厚生労働科学研究費補助金
第3次対がん総合戦略研究事業

乳癌患者における妊孕性保持支援のための治療選択および患者支援プログラム・関係ガイドライン策定の開発

平成24年度　総括研究報告書

研究代表者　清水　千佳子

平成　25（2013）年　5　月

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I. 総括研究報告書

厚生労働科学研究費補助金（第３次対がん総合戦略研究事業）
総括研究報告書

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研究要旨

日本人女性の年間乳癌罹患数60,000例のうち40歳未満の若年女性は4,000人に及び、中でも35-39才の年齢層での罹患数は増加している（2007)。乳癌初期治療では、化学療法による卵巣機能障害や長期内分泌療法は妊孕性の保持を困難にし、挙児希望のある患者はライフプランの変更が余議なくされる。

海外では American Society of Reproductive Medicine および American Society of Clinical Oncology が全てのがん患者に対し妊孕性保持の支援を推奨、ドイツでは FertiPROTEKT が組織され癌患者の妊孕性保持の品質管理を目指すなど、乳癌患者の妊孕性保持支援への取り組みが進んでいる。国内では、患者向けガイドライン、若年乳癌患者向けのウェブサイトを通して、患者への啓発は進んできたが、医療側からは、再発の不安、乳癌治療医と生殖医療のコミュニケーションの不足、診療時間の制約、パートナー不在などが、患者支援の現実的な障害として挙げられているが、具体的な支援のあり方についての議論は乏しい。

以上より、本研究班では、挙児希望を有する乳癌患者の意思決定と乳癌治療医と生殖医療医の円滑な協働の支援を目指して、乳癌患者の妊孕性保持に関する指針案の策定、リアルタイムでのコンサルテーション・システムの確立、妊孕性保持を希望した若年乳癌患者の乳癌の予後・生殖に関するアウトカムを評価するためのデータベース(DB)の構築を目的とした研究を開始した。初年度はガイドライン案のアウトラインの作成し、患者用冊子の妥当性評価を行った。

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A．研究目的

日本人女性の年間乳癌罹患数 60,000 例のうち40歳未満の若年女性は4,000人に及び、中でも 35-39 才の年齢層での罹患数は増加している（2007）。乳癌初期治療における薬物療法は生命予後を改善するが、化学療法による卵巣機能障害や長期内分泌療法は妊孕性の保持を困難にするため、挙児希望のある患者はライフプランの変更が余議なくされる。このため、乳癌薬物療法の選択において、患者との対話を重視し、サバイバーシップとのバランスをとるべきとの考え方が普及してきたが、"がん・生殖医療（Oncofertility）"の領域は海外においても比較的新しい研究領域である（図１）。

American Society of Reproductive Medicine (2005) および American Society of Clinical Oncology(2006)が全てのがん患者に対し妊孕性保持の支援を推奨した。ドイツでは、主要医療機関の癌治療医と生殖医療医により FertiPROTEKT が組織され(2006)、ガイドライン、定期的会合、登録システム、オンラインコンサルテーションシステムを通じて、癌患者の妊孕性保持の品質管理を目指している。2012 年には、International Society of Fertility Preservation(ISFP)より、リンパ腫・白血病・乳癌患者の妊孕性保持支援のシステム構築に関する指針が示された(J Assis Reprod Genet, e-pub 22 May 2012)。

国内では、患者向けガイドライン(日本乳癌学会 2006, 2009)、平成 21-23 年がん研究開発費「若年乳癌患者のサバイバーシップ支援プログラムの構築」班（大野）のウェブサイト（2011）を通じ、患者への啓発は進んできた。一方、平成 21-23 年度　厚労科研「がん患者及びその家族や遺族が抱える精神心理的負担による QOL への影響を踏まえた精神心理的ケアに関する研究」班（清水、加藤）が行った日本乳癌学会乳腺専門医および日本生殖医学会生殖専門医に対する意識調査(2010, 2011)では、再発の不安、生殖医療の照会先がないこと、診療時間の制約、生殖専門医の乳癌の知識不足、パートナー不在が、患者支援の現実的な障害として挙げられた。日本生殖医学会は「医学的介入により造精機能低下の可能性のある男性の精子の凍結保存」（2003）の指針を策定しているが、癌罹患女性の生殖医療の具体的指針はない。

以上より、乳癌治療医と生殖医療医との連携システムの構築は緊喫の課題である。国内の現状は、ISFP の示す指針（図2）の、Step 1、2 が完了した段階である。本研究では、Step 3（乳癌治療医と生殖医療医の正式な協力関係の樹立)を目指したい。具体的には、乳癌治療医と生殖医療医の協働の礎となる乳癌患者の妊孕性保持に関する指針の策定、リアルタイムでのコンサルテーション・システムの作成、妊孕性保持を希望した若年乳癌患者の乳癌の予後・生殖に関するアウトカムを評価するための DB の構築を目的とする。

本研究により、乳癌治療医と生殖医療医のコミュニケーションの促進、若年乳癌患者の癌治療と生殖医療の質の向上、ひいては個々の若年乳癌患者のサバイバーシップの質の向上が期待される。さらに DB に乳癌患者の生殖医療の治療成績や安全性に関するデータが蓄積できれば、将来の若年乳癌患者の治療選択において有用な情報源となる。また、乳癌患者での妊孕性支援システムのモデルは、他の成人悪性腫瘍、小児悪性腫瘍患者の妊孕性に関するサバイバーシップ支援の促進の一助となると考えられる。

図１　Medline 検索による文献数の推移

（検索語：“fertility preservation（妊孕性保持”）AND “breast cancer（乳癌）”）

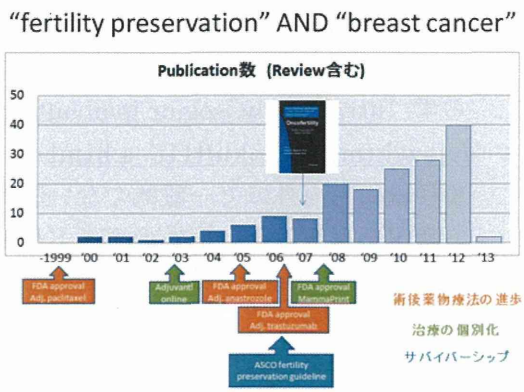
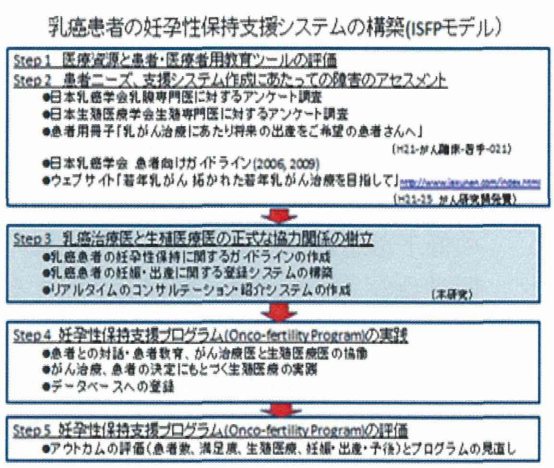


図 2 International Society of Fertility Preservation モデル



B．研究方法

初年度：乳癌治療医、婦人科医、生殖医療医により「乳癌患者の妊孕性保持に関するガイドライン」を検討し、リアルタイムでのコンサルテーション・紹介システムのモデルを構築する。

