Critical Review of Clinical Practice Guidelines for Fertility Preservation in Teenagers and Young Adults with Cancer

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Purpose: The 5-year survival of teenagers and young adults (TYAs; 13–24 years old) with cancer has continued to rise, but as a result more patients experience late effects of treatment, such as infertility. Advice regarding fertility preservation in relation to cancer is provided in numerous clinical practice guidelines, but the rigor of their development is unclear.

Methods: A systematic search was undertaken for clinical practice guidelines regarding fertility preservation in TYAs with cancer. All guidelines were reviewed according to the Appraisal of Guidelines for Research and Evaluation (AGREE-II) criteria. Five out of 13 identified guidelines scored over 75% in the “rigor of development” section and were further appraised. Content, scope, and consistencies between recommendations were also examined.

Results: All five of the reviewed guidelines encouraged oncologists to have discussions with their patients about potential fertility issues associated with treatment and available fertility preservation methods. The cryopreservation of sperm, oocytes, and embryos were all recommended as first-line interventions in postpubertal patients. Recommendations surrounding pre- or peripubescent adolescents were few, with many techniques only recommended as part of a clinical trial. The risk of subfertility associated with different treatment regimens was poorly described.

Conclusions: The methodology and development of guidelines describing fertility preservation in TYA cancer patients varied greatly. Methodological quality did not clearly influence key recommendations. Those involved with the development of guidelines are encouraged to clearly define their development methods to allow users to be confident of the quality.

Keywords: AGREE-II, fertility, guidelines, preservation

CANCER IN TEENAGERS AND YOUNG ADULTS (TYAs; 13–24 years old) is relatively rare, accounting for less than 2% of all cancers diagnosed across Europe and the United States.¹ Despite this, it is the most common cause of non-accidental death in this age group.^{2,3} The most frequently diagnosed cancers in TYAs are leukemias and lymphomas, central nervous system tumors, germ cell tumors, sarcomas, melanomas, and thyroid, breast, and other carcinomas.^{4,5} The 5-year survival has continued to rise, and is now more than 80% with aggressive multimodal treatment,⁶ but as a result, more patients experience late effects of their cancer treatment. One such effect is on a patient's ability to reproduce, but this is variable and depends on the patient's age when starting treatment, type of treatment administered, and cancer

site. Both pre- and postpubertal TYA patients are at risk from the toxic effects of treatment, and prepubertal patients may also be left with growth and secondary sexual characteristic deficiencies due to gonadal failure.

There are many methods of fertility preservation in relation to cancer described in the literature, and advice regarding offering these methods to patients is provided in numerous clinical practice guidelines. Clinical practice guidelines are defined as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances,”⁷ but not all guidelines are of a similar quality of development.^{8,9} Furthermore, information regarding guideline development protocol, methodology, and appraisal is universally poorly

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reported.¹⁰ When this information is not fully available, duplication of work for researchers and regulators—such as detailed interpretation and critical appraisal of results—ensues. This contributes little in terms of additional value to the end user.¹¹

Given the range of guidelines produced regarding fertility preservation in TYAs treated for cancer, we critically reviewed these documents for their methodological quality and assessed their recommendations regarding the preservation of fertility in the pre-, peri-, and post-treatment phases. This was undertaken to guide clinical practitioners in selecting appropriately robust documents for their use.

Methods

A systematic search of bibliographic and grey literature (not published in journals or indexed within databases) for clinical practice guidelines regarding fertility preservation in TYAs with cancer was undertaken, in addition to expert consultation. The literature search combined demographic-specific terms and the relevant disease—((teenage OR adolescent* OR young adults) AND (cancer OR malignan* OR neoplasm OR carcinoma OR leukaemia OR leukemia OR lymphoma))—with fertility and its preservation (fertility AND (preservation OR conservation)). The search was limited to clinical practice guidelines. The electronic databases MEDLINE (OVID: 1946 through May 2013), EMBASE (1974 through May 2013), and the Cochrane Library were searched. A thorough internet search was undertaken to ensure that eligible clinical practice guidelines not cataloged within bibliographic databases were included. Experts in the field of TYA oncology were also approached. A similar search strategy was used to identify fertility preservation guidelines for children and adults to ensure that no guidance relevant to TYAs was missed. In cases where multiple versions of a guideline were available, the latest version was appraised.

