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New Promising Strategies in Oncofertility

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Abstract

Introduction—Approximately 70,000 adolescent and young adults (AYA) are diagnosed with cancer each year. While advancements in treatment have led to improved prognosis and survival for patients, these same treatments can adversely affect AYA reproductive capacity. Localized treatments such as surgery and radiation therapy may affect fertility by removing or damaging reproductive organs, and systemic therapies such as chemotherapy can be toxic to gonads, (ovaries and testicles), thus affecting fertility and/or endocrine function. This can be traumatic for AYA with cancer as survivors often express desire to have genetic children and report feelings of regret or depression as a result of infertility caused by cancer treatments.

Areas Covered—Emerging technologies in the field of assisted reproductive technology offer new promise for preserving the reproductive capacity of AYA cancer patients prior to treatment as well as providing alternatives for survivors. The following review revisits contemporary approaches to fertility preservation as well newly developing technologies.

Expert Commentary—There are several advances in ART that hold promise for patients and survivors. However there are challenges that inhibit uptake including poor communication between providers and patients about risks and fertility preservation options; high costs; and lack of insurance coverage for fertility preservation services.

Keywords

Oncofertility; cancer; reproductive health; assisted reproduction techniques; fertility

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1. Introduction

Each year approximately 70,000 adolescent and young adults (AYA) are diagnosed with cancer in the United States and over one million internationally [1]. The age ranges of AYA vary by country and organization, but the most commonly used range is 15-39 years old, correlating with traditional reproductive age [1] [2]. While recent advancements in cancer treatment have led to improved prognosis and survival rates for cancer patients, cancer treatments can adversely affect reproductive capacity for AYA. Localized treatments such as surgery and radiation therapy may affect fertility by removing or damaging reproductive organs, and systemic therapies such as chemotherapy can be toxic to gonads, (ovaries and testicles), thus affecting fertility and/or endocrine function. This can be psychologically traumatic for AYA and as survivors AYA often express desire to have genetic children and report feelings of regret or depression as a result of sterility or infertility caused by cancer treatments [3]. Assisted reproductive technologies (ART) such as cryopreservation of gametes implemented prior to the administration of cancer treatment offer an opportunity for cancer patients to potentially preserve their fertility.

Multiple national and international organizations such as the American Society for Clinical Oncology (ASCO) [4], the American Academy of Pediatrics (AAP) [5], the American Society for Reproductive Medicine (ASRM) [6], and the European Society for Medical Oncology [7, 8] strongly suggest AYA and pediatric cancer patients receive counseling about potential loss of fertility and referrals to specialists to learn about fertility preservation options prior to the start of treatment. Yet many AYAs report not receiving counseling [9] and oncologists have reported both lack of training and discomfort in discussing fertility and preservation options.[10] A multi-site medical records abstraction study found that less than 50% of US oncologists documented having a discussion about fertility risk with AYA cancer patients or providing referrals to reproductive specialists [11]. Several studies have shown fertility is a priority for newly diagnosed cancer patients and AYA survivors report distress and anxiety about potential infertility. Additionally many of these survivors and families state they would have liked more information about this topic at the time of diagnosis [12-17]. AYA patients who receive timely fertility counseling, even if they do not pursue fertility preservation, report less regret than those who do not receive information prior to treatment [18, 19]. Rates of uptake of the use of fertility preservation methods for AYA cancer patients are not well documented. Although there is significant variability between centers and regions, it appears that ~30% of eligible AYA male patients bank sperm and 10-25% of AYA females opt for fertility preservation [9, 20-22]. Information is limited because to date there are no United States registries that collect data on the use of ART among patients diagnosed with cancer; however, the fertiPROTEKT network collects this information in German speaking countries [23].

Not all AYA patients will elect to preserve fertility prior to cancer treatments and some may retain their fertility and conceive naturally, while others may pursue alternative family building options post-cancer treatment such as adoption or oocyte donation, still others may embrace child-free living. Ultimately, counseling about potential fertility threats and the offer of fertility preservation/sparing options provides AYA cancer patients the opportunity for informed decision-making.

The following review briefly summarizes the history of fertility preservation including contemporary approaches as well newly developing technologies (Table 1) for AYA cancer patients and survivors and highlights the importance of these options for this population. While fertility loss also applies to pediatric (pre-pubertal) cancer patients, presently all fertility preservation options are experimental for this group. Table 2 provides a list of fertility preservation options for males and females (pre and post-pubertal) as well as alternative family building options.

2. Established Fertility Preservation Methods for Males

2.1 Sperm Banking

Sperm cryopreservation as a fertility preservation option for post-pubertal males with cancer is an effective and efficient way to retain reproductive progeny options. Typically, the semen sample is collected via masturbation and tested for quality to determine feasibility for cryopreservation. The ability to offer this option to patients prior to treatment requires access to a facility that can collect, test, and store the sperm. As a method to facilitate this option, some cancer centers established sperm banking programs for their patients [24].

