SPMR
SOCIEDADE PORTUGUESA DE MEDICINA DA REPRODUÇÃO

CENTRO DE PRESERVAÇÃO DA FERTILIDADE
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Fertility preservation: A multidisciplinary approach.

Prof. ª Doutora Teresa Almeida Santos (presidente da SPMR)

2006

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

Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Karen Hagerty, Lindsay N. Beck, Lawrence V. Brennan, and Kutluk Oktay

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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2013

Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Alison W. Loren, Pamela B. Mangu, Lindsay Nohr Beck, Lawrence Brennan, Anthony J. Magdalinski, Ann H. Partridge, Gwendolyn Quinn, W. Hamish Wallace, and Kutluk Oktay

A B S T R A C T

Purpose
To update guidance for health care providers about fertility preservation for adults and children with cancer.

Methods
A systematic review of the literature published from March 2006 through January 2013 was completed using MEDLINE and the Cochrane Collaboration Library. An Update Panel reviewed the evidence and updated the recommendation language.

Results
There were 222 new publications that met inclusion criteria. A majority were observational studies, cohort studies, and case series or reports, with few randomized clinical trials. After review of the new evidence, the Update Panel concluded that no major, substantive revisions to the 2006 American Society of Clinical Oncology recommendations were warranted, but clarifications were added.

Recommendations
As part of education and informed consent before cancer therapy, health care providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation. The discussion should be documented. Sperm and embryo cryopreservation as well as oocyte cryopreservation are considered standard practice and are widely available. Other fertility preservation methods should be considered investigational and should be performed by providers with the necessary expertise.

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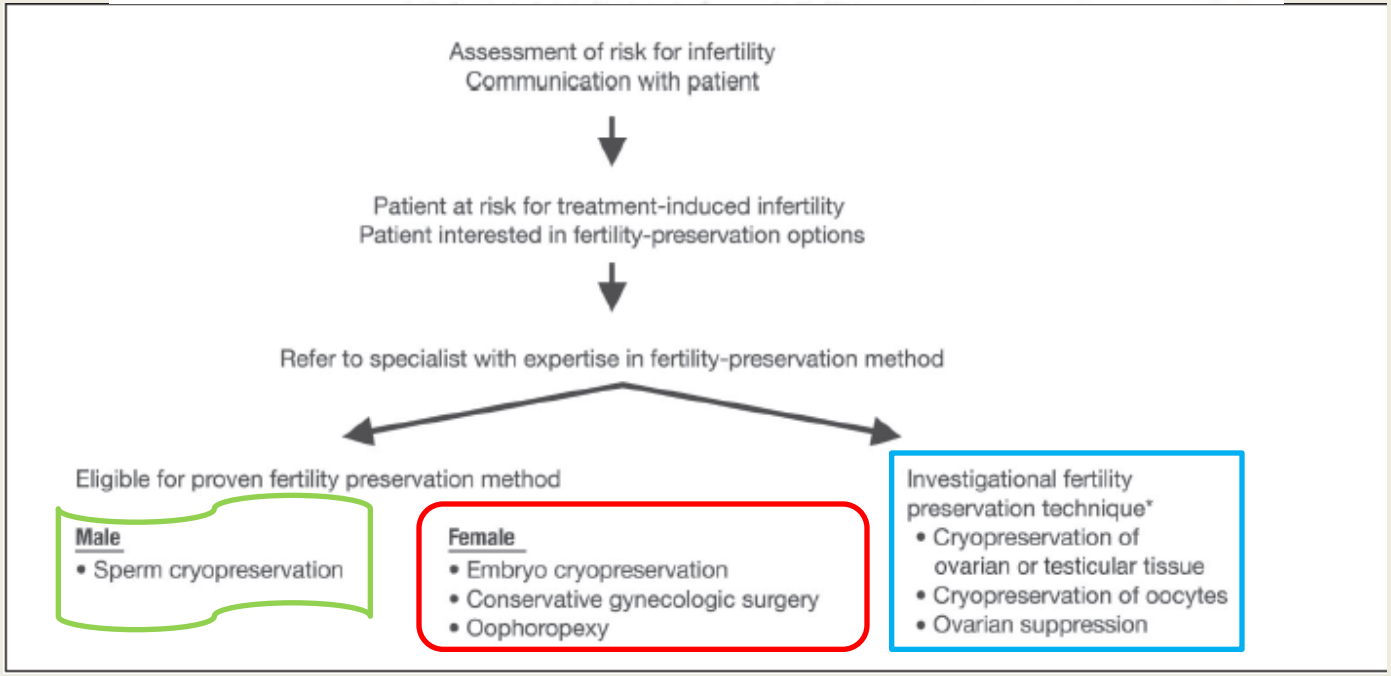
ASCO SPECIAL ARTICLE

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

Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Karen Hagerty, Lindsay N. Beck, Lawrence V. Brennan, and Kutluk Oktay



Epidemiology

- **1/250 adults is a survivor of a childhood cancer**;
- 700.000 new cancers/year in women (USA);
- **43.300 new cancers in 2008 (Portugal);**
- 8% under 40 years;
- 1/3 of young women exposed to chemotherapy develop ovarian failure.

Gonadotoxicity- chemotherapy

The nature and extent of gonadal damage depends on the:

- Drug;
- Dose received;
- Age of the patient.

The relative contribution of an individual drug is difficult to determine because most treatments are multidrug regimens.

Gonadotoxicity- radiotherapy

Testicular tissue is extremely sensitive to radiation

Doses as low as 0.1 Gy can cause oligospermia.
Reversible azoospermia with doses as low as 0.35 Gy.

The testes are rarely directly radiated, **even exposure due to scatter radiation** can have reproductive consequences.

Theoretical concern that cancer therapies have the potential to cause mutagenesis in the testes and therefore may impact the health of offspring.

Evidence of increased genetic problems, stillbirth or neonatal death in men treated with gonadal radiation as children was not found.

Table I Assessement of risk of subfertility after treatment for common cancers in childhood and adolescence (from Wallace *et al.*, 2005b).

