

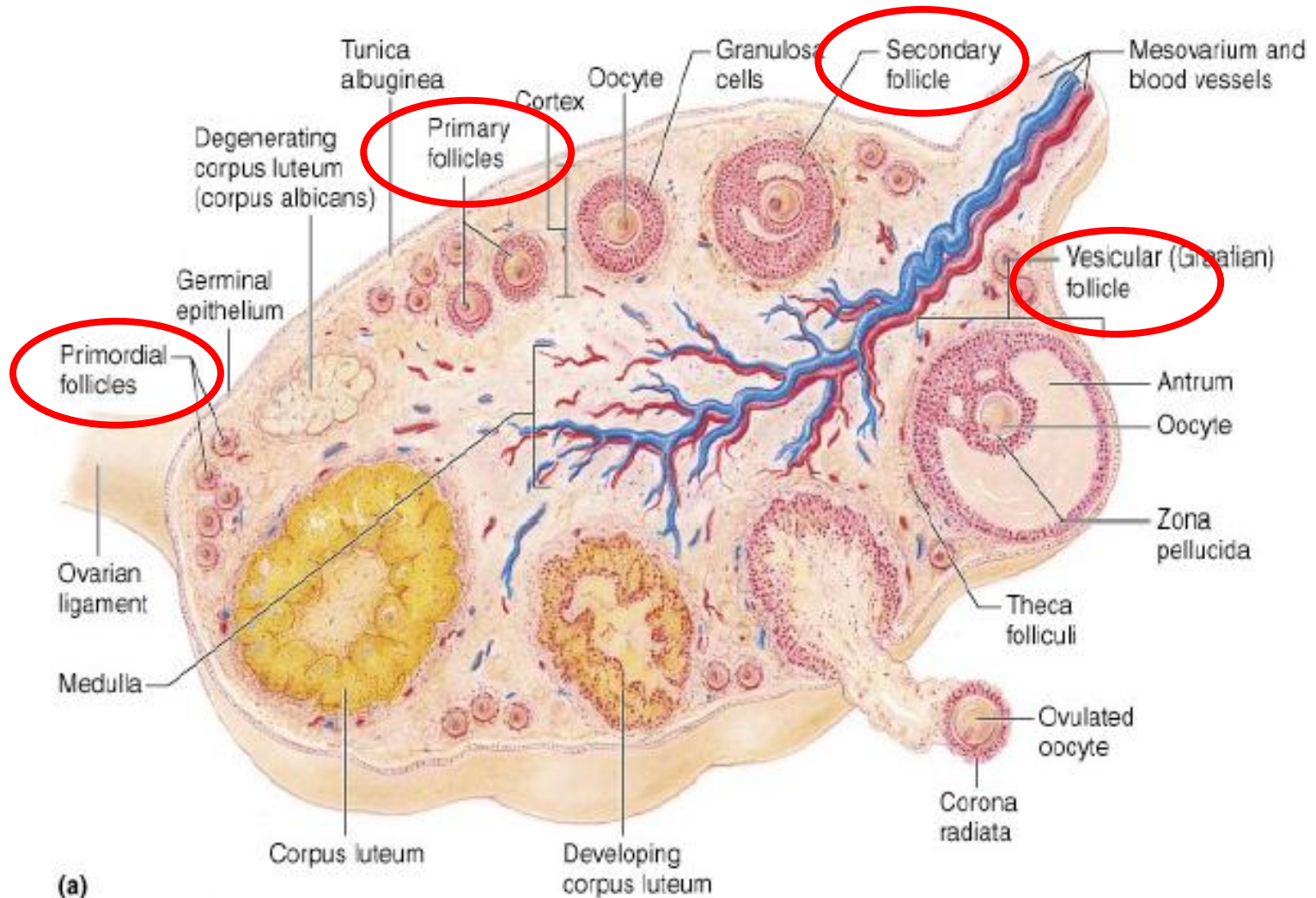
# La preservazione della fertilità: è oggi possibile ?

Fedro Peccatori, MD PhD  
Fertility and Procreation Unit in Oncology  
European Institute of Oncology,  
European School of Oncology,  
Milan, ITA



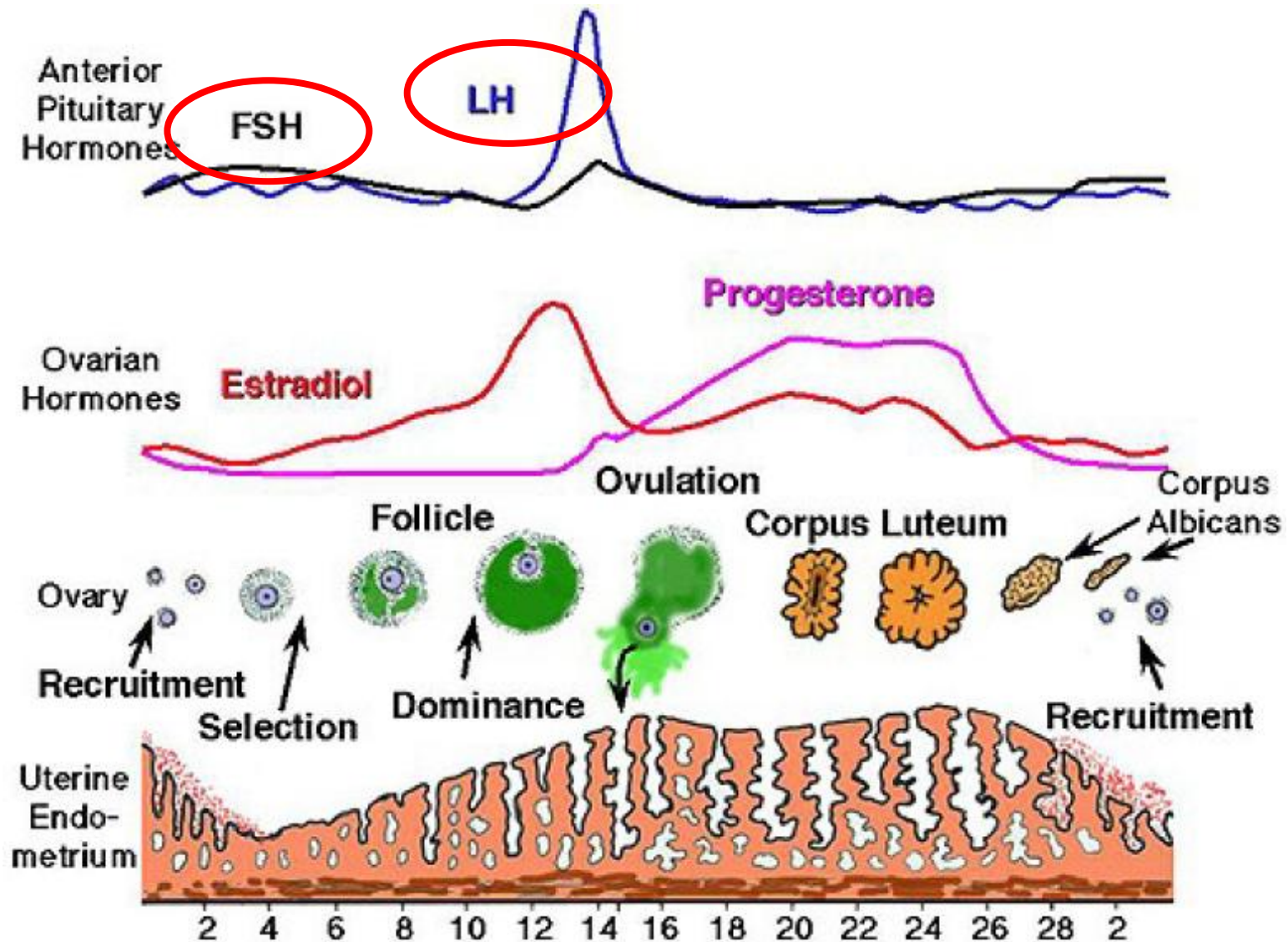
Carcinoma mammario: quando la donna è giovane  
Negrar, 24 Giugno 2015

# Foreword 1: the ovary

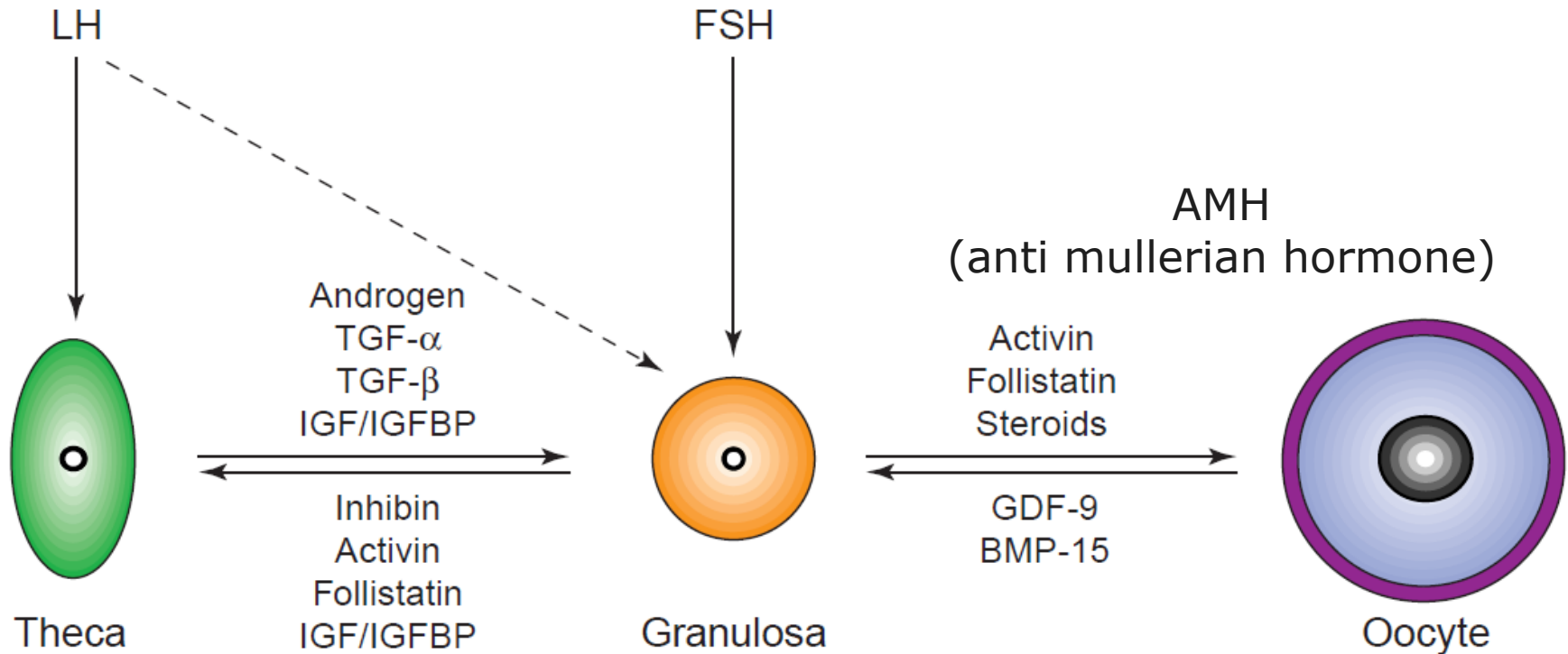


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# Foreword 2: the hypothalamus-ovarian axis

