



Fertility & breast cancer



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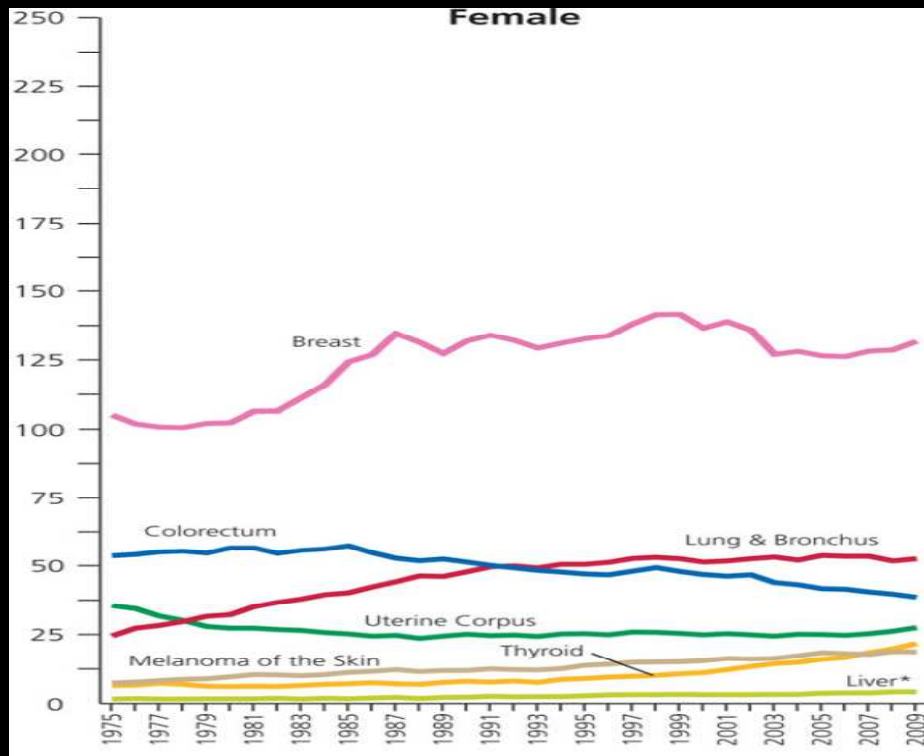
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ICBC 2013

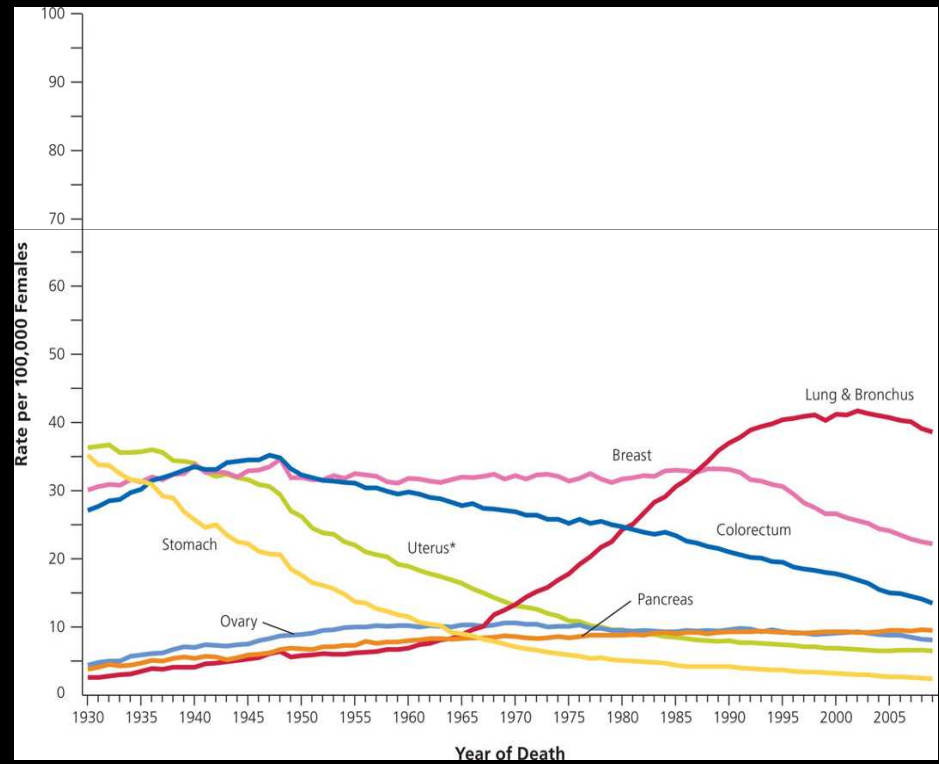


Breast Cancer

Incidence

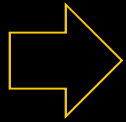


Mortality



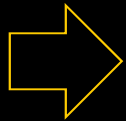


Breast cancer **Age < 40**



1/3 of cancers in women of childbearing age

Margulies et al., J Gynecol Obstet Biol Reprod 2012



4,000 new cases / year and 1,000 in females 25 -35 years old

Guérin et al., Bull Cancer.2010

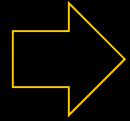


Highest Mortality ↓ in 35-39 years old

www.inca.fr



Pregnancy desire



Age of first pregnancy ↑ 30 years in France

Pison et al., Bull Cancer.2010



Survivors more concerned about future fertility than age and gravidity matched women

Ruddy et al., breast 2007



30% less toxic chemotherapy to help preserve fertility even at risk of increased cancer recurrence

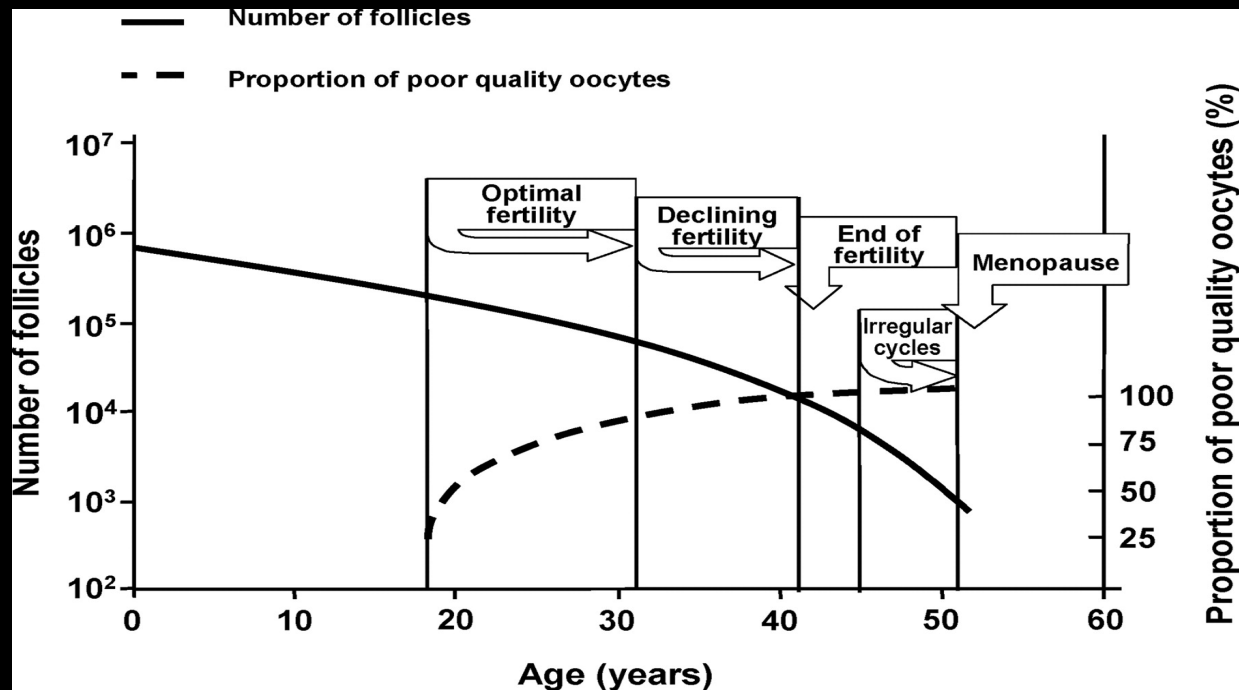
Partridge et al., J Clin Oncol 2004

Fertility after breast cancer is a major concern



Reproductive aging

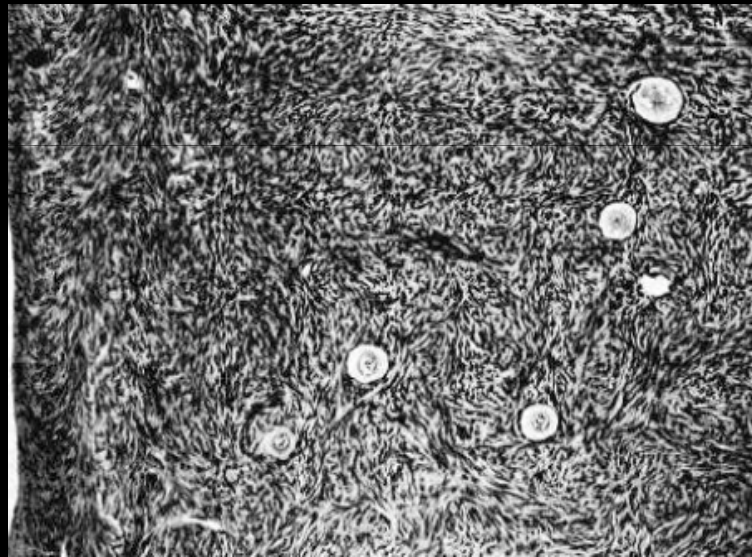
Dramatic decline of fecundity per cycle after 35 years