A recent systematic review of the use and effectiveness of sperm banking programs for cancer patients found an aggregated discard rate of 16% and 49% aggregated utilization rate that resulted in parenthood [25]. Studies examining the rates of men returning to use their cryopreserved sperm are low, ranging from 6% [26] to 10% [27]. The reasons for this low rate of return are not known but could be due to death of the patients or return of spermatogenesis (natural conception) [28, 29].

Sperm banking is generally recommended before the start of cancer treatment, as even a single treatment of chemotherapy can adversely affect sperm quality [4, 30]. Additionally, in some conditions, such as testicular germ cell tumors or Hodgkin's lymphoma, patients are oligo- or azoospermic even prior to treatment [30, 31]. Ejaculated semen yields the highest quality of sperm for cryopreservation, and producing semen via masturbation is the most cost effective means of procuring sperm; however, adolescent and adult males may experience developmental, religious, or physical barriers to producing an ejaculated sample [32-35].

Patients who are unable or unwilling to masturbate may have sperm extracted using microsurgical extraction or percutaneous aspiration of sperm from the epididymis or testis [36]. This is also an option for cancer survivors who are azoospermic, as sometimes there are a few errant sperm in the epididymis that can be collected [37, 38]. Electroejaculation (EEJ) offers an additional alternative for patients unable to masturbate to produce sperm, using electrical stimulation via a rectal probe to stimulate ejaculatory organs [34, 35, 39]. In 2000 researchers began clinical trials testing the viability and motility of cryopreserved and thawed testicular sperm from the testicular tissue, a process known as testicular sperm extraction (TESE). These current clinical trials are typically exclusive to the intracytoplasmic sperm injection (ICSI) procedure for pregnancy whereby a single sperm is injected directly into an egg [40, 41].

Live birth rates for male cancer survivors treated with intracytoplasmic sperm injection (ICSI) are comparable to that of males with general infertility [42]. In 2015, a male cancer patient diagnosed with a rare case of synchronous bilateral testicular cancer and azoospermia underwent TESE resulting in a live birth [43]. Clinical trials by Küpker et al. [44] used thawed testicular sperm in conjunction with ovarian hyperstimulation, finding that retrieved oocytes had 45% fertility and 30% clinical pregnancy rates. In many of these early cases [45], researchers made note of the potential and clinical evidence that pregnancy success rates using thawed testicular sperm were lower than rates with ejaculated sperm [46]. One study reported pregnancy rates of 44.2% for fresh and 43.6% for frozen sperm [47]. Though underused, sperm cryopreservation is still the primary fertility preservation technique for post-pubertal males; projected rates of uptake of sperm cryopreservation in male cancer patients are ~30% [20-22].

3. Experimental Fertility Preservation Methods for Males

3.1 Testicular Tissue and Sperm Extraction and Cryopreservation

Testicular tissue cryopreservation is an experimental fertility preservation method for pre- and post-pubertal males. For post-pubertal males, testicular tissue is surgically harvested and cryopreserved using slow freezing or vitrification [48]. Pre-pubertal boys who have not undergone spermatogenesis may elect to preserve spermatogonial stem cells (SSC), an experimental therapy that also carries the theoretical risk of “reseeding” malignant cancer cells, based on data from females [49]. The European Society of Human Reproduction (ESHRE) recommends that “in cases where no semen can be collected, the experimental techniques of cryopreservation of testicular tissue or suspensions of immature testicular cells including SSCs should be considered.” They further suggest that to “minimize trauma to the patient, the surgical recovery of testicular tissue should be combined with other interventions requiring anesthesia, such as bone marrow sampling or implantation of venous ports” [6, 50]. ASRM recommends that young boys and their parents receive counseling about the benefits of banking testes tissue for cryopreservation and later transplantation and that such offer be available only with an approved IRB protocol [51]. It should be noted that testicular tissue has a superior post-thaw viability rate (95%) as compared to SSC (66%) [52]. Reproductive potential of cryopreserved immature testicular tissue remains experimental and no one preservation protocol has been shown to be superior over any other published method.

4. Established Fertility Preservation Methods for Females

4.1 Embryo Cryopreservation

Research on human embryo cryopreservation was developed in the late 1980's following clinical trials of mouse oocyte cryopreservation. Embryo cryopreservation consists of the use of fresh or previously frozen oocytes fertilized with sperm in-vitro and then cryopreserved when the developing embryo reaches the blastocyst stage. Reviews by Loutradi et al (2008) and AbdelHafez et al (2010), suggest human embryos preserved through vitrification yield higher survival rates post-thaw than those preserved using a slow-freeze method [53, 54]. As a method of fertility preservation, embryo cryopreservation

yields pregnancy rates as high as 59% and a live birth rate of approximately 50% [55], depending on factors such as the age of the woman at the time of cryopreservation. As data in the US are not collected specifically among cancer patients and the use of cryopreservation, it is not known how or if these rates vary in this population. However, this method may pose several challenges to newly diagnosed cancer patients, as it requires contribution from a partner or sperm donor, as well as a post pubertal egg. In the US data are not collected specifically among cancer patients for the use of cryopreservation, it is not known how or if these rates vary in this population.

