

Fertility counselling: What are the options?

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Disclosures

- **Advisory board:** GSK, Celgene, Nanostring
- **Honoraria:** GSK, Novartis, Celgene, Nanostring
- **Research support:** Amgen

Case Description

- Mrs. “B” is a 34-year-old lawyer, diagnosed with a left breast cancer, for which she was subjected to a left lumpectomy and axillary dissection, after a positive SLN
- Pathology revealed:
 - Invasive duct carcinoma, grade III
 - pT₂ (2.7cm) pN₁ (2/13)
 - ER 90%, PgR 10%, HER2 –ve, Ki67 25%

Case Description

- No evidence of distant metastasis
- Other relevant history:
 - Married 6 months ago, no children
 - Regular menstrual cycles
 - Positive family history of breast cancer (cousin), BRCA testing pending
 - Perfect general health, no associated medical conditions

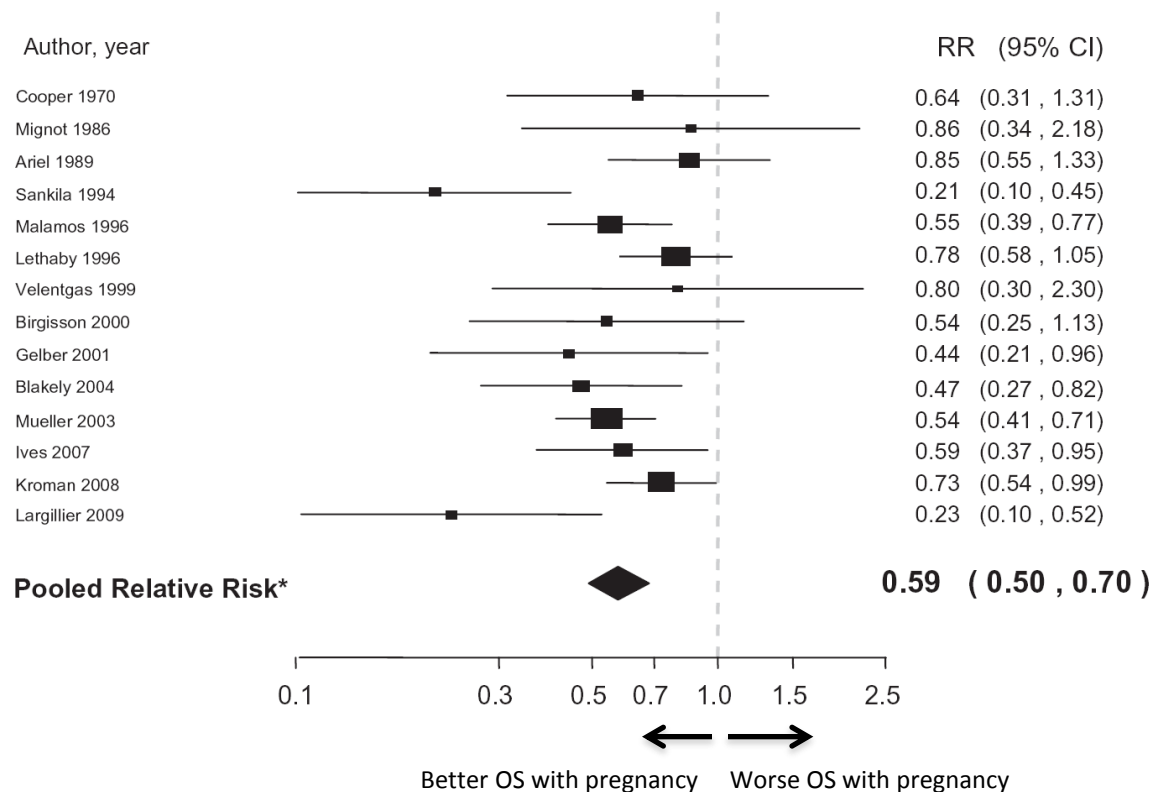
Case Description

- The patient was advised for adjuvant chemotherapy for 6 cycles to be followed by RTH and 5 years of endocrine therapy
- However, she was very much concerned regarding
 1. Safety of pregnancy in her case
 2. Her chances of future conception after chemo/hormonal therapy
 3. Whether it is possible to preserve her fertility

