

**31 MAIO
A 2 JUN
2018**

XIX CONGRESSO SUL-BRASILEIRO
DE GINECOLOGIA E OBSTETRÍCIA
IV JORNADA SUL-BRASILEIRA
DE MASTOLOGIA



Mesa Redonda 27: Infertilidade

Preservação da Fertilidade

01 de junho de 2018

16h15-17h35

Ricardo Nascimento

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Declaração de conflito

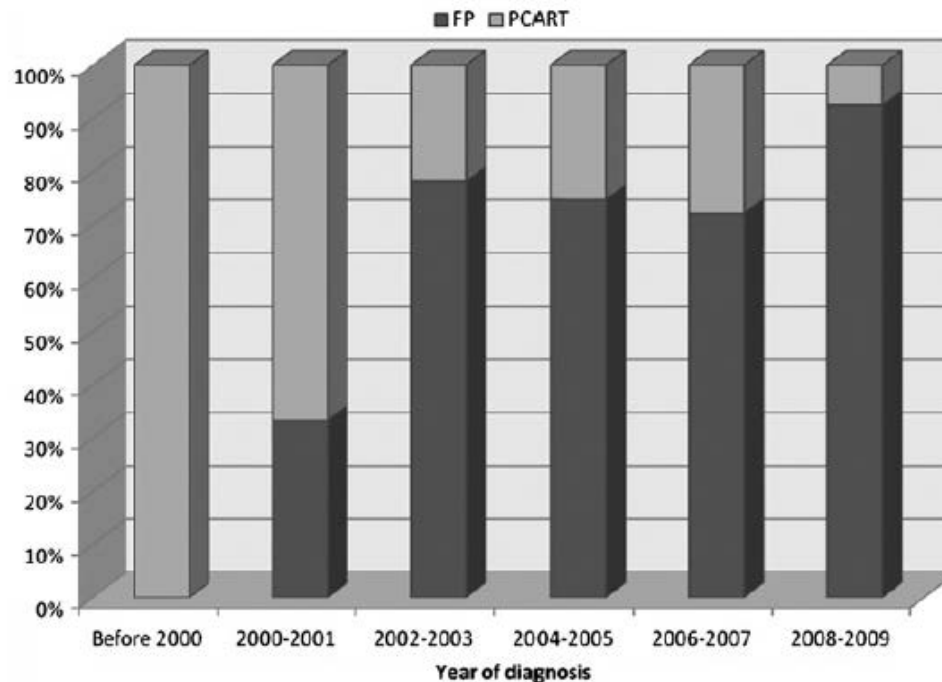
Não há conflito de interesses nesta
apresentação.

Preservação da Fertilidade

Assunto emergente:

- Por razões oncológicas
- Por razões pessoais

Proportion of referral for FP increased continually from 2000 to 2009.



Preservação da Fertilidade

“Fertility preservation”

Termo questionável, pois encerra uma promessa que nem sempre poderemos cumprir.

Seria melhor,

- **Postergação da fertilidade**
- **Prevenção da infertilidade**
- **Guarda de gametas**
- **Outro termo que representasse melhor?**

Fertility Preservation in Women

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

Table 1. 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

INDICAÇÕES

Panel 1: The Edinburgh selection criteria

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years
- A realistic chance of surviving for 5 years
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (from parents and, where possible, patient)
- Negative serology results for HIV, syphilis, and hepatitis B
- Not pregnant and no existing children

Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation

Indicações de Preservação da Fertilidade

Doenças malignas com quimio/radioterapia ou transplante de medula (Ciclo e Ifosfamida e Busulfan; radio >2Gy destrói 50% fols primários)

- **Hematológicas:** leucemia e Linfomas Hodgkin não Hodgkin
- **Ca da mama**
- **Sarcoma**
- **Alguns cânceres pélvicos** (colo, útero, ovário)

O risco de FOP varia com a reserva ovariana que varia com indivíduo e idade.

Indicações de Preservação da Fertilidade

Doenças benignas ou autoimunes:

- Doenças sistêmicas com quimio/radioterapia ou transplante de medula
- Ovários:
 - Tumores ovarianos bilaterais
 - Endometriomas grandes ou recorrentes
 - Torção ovariana
- Risco de falência prematura do ovário
 - História familiar
 - Síndrome de Turner

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

INDICAÇÕES PARA DOENÇAS NÃO ONCOLÓGICAS

Non-oncological conditions requiring fertility preservation.

Indication	Disease
Autoimmune diseases (6, 7)	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 (7, 8)	Autoimmune diseases unresponsive to immunosuppressive therapy Haematological diseases (sickle cell anaemia, thalassaemia major, plastic anaemia)
Medical conditions causing POI (9)	Altered hypothalamic–pituitary–gonadal axis (10, 11) Ovarian oophoritis Benign ovarian tumours Mosaic Turner's syndrome Fragile X Mental Retardation 1 (12) Galactosaemia (13) Beta-thalassaemia (14) Endometriosis (15)

Martinez. Update on fertility preservation. Fertil Steril 2017.

Indicações de Preservação da Fertilidade

Razões pessoais:

- Idade
- Postergação da Gravidez

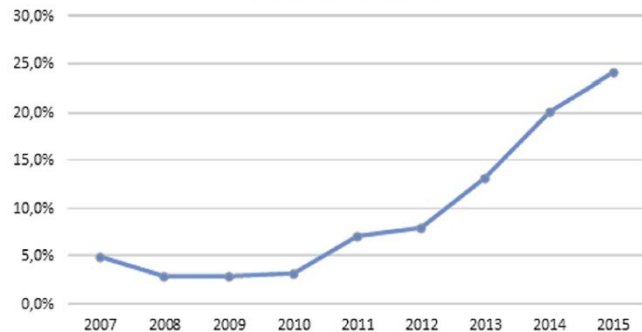
Oocyte vitrification as an efficient option for elective fertility preservation

Quando realizar?

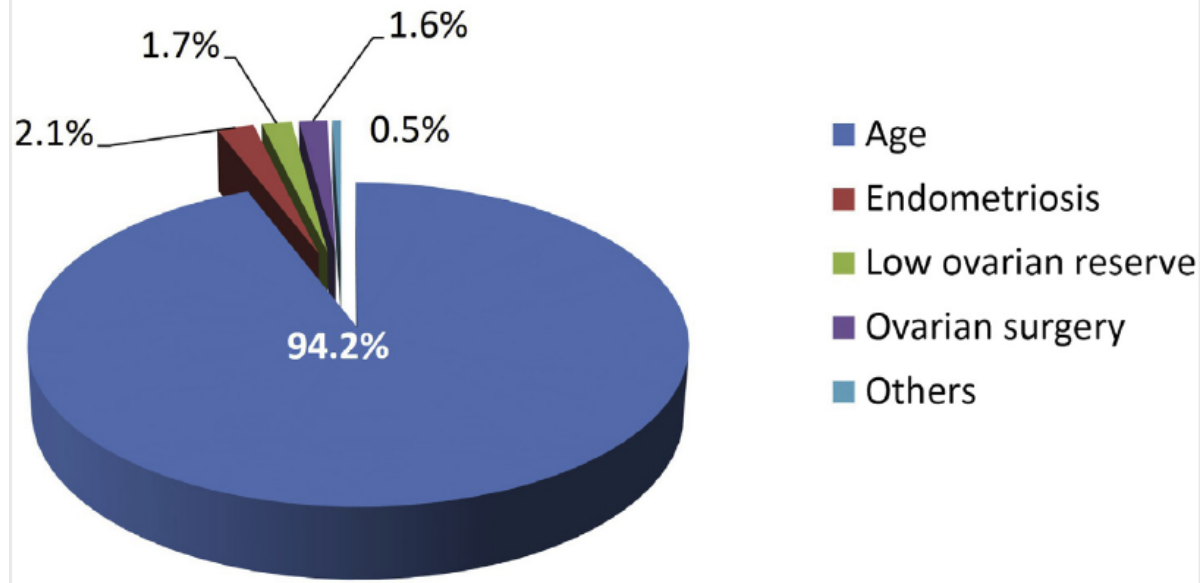
Ana Cobo, Ph.D.,^a Juan A. García-Velasco, M.D.,^b Aila Coello, Ph.D.,^a Javier Domingo, M.D.,^c Antonio Pellicer, M.D.,^d and José Remohí, M.D.^a