① 乳癌患者の妊孕性保持に関するガイドラインの作成

海外の乳癌およびその他の悪性腫瘍患者の妊孕性保持ガイドラインの検討し、国内の一般女性に対する不妊治療に関する産婦人科・生殖医療関連学会のガイドライン、「医学的介入により造精機能低下の可能性のある男性の精子の凍結保存」（2003）との整合性に配慮したガイドラインを作成する。

② 乳癌患者の生殖医療に関するリアルタイム・コンサルテーション・システムのモデル作成

医療者、患者を対象に平成21-23年度厚労科研「がん患者及びその家族や遺族が抱える精神心理的負担によるQOLへの影響を踏まえた精神心理的ケアに関する研究」班において作成した患者情報提供用小冊子「乳がん治療に際して将来の出産を御希望の患者さんへ」の内容の妥当性評価を行い、患者への妊孕性保持と医療者間のコミュニケーションを支援する情報提供ツールとして完成させる。

平成21-23年がん研究開発費「若年乳癌患者のサバイバーシップ支援プログラムの構築」班（大野）のウェブサイトを活用、拡充し（乳癌患者の生殖医療の受け入れ可能機関、医療者・患者向けQ&Aの公開など）、乳癌治療医が生殖医療医に対して患者の生殖医療支援に関してリアルタイムなコンサルテーションを実現できるようなシステムを構築する。

２年目：妊孕性保持を希望した若年乳癌患者の乳癌の予後・生殖に関するアウトカムを評価するためのデータベース(DB)の構築

① 乳癌患者の生殖医療とアウトカムのDB作成

DB作成に必要な項目の抽出し、オンラインによる患者登録システムを作成する。

② 妊孕性保持に関するガイドライン、DBに関する教育と普及
日本乳癌学会もしくは生殖医療関連学会等の協力を得て、ガイドラインと登録システムについての周知・啓発を図る。

③ DBの運用
妊孕性保持を希望した若年乳癌患者の乳癌の予後・生殖医療・生殖医療のアウトカムに関するDBの試験的な運用を開始する。登録が進んだ時点で、得られた情報を分析し、患者への情報提供ツール、医療者間コミュニケーションツールに情報を還元する。また臨床研究も検討する。

（倫理面への配慮）
ガイドラインの策定、DB の作成は、患者を直接対象とした研究ではないため患者に直接の不利益や危険性はない。DB への登録を開始した場合、疫学研究の倫理指針および個人情報保護法を遵守する。

C．研究結果

① 乳癌患者の妊孕性保持に関するガイドライン案の作成

a. 国内外のガイドラインの検討

既存の海外のガイドラインとして、American Society of Clinical Oncology, International Society of Fertility Preservation, Fertiprotektのガイドラインを検討した（資料１①-④）。これらのガイドラインの生殖医療の観点からみた問題点として、加齢に伴う卵の数と質の低下や母体保護の観点からみた出産年齢が加味されていないこと、生殖補助医療において本来評価されるべきアウトカムである生児獲得率への言及がないこと、LHRHアナログによる卵巣保護に関する論文においてはエンドポイントとなっている月経回復率が卵巣予備能の代替指標として不適切であることが挙げられた。このようなガイドライン自体の内的妥当性に関する問題があるほか、提供卵子による体外受精、代理出産が認められておらず（http://www.jsog.or.jp/about_us/view/html/kaikoku/H16_4.html）、養子縁組も海外ほど一般的でない国内の状況を考えると、海外のガイドラインをそのまま利用することは困難であり、独自のガイドラインの作成が必要であると考えられた。

国内では、資料２のごとく、医学的介入による男性の造精機能の低下に対する精子保存の指針が示されている（http://www.jsrm.or.jp/guideline-statem/guideline_2003_01.html）。胚および卵子の凍結保存に関しては、日本産科婦人科学会より見解が示されている（http://www.jsog.or.jp/ethic/hitohai_20100422.html）が、悪性腫瘍の治療など医学的介入による女性の卵巣機能の低下を想定した具体的指針ではない。同学会の「体外受精・肺移植に関する見解」（http://www.jsog.or.jp/about_us/view/html/kaikoku/H18_4_taigaijusei.html）では体外受精・胚移植は配偶者を有する女性を対象とすることが前提となっており、配偶者のいない女性に対する国内における例外的な取り組みとしてA-PART（The International Association of Private Assisted Reproductive Technology Clinics and Laboratories, 不妊・生殖補助医療国際学会）日本支部が、「複数施設における血液疾患未婚女性患者における卵子採取、ならびに凍結保存の臨床研究」（http://www.apartonline.info/japan/pdf/apart_2012_0423_2.pdf）を、

研究として実施している実態がある。

以上より、配偶子の取り扱いに関する基本的な考え方や、インフォームドコンセントにあたり癌治療医や生殖医療医が情報提供すべき内容に関しては、上述の国内の倫理規範に則ることが求められると考えるが、配偶者のいない乳癌患者への卵子保存に関する国内の基盤は脆弱であり、現実に臨床現場で遭遇することの多い未婚女性の卵子保存に関しては、卵子保存技術は技術的にも未確立であると考えられ、規範の整備や、登録制度の確立を含む研究的基盤の整備を考慮する必要があると考えられた。また、乳癌患者の妊孕性保持という観点からは、多くは35歳を超える妊娠・出産となると考えられることから、生殖年齢の解釈に関しても一定のコンセンサスが必要と考えられた。

さらに、がん患者に対する妊孕性保持に関連した懸念事項として、以下に示すような問題点が挙げられた。

・予後不良と考えられる患者の挙児希望が、児の福祉という観点から、社会的に許容されるものであるか？

・有効性に関するエビデンスが確立している薬物療法の省略や中断が患者への潜在的な不利益をもたらす可能性があるが、癌治療医の医療上の責任は問われる可能性はないか？

・がんの診断後短期間で意思決定が必要となる状況下で、患者に十分に情報を咀嚼し、自己決定できるのか？

b. 当研究班で作成するガイドライン案の構成の検討と作成手順

ガイドラインでは、①インフォームドコンセントにおける基本的な考え方、②必要な体制、③クリニカルクエスチョン、④倫理的・法的問題の４部構成とすることとした（資料3）。クリニカルクエスチョンについては、乳癌治療に関するクリニカルクエスチョン（生殖医療医の臨床的疑問）、生殖医療に関するクリニカルクエスチョン（乳癌治療医の臨床的疑問）に大別し、それぞれ乳癌治療医と生殖医療医が執筆を担当することとした。

クリニカルクエスチョンに対する本文・エビデンスレベル・推奨レベルの記載に関しては、Minds診療ガイドライン選定部会による「診療ガイドライン作成の手引き」を参考にして作成することとした。原案作成担当者は、各クリニカルクエスチョン文献検索を行い、アブストラクトフォームを作成、エビデンスレベルと推奨レベルを付与する。さらにグループ内・グループ間のピアレビュー、癌治療医・生殖医療医別のコンセンサス会議、全体のコンセンサス会議を経て最終案とすることとした。