Question 1: Safety of pregnancy after BC

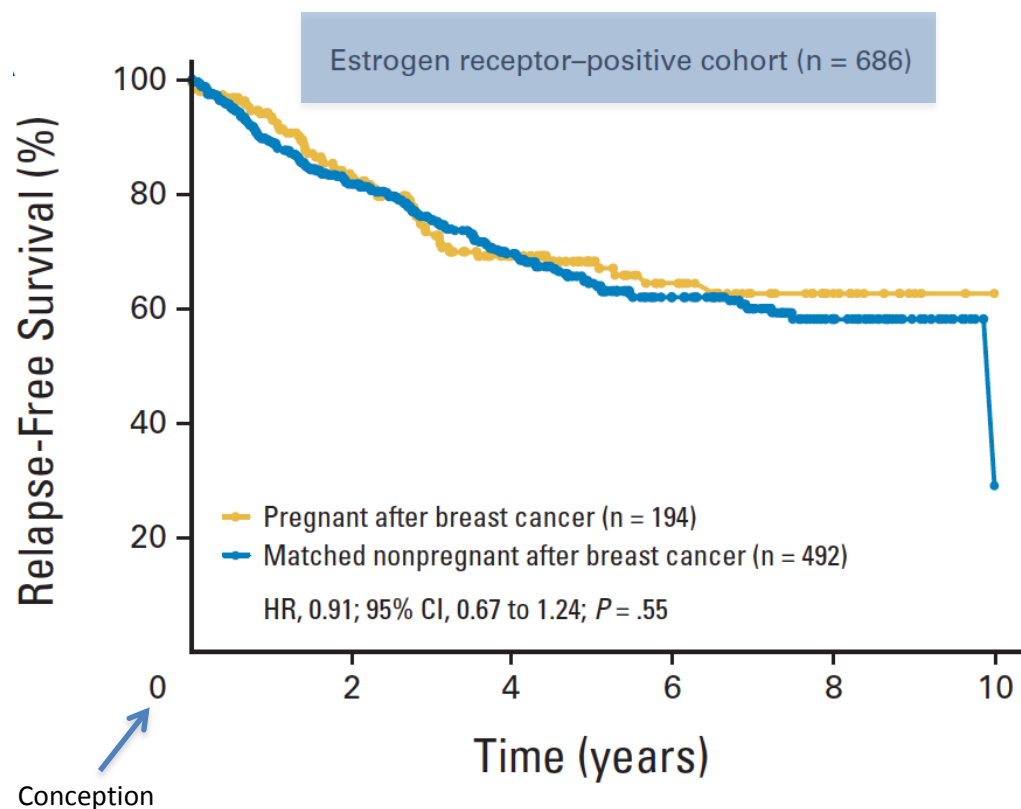
Not a good Idea !