- Pesquisa em pacientes FP por razões pessoais, doenças benignas e excluídas portadoras de câncer:

Trends of elective FP



Distribution of Elective FP cycles



Oocyte vitrification as an efficient option for elective fertility preservation

Quando realizar?

Ana Cobo, Ph.D.,^a Juan A. García-Velasco, M.D.,^b Aila Coello, Ph.D.,^a Javier Domingo, M.D.,^c Antonio Pellicer, M.D.,^d and José Remohí, M.D.^a

Pequisa em pacientes FP por razões pessoais ou doenças benignas e excluídas portadoras de câncer:

Fertil Steril 2016;105:755–64.

IDADE NA VITRIFICAÇÃO X TAXA CUMULATIVA DE NASCIDOS VIVOS

Survival and clinical outcomes according to age at time of vitrification, n (%).								
Age, y	Patients, n	Cycles, n	Survival rate, n (%)	CPR/cycle, n (%)	CPR/ET, n (%)	OPR/cycle, n (%)	OPR/ET, n (%)	Live births/patients, n (%)
Survival and clinical outcomes in patients aged <35 y and ≥36 y at vitrification								
≤35	32	41	257/272 (94.6) ^a	24/41 (58.5) ^a	24/39 (61.5) ^a	21/41 (51.2) ^a	21/39 (53.9) ^a	16/32 (50) ^a
≥36	105	150	750/910 (82.4) ^b	47/150 (31.3) ^b	47/118 (39.8) ^b	27/150 (18.0) ^b	27/118 (22.9) ^b	24/105 (22.9) ^b
Total	137	191	1,007/1,182 (85.2)	71/191 (37.1)	71/157 (45.2)	48/191 (25.1)	48/157 (30.5)	40/137 (29.2)
Survival and clinical outcomes according to different groups of age at vitrification								
≤29	6	9	59/62 (94.5) ^a	6/9 (66.6) ^a	6/9 (66.6) ^a	6/9 (66.6) ^a	6/9 (66.6) ^a	6/6 (100) ^a
30–34	20	23	155/161 (96.1) ^a	14/23 (60.9) ^a	14/21 (66.7) ^a	13/23 (56.5) ^a	13/21 (61.9) ^a	9/20 (45) ^b
35–39	84	127	601/734 (81.8) ^b	48/127 (37.8) ^b	48/112 (42.9) ^b	27/127 (21.3) ^b	27/112 (24.1) ^b	24/84 (28.5) ^b
≥40	27	32	192/225 (85.3) ^b	3/32 (9.8) ^c	3/15 (20) ^c	2/32 (6.3) ^c	2/15 (13.3) ^b	1 (3.7) ^c
Total	137	191	1,007/1,182 (85.2)	71/191 (37.1)	71/157 (45.2)	48/191 (25.1)	48/157 (30.5)	40/137 (29.2)

O mais cedo possível, ideal < 35 anos

Quando realizar?

Cinco pontos importantes para ter em mente, nas pacientes com Câncer:

- Tempo de 10 -12 dias até quimioterapia
- Pós puberdade
- Protocolo específico para sensibilidade hormonal
- Procedimento novo: qualidade destes ovócitos?
- Baixa taxa de nascidos vivos x não câncer

Determinants of access to fertility preservation in women with breast cancer

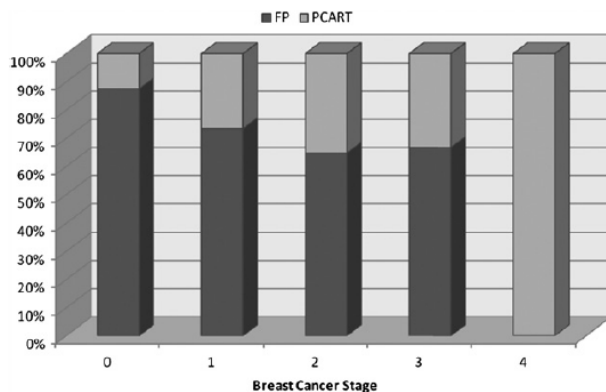
Fertility and Sterility® Vol. 95, No. 6, May 2011

Sanghoon Lee, M.D.,^a Elke Heytens, Ph.D.,^a Fred Moy, Ph.D.,^b Sinan Ozkavukcu, M.D.,^a and Kutluk Oktay, M.D.^a

Favorece encaminhamento precoce

- Estágio inicial
- Provir de Centro Academico
- História familiar de Cancer
- BRCA (ovários hipofuncionantes)

Proportion of referral for FP inversely associated with the stage of breast cancer.



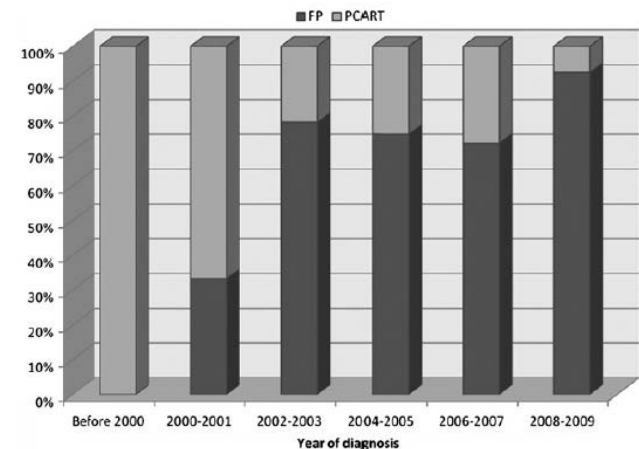
Lee. Access to fertility preservation. Fertil Steril 2011.

Não favorece encaminhamento precoce

- Idade

Muitos acreditam na recuperação da Fertilidade nas pacientes jovens

Proportion of referral for FP increased continually from 2000 to 2009.



Lee. Access to fertility preservation. Fertil Steril 2011.