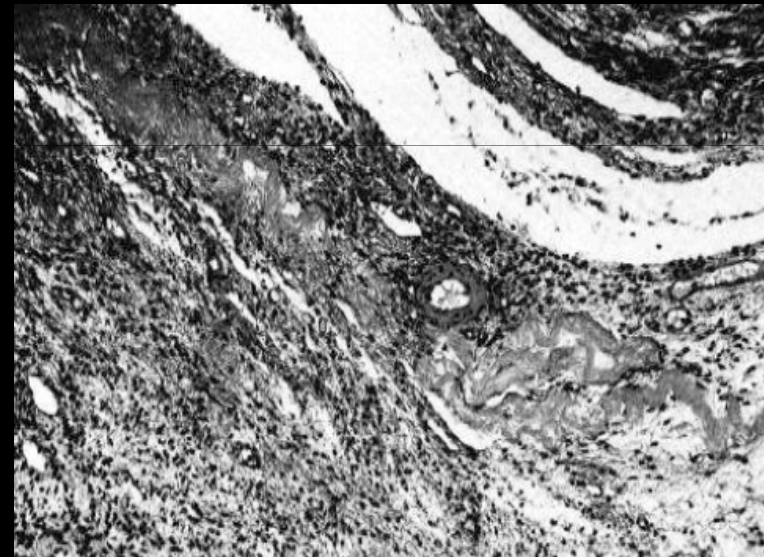


Gonadal toxicity of treatments

Ovarian toxicity



Before chemotherapy



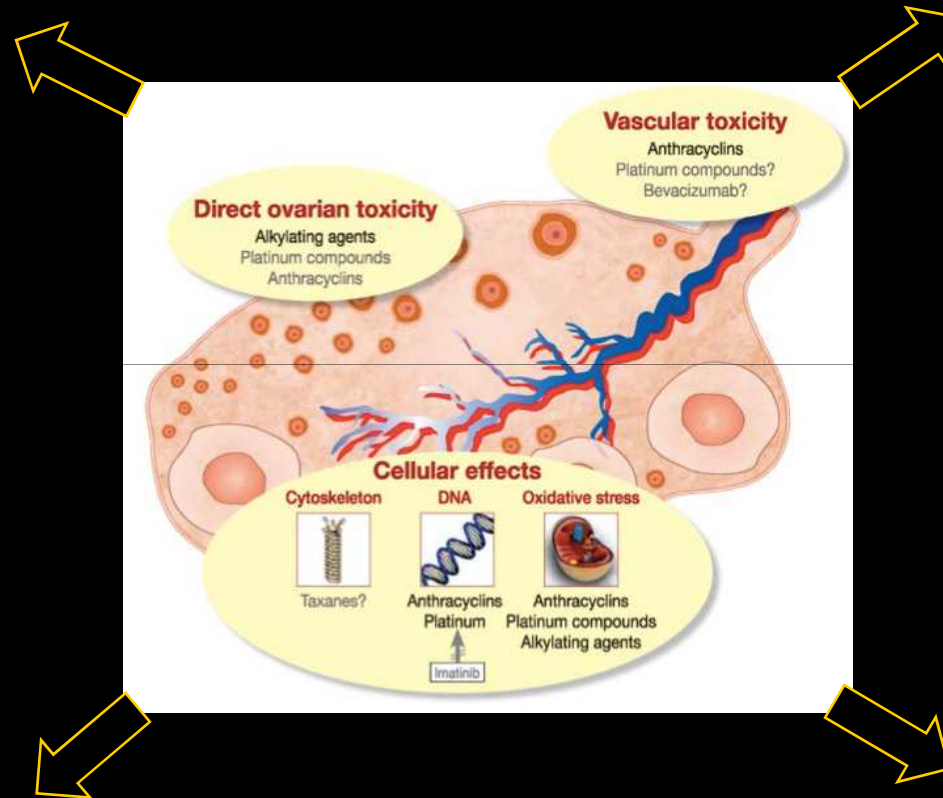
After chemotherapy



Gonadal toxicity of treatments

Ovarian tissue fibrosis

Vascular damage



Apoptosis of primordial and primary follicles

Follicular activation: burn-out

Oktaý et al., *Cancer Treat Rev* 2012

Blumenfeld et al., *Best Pract Res Clin Obstet Gynaecol.* 2012



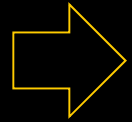
Type of chemotherapy

Risk of gonadotoxicity

High risk	Moderate risk	Low risk	Undetermined
Cyclophosphamide	Cisplatine	Methotrexate	Irinotecan
Cholarambucil	Adriamycine	5-Fluorouracil	Imatinib
Melphalan	Paclitaxel	Vincristine	
Busulfan		Actinomycin D	
Ifosfamide		Bleomycine	
Procarbazine			
Thiotepa			



Fecundity after cancer treatment



Assessment of the potential of fertility after CT remains a challenge

Multifactorial : tabacco, BMI, genetic

Natural fertility before chemotherapy often unknown



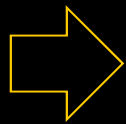
Current markers

Amenorrhea: a late marker

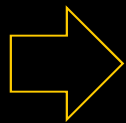
Markers of the follicular ovarian status



Chemotherapy-related amenorrhea



Short-term effect: acute ovarian insufficiency



Long-term effect: alteration of ovarian reserve



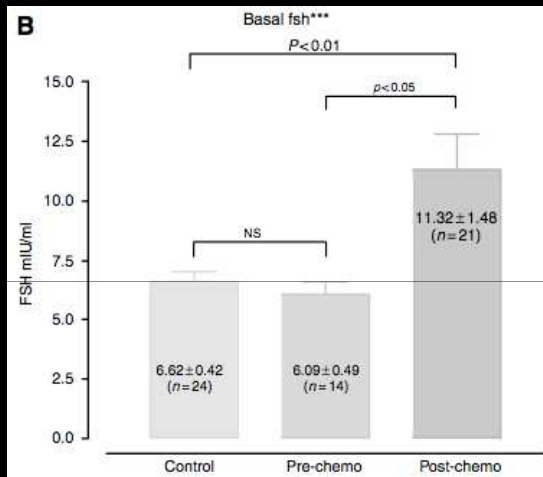
Type of chemotherapy

Regimen	Age	Risk of amenorrhea
AC 4 c Docetaxel 4 c <i>Swain et al., 2009</i>	40 – 49 31- 39 < 31	35% 12% 6%
AC - EC <i>Partridge et al. 2007; 2008</i> <i>Petrek et al. 2006</i>	> 40 30 – 39	30 – 70 % < 20 %
CMF, CEF, CAF 6 c <i>Pagani et al., 1998</i> <i>Goodwin et al., 1999</i> <i>Parulekar et al., 2005</i> <i>Partridge et al. 2007</i>	>40 30 – 39 < 30	>80% 30 – 70 % < 20 %
FEC 6 c <i>Roche et al., 2006</i>	> 40 < 40	73% 38%
MTX + FU		Very low
Monoclonal Antibodies		Little evidence
Taxanes		Little evidence

