Sociedade Brasileira de Mastologia
Regional Goiás

Preservação da Fertilidade em Pacientes com Câncer de Mama

HUMANA
medicina reprodutiva

Marta Finotti

Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Chemotherapy and radiation therapy often result in reduced fertility, and patients receiving gonadotoxic treatment should be informed of options for fertility preservation and future reproduction prior to such treatment. Reproduction in the context of cancer also raises a number of ethical issues related to the welfare of both patients and offspring. This document replaces the document titled, "Fertility preservation and reproduction in cancer patients," last published in 2005 (Fertil Steril 2005;83:1622–8). (Fertil Steril® 2013;100:1224–31. ©2013 by American Society for Reproductive Medicine.)

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Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion

The Ethics Committee of the American Society for Reproductive Medicine
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Fertil Steril® 2013; 100:1024-31

Aumentando a sobrevida e reduzindo a fertilidade

- ✓ Os avanços no tratamento tem possibilitado a sobrevida de pacientes jovens com câncer
- ✓ As taxas de sobrevida com 5 anos para o câncer de mama, doenças hematológicas, câncer testicular e outros canceres, que atingem pacientes jovens, pode ser de até 85 -90 %
- ✓ Entretanto o tratamento para estes tipos de câncer é altamente deletério á função reprodutiva em homens e mulheres
- ✓ O comprometimento do ovário no que tange ao uso de quimioterápicos é dependente da droga, dose do medicamento e da idade da paciente, na época do tratamento. Com doses cada vez menores podendo causar dano (IOP) a medida que a idade aumenta
- ✓ Com relação a radioterapia acontece o mesmo. O dano está diretamente relacionado a dose de irradiação, ao esquema de fracionamento e a idade

Aspectos Relevantes

- ✓ O profissional de saúde responsável pelo tratamento oncológico da paciente, **deve discutir o potencial risco de infertilidade** com o tratamento que será realizado e as **opções para preservação de fertilidade**

- ✓ É fundamental que o profissional esteja preparado para **discutir as opções de preservação da fertilidade** e **encaminhar para um especialista em Reprodução Humana**, antes do inicio do tratamento

- ✓ A discussão **deve ocorrer precocemente**, fazer parte do plano de tratamento, devendo **ser devidamente documentada**

Preservação da fertilidade: indicação médica ou social ?

- ✓ A **oncofertilidade é um campo interdisciplinar de estudo que busca interpor conhecimentos em oncologia e endocrinologia reprodutiva** para o aperfeiçoamento das estratégias de preservação da função reprodutiva em sobreviventes ao câncer

- ✓ A preservação de fertilidade pré-tratamento antineoplásico transita entre a **indicação médica**, baseada na intenção de profilaxia, e a **indicação social**, baseada no impacto biopsicossocial da incapacidade de procriar

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

Fertility Preservation in Women

Jacques Donnez, M.D., Ph.D., and Marie-Madeleine Dolmans, M.D., Ph.D.

N Engl J Med, 2017

Indications for Fertility Preservation

Malignant diseases requiring gonadotoxic chemotherapy, radiotherapy, or bone marrow transplantation

Hematologic diseases (leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma)

Breast cancer

Sarcoma

Some pelvic cancers

Nonmalignant conditions

Systemic diseases requiring chemotherapy, radiotherapy, or bone marrow transplantation

Ovarian diseases

- Bilateral benign ovarian tumors
- Severe and recurrent ovarian endometriosis
- Possible ovarian torsion

Risk of premature ovarian insufficiency

- Family history
- Turner's syndrome

Personal reasons

Age

Childbearing postponed until later in life

Human Reproduction, Vol.32, No.9 pp. 1802–1811, 2017
Advanced Access publication on July 21, 2017 doi:10.1093/humrep/dex218

human reproduction

ESHRE PAGES

Update on fertility preservation from the Barcelona International Society for Fertility Preservation–ESHRE–ASRM 2015 expert meeting: indications, results and future perspectives†,‡

Francisca Martinez*, on behalf of the International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group[1]

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Submitted on March 27, 2017; accepted on May 19, 2017

Table I **Non-oncological conditions requiring fertility preservation.**

Indication	Disease
Autoimmune diseases (Donnez and Dolmans, 2013; Bedaiwy and Botros, 2014)	Systemic lupus erythematosus (SLE) Behcet's disease Churg-Strauss syndrome (eosinophilic granulomatosis) Steroid resistant glomerulonephritis Granulomatosis with polyangiitis (formerly Wegener's granulomatosis) Inflammatory bowel diseases Rheumatoid arthritis Pemphigus vulgaris
Hematopoietic stem cell transplantation (Donnez and Dolmans, 2013, Joshi *et al.*, 2014)	Autoimmune diseases unresponsive to immunosuppressive therapy Haematological diseases (sickle cell anaemia, thalassaemia major, plastic anaemia)
Medical conditions causing POI (ESHRE POI Guideline Development Group, 2015)	Altered hypothalamic–pituitary–gonadal axis (Donnez and Kim, 2011, Harward *et al.*, 2013) Ovarian oophoritis Benign ovarian tumours Mosaic Turner's syndrome Fragile X Mental Retardation 1 (Gleicher *et al.*, 2015) Galactosemia (Fridovich-Keil *et al.*, 2011) Beta-thalassaemia (Roussou *et al.*, 2013) Endometriosis (Somigliana *et al.*, 2015)
Male genetic disorders	Klinefelter's syndrome (Bedaiwy and Botros, 2014)
Testicular damage (Stahl *et al.*, 2010)	
Gender reassignment procedures (Darney, 2008)	
Severe body trauma requiring surgical intervention	

POI, premature ovarian insufficiency.

Human Reproduction, 2017. Vol 32: 1802-1811

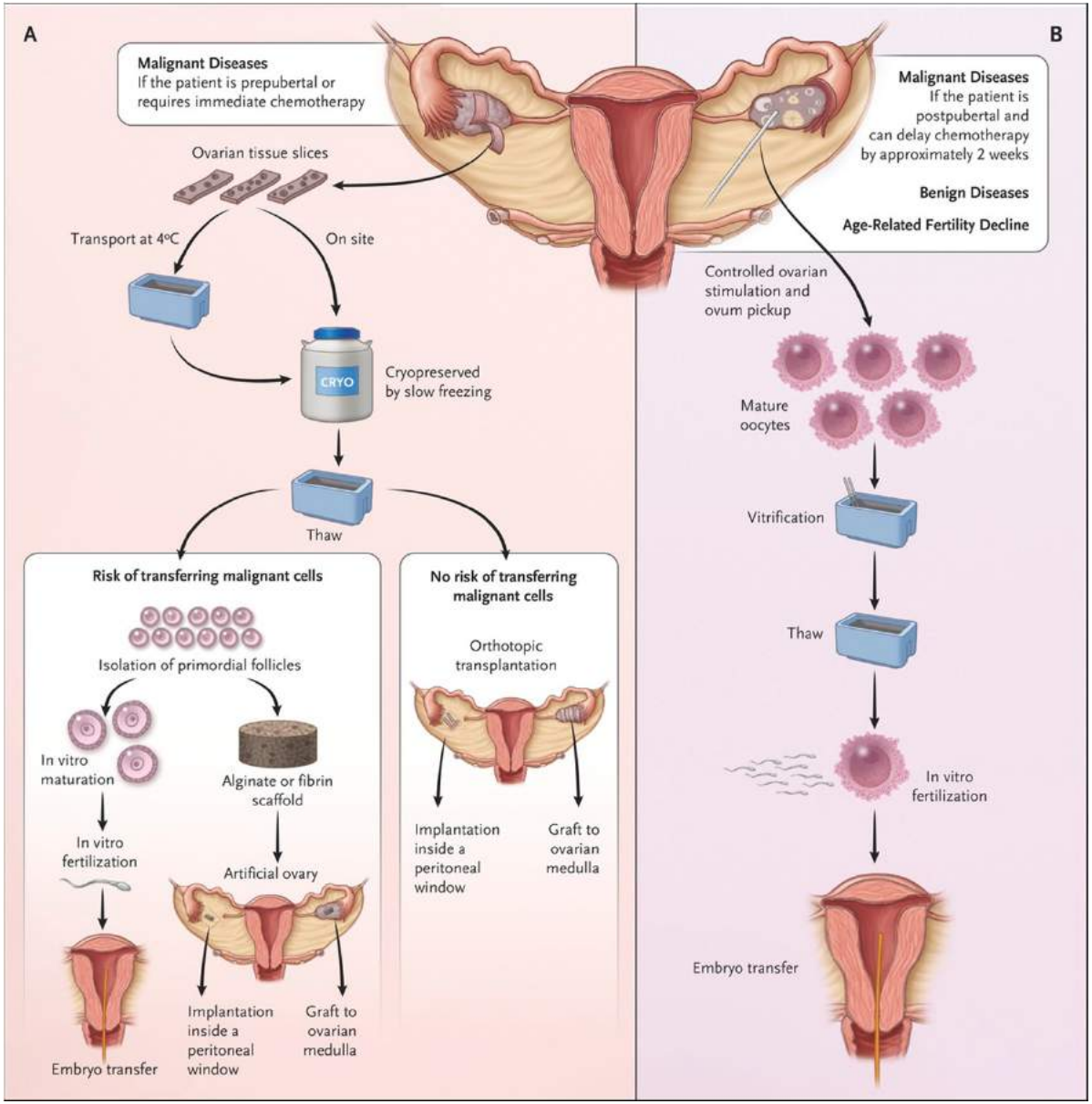
Métodos de preservação da fertilidade

♀

- Criopreservação de embriões
- Criopreservação de óvulos
- Transposição ovariana (ooforopexia)
- Supressão ovariana (GnRHa)?
- Preservação de tecido ovariano e reimplantação
- Maturação *in vitro* de oócitos

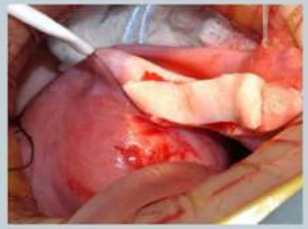
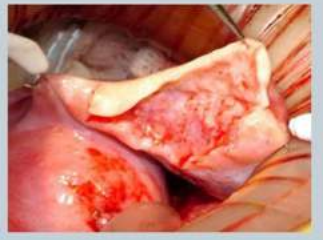
♂

