


Evidence-Based Recommendations for Fertility Preservation Options for Inclusion in Treatment Protocols for Pediatric and Adolescent Patients Diagnosed With Cancer

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Abstract

As survival rates improve for pediatric cancers, increased attention has been paid to late effects of cancer therapy, in particular, infertility. Fertility preservation options are available for pre- and postpubertal cancer patients; however, many providers lack knowledge regarding options. The aim of this article is to provide a comprehensive synthesis of current evidence and recommendations regarding fertility preservation options for children, adolescents, and young adults undergoing cancer treatment. A systematic search was performed to identify fertility preservation evidence. Fifty-three studies and 4 clinical guidelines were used for the review. Final recommendations consisted of 2 strong and 1 weak recommendation for both female and male fertility preservation options. The treatment team should be knowledgeable about fertility preservation so that they can educate patients and families about available fertility preservation options. It is important to consider and discuss all available fertility options with patients at the time of diagnosis.

Keywords

fertility preservation, cancer treatment, pediatric, adolescent, young adult

When chemotherapy was introduced into the care of children with cancer, the goal was focused solely on achieving remission. As multimodality therapies advanced and became more refined, survival rates rose, and the long-term consequences of cancer-directed therapies became more apparent. Subsequently, attention shifted to identifying and minimizing these long-term effects when possible. Long-term complications include effects on reproductive capacity following exposure to radiation to the gonads or pituitary or from the use of chemotherapy, particularly alkylating agents (Green et al., 2009, 2010). Patients and families have identified the threat of infertility as a major concern, and conversely, knowledge that efforts have been made to preserve future fertility can serve as a stimulus of hope (Saito, Suzuki, Iwasaki, Yumura, & Kubota, 2005; Schover, 2009). In patients determined to be at risk, assisted reproductive technologies, such as cryopreservation of gonadal tissue or gametes, can be used to safeguard against future infertility (Levine, Canada, & Stern, 2010).

Many challenges exist in providing comprehensive fertility preservation (FP) counseling and services to children and adolescents with cancer. Specific challenges include determining who is at risk for alterations in reproductive capacity and appropriate interventions based on sex, age, risk, and available patient resources. Research focusing on FP has confirmed that oncology patients and

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their health care team are often not aware of the effect of cancer treatment on fertility or the preservation options available (Woodruff, 2007). Educating patients and families on the side effects of treatment and interventions to minimize side effects is a primary responsibility of pediatric oncology health care providers. The goal of this article is to provide a comprehensive synthesis of current evidence for pediatric oncology health care providers about the FP options available for the pediatric, adolescent, and young adult patient undergoing treatment for a pediatric malignancy.

Evidence Review Methods

Evidence-Based Practice Review Team Selection and Composition

A call for evidence-based practice (EBP) projects was disseminated to the Children's Oncology Group (COG) Nursing Discipline membership, after EBP topic areas were developed to align with the Nursing Discipline's 5-year blueprint and organizing framework (Kelly, Hooke, Ruccione, Landier, & Haase, in press; Landier, Leonard, & Ruccione, 2013) and vetted with COG leadership and other key stakeholders (ie, COG committees such as the Survivorship-Outcomes Committee). The project team leaders (A.F. and B.L.) applied to develop evidence-based fertility preservation recommendations for children and adolescents with cancer, and after a competitive selection process, the proposal was selected for development. The evidence-based practice team for this project consists of 2 team leaders, 5 team members, and a group mentor. Members of the team include nurses, nurse practitioners, and 1 physician, all with interest and expertise in fertility preservation in this population. Team members are based at COG institutions across the United States. The group mentor is a doctoral prepared nurse who has experience with EBP reviews.

Question Development

The clinical concerns regarding fertility preservation were formed into PICOT questions to focus the systematic review. PICOT stands for Patient, Intervention or Issue of Interest, Comparison, Outcome, and Time (Melynck & Fineout-Overholt, 2011). Team leaders, with help from the group mentor, developed the following 2 PICOT questions to guide the EBP review: In pediatric and adolescent and young adult (AYA) individuals, what fertility preservation options can be used in pre- and postpubertal females immediately following a cancer diagnosis, before the initiation of cancer treatment? In pediatric and AYA individuals, what fertility preservation options can be used in pre- and postpubertal males immediately

following a cancer diagnosis, before the initiation of cancer treatment?