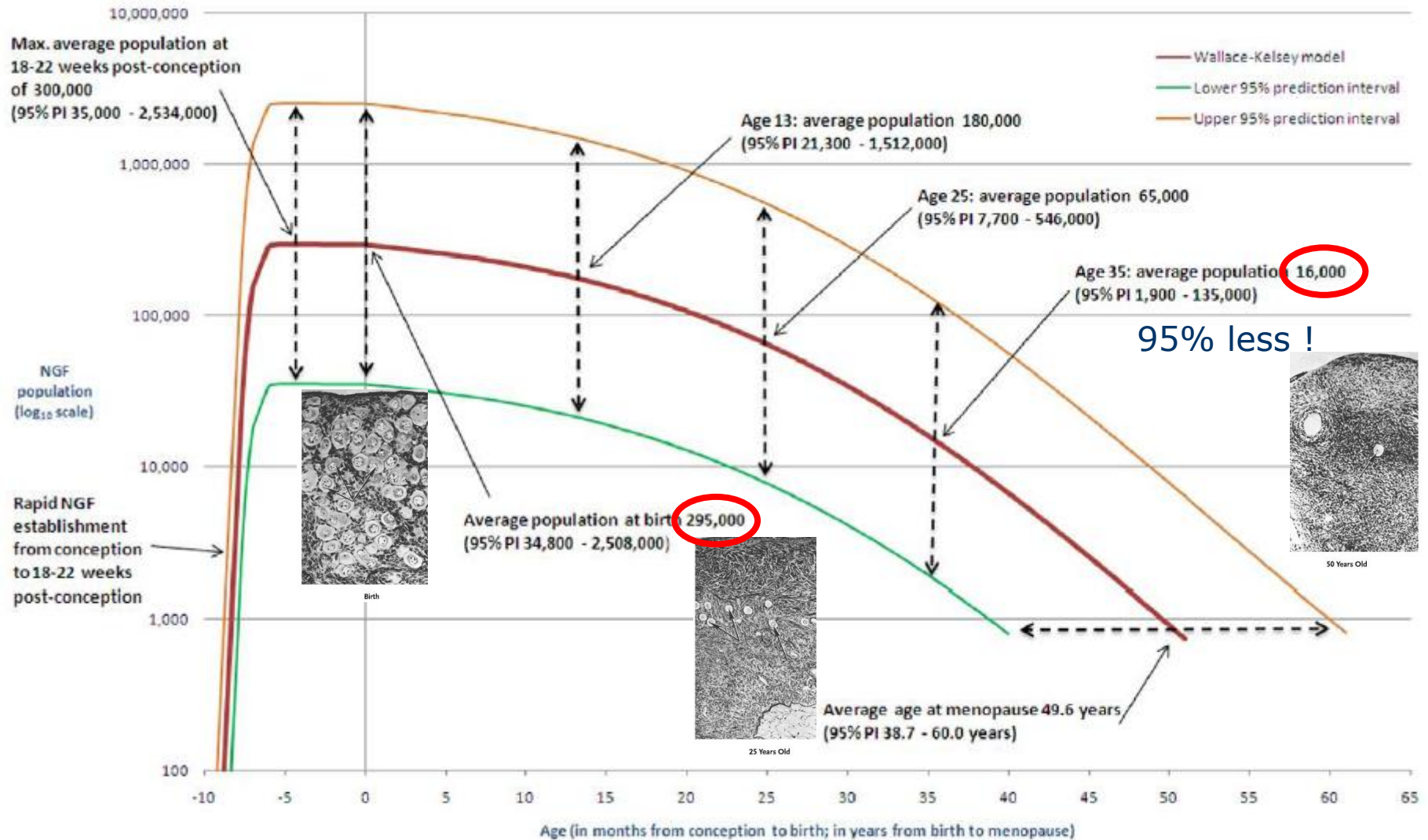


# Foreword 3: the paracrine factors

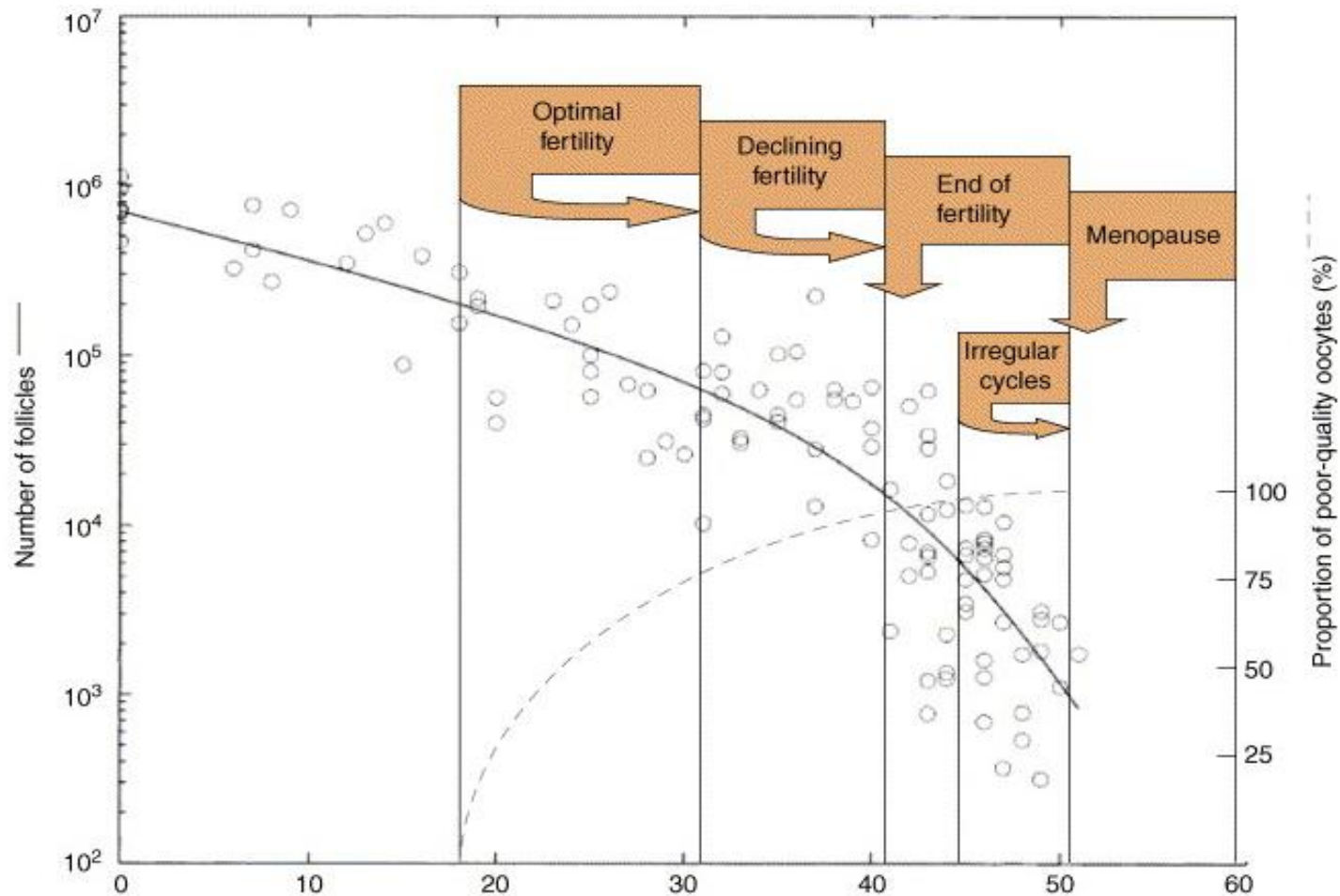




# Foreword 4: times goes by



# Foreword 5: fertility is not forever



Decrease in quantity and increase in poor-quality oocytes with age

# The clinical case

Anna, 36 y/o nullipara

No family history, no comorbidities

20/02/2015 Quadrantectomy and axillary dissection  
pT1c N1 (3/15 +In) G3 ductal infiltrating carcinoma  
ER 75% PgR 60% HER2 1+ Ki67 45% LVI +  
Lum B-like according to St Gallen

ECx4 ->wPTX x12 -> LHRHa+Exemestane x 5y

but...

# The clinical case





# The clinical case: 2 burning questions

What is the risk of chemotherapy-induced infertility ?  
Is there anything we can do to reduced it?



# Assessing the risk of infertility

## CRITICAL FACTORS:

- ✓ Age at diagnosis (oocyte quantity and quality)
- ✓ Drugs administered (schedule and dosage)
- ✓ Age at pregnancy (treatment duration)



Fertile Hope is a national LIVESTRONG initiative dedicated to providing reproductive information, support and hope to cancer patients and survivors whose medical treatments present the risk of infertility.

LIVESTRONG

## SAVE MY FERTILITY

An online fertility preservation toolkit for patients and their providers

About Save My Fertility Provider Pocket Guides Patient Fact Sheets

Home > Provider Pocket Guides >

### STARTING THE CONVERSATION

#### Fertility Preservation for Women Diagnosed with Cancer

#### Introduction

Many women of childbearing age who have been diagnosed with cancer think that preserving their fertility is important and want information about their options. However,



the Oncofertility<sup>®</sup> Consortium  
AT NORTHWESTERN UNIVERSITY



<http://oncofertility.northwestern.edu/about-us>

<http://www.savemyfertility.org/pocket-guides>

<http://www.fertilehope.org/tool-bar/risk-calculator-women-type.cfm>

# Assessing the risk of infertility

36 y/o

ECx4 -> wPTX x12 -> LHRHa+Exemestane x 5y

## Intermediate Risk

Approximately 30-70% of women develop amenorrhea post-treatment.

- CMF x 6 cycles in women ages 30-39  
(cyclophosphamide, methotrexate, 5-fluorouracil)
- CEF x 6 cycles in women ages 30-39  
(cyclophosphamide, epirubicin, 5-FU)
- CAF x 6 cycles in women ages 30-39  
(cyclophosphamide, doxorubicin, 5-FU)
- AC x 4 cycles in women ages 40 and older  
(doxorubicin, cyclophosphamide)

# Assessing the risk of infertility



Treatment	Age <30	Age 30-40	Age>40
AC x 4	--	13	57-63
CMF x 6	19	31-38	76-96
CAF/CEF x 6	23-47		80-89
TAC x 6	51		
AC x 4 -> T x 4	38 (15% age <40)		

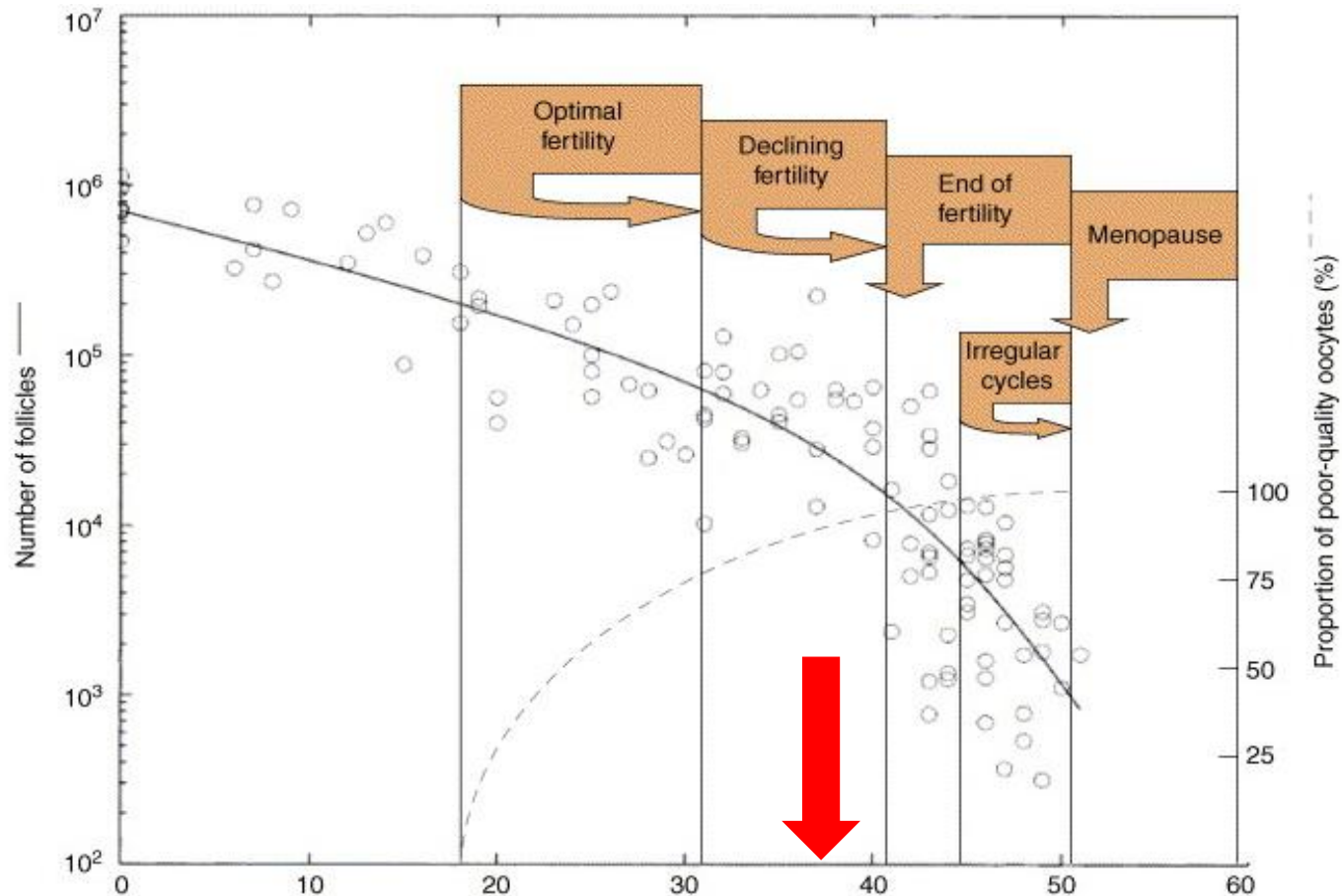
(Goodwin et al., JCO 1999; Burstein, H. J. et al. NEJM 2000; Nabholz et al., ASCO 2002; Parulekar et al., JCO 2005; Fornier et al., Cancer 2005; Petrek et al, JCO 2006)



