

Sessualità e fertilità

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Oncologia Medica A



BREAST CANCER and SEXUALITY(1)

- The experience of breast cancer has effect on quality of life, sexuality and body image
- Common side effects of chemotherapy, radiotherapy, mastectomy and hormone therapy include vaginal irritation and dryness, lowered libido, hair loss, nausea, vomiting, premature menopause and significant psychological disturbances
- Many women feel less attractive and have poor body images than their healthy counterparts
- Fifty percent of women have been shown to experience sexual difficulties following breast cancer treatment

BREAST CANCER and SEXUALITY(2)

-Pretreatment: before treatment sexual desire often decreases because both patient and partners are dealing with concerns about survival

-Treatment: the effects of cancer treatment include lack of desire, pain, and feeling sexually unattractive because of hair loss, loss of a body part, nausea, and weight loss or gain. Women may experience premature menopause, hot flashes and vaginal dryness

BREAST CANCER and SEXUALITY(2)

-Posttreatment: 50% of women continued to experience sexual difficulties they attributed to the breast cancer, such as feeling less sexually attractive, having difficulty becoming sexually aroused, having difficulty with orgasm and lubrication and feeling dissatisfied with their level of sexual activity.

BREAST CANCER and SEXUALITY(3)

Table 3. Percentage of Women Reporting Moderate to Serious Problems in MOS Domain-Specific Sexual Problems, Partner Interest, and Satisfaction

Outcome	Time Point											
	Prediagnosis*			Baseline			Follow-up 1			Follow-up 2		
	No.	%	<i>P</i>	No.	%	<i>P</i>	No.	%	<i>P</i>	No.	%	<i>P</i>
MOS												
Interest	40/209	19		87/208	42	< .0001	62/189	33	< .001	58/190	31	< .01
Arousal	35/205	17		64/196	33	< .0001	35/152	23	< .01	37/165	22	
Relaxation	24/203	12		63/191	33	< .0001	35/152	23	< .001	31/165	19	< .01
Orgasm	17/205	8		43/190	23	< .0001	23/148	16	< .01	28/164	17	< .01
Partner lacks interest	16/204	8		21/193	11		16/174	9		11/181	6	
Percentage reporting not satisfied†	—			29/207	14		30/152	20		30/163	18	

NOTE. *P* values are compared with prediagnosis.

Abbreviation: MOS, Medical Outcomes Study.

*Retrospective reporting of sexual function 6 months prior to diagnosis.

†Percent who reported 1 (not at all) or 2 (a little) satisfied on a 5-point scale of satisfaction.

BREAST CANCER and SEXUALITY(3)

Table 5. Mixed Model Results for Overall Sexual Problems

Variable	β	SE	P
Prediagnosis sexual function	0.43	0.04	< .0001
Physical well being	-.54	0.21	.0099
Social well being	-.83	0.26	.0015
Perceived sexual attractiveness	-6.89	1.02	< .0001
Radiation therapy	-5.67	2.11	.0076
Weeks since surgery*			
No current chemotherapy	0.04	0.12	.6998
Current chemotherapy	-.31	0.11	.0049
Effect of chemotherapy, weeks*			
6	10.90	3.43	.0016
12	8.75	2.73	.0015
18	6.61	2.23	.0032
24	4.47	2.06	.0307
30	2.33	2.30	.3129
36	0.18	2.85	.9491
42	-1.96	3.57	.5833
48	-4.10	4.38	.3490

*Interaction between time and chemotherapy was significant ($P = .0238$).

Dati in Italia

- 2008
 - N. casi donne età 20-84: 121.615
 - Tasso 527/100.000
 - N. casi donne età 20-39: 4.791 (4%)
 - Tasso: 67/100.000
 - Tumori più frequenti
 - Mammella (38%)
 - Tiroide (12%)
 - Melanoma (8%)
 - Cervice uterina (6%)
 - Colon retto (4%)
 - NHL (4%)



Cancro e fertilità nel carcinoma mammario

- Effetto della gravidanza sulla prognosi dopo diagnosi di cancro
- Tecniche di preservazione della fertilità in donne candidate a chemoterapia