Low risk <20%	Acute lymphoblastic leukemia
	Wilm's tumor
	Soft-tissue sarcoma: stage I
	Germ-cell tumors (with gonadal preservation and no radiotherapy)
	Retinoblastoma
	Brain tumor: surgery only, cranial irradiation <24 Gy
Medium risk	Acute myeloblastic leukemia
	Hepatoblastoma
	Osteosarcoma
	Ewing's sarcoma stage II or III
	Neuroblastoma
	Non-Hodgkin lymphoma
	Hodgkin's disease: alternating treatment
	Brain tumor: craniospinal radiotherapy, cranial irradiation >24 Gy
High risk >80%	Whole-body irradiation
	Localized pelvic radiotherapy
	Chemotherapy conditioning for bone-marrow transplantation
	Hodgkin's disease: treatment with alkylating-drugs
	Soft-tissue sarcoma: stage IV
	Metastatic Ewing's sarcoma

Table II Non-malignant pathologies with risk of POF.

Bone-marrow transplantation
Sickle cell anemia
Thalassemia major
Aplastic anemia
Autoimmune diseases unresponsive to immunosuppressive therapy
Autoimmune diseases requiring chemotherapy
Systemic lupus erythematosus
Rheumatoid arthritis
Behçet's disease
Wegener's disease
Multiple sclerosis
Ovarian pathologies
Recurrent ovarian cysts
Ovarian torsion
Endocrine or genetic diseases
Turner syndrome
Galactosemia
Family history of premature ovarian failure

Risk of Infertility in Men

Male infertility can result from:

1. Disease
2. Anatomic problems
3. Primary or secondary hormonal insufficiency
4. Damage or depletion of the germinal stem cells

The effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity

Azospermia typically surrogate for infertility

Possibilities

Displacing the ovaries from the radiation field

Ovarian supression with GnRHa

Embryo cryopreservation

Cryopreservation of ovarian tissue

- Autotransplantation (orthotopic or heterotopic)
- Transplantation to other hosts (xenotransplantation)
- Re-implantation of the ovary with its vascular pedicle
- Implantation of isolated primordial follicles

Men Have Sperm Banking!

Sperm cryopreservation

Freezing and banking sperm collected through masturbation, rectal electroejaculation, testicular aspiration or post-masturbation urine

If patient sick or with certain cancers (e.g., testicular cancer and Hodgkin)- sperm quality may be poor prior to treatment

Many patients have to start chemotherapy soon enough to limit the number of ejaculates

Still reasonable to make every effort to bank sperm- ICSI allows future use of small samples

Other “Options” for Men

Hormonal Gonadoprotection (e.g. GnRHa)

The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in male cancer patients

Evidence suggests **hormonal therapy in men is not successful in preserving fertility when highly sterilizing chemotherapy is given**

Potential future options:

Testicular tissue cryopreservation or reimplantation
Testis grafting with maturation in SCID mice

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

-Individual factors such as **disease, age, treatment type and dosages, and pre-treatment fertility** should be considered

- Patients should consider their options as soon as possible to maximize the likelihood of success

- Aside from hereditary genetic syndromes and *in utero* exposure to CT, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities

Fertility Preservation for Patients With Cancer: ASCO Practice Guideline Update

Adult males:

1. Present **sperm cryopreservation (sperm banking)** as the only established fertility preservation method.

2. **Do not recommend hormonal therapy in men**; it is not successful in preserving fertility.

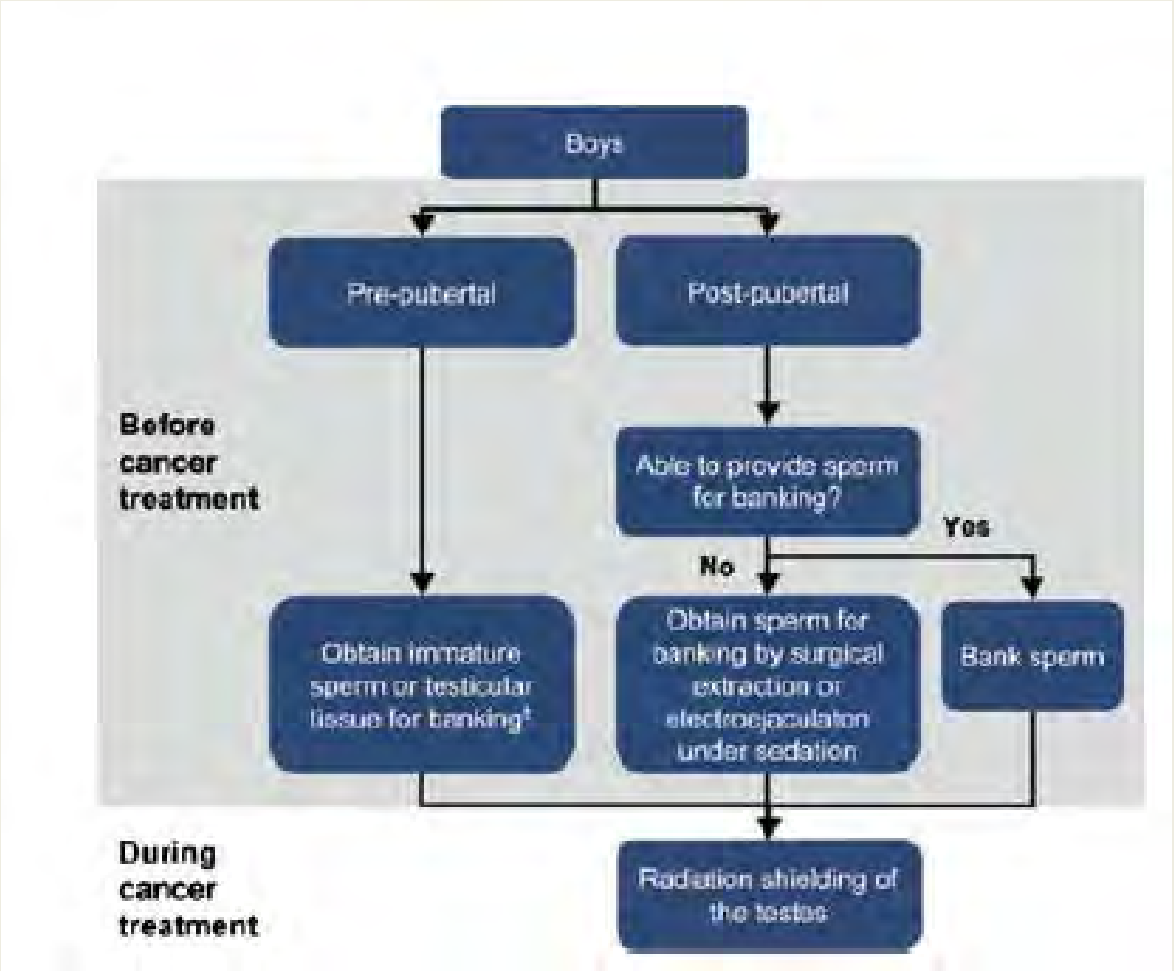
3. Inform patients that **other methods** (testicular tissue cryopreservation for the purpose of future reimplantation) **are experimental.**

4. Advise men of a **potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy**

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 post-masturbation 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.