- Criopreservação de espermatozoides
- Preservação de tecido testicular

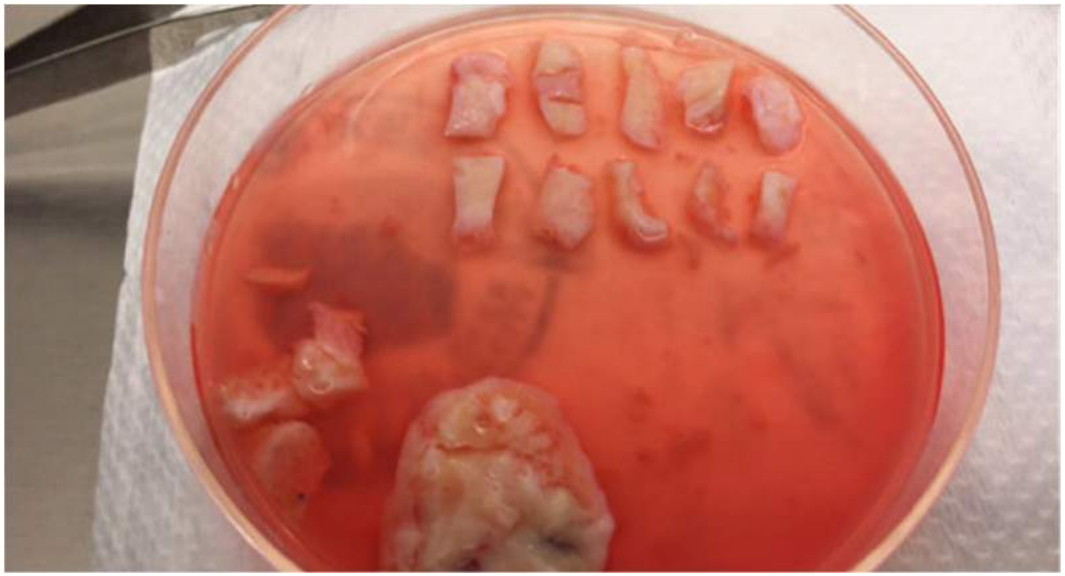


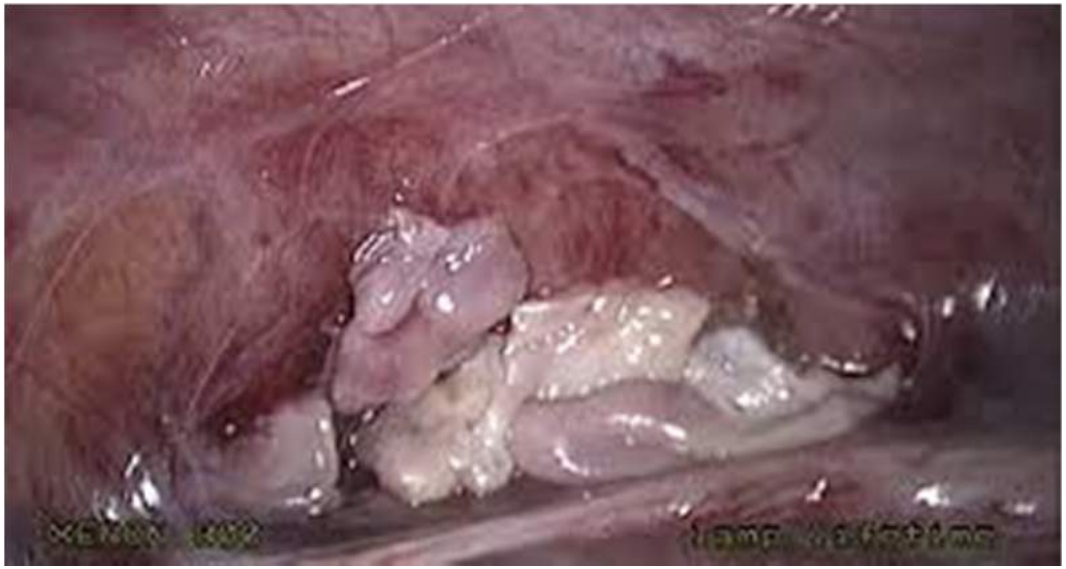
N Engl J Med 2017;377:1657-65

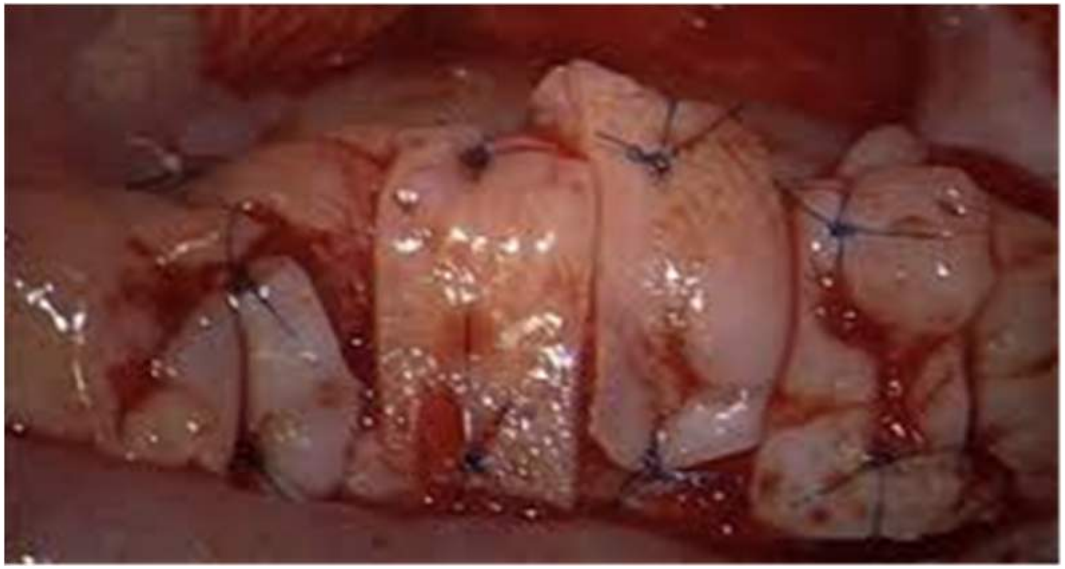
- American Society of Reproductive Medicine: 2014 Committee Opinion[1]
  - "an option in patients who must urgently undergo aggressive chemotherapy and/or radiation, or who have medical conditions requiring treatment that may threaten ovarian function and subsequent fertility. Ovarian tissue cryopreservation may be the only option for prepubertal girls undergoing such treatments. However, these techniques are still considered to be ***experimental*** and should be offered to carefully selected patients as an ***experimental protocol***".


[1]Fertil Steril. 2014 May;101(5):1237-43.







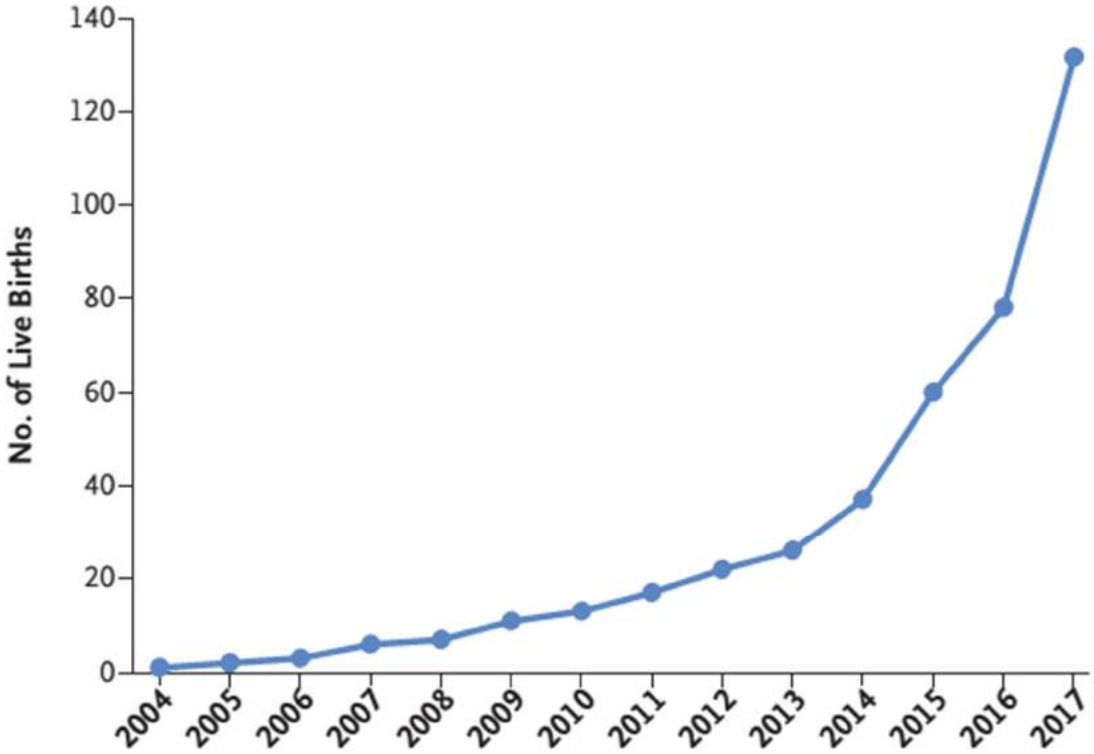
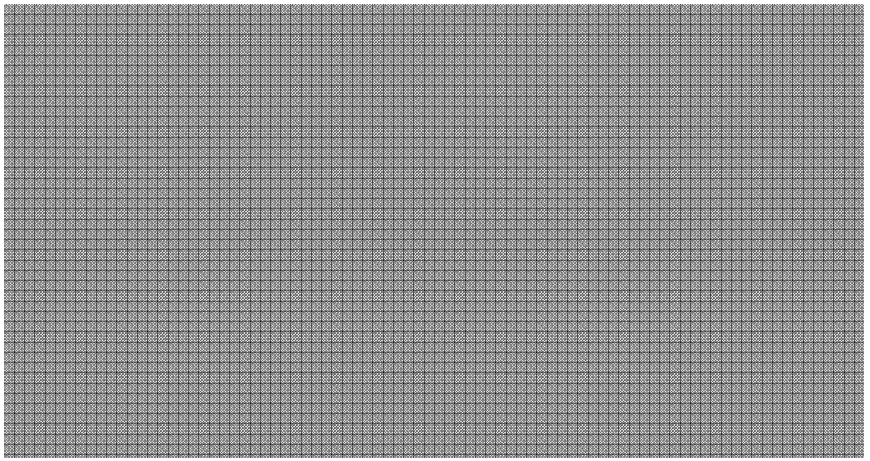
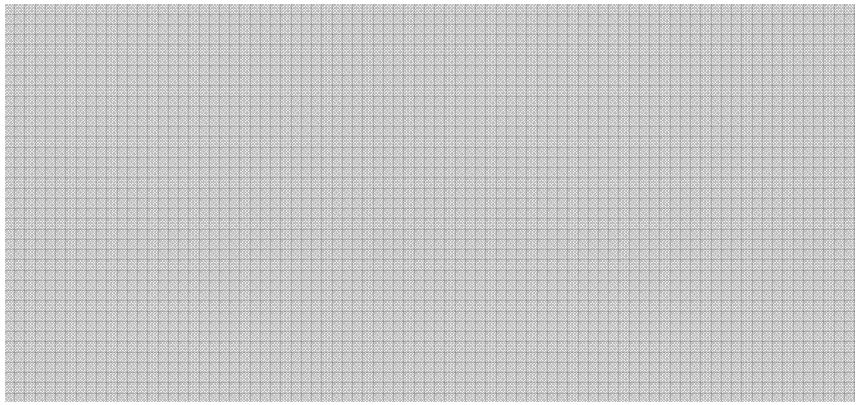


Figure 3. Reimplantation in an Orthotopic Site.

Since 2004, when the first pregnancy after reimplantation in an orthotopic site (namely, a site in the pelvic cavity) was reported, the number of live births has reached more than 130, showing a logarithmic increase during the past 2 years and highlighting the need to move from experimental studies to widespread clinical application.