Maternità in Italia

- Età media delle donne al parto del 1° figlio:

- 1981, 25 anni
- 1996, 28 anni

- Gravidanza oltre 35 anni

- 1990, 12%
- 1996, 16%

[Sabbadini LL. Gravidanza e parto. ISTAT Apr 2001]

- Si presume che **nel 2025 saranno il 25%**

[Astolfi P et al. Paediatr Perinat Epidemiol. 2002 Jan;16(1):67-72]



Preservazione delle fertilità in donne con carcinoma mammario

- 2008

- N. casi donne età 20-84: 37.947
 - Tasso 165/100.000
- N. casi donne età 20-39: 1.788 (4.7%)
 - Tasso: 25/100.000

Effects of pregnancy on outcome

Full-term pregnancies after breast cancer: 3-8%

Study	No. Pts	Outcome
Blakely Cancer 03	383	No adverse effect on survival
Gelber JCO 01	137	Decreased risk in pregnant w
Velentgas Cancer 99	53	No adverse effect on survival
Kroman Lancet 97	173	Decreased risk in pregnant w
Von Schoultz JCO 95	50	No adverse effect on survival
Sankila Am J Obst Gyn 94	91	No adverse effect on survival
Sutton Cancer 90	23	No adverse effect on survival
Malamos Oncology 96	21	No adverse effect on survival
Ariel Int Surg 89	47	No adverse effect on survival



Pregnancy after breast cancer: population based study

- 2539 women < 45 years with BC in 1982-2000
- 123 (5%) had at least one pregnancy
 - Live birth: 54%
 - 62 (50%) conceived within two years
 - HR of death: 0.59 (95%CI: 0.37-0.95; p=0.030)

Time to pregnancy (months)	Hazard ratio (95% CI)	P value
<6	2.20 (0.14-35.42)	0.579
6-24	0.45 (0.16-1.28)	0.135
>24	0.48 (0.27-0.83)	0.009



Effects of pregnancy on outcome

- Survival after breast cancer does not appear to be affected by pregnancy
- There may be a slight protective effect (?)
- “Healthy mother” bias: women who had pregnancies after breast carcinoma had earlier-stage disease, fewer positive lymph nodes



Pregnancy after treatment of breast cancer

- No evidence that cytotoxic drugs used prior to a pregnancy produce any adverse effects on fetal development
- Increased chance of spontaneous abortions (nearly 25%)
- Interval before attempting conception
 - Pregnancy should be deferred for at least two years after treatment



Pregnancy outcome – Risk of miscarriage

- 53 women with a pregnancy after BC
- Rate of **spontaneous abortion**: **24%**
- Frequency among **controls** (case-control study): **18%**
- Age-adjusted **RR** of miscarriage in the first 20 weeks associated with a history of BC: **1.7** (95% CI: 1.1-2.8)
- Potential explanations
 - Altered hormone profile, due to BC treatment, less able to support a pregnancy
 - Women who develop premenopausal BC may have an underlying higher risk of miscarriage