High oestrogen levels during pregnancy could stimulate BC to recur



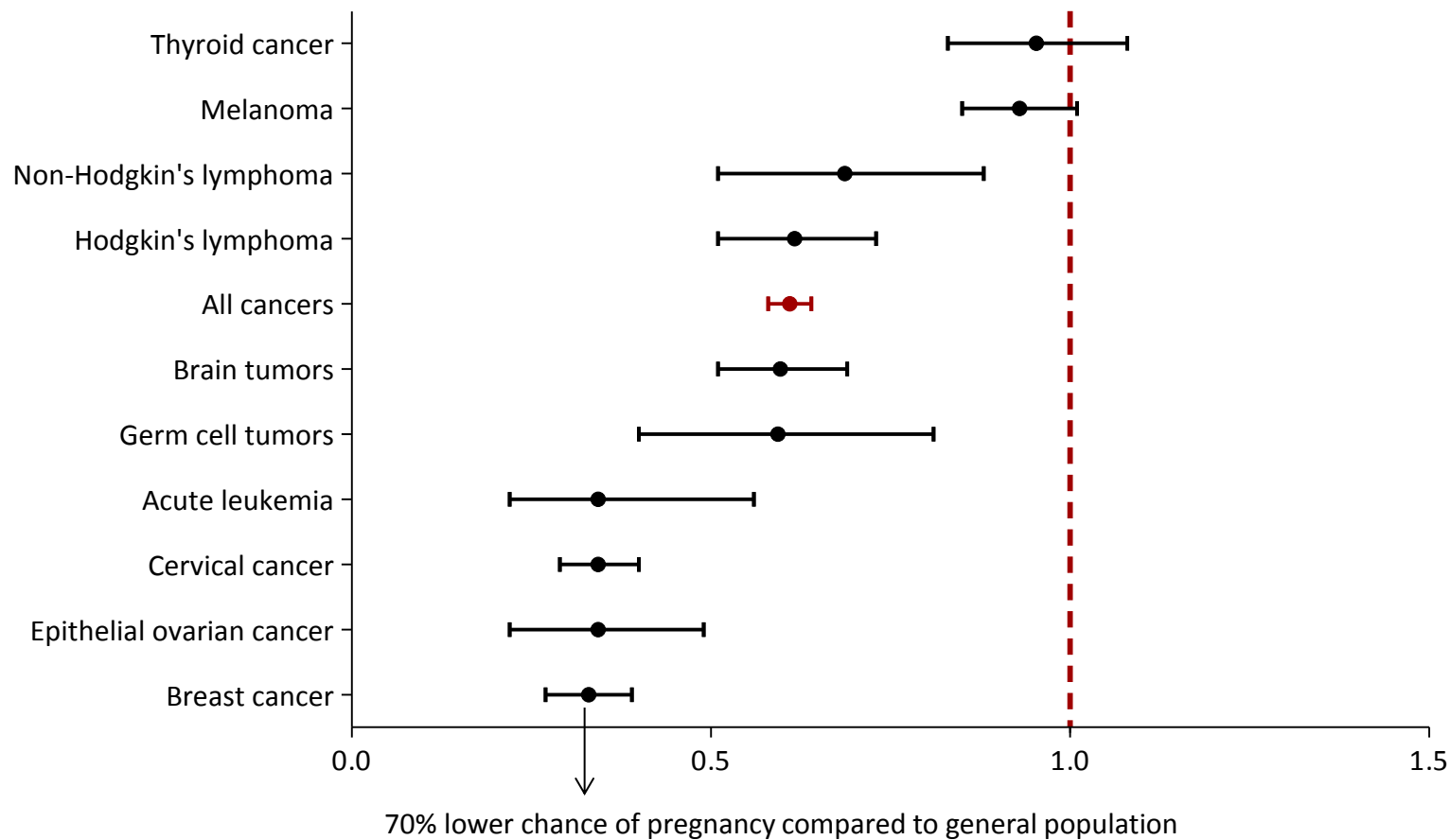
Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

Hatem A. Azim Jr, Niels Kroman, Marianne Paesmans, Shari Gelber, Nicole Rotmensz, Lieveke Ameye, Leticia De Mattos-Arruda, Barbara Pistilli, Alvaro Pinto, Maj-Britt Jensen, Octavi Cordoba, Evandro de Azambuja, Aron Goldhirsch, Martine J. Piccart, and Fedro A. Peccatori