N Engl J Med 2017;377:1657-65



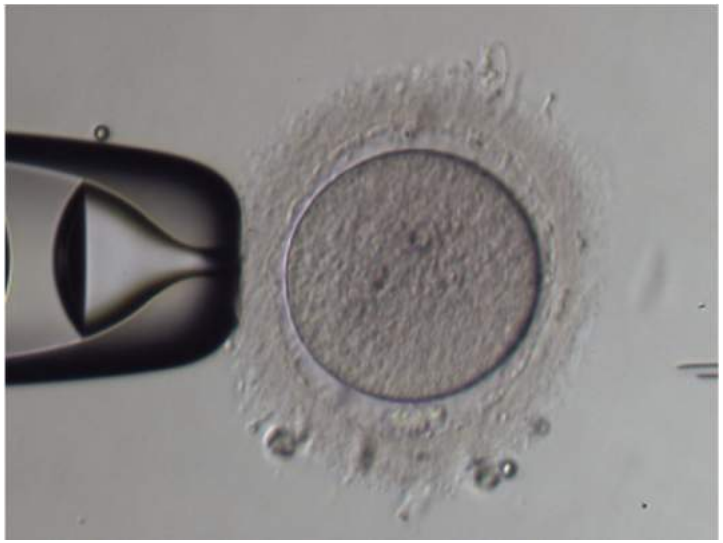
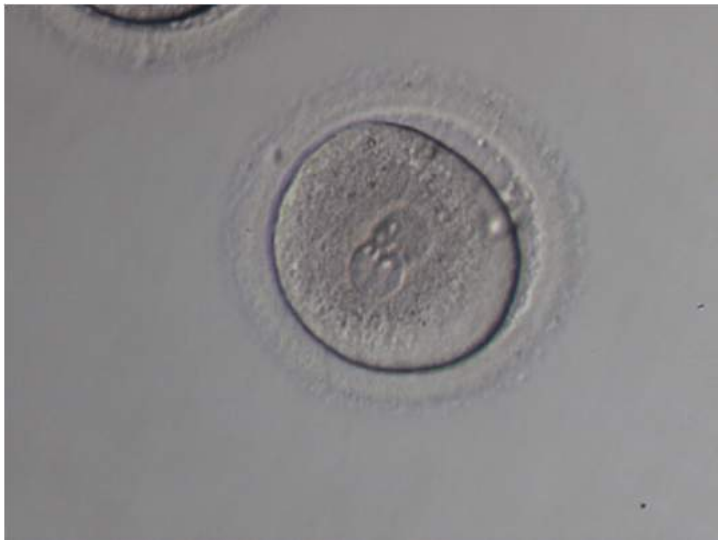
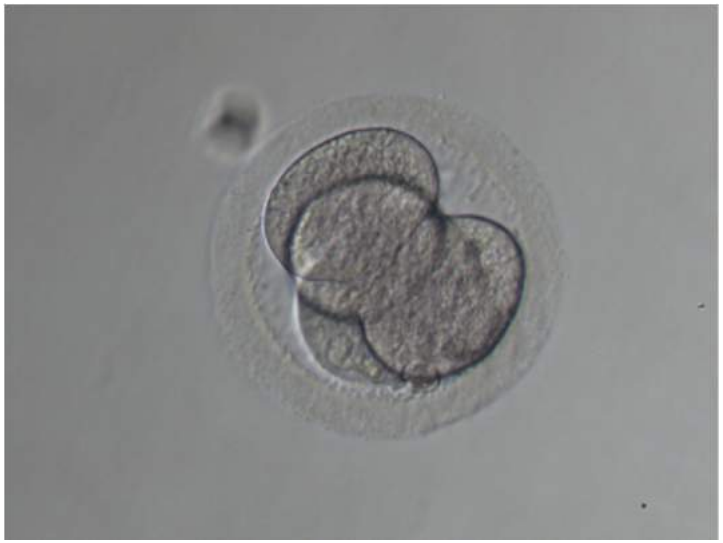
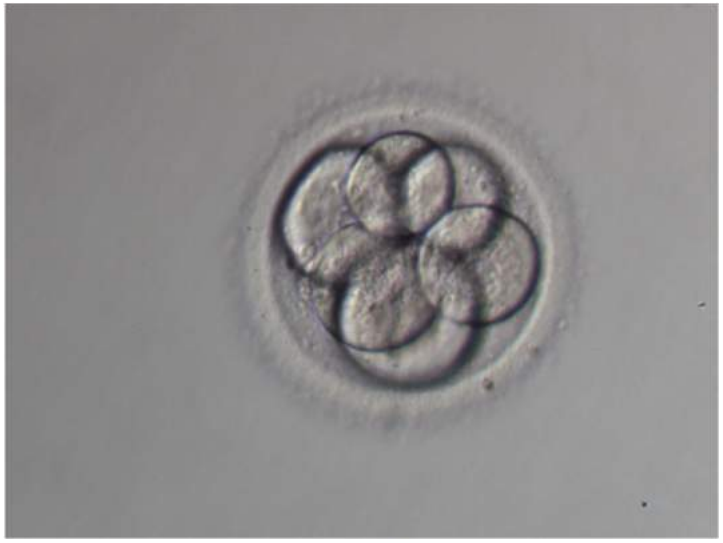
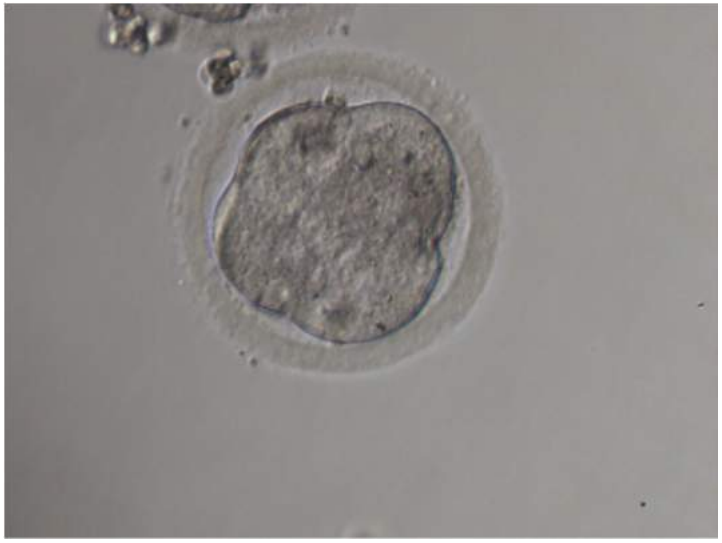
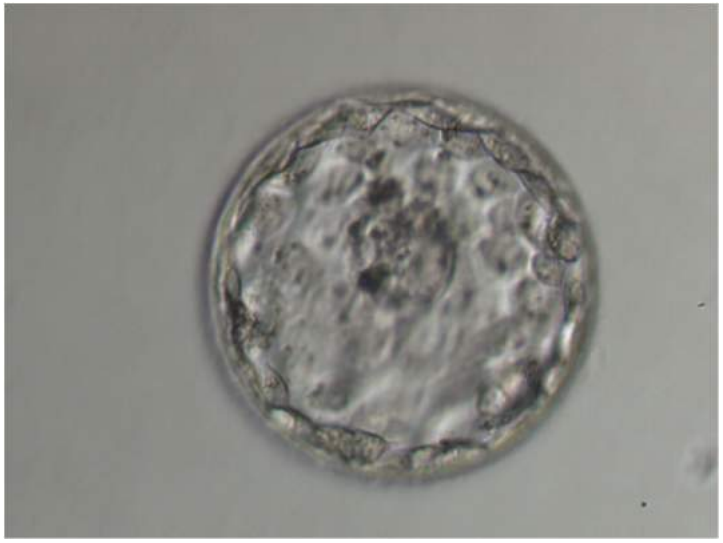


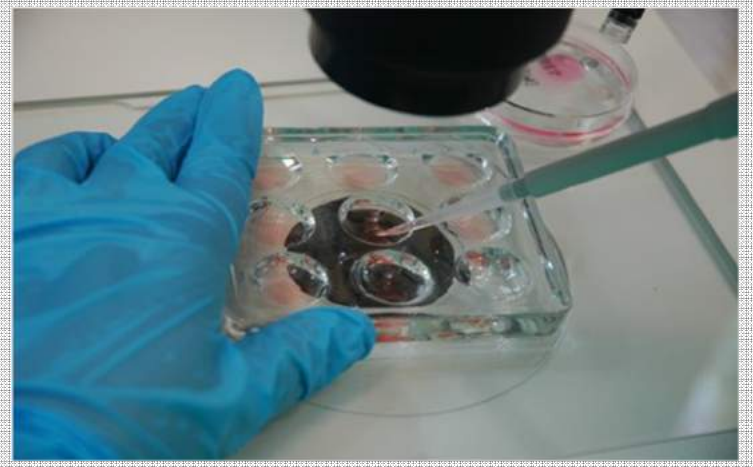
Congelamento de Embriões

- O congelamento de embriões é o método de preservação fertilidade mais usado em todo o mundo
- Sobrevivência embrionária ao descongelamento de até 80%
- Taxas de gravidez de 29 a 43%
- Taxa de nascidos vivos entre 22 e 32%, a depender da idade e de características individuais de melhor ou pior prognóstico reprodutivo

1-Check JH et al., Clin Exp Obstet Gynecol, 2012

2-Yuan Y et al., Hum Reprod, 2019



Congelamento de óvulos

- O congelamento de oócitos maduros assumiu recentemente grande importância
- Foi reconhecido no último consenso da Sociedade Americana de Oncologia Clínica, ao eliminar dilemas éticos que envolvem o congelamento de embriões, uma vez que não se pode excluir o risco de um desfecho letal na população oncológica.
- Em ciclos terapêuticos com oócitos criopreservados e posteriormente descongelados, as taxas de implantação e de gravidez variam de 10 a 60% e de 30 a 50%, respectivamente, com resultados reprodutivos muito próximos aos obtidos com embriões obtidos com gametas a frescos

Cobo A et al., Fertil Steril. 2013

Human Reproduction, Vol.32, No.9 pp. 1802–1811, 2017
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human reproduction

ESHRE PAGES

Update on fertility preservation from the Barcelona International Society for Fertility Preservation–ESHRE–ASRM 2015 expert meeting: indications, results and future perspectives†,‡

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Table II Clinical outcomes from fertility preservation techniques in women.

Author	FP technique	Women/Indication	Outcome
Dolmans *et al.* (2015)	Embryo cryopreservation	54/Cancer 33 returned/20 ET	22% LBR per ET Nine pregnancies Four deliveries
Oktay *et al.* (2015)	Embryo cryopreservation	33/Breast cancer 18 returned/55 ET	45% LBR per ET 26 pregnancies 18 deliveries
Cobo *et al.* (2015)	Oocyte vitrification	Ovum donation programme	6.5% oocyte-to-baby rate. CLBR increased with the number of oocytes used
Cobo *et al.* (2016)	Oocyte vitrification	Delaying childbearing or non-oncological medical conditions	50% LBR per patient in women ≤35 years old 22.9% LBR per patient in women >36 years old
Donnez *et al.* (2015)	Ovarian tissue cryopreservation		*N* = 111 cases, 32 conceived 29.0% LBR per patient

FP, fertility preservation; ET, embryo transfer; LBR, live birth rate; CLBR, cumulative live birth rate.

Human Reproduction, 2017. Vol 32: 1802-1811.

REPROD CLIM. 2017;32(1):31–38

SBRH
Sociedade Brasileira de Reprodução Humana

Reprodução & Climatério

http://www.sbrh.org.br/revista

Artigo de revisão

Indução de ovulação em pacientes com tumor estrogênio-dependente: diretrizes clínicas da Sociedade Brasileira de Reprodução Humana☆

Bruno Ramalho de Carvalho[a,b,*], *João Pedro Junqueira Caetano*[b,c], *Mário Cavagna*[d], *Ricardo Mello Marinho*[b,c], *Adelino Amaral Silva*[a,b] *e Hitomi Miura Nakagawa*[a]

[a] *Genesis Centro de Assistência em Reprodução Humana, Brasília, DF, Brasil*
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[d] *Centro de Referência em Saúde da Mulher, Hospital Pérola Byington, São Paulo, SP, Brasil*