All identified clinical practice guidelines were reviewed according to the Appraisal of Guidelines for Research and Evaluation (AGREE-II) criteria by two researchers (a TYA oncology consultant and an academic oncology trainee). The AGREE-II is an online appraisal tool used to assess the methodological rigor and transparency by which a guideline is developed.¹² The AGREE-II tool is comprised of 23 individual elements categorized into six groups: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The rigor of development category is split into eight statements:

- Systematic methods were used to search for evidence.
- The criteria for selecting the evidence are clearly described.
- The strengths and limitations of the body of evidence are clearly described.
- The methods for formulating the recommendations are clearly described.
- The health benefits, side effects, and risks have been considered in formulating the recommendations.
- There is an explicit link between the recommendations and the supporting evidence.
- The guideline has been externally reviewed by experts prior to its publication.
- A procedure for updating the guideline is provided.

Each statement is scored out of seven (1 = strongly disagree to 7 = strongly agree) to give a total score of 56.

Guidelines with a score of 75% (42/56) or better in the “rigor of development” section were then further assessed and narratively synthesized. Prior to commencing the study, the investigators agreed that this score was an acceptable cut-off, as no score breakdown is provided within the AGREE-II. If there was disagreement between the two researchers, a third independent researcher (a TYA oncology consultant) was consulted. Content, scope, and consistencies between recommendations were examined. Key elements of inconsistency were further explored, relating these areas to the quality of the guideline (overall AGREE-II score), the rigor of its development (AGREE-II subgroup score), the healthcare system within which the guideline was developed, and the evidence from which the recommendation was derived.

Results

Thirteen clinical practice guidelines directly relevant to fertility preservation in TYAs with cancer were identified. The guidelines were from the American Academy of Pediatrics (AAP; 2008),¹³ French Association for the Care of Oncological Support (AFSOS; 2013),¹⁴ American Society of Clinical Oncology (ASCO; 2013),¹⁵ British Fertility Society (BFS; 2003),¹⁶ Clinical Oncological Society of Australia (COSA; 2011),¹⁷ European Society of Medical Oncology (ESMO; 2009),¹⁸ International Society of Fertility Preservation (ISFP; 2012),¹⁹ National Comprehensive Cancer Network (NCCN; 2012),²⁰ French Institute of Cancer (NIC; 2012),²¹ National Institute for Health and Clinical Excellence (NICE; 2013),²² Royal Colleges of Physicians, Radiologists, and Obstetricians and Gynaecologists (“joint Royal Colleges;” 2007),²³ French Childhood Cancer Society (SFCE; 2013),²⁴ and the Scottish Intercollegiate Guidelines Network (SIGN; 2013).²⁵ All of the identified clinical practice guidelines and subsequent AGREE-II scores are detailed in Table 1.

Only five identified guidelines had sufficient evidence of rigor of development to warrant further appraisal. The five guidelines were the SIGN (rigor of development score = 91%), NICE (89%), COSA (88%), ASCO (84%), and AAP (77%) guidelines. All five guidelines had an overall AGREE-II score of 6 out of a possible 7. Results from the appraised guidelines are shown in Tables 2–4.

Male fertility preservation: postpubertal (Table 2)

All appraised guidelines recommended the cryopreservation of sperm as soon as possible in postpubertal males able to produce a semen sample, regardless of their type of treatment. Liquid nitrogen was the preferred method of freezing in the NICE guideline; no freezing method was discussed in the others. The NICE guideline recommended storing sperm for up to 10 years, and longer for those who remain at risk of significant infertility. In comparison, the American clinical practice guidelines (AAP and ASCO) stated that sperm samples should be stored for three years, with further storage incurring extra costs to the patient. The duration of storage—particularly relevant for younger patients, who may have many remaining years of potential parenthood—was not mentioned in the two remaining clinical practice guidelines.