# Assessing the risk of infertility

Treatment duration (age at pregnancy)

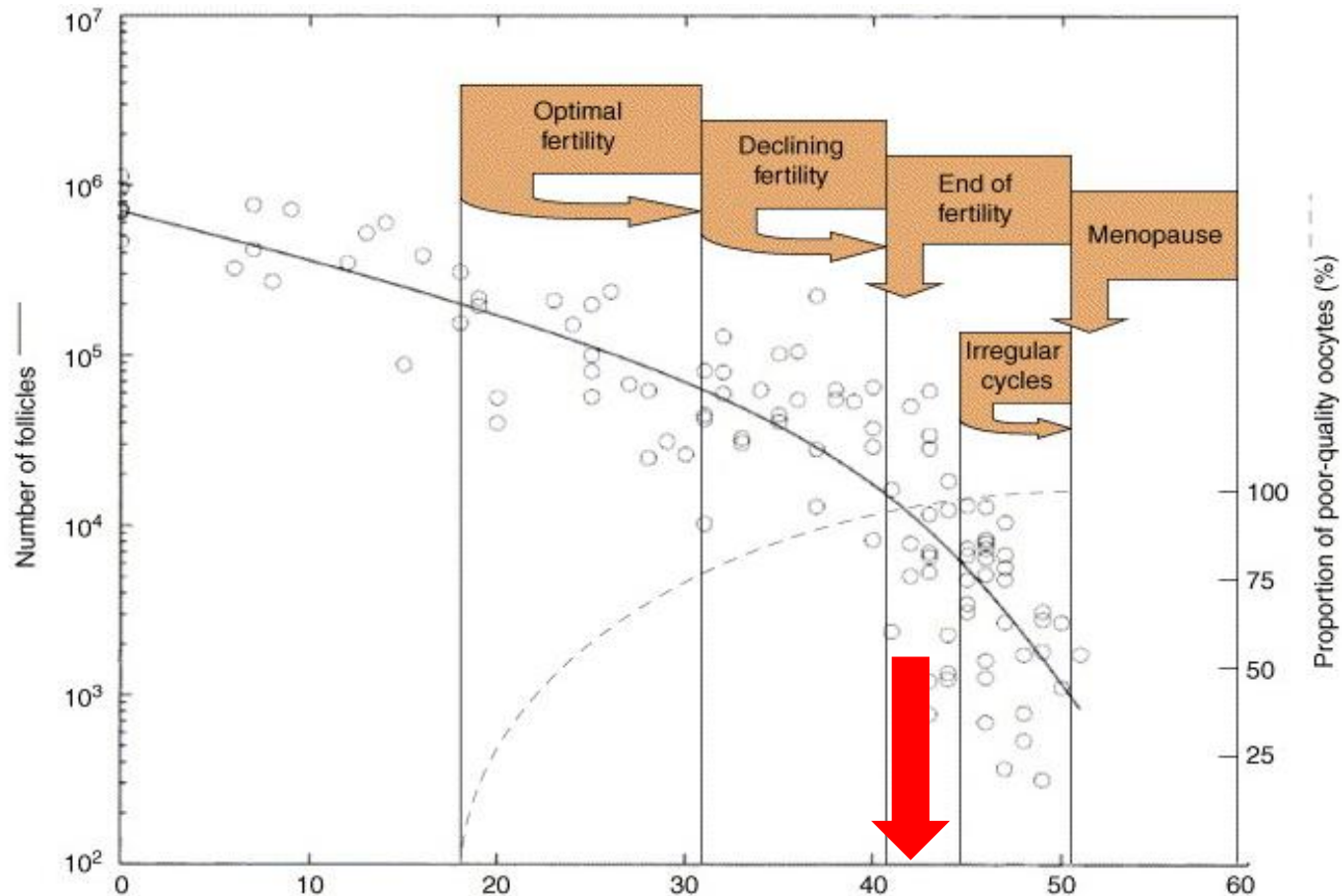
ECx4 -> wPTX x12 -> LHRHa+Exemestane x 5y



# Assessing the risk of infertility

Treatment duration (age at pregnancy)

ECx4 -> wPTX x12 -> LHRHa+Exemestane x 5y



# Is there anything we can do ?

## THINK PROACTIVELY !

- ✓ Inform the patient about the risk of infertility
- ✓ Refer her to the reproductive endocrinologist asap
- ✓ Consider egg/embryo freezing before chemotherapy
- ✓ If you're a believer, offer LHRHa during chemotherapy
- ✓ Discuss temporary interruption of endocrine treatment before Y5

# Inform the patient about the risk of infertility

Young women desiring future fertility should be counselled on available fertility preserving options before starting anticancer treatments. Counselling should be implemented soon after diagnosis, to allow prompt referral to fertility specialists [IV, B]. Age is the most important determinant of chemotherapy or radiotherapy-induced ovarian dysfunction

clinical practice guidelines

*Annals of Oncology* 24 (Supplement 6): vi160–vi170, 2013  
doi:10.1093/annonc/mdt1199  
Published online 27 June 2013

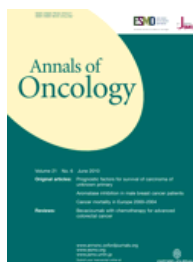
## **Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>**

F. A. Peccatori<sup>1</sup>, H. A. Azim Jr<sup>2</sup>, R. Orecchia<sup>3</sup>, H. J. Hoekstra<sup>4</sup>, N. Pavlidis<sup>5</sup>, V. Kesic<sup>6</sup> & G. Pentheroudakis<sup>5</sup>, on behalf of the ESMO Guidelines Working Group\*

<sup>1</sup>Fertility and Procreation Unit, Division of Gynaecologic Oncology, European Institute of Oncology, Milan, Italy; <sup>2</sup>Department of Medicine, BrEAST Data Centre, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; <sup>3</sup>Department of Radiotherapy, European Institute of Oncology, Milan, Italy; <sup>4</sup>Department of Surgical Oncology, University Medical Centre Groningen, Groningen, The Netherlands; <sup>5</sup>Department of Medical Oncology, University of Ioannina, Ioannina, Greece; <sup>6</sup>Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;

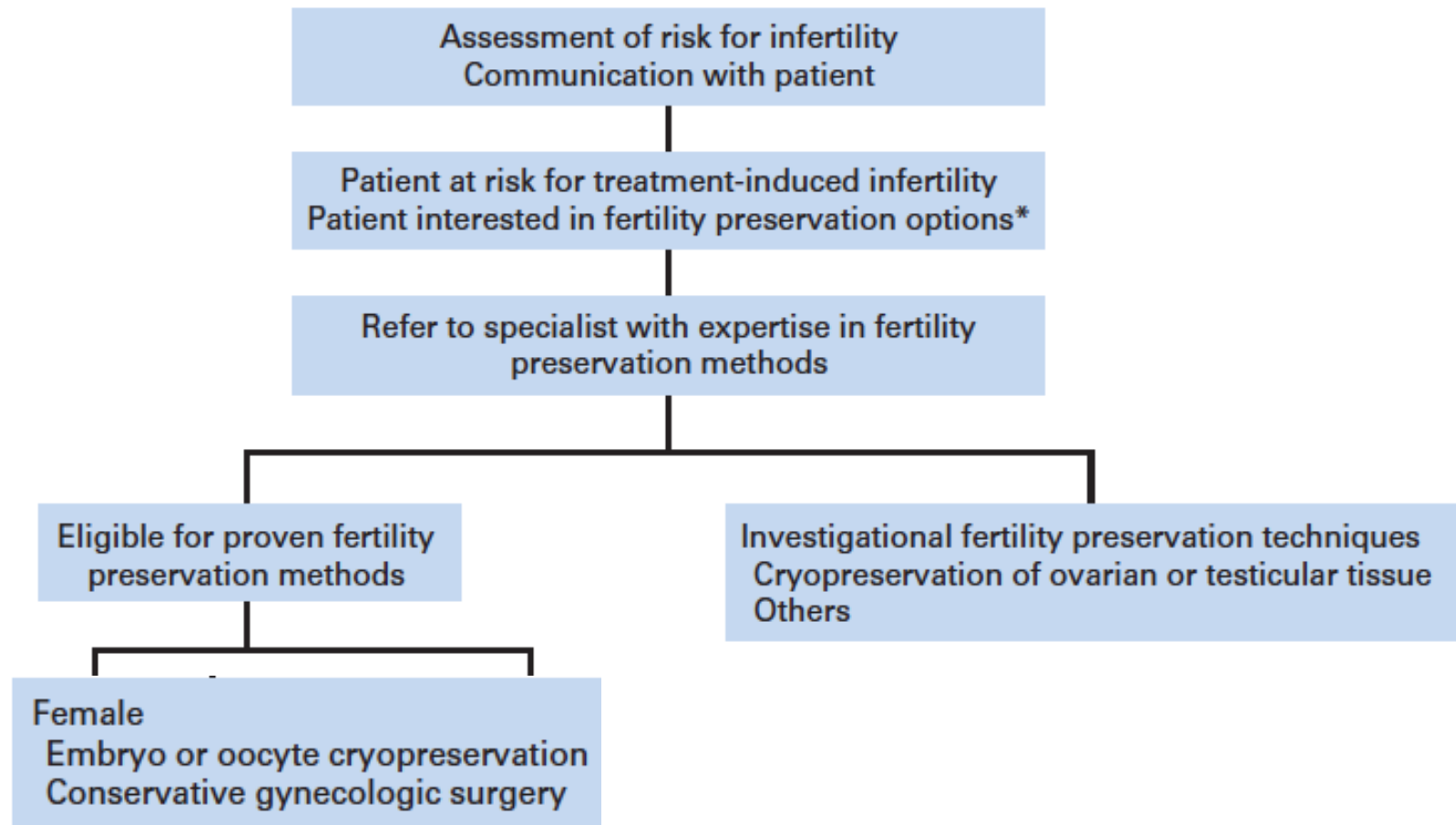
These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

2013





# Inform the patient about the risk of infertility



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

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

2013



# Early referral

VOLUME 28 • NUMBER 31 • NOVEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Value of Early Referral to Fertility Preservation in Young Women With Breast Cancer

Sanghoon Lee, Sinan Ozkavukcu, Elke Heytens, Fred Moy, and Kutluk Oktay

From the Institute for Fertility Preservation, New York Medical College/Westchester Medical Center; Graduate School of Basic Medical Sciences, New York Medical College, Valhalla, NY.

Submitted June 9, 2010; accepted August 10, 2010; published online ahead of print at www.jco.org on September 27, 2010.

Supported by Grant No. HD 053112 (K.O.) from the National Institutes of Health.

Presented in part at the 46th Annual Meeting of the American Society of Clinical Oncology, June 4-8, 2010, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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### A B S T R A C T

#### Purpose

To determine whether early referral to reproductive specialists improves fertility preservation (FP) outcomes and reduces delay in adjuvant treatment in young women with breast cancer.

#### Patients and Methods

A secondary analysis of a prospective database of patients with breast cancer undergoing ovarian stimulation (OS) for FP by oocyte or embryo cryopreservation was performed.