Additionally, the ability to cryogenically preserve human embryos has been associated with multiple ethical concerns such as ownership of embryos in the event of dissolution of a partnership or marriage or death of one partner, what to do with unused embryos, the use of embryos for research purposes or the legality and morality of donating embryos (adoption) to other families.

The 1989 case of *York vs. Jones* sparked the first debate over ownership of cryopreserved embryos and created legal turmoil for IVF patients, laboratories, and clinicians [56]. To summarize, the York's cryopreserved embryos at The Jones Institute for Reproductive Medicine. After repeated unsuccessful attempts at pregnancy, the couple transferred their remaining frozen embryo to a facility in their state of residence, California. The Jones Institute refused to make the transfer claiming this was a violation of the signed consent form, which only allowed three options for the fate of unused embryos: embryo donation to another family, embryo donation to science, or thawing the embryo without implantation. The consent form did not provide language for the allowance or restriction of institutional transfer of the embryo. Ultimately, the York's successfully defended their right to ownership of their embryo, and the court ruled the Jones Institute committed a breach of contract. This case continues to be cited in legal disputes over human embryo ownership.

4.2 Oocyte Cryopreservation

Oocyte cryopreservation is only an option for post-menarchal females, however this method offers an alternative method to embryo cryopreservation, and may be ideal for cancer patients who do not have a readily accessible partner or for whom the use of donor sperm is unacceptable. Oocyte cryopreservation is more precarious compared to embryo cryopreservation as it involves a higher risk of damage during the preservation process and yields slightly lower overall pregnancy rates. Oocyte cryopreservation collection success has shown freeze-thaw survival rates of 90% to 95%, and pregnancy-per-transfer rates of 50% to 65% in prospective studies [35, 55, 57-59]. Most recent statistics on success rates of oocyte cryopreservation rates are combined with embryo cryopreservation rates; however, data from the Italian national registry of IVF centers suggests that the rates of live births resulting from oocyte cryopreservation were slightly less than those of embryo cryopreservation [60, 61]. Live births from oocyte cryopreservation with vitrification have increased with newer techniques and current studies indicate no difference in perinatal outcomes or congenital anomalies among children born from frozen oocytes compared to those born from fresh IVF cycles or spontaneous pregnancies [62]. Presently no US registries collect data regarding pregnancies and/or live births from oocyte cryopreservation among cancer patients/

survivors. It is recommended that oocyte cryopreservation in the oncology population be presented with appropriate counseling [60]. Whereas oocyte cryopreservation was once considered an experimental procedure, requiring an approved IRB protocol, it is now widely available among reproductive endocrinology and infertility centers. ASRM updated their guidelines and recommendations to endorse egg freezing as an established method of fertility preservation for cancer patients in 2013, paving the way for potential insurance coverage [63].

Whether for oocyte or embryo cryopreservation, the use of ovarian stimulation has caused concern for women with hormone dependent cancers, such as breast cancer [64]. However, current practice supports ovarian stimulation utilizing tamoxifen or letrozole for patients with estrogen-sensitive cancers [64, 65]. A recent study in the Netherlands found no significant differences in breast cancer risk between non-IVF and IVF-treated women (73). Other studies have similarly reported little or no increased risk of recurrence (74), signaling relative safety.

4.3 Oophoropexy

Pelvic radiotherapy may lead to infertility in reproductive age female patients [66]. Oophoropexy, or ovarian transposition, offers an alternative method of fertility preservation for female patients undergoing pelvic radiation. In a non-oncologic context, oophoropexy is used to prevent recurrent ovarian torsion. Even in instances in which ovaries are outside of a direct radiation path, scatter doses can still cause ovarian failure in up to 50-90% of cases [67]. Oophoropexy removes ovaries from the direct field of radiation treatment (laparoscopically or with the use of mini-laparotomy), using placement that varies according to the patient's anatomy and the planned treatment [68]. At the conclusion of treatment, the ovaries are returned to their original position to allow return of reproductive function. Success rates range from 60 – 89% and are largely dependent on patient age, radiation dose, site, type of treatment and whether or not chemotherapy is also integrated in the treatment plan [69-71]. Reproductive and oncologic outcomes of robotically assisted laparoscopic ovarian transposition have proven this modality is safe. A recent study found that the use of robotically assisted laparoscopic ovarian transposition leads to preservation of ovarian function in two-thirds of patients with lower gastrointestinal cancer undergoing pelvic radiotherapy [72]. To prevent ovarian remigration, it is recommended that oophoropexy be timed to coincide with treatment. While oophoropexy is not feasible when chemotherapy is administered, it can be considered for pre- and post-pubertal females undergoing radiation therapy [69].