TABLE 1. ALL IDENTIFIED CLINICAL PRACTICE GUIDELINES FOR TEENAGERS AND YOUNG ADULTS WITH CANCER AND ASSOCIATED AGREE-II SCORES BY RIGOR OF DEVELOPMENT SCORE

Guideline author group and title	Country	Year	AGREE-II rigor of development score ¹	Overall AGREE-II score ²
<i>Scottish Intercollegiate Guidelines Network (SIGN): Survivors of childhood cancer</i>	United Kingdom	2013	51	7
<i>National Institute for Health and Clinical Excellence (NICE): Fertility—assessment and treatment for people with fertility problems (update)</i>	United Kingdom	2013	50	7
<i>Clinical Oncological Society of Australia (COSA): Fertility preservation for AYAs diagnosed with cancer—guidance for health professionals</i>	Australia	2011	49	6
<i>American Society of Clinical Oncology (ASCO): Recommendations on fertility preservation in cancer patients</i>	United States	2013	47	6
<i>American Academy of Paediatrics (AAP): Preservation of Fertility in Pediatric and Adolescent Patients With Cancer</i>	United States	2008	43	6
Royal Colleges of Physicians, Radiologists, and Obstetricians and Gynaecologists: The effects of cancer treatment on reproductive functions: guidance on management	United Kingdom	2007	36	5
European Society for Medical Oncology (ESMO): Cancer, fertility and pregnancy—clinical recommendations for diagnosis, treatment and follow-up	Europe	2009	29	3
British Fertility Society (BFS): A strategy for fertility services for survivors of childhood cancer	United Kingdom	2003	24	5
French Association for the Care of Oncological Support (AFSOS): Cancer and fertility preservation in men, women and children	France	2013	23	5
French Society of Childhood Cancer (SFCE): Recommendations for the preservation of fertility in children and adolescents treated for cancer	France	2013	23	5
National Comprehensive Cancer Network (NCCN): Adolescent and young adult oncology	United States	2012	23	4
Nationale Institut of Cancer (NIC): Effects of cancer treatment and fertility preservation	France	2013	23	2
International Society for Fertility Preservation (ISFP): Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer	International	2012	16	2

Note. Italics indicates the final appraised guidelines.

¹Maximum possible score=56.

²Maximum possible score=7.

AGREE-II, Appraisal of Guidelines for Research and Evaluation; AYAs, adolescents and young adults.

For postpubertal males unable to ejaculate or produce a suitable amount of semen, the COSA and ASCO guidelines recommended epididymal or testicular aspiration or biopsy. The AAP guideline described the evidence behind these methods (as well as electro-ejaculation and post-masturbation urine samples) as anecdotal (case reports); they are not mentioned in the remaining two guidelines.

Testicular shielding during radiotherapy was recommended in both the AAP and ASCO guidelines, but not in the others. Relocation of the testes was briefly mentioned in the AAP guideline, but not recommended. *In vivo* protection of the testes from chemotherapy using gonadotropin-releasing hormone (GnRH) analogues was not recommended in the two guidelines (AAP and ASCO) in which it was discussed.

Male fertility preservation: prepubertal (Table 3)

Although there is a minority of male TYA patients who are pre- or peripubertal, this group was poorly defined in the

guidelines, with no guideline differentiating pre- and peripubertal states or specific Tanner stages for their recommendations. Of the four guidelines that briefly discussed fertility preservation for this group, methods were either not recommended or supported only within a clinical trial. Testicular tissue preservation was not recommended in the AAP (2008) guideline, but was supported as part of a clinical trial in the more recent guidelines from COSA (2011), SIGN (2013), and ASCO (2013). Testicular shielding was recommended for use in prepubertal males by both guidelines produced in the United States (AAP and ASCO). These same two guidelines were the only ones to discuss GnRH analogues for prepubertal males, although they again did not recommend its use.

Female fertility preservation: postpubertal (Table 2)

In postpubertal females, oocyte and embryo cryopreservation were unanimously recommended as the first-line

TABLE 2. GUIDELINE RECOMMENDATIONS FOR FERTILITY PRESERVATION METHODS IN POSTPUBERTAL MALES AND FEMALES,
BY GUIDELINE SOURCE AND YEAR OF PUBLICATION