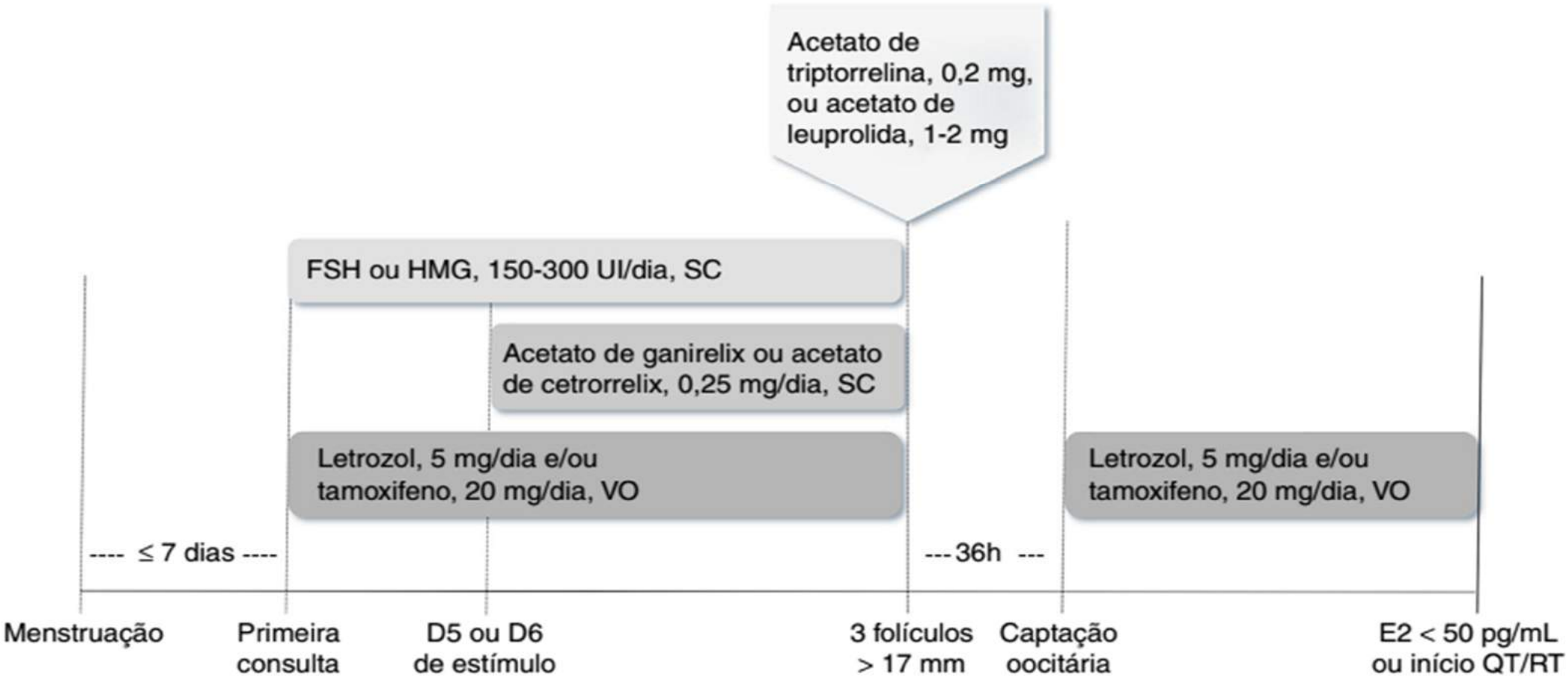
Tabela 1 – Risco de gonadotoxicidade ovariana estimado para diferentes combinações de agentes quimioterápicos antineoplásicos. Adaptado com autorização de Carvalho et al. (2014).[9]

	Alto risco amenorreia permanente >80% das expostas	Risco intermediário amenorreia permanente 20-80% das expostas	Baixo risco amenorreia permanente 20% das expostas	Risco pouco conhecido
Agentes isolados	Ciclofosfamida Busulfan Melphalan Clorambucil Dacarbazina Procarbazina Ifosfamida Thiotepa	Antracíclicos Cisplatina Carboplatina Ara-C (Citarabina)	Metotrexato Bleomicina 5-Fluorouracil Actinomicina-D Alacloides da Vinca Mercaptopurina Etoposide Fludarabina	Taxanos Oxaliplatina Irinotecan Anticorpos monoclonais Inibidores da tirosina-quinase
Agentes combinados e/ou radioterapia	Mostarda nitrogenada Altas doses Ciclofosfamida/Busulfan e transplante de células hematopoiéticas Irradiação ovariana CMF, CAF, CEF 6 ciclos mulheres >40 anos	CMF, CAF, CEF 6 ciclos mulheres 30-39 anos AC, EC 4 ciclos mulheres >40 anos	ABVD CMF, CEF, CAF 6 ciclos mulheres <30 anos MF CHOP, CVP Protocolos para leucemia mieloide, leucemia linfoide aguda AC 4 ciclos mulheres <40 anos	

AC, doxorrubicina + ciclofosfamida; CAF, ciclofosfamida + doxorubicina + fluorouracil; CEF, ciclofosfamida + epirrubicina + fluorouracil; CMF, ciclofosfamida + metotrexato + fluorouracil; MF, metotrexato + fluorouracil; EC, epirrubicina + ciclofosfamida; CHOP, ciclofosfamida + doxorrubicina + vincristina + prednisolone; CVP, ciclofosfamida + vincristina + prednisone; ABVD, adriamicina + bleomicina + vinblastina + dacarbazina.