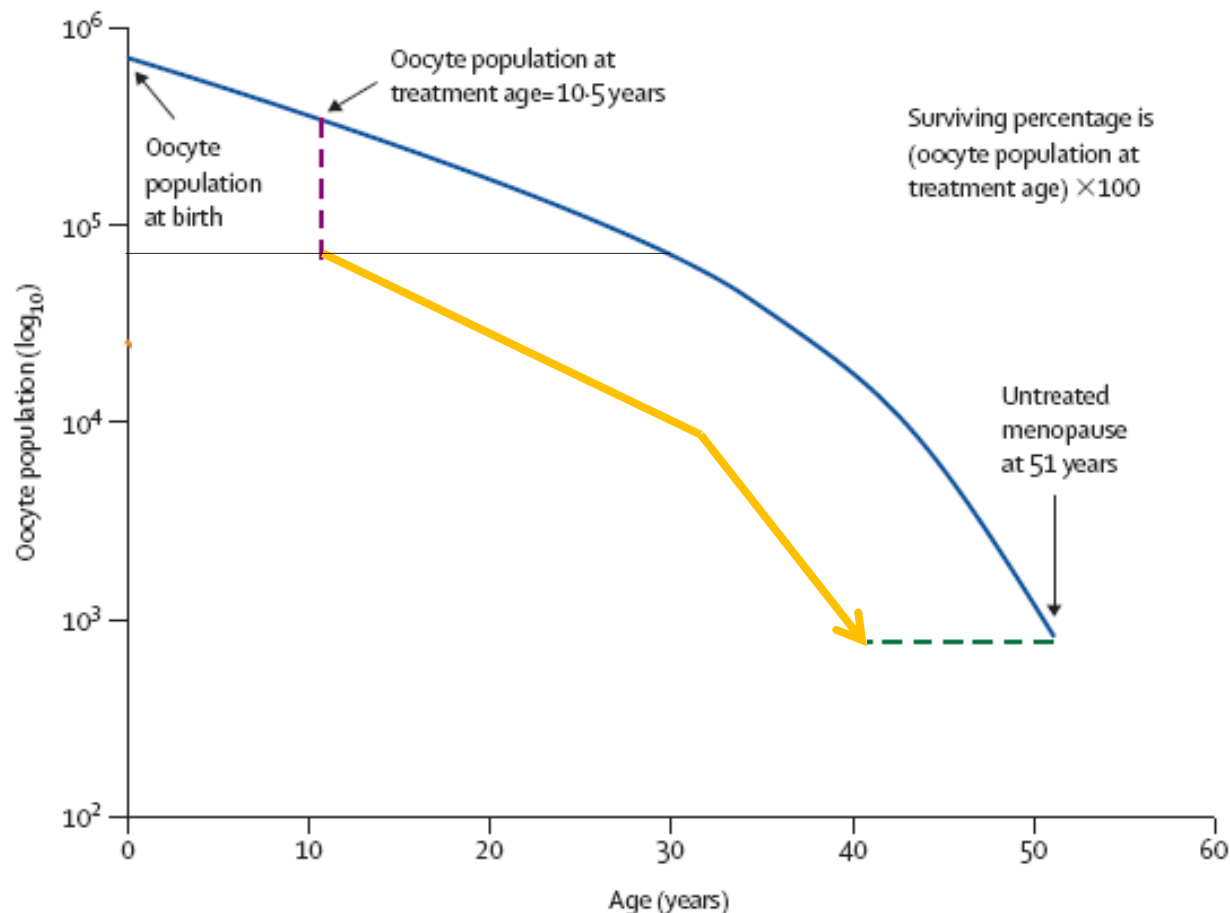
Median follow-up from date of conception: 4.7y
35% of patients were histological grade III
40% of patients were node-positive
80% of patients received adjuvant chemo

Question 2: Chances of future conception



	Age	Permanent Chemotherapy induced amenorrhea
CMF x 6	< 40	30 – 80%
	≥ 40	60 – 96%
AC x 4	< 40	13-30 %
	≥ 40	57-63 %
FEC/FAC x 6 - 8	< 40	10 – 25%
	≥ 40	80 – 90%
AC x 4 – T x 4	< 40	30 – 35%
	≥ 40	65 – 75%
TAC x 6		61.7%

Early menopause in patients who received chemo **even in those who resumed menses after ending therapy**

