncertainty. The lack of data on the precise risk of infertility from treatment and unmet information needs contribute to patients' uncertainty. At a time of high emotional distress, patients have to consider the importance to them of having a biologically related child; their comfort in using assisted reproductive technology; religious, cultural, and ethical beliefs; and the opinions and recommendations of clinicians, partners, and family members (4, 36). Decisions are often considered more difficult for females than for males as the procedures are more invasive, costly, and often require delaying treatment.

Financial considerations are often a significant factor influencing decision-making (53). The cost of undergoing FP is prohibitive for many patients, though there are significant international differences in reproductive healthcare coverage and access to fertility-related procedures. Access may also be limited by geographic location and access to specialized reproductive centers and insurance plan coverage.

Empirically-based Interventions

Although the importance of fertility for young cancer patients is now well accepted, the development of empirically-based interventions to improve clinical care and support patients facing infertility risks has lagged behind. Key factors that should be considered when building a FP program for patients facing infertility risks secondary to gonadotoxic cancer therapies have been reviewed elsewhere (52, 54).

At the provider level, at least one intervention has been developed targeting nurses working with adolescent and young adult cancer patients. An eight week, web-based communication skills program was shown to improve oncology nurses' perceived knowledge and confidence in communicating about reproductive health and FP with their patients (55–57). Larger trials are needed to evaluate the impact of provider-level interventions on patient-reported outcomes and the long-term uptake of institutional changes to enhance clinical care. Curriculums may also be adapted and tailored for different providers including psychologists, social workers, and child life specialists.

At the patient level, two decision aids have been developed for women with breast cancer considering FP before treatment (58, 59). Decision aid interventions appear to have promising benefits to patients' level of decisional conflict and post-treatment regret (58). This is consistent with a large body of literature supporting decision aids in the context of healthcare decision-making, particularly when there is uncertainty (60). Randomized controlled trials are needed to confirm these findings and determine whether decision aids may be generalized to other disease populations. Decision aid interventions may represent a feasible, low-cost strategy to support patient decision-making in many scenarios; however, there may be subgroups of patients who need more comprehensive programs of support and individualized attention. Working with a counselor or "decision coach" who provides individualized, nondirective guidance has been shown to significantly reduce decisional conflict and anxiety when patients perceive it as being useful (61). Further work should

explore how to feasibly build interventions that incorporate multiple specialties including reproductive health specialists, mental health or “decision support” counselors, and oncology providers.

Exploration of the ways in which psychosocial and decision support interventions may be translated to the pediatric oncology setting is also warranted (33). Murphy and colleagues have developed English and Spanish language pediatric FP brochures (62, 63), though the authors note that standardized education materials for pediatric patients and families are still not adequately available for most families. While parental education and decision support is essential, developmentally appropriate guidelines and resources to appropriately involve younger patients in treatment discussions also needs further development.

To date, long-term survivorship care plans have largely failed to incorporate comprehensive reproductive health counseling (41, 64). Survivors have recommended that clinicians be proactive in raising fertility at every clinic visit as relevant issues and need for resources may change over time (65).

Psychosocial Effects of Infertility and Fertility-related Distress

Newer evidence is consistent with the growing body of literature over the last decade demonstrating the negative psychosocial effects associated with post-treatment fertility problems among cancer survivors. These include long-term distress, fear, and anxiety; worries about dating, disclosure, and relating to peers; devastation with confirmed infertility and difficulty coping with uncertain reproductive capacity; fears about the safety of pregnancy and passing on a genetic risk for cancer to a future child (42, 49, 66). The extent and nature of fertility concerns may differ between males and females with females tending to be more distressed than males (49, 67, 68). Among female survivors, reproductive concerns are associated with moderate to severe depression (69); risk factors include younger age, nonwhite race, nulliparity and receipt of chemotherapy (70). Women who received fertility counseling by a reproductive specialist before treatment reported lower levels of post-treatment regret and better quality of life irrespective of whether they pursued FP (37, 71–73). Notably, some adolescent and young adult survivors have indicated continued fertility-related distress despite explicit reassurance from physicians that treatment had not affected their fertility (68).

Importantly, parents may overlook younger cancer patients’ fertility-related distress or misunderstand the nature of their concerns. Quinn et al. demonstrated that parents consistently underestimated their daughters’ level of reproductive concern, expecting them to be satisfied with survival (74). Klosky and colleagues reported that 44% of adolescent male survivors ranked having children as a “top 3 life goal,” though only 21% of mothers and 37% of fathers similarly ranked this for their sons (75).

Reproductive concerns may also increase in the years following treatment as young survivors reach development stages to consider long-term relationships and family-building. Gilleland et al. reported that most female survivors of childhood cancers and their parents who had received information on gonadotoxic risks were worried about fertility (71% and 97%, respectively) (76). While parental concern was constant across age groups, survivors’

accurate awareness of fertility risks and level of reproductive concern increased in older ages (pre-teen vs. adolescent vs. young adult age groups) (76). Lehmann et al. assessed male and female survivors at 3-, 4-, and 10-years post-diagnosis in which concerns about fertility/sterility only emerged in the final assessment and was shown to have a negative impact on dating and family planning (77). The need to improve clinical care and support patients in making decisions that are consistent with their values and future goals for childbearing is reinforced by the well-documented psychosocial difficulties many survivors face post-treatment.