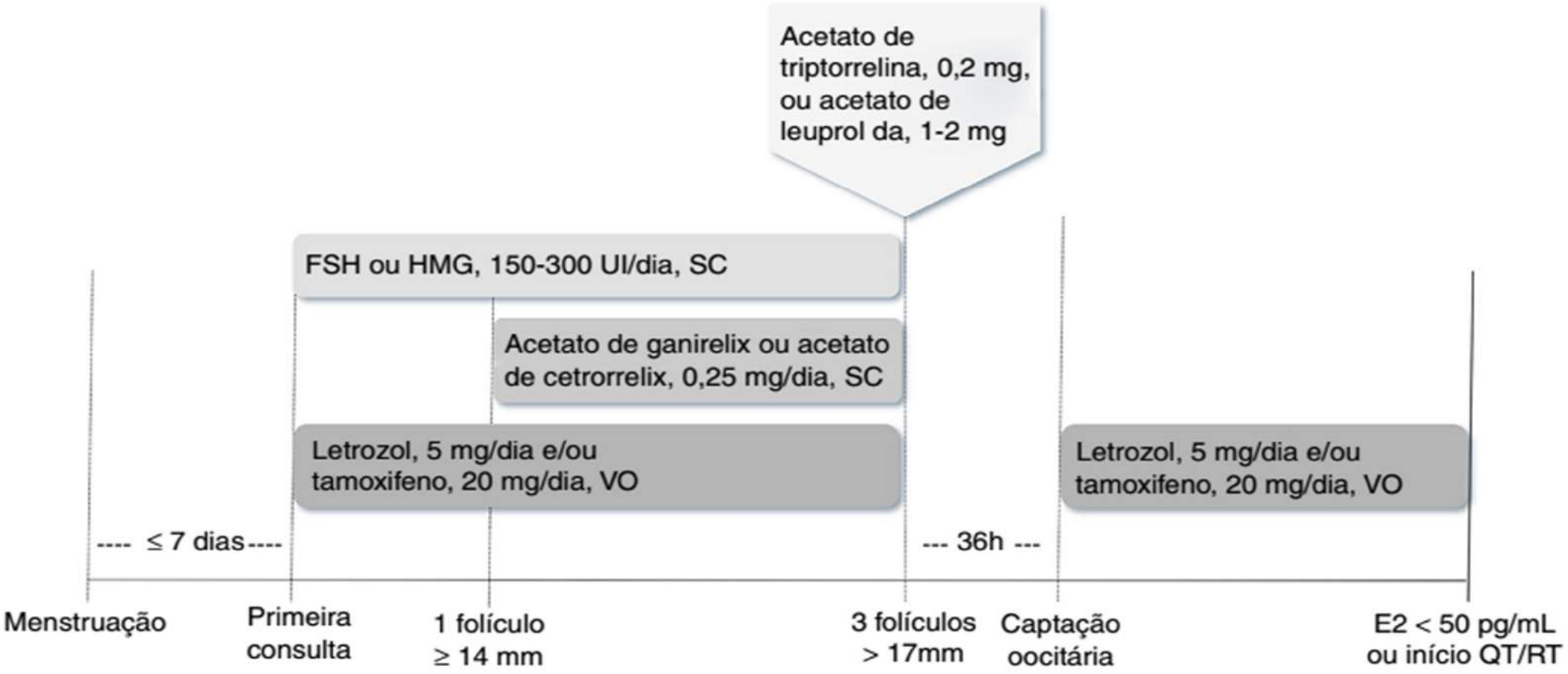
Reprod Clim. 2017;32(1): 31-38

Protocolo de início em fase folicular precoce, regime fixo



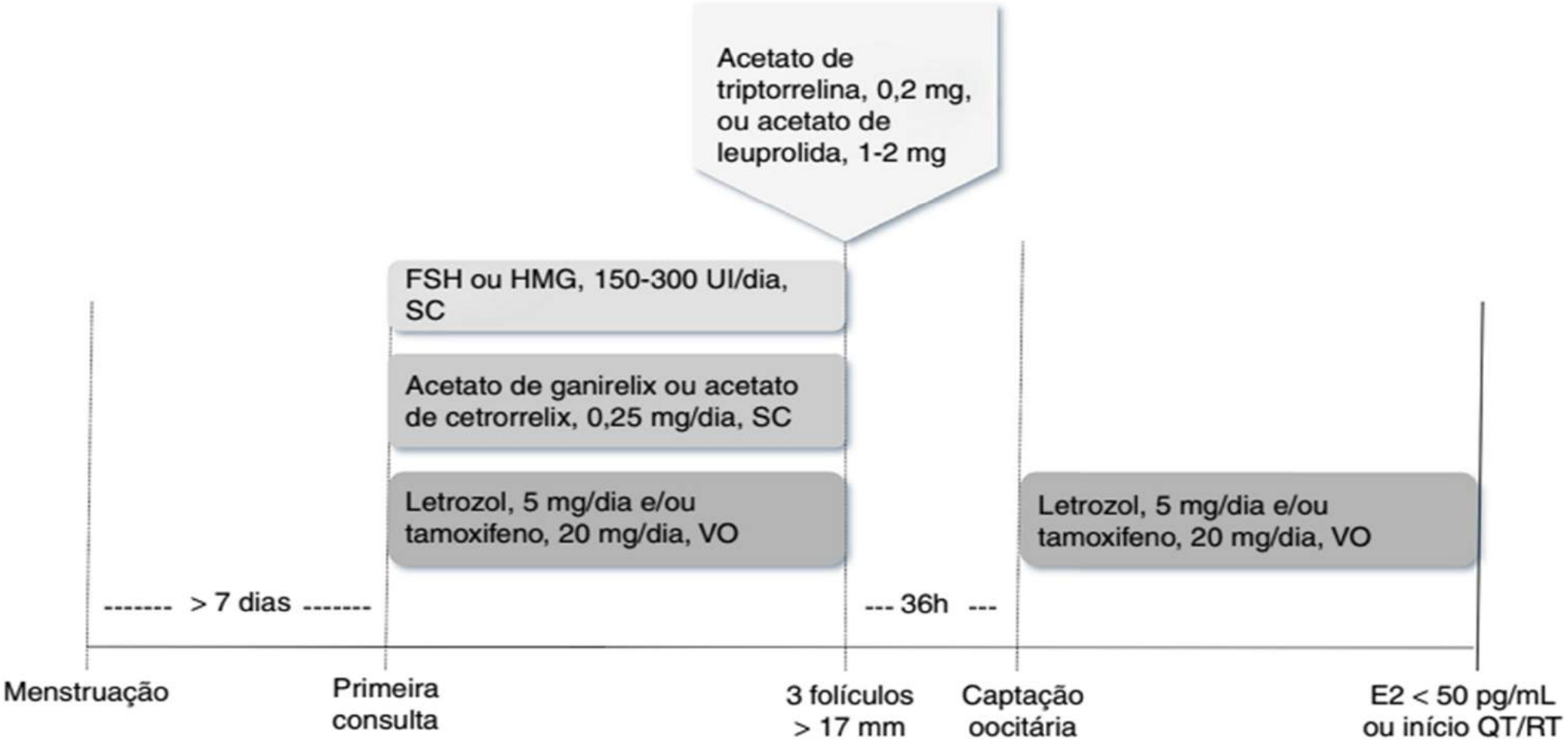
Reprod Clim. 2017;32(1): 31-38

Protocolo de início em fase folicular precoce, regime flexível



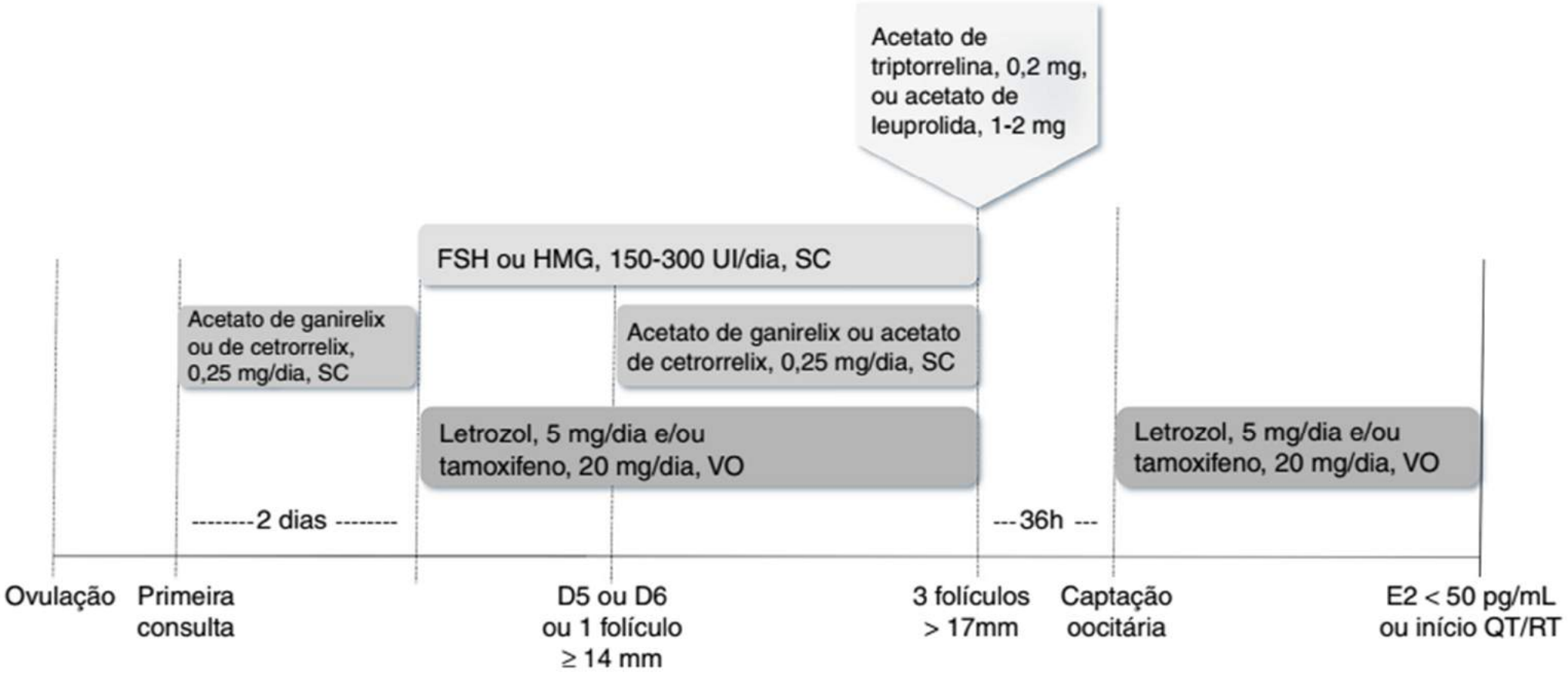
Reprod Clim. 2017;32(1): 31-38

Protocolo de início em fase folicular tardia, com dominância



Reprod Clim. 2017;32(1): 31-38

Protocolo de início em fase lútea



Reprod Clim. 2017;32(1): 31-38

ORIGINAL CONTRIBUTION

Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer

A Randomized Trial

Lucia Del Mastro, MD Luca Boni, MD Andrea Michelotti, MD Teresa Gamucci, MD Nina Olmeo, MD Stefania Gori, MD Monica Giordano, MD Ornella Garrone, MD Paolo Pronzato, MD Claudia Bighin, MD Alessia Levaggi, MD Sara Giraudi, MD Nicola Cresti, MD Emanuela Magnolfi, MD Tiziana Scotto, MD Carlo Vecchio, MD Marco Venturini, MD

Context Premenopausal patients with breast cancer are at high risk of premature ovarian failure induced by systemic treatments, but no standard strategies for preventing this adverse effect are yet available.

Objective To determine the effect of the temporary ovarian suppression obtained by administering the gonadotropin-releasing hormone analogue triptorelin during chemotherapy on the incidence of early menopause in young patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy.

Design, Setting, and Patients The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6) study, a parallel, randomized, open-label, phase 3 superiority trial, was conducted at 16 sites in Italy and enrolled 281 patients between October 2003 and January 2008. The patients were premenopausal women with stage I through III breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy. Assuming a 60% rate of early menopause in the group treated with chemotherapy alone, it was estimated that 280 patients had to be enrolled to detect a 20% absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin. The intention-to-treat analysis was performed by including all randomized patients and using imputed values for missing data.

Interventions Before beginning chemotherapy, patients were randomly allocated to receive chemotherapy alone or combined with triptorelin. Triptorelin was administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy.

Main Outcome Measure Incidence of early menopause (defined as no resumption of menstrual activity and postmenopausal levels of follicle-stimulating hormone and estradiol 1 year after the last cycle of chemotherapy).

Results The clinical and tumor characteristics of the 133 patients randomized to chemotherapy alone and the 148 patients randomized to chemotherapy plus triptorelin were similar. Twelve months after the last cycle of chemotherapy (last follow-up, August 18, 2009), the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of −17% (95% confidence interval, −26% to −7.9%; $P < .001$). The odds ratio for treatment-related early menopause was 0.28 (95% confidence interval, 0.14 to 0.59; $P < .001$).

Conclusion The use of triptorelin-induced temporary ovarian suppression during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause.

Trial Registration clinicaltrials.gov Identifier: NCT00311636

JAMA. 2011;306(3):269-276 www.jama.com

ORIGINAL ARTICLES: FERTILITY PRESERVATION

Check for updates

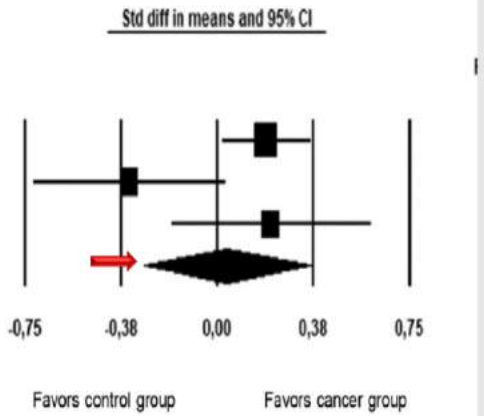
The impact of malignancy on response to ovarian stimulation for fertility preservation: a meta-analysis

Volkan Turan, M.D.,[a] Molly M. Quinn, M.D.,[b] Nurten Dayioglu, Ph.D.,[c] Mitchell P. Rosen, M.D.,[b] and Kutluk Oktay, M.D., Ph.D.[d,e]

A

	Cancer			Control			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		95% CI
Quinn et al, 2017(10)	19.10	12.44	191	16.80	11.97	398	42..34	0.19 (0.02, 0.36)
Almog et al, 2012 (8)	9.80	5.90	42	12..30	7.90	81	29..24	-0.34 (-0.72, 0.03)
Oktay et al, 2006(6)	12.40	7.00	47	11..10	5.50	56	28..42	0.21 (-0.18, 0.59)
Total	16.58	11.54	280	15.52	11.14	535	100..00	0,04 (-0.03, 0.36)

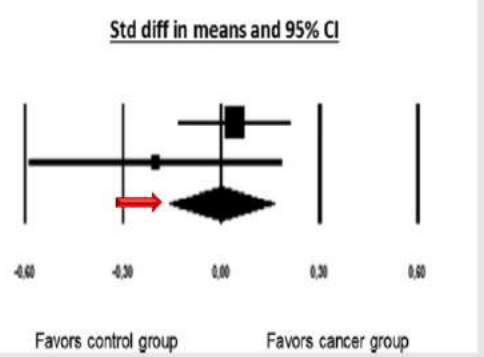
Heterogeneity:Tau^2=0.23; Chi^2= 6.67, df=2 (p=0.036); I^2=70%
Test for overall effect: Z=0.24 (p=0.812)



B

	Cancer			Control			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		95% CI
Quinn et al, 2017 (10)	13..50	9.7	191	13.10	10	398	83..54	0.04 (-0.13, 0.21)
Oktay et al, 2006 (6)	8.70	4.80	47	9.70	5.10	56	16.46	-0.20 (-0.59, 0..19)
Total	12.55	9.12	238	12.68	9.57	454	100.00	0.001 (-0..16, 0.16)

Heterogeneity:Tau^2= 0.00; Chi^2= 1.24 df=1 (p=0.265); I^2=19.54%
Test for overall effect: Z= 0.009 (p=0.993)



Subgroup analysis in women with breast cancer. Comparisons were made of the **(A)** mean number of total oocytes, and **(B)** mean number of mature oocytes between women with breast cancer and controls.

Turan. Ovarian response in cancer patients. Fertil Steril 2018.

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren

J Clin Oncol 36.

Table 1. Randomized Controlled Trials

First Author, Year, Trial	No. of Patients		Agents	Disease Sites	Follow-Up (years)	Primary Outcome	No. of Pregnancies (%)	*P*
	Enrolled	Evaluable						
Leonard, 2017, OPTION[9]	106	95	GnRHa	Breast	5.0*	POV	9 (9)	NR
	121	107	Control				6 (6)	
Demeestere, 2016[8]	65	32	GnRHa	Lymphoma	5.33	POF	17 (53.1)	NS
	64	35	Control				15 (42.8)	
Moore, 2015, POEMS[7]	126	105	GnRHa	Breast	4.1	POV	22 (21)	.03
	131	113	Control				12 (11)	
Lambertini, 2015, PROMISE-GIM6[6]	148	148	GnRHa	Breast	7.3	POV	8 (5)	NS
	133	133	Control				3 (2)	
Elgindy, 2013[5]	25	17	GnRHa	Breast	1.0	Resumption of menses	1 (4)	NS
	25	17	Control				1 (4)	
	25	17	GnRHa				1 (4)	NS
	25	17	Control				0 (0)	
Munster, 2012[4]	27	26	GnRHa	Breast	1.6	POV	0 (0)	NS
	22	21	Control				2 (10)	
Gerber, 2011[3]	30	30	GnRHa	Breast	4.0	Resumption of menses	1 (3)	NS
	31	30	Control				1 (3)	

Abbreviations: GnRHa, gonadotrophin-releasing hormone agonist; NR, not reported; NS, not significant; OPTION, Ovarian Protection Trial In Premenopausal Breast Cancer Patients; POEMS, Prevention of Early Menopause Study; POF, premature ovarian failure; POV, preservation of ovarian function; PROMISE-GIM6, Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients—Gruppo Italiano Mammella 6.

*Median not reported.

Table 3. Guidelines

Guideline	Recommendation
NCCN Breast Cancer 2017[21]	Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regard to the protective effect of GnRH agonist therapy on fertility.
NCCN AYA Oncology 2017[20]	Some data suggest that menstrual suppression with GnRH agonists may protect ovarian function. However, evidence that menstrual suppression with GnRH agonists protects ovarian function is insufficient, so this procedure is not currently recommended as an option for fertility preservation.
AIOM 2016[15]	Temporary ovarian suppression with LHRHa during chemotherapy should be recommended to all premenopausal patients with breast cancer undergoing chemotherapy who are interested in ovarian function and/or fertility preservation.
SEOM 2016[16]	The use of GnRHa could be an option to discuss with patients with early-stage receptor-negative breast cancer if embryo or oocyte cryopreservation not feasible. The use of GnRHa to preserve fertility in women with other cancer should not be recommended.
BCY2 2016[17]	The most recent data suggested a protective ovarian effect of LHRHa in both patients with hormone receptor–positive and –negative disease with no signal for harm from a breast cancer recurrence standpoint. The BCY2 Panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.
St Gallen 2015[18]	LHRH agonist therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women with ER-negative breast cancer undergoing chemotherapy.
ESMO 2013[19]	The use of GnRH analogs concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates in these cohorts are warranted.

Abbreviations: AIOM, Italian Association of Medicine; AYA, Adolescent and Young Adult; BCY2, International Consensus Conference for Breast Cancer in Young Women; ER, estrogen receptor; ESMO, European Society for Medical Oncology; GnRHa, gonadotrophin-releasing hormone agonist; LHRH, luteinizing hormone-releasing hormone; LHRHa, luteinizing hormone-releasing hormone agonists; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica.