Interval before attempting conception

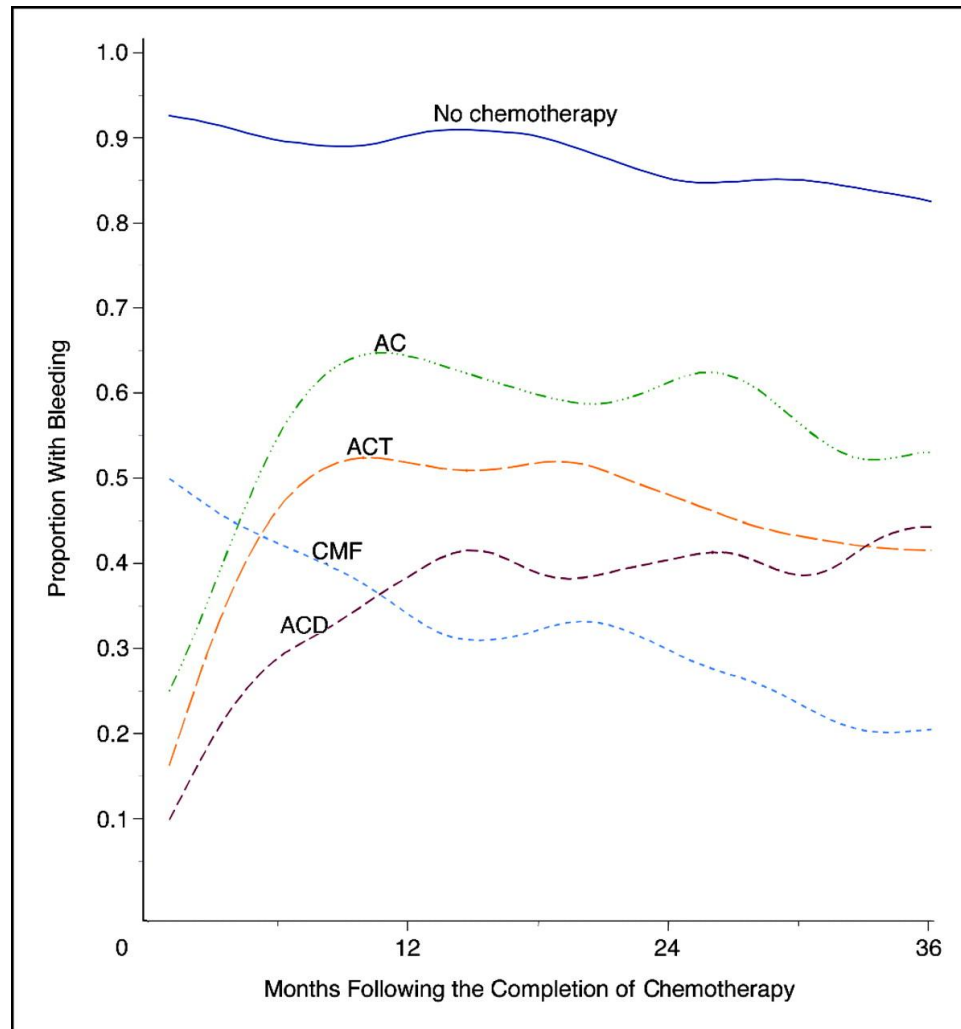
- Decisions about future conception should be **based on the prognosis for the individual woman**. The importance of timing correlates more with breast carcinoma prognosis than with any other effect that pregnancy may have on prognosis
- Pregnancy should be **delayed for at least two years** to differentiate women with a better chance of long-term survival from those with more aggressive disease
- As younger women have lower survival rates, those **< 33 years** might be advised to delay pregnancy for at least **three years**
- Women with **stage III** disease should consider deferring pregnancy for at least **five years**

Incidence of CT induced amenorrhea by regimen

Regimen	% pts developing amenorrhea
CMF x 6 (<i>Bines JCO 96</i>)	20-75
AC x 4 (<i>Bines JCO 96</i>)	34
MF x 6 (<i>Bines JCO 96</i>)	9
CEF x 6 (<i>Venturini JNCI 05; Levine JCO 98</i>)	50-60
FAC x6 (<i>Marty NEJM 05</i>)	51
TAC x 6 (<i>Marty NEJM 05</i>)	61
AC x 4 -> T x4 (<i>Fornier Cancer 05</i>)	15*

* Only <= 40 yrs pts; amenorrhea >= 12 months

Fig 3. Bleeding after chemotherapy by type of regimen



Petrek, J. A. et al. J Clin Oncol; 24:1045-1051 2006



Cancro e gravidanza

- Effetto della gravidanza sulla prognosi dopo diagnosi di cancro
- Tecniche di preservazione della fertilità in donne candidate a chemoterapia



Role of oncologist in advising patients about fertility issue

- Many oncologists either do not discuss the possibility of treatment-related infertility or do so suboptimally
 - At least half of female cancer survivors have no memory of a discussion of fertility at the time of their treatment disposition^{1,2,3,4}
- Raising this issue at the first encounter or at the time of diagnosis may not always be practical or wise. Clinician judgment to choose the timing