Boys
Pre-pubertal
Post-pubertal
Before cancer treatment
Able to provide sperm for banking?
Yes
No
Obtain immature sperm or testicular tissue for banking†
Obtain sperm for banking by surgical extraction or electroejaculation under sedation
Bank sperm
During cancer treatment
Radiation shielding of the testes

1. Sperm cryopreservation is an **established and successful method** of fertility preservation.

2. **All adolescent and young adult** males should be offered sperm cryopreservation prior to the onset of treatment.

3. Boys who are unable to produce semen through masturbation may undergo penile vibratory stimulation or rectal electrostimulation under anesthesia.

4. Additionally, sperm may be collected via testicular or epididymal aspiration.

For pre-pubescent males the only options available are experimental

1. Cryopreservation and *in vitro* maturation or transplantation of spermatogonial stem cells and testicular tissue has theoretical potential.

2. **There is no conclusive evidence that GnRH analogues are effective.**

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Porquê?

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Opinion statement

Oncofertility as a discipline plays an important, adjunctive role in the treatment of male patients with cancer. Despite recommendations by the American Society of Clinical Oncology, many clinicians managing malignancies in males fail to consistently incorporate fertility preservation as a routine aspect of health care. Providers involved in the treatment of oncologic patients should have an awareness of the impact of their prescribed treatments on reproductive potential, just as they would be knowledgeable of the potential deleterious effects of cancer therapies on vital organs such as the kidneys, lungs, and liver. Providers should then have a discussion with their patients regarding these potential adverse therapeutic effects or consult a fertility preservation specialist to discuss these matters and fertility preservation options with the patient. Cryopreservation of sperm remains an excellent option for male fertility preservation as it is readily available and results in storage of viable gametes for future use in the event of post treatment infertility. With the use of assisted reproductive techniques (ART), cryopreserved sperm may ultimately result in successful paternity, even in the setting of very low numbers of stored sperm. While sperm cryopreservation is usually an option for adolescent and adult males, fertility preservation in pre-pubertal males presents a more challenging problem. To date, no clinically proven methods are available to preserve fertility in these males. However, some centers do offer experimental protocols under the oversight of an IRB, such as testicular tissue cryopreservation in these males. The hope is that one day science will provide a mechanism for immature germ cells from the testicular tissue of these patients to be used *in vivo* or *in vitro* to facilitate reproduction. In closing, studies have

Barriers to Fertility Preservation in Male Adolescents With Cancer: It's Time for a Multidisciplinary Approach that Includes Urologists

Leena Nahata, Laurie E. Cohen, and Richard N. Yu

THERE IS A PAUCITY OF ADOLESCENT-APPROPRIATE EDUCATIONAL MATERIAL AND SPERM BANKING FACILITIES

Another barrier to fertility preservation in adolescents is the paucity of appropriate educational material and facilities. In a recent multicenter Canadian study, patients reported concerns regarding the restricted access to sperm banking units and the lack of adolescent-appropriate educational material.[6] Practitioners in a multicenter UK study found that the educational brochures at several institutions were difficult to read and understand; words such as "spermatogenesis" and "cryopreservation" were included in the pamphlets with no definitions.[20] Efforts to develop age-appropriate educational tools have begun, although they have yet to be validated in a larger patient populations.[21,22] These tools or similar materials could be incorporated into the fertility counseling sessions to help educate families about fertility preservation and facilitate the discussion between patients, families, and practitioners.

Another identified problem was the lack of suitable locations for adolescents to produce semen samples. A young teenager may have difficulty masturbating in an unfamiliar environment as it is, and even more so in the setting of a traumatic diagnosis,[20] especially when the facilities are suboptimal or when a parent is nearby.[13] Urologists may be instrumental in designing more age-appropriate brochures and facilities, and in preparing patients and families for challenges they may face during the banking process.

Barreiras
Limitações
Obstáculos

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PRACTITIONERS HAVE LITTLE TIME AND INADEQUATE KNOWLEDGE ABOUT THIS TOPIC

Semen cryopreservation was first established as a safe and effective method of fertility preservation in adults. During interviews with adult male cancer survivors, the amount of guidance that had been given by their health care providers was identified as the most important factor in the decision to bank sperm. The cancer survivors felt that practitioners should be clear and direct when discussing the risk for infertility, and should emphasize the importance of sperm banking. Patients who had not received this guidance often did not bank sperm and later expressed regret.[10] Schover et al found that men who had no memory of being told about sperm banking were

Barreiras
Limitações
Obstáculos

Physicians' lack of knowledge and failure to address the issues of infertility and sperm cryopreservation have also been identified as the most significant barriers to fertility preservation in the adolescent population.[7,10-12] Many reasons for failure to initiate the discussion have been identified by oncologists, including: the need to start treatment,[6] lack of time in a busy practice, difficulty finding convenient sperm banking facilities, and the belief that sperm banking would be too costly for patients.[7]

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Specific knowledge deficits have been identified

- Urologists can discuss other alternative measures for sperm acquisition, such as EEJ or TESE, for adolescents who are unable or unwilling to masturbate to produce a semen sample.

- Some oncologists overestimate the cost of sperm banking and the number of samples needed to make sperm banking worthwhile.