Table 2. Systematic Reviews

First Author, Year	Total Studies Included	RCTs Addressing Pregnancy	No. of Patients	Agents	No. of Pregnancies (%)	OR	95% CI	*P*
Munhoz, 2016[13]	7	NR	NR	GnRHa	NR	1.85	1.02 to 3.36	.04
			NR	Control	NR			
Elgindy, 2015[11]	10	8	427	GnRHa	30	1.63	0.94 to 2.82	NS
			412	Control	20			
Lambertini, 2015[12]	12	5	359	GnRHa	33 (9.2)	1.83	1.02 to 3.28	.041
			347	Control	19 (5.5)			
Turner, 2013[10]	12	4		GnRHa	6	NR	NR	NR
				Control	5			

Abbreviations: GnRHa, gonadotrophin-releasing hormone agonist; NR, not reported; NS, not significant; OR, odds ratio; RCT, randomized controlled trial.

Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Fertility and Sterility, 2017

KEY POINTS

1

- Clinicians should inform patients receiving potentially gonadotoxic therapies about options for fertility preservation and future reproduction prior to the initiation of such treatment. A collaborative multidisciplinary team approach is encouraged

2

- Established methods of fertility preservation include sperm cryopreservation in men and embryo and oocyte cryopreservation in women

3

- Due to technological advances made in the past decade, oocyte cryopreservation has become a viable option prior to gonadotoxic therapy for post pubertal girls, single women, and those who have moral or ethical objections to embryo freezing. Data, however, are still limited about long–term follow–up

4

- Experimental procedures such as cryopreservation of ovarian tissue in girls and women and testicular tissue in prepubescent males should be offered only in a research setting with institutional review board (IRB) oversight

KEY POINTS

5

- The data on the use of gonadotropin–releasing hormone analogs (GnRHa) for ovarian suppression have been conflicting; until definitive proof of efficacy is established, other fertility preservation options should be offered in addition to GnRHa treatment

6

- All available options should be offered and can be performed alone or in combination, often without causing significant delay to cancer treatment

7

- Concerns about the welfare of resulting offspring are not sufficient reasons to deny patients facing gonadotoxic treatments assistance in reproducing

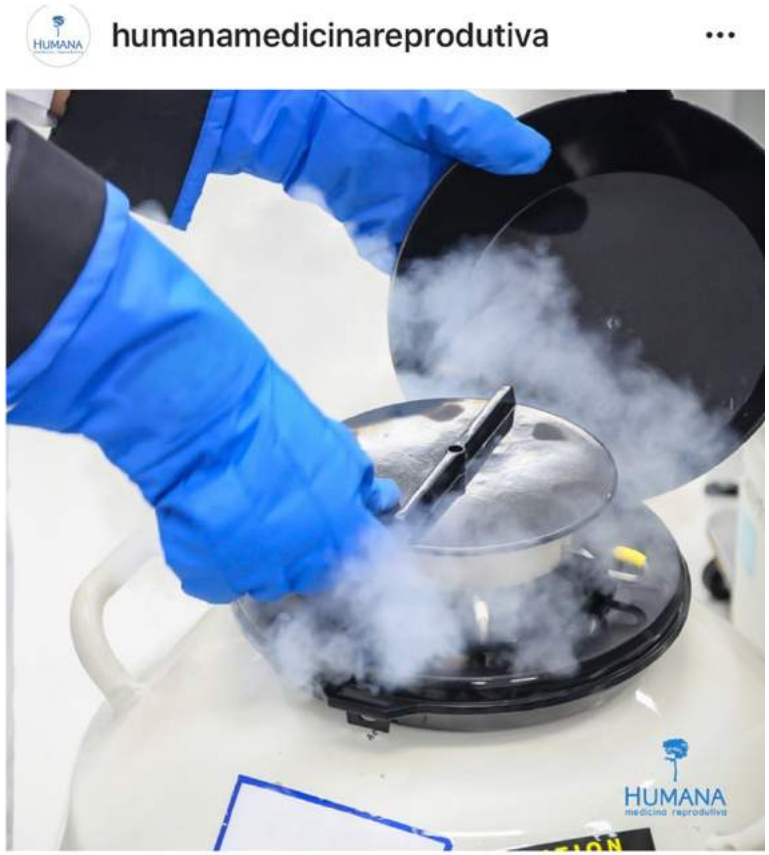
8

- Parents may act to preserve fertility of cancer patients who are minors if the child assents and the intervention is likely to provide potential benefits to the child

KEY POINTS

9

- Instructions should be specified about the disposition of stored gametes, embryos, or gonadal tissue in the event of the patient's death, unavailability, or other contingency



10

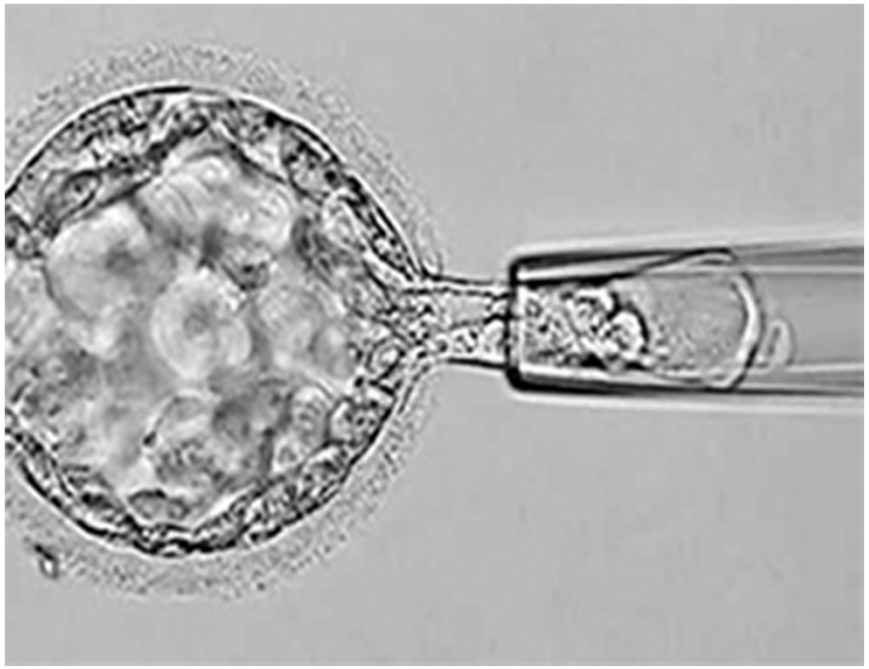
- Preimplantation genetic diagnosis (PGD) to avoid the birth of offspring with a high risk of inherited cancer is ethically acceptable

Escolha do embrião em pacientes mutadas

- ✓O diagnóstico genético pré implantacional (PGD), para evitar o nascimento de crianças com alto risco de câncer hereditário, é eticamente aceitável

Ethics Committee of American Society for Reproductive M. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. Fertil Steril 2013;100:54–7

Diagnóstico Genético Pré-implantacional
PGS e PGD (PGT-A e PGT-M)



- PGD (Pre-Implantation Genetic Diagnosis) e o PGS (Pre-Implantation Genetic Screening) são exames que podem ser utilizados nos processos de RA
- Objetivo de diagnosticar nos embriões a existência de alguma doença genética antes da implantação
- A diferença entre PGD e PGS está no tipo de análise genética realizada: PGD → examina doenças genética

  PGT-**A** (aneuploidia) e PGT-**M** (monogênica)

  PGS → examina doenças cromossômicas

BRCA mutations and reproduction

Hagit Daum, M.D.,[a] Tamar Peretz, M.D.,[b] and Neri Laufer, M.D.[c]

[a] Department of Genetic and Metabolic Diseases, [b] Sharett Oncology Institute, and [c] IVF Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Deleterious mutations in *BRCA1* or *BRCA2* genes have long been recognized as independent risk factors, mostly for breast and ovarian cancer. Numerous studies have evaluated the molecular processes involving these genes, the pathophysiology of BRCAness, follow up options and modes of prophylaxis. The fertility of *BRCA* carriers, however, has not been widely investigated. The aim of the present work is to review the literature pertaining to this issue. (Fertil Steril® 2018;109:33–8. ©2017 by American Society for Reproductive Medicine.)

Key Words: *BRCA*, preimplantation genetic diagnosis (PGD), premature ovarian insufficiency

- A mutação dos genes BRCA 1/2 tem interferência direta na fertilidade. A presença da mutação está diretamente relacionada com diminuição da reserva ovariana e a risco de IOP
- PGD é justificável em embriões de casais com mutações dos genes BRCA 1/2 do ponto de vista médico e ético
- Os pais tem o direito de querer evitar a possibilidade de transição da mutação aos seus descendentes
- O tema deve ser discutido e oferecido ao casal, entretanto os custos são elevados

Human Reproduction, Vol.33, No.2 pp. 181–187, 2018
Advanced Access publication on December 1, 2017 doi:10.1093/humrep/dex356

human reproduction OPINION

Fertility preservation in women harboring deleterious BRCA mutations: ready for prime time?

Fedro Alessandro Peccatori[1], Giorgia Mangili[2,*], Alice Bergamini[2], Francesca Filippi[3], Fabio Martinelli[4], Federica Ferrari[5], Stefania Noli[1,3,6], Emanuela Rabaiotti[2], Massimo Candiani[2], and Edgardo Somigliana[3,6]

[1]Fertility and Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology, Via S. Luca 8, 20122 Milan, Italy [2]Department of Obstetrics and Gynecology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy [3]Obstetrics and Gynecology Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via della Commenda 12, 20122 Milan, Italy [4]Gynecologic Oncology Unit, Fondazione IRCCS National Cancer Institute, Via G. Venezian, 1, 20133 Milan, Italy [5]Applied Research Division for Cognitive and Psychological Science, European Institute of Oncology, Via S. Luca 8, 20122 Milan, Italy [6]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Via Festa del Perdono, 20122 Milan, Italy

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criopreservação de ovócitos

Congelar a fertilidade

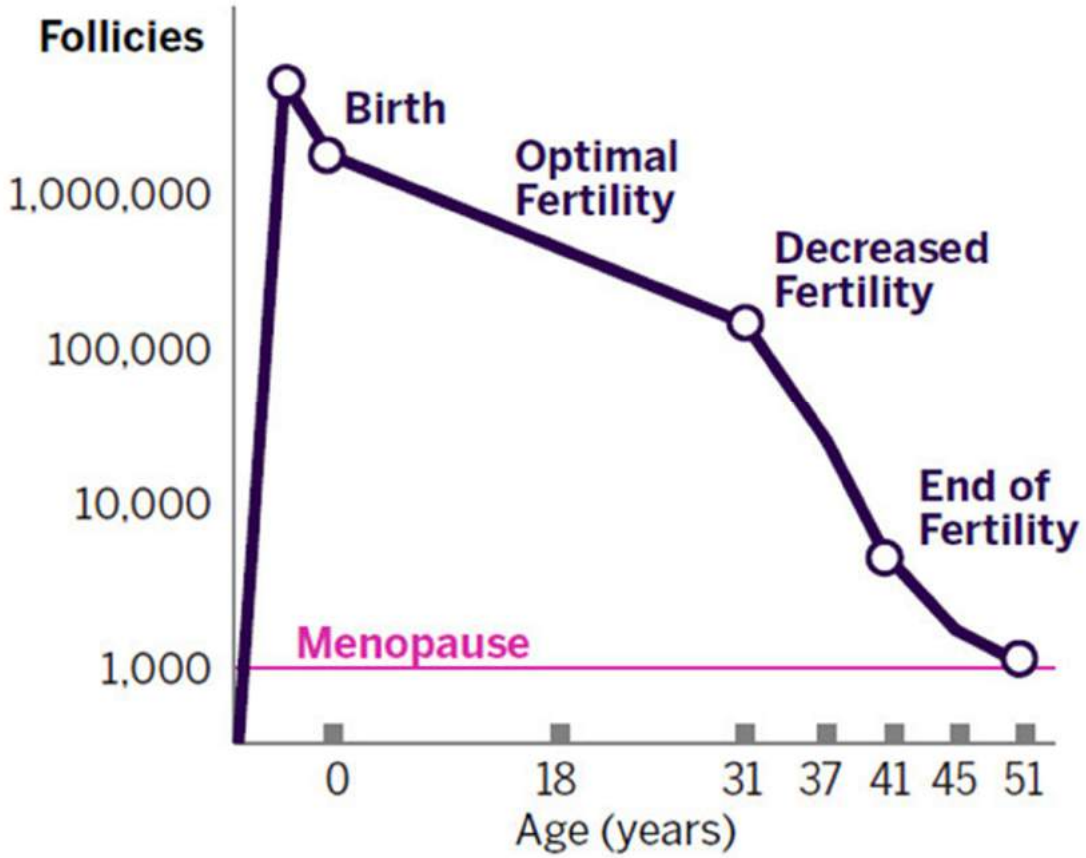
Está a nascer, nos EUA, uma revolução provavelmente equiparável à que ocorreu, nos anos 60, com a pílula: congelar os ovócitos para poder adiar a maternidade. Por cá, também já é possível fazê-lo.