ガイドラインの作成は、当研究班の班員に加え、日本がん・生殖医療研究会のメンバーに依頼することとした。

c. クリニカルクエスチョン

資料６にクリニカルクエスチョンおよび、内定した執筆担当者を示す。

② 乳癌患者の生殖医療に関するリアルタイム・コンサルテーション・システムのモデル作成

a. 患者情報提供用小冊子「乳がん治療に際して将来の出産を御希望の患者さんへ」の妥当性評価

平成 21-23 年度厚生労働科学研究補助金「がん患者及びその家族や遺族の抱える精神心理的負担によるQOLへの影響を踏まえた精神心理的ケアに関する

研究」班で作成した試作版患者用小冊子（B6 版、全 16 頁）の医療者からみた有用性と内容の妥当性の評価するため、任意の乳腺外科医、腫瘍内科医、生殖医療医（計 39 名）に送付し（資料 7、8、9）、25 人より回答を得た。

約 80%がパンフレットは「自分の役に立つ」「患者の役に立つ」と回答したが、内容のわかりやすさについた「わかりやすい」48%、「ふつう」30%、「少しわかりづらい」22%、「わかりづらい」0%であった。回答者より得た指摘事項を踏まえ、改訂版を作成した（資料 10、資料 11）。

b. データベースの構築

データベースの基盤に関する議論を行った。収集すべきデータとして以下の要素が挙げられた。

・患者の人口社会学的背景（年齢、パートナー・配偶者の有無、家族環境、就労の有無、年収、家族歴）

・乳癌の背景（臨床病期、ホルモン受容体、HER2、Ki67 など）

・乳癌治療の内容（推奨された治療、実施した治療、その期間）

・乳癌のアウトカム：　再発・転移、死亡

・治療前、治療後の卵巣機能評価（月経、E2, FSH, LH, AMH など）

・生殖医療の内容（実施タイミング、排卵誘発法、卵子凍結方法、体外受精の実施回数など）

・生殖医療のアウトカム：　妊娠、出産、児の予後

次年度に、当研究班でパイロット研究を実施することで合意した。

D．考察

乳癌患者の妊孕性保持に関するガイドライン案の作成に着手した。ガイドライン案の作成にあたっては、医療技術の科学的根拠だけでなく、インフォームドコンセントの在り方、既存の国内の倫理規範との整合性、がん・生殖医療の特殊性に配慮する必要があると考えられる。

患者用冊子は患者教育の一助となるだけでなく、乳癌治療医・生殖医療医の診療の効率化に役立つと考えられる。患者や市民・医療従事者の情報へのアクセスを容易にするため、今後、改訂版患者用冊子は、日本がん・生殖医療研究会および平成 21-23 年がん研究開発費「若年乳癌患者のサバイバーシップ支援プログラムの構築」班のウェブサイト「若年乳がん～拓かれた乳がん医療のために～」等にて公開する予定である。

未婚女性の卵子保存などに関する規範の整備や、登録制度の確立を含む研究的基盤を確立する必要があると考えられた。

E．結論

挙児希望を有する乳癌患者の意思決定と乳癌治療医と生殖医療医の円滑な協働の支援を目指して、乳癌患者の妊孕性保持に関するガイドライン案のアウトラインの作成し、患者用冊子の妥当性評価を行った。

F．健康危険情報

該当なし

G．研究発表

１．論文発表

田村宜子、清水千佳子。妊娠と乳癌薬物療法 現状と今後の展望（解説／特集)。
乳癌の診療、28(1),53-61,2013

２．学会発表

加藤友康、田村宜子、清水千佳子、坂東裕子、溝田友里、山本精一郎、藤原康弘
乳癌患者の生殖医療に関する生殖医療専門医の意識調査
第 27 回 日本女性医学学会学術総会、山形市 2012.10.14

加藤友康、清水千佳子、田村宜子、坂東裕子、溝田友里、山本精一郎、浅田義弘、藤原康弘
乳癌患者の生殖医療に関する生殖医療専門医の意識調査
第 50 回　日本癌治療学会学術集会、横浜市 2012.10.26

加藤友康、田村宜子、清水千佳子、坂東裕子、溝田友里、山本精一郎、藤原康弘
乳癌患者の生殖医療の課題：生殖医療医に対するアンケート調査より
第 57 回　日本生殖医療学会学術講演会・総会、長崎市 2012.11.9

田村宜子、清水千佳子、加藤友康、坂東裕子、溝田友里、山本精一郎、浅田義正、藤原康弘
挙児希望のある乳癌患者への情報提供ツールの開発
第 50 回　日本癌治学会学術集会　横浜市 2012.2.

Shimizu C, Kato T, Tamura N, Bando Y, Asada Y, Mizota Y, Yamamoto S, Fujiwara Y.
Perception and needs of reproductive specialists toward fertility preservation of young breast cancer patients.
2012 CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio Texas
(P2-11-02)

鈴木直
卵巣組織凍結を用いた妊孕性温存.
第 13 回横浜乳がんシンポジウム, 横浜市, 2012.10

鈴木直.
配偶子凍結、胚凍結、卵巣組織凍結などの問題点抽出
第 1 回 日本がん・生殖医療研究会, 川崎市, 2012.11

鈴木直.
研究会ならびに法人設立に関して, 第 2 回日本がん・生殖医療研究会,東京, 2013.1

大野真司
患者に向けガイドライン 2012 の改訂ポイント、第 20 回日本乳癌学会学術
総会、熊本、2012.6

大野真司
深き若年乳がん医療を考える、第 10 回日本乳癌学会九州地方会、長崎、2013.3

Ohno S,
Young Women Breast Cancer -Translational Research and Clinics, The 38th Annual Meeting of the Korean Cancer Association, Seoul, 2012.6

Ohno S,
What's New in Triple Negative, The 10th International Conference of the Asian Clinical Oncology Society, Seoul, 2012.6

Ohno S,
Ovarian Function Suppression and Effect of Chemotherapy Induced Menorrhea - Evidences and Guidelines, Korean Surgical International Symposium 2012, Seoul, 2012.12

H. 知的財産権の出願・登録状況

１．特許取得　　該当なし
２．実用新案登録　　該当なし
３．その他　　該当なし

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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

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A B S T R A C T

Purpose
To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer.

Methods
An expert panel and a writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature from 1987 to 2005 was performed, and included a search of online databases and consultation with content experts.

Results
The literature review found many cohort studies, case series, and case reports, but relatively few randomized or definitive trials examining the success and impact of fertility preservation methods in people with cancer. Fertility preservation methods are used infrequently in people with cancer.

Recommendations
As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists. Clinician judgment should be employed in the timing of raising this issue, but discussion at the earliest possible opportunity is encouraged. Sperm and embryo cryopreservation are considered standard practice and are widely available; other available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise.

Conclusion
Fertility preservation is often possible in people undergoing treatment for cancer. To preserve the full range of options, fertility preservation approaches should be considered as early as possible during treatment planning.

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INTRODUCTION

The diagnosis and treatment of cancer often poses a threat to fertility. Methods of fertility preservation are evolving quickly, yet little has been published in the medical oncology literature regarding this topic. Studies suggest that the ability to have biological children is of great importance to many people. Any oncologist seeing reproductive-aged patients for consideration of cancer therapy should be addressing potential treatment-related infertility with them or, in the case of children, with their parents. Yet, studies suggest that many oncologists either do not discuss the possibility of treatment-related infertility or do so suboptimally. Teaching in many fellowship programs covers sperm banking and techniques such as oophoropexy,[1] while little information is provided concerning other methods of fertility preservation.