Literature Search and Analysis

A systematic review of the literature was carried out by the team leaders and confirmed with a medical librarian. Databases used in the comprehensive review of the literature included Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, PubMed, OvidMedline, and the Cochrane Database of Systematic Reviews. The following search terms were used: cancer, carcinoma, neoplasm, malignant, tumor, oncology, fertility, semen, sperm, ovary, ovarian, preservation, cryopreservation, and transposition. In addition, reference lists of key articles were hand searched. Limits to the searches included the English language, any publication between the years 2002 and 2013, and involvement of human subjects.

A total of 1108 potential studies were identified from the searches. Articles were initially reviewed by title, and 850 articles were eliminated because they were not relevant to the PICOT questions. A total of 258 abstracts was screened. Abstracts were included in the EBP review if the study met the following inclusion criteria: (a) designed as research-based studies, case studies, systematic reviews, or meta-analyses, (b) consisted of study participants with a mean age of younger than or equal to 30 years, and (c) composed of a sample population where greater than 50% had a pediatric cancer diagnosis. Exclusion criteria included the following: (a) basic review article or (b) study participants who had ovarian carcinoma or breast cancer (diagnoses typically found in the adult population). Based on these criteria, 157 of the 258 abstracts were excluded. The remaining 101 articles were reviewed in full text for inclusion and exclusion criteria, and 53 met criteria for inclusion in this EBP review. Thirty studies discussed male fertility preservation options, and 23 studies examined female fertility preservation options. Search results are shown in Figure 1.

The 53 studies included in the review were divided into 2 groups, male and female, based on the sex of the patients studied and the fertility preservation option(s) discussed in the article. The articles were distributed among team members to review, summarize into matrix tables, and evaluate the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria. Using GRADE, literature is rated according to quality of evidence and labeled as high, moderate, low, or very low (Guyatt et al., 2011). The team leaders and mentor used summaries of the literature to create synthesized statements about each topic and used quality ratings to determine 1 overall quality of the evidence. Recommendation statements were then