		AAP (2008) ¹³	COSA (2011) ¹⁷	NICE (2013) ²²	SIGN (2013) ²⁵	ASCO (2013) ¹⁵
Male	Patient selection	All postpubertal male patients	All postpubertal male patients	All postpubertal male patients	All postpubertal male patients	All postpubertal male patients
	Cryopreservation Sperm	Included	Included	Included	Included	Included
	Duration of storage	Yes	Yes	Yes	Yes	Yes
	Method of freezing	Additional storage fees after 3 years	10 years or longer if remains at risk	10 years or longer if remains at risk	Not discussed	Additional storage fees after 3 years
	If no ejaculate?	Not recommended	Liquid nitrogen vapor	Liquid nitrogen vapor	Not discussed	Not discussed
	Radiotherapy	Not recommended	Not discussed	Not discussed	Not discussed	Testicular/epididymal aspiration or biopsy
	Shielding of testes	Included	Not discussed	Not discussed	Not discussed	Included
	Chemotherapy	Yes	Not discussed	Not discussed	Not discussed	Yes
	In vivo protection	Included	Not discussed	Not discussed	Not discussed	Included
		No (ineffective)	Not discussed	Not discussed	Not discussed	No (ineffective)
Female	Patient selection	All postpubertal female patients (time-dependent)	All postpubertal female patients (time-dependent)	“If they are well enough, it will not worsen their condition and there is enough time.”	Not discussed	All postpubertal female patients
	Cryopreservation Oocyte	Included	Included	Included	Included	Included
	Embryo	Yes	Yes	Yes	Yes	Yes
	Ovarian tissue	Experimental (yes in clinical trials)	Experimental (yes in clinical trials)	Not discussed	Experimental (yes in clinical trials)	Experimental (yes in clinical trials)
	Duration of storage	Storage fees	Not discussed	10 years	Not discussed	Not discussed
	Method of freezing	Not discussed	Not discussed	Vitrification	Not discussed	Not discussed
	Radiotherapy	Included	Included	Not discussed	Included	Included
	Transposition	Yes	No (no data)	Not discussed	No (no data)	Yes
	Shielding of ovaries	Yes	Not discussed	Not discussed	Not discussed	Not discussed
	Chemotherapy	Included	Included	Not discussed	Included	Included
	In vivo protection	No (ineffective)	Experimental (yes in clinical trials)	Not discussed	Experimental (yes in clinical trials)	No (ineffective)

AAP, American Academy of Pediatrics; ASCO, American Society of Clinical Oncology; COSA, Clinical Oncological Society of Australia; NICE, the National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

TABLE 3. GUIDELINE RECOMMENDATIONS FOR FERTILITY PRESERVATION METHODS IN PREPUBERTAL MALES AND FEMALES, BY GUIDELINE SOURCE AND YEAR OF PUBLICATION

		AAP (2008) ¹³	COSA (2011) ¹⁷	NICE (2013) ²²	SIGN (2013) ²⁵	ASCO (2013) ¹⁵
Male	Patient selection	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	Clinical trial participants	Selected cases
	Cryopreservation	Included	Included	<i>Not discussed</i>	Included	Included
	Testicular tissue	No	Experimental (yes in clinical trials)	<i>Not discussed</i>	Experimental (yes in clinical trials)	Experimental (yes in clinical trials)
	Duration of storage	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>
	Radiotherapy	Included	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	Included
	Shielding of testes	Yes	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	Yes
	Chemotherapy	Included	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	Included
Female	<i>In vivo</i> protection	No (ineffective)	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	No (ineffective)
	Patient selection	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	High risk of primary ovarian insufficiency	Selected cases
	Cryopreservation	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	Included	Included
	Ovarian tissue	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	Experimental (yes in clinical trials)	Experimental (yes in clinical trials)
	Duration of storage	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>
	Radiotherapy	Included	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>
	Shielding of ovaries	Yes	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>
	Chemotherapy	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>
	<i>In vivo</i> protection	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>	<i>Not discussed</i>

AAP, American Academy of Pediatrics; ASCO, American Society of Clinical Oncology; COSA, Clinical Oncological Society of Australia; NICE, the National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

approach, with embryo cryopreservation reserved for those with current partners. All but one of the guidelines (NICE) also mentioned ovarian tissue transplantation, though it was only recommended as part of a clinical trial. However, no guideline further defined the amount or form of tissue that should be preserved, nor did any guideline recommend a method of freezing or duration of sample storage.