The purpose of this guideline is to review the literature pertaining to fertility preservation options for men, women, and children undergoing cancer treatment, and to give guidance to oncologists about these issues. The focus is restricted to interventions aimed at fertility preservation; the guidelines do not address methods of fertility restoration after completion of cancer treatment nor the risks of assisted reproductive techniques, except those unique to cancer patients. The risks of pregnancy to parents and offspring after cancer treatment are reviewed only insofar as they might affect a person's desire to pursue fertility preservation methods before or during active cancer treatment.

Estimating the Risk of Infertility After Treatment for Cancer

Infertility is functionally defined as the inability to conceive after 1 year of intercourse without

contraception. Rates of permanent infertility and compromised fertility after cancer treatment vary and depend on many factors. The effects of chemotherapy and radiation therapy depend on the drug or size/location of the radiation field, dose, dose-intensity, method of administration (oral versus intravenous), disease, age, sex, and pretreatment fertility of the patient. Male infertility can result from the disease itself (best documented in patients with testicular cancer and Hodgkin's lymphoma), anatomic problems (eg, retrograde ejaculation or anejaculation), primary or secondary hormonal insufficiency, or more frequently, from damage or depletion of the germinal stem cells. The measurable effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity. In females, fertility can be compromised by any treatment that decreases the number of primordial follicles, affects hormonal balance, or interferes with the functioning of the ovaries, fallopian tubes, uterus, or cervix. Anatomic or vascular changes to the uterus, cervix, or vagina from surgery or radiation may also prevent natural conception and successful pregnancy, requiring assisted reproductive technology or use of a gestational carrier.

Male and female fertility may be transiently or permanently affected by cancer treatment or only become manifest later in women through premature ovarian failure. The panel wishes to emphasize that female fertility may be compromised despite maintenance or resumption of cyclic menses. Regular menstruation does not guarantee normal fertility as any decrease in ovulatory reserve may result in a lower chance of subsequent conception and higher risk of early menopause. Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened by premature menopause.

An estimated 1,372,910 people were diagnosed with cancer in 2005, of whom 4% (approximately 55,000) are under the age of 35.[2] The most common cancers diagnosed in people under the age of 40 years are breast cancer, melanoma, cervical cancer, non-Hodgkin's lymphoma, and leukemia.[3] The Panel recognizes that a table of all common cancer treatments with their associated risks of infertility is desirable. However, available data are poor and heterogeneous, so summarization was felt to be beyond the scope of this guideline. However, Tables 1[3A] and 2, and several additional references[4-12] illustrate the range of risks associated with several cancer therapies. The Panel noted that most of the available literature quantifying infertility risks reports rates of azoospermia and amenorrhea, though these are surrogate measures of infertility. In men and women, the greatest risks associated with chemotherapy involve the alkylating agents (particularly cyclophosphamide,

Table 1. Effects of Different Antitumor Agents on Sperm Production in Men[168]

Agents (Cumulative Dose for Effect)	Effect
Radiation (2.5 Gy to testis)	Prolonged azoospermia
Chlorambucil (1.4 g/m^2)	
Cyclophosphamide (19 g/m^2)	
Procarbazine (4 g/m^2)	
Melphalan (140 mg/m^2)	
Cisplatin (500 mg/m^2)	
BCNU (1 g/m^2)	Azoospermia in adulthood after treatment before puberty
CCNU (500 mg/m^2)	
Busulfan (600 mg/kg)	Azoospermia likely, but always given with other highly sterilizing agents
Ifosfamide (42 g/m^2)	
BCNU (300 mg/m^2)	
Nitrogen mustard	
Actinomycin D	
Carboplatin (2 g/m^2)	Prolonged azoospermia not often observed at indicated dose
Doxorubicin (Adriamycin) (770 mg/m^2)	Can be additive with above agents in causing prolonged azoospermia, but cause only temporary reductions in sperm count when not combined with above agents
Thiotepa (400 mg/m^2)	
Cytosine arabinoside (1 g/m^2)	
Vinblastine (50 g/m^2)	
Vincristine (8 g/m^2)	
Amsacrine, bleomycin, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine	Only temporary reductions in sperm count at doses used in conventional regioments, but additive effects are possible
Prednisone	Unlikely to affect sperm production
Interferon-α	No effects on sperm production
Examples of new agents:	Unknown effects on sperm production
Oxaliplatin	
Irinotecan	
Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)	
Tyrosine kinase inhibitors (erlotinib, imatinib)	
Taxanes	

NOTE. Reprinted and modified Table 54.6-3 with permission from DeVita, VT, Jr, Hellman S, and Rosenberg, SA. Cancer: Principles & Practice of Oncology (ed 7). Philadelphia, Pa, Lippincott Williams & Wilkins, 2005.
Abbreviations: BCNU, carmustine; CCNU, lomustine.

Table 2. Risks of Permanent Amenorrhea in Women Treated With Modern Chemotherapy and Radiotherapy

Degree of Risk	Cancer Treatment
High risk (> 80%)	Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan
	External beam radiation to a field that includes the ovaries
	CMF, CEF, CAF × 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)
Intermediate risk	CMF, CEF, CAF × 6 cycles in women age 30-39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)
	AC × 4 in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)
Lower risk (< 20%)	ABVD (doxorubicin/bleomycin/vinblastin/dacarbazine)
	CHOP × 4-6 cycles (cyclophosphamide/doxorubicin/vincristine/prednisone)
	CVP (cyclophosphamide/vincristine/prednisone)
	AML therapy (anthracycline/cytarabine)
	ALL therapy (multi-agent)
	CMF, CEF, CAF × 6 cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)
	AC × 4 in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)
Very low or no risk	Vincristine
	Methotrexate
	Fluorouracil
Unknown risk (examples)	Taxanes
	Oxaliplatin
	Irinotecan
	Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)
	Tyrosine kinase inhibitors (erlotinib, imatinib)

*These are general guidelines based on best available literature. Additional factors, particularly pre-treatment ovarian reserve,specific treatment regimen, and age determine individual risk for immediate infertility, or for premature ovarian failure after resumption of menses. Please see text for details.

ifosfamide, nitrosoureas, chlorambucil, melphalan, busulfan, and procarbazine). Total-body irradiation as used in myeloablative stem-cell transplantation is highly associated with infertility, while lesser doses or limited radiation fields have less gonadal toxicity.[13,14] Several agents are associated with a low or no risk of infertility: methotrexate, fluorouracil, vincristine, bleomycin, and dactinomycin. There are little human data available for the newer agents such as taxanes. Given the paucity of data regarding rates of male and female infertility following most current cancer treatments and the large number of patient factors that influence fertility, oncologists may have difficulty providing precise guidance to patients about their risks for infertility.

Questions The committee addressed the following clinical questions:

1. Are cancer patients interested in interventions to preserve fertility?
2. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?
3. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?
4. What is the role of the oncologist in advising patients about fertility preservation options?

Practice Guidelines Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide the following:

1. Improvement in outcomes
2. Improvement in medical practice
3. Means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where further research is needed

In formulating recommendations for fertility preservation options, ASCO considered these tenets of guideline development, emphasizing review of data from appropriately conducted and analyzed clinical trials. However, it is important to note that guidelines cannot always account for individual variation among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result. (Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe the use of procedures and therapies in clinical practice; they cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.)

METHODS

Panel Composition

The ASCO Health Services Committee (HSC) convened an Expert Panel consisting of experts in clinical medicine and research relevant to fertility preservation in cancer patients, including adult and pediatric oncology, obstetrics-gynecology, andrology, reproductive endocrinology and infertility, health services research,

psychosocial oncology, and bioethics. A patient representative was also part of the Panel. Panel members are listed in the Appendix.