Indiferente

- ocupação
- nacionalidade
- renda
- tto de fertilidade
- gravidez e aborto
- distancia

Possibilidades ao nosso alcance para a Preservação da Fertilidade

TABLE 4
Current Fertility Preservation Options

Method	Description	Investigational	Success Rates
Oocyte cryopreservation	Typically requires ovarian stimulation; oocytes harvested and frozen without fertilization	No	36%–61% ⁴⁷
Embryo cryopreservation	Typically requires ovarian stimulation; oocytes harvested and fertilized in vitro before cryopreservation	No	25%–40% ⁴⁸
Ovarian tissue cryopreservation	Surgically obtained ovarian tissue cryopreserved, then reimplanted	Yes	Not established in randomized controlled trial ⁴⁹
Immature follicle development	Isolation of immature oocytes from ovarian tissue; maturation of oocytes in vitro for future fertilization	Yes	Not established in randomized controlled trial ⁵⁰
Ovarian transposition	Transfixation of ovaries outside radiation field	No	Reduction of radiation to 5%–10% of expected dose ⁴
GnRH agonist	Ovarian suppression and protection	Yes	No benefit in randomized trials

Uso do GnRHa

Simulam estado pré puberal
Reduzem apoptose
Diminuem a perfusão ovariana

Cancer and fertility preservation:
international recommendations from
an expert meeting Lambertini et al. *BMC Medicine* (2016) 14:1

Recommendation 10 Ovarian suppression with the use
of LHRHa during chemotherapy should be considered a

Resultados de estudos controversos

Reserva ovariana pouco estudada

Retorno menstrual x gravidez

Ainda utilizado pelas vantagens

Considerado segunda linha

Associar a terapias eficazes

Iniciar 10 dias antes da QT

Table 1

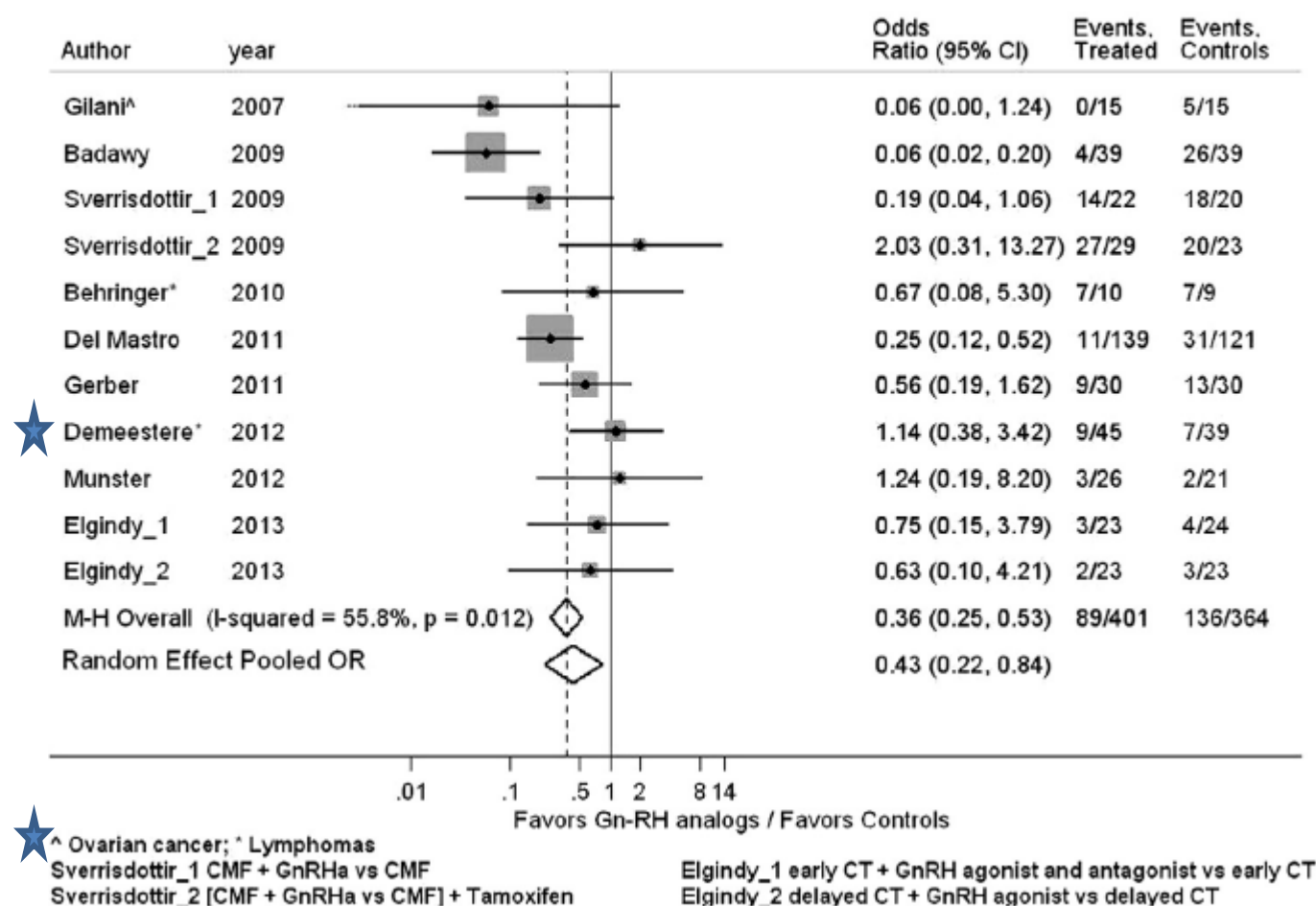
A review of the randomized trials literature and the outcomes for women who received GnRH agonists prior to chemotherapy, with the principal outcome of return of menses.

Reference (Author and Year)	Number of patients	GnRH Agonist	Cancer Type	Months Follow Up	% with menses- agonist vs control	P value
Blumenfeld 2008	111	triptorelin	hodgkin	24	96 vs 63	0.001
Badaway 2009	80	goserelin	breast	8	90 vs 33	0.001
Sverrisdottir 2009	260	goserelin	breast	24	36 vs 10	0.006
Gerber 2011	60	goserelin	breast	24	70 vs 57	0.28
delMastro 2011	281	triptorelin	breast	12	63 vs 50	0.03
Munster 2012	49	triptorelin	breast	18	88 vs 90	0.36

Cancer Treatment Reviews

Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: Systematic review and meta-analysis of randomized trials

L. Del Mastro et al. / Cancer Treatment Reviews 40 (2014) 675–683



Gonadotropin-releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early stage breast cancer: a systematic review and meta-analysis

Rodrigo R. Munhoz, MD^{1,2}, Allan A. L. Pereira, MD^{1,2}, André D. Sasse, MD³, Paulo M. Hoff, MD, FACP^{1,2}, Tiffany A. Traina, MD⁴, Clifford A. Hudis, MD⁴, and Ricardo J. Marques, MD⁵

Objective—To determine efficacy of GnRHa administered concurrently with chemotherapy for ovarian function preservation.

Results—Seven studies were selected, totaling 1047 randomized patients (856 evaluable patients).. The use of GnRHa was associated with a higher rate of recovery of regular menses after 6 months (OR = 2.41; 95% CI 1.40–4.15; $p = 0.002$) and at least 12 months (OR 1.85; 95% CI 1.33–2.59; $p = 0.0003$) following last chemotherapy cycle. The use of GnRHa was also associated with a higher number of pregnancies (OR 1.85; 95% IC 1.02–3.36; $p = 0.04$), although this outcome was not uniformly reported.

Conclusions and Relevance—GnRHa given with chemotherapy resulted in increased rates of recovery of regular menses and should be considered an option for ovarian function preservation in young women undergoing treatment for EBC. Additional outcomes related to ovarian function and fertility need to be further investigated.