Methods of fertility preservation for females other than cryopreservation were deemed to be experimental when mentioned, with encouragement for patients to participate in clinical trials if appropriate. The AAP and ASCO guidelines recommended ovarian transposition (oophoropexy) to preserve ovarian endocrine function in pelvic radiation therapy, however, the COSA and SIGN guidelines stated that data on its efficacy within clinical practice is lacking and thus did not recommend it; it was not mentioned in the NICE guideline. Ovarian shielding was recommended by AAP but was not mentioned in the other guidelines. GnRH analogues were a recommended method (within the context of clinical trials) in the COSA (2011) and SIGN (2013) guidelines, however, the AAP (2008) and ASCO (2013) guidelines recommended that GnRH analogues should not be used, as they were not considered an effective method of fertility preservation.

Female fertility preservation: prepubertal (Table 3)

The subject of fertility preservation in prepubertal girls was not discussed in two of the five clinical practice guidelines (COSA and NICE), and the remaining three (ASCO, SIGN, and AAP) stressed that any method used should take place only within a clinical trial. Ovarian tissue cryopreservation should be offered only in “selected cases” and to those at “high risk of primary ovarian insufficiency.” The

AAP guideline recommended ovarian shielding when possible. Hormonal suppression using a GnRH analogue was not discussed by any of the guidelines. Oncologists were encouraged to be open and honest with both the patient and parents regarding the experimental nature of these methods.

Additional information (Table 4)

The five appraised guidelines all encouraged oncologists to be open in discussing with their patients that treatment will affect fertility to varying degrees. All but the NICE guideline recommended that fertility counseling and psychological support be offered prior to treatment. Those four guidelines also recommended a multidisciplinary team approach to the management of fertility issues. Written information for patients was encouraged in the COSA, NICE, and SIGN guidelines, but not specified within the remaining two.

The AAP and COSA guidelines expected oncologists to have sufficient knowledge to discuss potential fertility issues associated with a treatment and available fertility preservation methods with their patients. These guidelines also stressed that a fertility specialist should be involved to continue these discussions and further explore preservation issues if required. The NICE and SIGN guidelines, which did not differentiate particular professional roles, recommended early referral to a fertility specialist and do not make any mention of oncologists discussing fertility preservation with their patients. ASCO recommended that the “health care provider” should discuss fertility preservation methods and/or early referral to fertility specialists. No guideline gave specific timeframes for specialist referral.

Three guidelines (COSA, SIGN, and ASCO) recommended that pregnancies subsequent to cancer treatment should be

TABLE 4. GUIDELINE RECOMMENDATIONS FOR RECOMMENDED TOPICS OF DISCUSSION BETWEEN PHYSICIAN AND PATIENT, BY GUIDELINE SOURCE AND YEAR OF PUBLICATION

Topic	AAP (2008) ¹³	COSA (2011) ¹⁷	NICE (2013) ²²	SIGN (2013) ²⁵	ASCO (2013) ¹⁵
Fertility will be affected by treatment	Yes	Yes	Yes	Yes	Yes
Give written information	Not discussed	Yes	Yes	Yes	Not discussed
Offer fertility counseling and psychological support	Yes in moderately distressed people	Yes	Not discussed	Yes	Yes
Who should discuss fertility preservation methods?	Oncologist or fertility specialist	Oncologist or fertility specialist	Fertility specialist	Fertility specialist	Healthcare providers or fertility specialist
No known risk of genetic abnormalities in offspring	Yes	Not discussed	Not discussed	Yes	Yes
No known increased risk of recurrent disease associated with fertility preservation methods	Yes	Not discussed	Not discussed	Not discussed	Yes
Manage subsequent pregnancy as high-risk	Not discussed	Yes	Not discussed	Yes	Yes
Ownership/destruction of stored gametes if patients dies	Yes	Not discussed	Not discussed	Not discussed	Not discussed

AAP, American Academy of Pediatrics; ASCO, American Society of Clinical Oncology; COSA, Clinical Oncological Society of Australia; NICE, the National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

managed as high-risk. AAP, SIGN, and ASCO also recommended reassuring patients that there is no evidence of an increased risk of cancer or birth/genetic defects in children born from fertility preservation methods and assisted reproduction. Only ASCO recommended discussing with patients that current fertility preservation methods do not raise the risk of disease recurrence. The ownership and/or destruction of stored gametes if a patient dies was mentioned in the AAP guideline, but not the others. ASCO described the individual cytotoxic treatment regimes and their associated effects on fertility in a data supplement; no other guidelines included this information.