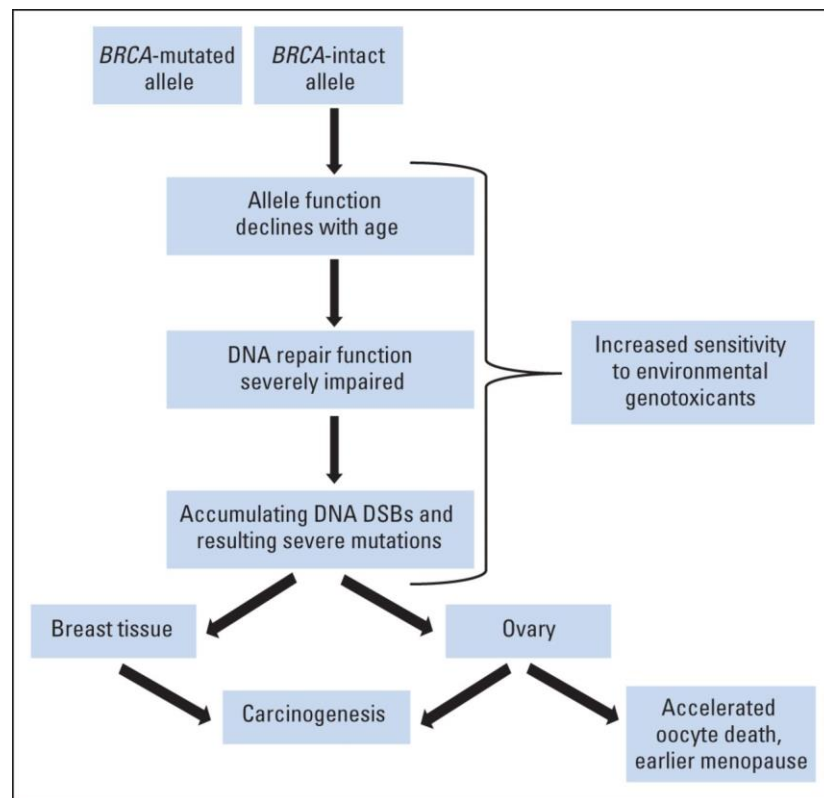


Comparison of Age at Natural Menopause in *BRCA1/2* Mutation Carriers With a Non-Clinic-Based Sample of Women in Northern California

Wayne T. Lin, MD, MPH^{1,2}; Mary Beattie, MD³; Lee-may Chen, MD¹; Kutluk Oktay, MD⁴; Sybil L. Crawford, PhD⁵; Ellen B. Gold, PhD⁶; Marcelle Cedars, MD¹; and Mitchell Rosen, MD¹

Frequency of premature menopause in women who carry a *BRCA1* or *BRCA2* mutation

Amy Finch, Ph.D.,^a Adriana Valentini, M.D.,^a Ellen Greenblatt, M.D.,^b Henry T. Lynch, M.D.,^c Parviz Ghadirian, Ph.D.,^d Susan Armel, M.S.,^e Susan L. Neuhausen, M.D.,^f Charmaine Kim-Sing, M.D.,^g Nadine Tung, M.D.,^h Beth Karlan, M.D.,ⁱ William D. Foulkes, Ph.D.,^j Ping Sun, Ph.D.,^a Steven Narod, M.D.,^a and Members of the Hereditary Breast Cancer Study Group



Premature menopause in patients with *BRCA1* gene mutation

Izabella Rzepka-Górska · Bogusław Tarnowski ·
Anita Chudecka-Głaz · Bohdan Górski ·
Dorota Zielińska · Aleksandra Tołoczko-Grabarek