4.4 Pre-Implantation Genetic Diagnosis (PGD)

Pre-implantation Genetic Diagnosis (PGD) allows for genetic testing of embryos. Using ART techniques, embryos are tested to diagnose the presence or absence of specific inherited mutations from either parent's genetic material. Typically, embryos that do not carry the specific mutation are subsequently transplanted to a woman's uterus for implantation, however some couples do opt to implant affected embryos or those with inconclusive results; such decisions have been deemed ethical [73]. PGD is beneficial for individuals with genetic conditions such as familial adenomatous polyposis (FAP) and

hereditary cancer syndromes such as BRCA and retinoblastoma, allowing for pre-emptive identification of inherited mutations and avoiding the dilemma of decision making concerning potential termination of the pregnancy. Limitations of PGD include additional time and expense for testing, in addition to standard in vitro fertilization expenses. The accuracy of these procedures depends on the technique, the type of condition being tested, the age of the parents, and the experience of the laboratory. In general, false positive rates have been estimated between 0 and 4.9% [74]. False negatives range from 1 to 4.9% [75].

5. Experimental Fertility Preservation Methods for Females

5.1 Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation attempts to preserve eggs within the ovarian follicles, where a large number of eggs are housed. Tissue is harvested prior to cancer treatment laparoscopically and frozen. After the conclusion of treatment, the tissue is thawed and transplanted back into the patient. Efficacy of the ovarian tissue increases when it is returned to the original site of the biopsy, where remnants of the ovarian cortex are still present [76]. Ovarian tissue preservation offers distinct advantages, including no requirement for prior ovarian stimulation (thus accommodating immediate commencement of cancer therapy), and promotes recovery of endocrine and reproductive functioning, although it is not currently being used for these purposes in the United States [77].

Pregnancy rates of ~25% have been reported cancer survivors [35, 55]. In a recent study among post-menarchal women who had completed cytotoxic therapy, the live birth rate was 23% after a first transplantation and premature ovarian insufficiency [78]. According to the ASRM, ovarian tissue cryopreservation is one of the best options for female cancer patients who require immediate cancer therapy and do not have time to pursue established methods of fertility preservation such as embryo or oocyte cryopreservation or who are pre-pubertal and do not have mature oocytes to harvest [69, 79]. In 2016, the first live birth resulting from cryopreserved pre-pubertal tissue was reported in London [80].

New research suggests that conducting oocyte aspiration in post-pubertal females before ovarian tissue cryobanking is safe and yields more oocytes with a better maturation rate than ovarian tissue cryobanking alone [76]. When the transplanted tissue is sufficiently vascularized and supported by functioning ovaries, spontaneous pregnancy is possible. While this technology carries great promise, it also carries a potential risk of “reseeding” malignant cells from the transplanted tissue for women diagnosed with ovarian and hematological cancers, thereby increasing the risk of recurrence [79].

5.2 In Vivo Maturation

In-vivo maturation (IVM) is an experimental fertility preservation method for post-pubertal females in which immature oocytes, from hormonally unstimulated or minimally primed follicles are collected. Immature oocytes are collected from small antral follicles before spontaneous ovulation, and oocytes then mature in vitro after which routine in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) and embryo transfer can be performed. The immature eggs are matured in the laboratory for 24-48 hours using culture

medium with added small quantities of hormones. The procedure is safe and because hormonal stimulation has not been done, the risk of ovarian hyperstimulation syndrome theoretically is reduced. IVM may also be less costly as there is no need for medications to stimulate the ovaries.

The first pregnancy from IVM oocytes occurred in 1991 [81], and pregnancy success rates are comparable to IVF [82]. IVM also requires no waiting period prior to the commencement of treatment. Xiao and colleagues recently proposed a two-step follicle culture process thought to promote growth and hormone production and further support follicle and oocyte maturation [83]. Recent studies have proposed utilizing IVM in concert with other fertility preservation techniques such as ovarian tissue preservation [84]. Such an approach, utilizing vitrified immature oocytes in pre-pubertal cancer patients avoids the risk of “reseeding” cancer.

IVM may also be an ideal technique for women requiring emergency oocyte preservation prior to the start of treatment, especially in cases where there is not adequate time to undergo ovarian stimulation. In a recent study comparing IVM rates of cumulus-oocyte complexes (COCs) between breast cancer patients seeking urgent fertility preservation and those recovered in the follicular or luteal phase of a cycle, maturation rates were comparable (43.1%) [85]. IVM is still experimental and there is a dearth of research on outcomes, however new technological advancements, such as pretreatment with GnRHa [82], may refine the utility of this technique.

6. Methods for Alternative Family Building

6.1 Donation of Reproductive Gametes

Due to the advancements in cryotechnology and assisted reproduction in humans, gametes can be stored for various periods of time to preserve reproductive potential for personal future use, or donated to others.

6.2 Egg Donation

In the event that a woman can no longer produce eggs or does not have viable eggs, she may elect to use oocytes donated by another woman. The use of egg, or oocyte, donation began around the early 1980s, and the first successful pregnancy from a donated egg occurred in 1984 [86]. Prior to this technique, frozen embryo donation was the only possible option to achieve pregnancy for a sterile woman.