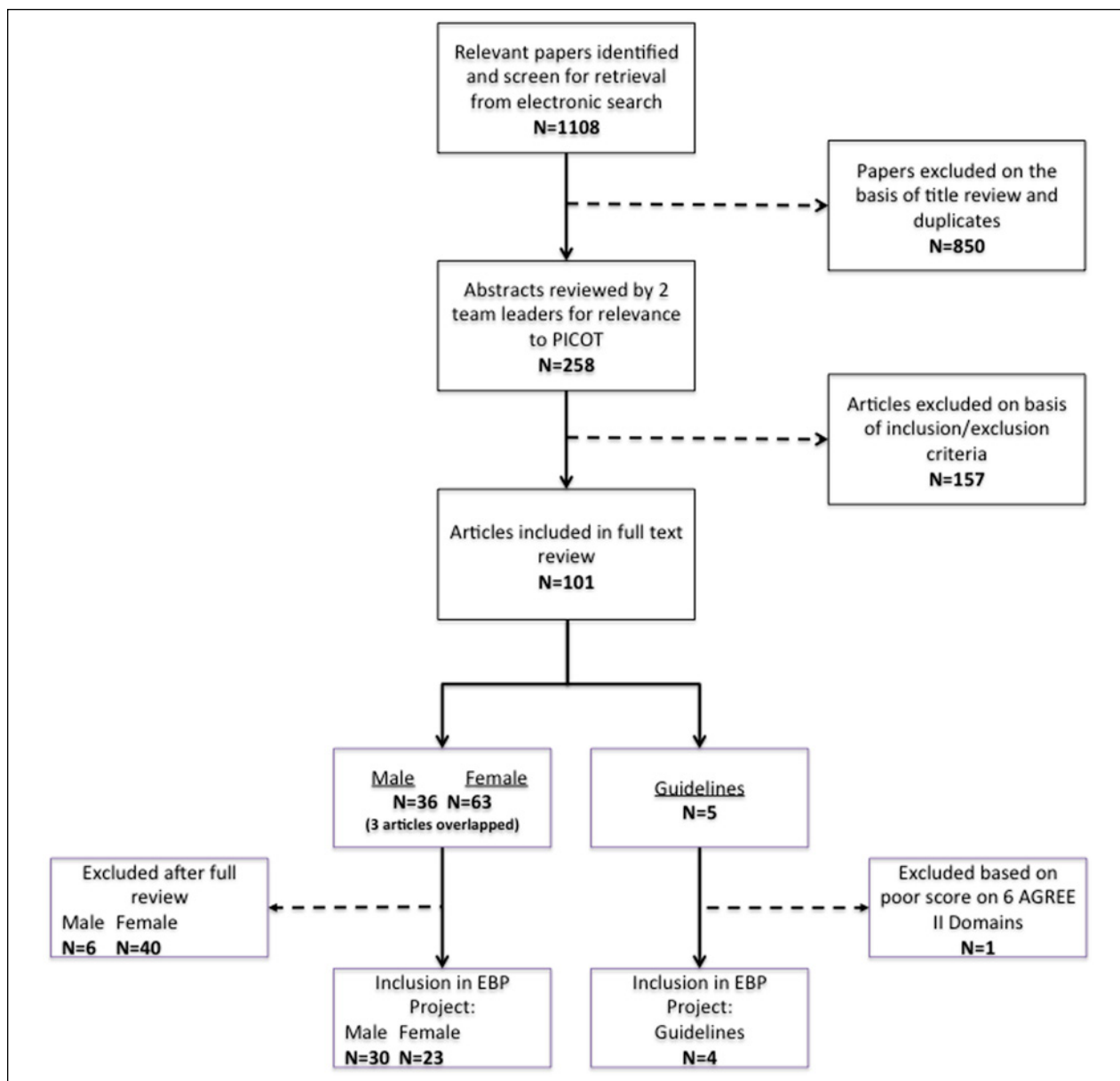


Figure 1. Search results.

developed from the synthesized evidence and were labeled as strong or weak, as described in the introduction article of this journal issue. The strength of each recommendation was determined by the desirable and undesirable effects of the evidence and made independently of the quality level of the evidence (Andrews et al., 2013).

Clinical Guideline Search

In addition to the database searches, a comprehensive search for clinical guidelines was conducted by 1 team member by searching relevant professional organizations and governmental agency websites (ie, National

Guideline Clearinghouse). Five guidelines, pertinent to both male and female fertility preservation options, were identified from the search. The clinical guidelines were reviewed using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool to assess the methodological rigor of the guidelines (Cluzeau et al., 2003). The tool’s criteria evaluated 6 domains of the guidelines: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each guideline was independently reviewed by a team leader and the mentor using the AGREE II tool, and significant differences of scores were discussed between the 2 individuals until agreement

Table 1. Embryo/Oocyte Cryopreservation Evidence.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Postpubertal feasibility	Oocytes can be retrieved with ovarian hyperstimulation and cryopreserved as fertilized (embryo) or not fertilized (oocyte) in postpubertal females	ASRM, 2005; ASRM 2013; Coccia, 2012; Loren, 2013	Not applicable
	4-22 oocytes have been retrieved per ovarian hyperstimulation cycle	Huser, 2012; Kamath, 2011; Rossi, 2011	Very low–low
Pre- or peripubertal feasibility	Oocyte harvesting is possible with 7-17 oocytes retrieved per ovarian hyperstimulation cycle in pre- or peripubertal females	Reichman, 2012; Revel, 2009	Very low

was reached. Ratings among the 2 individuals were then averaged for a combined score for each of the 6 domains. As no cut-off criteria have been determined for the AGREE II tool (Cluzeau et al., 2003), the team leader and mentor discussed final score results to determine if the clinical guideline was acceptable for use. Five clinical guidelines were assessed using the AGREE II tool and 4 guidelines met criteria to be included. Guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the American Society for Reproductive Medicine (ASRM) were included in this EBP project. In 2013, ASRM updated guidelines regarding oocyte cryopreservation, and these were included in the EBP review.

Review of the Evidence

Fertility Preservation Options for Females—Pre- and Postpubertal

Four methods of female FP were noted in the literature: embryo/oocyte cryopreservation, oophoropexy, ovarian tissue cryopreservation, and hormone suppression. Options for FP are influenced by several factors including the patient's sexual development status, time frame to begin treatment, and the patient and family's desire to undergo FP treatments that might be time-consuming and costly (Levine et al., 2010).

Embryo/Oocyte Cryopreservation

The literature addressing embryo and oocyte cryopreservation included 5 articles, 3 guidelines, and 1 amendment to clinical guidelines (Table 1). Both FP embryo and oocyte cryopreservation require medications to stimulate the ovaries to produce oocytes, which are harvested through a surgical procedure and then cryopreserved. Ovarian stimulation requires days to weeks and may not be feasible if cancer treatment must be initiated emergently (Ginsberg et al., 2008). The expenses associated

with the ovarian stimulation, surgical procedure, and annual storage fees may deter this FP option for some patients (Levine et al., 2010).