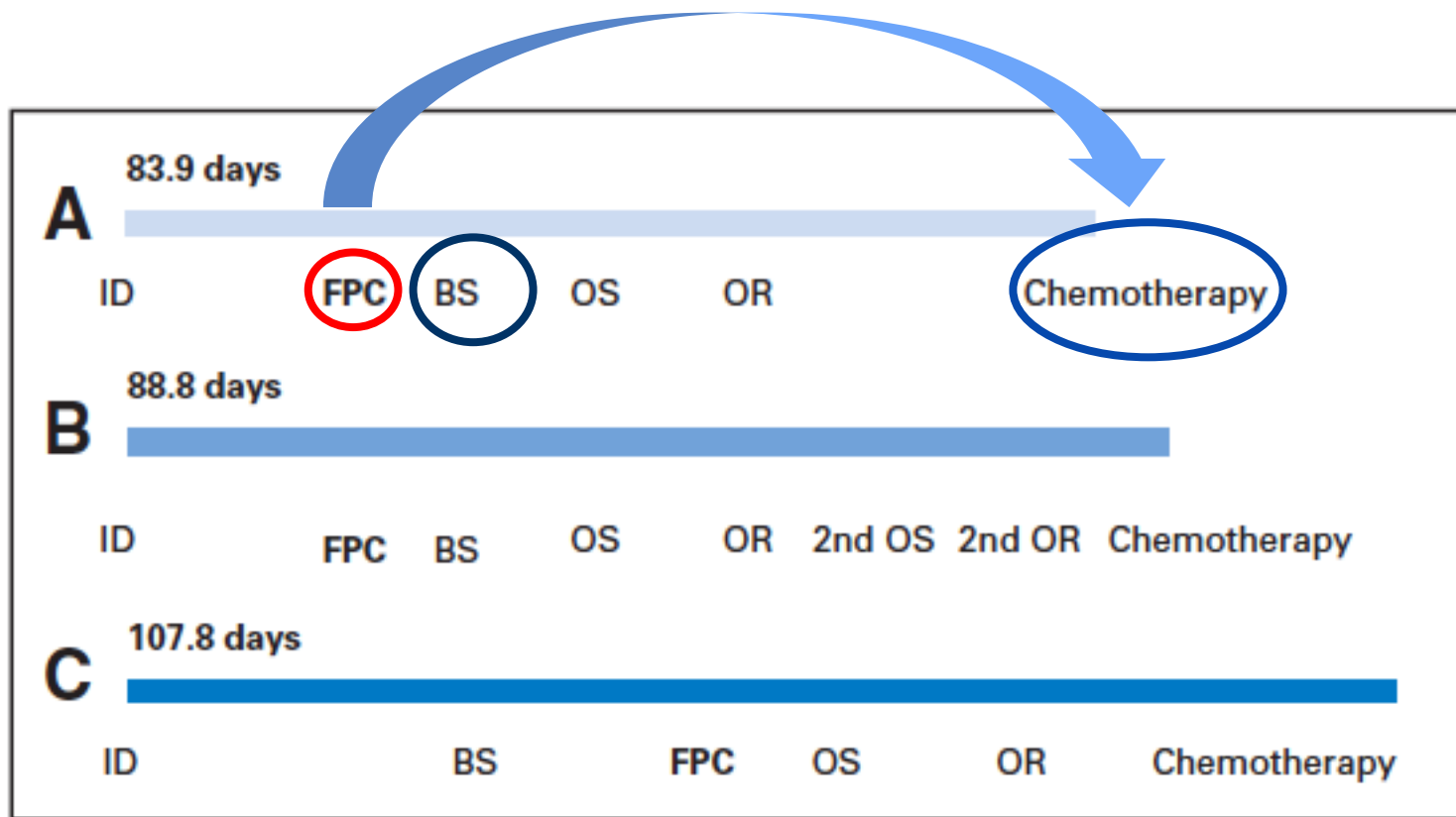
#### Results

Of the 154 patients, 93 met the inclusion criteria (mean age,  $35.2 \pm 4.4$  years). Thirty-five of the 93 patients were referred before breast surgery (PreS), and 58 patients were referred after surgery (PostS). The time periods from initial diagnosis (ID) to initiation of OS ( $42.6 \pm 27.7$  days for PreS v  $71.9 \pm 30.7$  days for PostS;  $P < .001$ ) and from ID to initiation of chemotherapy ( $83.9 \pm 24.3$  days for PreS v  $107.8 \pm 42.9$  days for PostS;  $P = .045$ ) were significantly shorter for the PreS group versus the PostS group. Nine (25.7%) of 35 patients in the PreS group versus one (1.7%) of 58 patients in the PostS group were able to undergo two FP cycles ( $P < .001$ ), resulting in an increased yield of oocytes in the PreS group (18.2% [93 of 511 oocytes] v 0.6% [five of 800 oocytes], respectively;  $P < .001$ ) and embryos (17.2% [40 of 233 embryos] v 0.6% [two of 357 embryos], respectively;  $P < .001$ ). Patients who had an oocyte retrieval within 5 weeks of the surgery were able to complete a second cycle within 9 weeks of the surgery.

#### Conclusion

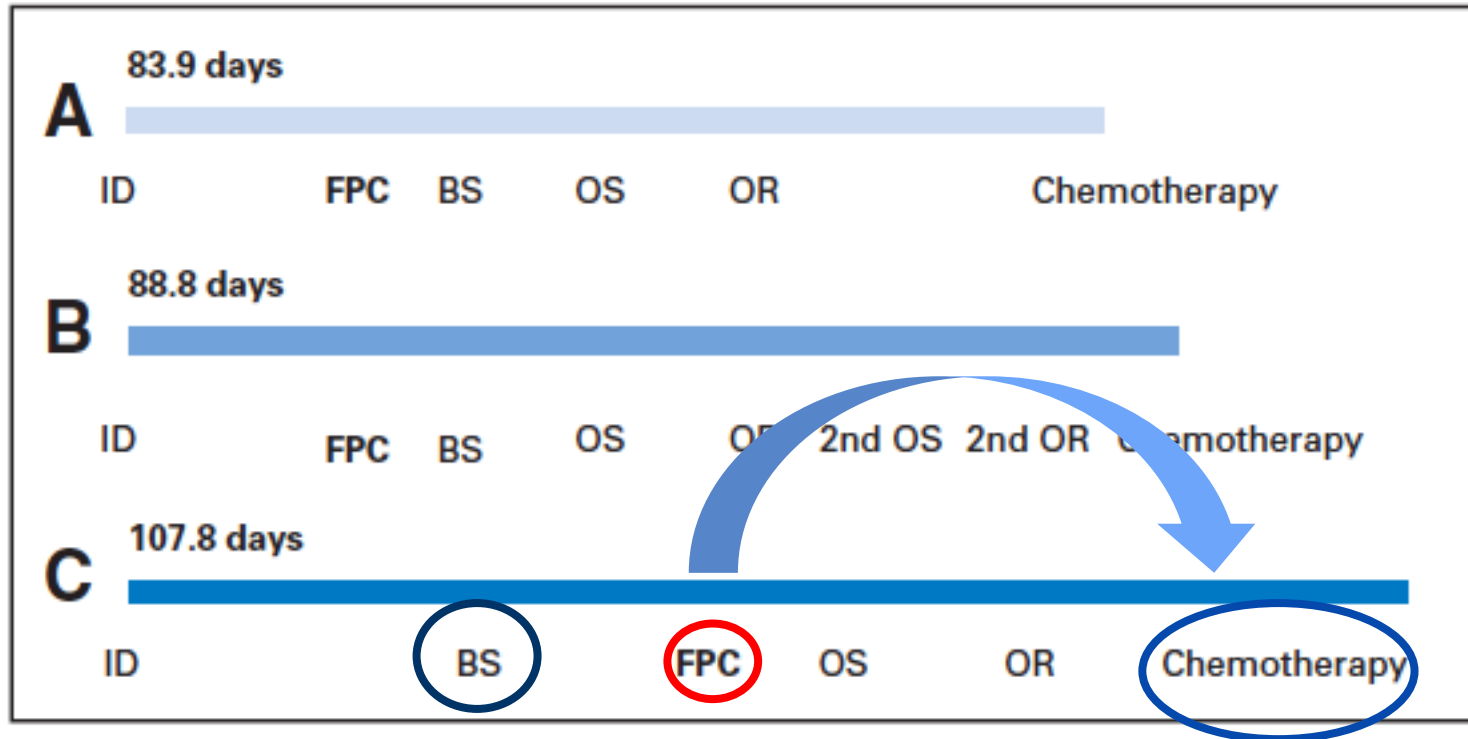
FP referral before breast surgery enables earlier initiation of cryopreservation cycles and chemotherapy and, when appropriate, multiple FP cycles. Women who can undergo multiple cycles may be at advantage for FP because of a larger number of oocytes or embryos cryopreserved. This is the first study demonstrating the benefit of early FP referral in patients with cancer.

# Early referral



ID: initial diagnosis, FPC: fertility preservation counseling  
BS: breast surgery, OS/OR: ovarian stimulation/oocyte retrieval

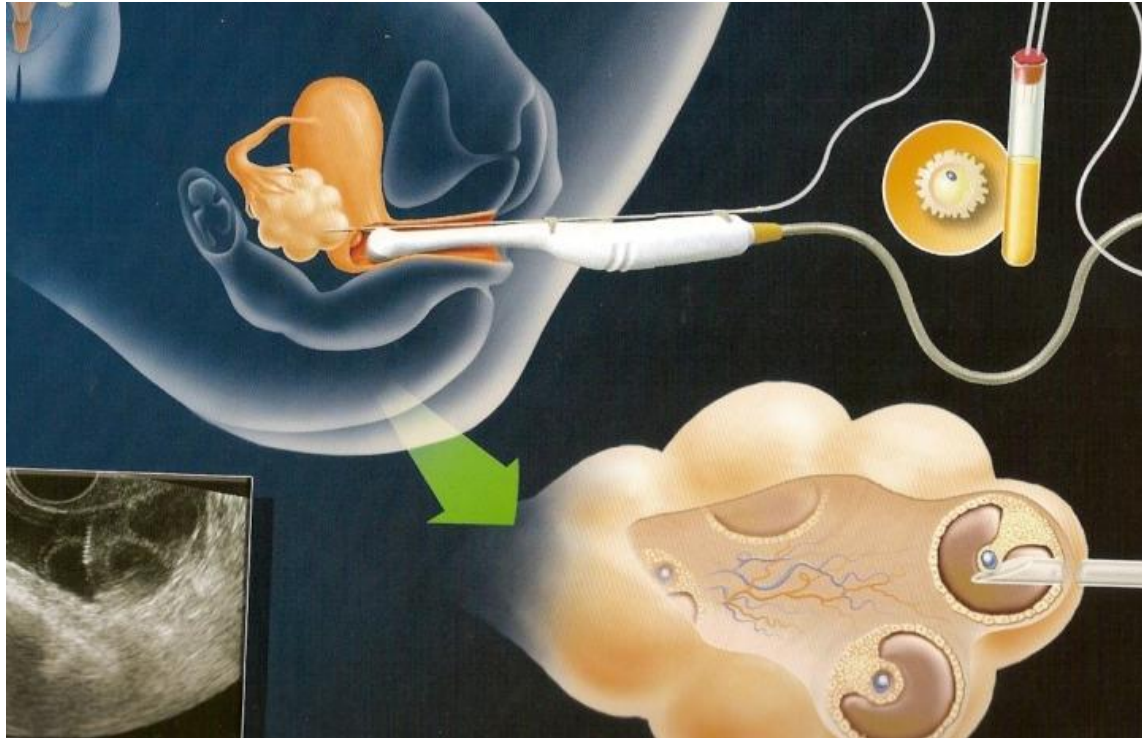
# Early referral



ID: initial diagnosis, FPC: fertility preservation counseling  
BS: breast surgery, OS/OR: ovarian stimulation/oocyte retrieval



# Consider egg/embryo freezing before chemo



Gonadotrophin administration

Oocytes pick up



Oocytes freezing

IVF/ICSI and embryo freezing

# Oocyte cryopreservation

*John K. Jain, M.D., and Richard J. Paulson, M.D.*

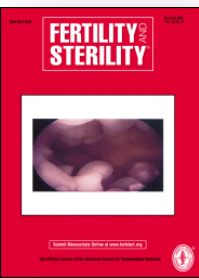
Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Southern California Keck School of Medicine, Los Angeles, California

## Success rates of selected recently reported series using slow-freeze and vitrification methods.

Author (y; reference no.)	Method	Survival rate, n (%)	Fertilization rate, n (%)	No. of oocytes per pregnancy
Fabbri (2001 [35])	Slow-freeze	796/1,502 (53)	632/796 (79)	94
Chen (2005 [36])	Slow-freeze	119/159 (75)	80/119 (67)	23
Boldt (2006 [46])	Slow-freeze (sodium depleted)	218/361 (60)	134/218 (61)	26
Yoon (2003 [56])	Vitrification	325/474 <sup>a</sup> (68.6)	142/198 (71.7)	79
Kuwayama (2005 [58])	Vitrification	58/64 (91)	52/58 (90)	5

<sup>a</sup> Cryopreserved and thawed cumulus–oocyte complexes.

90% vitality and fertilization after thawing  
8-12 frozen oocytes - 30% probability of a baby



# *Oocyte/embryo freezing: pros and cons*

Good reproductive outcome

Limited invasiveness



---

Delay in chemotherapy start (?)