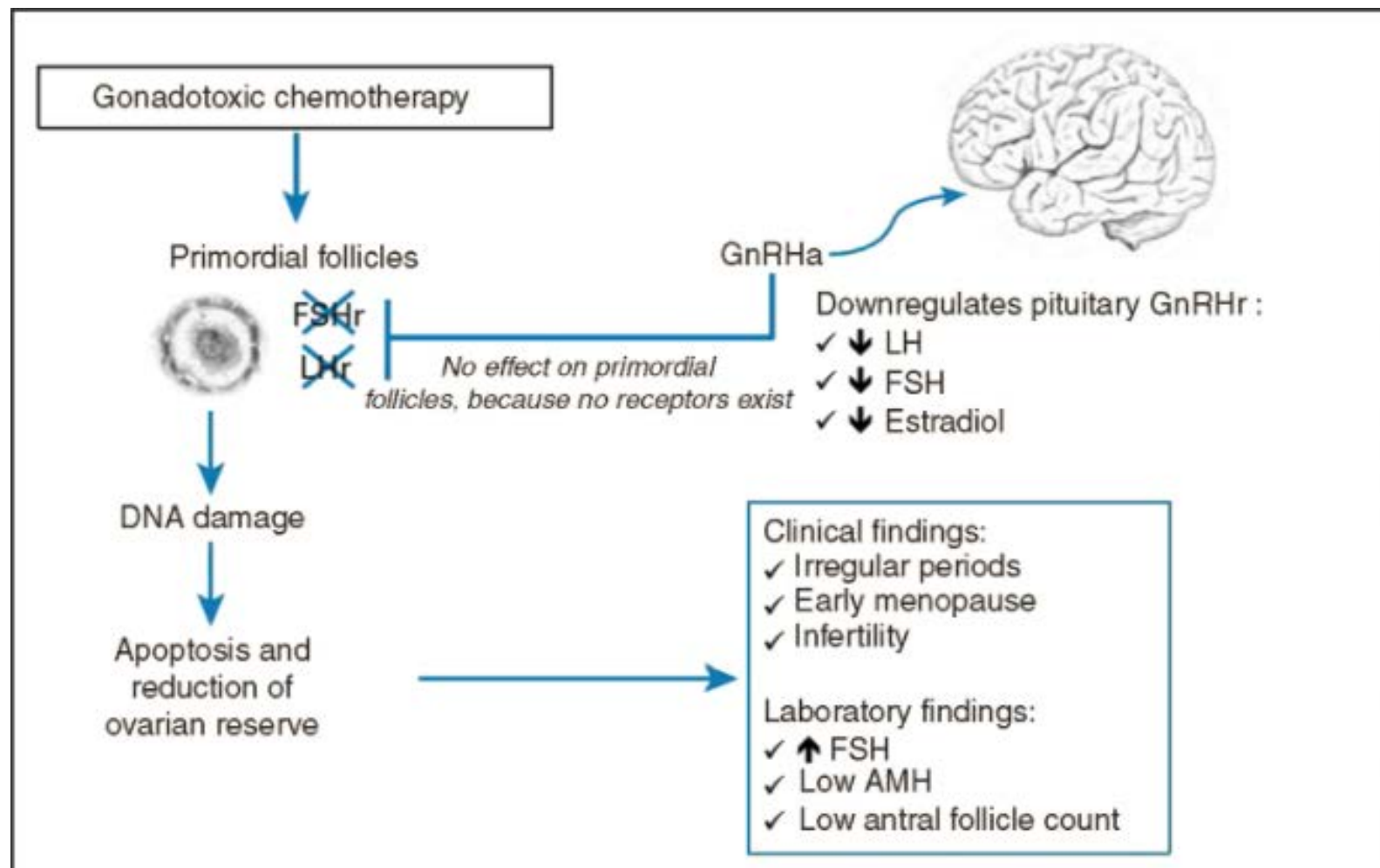
Goserelin does not preserve ovarian function against chemotherapy-induced damage

K Oktay ✉, E Taylan, K A Rodriguez-Wallberg, G Bedoschi, V Turan, F Pacheco

Annals of Oncology, Volume 29, Issue 2, 1 February 2018, Pages 512–513,

<https://doi.org/10.1093/annonc/mdx695>

Published: 03 November 2017



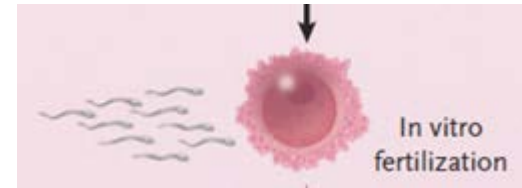
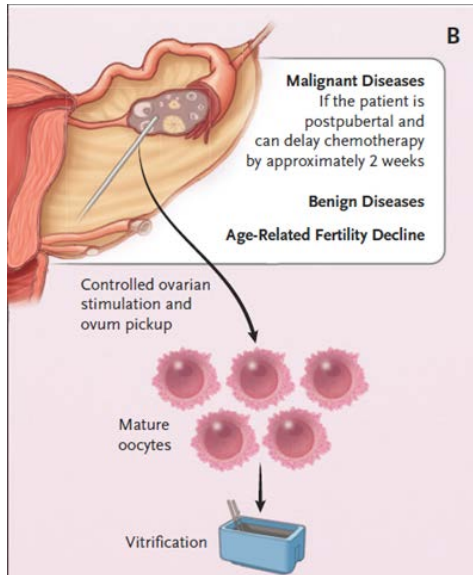
Transposição cirúrgica dos ovários

Radioterapia localizada: colo e linfomas

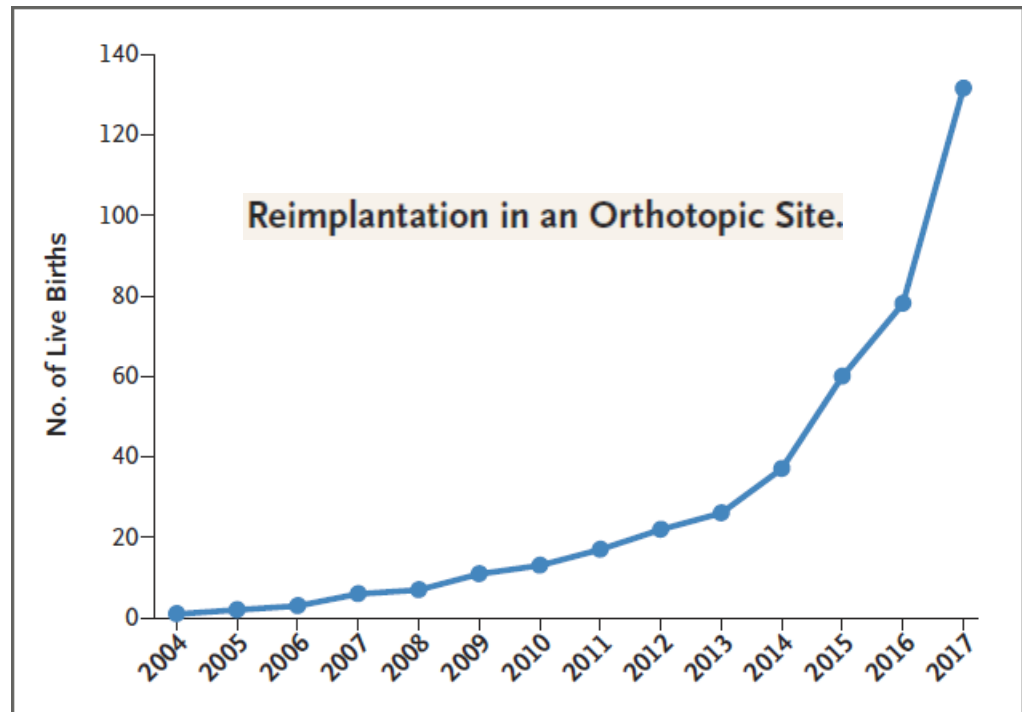
- Deve ser feita próximo do período da radiação pois tem risco de remigração.
- A chance de preservação a curto prazo é de 50-80%.
- IMPORTANTE:
 - Preservar a vascularização ovariana, evitando estiramentos e acotovelamentos: isquemia.
 - Facilitar o acesso se houver necessidade de aspiração de óvulos
 - Criopreservar fragmento de ovário