Conclusions

Recent evidence has highlighted the difficulties many patients face when their cancer treatments require gonadotoxic therapies and the barriers that prevent optimal management of fertility issues in clinical care. Cancer care settings need to establish systems to ensure that fertility is adequately addressed (78). Examples of fertility programs in different kinds of clinical settings have been published (54). Given the long-term regret and distress associated with confirmed and potential infertility post-treatment, an important focus of future research should be to develop strategies to ensure patient education and facilitate informed decisions consistent with patients' personal values and future reproductive goals.

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Key Points

- Decisions about fertility preservation are often difficult for young cancer patients to make and for females in particular, may be wrought with uncertainty, conflict, and lead to long-term regret and distress in survivorship.
- There are a number of barriers to addressing fertility in the context of cancer care based on provider-, situational- and patient-level factors; barriers may vary worldwide depending on sociocultural and policy-level differences across countries.
- Further work is needed to develop empirically-based interventions to train providers to appropriately address fertility with their patients and to support patients making decisions about fertility preservation.
- Recent evidence suggests reproductive concerns and fertility-related distress may occur even when patients do not receive gonadotoxic therapies and despite providers' reassurance (68), highlighting the need for comprehensive and ongoing reproductive health counseling throughout the cancer continuum.

Table 1**Fertility Preservation Options for Males**

Sperm Banking (freezing of sperm)

- Ejaculation: Semen specimen obtained by masturbation
 - Electroejaculation: Semen specimen obtained by electrical stimulation of ejaculation; a mild electrical current is emitted from a rectal probe positioned over the prostate gland; performed by a reproductive urologist under anesthesia
 - Testicular sperm extraction: Small pieces of testicular tissue are removed by biopsy or aspiration; tissue examined for sperm to be extracted directly from the tubules; performed by a reproductive urologist under anesthesia
-

Testicular Tissue Freezing

- Small pieces of testicular tissue are removed by biopsy; performed by a reproductive urologist under anesthesia
 - Experimental
 - The only option for pre-pubertal males
 - Technique for future use could be re-implantation of tissue or in vitro maturation of sperm; no children have yet been born using frozen testicular tissue
-

Testicular Shielding

- For use in males receiving pelvic or inguinal radiation without intent to treat the testes
 - A clam shell like device is positioned around the scrotal sac each day of treatment to reduce testicular exposure to radiation
-

Note. Information from (13–19)

Table 2**Fertility Preservation Options for Females****Embryo Freezing**

- Embryos created by in vitro fertilization (IVF) after a cycle of ovarian stimulation and transvaginal retrieval of mature eggs
- Process take two to three weeks

Egg Freezing

- Eggs obtained after a cycle of ovarian stimulation and transvaginal retrieval of mature eggs
- Process take two to three weeks

Ovarian Tissue Freezing

- Ovarian cortex obtained by unilateral or partial oophorectomy
- Experimental
- The only option for pre-pubertal females
- Also an option for post-pubertal females unable to undergo embryo or egg freezing
- Technique for future use could be re-implantation of tissue or in vitro maturation of primordial follicles; about 25 children have been born world-wide after re-implantation of tissue

Ovarian Transposition

- For use in females receiving pelvic or inguinal radiation without intent to treat the ovaries
- Repositioning of the ovaries outside of the radiation treatment field to reduce ovarian exposure to radiation
- If fallopian tubes are dissected from uterus, patient cannot conceive naturally

Ovarian Suppression

- Administration of GnRH agonist (e.g., leuprolide) during chemotherapy to suppress recruitment and maturation of follicles
- Experimental (off-label use); studied primarily in women with breast cancer and lymphoma

Alternative Treatment for Early Stage GYN Cancers

- Only appropriate for select patients with early stage disease Cervical cancer: radical trachelectomy instead of hysterectomy
- Ovarian cancer: unilateral oophorectomy instead of bilateral oophorectomy
- Endometrial cancer: progestin therapy instead of hysterectomy

Note. Information from (8, 20–28)

Table 3**Alternative Family Building Options****Donor Sperm**

- Provided by healthy young men who deposit semen to a sperm bank where it is frozen and stored for others to use
- Donors are generally anonymous, although a variety of physical and personal characteristics are shared to help people select a donor
- If female partner has no fertility problems, intrauterine insemination (IUI) is used to attempt pregnancy

Donor Eggs

- Provided by healthy young women who undergo ovarian stimulation and egg retrieval to obtain eggs for others to use
- After retrieval, the eggs are fertilized and the resulting embryo is transferred into the uterus of the intended parent to attempt pregnancy.
- The mother has no genetic relationship, but can experience pregnancy and child birth, and the child will have a genetic relationship with the father

Donor Embryos

- Created by couples who underwent IVF for infertility, have completed building their families, and now have extra embryos they choose to donate to others rather than discard
- Neither parent will have a genetic relationship with the child, but the mother can experience pregnancy and child birth

Surrogacy with a Gestational Carrier

- For females unable to carry a pregnancy (e.g., post hysterectomy or high dose pelvic radiation) or for whom it would be unsafe to carry a pregnancy (e.g., late effects of treatment, risk of recurrence, metastatic disease)
- Embryos or created via in vitro fertilization (IVF), using parents' gametes or donor gametes, and embryo is transferred to the uterus of another woman to carry the pregnancy

Adoption

- A cancer history does not disallow someone from adopting, but they generally must be healthy and cancer free for at least a few years

Note. Information from (30)