Relatively high estrogen levels (3-7 days)

# Breast cancer and fertility preservation: what can be done (in ER+ tumours) ?

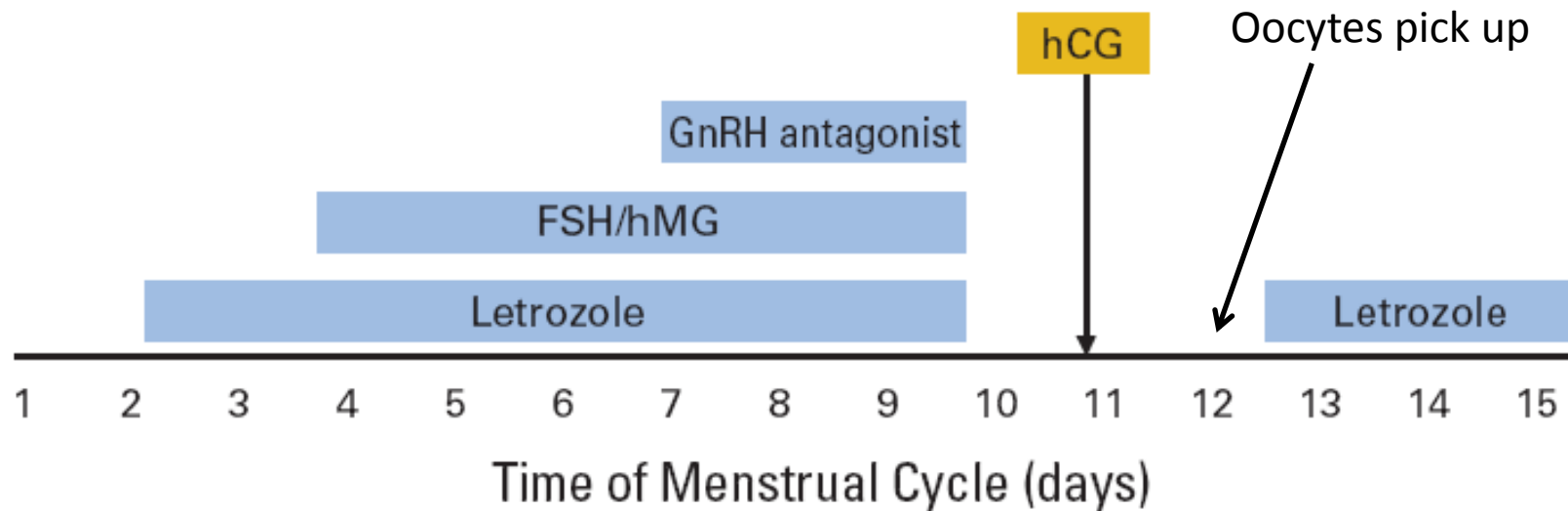
However, concerns about the safety of markedly elevated estrogen levels associated with conventional ovarian stimulation using follicle-stimulating hormone (FSH) have limited enthusiasm for this strategy. Does a relatively brief exposure to high estrogen levels affect risk of recurrence in young women with newly diagnosed early breast cancer?

## Fertility After Breast Cancer: Questions Abound

Ann H. Partridge and Eric P. Winer, *Dana-Farber Cancer Institute and Brigham and Women's Hospital and Harvard Medical School, Boston, MA*



# Controlled ovarian stimulation: Letrozole



**Fig 1.** Protocol for ovarian stimulation with letrozole and gonadotropins in patients diagnosed with breast carcinoma. In this regimen, letrozole is initiated on the second day of menstrual cycle and gonadotropins are started 2 days later. A gonadotropin-releasing hormone (GnRH) antagonist is administered when estradiol levels reach  $\geq 250$  pg/mL or the lead follicle size reaches 14 mm. Human chorionic gonadotropin (hCG) is administered when the leading follicle reaches 19 to 20 mm in diameter. Letrozole treatment is restarted after oocyte retrieval until the estradiol levels are lower than 50 pg/mL. FSH, follicle-stimulating hormone;

## 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

# Controlled ovarian stimulation: Letrozole

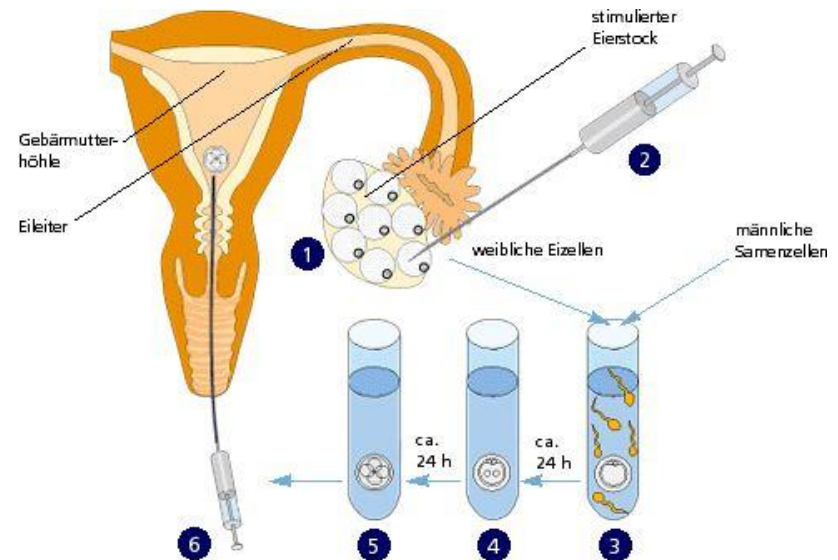
79 patients

Mean age:  $36.1 \pm 3.8$

N-: 62%

ER+: 81%

HER-2+: 26%



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

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# Controlled ovarian stimulation: Letrozole

Peak estradiol levels 58.4-1.166 pg/ml  
(mean  $405.94 \pm 256.64$  pg/ml)

Average number of oocytes retrieved  $10.3 \pm 7.75$

Average number of frozen embryos  $5.97 \pm 4.97$

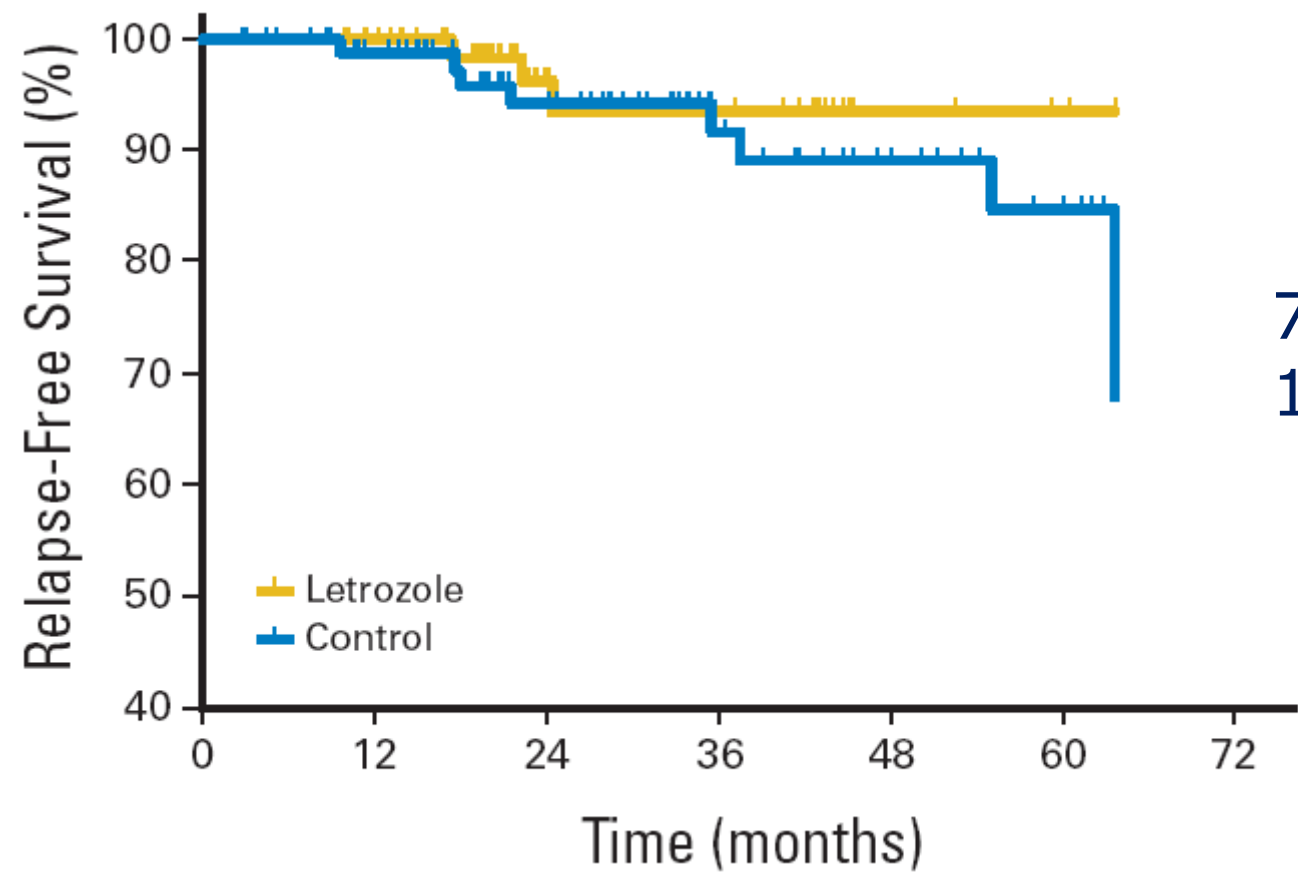
Median time from surgery to systemic Rx 45 d

10 embryo implanted, 5 deliveries.

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*

# Controlled ovarian stimulation: Letrozole



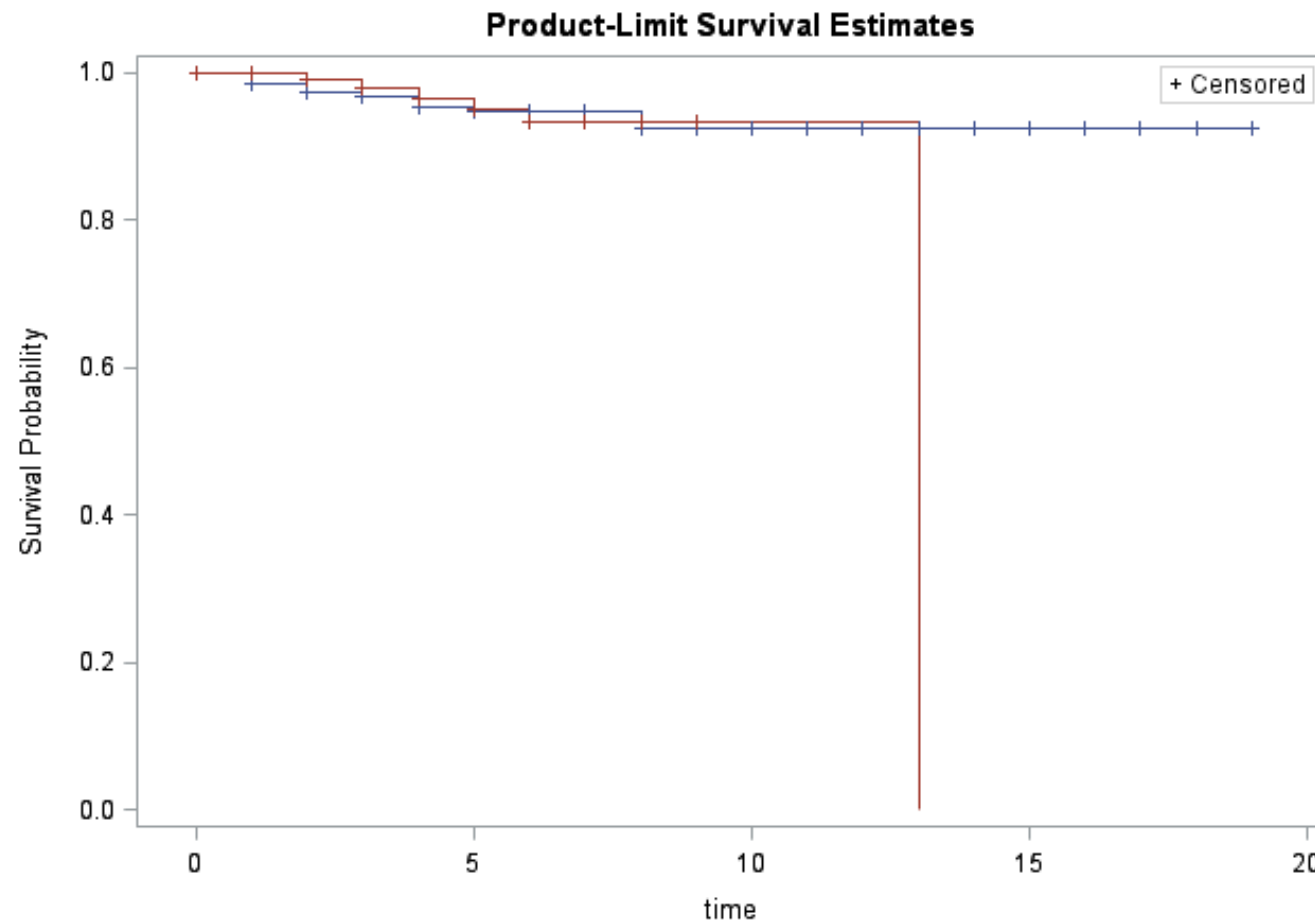
79 letrozole  
136 controls

No. of patients at risk						
Letrozole	79	74	37	18	7	5
Control	136	81	56	38	26	19