Métodos de Preservação da Fertilidade reconhecidos pela Sociedade Americana de Medicina Reprodutiva

Fertil Steril 2013;100:1224-31.



Experimental: nova técnica?
Recupera atividade ovariana 95%
Dura 4 a 5 anos
Primeira gravidez em 2004



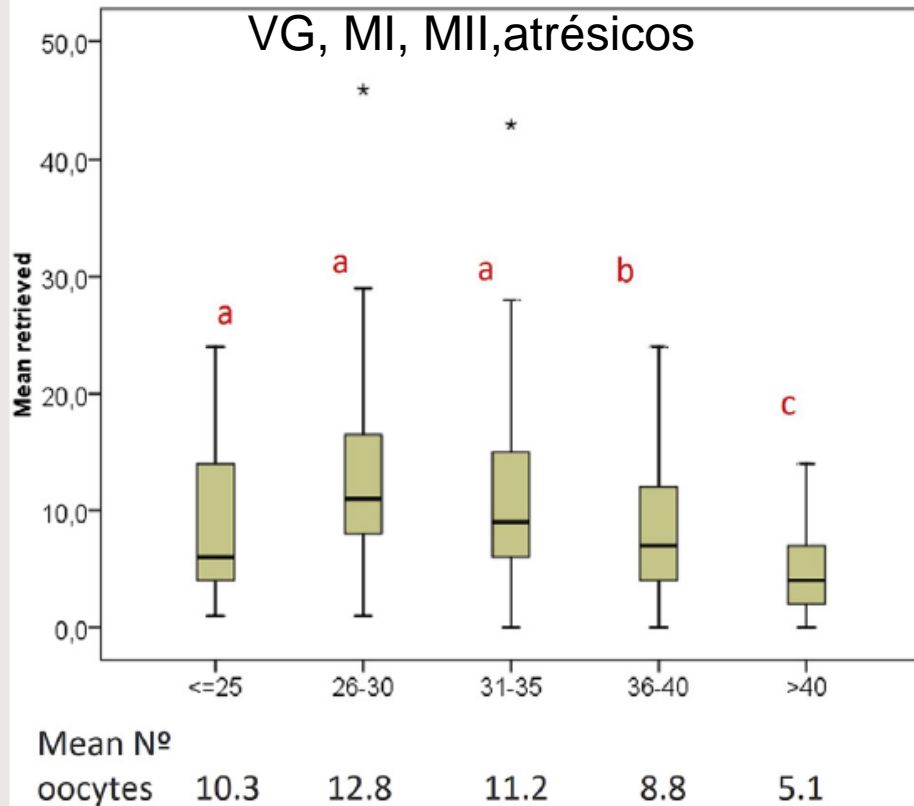
Oocyte vitrification as an efficient option for elective fertility preservation

Número de óvulos obtidos e vitrificados conforme a idade

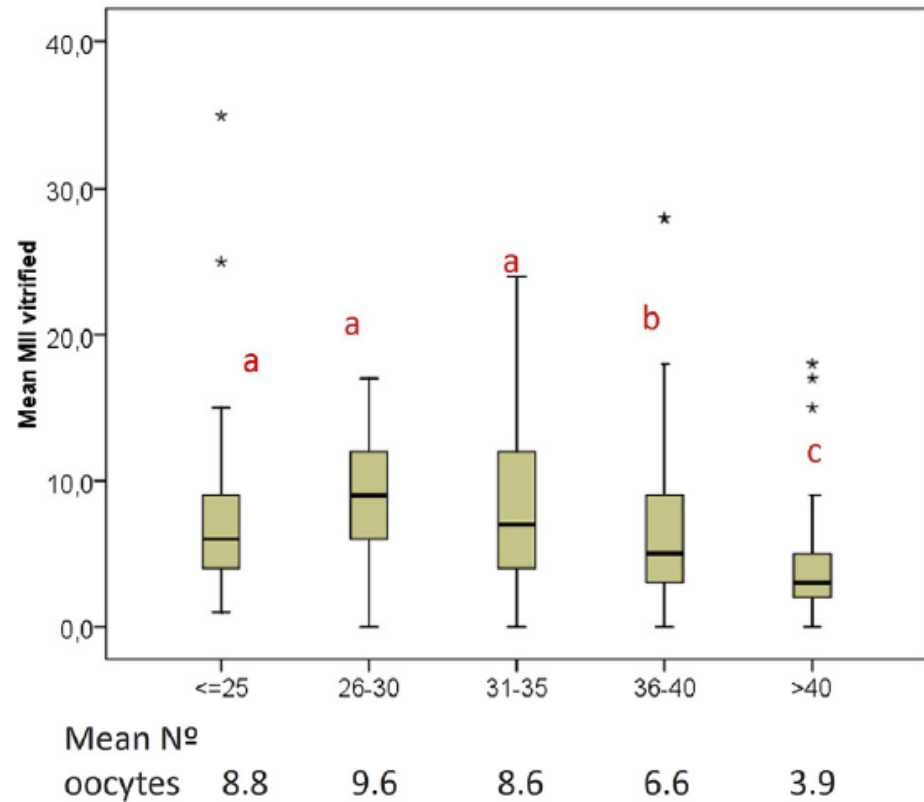
Ana Cobo, Ph.D.,^a Juan A. García-Velasco, M.D.,^b Aila Coello, Ph.D.,^a Javier Domingo, M.D.,^c Antonio Pellicer, M.D.,^d and José Remohí, M.D.^a