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É possível fazer melhor…

Improved Fertility Preservation Care for Male Patients With Cancer After Establishment of Formalized Oncofertility Program

Kunj R. Sheth, Vidit Sharma, Brian T. Helfand, John Cashy, Kristin Smith, Jason C. Hedges, Tobias S. Köhler,* Teresa K. Woodruff and Robert E. Brannigan†

From the Departments of Urology (KRS, VS, BTH, JC, JCH, REB) and Obstetrics and Gynecology (KS, TKW), Feinberg School of Medicine, Northwestern University, Chicago and Division of Urology, Department of Surgery, Southern Illinois University School of Medicine (TSK), Springfield, Illinois

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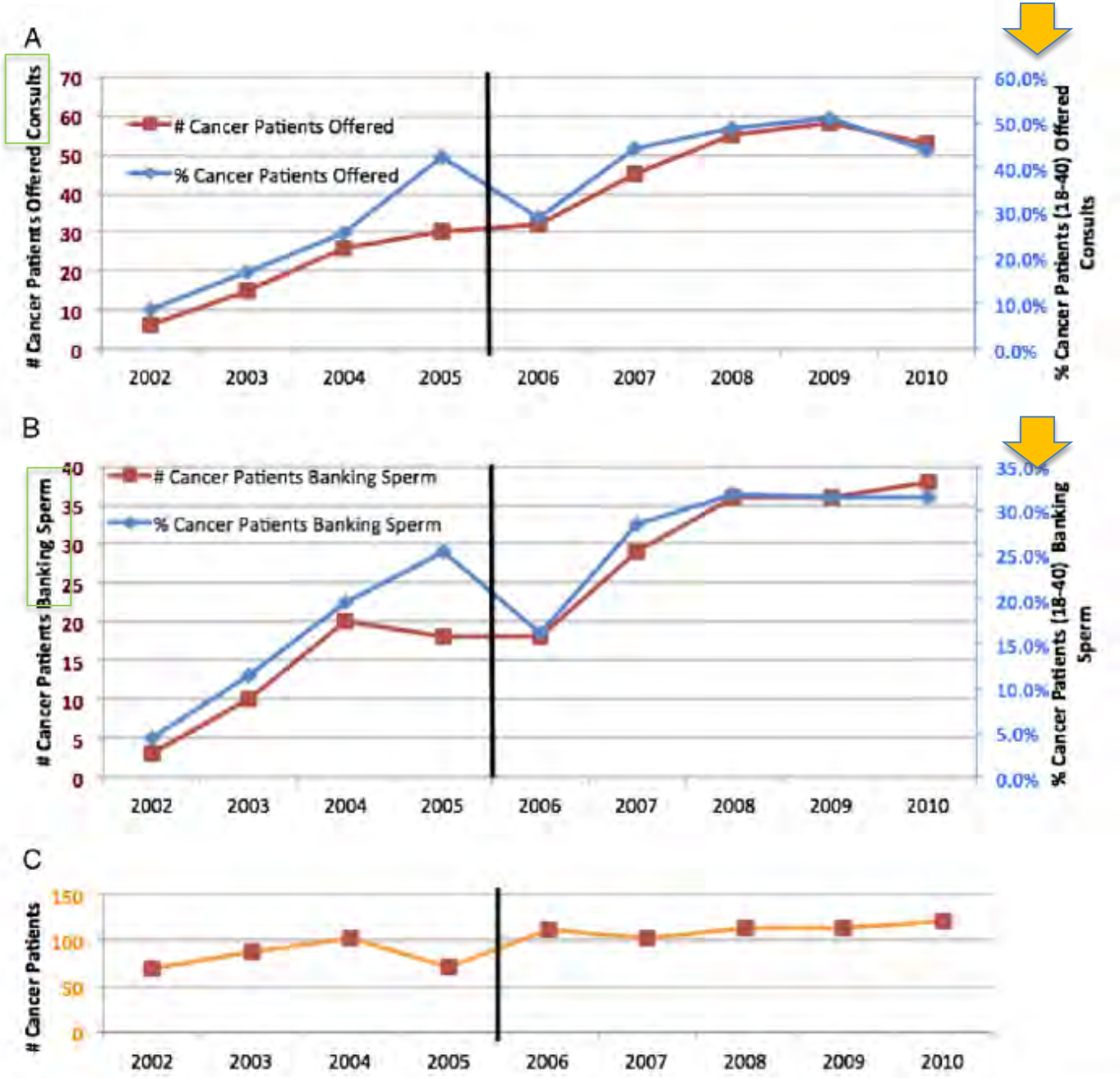

Figure 3. Fertility preservation use in men 18 to 40 years old before and after establishing formalized oncofertility program. *A* and *B*, number of patients increased after program was formalized in 2006 (vertical line). *C*, number of men 18 to 40 years old diagnosed with cancer.

