INTRODUCTION

Infertility is of paramount concern and a significant source of distress for survivors of childhood cancer [1–4]. Recognizing the importance of this issue, the American Society of Clinical Oncology (ASCO) developed guidelines in 2006, updated in 2013, recommending the discussion of fertility issues, including fertility preservation (FP), to all patients in whom fertility may be affected [5]. Although investigational, disclosure of methods available for children should be made accessible to parents. Understandably complex, we strive to review existing technologies and barriers preventing implementation and provide strategies on how to approach this with patients.

Effect of Cancer Treatment on Female Fertility

Treatment of childhood cancer may involve combinations of surgery, chemotherapy with alkylating agents, radiotherapy (RT), and/or bone marrow transplant. With the exception of non-pelvic surgery, these treatments can adversely impact ovarian function [6]. Ovaries are susceptible to cancer treatment due to the finite number of non-renewable germ cells present from birth [7].

Pelvic RT specifically causes expedited ovarian follicle atresia, resulting in the destruction of the follicular pool, ultimately leading to premature ovarian failure. Additionally, pelvic RT may cause uterine scarring and reduced uterine blood flow, diminishing the volume of the developing endometrium [8–10]. RT has a greater overall effect on the uterus in prepubertal females. Women who receive RT post-puberty have more developed, larger uteri and a higher chance of having live births than those who have undergone prepubertal RT [3,8]. Thus, a uterus radiated in early childhood may not be capable of carrying a fetus to term. The effect of RT on fertility is dose-dependent [11]. RT to the hypothalamic–pituitary axis also affects fertility, as an intact hypothalamic–pituitary axis is essential for ovulation and natural conception.

Chemotherapy agents, especially alkylating agents, cause significant DNA damage by inducing cross-linkages and breaking single-strand DNA [9]. Histological evaluation of ovarian tissue taken from patients exposed to chemotherapy agents provides circumstantial evidence of damage with decreased or complete absence of follicles, as well as stromal fibrosis and damage to ovarian blood vessels [10,12]. Patients treated with alkylating agents have a fourfold higher risk of ceased ovarian function when compared to those treated with other chemotherapy agents [6]. Although gonadotoxicity and age have an inverse relationship in females (i.e., the higher the patient’s age, the lower the dose of chemotherapy that causes ovarian failure), there is no evidence to support that the prepubescent ovary is safe from chemotherapy damage [7]. Platinum agents, such as cisplatin and carboplatin, as well as anthracyclines, most notably doxorubicin, present a lower, but not negligible risk of gonadotoxicity than alkylating agents [13,14]. Assessment of the damage done by individual chemotherapy agents is difficult due to the frequent use of multimodal regimes, confounded further by the constantly evolving treatment schedules.

Hematopoietic stem cell transplantation (HSCT) is a common form of treatment for hematological malignancies; the success of this treatment is closely correlated to a dose–response relationship with chemotherapy [6]. The conditioning regimes used in HSCT include high-dose chemotherapy with or without the addition of total body RT. Doses of chemotherapy vary depending on whether the intent is myeloablative versus nonmyeloablative. Patients cured with myeloablative HSCT have a very high risk of developing permanent ovarian failure, demonstrated by several studies. Most notably, Thibaud et al., studied 31 females ranging in age from 3.2 to 17.5 years at diagnosis, who underwent HSCT with or without RT. Females who menstruated prior to treatment suffered from permanent amenorrhea and 6 years post-treatment of HSCT, 80% of
the female patients had permanent ovarian failure [15]. Conditioning regimens, including the combination of busulfan-cyclophosphamide (Bu-Cy), render females at substantial risk for ovarian failure [6]. In adult females treated with Bu-Cy (mean age of 38 years using 200 mg/kg of Cy), only one out of 73 patients recovered ovarian function [16]. In contrast, nonablative chemotherapy regimens often used in autologous transplantation proved to be effective in treating primary disease (i.e., lymphoma), while also providing substantial FP advantage. Of the 30 women treated, 10 were able to have successful pregnancies post-HSCT [17]. Although similar comparisons are not available for younger females, these studies indicate an extremely high risk of persistent ovarian failure, especially after myeloablative HSCT.

In summary, females undergoing pelvic RT and myeloablative BMT are at the highest risk for permanent ovarian failure and should be the population for the greatest consideration of FP procedures prior to the commencement of therapy.

**Detecting Ovarian Failure After Cancer Treatment**

There are two major subcategories of ovarian failure: acute ovarian failure (AOF) and premature ovarian failure (POF) [18]. Patients who lose ovarian function during cancer therapy or shortly after its completion are classified as having AOF. Patients who retain ovarian function after therapy completion and then experience menopause before the age of 40 are classified as having POF [19–22]. In pediatrics, POF is by far the greatest concern as otherwise healthy girls experience menopause before the age of 40, which is considered as a rare event in normal females. The incidence of POF varies from 2.4% in prepubertal to 6.3% in postpubertal girls [19–22].