Discussion

Of the 13 identified guidelines detailing fertility preservation recommendations for TYAs with cancer, only five demonstrated a high standard of development (>75% rigor of development score).

First-line recommendations

While no two guidelines were the same, all five high-quality guidelines shared very similar first-line recommendations for postpubertal patients: sperm, oocyte, and embryo cryopreservation. There were however, differences in the recommended duration of storage, ranging from 10 years in the NICE guideline to only three years in the ASCO and APP guidelines. This can, in part, be explained by the healthcare systems in which the clinical practice guidelines were created. The majority of the healthcare offered in the United States and Australia is insurance-based, leading to additional fees for longer storage durations, which may markedly disadvantage younger patients and those early in their careers who are not financially secure. In contrast, the United Kingdom and Europe healthcare systems are largely based around a national service that may cover these additional costs.

Second-line recommendations

Recommended second-line approaches were more varied in both male and females. For postpubertal males, when an ejaculate could not be obtained, testicular and epididymal aspiration or biopsy were recommended in the COSA and ASCO guidelines. The earliest guideline appraised (AAP, 2008), which may have been limited by the available data at the time, described these methods, together with post-masturbation urine samples and electro-ejaculation, as limited to case reports. The topic of non-ejaculatory infertility was not covered by either of the guidelines out of the United Kingdom (NICE and SIGN), which may highlight geographical differences in the availability and cost of experimental and expensive techniques.

In pre- or peripubescent boys, testicular tissue cryopreservation was not recommended in the relatively earlier (2008) AAP guideline, but was recommended within the confines of a clinical trial in the more recent COSA (2011) and SIGN and ASCO (both 2013) guidelines. While this technique has proved promising in animal studies, no successful human live births have yet been reported.²⁶

For postpubertal females, there is a smaller evidence base surrounding methods other than cryopreservation, with many still experimental and only available as part of a clinical trial.

Ovarian transposition (oophoropexy) during radiotherapy is only feasible with selected radiation fields and certain cancer locations,²⁷ though it was recommended in both guidelines from the United States (AAP and ASCO), but not those from Europe (SIGN) or Australia (COSA); it not mentioned by NICE. Ovarian shielding—a simple and conservative method of preserving fertility, although technical issues limit its use²⁸—was recommended by only the AAP.

Ovarian tissue cryopreservation and *in vivo* protection using GnRH analogues remain experimental techniques over the six-year span of the appraised guidelines (2008–2013). The first live birth in a postpubertal woman using ovarian tissue cryopreservation and subsequent orthotopic transplantation was described in 2004.²⁹ Unfortunately its widespread use may have been hampered by increased tissue fragility and risk of reintroducing cancer cells; however, the use of vitrification freezing (rapid cooling in liquid nitrogen) may improve viability of the tissue.³⁰ Non-ovarian tumors affecting patients of reproductive age seem to have a relatively low potential to metastasize to the ovary.³¹ However, a recent systematic review by Bastings et al. concluded that patients diagnosed with leukemia may not be suitable for ovarian tissue cryopreservation, and there is also some concern for patients with endometrial, colorectal, or gastric cancers.³² Ovarian tissue should be screened for metastases using a range of histological and biochemical markers before cryopreservation.³³ GnRH analogues on the other hand, have been long established for *in vitro* fertilization to down-regulate the ovaries. However, their successful application in protecting the ovaries or testicles against the toxic effects of chemotherapy has been limited.

In prepubertal girls, the only fertility preservation method recommended was ovarian cryopreservation as part of a clinical trial. However, no successful live births after using this technique have been documented to date.

Discussing fertility preservation methods

All the guidelines expected oncologists to be knowledgeable about potential fertility issues associated with a particular cancer treatment. Despite this, Duffy et al.'s 2005 study asking oncologists about their confidence having fertility discussions with their patients found that over a third of oncologists were not confident in their knowledge.³⁴ The earlier guidelines from AAP (2008) and COSA (2011) recommended that oncologists discuss potential fertility preservation techniques with their patients; in contrast, the most recent guidelines—NICE, SIGN and ASCO (all 2013)—recommended early referral to a fertility specialist with no obligation to discuss fertility preservation with their patients. This may reflect that too few oncologists routinely discuss fertility preservation,³⁵ instead routinely referring patients to a fertility specialist.³⁶ Alternatively, as the topic of onco-fertility grows and develops, together with a greater public awareness, the attitudes and practices of oncologists may have shifted to include fertility specialists early to maximize the chance of fertility preservation with optimum treatment times.