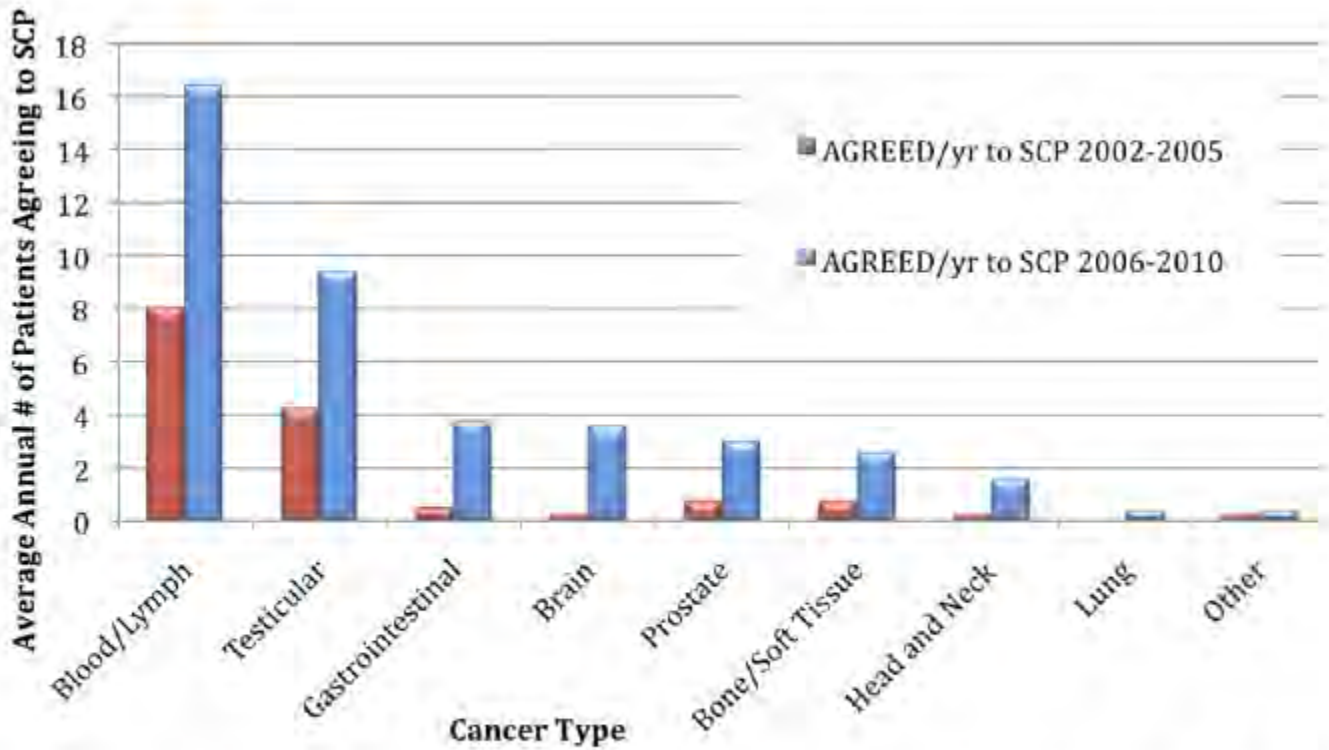

Figure 4. Average annual number of patients who agreed to SCP by cancer type from 2002 to 2005 vs 2006 to 2010. Average number increased after program formalization.

RISKS?

1. **Risks of the technique;**

1. **Risk of transmission of neoplastic cells;**

1. **Risks of pregnancy after fertility preservation treatment:**

   - Germline mutations and increased risk of genetic abnormalities in offspring - **NO**;
   - Miscarriage, stillbirth and malformations (incresed only if RT).

Risks of pregnancy after fertility preservation treatment

Concerns that potentially mutagenic chemotherapy and radiotherapy may cause germline mutations and an increased risk of genetic abnormalities in offspring of cancer survivors (Boice et al., 2003; Winther et al., 2004).

Risks of the technique

- No evidence that fertility preservation compromises the success of cancer therapy or affect a survivor’s health.
- Reimplantation of ovarian cortex carries the risk of transmission of neoplastic cells.
- Methods to detect residual tumoral involvement are becoming increasingly effective.

Cancer therapies do not confer a greater risk of inherited genetic disease in offspring

- Numerous studies (Hawkins, 1991; Byrne et al., 1998; Nagarajam and Robison, 2005; Rees et al., 2006) investigated the incidence of cancer in the offspring of cancer survivors and found **minimal or no increased risk of cancer development**.

Fertility preservation options must be discussed even in children

The most common reasons given for **not discussing fertility preservation options**:

- Not at significant risk - 29%;
- Too young - 27%;
- Techniques unproven - 22%;
- No facilities - 10%;
- No funding - 8%.

Ovarian/testicular cryopreservation in children

- ASCO (2006; 2013) recommended that oncologists address the possibility of infertility in patients treated during their reproductive years and be prepared to discuss fertility preservation options or refer patients to reproductive specialists.

- However, there is no consensus or directive on the age at which reproductive potential is actually reached

- Unclear how this can be applied to cancer patients under 18 years.

Preservation of fertility potential in boys when freezing sperm is impossible

In the hope that future technologies can utilize their immature gametes, **there may be benefits in considering gonadal tissue preservation** for children prior to chemo or radiotherapy.

- Transplantation back into the inactive testis;
- Maturation *in vivo* in another host;
- *In vitro* spermatogenesis.

Questions?

Chemotherapy prior to cryopreservation

- Hope of eradicating neoplastic cells in the ovary before the tissue is cryopreserved, especially in hematological cancers.

- However, one cannot exclude a gonadotoxic effect of this initial chemotherapy.

And if a girl/boy has already undergone chemotherapy?

- Even in this situation, **cryopreservation of ovarian cortex can be proposed** if a greater gonadotoxic risk is required.

- As follicle density is higher in children, there is a high probability of recovering intact follicles, even after several courses of chemotherapy.

National recommendations: CNPMA

cnpma
conselho nacional de procriação medicamente assistida

RECOMENDAÇÃO PARA A INSTALAÇÃO DE CENTROS DE PRESERVAÇÃO DA FERTILIDADE NO SERVIÇO NACIONAL DE SAÚDE PARA DOENTES SUJEITOS A TERAPÊUTICAS DO FORO ONCOLÓGICOS

A propósito do debate acerca da aplicabilidade das técnicas de PMA e sublinhando o contributo social e a relevância ética da realização plena da maternidade e da paternidade, o Conselho Nacional de Procriação Medicamente Assistida (CNPMA) entende por bem manifestar de novo a sua posição relativamente à necessidade de instituir no Serviço Nacional de Saúde uma estrutura dedicada à preservação da fertilidade para doentes que venham a ser submetidos a terapêuticas do foro oncológico.

Atendendo à repercussão dos tratamentos oncológicos na função reprodutiva, aliada à felizmente crescente taxa de sobrevivência dos pacientes sujeitos a estas terapêuticas, torna-se cada vez mais urgente reconhecer a preservação da fertilidade como parte integrante da promoção da qualidade de vida destes doentes.

National recommendations: CNPMA

É por isso indispensável organizar, no âmbito do Serviço Nacional de Saúde, uma estrutura/unidade/centro vocacionada e dedicada à recolha e criopreservação de espermatozóides, óvulos e/ou tecido ovárico para uso futuro dos doentes indicados para terapêuticas do foro oncológico.

National recommendations: CNPMA

O CNPMA considera que os centros cuja instalação agora se recomenda se deverão localizar em estruturas hospitalares que pelas características da sua actividade e por condições de multidisciplinaridade e elevada diferenciação reúnam as sinergias, as condições técnicas e as competências na área laboratorial humana indispensáveis. Sem prejuízo da ponderação de outras hipóteses, o CNPMA sugere que a instalação de uma tal estrutura/unidade/centro (fisicamente distinta do centro de PMA), teria todo o cabimento que ocorresse em Hospitais agregados a Faculdades de Medicina e respectivos Institutos de ciências básicas na área da Medicina Molecular, e que, nomeadamente, possam dispor de Serviços que têm como missão o tratamento de doenças do foro oncológico, com um número significativo de pacientes, e também de doenças da área da Hematologia e doenças reumatismais graves, cuja terapêutica é, em todos esses casos, igualmente lesiva para as células reprodutoras.