Selection of an oocyte donor is left primarily to the individual or couple who receive the oocyte. Since the late 1980s and continuing today, research on oocyte donor selection emphasizes the need for medical and psychosocial considerations when choosing a donor [87, 88]. For both the recipient of donated oocytes and the donor, a standard medical examination, reproductive history, and psychological evaluation are recommended. It is also recommended that a psychological evaluation of the spouses be conducted. The ASRM also notes that state requirements may differ from their recommendations, and those held by the FDA, so laboratories must be aware of the guidelines specific to their state [89].

There are some ethical concerns with the use of egg donation, such as the ability for anonymity of the donor, compensation for egg donation, and retraction of waiving parental rights on behalf of the donor. In 1990, the American Fertility Society (AFS) explicitly denied the compensation of egg donors [90], but currently compensation is generally offered to egg donors. The Ethics Committee of the ASRM has guidelines for the process and amount of compensation for oocyte donors, as well as caution for repetitive donors [91].

6.3 Sperm Donation

Men who are sterile or who have a history of familiar deleterious genetic mutations and do not wish to pass this on to future progeny have the option to use donor sperm to impregnate their partner. Sperm donation is a process that transplants the donor sperm either directly to a woman (insemination) or to harvested oocytes via IVF, to achieve pregnancy. The use of donor sperm to overcome human, male infertility can be traced back as far as 1884, following the first use of artificial insemination by physician J. Marion Sims in 1866 [92].

Sperm donation allows for several advantages, such as the ability to allow other individuals, related or not, access to gametes to overcome an infertility issue. When presented with time constraints and lack of privacy, cancer patients may opt to use donated sperm from a sperm bank or close friends. Men can also receive payment for donating sperm.

In the United States, sperm donors can choose to remain anonymous. There are ethical considerations regarding anonymity of the donor, a practice exclusive to the United States. Anonymous sperm donation, which may inhibit the ability for offspring to know their medical history, has resulted in serious ethical issues such as paternity lawsuits, the ability for a single donor to father over 100 children [93], and consanguinity resulting from unintentional inbreeding [82].

6.4 Gestational Surrogacy

A gestational carrier, or surrogate, is “a woman who bears a child who is genetically unrelated to herself for an individual or couple who intend to be the legal, rearing parents(s) of the child” [94]. Gestational surrogacy is an optimal alternative for female cancer patients who have undergone hysterectomies or pelvic/abdominal radiation, or for any woman who cannot carry a pregnancy. Unlike traditional surrogacy, which used the genetic material (oocyte of the gestational carrier), gestational surrogacy utilizes the gametes from the intended parents. Gestational surrogacy requires in vitro material to transfer gamete material from the mother and father to the gestational carrier for transplantation and pregnancy.

Gestational surrogacy raises a number of ethical concerns for the rights of the carrier, including reasonable economic compensation, access to medical treatment, psychological support and informed consent. State laws regarding gestational surrogacy continue to develop and often require the carrier use none of her own genetic material to avoid potential legal issues regarding kinship and parentage rights. With the revision and amendment of the Uniform Parentage Act in 2000 and 2002, respectively, and the Model Assisted Reproductive Technologies Act (MARTA), the gestational carrier agreement, or consent form, received more legitimacy in legal disputes [95].

However, state laws remain highly variable, and not all are subject to the gestational agreement prior to the ART procedure. There are 11 states that adopted the Uniform Parentage Act: Alabama, Delaware, Illinois, Maine, New Mexico, North Dakota, Oklahoma, Texas, Utah, Washington, and Wyoming [96], and other states have some form of a similar act that serves a similar function. What this means is that not all 50 states define the parent-child relationship in the same way, especially when it comes to ART with the use of a third-party.

This lack of statutory congruence can be a particularly troubling concern considering potential for inter-state surrogacy agreements, as some states, such as Washington, prohibit the compensation of a gestational carriers and uphold that restriction in cases of inter-state agreements [97]. Interstate agreements can also affect the legal parentage of the resulting child in surrogacy arrangements. For example, Arizona and New York forbid gestational surrogacy contracts and in New York, anyone involved in the process (lawyers, couples) can be fined. In this example, a couple wishing to use a carrier would have to find one in a state allowing surrogacy and in some cases, legally adopt the child once he or she is born [98].

6.5 Embryo Adoption

Embryo adoption is the process of an individual or couple using a frozen embryo from another couple; the embryo is implanted in the recipient woman's uterus. Typically, these frozen embryos are “surplus” from the donating couples' IVF attempt. This process has also been described as giving birth to your adopted child. In contrast to traditional adoptions, the human embryo is defined as property in most states, with only a few states, such as Louisiana, designating the embryo as having “juridical personhood” [99, 100]. Embryo adoption and ownership is governed by property law more often than family law. Embryo adoption may be of interest to cancer survivors who want the experience of pregnancy and giving birth, but are unable to conceive traditionally. Couples who have concerns about deleterious familial genetic mutations also express interest in embryo adoption.