Individual cytotoxic agents

The ASCO (2013) guideline was the only appraised clinical practice guideline to outline (in a data supplement) the

different effects of each cytotoxic and radiotherapy regime on sperm function and the risk of permanent amenorrhea.

It is of note that some of the unappraised guidelines—ESMO, SFCE, and AFSOS—separated cytotoxic agents into high, intermediate, low, and unknown risk of causing infertility. Two of the guidelines from the United Kingdom (BFS and joint Royal Colleges) listed not only the cytotoxic agents that increased the risk of gonadotoxicity but also the risk associated with each malignancy. This may help oncologists and fertility specialists better inform their patients, and it is a lack of demonstrated rigor of development in these guidelines that has identified this as a gap in clinical practice guideline content.

Strengths and limitations

Strengths of our study were that all reviewed guidelines went through a rigorous scoring process using the AGREE-II tool, which is internationally recognized for assessing clinical guideline quality. This allowed for an in-depth analysis of the consistencies and differences between fertility preservation guidelines relevant to TYAs, although some clinical practice guidelines' lack of published methods resulted in them having a lower score. Key recommendations were also summarized.

Limitations of our study include using only two researchers to review each guideline, with a third consulted if no agreement was reached. The AGREE-II tool suggests using 2–4 reviewers to increase the reliability of the assessment. In addition, a cut-off rigor of development score of 75% was chosen prior to guideline appraisal. This was arbitrarily chosen as no cut-off is provided by the AGREE-II tool, but may have excluded some high-quality guidelines. Lastly, a number of reviewed guidelines did not publish their criteria for selecting evidence or their methods for formulating the recommendations within the guideline itself. Sometimes this data is published within a supplement, and although the authors' best efforts were made to identify them, some may have been missed.

Conclusion

There are many clinical practice guidelines on the topic of fertility preservation in TYA cancer patients available from authoritative sources, particularly from the United States, Europe, and Australia. We found that reported methodology and development varied greatly, but methodological quality did not clearly influence key recommendations. Data available to each guideline's panel at the time of development and publication undoubtedly affected their final recommendations, as seen when comparing the APP's guidelines from 2008 guideline with the more recent ones from ASCO and SIGN in 2013. However, as it can take up to 17 years for research findings to translate into clinical practice, this process is slow and predictable.³⁷ The majority of high-quality guidelines we reviewed lacked clear details about the individual chemotherapy agents that lead to infertility. This is due, in part, to a lack of strong data characterizing the risk of each individual chemotherapy agent to fertility. However, this has started to emerge as detailed in the ASCO (2013) guideline's data supplement.

All five appraised guidelines recommended the cryopreservation of sperm, oocytes, and embryos as first-line fertility

preservation interventions for postpubertal patients. Ovarian tissue cryopreservation was recommended as an experimental technique. However, recommendations surrounding fertility preservation for pre- or peripubescent adolescents were few and experimental, with many guidelines offering little or no advice.

Oncologists caring for TYA patients with cancer should continue to use a regionally-relevant clinical practice guideline, as each of the appraised guidelines had similar first-line recommendations, regardless of their reported methodological quality. However, the risk of subfertility with different treatment regimens is poorly described. As understanding about the fertility impacts of various chemotherapy agents improves, this is an area that needs to be developed in subsequent guideline iterations. Practicing oncologists must be aware that not all guidelines are created using the same methodology and that there can be wide variability in the techniques used. These were the main driving forces for the Institute of Medicine to publish standards in 2011 for developing trustworthy clinical practice guidelines.³⁸ The main themes in their publication were: establishing transparency, management of conflict of interest, guideline development group composition, clinical practice guideline–systematic review intersection, establishing evidence foundations and rating strength of recommendations, articulation of recommendations, external review, and guideline updating.

To improve transparency in their recommendations, those involved with the development of clinical practice guidelines for TYAs with cancer are encouraged to prospectively define and make available their development methods. This ensures that end users can be confident of the quality of the final guidelines produced.

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