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5 CONGRESSO FIGUEIRA DA FOZ

3 a 5 Outubro 2013

CURSOS

- Preservação da Fertilidade - uma abordagem multidisciplinar / Fertility preservation: a multidisciplinary approach.

Coordenadoras: Teresa Woodruff e Teresa Almeida Santos

- Technical aspects of fertility preservation and the experience in the Center for Fertility Preservation of C.H.U.C., E.P.E. - Teresa Almeida Santos

- Infertility risk in oncology patients: the role of information in supporting the fertility preservation decision - Cristina Silva e Ana Cristina Rama

- The importance of shared decision-making process regarding fertility preservation in oncology patients - Cláudia Melo e Cristina Canavarro

- Oncofertility Consortium®: An overview - Teresa Woodruff

- Andrologia

Coordenador: Belmiro Parada

A - Infertilidade: estudo do factor masculino

1. Aspectos clínicos: quais as perguntas a fazer? Quais os dados mais relevantes do exame físico? Belmiro Parada (Serviço de Urologia e Transplantação Renal; Serviço de Medicina da Reprodução Centro Hospitalar e Universitário de Coimbra)

2. Que exames auxiliares de diagnóstico podem ser úteis? Em que circunstâncias?
Pedro Eufrásio (Serviço de Urologia; Hospital de São Teotónio, Viseu)

B - Infertilidade: abordagem terapêutica do factor masculino

1. Varicocelo: quando e como tratar? Quais os benefícios expectáveis?
Frederico Furriel (Serviço de Urologia, CHUC)

2. Endocrinopatias: quais as mais prevalentes e como tratá-las?
Bruno Pereira (Serviço de Urologia, Centro Hospitalar Cova da Beira, Covilhã)

3. As técnicas de colheita de gâmetas: experiência de um Centro
Gustavo Gomes (Serviço de Urologia, CHUC)

4. As terapêuticas empíricas: simples placebo?
Pedro Eufrásio (Serviço de Urologia; Hospital de São Teotónio, Viseu)

C - Infertilidade: a importância da multidisciplinaridade e da comunicação dentro da Equipa

1. A abordagem dinâmica no estudo e tratamento de ambos os elementos do casal: de que forma a situação clínica de um influencia toda a estratégia terapêutica e diagnóstico do outro?
Belmiro Parada; Doutora Teresa Almeida Santos; Daniela Couto

2. O diálogo entre "laboratório" e "clínica"
Ana Paula Sousa

3. O conflito nas relações: Consulta de Psicologia
Mariana Moura Ramos (Psicóloga)

5 CONGRESSO
3 a 5 de Outubro 2013
FIGUEIRA DA FOZ
CENTRO DE ARTES E ESPECTÁCULOS

SPMR 35 ANIVERSÁRIO 1978-2013
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Series in young ages

Table III Series of ovarian cortex cryopreservation in children.

Authors	Patients (*n*)	Age (years)		Patients under 16 years		Patients under 10 years	
		Range	Mean	*n*	%	*n*	%
Feigin *et al.* (2007)	23	5–17.5	13.5	NA	NA	NA	NA
Poirot *et al.* (2007)	47	0.8–15	6.1	47	100	38	81
Anderson *et al.* (2008b)	36	5–35	19.2	11	31	3	8
Revel *et al.* (2009)	19	5–20	15.3	8	42	2	11
Oktay and Oktem (2009)	26	4–21	14.3	9	35	6	23
Borgström *et al.* (2009)	57	8–19.8	14.4	40	70	4	7
Jadoul *et al.* (present publication)	58	0.8–15.8	10.4	58	100	21	36

Cancer treatment takes priority over potential restoration of fertility, but the chance to preserve fertility may greatly enhance the quality of life of young cancer patients and their parents.

Cases: 2008-2011

Date of the 1st Appointment	Health Institution of Origin	Age	Marital Status	Profession	Diagnosis	Fertility Preservation Technique
July/2008	CHUC, Coimbra	25	Married	Architect	Hodgkin's Lymphoma	Ovarian tissue
November/2008	Hospital da Luz, Lisbon	32	Civil union (4Y)	Unemployed	Colon cancer	Ovarian tissue
June/2009	CHUC, Coimbra	40	Single	Lawyer	Ovarian cancer	Ovarian tissue
July/2009	CHUC, Coimbra	22	Single	Unemployed	Ovarian cancer	Ovarian tissue
February/2010	CHUC, Coimbra	17	Single	Student	Leukemia	Ovarian tissue
April/2010	Maternidade BB, Coimbra	14	Single	Student	Teratoma	Ovarian tissue
June/2010	CHUC, Coimbra	28	Married	Electronic Engineer	Hodgkin's Lymphoma	Ovarian tissue
July/2010	Hospital São José, Lisbon	23	Single	Journalist	Breast cancer	Ovarian tissue
August/2010	CHC, Coimbra	26	Single	Student	Kidney failure	Ovarian tissue
August/2010	Maternidade BB, Coimbra	22	Civil union (1Y)	Waitress	Lupus	Ovarian tissue
October/2010	CHUC, Coimbra	15	Single	Student	Nasopharyngeal cancer	Ovarian tissue
October/2010	CHUC, Coimbra	32	Divorced	Cashier	Non-Hodgkin's Lymphoma	Ovarian tissue and oocytes
April/2011	Hospital de Guimarães	26	Single	Student	Bowel cancer	Ovarian tissue and oocytes
May/2011	CHUC, Coimbra	36	Single	Education auxiliary	Breast cancer	Ovarian tissue
June/2011	Hospital São Teotónio, Viseu	36	Civil union (6Y)	Administrative	Breast cancer	Ovarian tissue and embryos
June/2011	CHUC, Coimbra	28	Single	Pharmacist	Non-Hodgkin's Lymphoma	Ovarian tissue
September/2011	CHUC, Coimbra	20	Single	Student	Hodgkin's Lymphoma	Ovarian tissue
October/2011	IPOFG Coimbra	22	Single	Student	Ewing's Sarcoma	Ovarian tissue
November/2011	CHUC, Coimbra	22	Single	Student	Hodgkin's Lymphoma	Ovarian tissue