Oocytes may be preserved unfertilized as an oocyte or undergo fertilization to create an embryo. Fertilization requires sperm to fertilize the oocytes prior to freezing (Agarwal & Chang, 2007) and therefore may not be a feasible option for AYA patients who do not have a life partner or for whom the use of donor sperm for fertilization is not an option. The American Society of Clinical Oncology, ASRM, and NCCN all endorse embryo cryopreservation as a FP option for postpubertal females at risk for infertility secondary to treatment (ASRM, 2005; Coccia et al., 2012; Loren et al., 2013).

Until recently, oocyte harvesting and cryopreservation was deemed an experimental method of FP in both the oncology and general infertility population; however, ASRM recently revised FP guidelines for cancer patients. The American Society for Reproductive Medicine and Society for Assisted Reproductive Technology (2013) stated that pregnancy rates following oocyte cryopreservation are similar to embryo cryopreservation; therefore, oocyte preservation is no longer experimental for postpubertal females. The 2013 ASCO guidelines concur with the 2013 ASRM statement (Loren et al., 2013).

Oocyte harvesting and cryopreservation is a viable option in postpubertal female patients at risk for infertility who do not wish to freeze embryos. Recent studies confirm that ovarian hyperstimulation can produce oocytes in postpubertal females (Kamath, Londhe, Muthukumar, & George, 2011; Rossi, Ashby, & Srouji, 2011). A recent study of 154 women who were newly diagnosed with cancer found that both embryo and oocyte cryopreservation are feasible methods to preserve reproductive potential prior to gonadotoxic cancer treatment (Huser et al., 2012). Two studies also report the possibility of oocyte harvesting in prepubertal females (Reichman, Davis, Zaninovic, & Rosenwaks, 2012; Revel et al., 2009). Successful oocyte harvesting was performed in a case report of a 13-year-old pre-menarcheal female with Tanner III breast

Table 2. Oophoropexy Evidence.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Clinical use	Oophoropexy is an option for females receiving pelvic radiation	Coccia, 2012; Loren, 2013; Terenziani, 2009	Low
Outcomes	14 pregnancies in 11 women who underwent oophoropexy as adolescents prior to Hodgkin lymphoma treatment	Terenziani, 2009	Low
	3 pregnancies in 11 women who underwent oophoropexy prior to radiation therapy	Gareer, 2011	Low
	Ovarian protection in 5 adolescents who underwent oophoropexy prior to craniospinal radiation	Kung, 2008	Very low

development and Tanner I pubic hair growth (Reichman et al., 2012). A 2009 cohort study of 19 patients ages 5 to 20 years reported successful oocyte aspiration during ovarian tissue cryopreservation (Revel et al., 2009). In this study, oocytes were retrieved, matured, and cryopreserved in both pre- and postpubertal patients.

Oophoropexy

Oophoropexy is the surgical relocation of the ovary or ovaries outside of the radiation field. This method of FP may be used in either pre- or postpubertal females only if the ovary or ovaries are in the radiation field and do not require radiation as part of cancer therapy. To be effective, oophoropexy must be performed prior to start of radiation therapy. This method does not protect the ovaries from gonadotoxic effects due to chemotherapy (Lee, 2007).

Three articles and 2 clinical guidelines supported the use of oophoropexy in pediatric and AYA patients (Table 2). Fourteen pregnancies were reported in 11 women who underwent oophoropexy prior to pelvic radiation for treatment of Hodgkin lymphoma (Terenziani et al., 2009). Furthermore, a 2011 study reported that 3 out of 11 patients had successful, full-term pregnancies following oophoropexy (Gareer, Gad, & Gareer, 2011). In addition to protecting patients undergoing pelvic radiation, oophoropexy is a feasible FP option prior to craniospinal radiation with ovarian protection noted among 5 adolescents ages 11 to 17 years (Kung, Chen, Huang, Ho, & Cheng, 2008). Both ASCO and NCCN endorse oophoropexy as an option for females receiving pelvic radiation (Coccia et al., 2012; Loren et al., 2013).