Retrieved oocytes

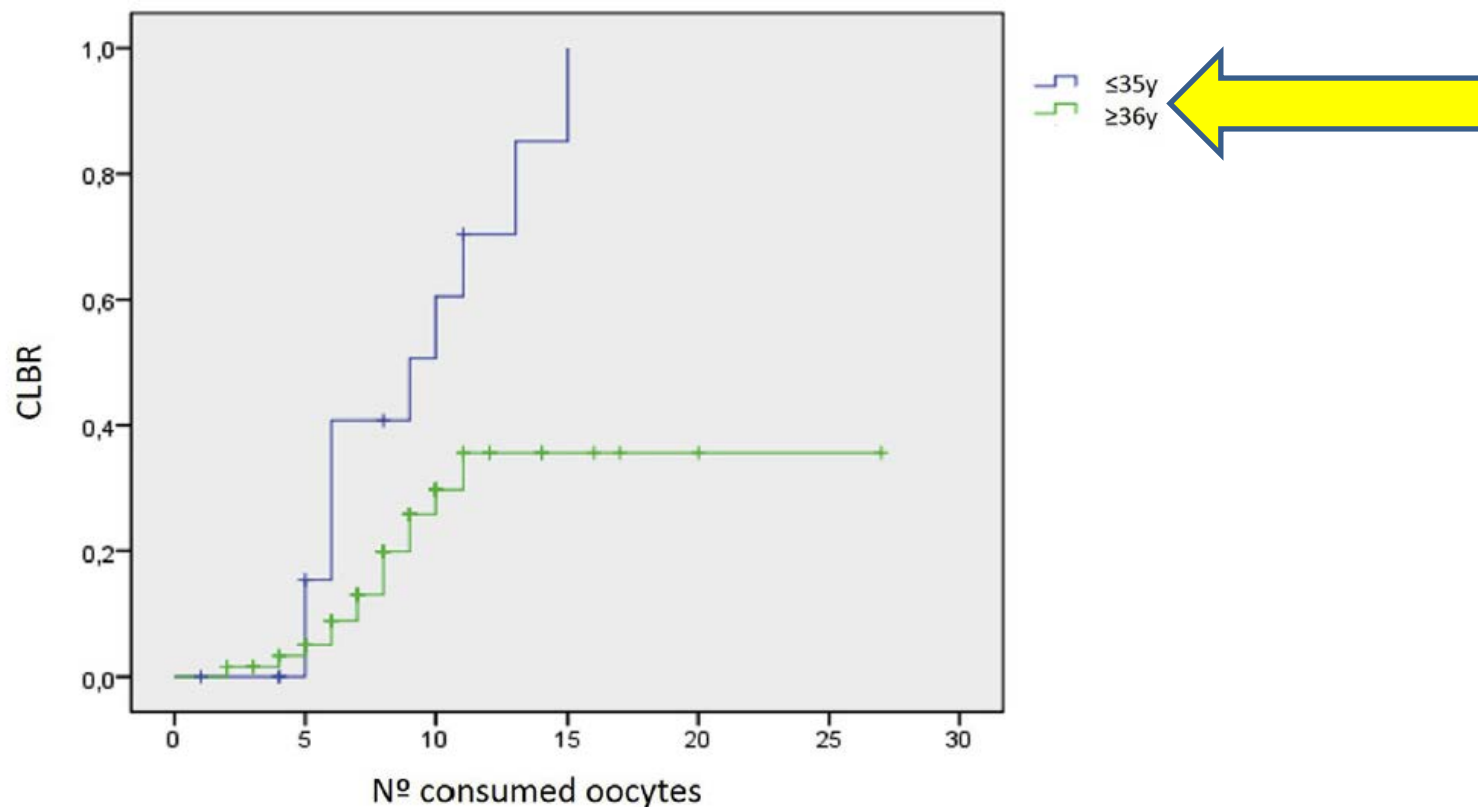
VG, MI, MII,atréxicos



Vitrified MII oocytes



CLBR according to age (≤ 35 vs ≥ 36) and N° oocytes consumed



≤ 35 years old

oocytes	CLBR (IC95%)
5	15,4 (-4.2-35.0)
8	40,8 (13.2-68.4)
9	50,6 (31.6-79.6)
10	60,5 (34.5-89.5)
15	85,2 (60.5-100)

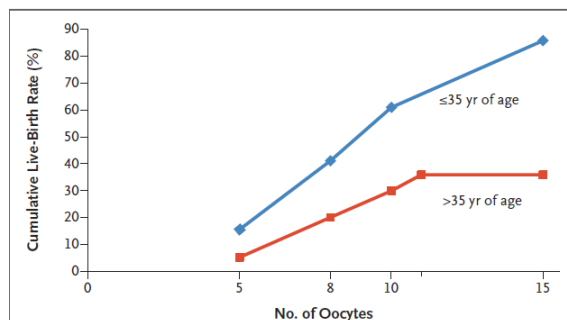


Figure 2. Cumulative Live-Birth Rates with 5 to 15 Oocytes, According to Age.

≥ 36 years old

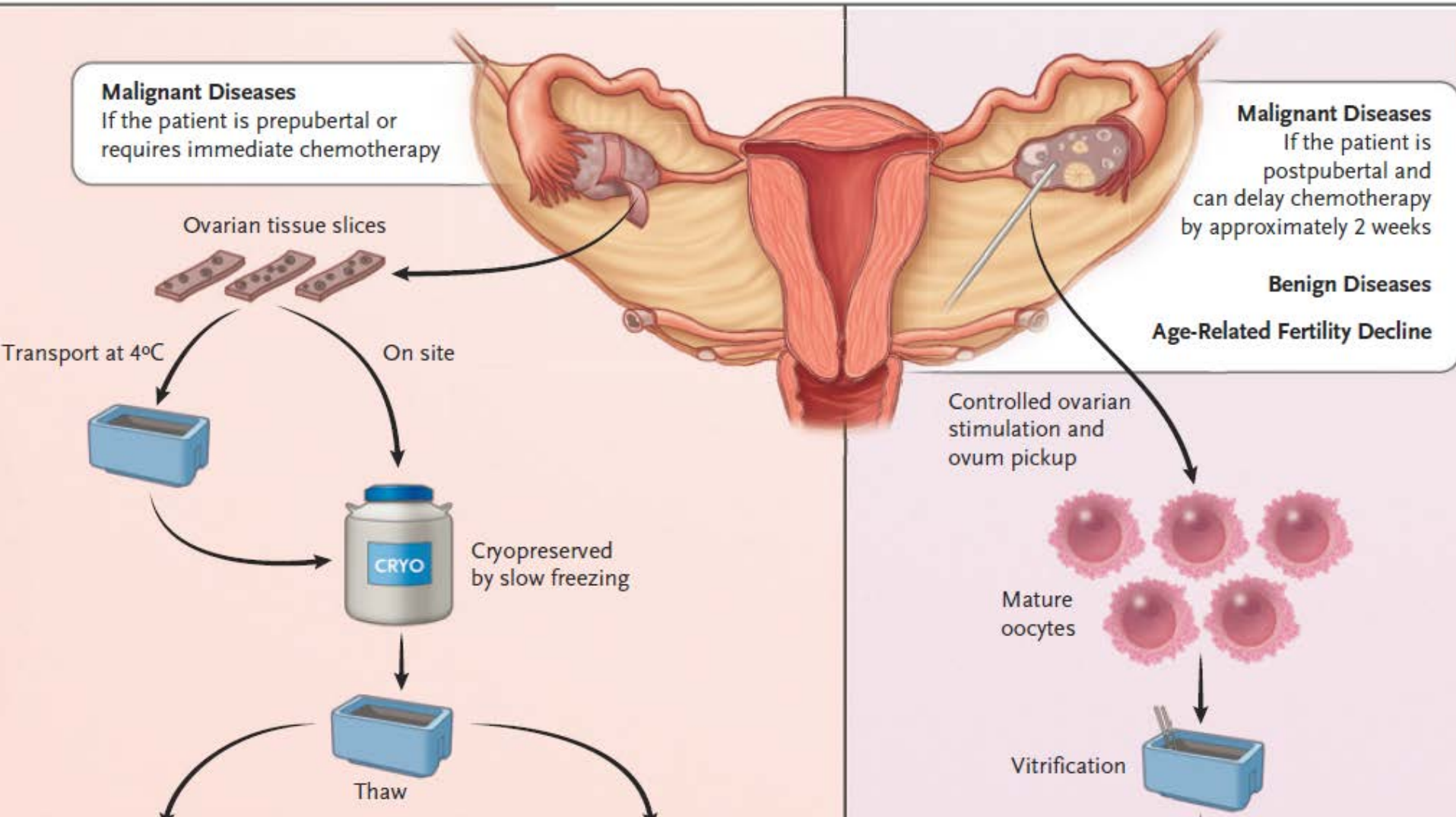
oocytes	CLBR (95% CI)
5	5,1 (-0.6-10.7)
8	19,9 (8.7-31.1)
9	25,8 (12.7-38.9)
10	29,7 (15.2-34.2)
11	35,6 (18.4-52.8)