Cases: 2012

Date of the 1st Appointment	Health Institution of Origin	Age	Marital Status	Profession	Diagnosis	Fertility Preservation Technique
January/2012	IPOFG Coimbra	27	Civil union (10Y)	Economist	Dysgerminoma	Embryos
February/2012	IPOFG Coimbra	28	Single	Waitress	Breast cancer	Ovarian tissue and oocytes
February/2012	IPOFG Lisbon	25	Single	Nutritionist	Hodgkin's lymphoma	Embryos and oocytes
February/2012	Hospital do Funchal, Madeira	34	Married	Jurist	Transversal myelitis	Embryos and oocytes
March/2012	CHUC, Coimbra	28	Single	Doctor	Sarcoma	Ovarian tissue
June/2012	IPOFG Lisbon	34	Civil union (2Y)	Assistant	Breast cancer	Embryos
August/2012	IPOFG Lisbon	32	Married	Administrative	Breast cancer	Embryos
October/2012	IPOFG Lisbon	31	Divorced	Nurse	Breast cancer	Oocytes
November/2012	Hospital de Guimarães	30	Single	Lawyer	Breast cancer	Oocytes
December/2012	CHUC, Coimbra	30	Single	Human resources	Breast cancer	Ovarian tissue
December/2012	IPOFG Lisbon	28	Single	Pharmacist	Breast cancer	Oocytes

Cases: 2013...

Date of the 1st Appointment	Health Institution of Origin	Age	Marital Status	Profession	Diagnosis	Fertility Preservation Technique
January/2013	IPOFG Lisbon	38	Single	Administrative	Breast cancer	Oocytes
February/2013	Hospital de Guimarães	22	Single	Student	Non Hodgkin's lymphoma	Ovarian tissue
March/2013	Hospital das Calda da Raínha	33	Married	Machine operator	Breast cancer	Oocytes
May/2013	IPOFG Lisbon	33	Married	Professor	Breast cancer	Embryos
May/2013	IPOFG Lisbon	13	Single	Student	Ewing's Sarcoma	Ovarian tissue
May/2013	CHUC, Coimbra	17	Single	Student	Sarcoma	Ovarian tissue
May/2013	IPOFG Lisbon	15	Single	Student	Ewing's Sarcoma	Ovarian tissue and oocytes
May/2013	CHUC, Coimbra	33	Married	Student	Hodgkin's lymphoma	Embryos
June/2013	Private practice, Coimbra	26	Single	Student	Ovarian tumor borderline	Oocytes
June/2013	CHUC, Coimbra	36	Single	Doctor	Breast cancer	Oocytes
June/2013	IPOFG Coimbra	35	Single	Lawyer	Breast cancer	Oocytes
June/2013	CHUC, Coimbra	29	Married	Waitress	Ovarian tumor borderline	Oocytes
July/2013	CHUC, Coimbra	26	Civil union (5Y)	Assistant	Sarcoma	Oocytes
August/2013	CHUC, Coimbra	31	Single	Doctor	Hodgkin's lymphoma	Oocytes
August/2013	CHUC, Coimbra	33	Single	Archeologist	Breast cancer	Oocytes
August/2013	CHUC, Coimbra	32	Civil union (11Y)	Student	Non Hodgkin's lymphoma	Embryos and oocytes
September/2013	CHUC, Coimbra	26	Civil union (1Y)	Analyst	Breast cancer	Oocytes
September/2013	IPOFG Lisbon	29	Civil union (2Y)	Administrative	Breast cancer	Oocytes

CENTRO DE PRESERVAÇÃO DA FERTILIDADE
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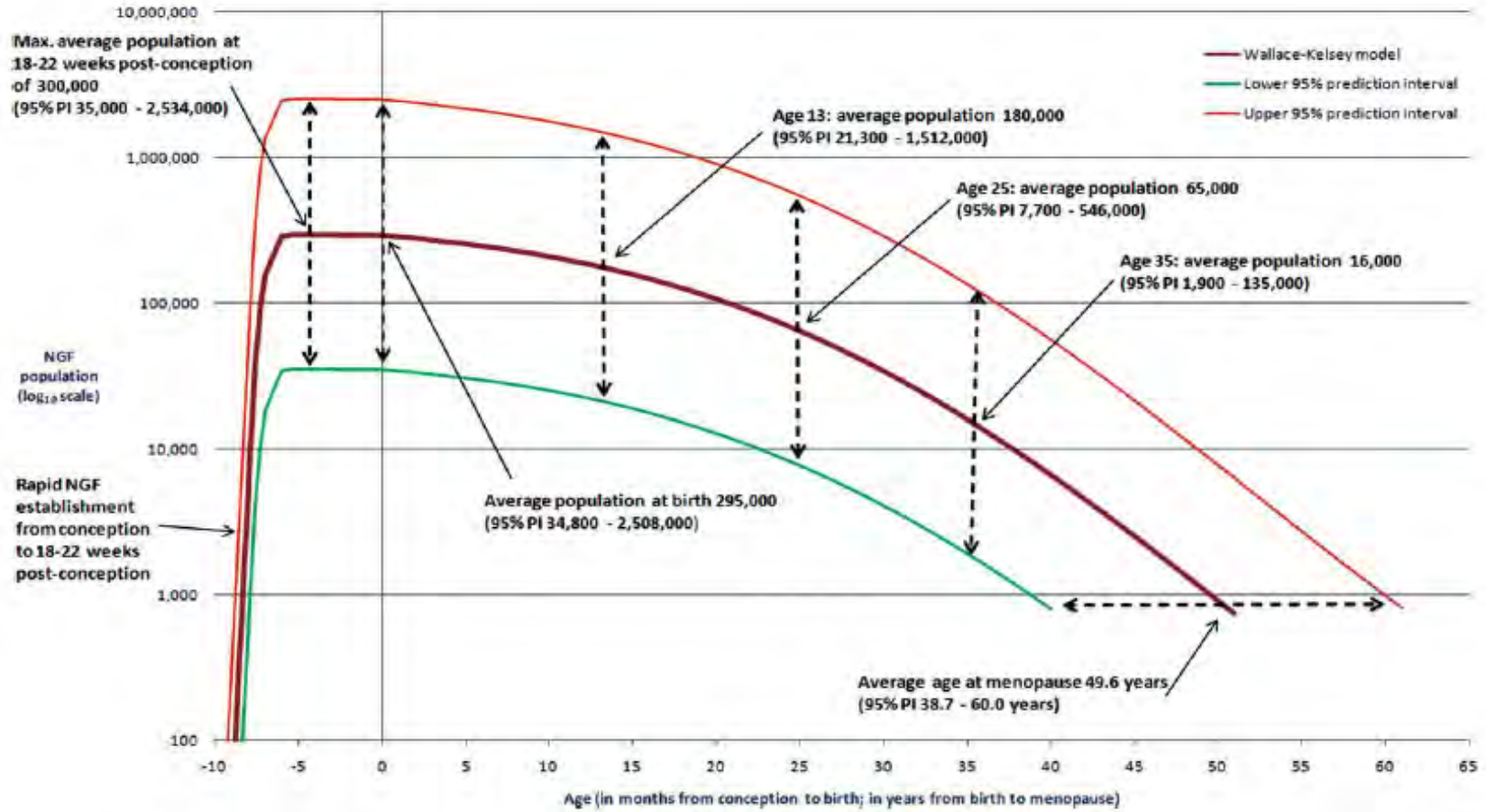