POR **MANUELA VASCONCELOS**
COLABORAÇÃO E REVISÃO CIENTÍFICA

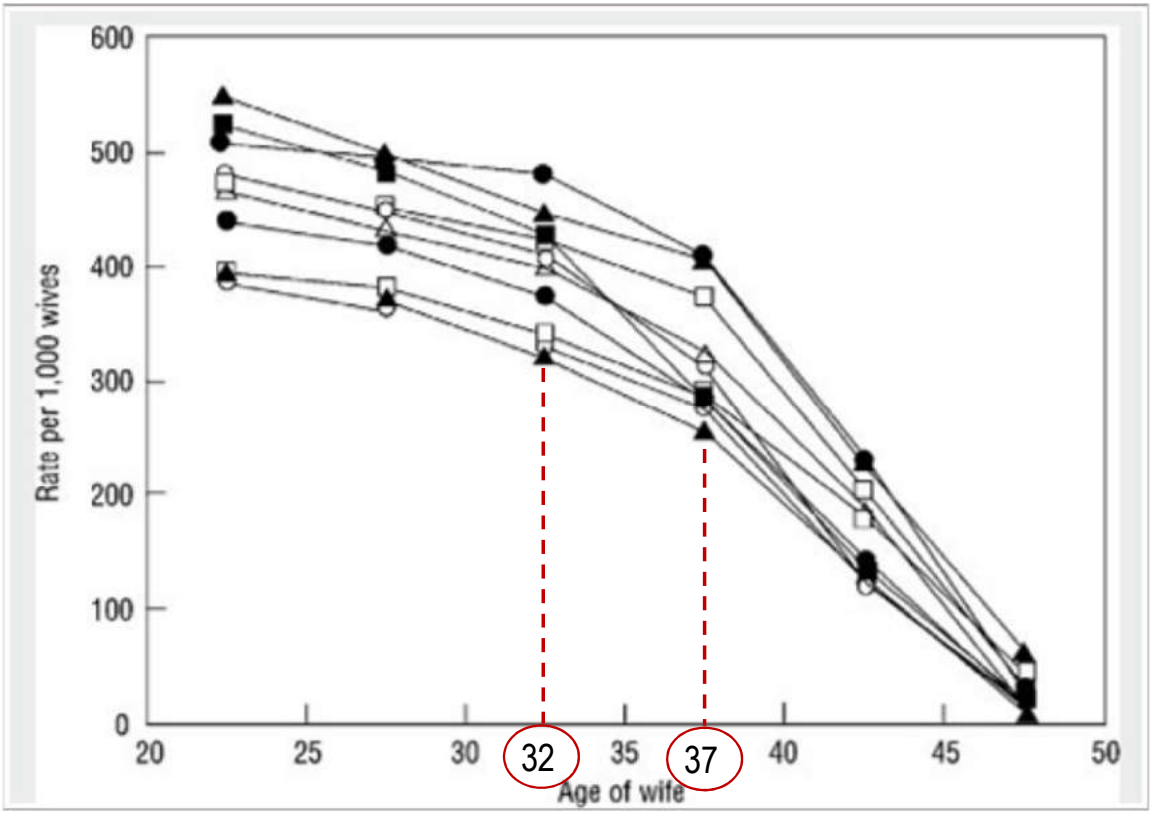
PROF. ANA TERESA SANTOS
Presidente da Sociedade Portuguesa de Medicina da Reprodução

PROF. CÂNDIDO TOMÁS
Diretor clínico do centro de fertilidade AVA Clinic

Natural Decline of Ovarian Reserve

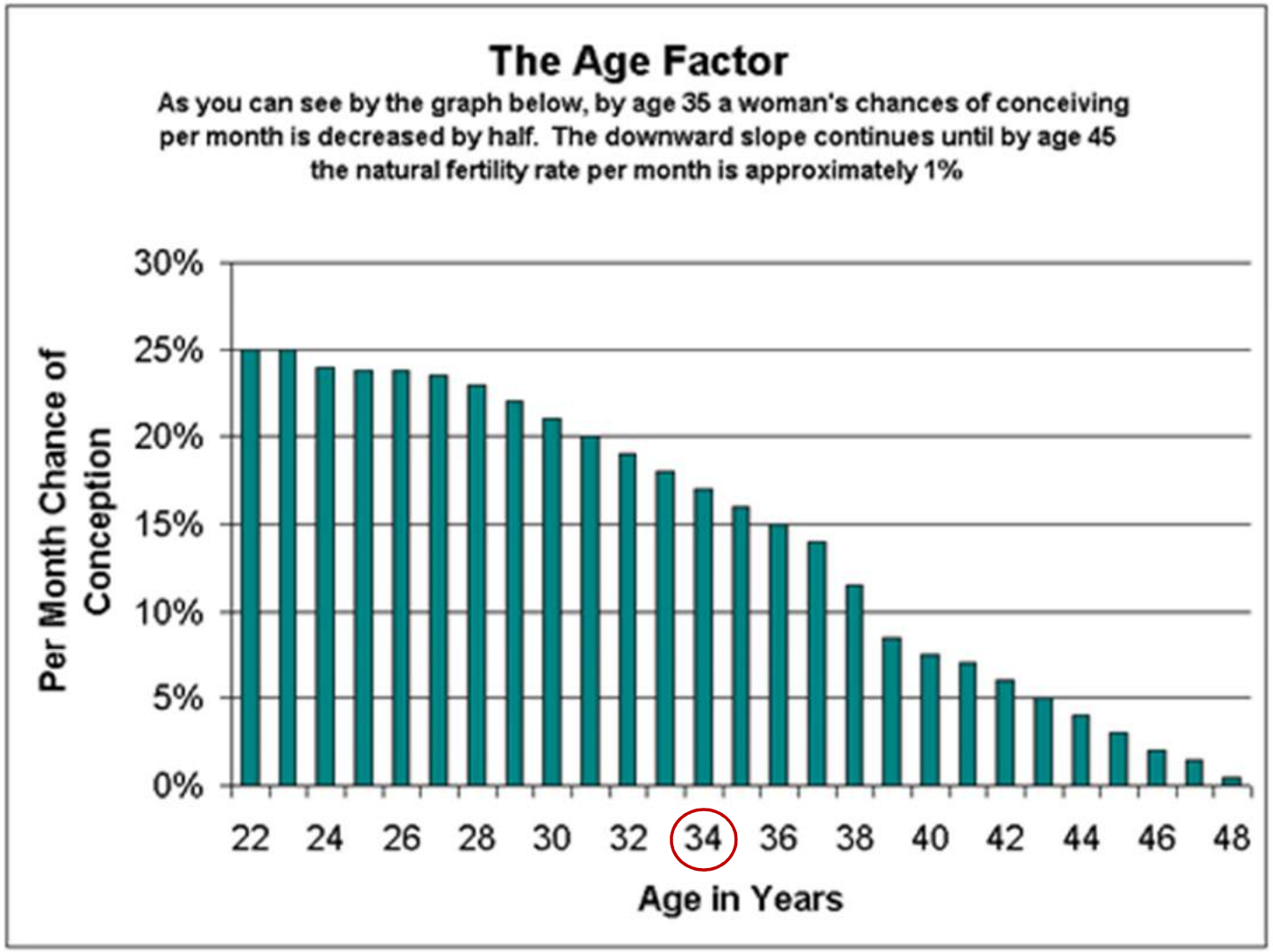


Source: Source: The American Society for Reproductive Medicine



Marital fertility rates by 5-year age groups. The ten populations (in descending order at age 20–24 years) are Hutterites, marriages in 1921–1930 (▲); Geneva bourgeoisie, husbands born 1600–1649 (■); Canada, marriages in 1700–1730 (●); Normandy marriages in 1760–1790 (○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840–1859 (△); Normandy, marriages in 1674–1742 (●); Norway, marriages in 1874–1876 (□); Iran, village marriages in 1940–1950 (▲); Geneva bourgeoisie, husbands born before 1600 (○). From Menken J, Trussell J, Larsen U. Age and fertility. Science 1986;233:1389–94. Reprinted with permission from AAAS.

Pratice Committee. Committee Opinion No. 589. Fertil Steril 2014



ACOG Committee Opinion – Female Age Related Fertility Decline, N.589, 2014

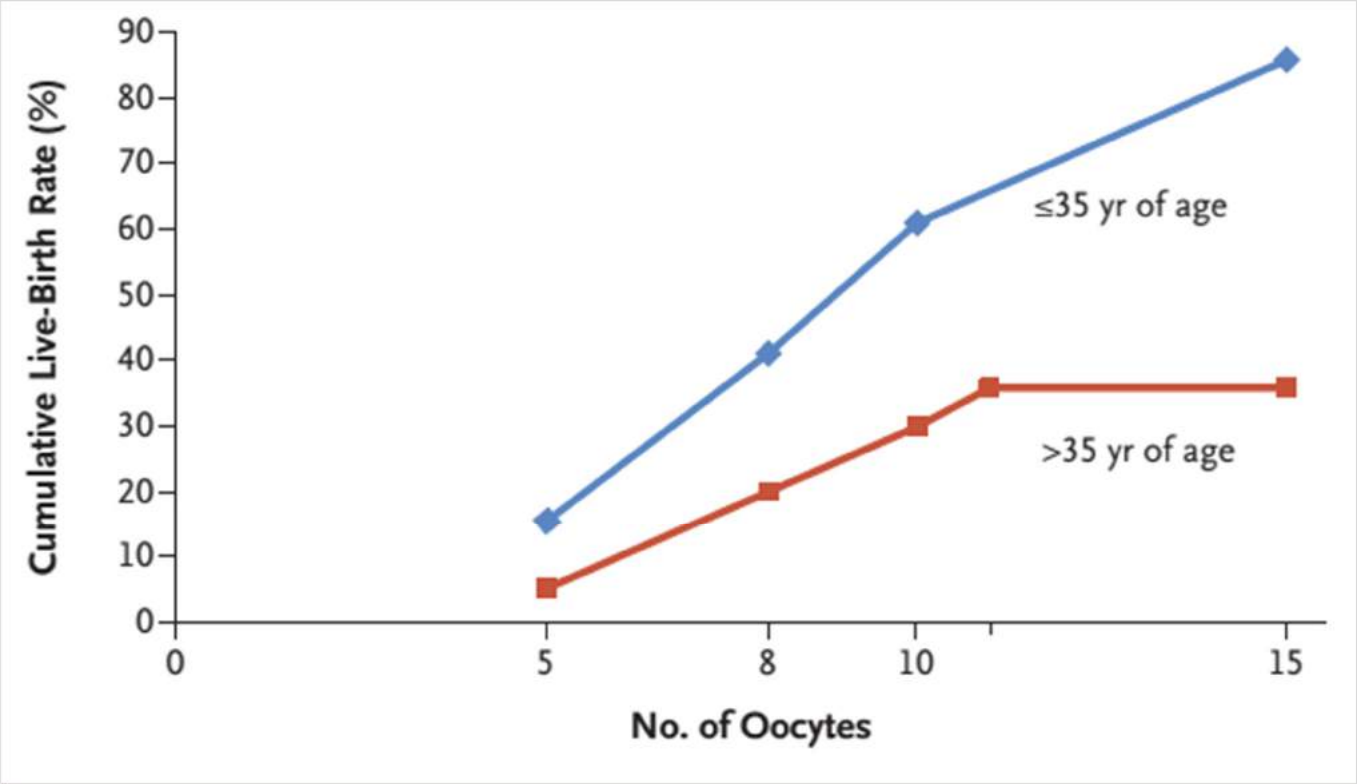
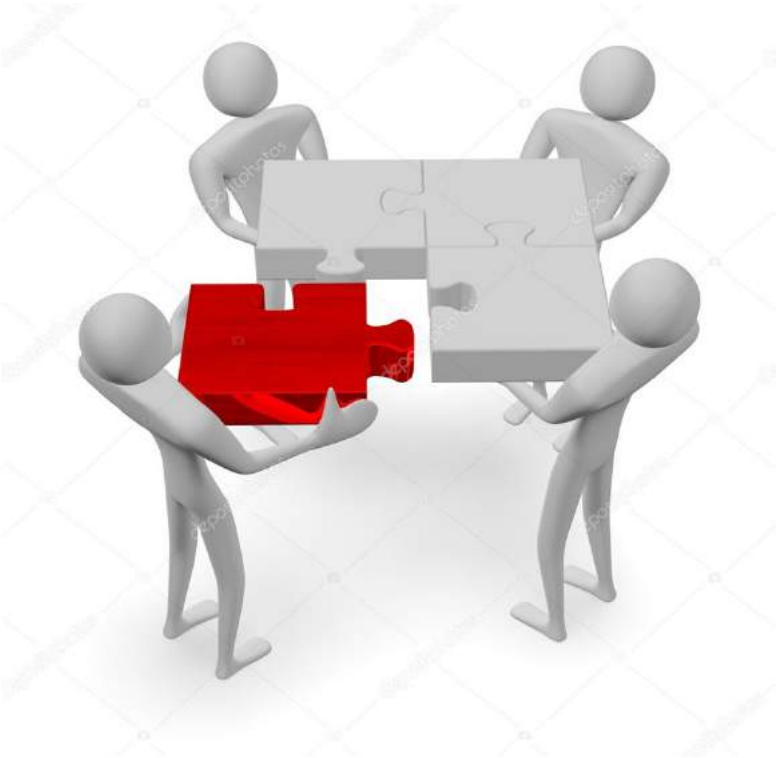