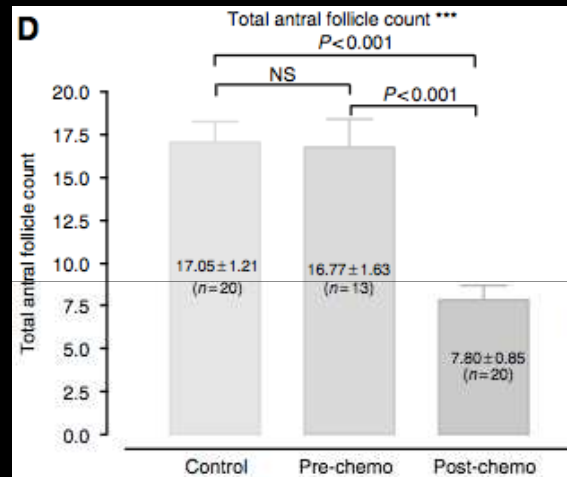


Premature ovarian failure after CT

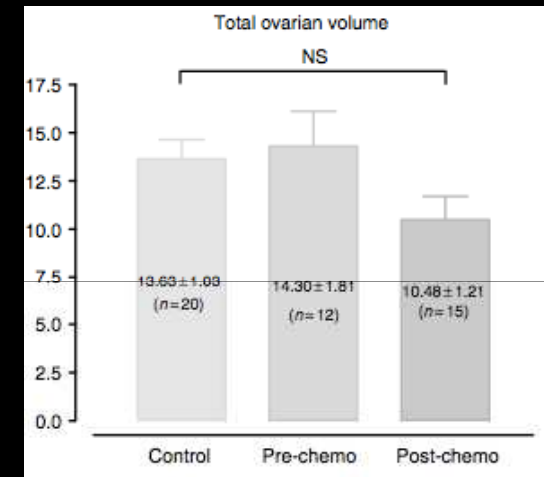
FSH



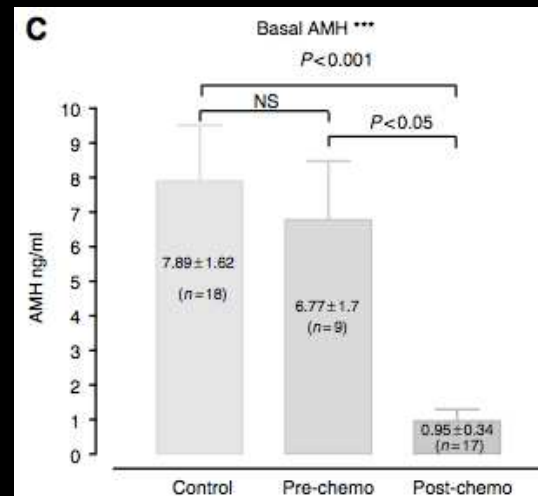
AFC



Ov. vol

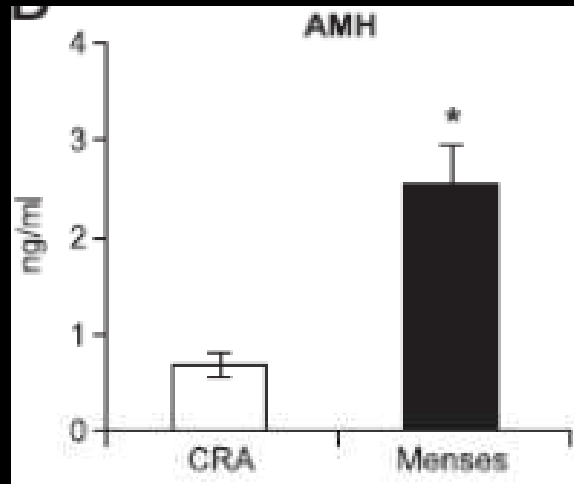


AMH



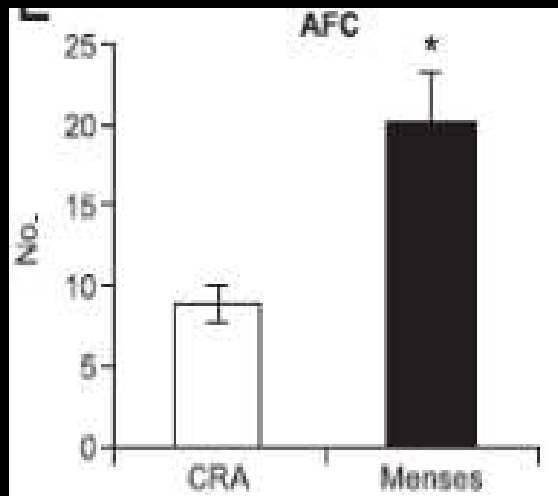


Premature ovarian failure after CT



All women with AMH < 1.9 ng/ml became amenorrheic

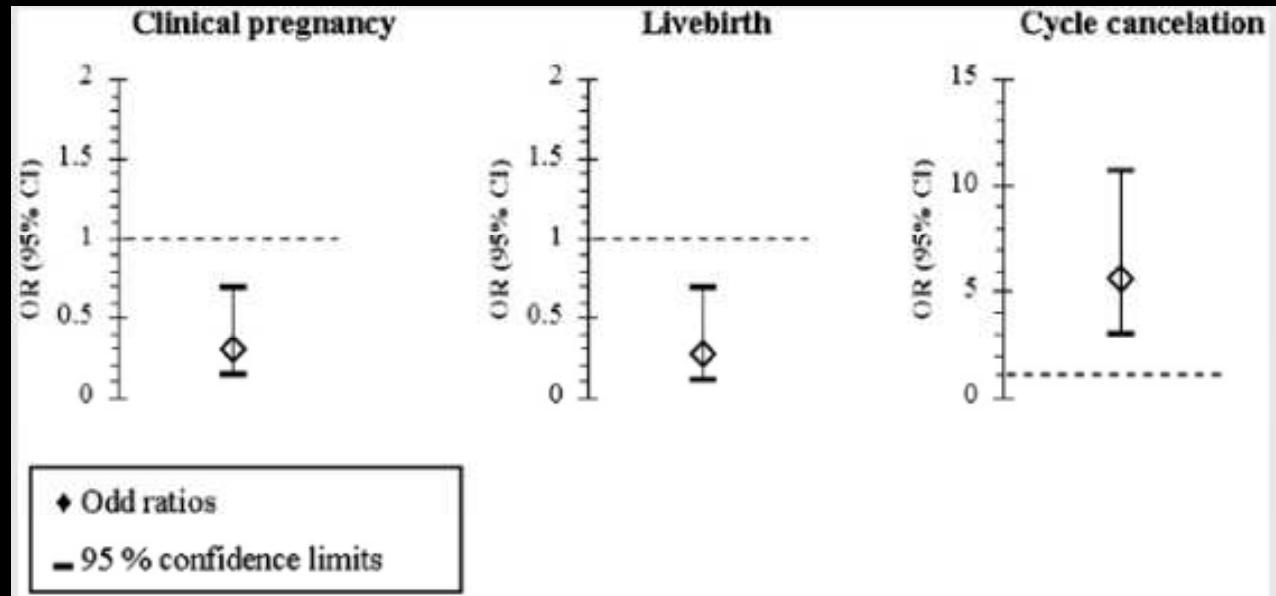
AMH can predict long-term ovarian activity after chemotherapy



Women with ongoing menses had higher AFC



Premature ovarian failure after CT

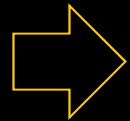


Poor ART outcome in cancer survivors

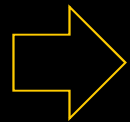


Breast cancer treatment & impact on fertility

2 possible impacts on patients' fertility



Ovarian toxicity of treatments



Postponing motherhood & facing the burden of natural ovarian aging



Breast cancer treatment & impact on fertility

Age

Baseline
fertility

Follicular
ovarian status

FERTILITY PRESERVATION

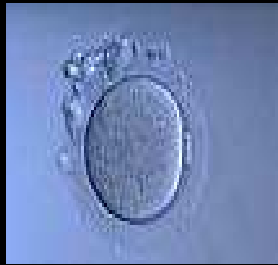
Chemo regimens &
sensitivity /chemo

Natural ovarian
aging

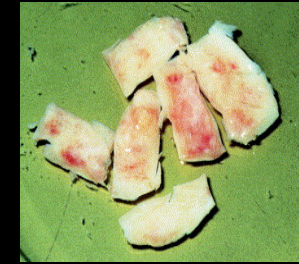
Lower pregnancy
rates after ART in
cancer survivors