Fertility Preservation in Women

The NEW ENGLAND JOURNAL of MEDICINE

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

N ENGL J MED 377;17 NEJM.ORG OCTOBER 26, 2017

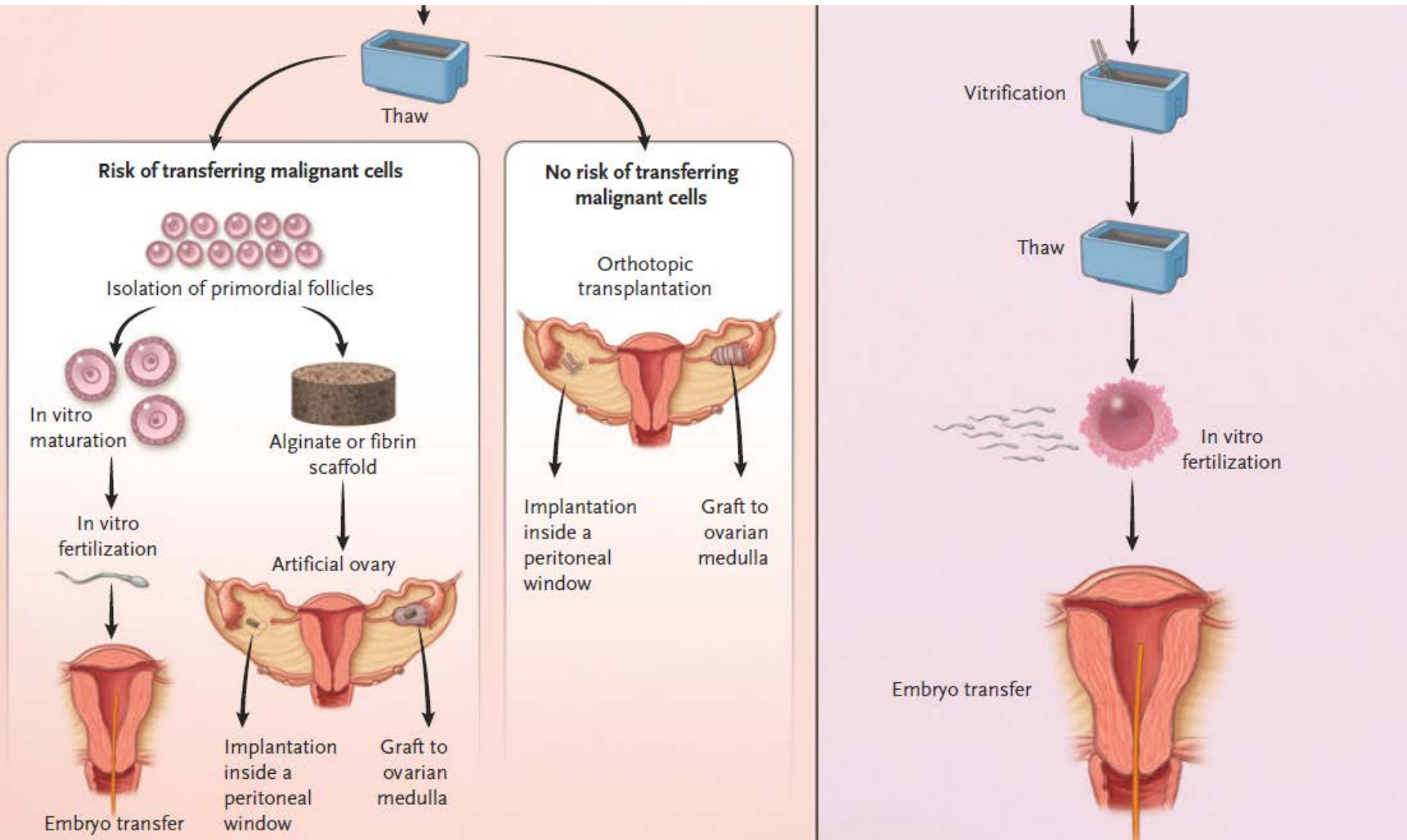


Fertility Preservation in Women

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N ENGL J MED 377;17 NEJM.ORG OCTOBER 26, 2017



Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer

Alexandra W. van den Belt-Dusebout, PhD; Mandy Spaan, MSc; Cornelis B. Lambalk, MD, PhD;

Table 3. Invasive Breast Cancer Risk According to Fertility Treatment and Reproductive Characteristics^a

	No. of Breast Cancers ^a	No. of Women	No. of Person-Years	Adjusted HR (95% CI) ^b	P for Trend
IVF exposure					
Non-IVF	220	5590	131 589	1 [Reference]	
IVF	619	19 158	378 683	1.01 (0.86-1.19)	
Subfertility diagnosis ^c					
Male factor	152	4873	95 989	1 [Reference]	
Tubal factor	248	7114	147 902	0.97 (0.79-1.19)	
Hormonal factor or other	150	4020	81 798	1.12 (0.89-1.40)	
Unexplained	151	4142	83 654	1.03 (0.83-1.30)	
Missing	138	4959	100 926	0.85 (0.68-1.08)	

Key Points

Question What is the long-term risk of breast cancer after ovarian stimulation for in vitro fertilization (IVF)?

Findings In this cohort study that included 25 108 women who underwent fertility treatments with a median follow-up of 21.1 years, breast cancer risk in IVF-treated women was not significantly different from that in the general population or in women who underwent other fertility treatments.

Meaning These findings are consistent with the absence of a significant increase in long-term risk of breast cancer among IVF-treated women.

Coorte de 25.108 mulheres com FIV
Período de 21,1 anos.