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation (OTC) is an experimental method of FP and is the only cryopreservation option available to prepubertal females (Gosiengfiao, 2007; Gracia & Ginsberg, 2007; Wallace, 2011). This FP method requires removal of tissue from part or all of an

ovary, which is then cryopreserved for future use. One option for future use includes reimplanting part of or the entire ovary into the patient to restore either hormonal function or fertility (Lee, 2007).

A total of 12 articles and 3 clinical guidelines met inclusion criteria for OTC (Table 3). Because this technique requires surgery and the benefit to the patient is not yet established, ASCO and ASRM guidelines state that OTC should be offered only in research that has been approved by an Institutional Review Board (IRB) (ASRM & Society for Assisted Reproductive Technology, 2013; Loren et al., 2013). National Comprehensive Cancer Network guidelines state that OTC is an investigational method of FP and the possibility of reseeding cancer through reimplanted tissue exists (Coccia et al., 2012).

One concern for OTC is delaying the onset of treatment due to the oophorectomy procedure. Several studies show no significant delay in treatment and the ovarian tissue harvest may be bundled with other procedures such as venous port placement (Babayev, Arslan, Kogan, Moy, & Oktay, 2013; Feigin, 2007; Gracia et al., 2012; Rosendahl et al., 2008). Adult survivors of childhood cancer, younger than 18 years of age at the time of the OTC, report satisfaction with their decision to pursue OTC (Rosendahl et al., 2008).

A large descriptive study of 154 female patients with newly diagnosed cancer demonstrates that OTC is a viable option for women; however, all ovarian tissue from these women remains cryopreserved, so outcomes are unavailable (Huser et al., 2012). A 2007 observational study reports that patients who have received chemotherapy prior to OTC may still benefit from OTC if receiving gonadotoxic treatment, provided previous treatment was nonsterilizing (Meirow et al., 2007). There are 2 case reports of live birth following reimplantation of harvested ovarian tissue following cancer treatment. The 2 cases involved a 17-year-old female and a 24-year-old female who both underwent OTC prior to hematopoietic stem cell transplantation (Demeestere, Simon, Emiliani, Delbaere, & Englert, 2007; Donnez et al., 2011). In

Table 3. Ovarian Tissue Cryopreservation.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Feasibility	No significant treatment delay and harvest can be bundled with other procedures	Babayev, 2013; Feigin, 2007; Gracia, 2012; Rosendahl, 2008	Low
Malignancy risk	8 out of 26 ovarian tissue samples had leukemia cells	Rosendahl, 2010	Low
	Ovarian tissue from 24 Hodgkin lymphoma patients had no cancer cells	Seshadri, 2006	Low
Outcomes	Patients satisfied with ovarian tissue cryopreservation decision	Rosendahl, 2008	Low
	Unknown, tissue remains cryopreserved	Huser, 2012	Low
	Endocrine function restored after reimplantation of ovarian tissue	Donnez, 2008	Very low
	One live birth reported in each case study	Demeestere, 2007; Donnez, 2011	Very low
	Retrieval of immature oocytes from ovarian tissue cryopreservation is feasible	Huang, 2008	Very low

Table 4. Hormone Suppression Evidence.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Outcomes	Efficacy is not proven	Coccia, 2012; Loren, 2013	Not applicable
	No ovarian protection in patients with Hodgkin lymphoma	Behringer, 2010; Nitzschke, 2010	Very low–low
	Ovarian protection only with less gonadotoxic treatment	Huser, 2012	Low
	Ovarian protection in women receiving treatment for Hodgkin lymphoma	Falorio, 2008	Low
	Decreased gonadotoxicity in patients undergoing stem cell transplant with lymphoma but not leukemia	Blumenfeld, 2012	Low

addition, endocrine function was restored in 5 women when ovarian tissue was reimplanted following treatment completion (Donnez et al., 2008).

If malignant cells are present in the ovary, there is a risk of reseeding the malignancy if the ovary is reimplanted (Rosendahl et al., 2010). Thus, research is ongoing to develop techniques to mature follicles into oocytes that may be fertilized through in-vitro fertilization, allowing for pregnancy to occur without the risk of reseeding a malignancy (Gosiengfiao, 2007). In a retrospective study, polymerase chain reaction (PCR) of previously cryopreserved ovarian tissue showed that 8 out of 26 samples had leukemia cells present (Rosendahl et al., 2010). However, another retrospective analysis of ovarian tissue harvested in 24 Hodgkin lymphoma patients did not show any evidence of cancer cells (Seshadri et al., 2006).