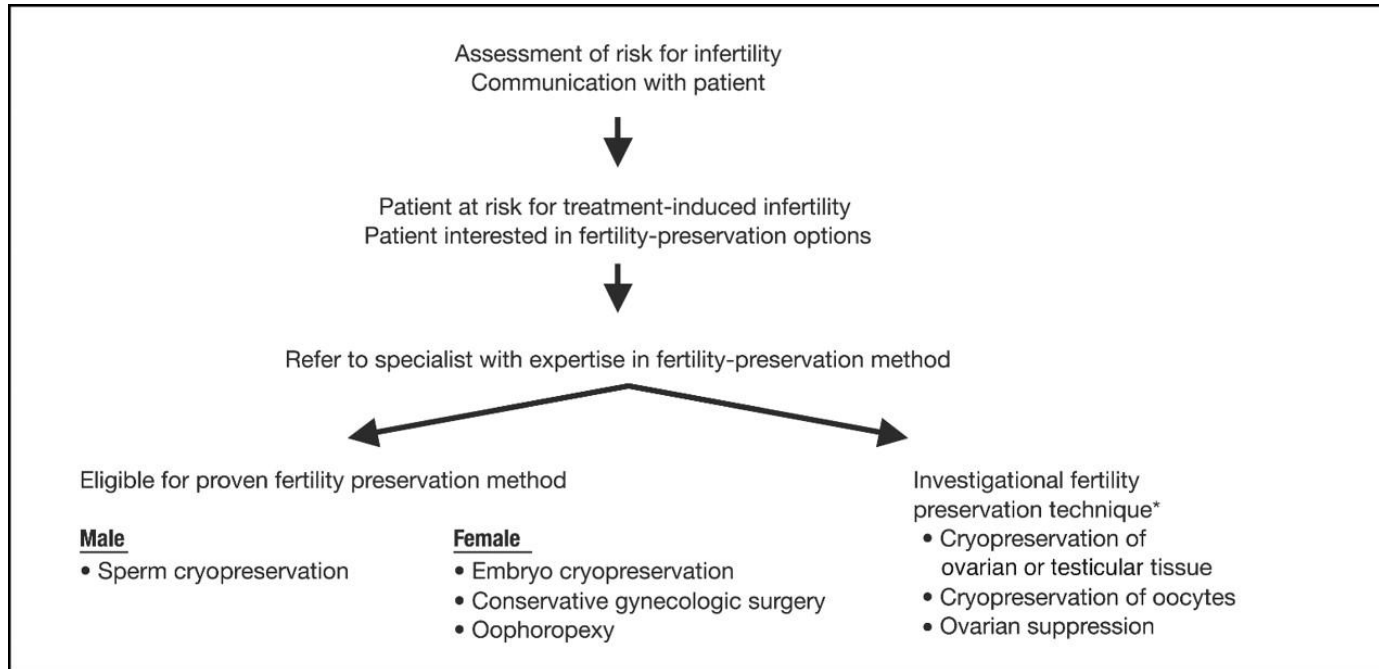


Infertility in female cancer patients

- Infertility: inability to conceive after 1 year of intercourse without contraception
- Increased risk of emotional distress in cancer survivors who become infertile because of their treatment
- Young women with breast cancer may choose a less toxic regimen of CT even if it confers slightly less protection from recurrence¹

1. Partridge JCO 22: 4174-83, 2004

Fig 1. Flow diagram



Lee, S. J. et al. J Clin Oncol; 24:2917-2931 2006

Fertility in young cancer patients

- 4% of people with cancer are under the age of 35 (<http://www.seer.cancer.gov/statfact>)
- The most common cancer diagnosed in people under the age of 40 years:
 - Breast cancer
 - Melanoma
 - Cervical cancer
 - NHL
 - Leukemia

Fertility preservations options in females candidates for RT/S on reproductive organs

Intervention	Definition	Comment	Considerations
Gonadal shielding during RT (S)	Use of shielding to reduce the dose of radiation	Case series	Only possible with selected radiation fields and anatomy
Ovarian transposition (S)	Surgica reposition of ovaries away from the radiation fiels	Large cohort studies; 50% chance of success	Same day outpatient surgical procedure
Trachelectomy (S)	Surgical removal of the cervix while preserving the uterus	Large case series and case reports	Inpatient surgical procedure
Other conservative gynecologic surgery (S/I)	Minimization of normal tissue resection	Large case series and case reports	Expertise may not be widely available