Sem aumento risco de Ca da mama

Successful Oocyte Cryopreservation in Reproductive-Aged Cancer Survivors

Sarah Druckenmiller, BA, Kara N. Goldman, MD, Patty A. Labella, BS, M. Elizabeth Fino, MD, Antonia Bazzocchi, MD, and Nicole Noyes, MD

Table 4. Live Births From Oocyte Thaw Cycles Completed in Cancer Survivors

Neonate No.	Maternal Age at Cryopreservation (y)	Maternal Cancer Diagnosis	Cryopreservation Method	Day of Embryo Transfer	Maturation of Transferred Embryo(s)	Length of Gestation (wk)	Birth Weight (g)
1	28	Gynecologic	Vitrification	5	Blastocyst	33.0	2,087
2	28	Gynecologic	Vitrification	5	Blastocyst	33.0	1,452
3	33	Breast	Slow cooling	3	Cleavage	40.8	2,858
4	40	Breast	Slow cooling	3	Cleavage	38.6	3,357
5	39	Breast	Slow cooling	5	Blastocyst	39.0	3,311

Futuro da Preservação da Fertilidade

1. Prevenção:

- GnRha
- Nanoencapsulamento dos gonadotóxicos com alvo no tumor
- Imunomoduladores : evitam “burnout” da quimioterapia como AS101 e esfingosina-1-fosfato que evita apoptose
- Contínua descoberta de drogas melhores

Futuro da Preservação da Fertilidade

2. Enxertos alográficos

- Irmãs gêmeas
- Irmãs geneticamente diferentes(2011)
especialmente naquelas com transplante de medula óssea.

3. Células tronco ovarianas

(interferências no genoma)

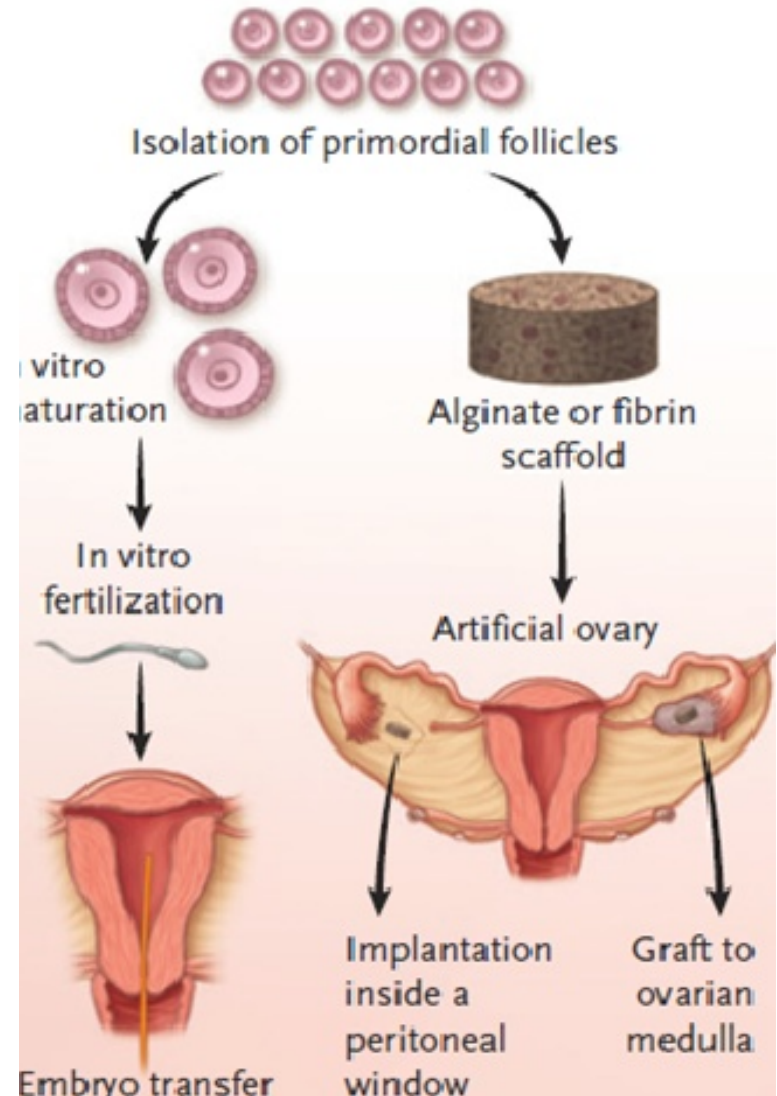
Futuro da Preservação da Fertilidade

3. Ovário artificial

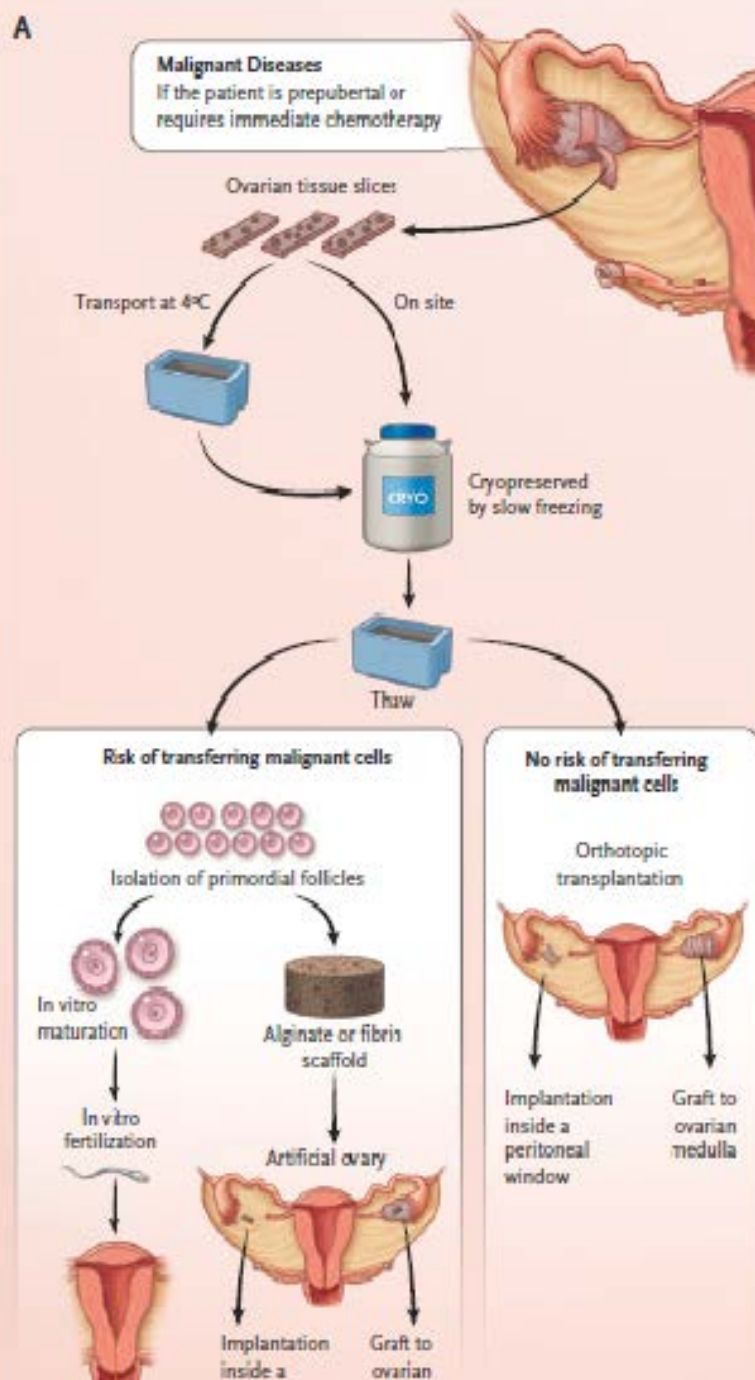
(estudos em ratos e de óvulo humano em ratos imunodeficientes)

4. Desenvolvimento in vitro de folículos primordiais

(meios de cultura sequenciais)



A



B