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

# Controlled ovarian stimulation: Letrozole



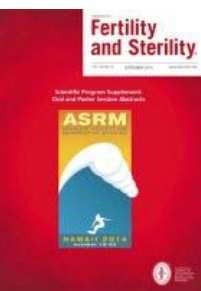
At median FU 5 years (unpublished)

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

## Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies

Dror Meirow, M.D.,<sup>a</sup> Hila Raanani, M.D.,<sup>a</sup> Ettie Maman, M.D.,<sup>a</sup> Shani Paluch-Shimon, M.B., B.S., M.Sc.,<sup>b</sup> Moran Shapira, B.Sc.,<sup>a</sup> Yoram Cohen, M.D.,<sup>a</sup> Irena Kuchuk, M.D.,<sup>b</sup> Ariel Hourvitz, M.D.,<sup>a</sup> Jacob Levron, M.D.,<sup>a</sup> Michal Mozer-Mendel, M.D.,<sup>b</sup> Masha Brengauz, Ph.D.,<sup>a</sup> Hana Biderman, B.Sc.,<sup>a</sup> Daphna Manela, R.N.B.A.,<sup>a</sup> Raphael Catane, M.D.,<sup>b</sup> Jehoshua Dor, M.D.,<sup>a</sup> Raoul Orvieto, M.D.,<sup>a</sup> and Bella Kaufman, M.D.<sup>b</sup>



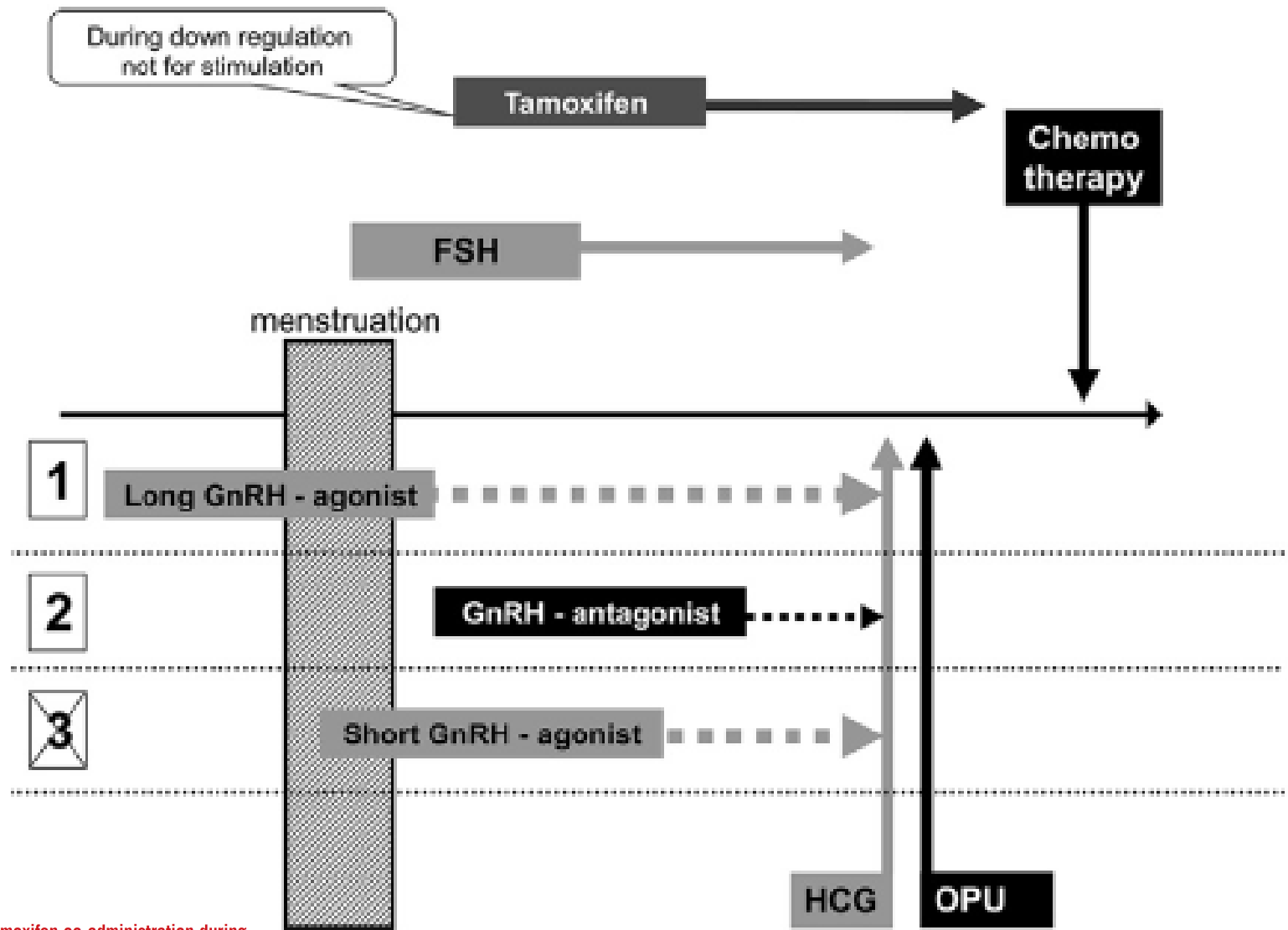
Fertil Steril. 2014 Aug;102(2):488-495.



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# Controlled ovarian stimulation: Tamoxifen



**Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies**

Orsi Mészáros, M.D.,<sup>1</sup> Hiba Barakat, M.D.,<sup>2</sup> Eric Mennin, M.D.,<sup>3</sup> Shari Paley-Shimon, M.B., B.S., M.Sc.,<sup>4</sup> Meera Shetty, B.Sc.,<sup>5</sup> Yoram Cohen, M.D.,<sup>6</sup> Yoram Kupchik, M.D.,<sup>7</sup> David Horowitz, M.D.,<sup>8</sup> Jacob Levron, M.D.,<sup>9</sup> Michael Moser-Mandel, M.D.,<sup>10</sup> Marika Storgaard, Ph.D.,<sup>11</sup> Hans Billeman, B.Sc.,<sup>12</sup> Daphne Mandel, R.N.B.A.,<sup>13</sup> Raphael Cohen, M.D.,<sup>14</sup> Jonathan Orr, M.D.,<sup>15</sup> Pascal Oudinet, M.D.,<sup>16</sup> and Sella Kaufman, M.D.<sup>17</sup>

Fertility and Sterility



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# Controlled ovarian stimulation: Tamoxifen

- 70 patients, 76 cycles
- 48 cycles with TAM, 28 cycles without TAM
- Median age 33.6 y (range: 24-43), 58%=ER+
- No difference in outcome for the 4 groups, with 4.3% late mortality
- Fertility preservation with controlled ovarian stimulation and TAM is safe (and effective !)



**Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies**

David M. Mittleman, M.D.,<sup>1</sup> Hui Bao, M.D.,<sup>2</sup> Eric M. Mittleman, M.D.,<sup>3</sup> Shari Pakuch-Shimron, M.B., B.S., M.Sc.,<sup>4</sup> Meera Shetty, B.Sc.,<sup>5</sup> Yoram Cohen, M.D.,<sup>6</sup> Yoram Kupchik, M.D.,<sup>7</sup> David Horowitz, M.D.,<sup>8</sup> Jacob Levron, M.D.,<sup>9</sup> Michael Mittleman, M.D.,<sup>10</sup> Marika Strogatz, Ph.D.,<sup>11</sup> Hans Billewicz, B.Sc.,<sup>12</sup> Daphna Marmel, R.N.B.A.,<sup>13</sup> Raphael Cohen, M.D.,<sup>14</sup> Jonathan Orr, M.D.,<sup>15</sup> David Oren, M.D.,<sup>16</sup> and David M. Mittleman, M.D.<sup>17</sup>



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# If you're a believer, offer LHRHa during chemo



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## Cancer Treatment Reviews

journal homepage: [www.elsevierhealth.com/journals/ctrv](http://www.elsevierhealth.com/journals/ctrv)



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

Lucia Del Mastro<sup>a,\*</sup>, Marcello Ceppi<sup>b,1</sup>, Francesca Poggio<sup>c,2</sup>, Claudia Bighin<sup>c,3</sup>, Fedro Peccatori<sup>d,4</sup>, Isabelle Demeestere<sup>e,5</sup>, Alessia Levaggi<sup>a,2</sup>, Sara Giraudi<sup>a,6</sup>, Matteo Lambertini<sup>c,2</sup>, Alessia D'Alonzo<sup>a,2</sup>, Giuseppe Canavese<sup>f,7</sup>, Paolo Pronzato<sup>c,8</sup>, Paolo Bruzzi<sup>b,9</sup>

<sup>a</sup> *UO Development of Innovative Therapies, Medical Oncology Department, IRCCS AOU San Martino-IST, National Institute for Cancer Research, Genova, Italy*

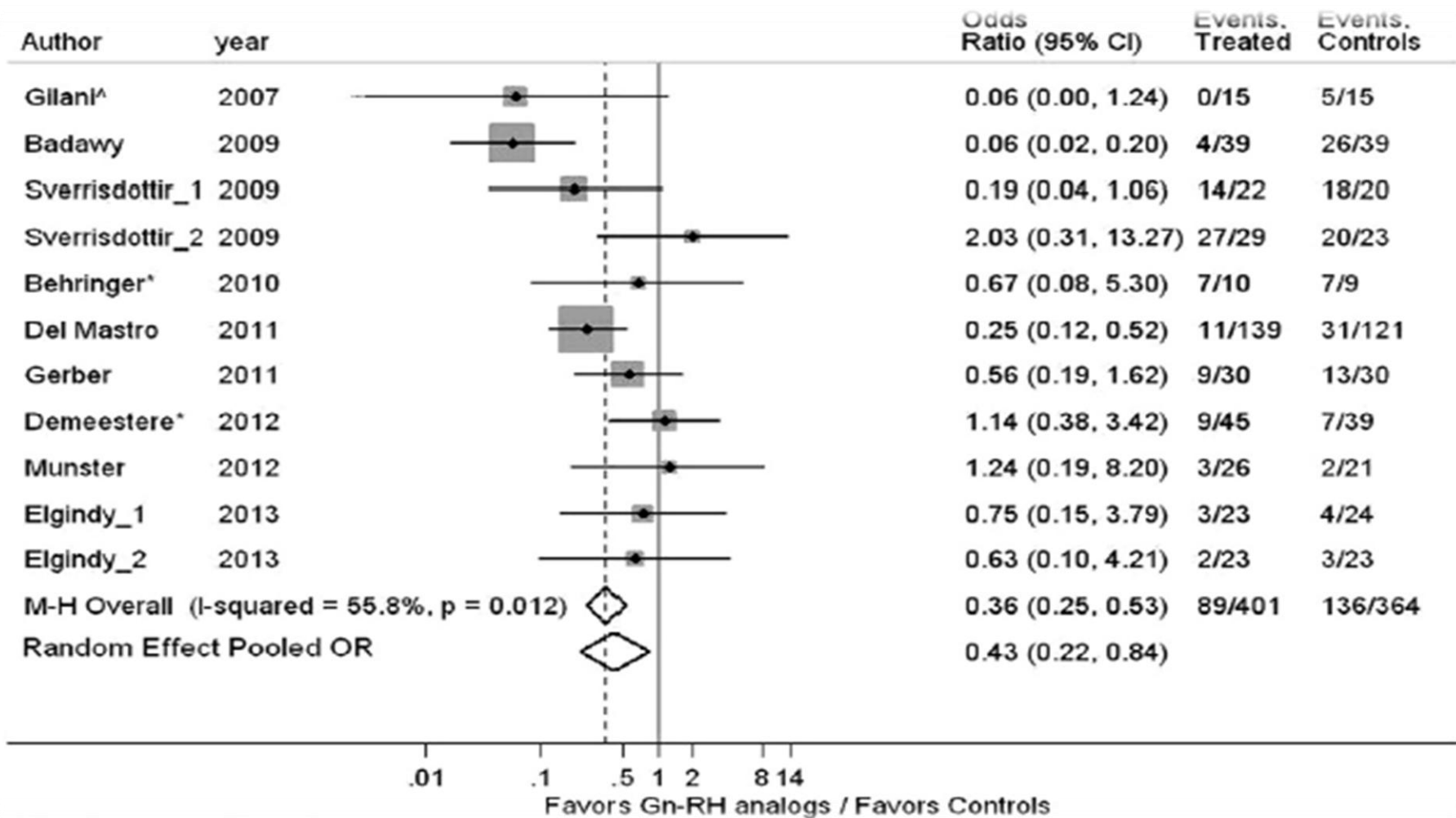
<sup>b</sup> *UO Clinical Epidemiology, IRCCS AOU San Martino-IST, National Institute for Cancer Research, Genova, Italy*