Literature Review and Analysis

The following electronic databases were searched from 1987 through March 2005: MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library. The National Cancer Institute's (NCI) PDQ database of clinical trials, and the National Library of Medicine's (NLM) *ClinicalTrials.gov* database were also searched for ongoing trials. Results were supplemented with hand searching of selected reviews and personal files. The following MeSH terms and text words were used in a core search: "fertility," "infertility," and "neoplasms." In separate searches, results were cross-referenced with "pregnancy," "pregnancy outcomes," "reproductive techniques," "premature ovarian failure," and "premature menopause." Supplemental searches were done for each intervention using terms specific for that intervention (eg, "sperm banks," "semen preservation"). Due to the very limited number of randomized controlled trials in this field of research, study design was not limited to randomized controlled trials, but was expanded to include cohort designs, case series, and where no other data were available, case reports and selected abstracts. Letters, commentaries, and editorials were excluded.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the study discussed a fertility intervention and reported primary data; and (2) the study population consisted of cancer patients scheduled for or undergoing cancer treatments that threaten fertility (other populations could be considered where data were lacking in cancer patients). Articles were excluded from further consideration if they did not report specifically on a fertility intervention and did not report primary data. However, due to the limited nature of the data in many areas, the Panel made an a priori decision to also retain high-quality reviews or background papers, and these articles were described as such in the coding process.

An initial article abstract screen was performed by ASCO staff. The ASCO Panel reviewed all remaining potentially relevant abstracts identified in the original literature searches to select studies pertinent to its deliberations. Two Panel members independently reviewed each abstract for its relevance to the clinical questions, and disagreements were resolved by third-party review. Full text articles were then reviewed for all selected abstracts. The Panel designed a coding sheet to complete the review of identified potentially relevant studies, and the Co-Chairs assigned each Panel member a subset of articles to review. Data were extracted on the source of the threat to fertility, the intervention being considered, the outcomes assessed, the number of patients and types of cancer, and study design. Primary outcomes of interest included pregnancies and live births, but the following were also considered: fertility maintenance; resumption/maintenance of menses; number of oocytes recovered; number of embryos recovered; fertilization rates; and in vitro fertilization (IVF) outcome. Also considered were the risks associated with the fertility intervention, quality of life, patient and/or family satisfaction, patient education or increased awareness, and economic evaluation (eg, cost-effectiveness, cost utility).

Consensus Development Based on Evidence

The entire Panel participated in monthly teleconferences. Preliminary teleconferences refined the questions addressed by the guideline; subsequent teleconferences addressed the process of the systematic review and the allocation of writing assignments for respective sections. All members of the Panel participated in the preparation of the guideline. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the Health Services Committee (HSC) and by the ASCO Board of Directors before dissemination.

Guideline and Conflict of Interest

All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Revision Dates

At annual intervals, the Panel Co-Chairs and two Panel members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline to the HSC and the ASCO Board for review and approval.

RESULTS

Literature Search

Preliminary searches identified 1,675 potential articles. The initial abstract screen performed by ASCO staff eliminated 807 abstracts that failed to meet any of the inclusion criteria. The ASCO Panel conducted dual independent review of all remaining 868 potentially relevant abstracts identified in the original systematic review. The Panel eliminated 463 abstracts at this stage of the review; the remaining 405 articles were reviewed in full for the interventions and outcomes described above. One hundred twenty-nine articles that did not report primary data on a fertility preserving intervention were excluded from further consideration. Two hundred thirty-three articles met the inclusion criteria, and an additional 43 articles met the a priori criteria as supplementary studies or reviews.

A meta-analysis was not performed because the studies were judged to be too small and heterogeneous for meaningful quantitative synthesis.

Cohort studies or case series were identified in embryo and oocyte cryopreservation, ovarian tissue preservation, conservative surgical treatment of tumors, ovarian transposition (during radiotherapy), trachelectomy, sperm banking, rectal electroejaculation, hormonal manipulation, intracytoplasmic sperm injection, and testicular sperm extraction. Case reports were available for the other methods of fertility preservation.

Of the outcomes assessed, 111 studies reported on pregnancies, live births, or IVF outcome. Of these 111 studies, the majority were case series or case reports.

Limitations of the Literature

Review of the fertility preservation literature reveals a paucity of large and/or randomized studies. Most data come from cohort studies, case series, small nonrandomized clinical trials or case reports. Fertility preservation methods are still applied relatively infrequently in the cancer population, limiting greater knowledge about success and effects of different potential interventions. Other than risk of tumor recurrence, less attention is paid to the potential negative effects (physical and psychological) of fertility preservation attempts.

Little is known about the emotional impact of infertility or utilization of fertility preservation options on cohorts that are diverse in ethnicity and socioeconomic status, groups that face even greater barriers to fertility preservation.[15,16]

The Panel encourages additional well-designed studies evaluating methods of fertility preservation in people with cancer to help answer these questions. However, the Panel also notes that the traditional gold standard of randomized, controlled, and blinded therapeutic studies may not be possible in this area.

I. Are Cancer Patients Interested in Fertility Preservation Interventions?

The available evidence suggests that fertility preservation is of great importance to many people diagnosed with cancer, and that infertility resulting from cancer treatment may be associated with psychosocial distress. Although cancer survivors can become parents through options such as adoption and third-party reproduction (using gamete donation or a gestational carrier),[17] most prefer to have a biological offspring,[18-20] even if they have concerns about birth defects that could be caused if the parent had cancer treatment before conception[21] or anxiety about their own longevity or their child's lifetime cancer risk. One study in men suggested that having banked sperm was a positive factor in coping emotionally with cancer, even if samples were never used.[22] Cancer survivors who are free of disease typically view themselves as healthy enough to be good parents, and in fact view their experience of illness as one that can enrich their parental role. Most put a higher value on family closeness after cancer and believe they are less bothered by daily stresses.[19,20,23] It may be impossible for physicians to know how important fertility preservation is to their patients unless they ask, since many patients may not bring up the topic. A recent report by the President's Cancer Panel recommends that all cancer patients of reproductive age be informed about the possibility of treatment-related infertility.[24] Figure 1 and Table 3 provide guidance to oncologists in initial discussions.

Surveys of cancer survivors have identified an increased risk of emotional distress in those who become infertile because of their treatment.[19,20,25-28] These studies mirror what has been observed in infertile noncancer populations where research clearly shows that long-term quality of life is affected by unresolved grief and depression,[16] as well as reduced life satisfaction and increased anxiety.[29-31] Some evidence suggests that patients may choose a less efficacious treatment strategy in order to avoid greater toxicity and long-term complications. For example, if given a choice, young women with early-stage breast cancer may choose a less toxic regimen of chemotherapy even if it confers slightly less protection from recurrence.[27]

Parents may also be interested in fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand, but potentially traumatic to them as adults. Use of established methods of fertility preservation (semen cryopreservation and embryo freezing) in postpubertal minor children requires patient assent and parental consent. Unfortunately, the modalities that are available to prepubertal children to preserve their fertility are limited by patients' sexual immaturity and are essentially experimental. Efforts to preserve fertility of children using experimental methods should only be attempted under institutional review board (IRB)–approved protocols, where proper attainment of informed consent from a legally authorized representative(s) (ie, parent[s] or guardian[s]) and of childhood assent can be ensured.[32-34] It has been suggested that to overcome some of the practical obstacles involved in studying experimental fertility preservation in children, the consent process should be performed in two stages.[35-36] The decision to harvest gametes would be made at the time of cancer treatment, and consent for the procedure would rely on parents/guardians. The decision of how to use the gametes after they have been isolated could be made at a future point by the patient. Then, the adult patient would be better able to express personal preferences about the handling of the tissue.