There are some benefits to embryo adoption over traditional adoption. There is no danger the birth mother will change her mind and there are not the high fees and long wait times associated with international or private adoption. There is roughly a 40% success rate with embryo adoption to yield a live birth [101]. Potential adoptive parents often worry that children born from frozen embryos are at a higher risk of birth defects. Studies have shown children born from cryo-preserved embryos do not experience birth defects at any higher rate than children conceived naturally [102].

There are many legal disputes referring to the status of legal parentage of the recipient of the embryo and the resulting child. The use of a written, signed contract in legal disputes referring to parentage rights, ownership of the embryo, and especially disposal methods of surplus embryos is a growing trend, but one that some law researchers suggest can be misleading to the consenting parties as they navigate through the laborious process of assisted conception [103].

6.6 Traditional Adoption

Adoption is an alternative for parenthood for everyone, regardless of a cancer diagnosis. Some individuals and couples prefer traditional adoption over having their own genetic child for a variety of reasons and this trend is on the upswing [104]. US domestic adoption is not restricted to traditional male/female couples and is permitted for single people as well as same-sex couples. International adoption is usually not permitted to anyone other than traditional heterosexual couples and has become more restrictive for US citizens in the past 5 years [104].

Adoption is a viable option for cancer survivors who did not have an opportunity to preserve gametes or are poor candidates for ART. Cancer survivors may choose to research adoption option in lieu of undergoing invasive procedures or after failed attempts to utilize ART. Generally, AYA survivors should be cancer-free for five years before attempting adoption.

A recent study by Quinn et al evaluating a national training program for oncology nurses, identified that adoption can be challenging for cancer survivors and they may face obstacles not experienced by those without a cancer history [105]. This study found some agencies restrict adoption to cancer survivors or require them to provide a letter from their physician attesting to their cancer-free status [105]. The publication noted it was potentially discriminatory, likening it to restricting employment opportunities for people with disabilities and in violation of the Americans with Disabilities Act of 1990 [105]. The authors contend “there is no evidence to suggest that a cancer survivor or a parent with any kind of disability is any less able than an individual without a disabling health condition or cancer history to raise children in a loving, caring, and protective manner.” [105].

7. Future Directions

7.1 Expanding knowledge about current technologies

Just as the status of oocyte preservation has changed from “experimental” to “established” in the past five years, studies assessing outcomes of experimental procedures (such as oocyte and testicular tissue preservation) should be prioritized over the next decade. These methods will inevitably be used more and more frequently, given that they are the only option for males and females prior to puberty, and also for post-menarchal females when cancer treatment is urgent. Additionally, more research is needed to better understand perceived benefits and barriers to fertility preservation, in addition to examining why utilization of stored sperm is so low.

Currently, the majority of research with regard to fertility, particularly among childhood cancer survivors, demonstrates regret about missed opportunities for fertility preservation prior to treatment. Little is known about biological and psychosocial outcomes among youth who do opt for various fertility preservation technologies, both established and experimental. Psychosexual development also remains understudied in this population, and has important implications for fertility and family planning. Finally, although the optimal time for fertility preservation is generally prior to treatment initiation, there may be cases in which post-treatment preservation can and should be considered in both males and females, though data regarding success rates are currently limited [16, 106].

7.2 Developing and utilizing new technologies

Several other technologies hold promise for new directions in fertility preservation for AYA with cancer. While gonadotropin-releasing hormone (GnRH) agonists have shown conflicting results over the years [107] and were not recommended in the most recent ASCO guidelines of 2013, a few novel approaches have since shown some success. GnRH agonists have been used as part of chemotherapy regimens in females to lower the toxicities of chemotherapy on ovarian follicles and oocytes. Two recent studies demonstrated protective effects of GnRH agonists, with a highly significant reduction in amenorrhea and ovarian insufficiency in women with breast cancer [108, 109]. Other studies have also examined the use of agents that may protect oocytes against gonadotoxic therapies. For example, a mouse model study showed the drug imatinib mesylate had a clear protective effect and reduced the percentage of unhealthy follicles in mice where oocytes cisplatin was administered [110]. These findings are promising and indicate that different chemotherapy drugs, such as cisplatin and doxorubicin, may induce follicle loss using different pathways and require tailored treatments to protect the ovary.

The recent design of a diagnostic panel of breast cell contamination by reverse-transcription polymerase chain reaction (RT-PCR), immunohistochemical analysis, in vitro invasion assay and xenotransplantation assayed in ovarian tissue from breast cancer patients may allow for safer ovarian tissue cryopreservation and transplantation in breast cancer survivors [111].