Younger patients have a larger pool of oocytes; thus, the relative decline in ovarian function due to cancer treatment is less than in older women. The ovary can still support regular ovarian cycles with the reduced amount of follicles for a variable amount of time post-puberty [23]. However, premature follicle depletion will result in early menopause [24]. As such, POF also increases the risk of osteoporosis and cardiovascular disease [18,23]. In one study, a follow-up of women treated with RT and chemotherapy for cancer at the age 20 and younger showed that 42% had reached menopause by age 31 [24]. Approximately 40% of postpubertal women treated with alkylating agents require hormone replacement therapy for POF [6].

Ovarian failure precludes the possibility of conception, leaving survivors without the ability to conceive biological children. The long-term follow-up guideline issued by the Children’s Oncology Group recommends regular screening of both prepubertal and postpubertal females [18,21]. In prepubertal survivors, menstrual history, onset/tempo of puberty, and Tanner stage should be evaluated annually until sexual maturity is reached. In postpubertal females, menstrual and pregnancy history, as well as any menstrual changes, should be evaluated. In patients experiencing delayed puberty, irregular menses, amenorrhea, and/or clinical symptoms of estrogen deficiency, levels of luteinizing hormone, follicle-stimulating hormone (FSH), antimüllerian hormone (AMH), and estradiol should be investigated.

There is controversy, however, on how best to assess ovarian function in adolescents. Several studies have shown that survivors of solid tumors and hematologic malignancies have chronically high levels of FSH and demonstrate amenorrhea, indicative of ovarian failure [15,22,25,26]. Despite these findings, pregnancies in childhood cancer survivors with these symptoms have been well reported; hence, neither FSH levels nor menstrual cyclicity post-cancer treatment is a reliable predictor of conception [15,20]. However, many limitations to these studies continue to preclude our ability to offer counseling with the precision required to accept intervention. Our philosophy remains that the delivery of information regarding the potential risk should be uniform, even if the decision to undergo procedures is not.

In recent years, serum AMH has been established as a novel marker for ovarian reserve [27]. The early finding of AMH serum levels diminishing with age lead to the hope of using this marker as a predictor of POF in female cancer survivors; AMH levels, as a predictor of age of menopause, in adult women has confirmed this as a feasible indicator [28–31]. Although AMH is now described as a useful marker for determining the ovarian reserve of adult survivors of cancer, fewer data are available for its use among survivors of childhood cancer [2,32]. Two studies have examined AMH serum levels in survivors of childhood Hodgkin’s lymphoma, solid tumors, and hematological malignancies. These studies confirm that AMH levels were indeed indicative of limited ovarian reserve in contrast to FSH and estradiol levels that did not vary from the healthy controls [33,34].

**Fertility Preservation Options**

If a sexually mature, young woman of reproductive age is seeking FP, standard options for oocyte or embryo cryopreservation exist. However, offering these techniques to postpubertal adolescents is associated with additional challenge as the techniques required to acquire oocytes involves intravaginal instrumentation. The alternative to oocyte cryopreservation (OC) involves ovarian tissue cryopreservation (OTC).

**Oocyte Cryopreservation**

Advances in OC from adult women have resulted in over 900 live births over the last three decades [35]. There are many barriers to the adoption of OC into standard of care for adolescent cancer patients, which will be discussed. Firstly, OC requires time for ovarian stimulation and egg harvest, which can be a problem within the context of urgency to start cancer treatment. Mature OC requires ovarian hyperstimulation procedures in order to maximize the number of mature oocytes, which can be aspirated. Whereas in the past, ovarian stimulation could only start in the early follicular phase of a menstrual cycle; newer, more rapid stimulation protocols have halved the usual 4-week process allowing for “random start” for ovarian stimulation. Cancer treatment can usually begin the day after oocyte collection [35–37]. However, even a 2-week delay in cancer treatment is often not feasible since most pediatric cancers are aggressive, or patients are too unwell to tolerate the delay [38]. Secondly, oocytes are harvested by inserting a needle transvaginally, which passes into the pelvis in order to access the ovarian cortex [39]. This is a painful procedure, which requires sedation even in adult women and specialized equipment which is not often available in pediatric hospitals. Most adolescents, despite their sexual maturity, may find this procedure emotionally and physically intolerable in the absence of a general anesthesia. Prepubertal females are not yet ovulating due to the lack of maturity of the hypothalamic–pituitary axis negating the possibility of OC.