II. What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Males?

The Panel reviewed the available information supporting sperm cryopreservation, testicular hormonal suppression, and

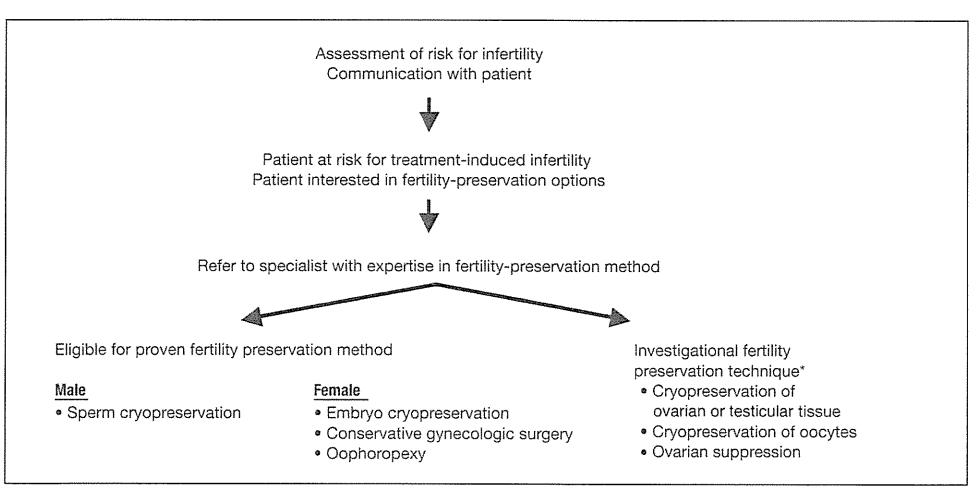

Fig 1. Flow diagram. *Clinical trial participation encouraged.

Table 3. Points of Discussion Between the Patient and Physician: Fertility Preservation Methods in Cancer Patients

- Cancer and cancer treatments vary in their likelihood of causing infertility. Individual factors such as disease, age, treatment type and dosages, and pretreatment fertility should be considered in counseling patients about the likelihood of infertility.
- Patients who are interested in fertility preservation should consider their options as soon as possible to maximize the likelihood of success. Some female treatments are dependent upon phase of the menstrual cycle and can only be initiated at monthly intervals. Discussion with reproductive specialists and review of available information from patient advocacy resources (for example, FertileHope, the Lance Armstrong Foundation/Livestrong, the Susan G. Komen Breast Cancer Foundation) can facilitate decision-making and treatment planning.
- The two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for males and embryo freezing for females. Conservative surgical approaches and transposition of ovaries or gonadal shielding prior to radiation therapy may also preserve fertility in selected cancers. At this time (2006), other approaches should be considered investigational.
- Data are very limited, but there appears to be no detectable increased risk of disease recurrence associated with most fertility preservation methods and pregnancy, even in hormonally sensitive tumors.
- Aside from hereditary genetic syndromes and in utero exposure to chemotherapy, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities in the progeny.
- Treatment-related infertility may be associated with psychosocial distress, and early referral for counseling may be beneficial in moderately distressed people.

testicular tissue cryopreservation. The available evidence suggests that sperm cryopreservation is an effective method of fertility preservation in males treated for cancer. In contrast, gonadoprotection through hormonal manipulation is ineffective. Testicular tissue or spermatogonial cryopreservation and transplantation or testis xenografting are in the early phases of experimentation and have not yet been successfully tested in humans. Table 4 summarizes the fertility preservation options in males. The Panel notes that available interventions are unlikely to delay initiation of cancer treatment once a patient is successfully referred.

Sperm cryopreservation. Due to recent advances in IVF technology and sperm banking procedures, even men with extremely reduced sperm count and motility are candidates for sperm cryopreservation. It is strongly recommended that sperm be collected before initiation of cancer therapy because the quality of the sample and sperm DNA integrity may be compromised even after a single treatment session.[37,38] In addition, depending on the type of cancer—particularly testicular cancer and Hodgkin's lymphoma[39]—and the overall condition of the patient, sperm quality may be poor even in patients who have not yet started treatment.[37,38,40,41] Many patients have to start chemotherapy immediately or soon enough to limit the number of ejaculates to one or two samples. Even in these instances, it is reasonable to make every effort to bank sperm[38] since recent progress in andrology laboratories and in the use of assisted reproductive techniques, particularly the technique of intracytoplasmic sperm injection (ICSI) allows the successful freezing and future use of a very limited amount of sperm. There are case reports and small case series of successful collection of sperm from a postmasturbation urine sample, rectal electroejaculation under anesthesia,[42,43] and testicular sperm aspiration,[44] but these are uncommon and/or investigational methods. Oncologists should make every effort to discuss sperm banking with appropriate patients,[38,45-47] though a recent survey[48] suggests

Table 4. Summary of Fertility Preservation Options in Males

Intervention	Definition	Comment	Considerations
Sperm cryopreservation (S) after masturbation	Freezing sperm obtained through masturbation	The most established technique for fertility preservation in men; large cohort studies in men with cancer	• Outpatient procedure • Approximately $1,500 for three samples stored for 3 years, storage fee for additional years*
Sperm cryopreservation (S) after alternative methods of sperm collection	Freezing sperm obtained through testicular aspiration or extraction, electroejaculation under sedation, or from a postmasturbation urine sample	Small case series and case reports	Testicular sperm extraction-outpatient surgical procedure
Gonadal shielding during radiation therapy (S)	Use of shielding to reduce the dose of radiation delivered to the testicles	Case series	• Only possible with selected radiation fields and anatomy • Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs
Testicular tissue cryopreservation Testis xenografting Spermatogonial isolation (I)	Freezing testicular tissue or germ cells and reimplantation after cancer treatment or maturation in animals	Has not been tested in humans; successful application in animal models	Outpatient surgical procedure
Testicular suppression with gonadotropin releasing hormone (GnRH) analogs or antagonists (I)	Use of hormonal therapies to protect testicular tissue during chemotherapy or radiation therapy	Studies do not support the effectiveness of this approach	

Abbreviations: S, standard; I, investigational.
*Costs are estimates.

that oncologists lack knowledge about recent advances in assisted reproductive techniques.

Sperm cryopreservation in boys and young men involves additional considerations. Spermarche, the production of sperm, occurs at approximately 13 to 14 years, but once sperm are present, the patient's age does not seem to affect quality of sperm produced.[49] However, prepubertal boys have not yet developed gametes, and collection of semen through masturbation in adolescents may be compromised by embarrassment and issues of informed consent. For example, one study suggested adolescent boys may be more successful if a parent does not accompany them to the sperm bank.[50]

Hormonal gonadoprotection. The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients. Hormonal therapy in men is not successful in preserving fertility when highly sterilizing chemotherapy is given,[51,52] nor did it speed recovery of spermatogenesis in 18 men after nonsterilizing treatment compared to concurrent controls.[53,54] Based on observations in rats, a small prospective study evaluated the effects of hypothalamic-pituitary-gonadal suppression plus testosterone in seven men rendered azoospermic after chemotherapy or radiation treatment for childhood cancer. No recovery of spermatogenesis was seen after 12 weeks of suppression.[55] In contrast, a very small study evaluating testosterone in men without cancer treated with cyclophosphamide for glomerulonephritis suggested some benefit.[56]

Other methods to preserve male fertility. Other methods, such as testicular tissue cryopreservation and reimplantation[57] or grafting of human testicular tissue to SCID mice to facilitate spermatogenesis,[58,59] remain experimental and have not been tested in humans. Of note, such approaches are also the only methods of fertility preservation potentially available to prepubertal boys.