<sup>c</sup> *Medical Oncology A, IRCCS AOU San Martino-IST, National Institute for Cancer Research, Genova, Italy*

<sup>d</sup> *Fertility and Reproduction Unit, Department of Medicine, European Institute of Oncology, Milano, Italy*

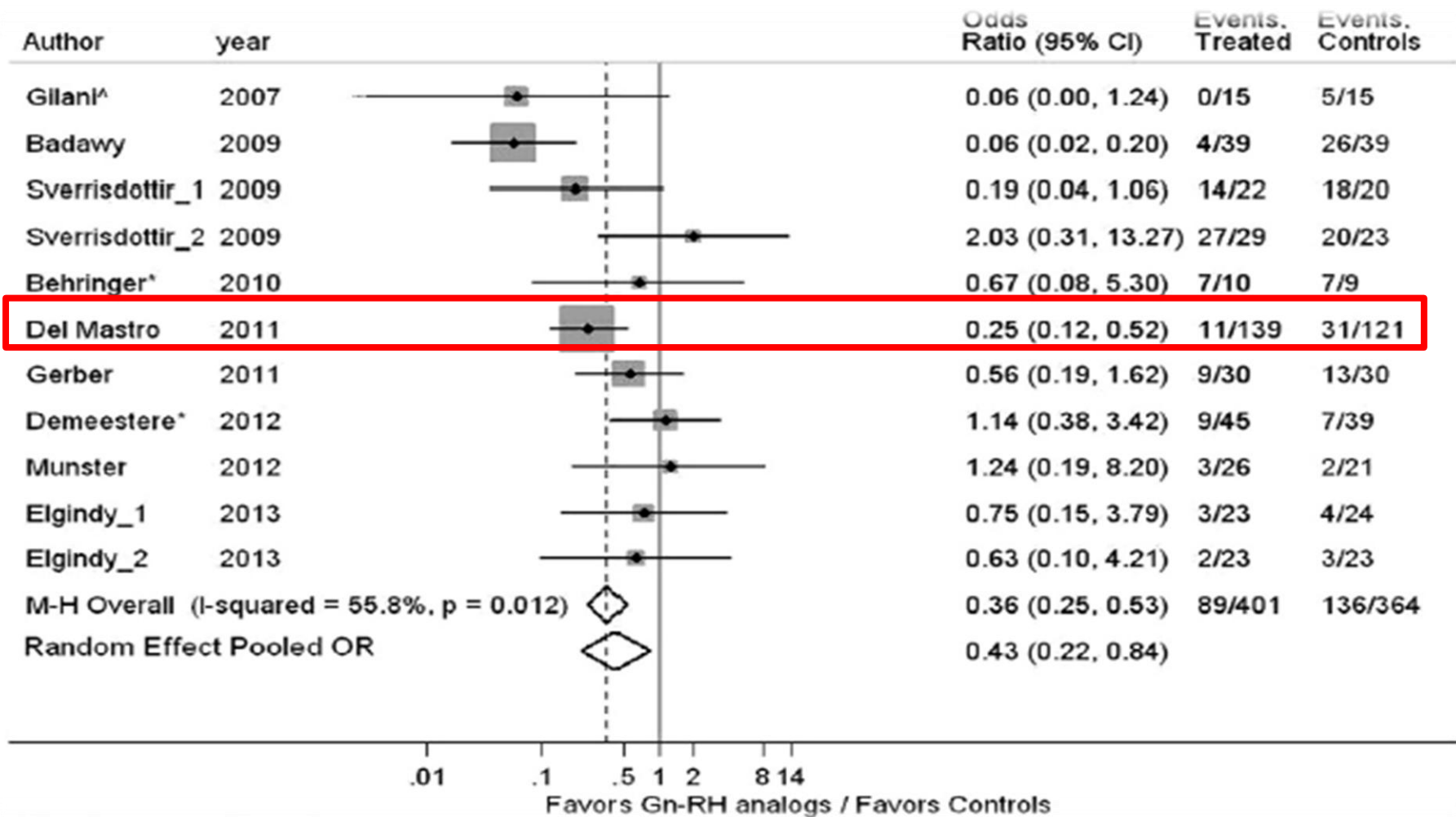
<sup>e</sup> *Research Laboratory on Human Reproduction, Université Libre de Bruxelles, Brussels, Belgium*

<sup>f</sup> *Breast Surgery Unit, IRCCS AOU San Martino-IST, National Institute for Cancer Research, Genova, Italy*



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

Lucia Del Mastro<sup>a,\*</sup>, Marcello Ceppi<sup>b,1</sup>, Francesca Poggio<sup>c,2</sup>, Claudia Bighin<sup>c,3</sup>, Fedro Peccatori<sup>d,4</sup>, Isabelle Demeestere<sup>e,5</sup>, Alessia Levaggi<sup>a,2</sup>, Sara Giraudi<sup>a,6</sup>, Matteo Lambertini<sup>c,2</sup>, Alessia D'Alonzo<sup>a,2</sup>, Giuseppe Canavese<sup>f,7</sup>, Paolo Pronzato<sup>c,8</sup>, Paolo Bruzzi<sup>b,9</sup>



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

Lucia Del Mastro<sup>a,\*</sup>, Marcello Ceppi<sup>b,1</sup>, Francesca Poggio<sup>c,2</sup>, Claudia Bighin<sup>c,3</sup>, Fedro Peccatori<sup>d,4</sup>, Isabelle Demeestere<sup>e,5</sup>, Alessia Levaggi<sup>a,2</sup>, Sara Giraudi<sup>a,6</sup>, Matteo Lambertini<sup>c,2</sup>, Alessia D'Alonzo<sup>a,2</sup>, Giuseppe Canavese<sup>f,7</sup>, Paolo Pronzato<sup>c,8</sup>, Paolo Bruzzi<sup>b,9</sup>



# If you're a believer, offer LHRHa during chemo

## 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 Camucci, 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.

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**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 resump-





# Ovarian function outcome

281 pts

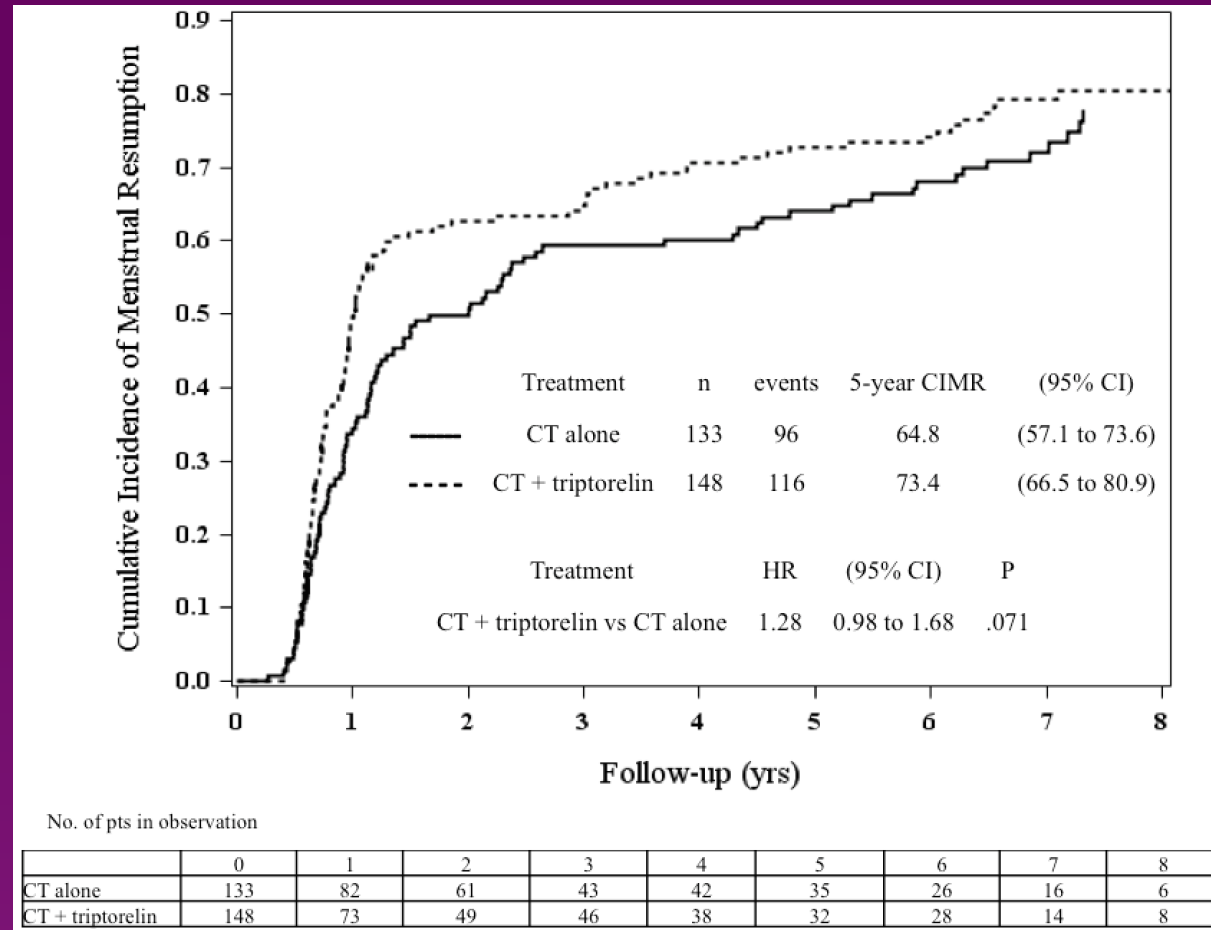
	CT alone N=133	CT + Triptorelin N=148	Absolute difference (95% CI)	P value
No resumption of menses and post-menopausal or unknown levels of FSH and E2, 1 year after the end of CT (primary end-point)	25.9%	8.9%	-17% (from -26 to -7.9)	<.001

Courtesy of L Del Mastro



Del Mastro L, Boni L, Michelotti A et al JAMA 2011

# Current Analysis: Long-term Ovarian Function



The use of LHRH analog increased the probability for menstrual resumption at longer follow-up, although non-statistically significantly

(HR=1.28; 95% CI 0.98-1.68, p=.071)

# Current Analysis: Pregnancies

Median follow up: 7.3 years (6.3 - 8.2 years)

	Chemotherapy alone arm (n=133)	Chemotherapy + triptorelin arm (n=148)
No. pregnancies	3	8
Incidence rate per 100 person-years (range)	0.4 (0.1 – 1.1)	0.9 (0.4 – 1.8)
No. abortions (type)	-	1 (induced abortion) 2 (miscarriages)
No. live births	3	5

The use of LHRH analog increased the probability for becoming pregnant, although non-statistically significantly

(HR=2.56; 95% CI, 0.68 to 9.60, p=.142)

# If you're a believer, offer LHRHa during chemo

## ORIGINAL ARTICLE

### Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

Halle C.F. Moore, M.D., Joseph M. Unger, Ph.D., Kelly-Anne Phillips, M.D., Frances Boyle, M.B., B.S., Ph.D., Erika Hitre, M.D., David Porter, M.D., Prudence A. Francis, M.D., Lori J. Goldstein, M.D., Henry L. Gomez, M.D., Carlos S. Vallejos, M.D., Ann H. Partridge, M.D., M.P.H., Shaker R. Dakhil, M.D., Agustin A. Garcia, M.D., Julie Gralow, M.D., Janine M. Lombard, M.D., John F. Forbes, M.B., B.S., Silvana Martino, D.O., William E. Barlow, Ph.D., Carol J. Fabian, M.D., Lori Minasian, M.D., Frank L. Meyskens, Jr., M.D., Richard D. Gelber, Ph.D., Gabriel N. Hortobagyi, M.D., and Kathy S. Albain, M.D., for the POEMS/S0230 Investigators