Modified from Lee; JCO 24: 2917-2931, 2006

S= standard; I= investigational

Risk of permanent Amenorrhea in Women treated with Modern Chemotherapy (ASCO rec , JCO 24: 2917-31; 2006)

Degree of Risk	Cancer Treatment
High Risk (> 80%)	CMF, CEF, CAF x 6 cycles in women age 40 and older Haematopoietic stem cell transplantation with Cyclophosphamide/total body irradiation or Cyclophosphamide/Busulfan
Intermediate Risk	CMF, CEF, CAF x 6 cycles in women age 30-39 and older AC x 4 in women age 40 and older
Lower risk (<20%)	ABVD CHOP x 4-6 cycles CVP AML and ALL therapy CMF, CEF, CAF x 6 cycles in women age < 30 AC x 4 in women age < 40
Very low or no risk	Vincristine; Methotrexate; Fluorouracil
Unknown risk (eg)	Taxanes; Oxalipaltin; Irinotecan Monoclonal antibodies (Trastuzumab, Bevacizumab, Cetuximab) TKI (Erlotinib, Imatinib)

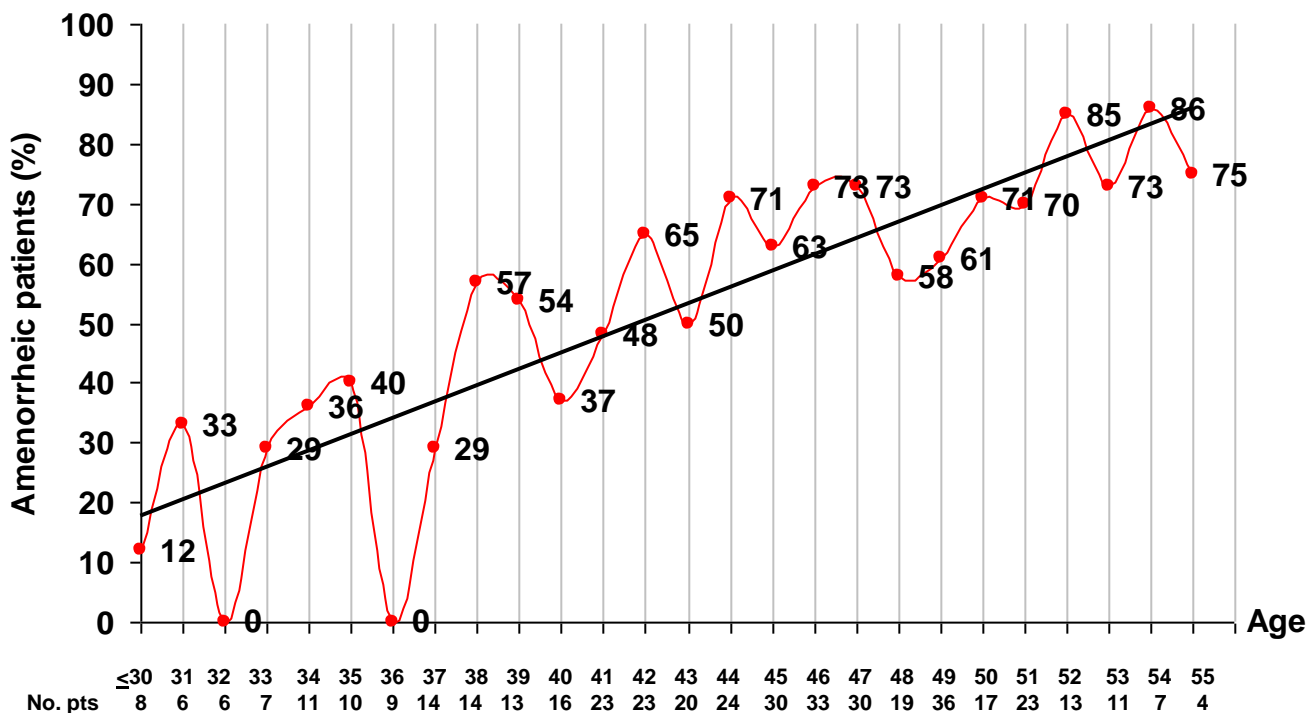


Preservazione delle fertilità in donne con carcinoma mammario

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Incidence of CT-induced amenorrhea among 423 premenopausal pts treated with CEF for 6 cycles