Other considerations of fertility preservation options in males. Epidemiological studies confirm that most young male patients with cancer are not referred for sperm banking.[12,37,38] Reasons for this apparent underutilization are likely multifactorial. Physicians may not discuss or emphasize opportunities to preserve fertility before treatment.[60] Psychological, logistic and financial constraints on patients may further limit sperm banking. Men may be traumatized about their diagnosis or lack interest in fertility preservation at the time of diagnosis. However, two recent surveys suggest that for men who desire future children, lack of timely information is the most common reason for not banking sperm.[19,20] Responsibility for organizing an appointment with the cryopreservation laboratory often falls to the patient. Most insurance companies in the United States do not cover sperm cryopreservation. However, even in the United Kingdom, where the national health system subsidizes sperm banking for young cancer patients, many young men are not given referrals.[61]

Even when sperm is banked, most studies suggest that a minority (up to 30%, but $<$ 10% in most cohorts) of men return to use their stored specimens.[41,62-64] Storage fees are rarely a reason that men have cryopreserved semen destroyed.[65]

In the absence of a heritable cancer syndrome, there is no evidence that a prior history of cancer increases the rate of congenital abnormalities or cancer in a man's offspring.[66] However, recent studies suggest the sperm of untreated men with cancer may have poor DNA integrity even before treatment.[67,68] Small studies suggest transient higher rates of aneuploidy after chemotherapy and radiotherapy,[69-71] though DNA integrity of sperm seemed similar to age-matched controls in one cohort of pediatric cancer survivors.[72] Men should be advised of a possible, not yet quantifiable, higher risk of genetic damage in sperm stored after diagnosis of cancer or initiation of cancer therapy. In noncancer populations, there is no evidence of an increased risk of adverse outcomes if cryopreserved rather than fresh sperm are used for assisted reproductive techniques. Intracytoplasmic sperm injection (ICSI) allows successful fertilization with a single sperm but has raised concerns about the health of offspring conceived by this method. Although no studies have shown an increased rate of adverse outcomes compared with traditional in vitro fertilization techniques (both may be associated with a higher rate of major birth defects than unassisted conception),[73] the technique is relatively new, and long-term follow-up of progeny is recommended.[74,75]

III. What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Females?

Fertility preservation options in females depend on the patient's age, type of treatment, diagnosis, whether she has a partner, the time available and the potential that cancer has metastasized to her ovaries.[76] The panel reviewed the available information supporting embryo and oocyte cryopreservation (with or without hormonal stimulation), ovarian tissue cryopreservation, ovarian suppression, ovarian transposition, and trachelectomy. Conservative surgical and radiation therapy approaches to specific cancers are also available but are not discussed further. Table 5 summarizes the options for fertility preservation in females. The Panel notes that due to requirements for scheduling and procedures, some interventions may entail a delay in cancer treatment and wishes to emphasize that early referral to a subspecialist can minimize this delay.

Embryo cryopreservation. Embryo cryopreservation is considered an established fertility preservation method as it has routinely been used for storing surplus embryos after in vitro fertilization for infertility treatment. This approach typically requires approximately two weeks of ovarian stimulation with daily injections of follicle-stimulating hormone from the onset of menses. Follicle development is monitored by serial ultrasounds and blood tests. At the appropriate time, an injection of HCG is administered to start the ovulatory cascade, and oocytes are subsequently collected by ultrasound guided transvaginal needle aspiration under intravenous sedation. Oocytes are fertilized in vitro and cryopreserved after fertilization. Because stimulation must be started at the onset of menses and takes two weeks, a delay of 2 to 6 weeks in chemotherapy initiation may be required if reproductive specialists do not see women early in their menstrual cycle. Most insurance companies do not offer assisted reproductive techniques as benefits so this approach may be associated with high out-of-pocket costs for most women. A partner or sperm donor is also required.

Live birth rates after embryo cryopreservation depend on the patient's age and the total number of embryos cryopreserved and may be lower than with fresh embryos. Oocyte collection can be performed without ovarian stimulation ("natural cycle-IVF") but the embryo yield is extremely low.[77,78] For women with hormone-sensitive tumors,[79] alternative hormonal stimulation approaches such as letrozole or tamoxifen have been developed to theoretically reduce the potential risk of estrogen exposure. Short term breast cancer recurrence rates after ovarian stimulation using letrozole or tamoxifen concurrent with follicle stimulating hormone (FSH) administration have been compared to nonrandomized controls and no increase in

Table 5. Fertility Preservation Options in Females

Intervention	Definition	Comment	Considerations*
Embryo cryopreservation (S)	Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation	The most established technique for fertility preservation in women	• Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle • Outpatient surgical procedure • Requires partner or donor sperm • Approximately $8,000 per cycle, $350 per year storage fees
Oocyte cryopreservation (I)	Harvesting and freezing of unfertilized eggs	Small case series and case reports; as of 2005, 120 deliveries reported, approximately 2% live births per thawed oocyte (3-4 times lower than standard IVF)	• Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle • Outpatient surgical procedure • Approximately $8,000 per cycle, $350/yr storage fees
Ovarian cryopreservation and transplantation (I)	Freezing of ovarian tissue and reimplantation after cancer treatment	Case reports; as of 2005, two live births reported	• Not suitable when risk of ovarian involvement is high • Same day outpatient surgical procedure
Gonadal shielding during radiation therapy (S)	Use of shielding to reduce the dose of radiation delivered to the reproductive organs	Case series	• Only possible with selected radiation fields and anatomy • Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs
Ovarian transposition (oophoropexy) (S)	Surgical repositioning of ovaries away from the radiation field	Large cohort studies and case series suggest approximately 50% chance of success due to altered ovarian blood flow and scattered radiation	• Same day outpatient surgical procedure • Transposition should be performed just before radiation therapy to prevent return of ovaries to former position • May need repositioning or in vitro fertilization (IVF) to conceive
Trachelectomy (S)	Surgical removal of the cervix while preserving the uterus	Large case series and case reports	• Inpatient surgical procedure • Limited to early stage cervical cancer; no evidence of higher cancer relapse rate in appropriate candidates • Expertise may not be widely available
Other conservative gynecologic surgery (S/I)	Minimization of normal tissue resection	Large case series and case reports	• Expertise may not be widely available
Ovarian suppression with gonadotropin releasing hormone (GnRH) analogs or antagonists (I)	Use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy	Small randomized studies and case series. Larger randomized trials in progress	• Medication given before and during treatment with chemotherapy • Approximately $500/mo