A final strategy involving OTC consists of combining OTC with retrieval of oocytes from the excised ovarian tissue. A retrospective study of 4 females reported 11 oocytes retrieved from their ovarian tissue with a greater number of oocytes retrieved from the younger patient's tissue (ages 18 and 21 years vs ages 35 and 38 years) (Huang, Tulandi, Holzer, Tan, & Chian, 2008).

Hormone Suppression

The administration of gonadotropin-releasing hormone analogs (GnRHa) to protect the ovaries from the effects of gonadotoxic treatment was evaluated in 5 studies and cited in 2 clinical guidelines (Table 4). This method of FP is thought to put the ovaries in a prepubertal state, preventing ovulation and thus preserving the number of oocytes in the ovary. The American Society of Clinical Oncology (2013) does not endorse GnRHa as a FP method (Loren et al., 2013). The National Comprehensive Cancer Network stated that posttreatment pregnancy rates are not improved with hormone suppression (Coccia et al., 2012). A phase II clinical trial was closed prematurely when an interim analysis of 23 patients did not demonstrate that GnRHa or oral contraceptives maintain ovarian reserve (Behringer et al., 2010). Another study found that GnRHa were protective only in patients receiving less gonadotoxic chemotherapy (Huser et al., 2012). Two studies examining GnRHa use in patients with Hodgkin lymphoma had conflicting results regarding efficacy. A case control study of 30 women (10 received GnRHa with chemotherapy treatment, 10 received

chemotherapy without GnRHa, and 10 received GnRHa without chemotherapy) reported no ovarian protection from the GnRHa during chemotherapy (Nitzschke et al., 2010). In a retrospective study of 61 patients who all received GnRHa during their treatment for Hodgkin lymphoma, 50 women resumed menses, 22 women conceived, and 7 women developed acute ovarian failure (Falorio, Angrilli, & Fioritoni, 2008). Gonadotropin-releasing hormone analogs use in conjunction with stem cell transplantation may decrease gonadotoxicity and premature ovarian failure in patients with lymphoma, but it is not shown to be effective in females with a leukemia diagnosis (Blumenfeld, Patel, Leiba, & Zuckerman, 2012).

Fertility Preservation Options for Females— Recommendations

Embryo/oocyte cryopreservation. The existing evidence for embryo/oocyte cryopreservation as a FP method is of moderate quality. There is a strong recommendation that embryo/oocyte cryopreservation should be offered to postpubertal females at risk for infertility as a method of preserving fertility prior to cancer treatment.

Oophoropexy. There is a moderate quality of evidence available for oophoropexy in females receiving ovarian radiation exposure. There is a strong recommendation for the use of oophoropexy prior to radiation therapy in females who will receive ovarian radiation exposure.

Ovarian tissue cryopreservation. The evidence supporting ovarian tissue cryopreservation is of low quality. There is a weak recommendation that OTC, an experimental procedure, should be offered to pre- and postpubertal females as a fertility preservation method prior to treatment only as part of an IRB-approved protocol.

Hormone suppression. There is low quality and contradictory evidence regarding the use of hormone suppression as a FP option. Efficacy and endorsement by ASCO and ASRM are lacking. No recommendation is given regarding hormone suppression as a method of FP.

Fertility Preservation Options for Males— Pre- and Postpubertal

Sperm banking via masturbation. Obtaining semen for cryopreservation via masturbation is a common FP modality used for postpubertal males undergoing treatment for cancer. The literature search yielded 28 original studies, including 16 descriptive studies, 2 case reports, and 10 retrospective reviews that evaluated sperm banking via masturbation (Table 5). The studies indicated that postpubertal males can effectively collect and freeze sperm via masturbation prior to starting treatment for

cancer (Bahadur et al., 2002; Bashore, 2007; Chang, Chen, Chen, & Hsieh, 2006; Chong, Gupta, Punnett, & Nathan, 2010; Ginsberg et al., 2008; Hagenäs et al., 2010; Kamischke, Jurgens, Hertle, Berdel, & Nieschlag, 2004; Menon et al., 2009; Meseguer et al., 2006; Neal et al., 2007; Postovsky et al., 2003; van Casteren, Dohle, et al., 2008; van Casteren, van Santbrink, van Inzen, Romijn, & Dohle, 2008; van der Kaaij et al., 2009; Williams et al., 2009). The timing of the referral to bank sperm is critical, since there is often an urgency to start cancer treatment as soon as possible following a cancer diagnosis (Kamath et al., 2011), and sperm banking should be done prior to the initiation of any cancer treatment (Bahadur et al., 2005; Liguori et al., 2008).