The first uterine transplant resulting in a successful pregnancy occurred in 2013 in Sweden, although the woman was not a cancer patient [112]. To date a clinical trial has shown that among 7 women receiving a successful uterine transplant, 4 have resulted in a live birth [113]. This holds future opportunity for women whose uterus was removed or was damaged by cancer treatment, to experience pregnancy. Researchers are also exploring the creation of an engineered ‘artificial ovary’ for transplantation [114]. “This artificial ovary comprises follicles isolated from a patient’s cryopreserved ovarian tissue, along with other ovarian cells, which are assembled on a 3D matrix scaffold; the resulting structure would allow follicles to grow within an ovary-like environment and would potentially restore both fertility and endocrine function once transplanted into the patient” [115].

A highly novel but early stage investigation is the use of oogonial stem cells embryonic stem cells or pluripotent stem cells, which also carry genetic material. These methods have been successful in mouse models but have not yet been explored in humans and their use is controversial [116].

Fertility preservation modalities have greatly evolved over the last decades, with newly emerging technologies providing ever-increasing options for cancer patients. While additional research is needed to explore the viability of experimental treatments, current findings in oncofertility have signaled rapid innovation in fertility preservation modalities. The potential for future reproduction in those experiencing infertility due to cancer or other gonadotoxic treatments is a vibrant field, holding great promise as the numbers of survivors also increases.

8. Expert Commentary

While several emerging technological advances in ART hold potential for patients and survivors, there are challenges that inhibit uptake. The first is lack of communication about fertility preservation. Multiple studies have shown patients do not recall learning about potential infertility and an equal number of studies show oncology providers are not comfortable discussing this topic with patients. Whether or not providers are talking to patients but they do not remember, is not known. It has been well established that patients often do not hear anything else after they learn they have cancer. At the same time, provider documentation of discussions of fertility and referrals to specialists is low [11], with less than 50% of eligible patients having a note in their chart about fertility discussions or referrals.

Providers' discomfort on the topic can be attributed to many factors such as lack of knowledge, belief the patient is ineligible for preservation or disinterested, or concerns about the patients' prognosis. However, a recent study showed patients who learned about fertility loss and prevention prior to their treatment had less regret and grief, even among those who opted not to preserve fertility, than those for whom fertility was not discussed. There are training programs to help providers improve their communication skills in these areas. An example of one such program is the ENRICH/ECHO [117], which trains nurses, social workers, psychologists and physician assistants through on-line training. Other programs such as ASCO's Focus under Forty [118] offer training aimed at physicians.

Communication is a key part of improving reproductive options in oncofertility but learning about it is only half the battle. The costs for using fertility preservation options such as sperm banking (average cost \$350, yearly storage fee \$300) and oocyte cryopreservation (average costs \$10,000, yearly storage fee \$800) are often cost prohibitive for many young patients. It is important to note these fees are solely for the collection and storage of gametes; additional costs are involved when survivors return to use their stored gametes to attempt pregnancy. In most cases, these costs are not covered by insurance [119], although some fertility centers offer reduced pricing for patients with cancer. Recently several large employers such as Facebook and Google [120] have offered "social egg freezing" at no charge to their female employees, sparking increased debate over the feasibility of providing insurance coverage for fertility preservation utilized for cancer-related infertility.

Even when patients are educated about potential loss of fertility and reproductive options, finding a qualified oncofertility specialist in the midst of a health crisis can be challenging. Some cancer centers have established oncofertility programs for their patients with navigators, or alliances with academic physicians [121, 122]. In the absence of these types of arrangements, a new GPS locator system – Fertility Scout [123] – enables patients or providers to identify specialists for the specific service needed based on geographic location and an appointment can be scheduled online, within 48 hours.

Finally, decision-making concerning fertility preservation is a highly complex process, even if patients are educated about their options and have the financial means to utilize fertility preservation. Decision-making processes for females is especially difficult for females as

fertility preservation procedures requires invasive procedures. In addition, there are several ethical concerns for patients and their providers to consider. Several female cancer survivors have faced the dilemma of not using their stored oocytes or embryos because they never found a partner and elected not to pursue parenting alone. For other couples, the end of the relationship led to legal battles over the use or destruction of stored gametes. In other cases, patients may have completed their families, either through natural conception or through the use of fertility preservation, and are subsequently faced with the need to decide the fate of remaining stored gametes. Patients may feel stymied by the choice to either destroy or donate their unused gametes to other couples.

Despite the challenges of fertility preservation and family building for cancer patients and survivors, the benefits of uptake outweigh the barriers. Patient education and shared decision making concerning fertility preservation uptake do not occur routinely but are ideals that all providers should strive for when counseling cancer patients. Even in the event a patient's fertility can't be saved, research has shown that patient's experience less regret and depression when properly informed of risks, benefits and options.