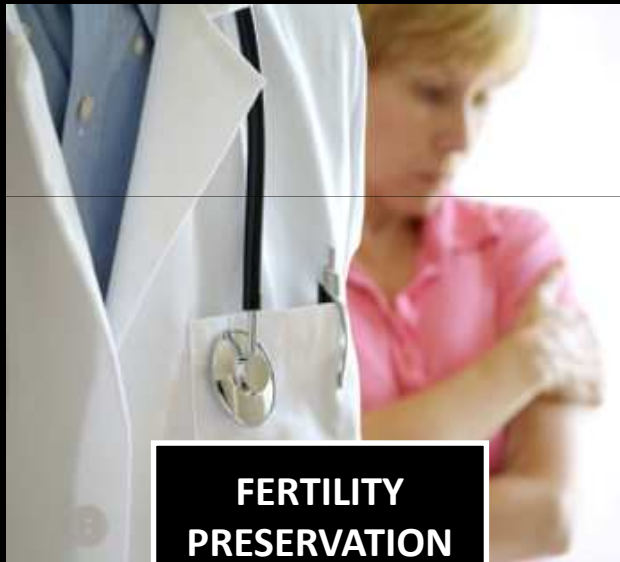
Fertility preservation



Oocyte cryopreservation



Ovarian tissue cryopreservation



**FERTILITY
PRESERVATION**

Embryo cryopreservation



Medical treatment



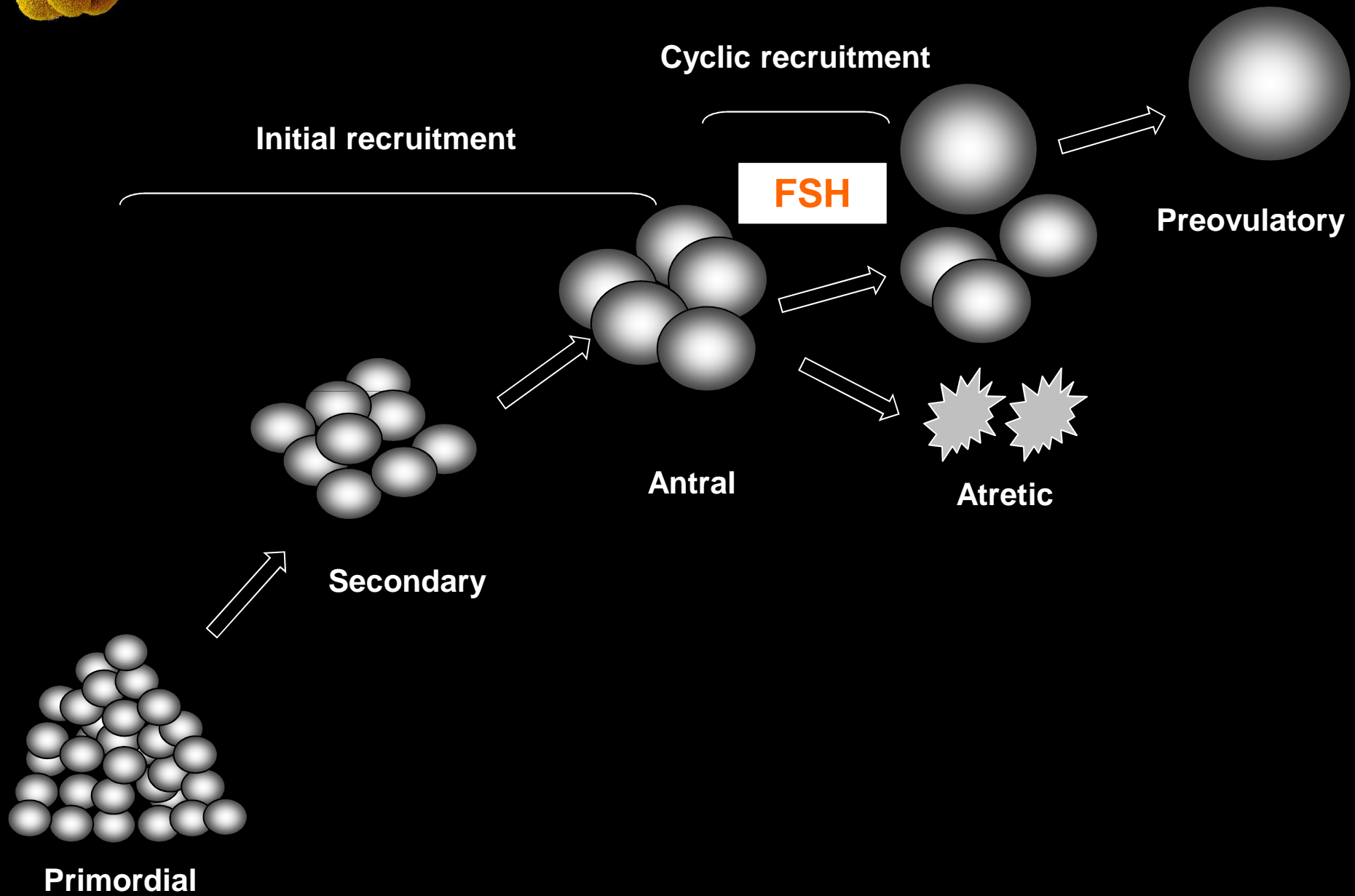


Fertility preservation

GNRH AGONISTS

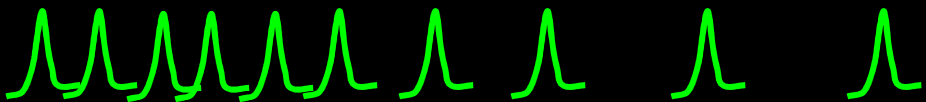


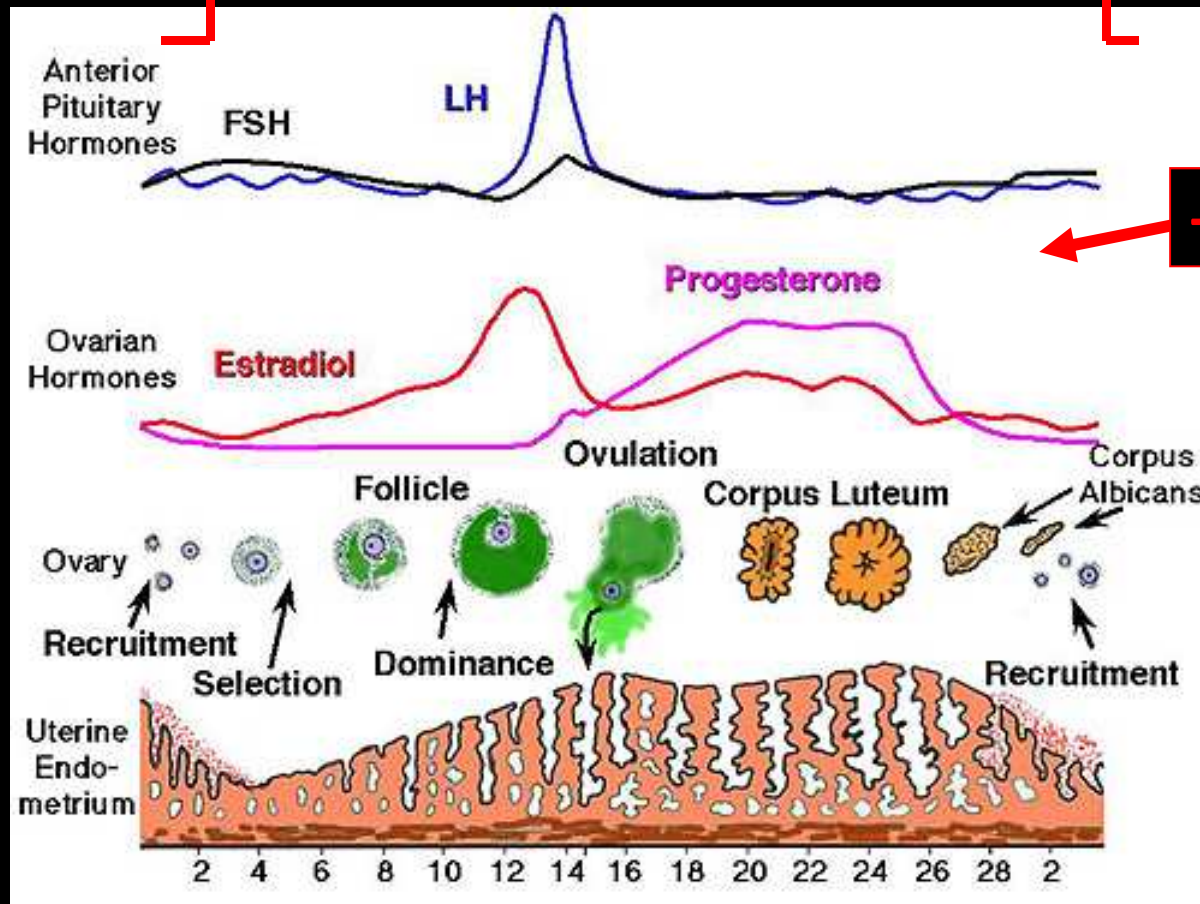
Folliculogenesis



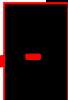


GnRH_a Mechanism

Hypothalamus  GnRH



GnRH analogues





GnRHa for FP

Advantages

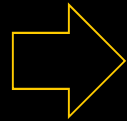
- No delay
- No ovarian stimulation
- No surgery
- Contraceptive
- Amenorrhea induced → ↓ hemorrhagic phenomenons

Drawbacks

- Estrogen deprivation
- Short term effects: flush, vaginal dryness
- Long term effects: decrease of bone mineral density