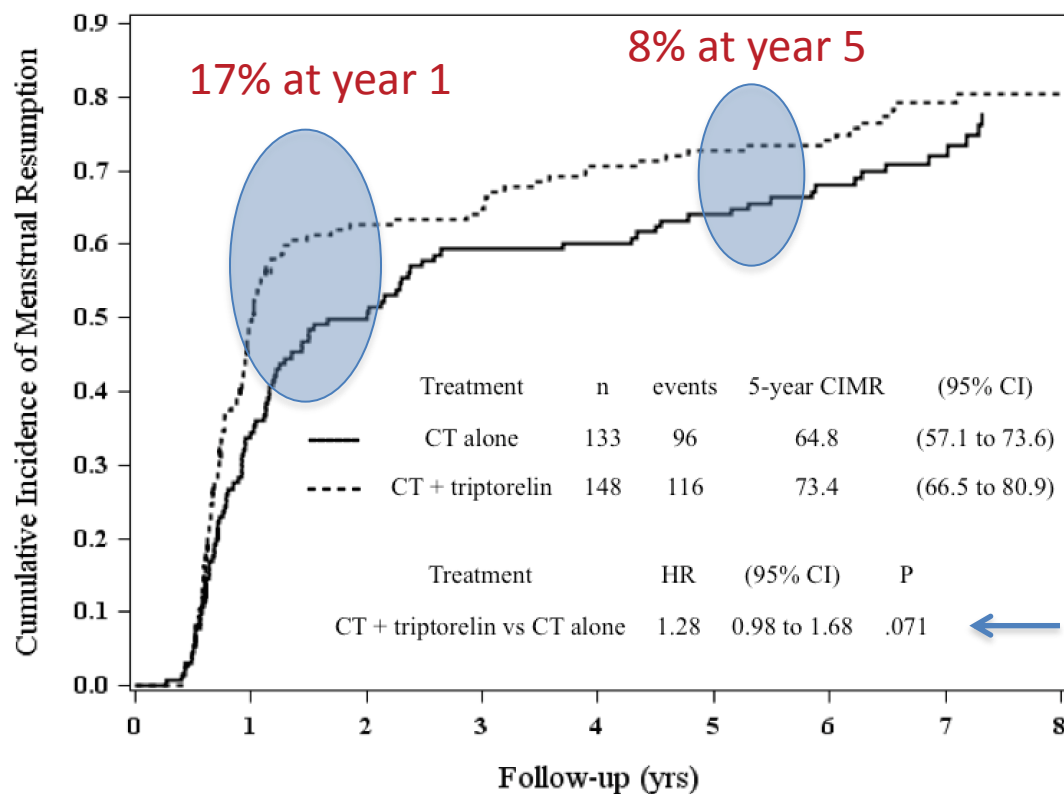
Question 3: What are the fertility preservation options?

	Oocyte cryopreservation	Embryo cryopreservation	Ovarian tissue cryopreservation	Ovarian suppression by GnRHa
Define	Harvest, freeze unfertilized eggs	Harvest eggs , IVF and freeze embryos	Freeze ovarian tissue and re-implant after cancer therapy	Use GnRHa during chemotherapy
Standard?	Yes	Yes	No	No
Need ovarian stimulation?	Yes	Yes	No	No
Delay starting therapy?	Yes	Yes	No	No
Need surgery?	Yes	Yes	Yes	No
Preserve ovarian function?	No	No	Yes	Menses
Available in all centres	No	No	No	No

Are GnRH Analogues reliable as a fertility preservation method?

	Del Mastro et al; JAMA 2011	Gerber et al; JCO 2011	Munster et al; JCO 2012	Moore et al; ASCO 2014
Country	Italy	Germany	US	International
Number	281	61	49	135
Median age	39	36	39	38
Chemotherapy	Any chemo	AC-T	AC-T or FEC	Any chemo
LHRH agonists/28d	Triptorelin	Goserelin	Triptorelin	Goserelin
ER status	Any	Negative	Any	Negative
1ry end point: Amenorrhea at	12 months	6 months	12 months	24 months
% resuming menses	LHRH: 91% No LHRH: 74% POSITIVE	LHRH: 56% No LHRH: 70% NEGATIVE	LHRH: 88% No LHRH: 90% NEGATIVE	LHRH: 92% No LHRH: 78% POSITIVE