Figure 2. Cumulative Live-Birth Rates with 5 to 15 Oocytes, According to Age.

The cumulative live-birth rate increases with the number of oocytes and is higher among younger women (≤35 years of age) than among older women (>35 years of age). Data are from Cobo et al.[26]

N Engl J Med 2017;377:1657-65

Considerações finais



- ✓ Cada caso tem sua própria estratégia de tratamento → **Individualização Terapêutica**
- ✓ A esperança de **poder gerar uma criança após um câncer é fator de melhoria da autoestima** e pode até mesmo **contribuir para a melhor aceitação do tratamento antineoplásico** e seus efeitos adversos
- ✓ O **risco de insucesso** deve ser esclarecido
- ✓ A **interdisciplinaridade** torna-se fundamental para a **abordagem adequada em oncofertilidade**
- ✓ **Integrando-se a atuação de médicos** oncologistas, ginecologistas e especialistas em reprodução humana, psicólogos, assistentes sociais e demais profissionais de saúde **as decisões, certamente, serão acertadas**

Câncer
A fertilidade em risco

INSTITUTO VERHUM
VÍDEO ENDOSCOPIA E REPRODUÇÃO HUMANA

Câncer. A fertilidade em risco.

Com o avanço tecnológico nos diagnósticos dos diferentes tipos de câncer, a detecção precoce da enfermidade se tornou uma realidade. Isso resultou em maior eficácia do tratamento, que se refletiu na melhoria da expectativa de vida para um elevado percentual de pacientes, especialmente crianças, adolescentes e jovens.

Na busca pela cura da doença, muitas conseqüências tardias do tratamento são esquecidas. A infertilidade em homens e mulheres é uma delas. Em muitos casos os danos são irreversíveis e a gravidez pode não se tornar realidade.

Os tratamentos com cirurgias, quimioterapia e radioterapia são indicados em vários casos de câncer e também, em doenças como o lúpus eritematoso sistêmico e a esclerose múltipla. O impacto desses tratamentos sobre a função ovariana pode ser percebido a curto prazo, por distúrbios menstruais e, a longo prazo, por menopausa precoce. Para o sexo masculino, a quimio e a radioterapia são igualmente danosas, podendo levar a alterações hormonais e a infertilidade.

A agressão ao ovário depende do tipo de quimioterápico escolhido, dose utilizada, duração do tratamento e a idade da paciente.

O avanço da medicina já permite o uso de técnicas inovadoras que preservam a fertilidade. Entre as técnicas disponíveis para as mulheres, destacam-se a transposição ovariana, a fertilização "in vitro" (FIV) com o congelamento de embriões ou óvulos, o congelamento de tecido ovariano e a aplicação de hormônios que protegem ovário. Para os pacientes do sexo masculino uma técnica disponível, eficaz e relativamente barata é o congelamento de sêmen.

A transposição ovariana consiste em reduzir a exposição dos ovários à irradiação, fixando-os atrás do útero ou retirando-os do campo de irradiação, traves da técnica de vídeo laparoscopia.

Na fertilização "in vitro" o procedimento todo pode ser realizado entre 15 e 30 dias. Com medicamentos, os ovários são estimulados a recrutar vários folículos, seguido pela coleta dos óvulos, fertilização dos mesmos em ambiente laboratorial e congelamento dos embriões para transferência após a cura do câncer.

Para as pacientes solteiras que não desejam utilizar sêmen de doador, uma opção é o congelamento de óvulos que apresenta resultados progressivamente positivos.

No congelamento de tecido ovariano, técnica ainda experimental, parte do ovário ou o ovário por inteiro é retirado através da vídeo laparoscopia e congelado em pequenos fragmentos. Após a cura do câncer, o material é descongelado e transplantado para a paciente.

As crianças formam um grupo especial de pacientes que também está exposto às conseqüências do tratamento para o câncer. Em função da tenra idade, seria inviável a indução da ovulação para congelamento de óvulos ou embriões, assim sendo as técnicas disponíveis seriam a transposição ovariana e o congelamento de tecido ovariano.

Para preservar o futuro reprodutivo dos homens, o congelamento de sêmen, além de ser relativamente de baixo custo, é o método mais seguro para garantir a reprodução após o tratamento contra o câncer.

Aconselha-se aos pacientes em idade de fértil e que necessita de tratamento quimio e radioterápico ou para aqueles que são responsáveis por uma pessoa de menor idade em via de realizar um tratamento antineoplásico, a conversar com o médico para saber se há indicação para o aconselhamento reprodutivo. Se já realizou um destes tipos de tratamento e deseja saber a repercussão sobre a fertilidade um especialista em Reprodução Humana deve ser procurado.

Movimento da FERTILIDADE

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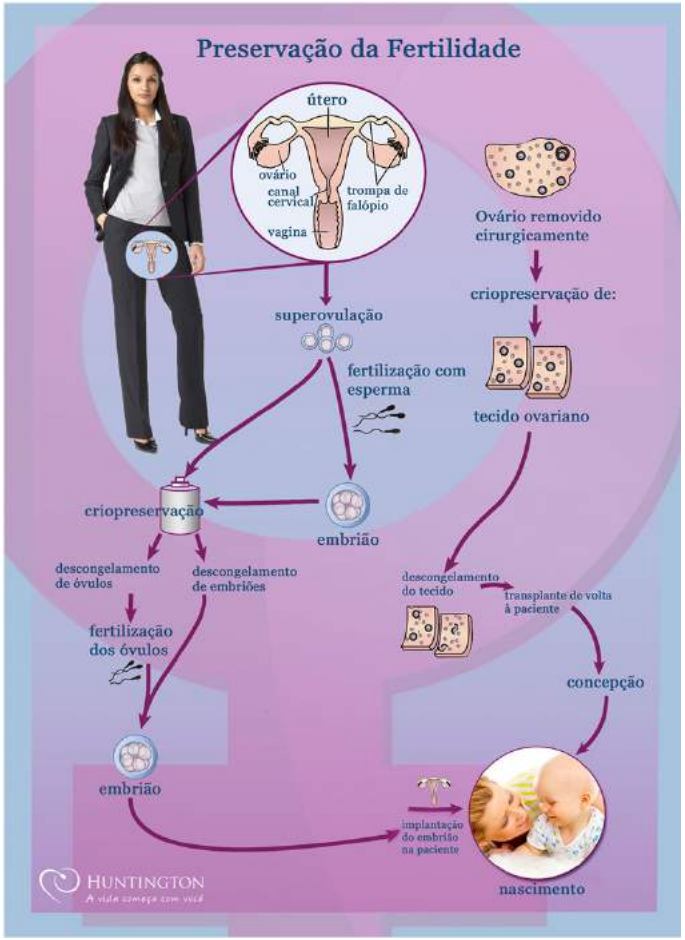

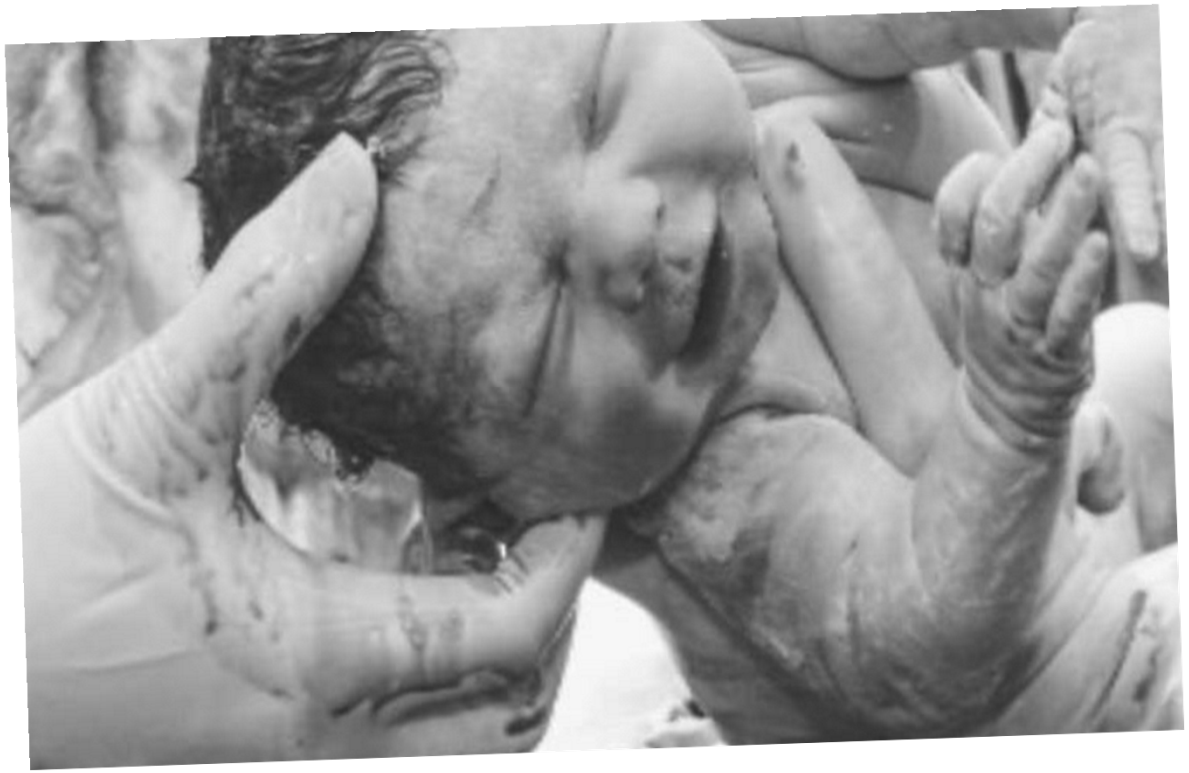


Obrigada!!