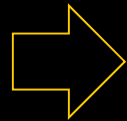
GnRH α for FP



Badawy A. Fertility and Sterility. 2009

Follow-up: 5 month

Bias +++



ZIPP study

Sverrisdottir A. et al., Breast Cancer Res Treat 2009



PROMISE-GIM6 study

No adjustment for tamoxifen

Del Mastro et al., JAMA 2011



GnRH α for FP



OPTION assay

Resumption of menstrual cycles in patients < 40 years

65% vs. 84%, $p < 0.05$

Leonard et al., J Clin Oncol 2010

ZORO assay

Resumption of menstrual cycles

70% vs. 56.7%, NS

Gerber, et al., J Clin Oncol 2011



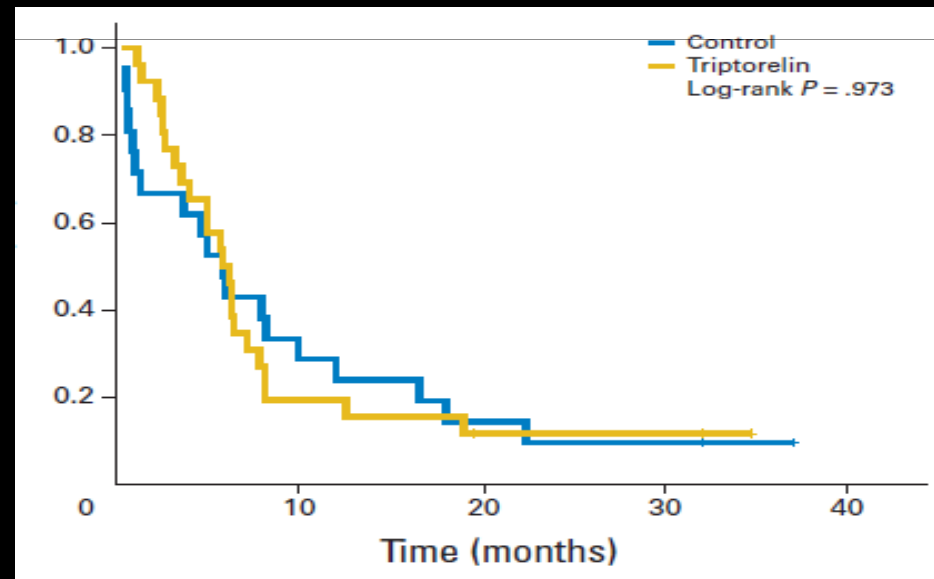
GnRHa for FP



Breast cancer, +/- tamoxifen

Adjustment according to the HR status

the trial was stopped for futility



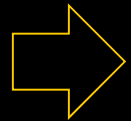
Munster et al., J Clin Oncol 2012



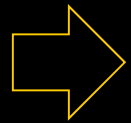
GnRHa for FP



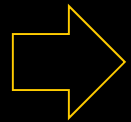
The use of GnRH analogs for ovarian protection remains controversial and continues to be investigated



Decreasing ovarian vascularization



Chemotherapy is gonadotoxic in prepubertal girls



Inhibiting FSH *simply won't do*

Routine administration, outside of a clinical trial, is currently not recommended

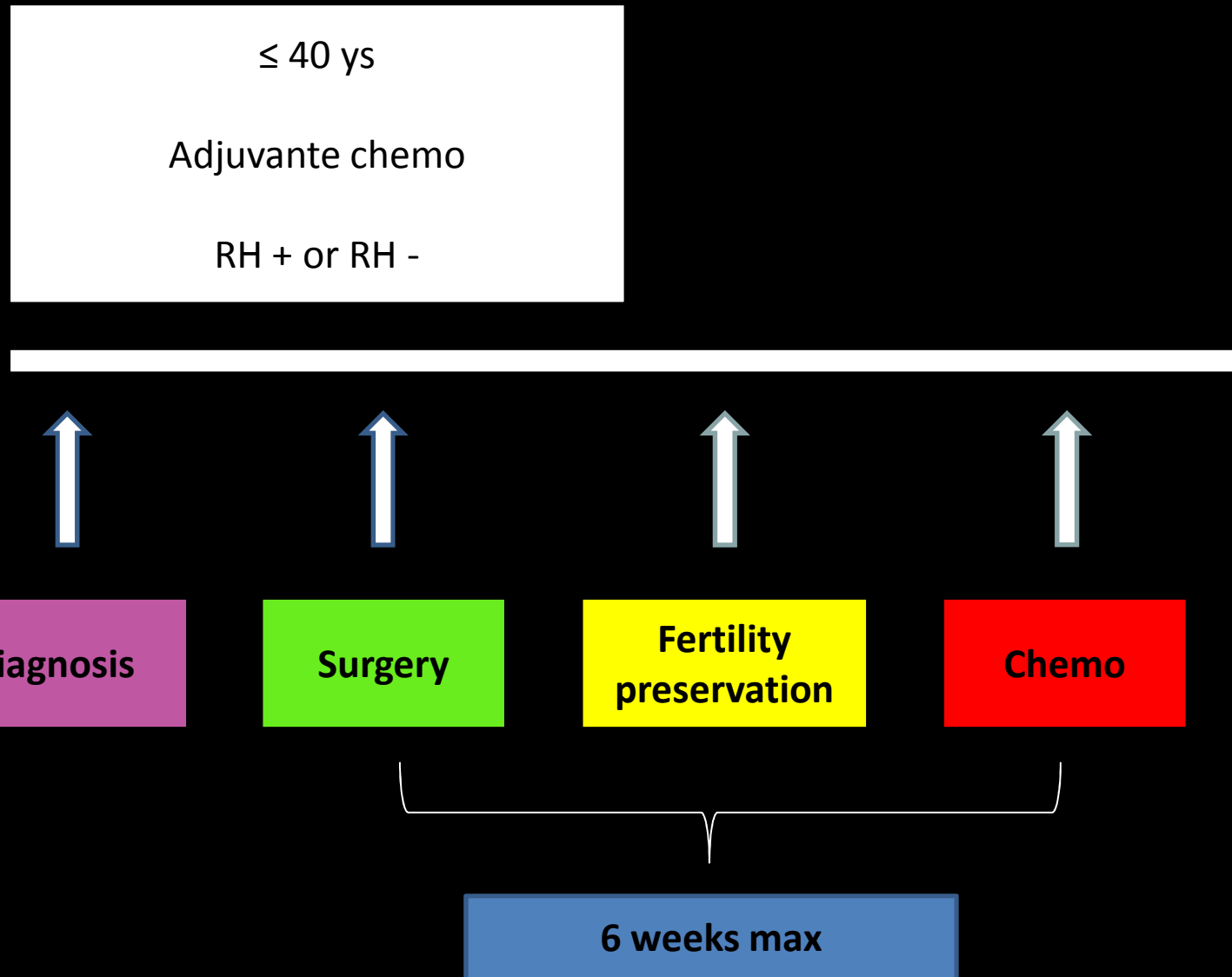


Fertility preservation

CONTROLLED OVARIAN STIMULATION



Chronology



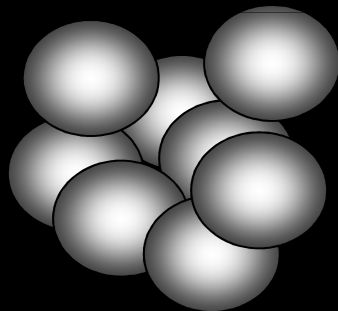


COS

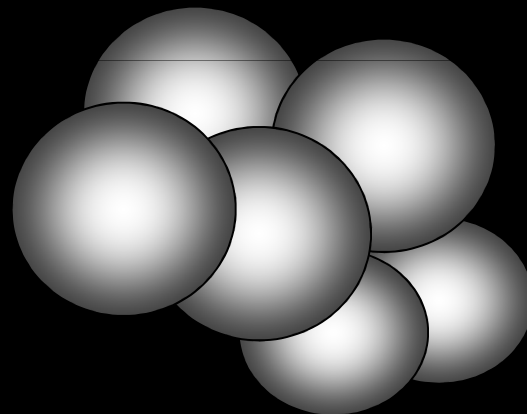
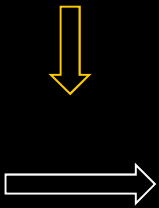
Controlled ovarian stimulation

Serum E2 levels ↑↑

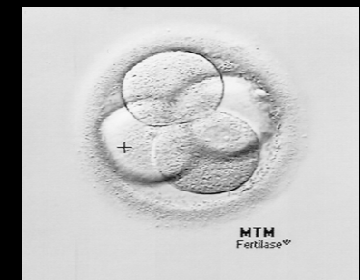
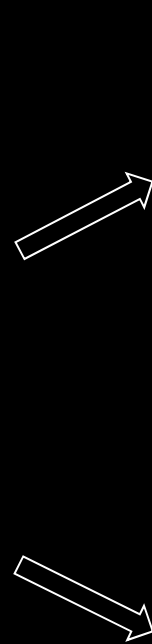
Exogenous FSH administration