Abbreviations: S, standard; I, investigational.
*Costs are estimates

cancer recurrence rates has been noted in these initial studies.[77,78] Only a small percentage of cancer survivors have yet returned to utilize their embryos but the initial pregnancy rates are encouraging.[77,79] Nevertheless, long-term follow-up with a larger number of patients is needed to evaluate the safety and efficacy of this approach. The panel also notes that letrozole and tamoxifen should not be given to a woman after pregnancy is established.[80,81] Recently, standard ovarian stimulation with coapplication of a progestin-releasing IUD has been reported to allow successful preservation of embryos in a patient with endometrial cancer.[82]

Oocyte cryopreservation. Cryopreservation of unfertilized oocytes is another option for fertility preservation, particularly in patients for whom a partner is unavailable, or who have religious or ethical objections to embryo freezing. The oocytes are thawed later and fertilized in vitro. Ovarian stimulation and harvesting requirements are identical to those of embryo cryopreservation, and thus this technique is associated with similar concerns regarding delays in therapy and potential risks of short-term exposure to high hormonal levels. As with embryo cryopreservation, letrozole or tamoxifen can be used. Research indicates that unfertilized oocytes are more prone to damage during cryopreservation procedures than embryos, and as a result, the overall pregnancy rates may be lower than standard IVF procedures.[83] There have been approximately 120 deliveries with this approach,[83] and efforts to improve the efficiency of cryopreservation may increase success rates.[84,85] Further research is needed to delineate the current success rates and safety, as well as to improve the efficiency

of this procedure. Oocyte cryopreservation should only be performed in centers with the necessary expertise, and the Panel recommends participation in IRB-approved protocols.

Ovarian tissue cryopreservation. Ovarian tissue cryopreservation is an investigational method of fertility preservation but has the advantage of requiring neither a sperm donor nor ovarian stimulation. Ovarian tissue is removed laparoscopically, a one hour outpatient procedure that requires general anesthesia, and frozen. At a later date, the ovarian tissue is thawed and reimplanted. Primordial follicles can be cryopreserved with great efficiency[86,87] but because of the initial ischemia encountered after ovarian transplantation, a quarter or more of these follicles might be lost, as shown in xenografting studies.[88] To offset this relatively large loss, typically the cortex from an entire ovary is cryopreserved in adults. The benefit of ovarian cryopreservation for women older than 40 years of age is very uncertain because there are too few primordial follicles remaining.[89] Ovarian tissue cryopreservation has been performed in humans for less than a decade, and the first ovarian transplant procedure was reported in 2000.[90] Ovarian tissue can be transplanted orthotopically to pelvis[90-94] or heterotopically to subcutaneous areas such as the forearm or lower abdomen,[95,96] and initial studies reported restoration of ovarian endocrine function after both types of transplantation.[90,93,94,96,97] There have been two reports of live births from orthotopic ovarian transplantation in cancer patients; one conceived spontaneously[91] and the other as a result of in vitro fertilization.[92] In addition, a live birth occurred when fresh ovarian tissue was transplanted between identical twins because of unexplained premature ovarian failure in the recipient, not related to cancer.[98]

One concern with reimplanting ovarian tissue is the potential for reintroduction of cancer cells. In patients without evidence of systemic metastasis to other organs, the likelihood of occult ovarian metastasis appears to be low in the majority of cancers seen in young females,[99,100] and there are no reports of cancer recurrence after ovarian transplantation although fewer than 20 procedures are reported thus far. Thus, ovarian tissue screening to detect malignant cells should be performed to minimize the risk of inadvertent transfer with the ovary. In patients with high risk of ovarian involvement, xenografting and ex vivo follicle growth are experimental but not yet practical possibilities.[101]

Ovarian cryopreservation and transplantation procedures should only be performed in centers with the necessary expertise under IRB-approved protocols that include follow-up for recurrent cancer.

Ovarian suppression. Ovarian suppression through gonadotropin-releasing hormone (GnRH) agonist or antagonist treatment during chemotherapy is highly controversial as a method to maintain fertility. A small study evaluating 54 patients compared with retrospective controls suggested a benefit in preserving menstrual function from ovarian suppression with GnRH analogs in women undergoing chemotherapy for Hodgkin's and non-Hodgkin's lymphoma,[102] but a small prospective study of 18 women receiving chemotherapy for Hodgkin's lymphoma did not show a benefit of this approach.[52] Retrospective studies have been criticized for longer follow-up time and higher incidence/dose of usage of alkylating agents in controls.[100] Two small case series of 64 and 24 cancer patients without controls report resumption of menses and/or pregnancies after ovarian suppression.[103,104] Small observational studies also suggest that oral contraceptives may help preserve ovarian function when given during chemotherapy.[105,106] Large randomized clinical studies of ovarian suppression should be performed with fertility preservation, not just menstruation, as the outcome measure. The Southwest Oncology Group is currently conducting a trial aimed at preventing early ovarian failure with GnRH agonists among women with hormone-receptor negative breast cancer who receive chemotherapy. The German Hodgkin's Lymphoma Study Group is conducting a randomized phase II trial evaluating GnRH agonists and oral contraceptives to preserve fertility in women treated for advanced Hodgkin's lymphoma.[105]

Anecdotally, because GnRH analogs are readily available, this strategy has been used widely without clear evidence for efficacy or full understanding of the potential risks and benefits, especially in women with hormone sensitive tumors. At this time, since there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and other means of ovarian suppression on female fertility preservation, women interested in ovarian suppression for this purpose are encouraged to participate in clinical trials.

Ovarian transposition. Ovarian transposition (oophoropexy—surgically moving ovaries as far as possible from the radiation field) can be offered when pelvic radiation is used for cancer treatment. The procedure can be done laparoscopically if laparotomy is not needed for the primary treatment of the tumor.[107-109] Because of the risk of remigration of the ovaries, this procedure should be performed as close to the radiation treatment as possible.[110] The overall success rate as judged by preservation of short-term menstrual function is approximately 50%. Scatter radiation and alteration of ovarian blood supply appear to be the main reasons behind the failures.[107,111,112] Total radiation dose and the dose received by the "less-irradiated" ovary also affect the outcome.[113] Ovarian repositioning may not always be needed to restore fertility, as spontaneous pregnancies have been reported in women with transposed ovaries.[114] If infertility develops and in vitro fertilization is needed after ovarian transposition however, the performance of oocyte retrieval becomes more complicated.[112] In this case, either a second procedure is needed to reposition the ovaries to pelvis,[114] or egg collection will have to be performed percutaneously with the risk of reducing the efficiency of this procedure.[112] Other risks include ovarian dysfunction leading to ovarian cysts and the theoretical risk of increased difficulty diagnosing ovarian cancer if the ovaries are no longer palpable on bimanual examination.

Conservative gynecologic surgery. It has been estimated that nearly 50% of women diagnosed with cervical carcinoma under the age of 40 are eligible for radical trachelectomy, a procedure in which the cervix is resected but the uterus is spared.[115] The procedure is typically performed vaginally with laparoscopic assistance, but an abdominal variant has also been described.[116] It has been suggested that the procedure be restricted to stage 1A2-IB disease with less than 2 cm in diameter and less than 10 mm invasion.[117,118] The recurrence rates following radical trachelectomy appear to be similar to that of radical hysterectomy but no randomized study exists.[119] To date, at least 236 women underwent the procedure with 63 live births resulting.[120] There is an increased risk in midtrimester losses and preterm birth.[121,122] There is also a higher incidence of infertility due to cervical abnormalities, which would require the use of assisted reproduction technologies.[117,123]

In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery and/or lower dose chemotherapy with the intent of sparing the