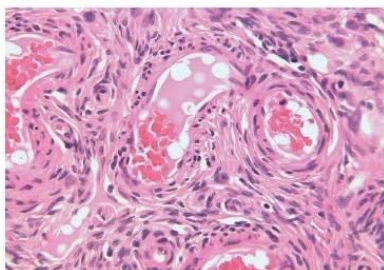
Long-term outcome after LHRH administration with chemo – ?? reduced benefit overtime



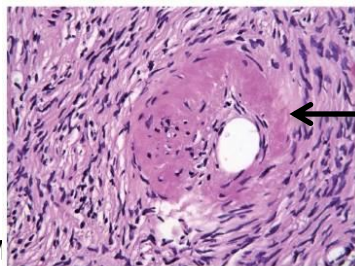
Resuming menses is a poor surrogate for adequate ovarian reserve

	Survivors	Controls	P-value
Antral Follicle Count	5.2	11.3	0.0042
AMH	0.57	1.77	0.0004
FSH	11.56	8.04	0.02
Inhibin B	24.3	46.6	0.02
Estradiol	126.0	38.8	0.14

No chemo



Non-sterile doses of chemo



Thickening & hyalinization
of cortical vessels

Fertility Preservation in Breast Cancer Patients: A Prospective Controlled Comparison of Ovarian Stimulation With Tamoxifen and Letrozole for Embryo Cryopreservation