Antral follicles



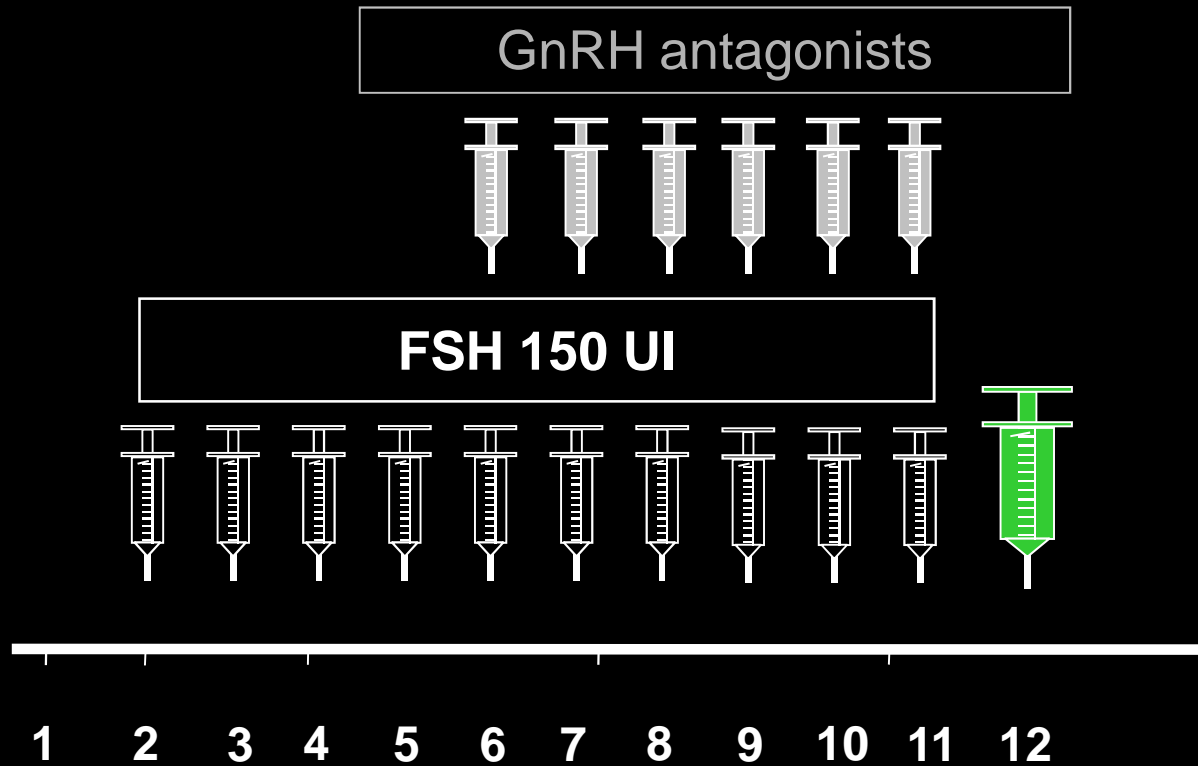
Preovulatory follicles



About 10 days

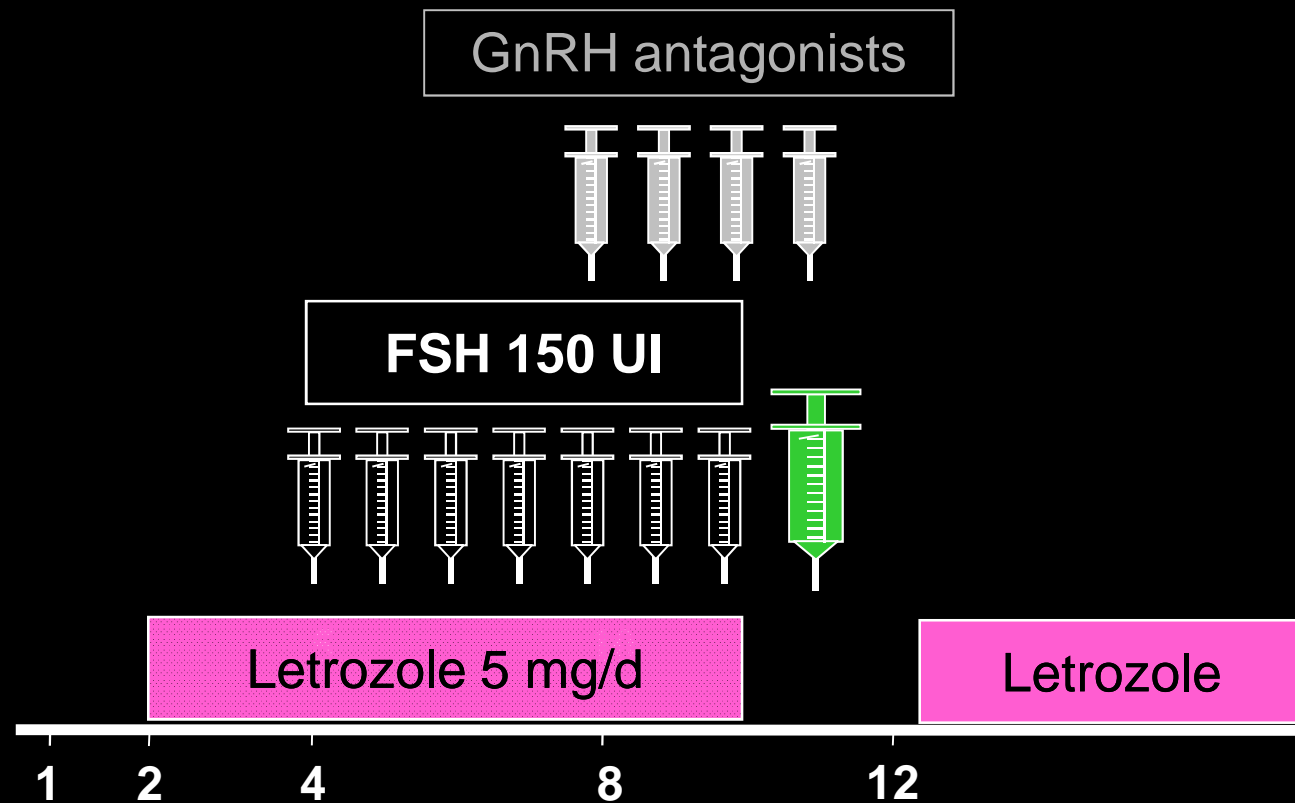


GnRH antagonist protocol





Ovarian stimulation aromatase inhibitors





Ovarian stimulation aromatase inhibitors

VOLUME 26 · NUMBER 16 · JUNE 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Safety of Fertility Preservation by Ovarian Stimulation With Letrozole and Gonadotropins in Patients With Breast Cancer: A Prospective Controlled Study

Amr A. Azim, Maria Costantini-Ferrando, and Kutluk Oktay

79 FP candidates vs. 136 controls

COH duration: 9.87 ± 2.28 days

Peak serum E₂ levels: 58.4 – 1166 pg/mL

Mean number of oocytes retrieved: 10.3 ± 7.75

Mean number of oocytes or embryos cryopreserved: 5.97 ± 4.97

No increased risk of recurrence at 23.4 months (3% vs. 8%, NS)

Azim et al., J Clin Oncol 2008



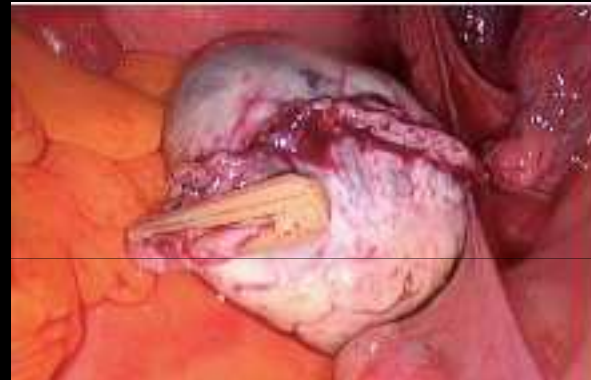
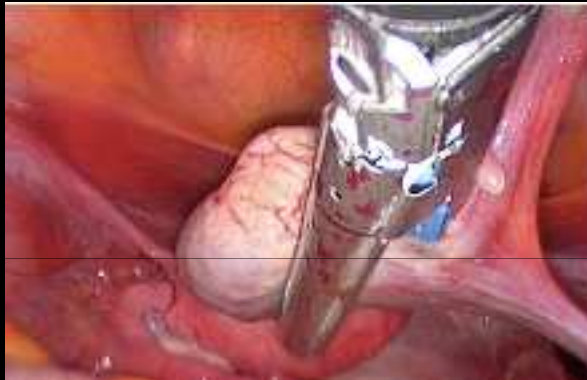
Fertility preservation

OVARIAN TISSUE CRYOPRESERVATION



Background

Ovarian tissue cryopreservation





Births after frozen ovarian tissue transplantation

Worldwide frozen ovarian cortical tissue transplantations live births.