It is also important to consider the psychological stressors associated with being told about a new cancer diagnosis and that infertility is a potential late effect of cancer treatment. Findings from several studies support the importance of counseling patients regarding their risk for fertility issues and educating providers regarding potential fertility preservation options available (Glaser, Phelan, Crawshaw, Jagdev, & Hale, 2004; Magelssen et al., 2005; Nahata, Cohen, Lehmann, & Yu, 2013). Babb et al. (2012) indicated that, fortunately, at many institutions, these conversations already take place and there is a high rate of discussion with newly diagnosed patients regarding infertility. Having the ability to bank sperm has been shown to be comforting to patients with cancer (Bonetti, Pasqualotto, Queiroz, Iaconell, & Borges, 2009), and most important, survivors who banked sperm prior to treatment have successfully fathered children using the cryopreserved semen (Babb et al., 2012; Bizet et al., 2012; Schmidt et al., 2004; van Casteren, Dohle, et al., 2008; van Casteren, van Santbrink, et al., 2008). However, despite expert consensus endorsing sperm banking, as well as the relative ease and high success rates associated with sperm banking, the overall rate for referral and usage of assisted reproductive techniques in patients who cryopreserved sperm remains low (Chung et al., 2004; Ragni et al., 2003).

In addition, 3 clinical guidelines supported sperm banking as an established method of fertility preservation for postpubertal males and advised that sperm banking should be discussed with and offered to all postpubertal males prior to receiving cancer treatment (ASRM, 2005; Coccia et al., 2012; Loren et al., 2013).

Sperm banking via alternative methods. Obtaining semen for cryopreservation via methods other than masturbation, such as urine collection after retrograde ejaculation, electro-ejaculation, and testicular sperm extraction (TESE), is an option for postpubertal males who are unable to ejaculate via masturbation. The evidence to support this intervention was of low quality according to the GRADE criteria. Three articles discussed this method (Table 6). Two studies were descriptive, 1 study was a

Table 5. Sperm Banking via Masturbation Evidence.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Collection feasibility	65%-98% of pubertal males produced semen sample prior to cancer treatment	ASRM, 2005; Bahadur, 2002; Bashore, 2007; Coccia, 2012; Hagenäs, 2010; Kamischke, 2004; Loren, 2013; Menon, 2009; Meseguer, 2006; Postovsky, 2003; van Casteren, Dohle, 2008; van Casteren, van Santbrink, 2008	Low-moderate
Semen collection	Mean sperm count = 40-56 mil/mL; median motility = 38%-50%	Chang, 2006; van Casteren, van Santbrink, 2008; van der Kaaij, 2009; Williams, 2009	Low-moderate
	Testicular volume correlates with sperm concentration and motility	Hagenäs, 2010	Moderate
Semen quality	No difference in semen quality prior to cancer treatment based on oncology diagnosis	Ginsberg, 2008; Menon, 2009; Meseguer, 2006	Low-moderate
	Semen quality does differ prior to cancer treatment based on oncology diagnosis	Bahadur, 2002; Chang, 2006; Neal, 2007; Postovsky, 2003	Low-moderate
Sperm banking discussions	Sperm banking should occur prior to initiation of cancer therapy	Bahadur, 2005; Glaser, 2004; Kamath, 2011; Liguori, 2008; Magelssen, 2005; Nahata, 2013	Very low-moderate
	Majority of initial discussions occur with parents and adolescent together; many facilities use educational pamphlet	Chong, 2010; Ginsberg, 2008	Low-moderate
Sperm banking outcomes	Ability to sperm bank is comforting to patients	Babb, 2012; Bonetti, 2009	Low-moderate
	23%-72% pregnancy success among use of banked sperm	Babb, 2012; Bizet, 2012; Schmidt, 2004; van Casteren, van Santbrink, 2008	Low-moderate

Table 6. Sperm Banking via Alternative Methods Evidence.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Feasibility	Urine collection after retrograde ejaculation, electro-ejaculation, and testicular sperm extraction are options for postpubertal males who are unable to ejaculate via masturbation	ASRM, 2005; Glaser, 2004; Hagenäs, 2010; van Casteren, Dohle, 2008	Low

retrospective review, and 1 guideline mentioned this method as a potential option. The studies showed that semen can be successfully collected and cryopreserved using alternative methods (Glaser et al., 2004; Hagenäs et al., 2010; van Casteren, Dohle, et al., 2008) and that these methods are available, accepted, and utilized at a number of pediatric treatment centers (Glaser et al., 2004). One clinical guideline also recommended sperm banking via alternative methods such as electro-ejaculation and testicular sperm extraction for patients in whom ejaculation by masturbation is not possible (ASRM, 2005).