Figure 1. Illustrative examples of nongrowing follicles (NGF) populations predicted by our model are shown. The average NGF population at ages 20 weeks after conception, birth, 13 years, 25 years, and 35 years is given, together with the respective 95% prediction intervals (95% PI). The predicted average age at menopause (49.6 years) is also shown, together with the 95% PI. Abbreviations: Max, maximum. Reprinted with permission from Wallace WH, Kelsey TM. Human ovarian reserve from conception to menopause. *PloS One*. 2010;5:e8772.

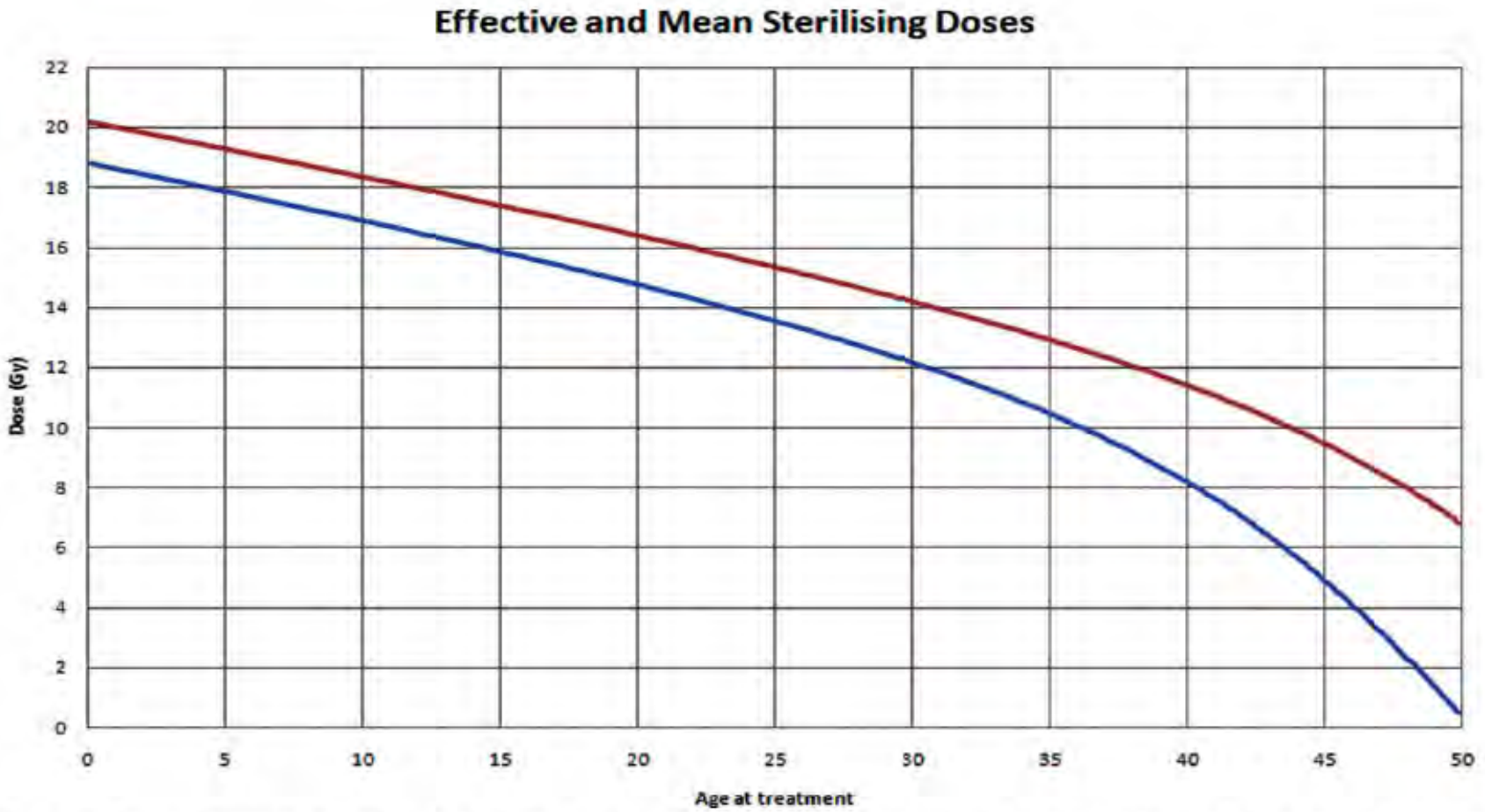

Figure 2. Based on our understanding of the radiosensitivity of the human oocyte and our knowledge of the natural decline in primordial follicles with increasing age, we provide effective (red line) and mean (blue line) estimates of the dose required to sterilize a patient at a known age of treatment. Abbreviations: Gy, gray. Reprinted with permission from Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys*. 2005;62:738-744