9. Five-year view

As we have noted in our review, reproductive science has leapt forward dramatically, enabling exploratory attempts to engineer the female ovary along with successfully yielding a live birth from pre-pubertal tissue cryopreservation. We speculate that these developments will continue to progress over the next five years, bringing scientists even closer to the knowledge needed to engineer replacement gonadal organs and tissues that may be implanted and utilized once a patient's treatment has ended. We further prognosticate that clinicians will develop less invasive means of collecting reproductive materials, and that newly emerging technologies will allow for the engineering of new regenerative matter yielded from smaller samples. It is also likely that new protective mechanisms, beyond ovarian transposition may be developed to simulate a protective shield against potentially toxic cancer treatments. Given the shifting landscape of social change and demographic data revealing an increasing shift in older-aged first time mothers, it is also likely that social egg freezing will routinely be covered by employers and potentially reduce costs associated with this procedure. As cost continues to be a barrier in uptake in fertility preservation services, insurance coverage is pertinent for cancer patients [124]. Currently, advocacy groups such as the Alliance for Fertility Preservation, are making efforts in some states to pass legislation that would ensure fertility preservation for cancer patients is covered by insurance companies [125]. It is our hope and belief that in the next five years, these legislative efforts will have come to fruition and that this initiative continues in an upward trajectory.

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10. Key issues

- Cancer and associated treatments can render AYA and pediatric patients sterile or with sub-fertility. Loss of fertility and the inability to have a biologic child negatively impacts quality of life in AYA survivors.
- There are established methods to preserve fertility for post-pubertal patients. The only established fertility preservation method for post-pubertal males is sperm cryopreservation. The established methods for post-pubertal females are oocyte and embryo cryopreservation and in certain cases ovarian transposition, shielding, and reproductive sparing surgery.
- There are experimental methods for pre-pubertal children. These include testicular tissue cryopreservation for boys, and ovarian tissue cryopreservation for girls. Post-pubertal women may also consider ovarian tissue cryopreservation as a fertility preservation method and to reduce the effects of premature menopause. All experimental methods require an approved IRB protocol and informed consent.
- The field continues to move forward and there are new techniques on the horizon such as: improvements in GnRH agonists as part of chemotherapy regimens, in vitro invasion assay and xenotransplantation assayed uterine transplants, and the use of oogonial stem cells, embryonic stem cells or pluripotent stem cells.

Table 1
Chronology of Assisted Reproductive Technology

Date	Type of Technology
1600s	Use of cryobiology for animal husbandry
1866	1 st use of artificial insemination
1880s	Use of donor sperm for artificial insemination
1949	Use of glycerol for increased storage of genetic material via cryopreservation
1950s	Animal trials for ovarian tissue cryopreservation
1953	Successful retrieval of frozen sperm and successful pregnancies of frozen sperm; use of liquid nitrogen (LN ₂) for increased storage with decreased motility loss
1958	Freezing and thawing of viable mouse oocytes
1977	1 st successful birth of a mouse from thawed oocyte
1980s	Human embryo cryopreservationHuman oocyte donation
1983	1 st pregnancy from donated egg
1990s	Use of nitrogen vapor to reduce viral cross-contaminations in human spermClinical trials of pregnancy success from surgically removed testicular sperm (non-frozen)
1996	Cryopreservation of human ovarian tissue for fertility preservationCryopreservation of testicular tissue and extraction of testicular sperm for fertilization using intracytoplasmic sperm injection (ICSI)
2000	Clinical research for testicular tissue (testicular sperm) cryopreservation
2004	1 st live birth from ovarian tissue cryopreservation (Belgium)
2013	Reclassification of oocyte cryopreservation as non-experimental.

Table 2
Fertility Preservation and Alternative Family Building Options Requirements, Benefits, and Barriers

Requirements		Benefits	Barriers
Males			
Sperm Cryopreservation	Post-pubertal	Low cost, out or in-patient banking	Patient may not be well enough, masturbation may not be acceptable
Sperm extraction	Post-pubertal	Viable option if masturbation is not possible or acceptable	In-patient surgery
Testicular tissue cryopreservation	Pre-pubertal	Unknown	Experimental
Females			
Ovarian transposition	Pre or post pubertal	Option for those receiving pelvic radiation only	Out-patient surgery
Fertility sparing surgery	Post pubertal	Pregnancy rate~50%, preserve reproductive capacity	Only for certain GYN cancers
Embryo cryopreservation	Post pubertal, donor sperm or partner	Pregnancy rate~60%, standard procedure	High costs, time required may delay treatment, sperm donor or partner may not be acceptable
Oocyte cryopreservation	Post-pubertal, ovarian stimulation	Pregnancy rate~50%, standard procedure, culturally sensitive, no donor required	High cost, time required may delay treatment
Ovarian tissue cryopreservation	Pre or post pubertal	Pregnancy rate~25%, will not delay treatment	Out-patient surgery, possibility of reseeded, experimental
Alternative Family Building Options			
Adoption private or state agency	Varies by state	Adopt infants through teens	Costs, may be extra challenge for cancer survivors
Gestational Carrier	For women who cannot or should not carry a pregnancy	Can use own gametes or donor	Costs, state laws vary
Donor egg or sperm	Varies by state	Donor banks can select similar racial/ethnic characteristics	Costs