**Ovarian Tissue Cryopreservation**

OTC proves advantageous as it can be offered at any time, with less delay to starting cancer therapy. In this process, strips of ovarian
cortical tissue are harvested by minimally invasive laparoscopic surgery under a general anesthesia. The amount of tissue required for optimal FP – that is the whole ovary or merely strips from the ovarian cortex – is unclear; however, the latter option is generally preferred in pediatric patients [40,41]. The harvested tissue is sliced into thin cortical strips in the laboratory and frozen. Examination of the viability of the freeze-thawed tissue has shown that the primordial follicles have survival rates that range between 10% and 85%, demonstrating that the follicles, which contain oocytes much smaller than their mature counterpart, are tolerant to the freeze–thaw process [42].

There are only a few centers worldwide demonstrating successful live births using OTC [43–45]. Restoration of ovarian function from postpubertal OTC was observed 3–6 months post-reimplantation, documented by an increase in estradiol and decreased FSH [46]. These findings were consistent among human, mice, and sheep ovarian postpubertal implant recipients [47]. In certain oncology patients, however, there is a significant concern for the risk of reintroducing cancer cells with reimplantation, and in fact, should not be performed for most pediatric malignancies [48]. The issue of ovarian transplantation in cancer patients remains an issue of debate among both the oncologists and the fertility experts.

OTC is the only method of FP available for prepubertal females, but an additional consideration applies. Tissue harvested from prepubertal females contains only immature follicles, which would need to be isolated from the tissue, matured in the laboratory, and when fully grown into mature follicles, the oocyte can be extracted and fertilized with sperm, with the resulting embryo being implanted into the uterus of the patient in hope of a successful pregnancy [25,49]. However, there is no precedent to date of a live birth using this method. The current scientific hurdle is to devise a method to grow the follicles and support the mature oocyte until in vitro fertilization can be performed. Patients with complete ovarian failure would also require endocrine management to carry a successful pregnancy.

In summary, options for FP remain limited for female pediatric patients. Having said this, the delivery of information regarding the possible risk of AOF and POF should always be presented (endorsed by ASCO guidelines). Institutional practices will vary, but every effort should be made to explore local opportunities for tissue harvesting and cryopreservation, and these options should be discussed with families. It is not unethical to disclose technologies that may not be available, and even to discuss those which are unproven technology. Our own practice is to attempt tissue harvesting whenever possible in females receiving pelvic RT and/or myeloablative BMT, which will almost certainly result in permanent ovarian failure. In other patients, who are at risk only of POF, rather than AOF, we have been advocating formal assessment of ovarian function in survivorship and a second opportunity in young adulthood for OC, if there is suggestion of early ovarian function decline. Further research in the value of this approach is required.

Further Challenges of FP Discussions With Females

One major obstacle to discussing FP with cancer patients and their families is the timing of these discussions. They are challenged to understand the biological and technical aspects of FP in order to quickly make decisions about next steps, all within the emotional context of a new cancer diagnosis. As a result, although oncologists may mention FP, patients rarely recall this detail later [50]. At the time of diagnosis, many patients and their parents lack basic knowledge of fertility issues, resulting in a greater decisional conflict, which ultimately negatively impacts the quality of decision making [26]. The distress associated with non-disclosure is so significant for families that even if an opportunity at diagnosis was missed, the topic should be raised during therapy. There are many reasons not to pursue FP procedures including invasiveness, unproven technology, cost, delay to start a treatment, or relatively low risk of POF; however, we believe that families still deserve hearing the information. They will likely discover examples of OTC (or OC) on the internet and wonder why these topics were not discussed. Furthermore, it is important to continue to remind young women of their reproductive potential and ovarian function assessment once in survivorship clinics, in case these discussions either did not happen at cancer diagnosis, happened with their parents, or have since been forgotten.

Financial Implications

Similar to adult patients, the cost of the procedures and storage present an added challenge regarding FP. These costs are not uniformly covered by the patients’ private insurance or public healthcare, despite the well documented psychological effects of infertility on their well-being [51–53]. There is currently no law that requires third-party reimbursement of the required procedures and storage; and although national non-profit organizations may provide funds to help partially subsidize the cost — especially for procedures in females — costs can be prohibitive [51,54–58].

The expense for OTC can be broken down into three parts: (i) procedure to retrieve tissue (done via laparoscopy under a general anesthesia); (ii) ovarian tissue pathologic evaluation and cryopreservation; and (iii) the annual cost of ovarian tissue storage (potentially for many years) [59,60]. The combined cost of laparoscopy, tissue retrieval, anesthesia, cryopreservation, and the first year of storage can be estimated at $5,538 (USD) [61]. As the procedure is performed using laparoscopy, it can be performed on an outpatient basis to keep costs as low as possible [62]. The annual expense of ovarian tissue storage is approximately $350–$500 [63]. This can represent a heavy financial burden for the patient’s family, especially when the procedure is still deemed experimental and it is unclear whether and when the tissue will be utilized. Lastly, even if the tissue is successfully harvested and cryopreserved, there will be important financial demands when attempting to employ the tissue for assisted reproduction.