Kutluk Oktay, Erkan Buyuk, Natalie Libertella, Munire Akar, and Zev Rosenwaks

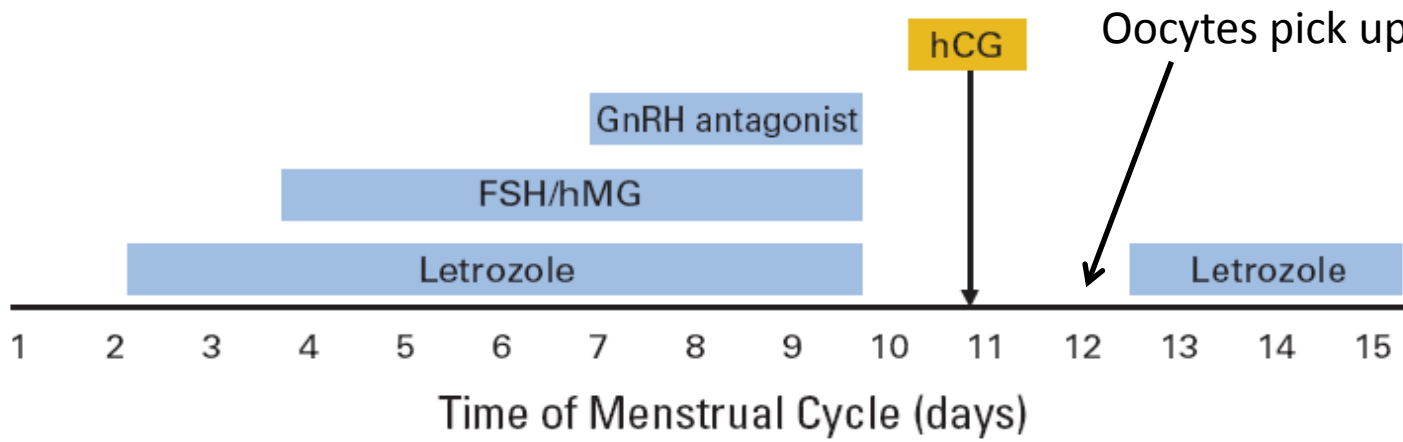
N=60

Variable	Mean \pm Standard Deviation		
	Tam-IVF (a)	TamFSH-IVF (b)	Letrozole-IVF (c)
Age, years	36.6 \pm 1.6	38.3 \pm 1.9	38.5 \pm 1
Baseline FSH, mU/mL	9.4 \pm 1.5	9.4 \pm 1.5	6.2 \pm 1.1
→ PeakE ₂ , pg/mL†	419 \pm 39	1,182 \pm 271	380 \pm 57
→ Total follicles, No.	2 \pm 0.3	6 \pm 1	7.8 \pm 0.9
Follicle > 17 mm, No.	1.2 \pm 0.1	2.6 \pm 0.4	3.2 \pm 0.4
Total oocytes, No.	1.7 \pm 0.3	6.9 \pm 1.1	12.3 \pm 2.5
→ Mature oocytes, No.	1.5 \pm 0.3	5.1 \pm 1.1	8.5 \pm 1.6
→ Total embryos, No.	1.3 \pm 0.2	3.8 \pm 0.8	5.3 \pm 0.8

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

N=217 (79 underwent controlled ovarian stimulation; 81% ER+, 38% N+)

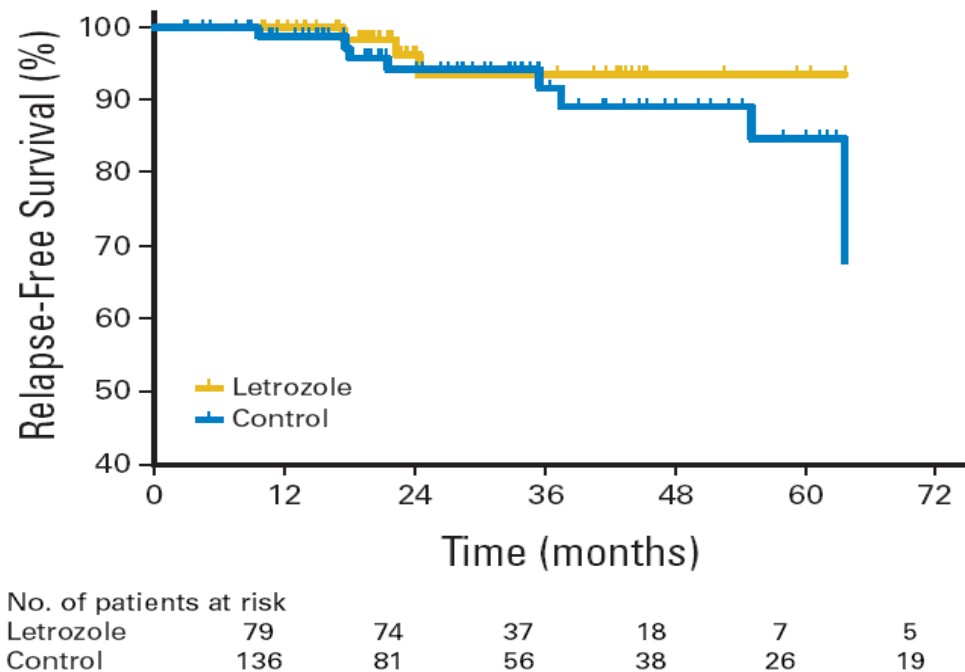


Average number of oocytes retrieved: 10.3 ± 7.75

Average number of frozen embryos: 5.97 ± 4.97

Median time from surgery to systemic Rx: **45 days** (vs. 33 in controls; $p < 0.01$)

10 embryo implanted, 5 deliveries



Pregnancy in breast cancer survivors & effect of assisted reproduction

	Spontaneous pregnancy (N=74)	Assisted reproduction (N=20)
Histological grade III	47 (63%)	5 (25%)
Positive nodal status	31 (42%)	6 (30%)
ER-positive	41 (55%)	15 (75%)

	Spontaneous pregnancy (N=74)	Assisted reproduction (N=20)
Median age at conception	37 years	41 years
Miscarriage	11 (12%)	6 (24%)
Twin pregnancy	2 (3%)	3 (16%)

	Spontaneous pregnancy (N=74)	Assisted reproduction (N=20)
Median FU after conception	55 months	34 months
Relapse	13 (17%)	2 (10%)
Death	6 (8%)	1 (5%)

clinical practice guidelines

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Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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