Case no.	Diagnosis	Age at cryopreservation (y)	Chemotherapy before cryopreservation	Conception	Babies	Authors
1	Hodgkin's lymphoma	25	No	Natural	1	Dommez et al.
2	Neurotumor	19	No	Natural	1	Dommez et al.
3	Non-Hodgkin's lymphoma	28	Yes	IVF-ET	1	Merow et al.
4	Hodgkin's lymphoma	24	Yes	Natural	2	Demeestere et al.
5	Ewing sarcoma	27	No	IVF-ET and natural	2	Andersen et al.
6	Hodgkin's lymphoma	25	Yes	IVF-ET	1	Andersen et al.
7	Premature ovarian failure	25	No	Natural	1	Silber et al.
8	Hodgkin's lymphoma	20	No	Natural	2	Silber et al.
9	Polyangitis	27	Yes	IVF-ET	1	Piver et al.
10	Breast cancer	36	No	IVF-ET	2	Pellicer et al.
11	Sickle cells	27	No	Natural	1	Piver et al.
12	Thalassemia	19	No	IVF-ET	2	Revel et al.
13	Hodgkin's lymphoma	27	Yes	Ovulation induction	1	Dittrich et al.

Note: Total, 13 patients and 18 babies.

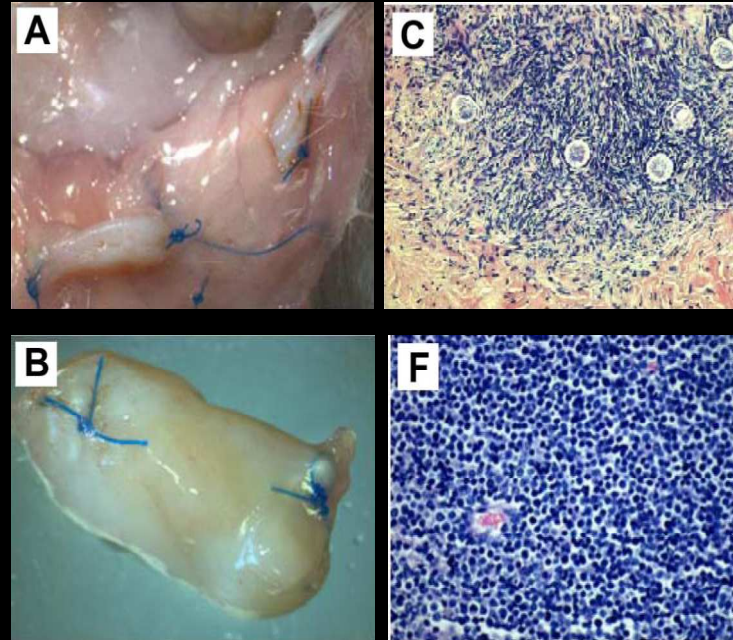
Grynberg. Ovarian and follicle transplantation. Fertil Steril 2012.

13 women, 18 babies

Grynberg et al., Fertil Steril 2012



Ovarian tissue graft



Risk of micrometastasis (Hematological diseases, breast cancer)



Ovarian tissue graft

IN VITRO MATURATION



IVM. History

- ➔ 1930s: in vivo and in vitro maturation of mammalian oocytes
Pincus & Enzmann, Journal of experimental Medicine, 1935
Pincus & Saunders, Ann Rec, 1939

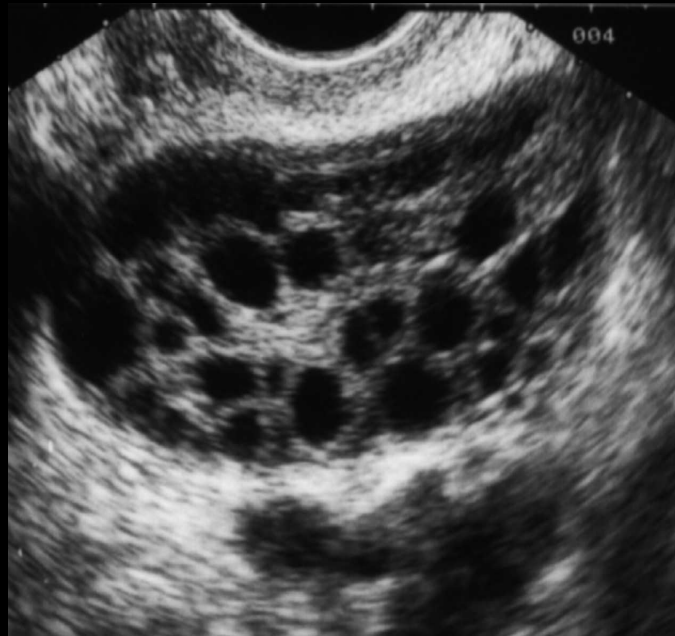
- ➔ First pregnancy after IVM of oocyte « rescued » from an IVF cycle
Veek et al., Fertil Steril 1983

- ➔ First pregnancy after IVM of oocyte in an oocyte recipient
Cha et al., Fertil Steril 1991

- ➔ First pregnancy after IVM of oocyte in a PCOS patient
Chian et al., Fertil Steril 1994



Rational



PCOS

Avoid potential side effects of COS

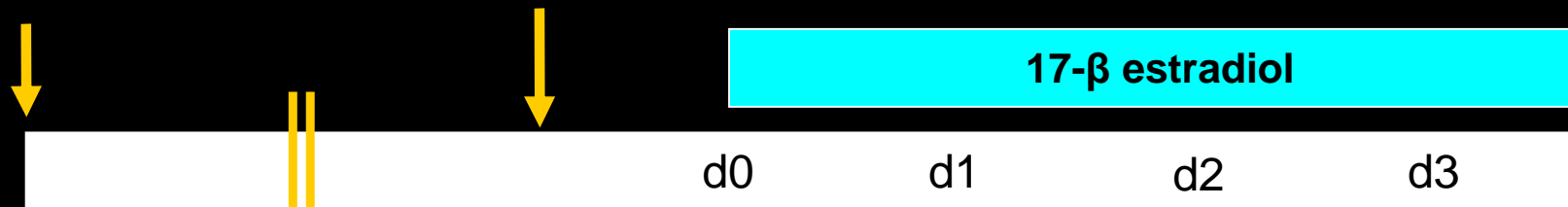
- ↓ OHSS
- ↓ Weight gain
- ↓ Breast tenderness
- ↓ Mood swing
- ↓ Cost



Protocol

Cycle d1

10.000 UI hCG

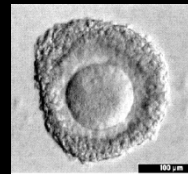


17-β estradiol

Monitoring



Oocyte retrieval



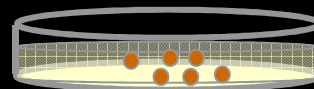
ICSI



ICSI



ET





IVM

Nuclear maturation



Prophase I: VG



Métaphase I: GVBD

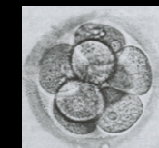


Métaphase II: 1st PG extrusion

Cytoplasmic maturation

Stock RNAm and proteins

Support the first steps of embryo development



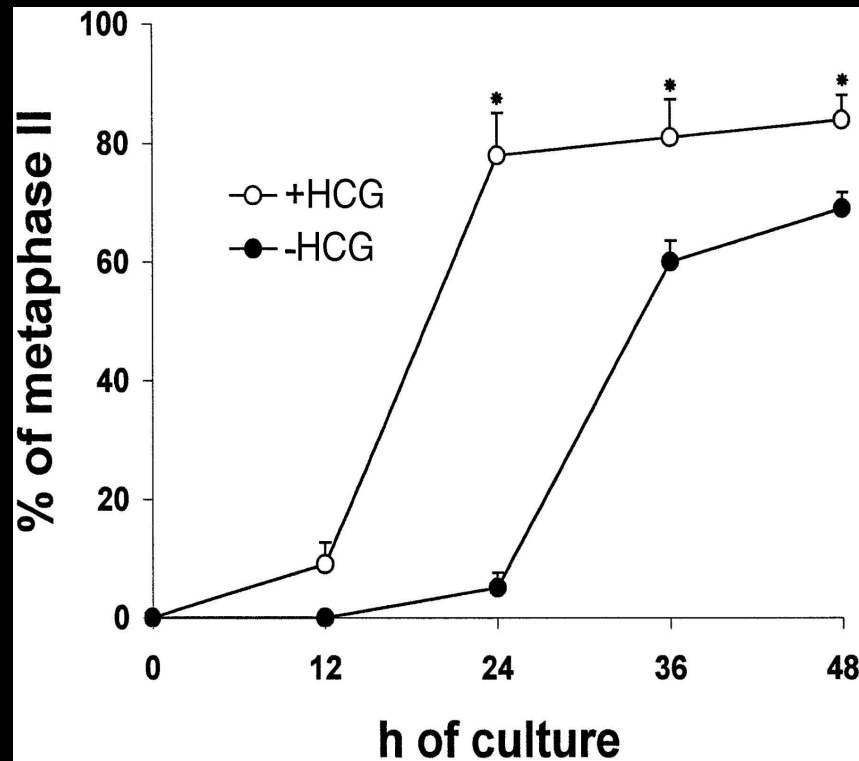
Genome

Quiescent

Active



hCG priming



Increased maturation rates

Increased fertilization rates

Increased implantation rates



IVM results

Cycles of IVM (n)	25
Age (y)	35.4 ± 4.7
Mean oocytes retrieved (n)	10.3 ± 5.4
Maturation rate (%)	84
Fertilization rate (%)	87
Clivage rate (%)	95
Embryos transferred (n)	2.9 ± 0.6
Clinical pregnancy – no (%)	10 (40)

Chian et al., NEJM 1999



IVM results

Cycles characteristics and outcomes of IVF versus IVM.