Effect of Infertility on Well-being

Infertility has been shown to cause emotional distress, lower quality of life, and can cause psychological disorders, such as post-traumatic stress disorder [41,64]. Specifically in cancer patients, survivors demonstrate a strong desire to have biological children and many have the perception that their cancer experience will make them better parents [31]. For example, cancer places further emphasis on the importance of family closeness, especially child–parent relations [1,41,65]. Emotions of young cancer patients, not given information on FP pretreatment, have been reported to have been ranging from profoundly angry, to disappointed, feeling overwhelmed and distressed [2,3]. It has also been demonstrated that perceived infertility in cancer patients leads to lower rates of marriage and higher divorce rates [9].

Pediatr Blood Cancer DOI 10.1002/pbc
Due to lack of knowledge about FP, patients and their families often have false misconceptions about the methods and expenses associated with FP, and the risk of their own cancer reoccuring due to FP technologies [66]. Knowledge translation is key in all cancer patients regardless of age; in order address these fears and misunderstandings and unnecessary stress.

In pediatric oncology, the illusion of normality remains a significant worry for patients and parents alike: this extends to fertility. For example, if a childhood cancer patient were to be infertile from treatment, they would have to navigate the timing of disclosure of their infertile state to their sexual partner, potentially compromising the normalcy they had gained since being off treatment [67].

Healthcare Professional Perspectives

Despite the knowledge of the negative effects of infertility on well-being, too few pediatric patients are referred for FP procedures. The challenges outlined earlier weigh heavily on the minds of healthcare professionals responsible for the care of pediatric patients. In a US survey of pediatric oncologists, 73% of respondents agreed that all pubertal female patients should be referred to a fertility specialist prior to treatment; however, only 23% of oncologists consistently made the referral [68]. No data were available on the referral rates of prepubertal females, which likely would be significantly lower. Over 90% of pediatric nurses also felt strongly that patients should be informed of FP options; however, 73% admitted that they discussed the topic less than 10% of the time [69].

Several barriers affect healthcare professionals’ likelihood of discussing FP, including lack of knowledge or awareness of expedited FP practices, patient factors (aggressiveness of their cancer, chance of survival), and cost [68,70–72]. Oncologists find it difficult to judge how important FP is to their patient/family if they do not bring up the topic themselves [50]. The failure of patients to ask about FP is often due to their focus on the cancer diagnosis, ignorance of fertility affects of cancer treatment, or fear of FP delaying their treatment leading to higher incidences of morbidity/mortality [38,67,71].

Our experience suggests that nominating an ‘FP Champion’ at each institution is very helpful in addressing these institutional barriers. This healthcare professional can be responsible for keeping up to date with the literature, making formal connections with local fertility units and facilitating dissemination of information to professionals and families, helping with complex referrals, and coordinating care with pediatric urologists and gynecologists who will be responsible for tissue acquisition.

SUMMARY AND RECOMMENDATIONS

In light of the new ASCO guidelines, and given the clear risks to female fertility associated with standard cancer therapies, it is important that physicians understand how to discuss fertility risks and preservation procedures with patients and their families prior to beginning the treatment. It is especially important to include young and adolescent patients in fertility conversations, who often feel they do not have enough say in their medical care.

It is clear that many challenges exist when discussing FP in underage females. The need to better understand the issues associated with FP and pediatric cancer patients is swiftly moving up the survivorship agenda, and based on the reviewed literature, there is a patient’s demand for information on FP from their healthcare team [26,27,31]. Yet there remains a disconnection between this demand and supply of information. Moreover, it is clear that in both Canada and the United States, education materials about FP may not be readily available, or as easily comprehensible as both patients and parents would like [63,72].

The discussion of FP should be included into standard clinical care in all children diagnosed with cancer. The actual process of obtaining services will depend on the many factors discussed previously; however, the delivery of information, should be consistent. Having an “FP Champion” in each center may provide an inexpensive and efficient way to help facilitate information delivery to staff and families. Furthermore, a connection with a fertility clinic has been shown to be a strong predictor of likelihood of FP referral and should be encouraged [73]. Fertility should be revisited in survivorship as there may still be an opportunity for preservation, especially in young women who have declining ovarian function. Regardless of the obstacles in discussing FP, the healthcare professional team is responsible for fully informing their patient and the patient’s family about the infertility risks associated with cancer therapy and FP procedures available, despite their experimental state, in order to ensure equal access to care and overall well-being of survivors and their families. This discussion will change as research progresses.

REFERENCES

Female Fertility Preservation for Pediatric Oncologists