Testicular Tissue Cryopreservation

Testicular tissue cryopreservation, an emerging fertility preservation method, is available for pre- and postpubertal males. This is the only practical method for preserving

sperm in prepubertal males, yet it remains entirely experimental for this age group. This method involves surgically removing a small piece of testicular tissue and then cryopreserving and storing the specimen. In postpubertal males, the tissue can be thawed, and then mature sperm is extracted and used for in-vitro fertilization. However, the immature gametes in the testicular tissue from prepubertal males have yet to be matured for fertility preservation purposes (Keros et al., 2007). Similar to females, there may be a risk of reseeding malignant cells if the malignant tissue is reimplanted (Babayev et al., 2013). Three articles discussed this method in the literature (Table 7). This procedure is feasible for tissue cryopreservation (Keros et al., 2007). This FP method can be bundled with another procedure such as a central line placement and does not significantly increase operation or anesthesia time (Babayev et al., 2013). In addition, the testicular

Table 7. Testicular Tissue Cryopreservation Evidence.

Theme	Findings	References (First Author, Year)	Quality of Evidence
Feasibility	No complications related to procedure and can be bundled with other surgical procedures	Babayev, 2013; Keros, 2007	Low
	Established for postpubertal males but experimental for prepubertal males	ASRM, 2005; Coccia, 2012; Loren, 2013	Not applicable
Malignancy risk	Risk of reseeding malignant cells if malignant tissue is reimplanted	Babayev, 2013	Low
Outcomes	Sperm extraction from postpubertal males' tissue but prepubertal males' tissue not yet used	Glaser, 2004; Keros, 2007	Low–moderate

tissue cryopreservation is available at centers throughout the world (Glaser et al., 2004). There were 3 clinical guidelines that mention this method and emphasize that it is currently experimental, but it may be an alternative for fertility preservation for prepubertal males in the future (ASRM, 2005; Coccia et al., 2012; Loren et al., 2013).

Fertility Preservation Options for Males—Recommendations

Sperm banking. The evidence was of moderate quality, supporting sperm banking as a fertility preservation option for postpubertal males. Thus, there is a strong recommendation that referral to a sperm bank and cryopreservation of semen obtained by masturbation should be offered to all postpubertal adolescent and young adult males as a method of preserving fertility prior to cancer treatment.

Sperm banking via alternative methods. Obtaining sperm via alternative methods is a feasible option to preserve fertility in postpubertal males who are unable to masturbate prior to starting treatment for cancer. There is a strong recommendation that sperm banking via alternative methods be offered to postpubertal males who are unable to sperm bank via masturbation prior to cancer therapy to preserve their fertility. Although the available evidence is of low quality, this FP method received a strong recommendation because the desirable effects clearly outweigh the undesirable effects (Guyatt et al., 2011).

Testicular tissue cryopreservation. Testicular tissue cryopreservation is an experimental option available for pre- and postpubertal boys to preserve fertility prior to cancer therapy. The overall evidence is very low quality. Because this method is relatively new with limited available data, there is a weak recommendation that testicular tissue cryopreservation, an experimental method to preserve fertility, should be offered to pre- and postpubertal males

prior to starting cancer therapy. It should be offered only as part of an IRB-approved clinical trial.

Recommendations for Nursing Practice

Decisions regarding fertility preservation are highly personal and may be difficult to make at the time of cancer diagnosis. Families are faced with a number of concerns for the immediate and future health and well-being of the child. Nurses serve as both advocate and educator for families and the patient. Therefore, many families look to nurses for information regarding decisions such as fertility preservation.

The treatment team should be able to inform patients and families of the potential for infertility based on treatment and the options available for FP prior to treatment. Quality improvement programs should be in place, assuring that fertility preservation options are discussed with patients and their parents and appropriate fertility preservation options are made available prior to initiation of cancer treatment, according to patient and family preference.

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