	IVF group (n = 97)	IVM group (n = 97)	P value
Cycle			
Follicles retrieved	22.2 ± 9.0	35.3 ± 18.6	< .0001
Eggs retrieved	17.2 ± 9.9	15.8 ± 7.2	NS
Oocytes/follicle	75.7	48.8	< .0001
Maturation rate	—	65.01	—
Mature oocytes obtained ^a	12.3 ± 6.2	11.2 ± 7.0	NS
Fertilization rate	61.5	62.9	NS
Cleaving embryos	9.6 ± 5.8	6.4 ± 4.8	< .0001
Embryos transferred	1.7 ± 0.6	1.9 ± 0.4	.0043
Day 2	8	13	NS
Day 3	58	80	.0008
Day 5	24	0	< .0001
No transfer	7 ^b	4 ^d	NS
Embryos frozen	2.6 ± 3.2	1.4 ± 2.7	.0058
Outcome			
Biochemical pregnancy	63.9 (62)	28.9 (28)	< .0001
Clinical pregnancy ^b	50.5 (49)	19.6 (19)	< .0001
Miscarriage	12.2 (6)	15.8 (3)	NS
Live birth rate	48.3 (43)	16.5 (16)	< .0001
Implantation rate	39.4	12.9	< .0001
Twins	25.6 (11)	25 (4)	NS



Impaired endometrium

Non-hCG-primed IVM system in PCOS

Comparative clinical outcomes of fresh and vitrified-warmed IVM embryo transfer.

	Fresh	Vitrified-warmed	P value
Clinical pregnancy rate	5/53 (9.4%)	7/22 (31.8%)	.033
Positive hCG	7/53 (13.2%)	9/22 (40.9%)	.008
Implantation rate	5/72 (6.9%)	7/32 (21.9%)	.043

Poorly when embryos are transferred in a fresh cycle.



Neonatal outcome

	RR	95%CI
IVM	1.19	0.35-3.25
IVF	1.01	0.52-1.90
ICSI	1.41	0.72-2.68

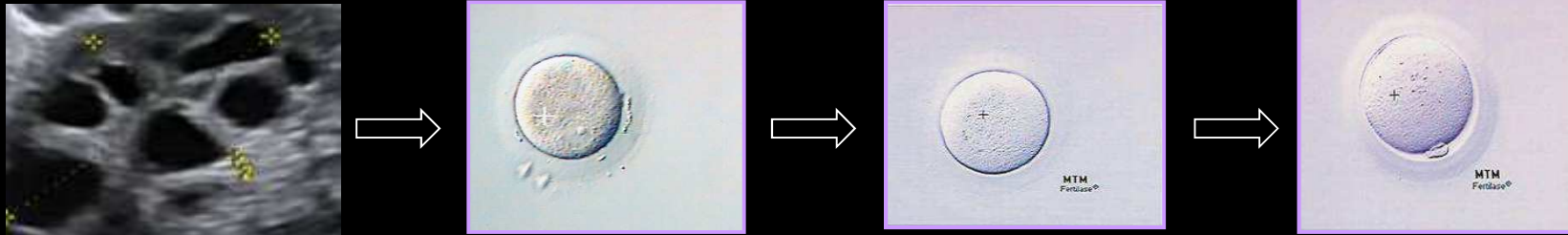
No increased rate of congenital abnormalities

Buckett et al., Obstet Gynecol 2007



Background

In vitro maturation of oocytes



No controlled ovarian stimulation

No increased serum E₂ levels

No time requirements

An alternative approach for fertility preservation



Background

IVM Follicular vs. Luteal phase

	Follicular phase n=13	Luteal phase n=5	P
No of oocytes aspirated	17.3 ± 13.5	12.8 ± 8.4	NS
Range	4 - 44	3 - 38	NS
MII oocytes after 24h	4.5 ± 3.8	4.0 ± 5.7	NS
Total MII oocytes	9.5 ± 7.73	7.0 ± 7.6	NS
Maturation rate, %	57.8 ± 29.2	48.6 ± 18.3	NS
Fertilization rate, %	63.2 ± 27.3	69.2 ± 47.4	NS
Mean total oocyte and embryo cryopreservation	7.8 ± 7.5	6.4 ± 6.6	NS



IVM for FP in breast cancer patients ***Clamart***

Prospective study

102 breast cancer patients, candidates for urgent fertility preservation using IVM

Inclusion criteria

➡ 2 ovaries

➡ No previous chemotherapy



Results

	Follicular phase (n=60)	Luteal phase (n=42)	<i>P</i>
Age (years)	32.4 ± 4.3	31.1 ± 4.9	0.513
BMI (Kg/m²)	22.1 ± 3.7	22.3 ± 3.1	0.778
Gestivity			0.904
• 0	31 (52)	22 (56)	
• 1-2	24 (40)	14 (36)	
• > 2	5 (8)	3 (8)	
Parity			0.885
* 0	42 (70)	28 (72)	
• 1-2	13 (22)	9 (23)	
• >2	5 (8)	2 (5)	
Menstrual cycles			
• Regular	52 (87)	29 (74)	
• Irregular	8 (13)	10 (26)	
Serum P₄ levels (ng/mL)	0.14 ± 0.5	3.52 ± 0.8	0.001
AFC	17.4 ± 7.7	18.9 ± 11.1	0.710
Serum AMH levels (ng/mL)	3.3 ± 2.0	3.9 ± 2.8	0.451



Results

	Follicular phase n=60	Luteal phase n=42	<i>P</i>
No immature oocytes recovered	8.4 ± 5.0	9.2 ± 6.7	0.426
Oocytes output rate (%)	48.7 ± 4.8	47.3 ± 5.0	0.643
Maturation rate at 24h (%)	72.2 ± 3.1	70.3 ± 2.3	0.752
Maturation rate at 48h (%)	7.0 ± 2.9	8.4 ± 1.7	0.618
Total maturation rate (%)	79.2 ± 2.5	78.7 ± 2.0	0.913
No mature oocytes	6.9 ± 3.7	7.4 ± 5.2	0.131
Fertilization rate (%)	78.7 ± 2.8	78.7 ± 2.0	0.597



Conclusion

1 Breast cancer is **frequent** in the young population

W

2 Young breast cancer patients show **concerns regarding future fertility** and ask for fertility preservation

h

3 Pregnancy is **safe** after breast cancer↑

y



Conclusion

4

Gonadotoxicity of chemotherapy, combined with physiological ovarian aging may alter the fertility potential, both natural and with ART

W

5

Currently there is **no adequate tool** to correctly predict fertility in a patient diagnosed with breast cancer

h

6

Many **fertility preservation** options are available

y

Oocyte cryopreservation



Ovarian tissue cryopreservation

Risk of micrometastasis

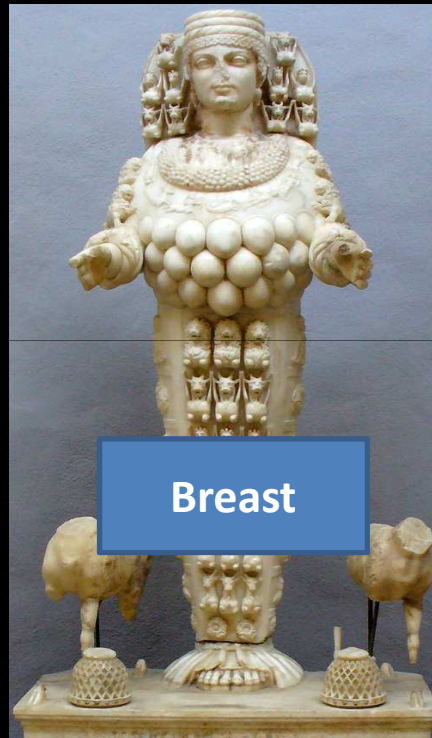
Problem in BRCA1 patients

Moderate ovarian toxicity of FEC/T

Oophorectomy after 30 ys

Efficiency +++

COS and increased E₂ levels



Breast

Medical treatment

Easy

Efficiency?

Inocuity?

Embryo cryopreservation





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