## ABSTRACT

#### BACKGROUND

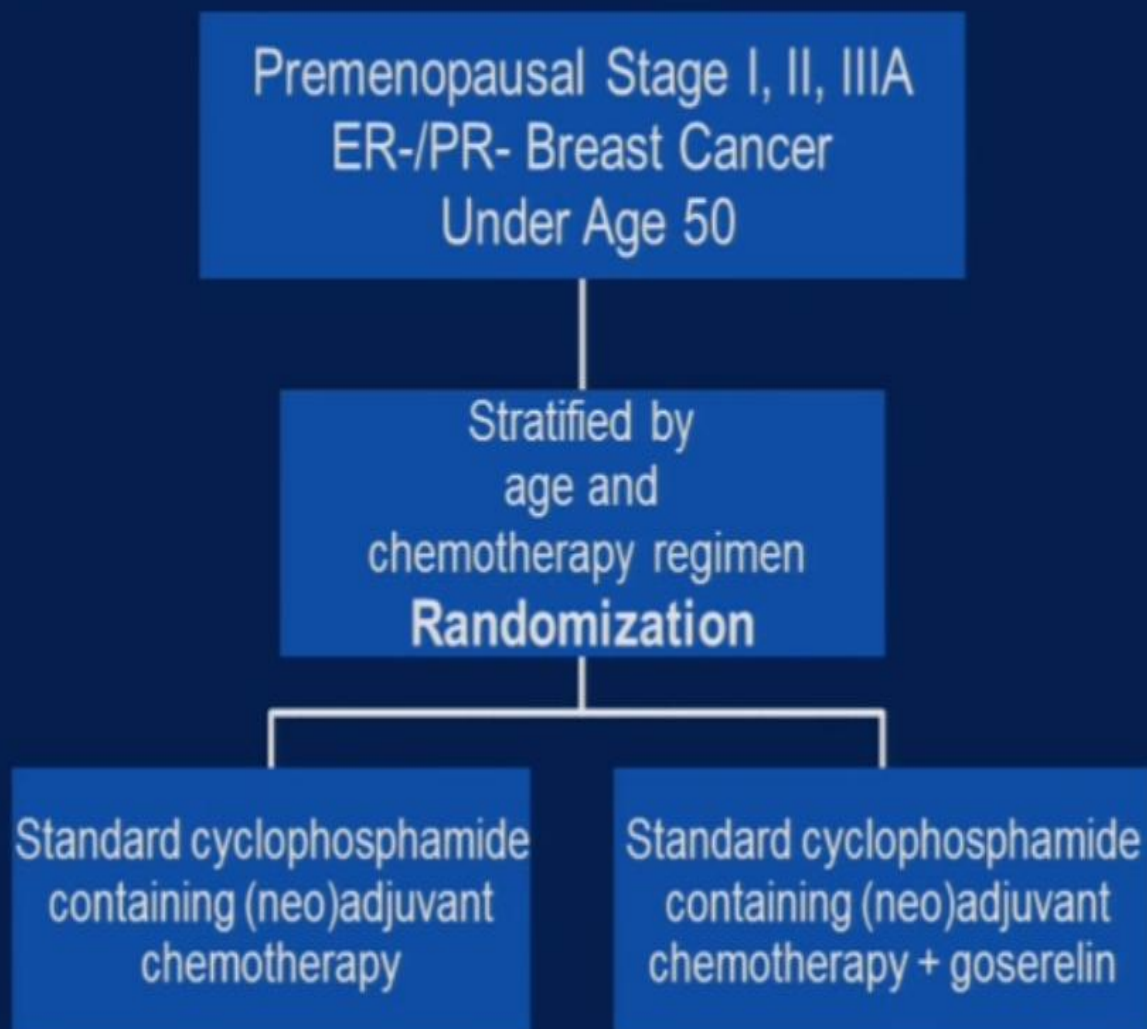
Ovarian failure is a common toxic effect of chemotherapy. Studies of the use of gonadotropin-releasing hormone (GnRH) agonists to protect ovarian function have shown mixed results and lack data on pregnancy outcomes.

#### METHODS

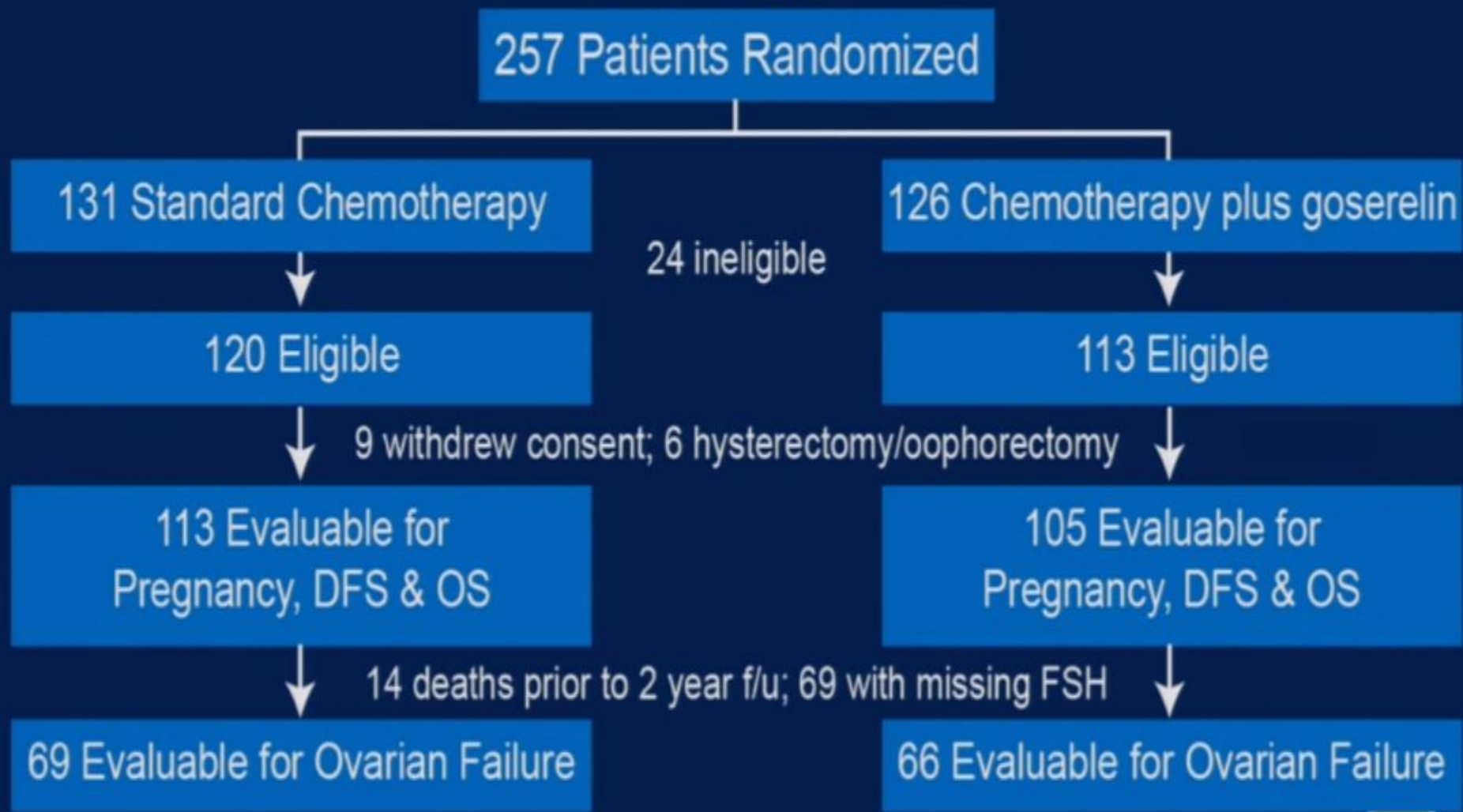
We randomly assigned 257 premenopausal women with operable hormone-receptor-negative breast cancer to receive standard chemotherapy with the GnRH agonist goserelin (goserelin group) or standard chemotherapy without goserelin (chemotherapy-alone group). The primary study end point was the rate of ovarian failure at 2 years, with ovarian failure defined as the absence of menses in the preceding 5 months and levels of follicle-stimulating hormone (FSH) in the postmenopausal



# POEMS/S0230 Schema



# POEMS Consort Diagram





# POEMS Ovarian Failure

	Standard Chemotherapy	Chemotherapy + Goserelin
Ovarian failure at 2 years	15/69 = <b>22%</b>	5/66 = <b>8%</b>

## Logistic Regression Results:

Analysis	Odds Ratio	95% CI	p-value	
			One-sided	Two-sided
Univariate	0.30	0.10 – 0.87	p=.01	p=.03
<b>Stratified*</b>	<b>0.30</b>	<b>0.09 – 0.97</b>	<b>p=.02</b>	<b>p=.04</b>
Multivariate*	0.36	0.11 – 1.14	p=.04	p=.08

\*Accounting for age and regimen through stratification ("Stratified") or covariate ("Multivariate") adjustment, respectively

# POEMS Pregnancy

	Standard Chemotherapy n=113	Chemotherapy + Goserelin n=105	Adjusted OR	Adjusted P-value
Attempted pregnancy	18 (16%)	25 (24%)		p=.12
Achieved pregnancy	12 (11%) <b>66%</b>	22 (21%) <b>88%</b>	2.45	p=.03
Patients with $\geq 1$ delivery	8 (7%)	16 (15%)	2.51	p=.05
Delivery or ongoing pregnancy	10 (9%) <b>55%</b>	19 (18%) <b>76%</b>	2.45	p=.04
Total number of babies	12	18		
Ongoing pregnancies	3	5		
Total adverse events				
Miscarriages	5	4		
Elective termination	3	2		
Delivery complication	2	2		

# If you're a believer... Offer LHRHa during chemo

- Consistent 15% amenorrhea reduction after LHRHa+CT vs CT
- Possible increased pregnancy rates
- Both in ER+ and ER- breast cancer patients

## 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

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Tiziana Scotto, MD

Carlo Vecchio, MD

Marco Venturini, MD

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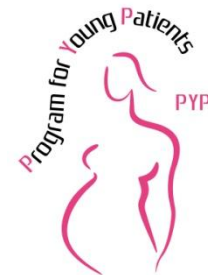
N Engl J Med 2015;372:923-32.

DOI: 10.1056/NEJMoa1413204

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# Discuss temporary interruption of ET



A single-arm, phase II trial evaluating the pregnancy outcomes and safety of interrupting endocrine therapy for young women with endocrine responsive breast cancer who desire pregnancy.

**P**regnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine responsive breast cancer (**POSITIVE**).

Study chair: Olivia Pagani (IBCSG/IOSI)



IBCSG

## TRIAL SCHEMA

- ✓ ER+ early breast cancer
- ✓ <43 years at enrolment
- ✓ Completing 18-30 months of ET
- ✓ (SERMs alone, LH-RH analogue + SERM or AIs)

### Pregnancy desire

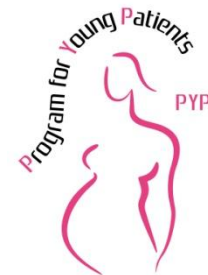
1. Treatment interruption
2. 3 months' wash out
3. 2 years' break to allow:  
conception, delivery  $\pm$   
breast feeding or  
pregnancy failure



Resume ET to 5-10 years  
according to individual risk,  
institutional policy and patient's  
preference



# ENDPOINTS



## Primary:

- Breast cancer free interval (BCFI) defined as the time from enrollment in the phase II trial to BC relapse. BC relapse will be the primary measure of safety being evaluated

## Secondary:

- Pregnancy outcome (i.e. full term pregnancy, abortion, miscarriage, ectopic, stillbirth rates, caesarean section)
- Offspring outcome (i.e. preterm birth, low birth weight, births defects rates)



# CORRELATIVE RESEARCH



## Screening/eligibility:

Patients with **ER+**  
early breast cancer

**≤42 years** at  
enrollment

**Completing 18-30  
months of ET** (SERMs  
alone, GnRH analogue  
+ SERM or AIs) <sup>1</sup>

**Pregnancy desire**

**Stop  
ET <sup>2</sup>**

**E  
N  
R  
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L  
M  
E  
N  
T**

3 months  
wash out

Up to 2 years' break to allow  
conception, delivery ± breast feeding

ET  
resumption  
to complete  
5 (-10) yrs

Follow-up

<sup>1</sup> ± CT

<sup>2</sup> No more than 1 month prior enroll.

Plasma for ctDNA

Serum for  
ovarian function  
(AMH, FSH,E2)  
Serum PRL/TSH  
Transvaginal US  
(Optional AFC)

Serum progesterone  
Plasma for ctDNA  
Transvaginal US  
(AFC optional)

Selected centers:  
Endometrial biopsy

Serum for ovarian  
function (AMH,  
FSH,E2)  
Serum PRL/TSH

3-6 months post ET restart:  
Plasma for ctDNA

2<sup>nd</sup> trimester of pregnancy: Plasma for ctDNA

**Translational  
research**

# Conclusions

- ✓ Chemotherapy may impair ovarian function.  
Age, drug type and dosage are the critical factors
- ✓ Early oncofertility counseling and prompt referral to the reproductive endocrinologist are essential for effective fertility preservation
- ✓ Egg or embryo freezing before chemotherapy +LHRHa administration can be used to improve results
- ✓ Dedicated research protocols for young women with cancer are warranted

# Grazie !

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Carcinoma mammario: quando la donna è giovane  
Negrar, 24 Giugno 2015