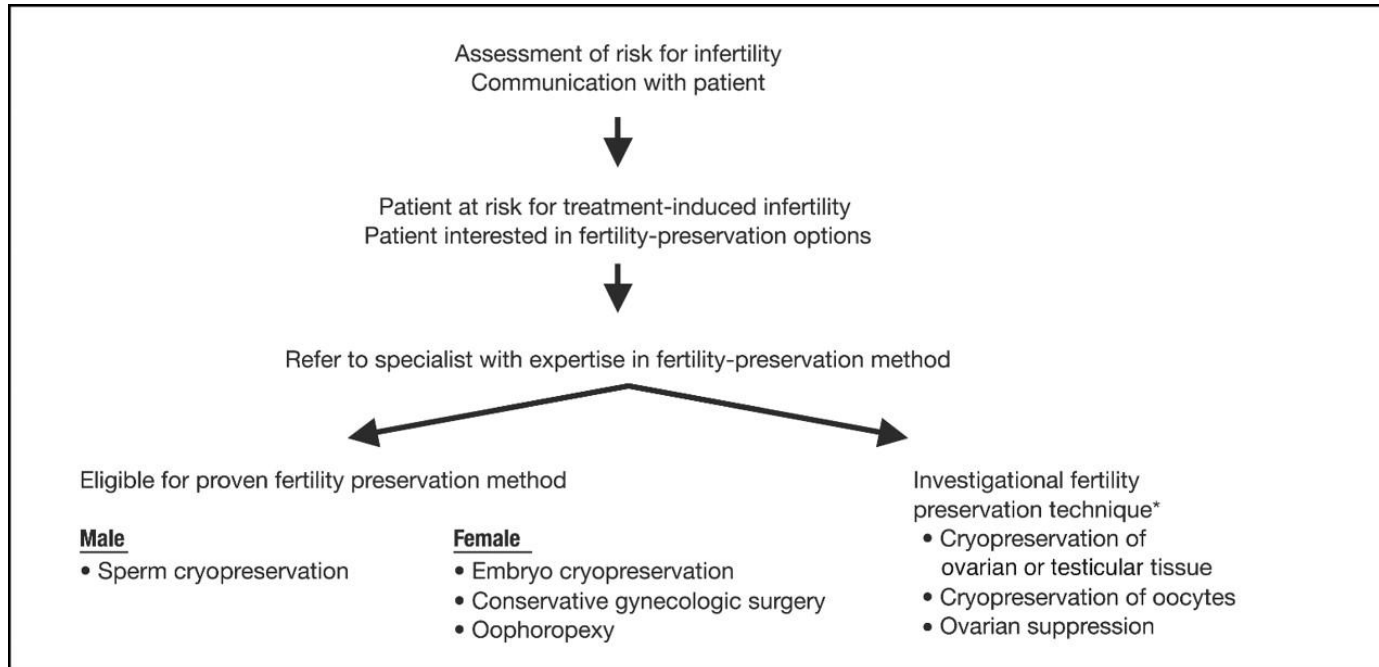


Ovarian function/fertility preservation options in breast cancer patients

Intervention	Definition	Fertility preservation	Preservation of ovarian function
Embryo cryopreservation	Harvesting eggs,IVF, embryo criopreservation	+ ? Small case series	no
Oocyte cryopreservation	Harvesting and freezing of unfertilized eggs	? Small case series, case reports; 2% live birth per thawed oocyte	no
Ovarian cryopreservation and transplantation	Freezing of ovarian tissueand reimplantation	? Only 2 live birth reported	? Limited life span of ovarian tissue
Ovarian suppression with GnRH analogs or antagonists	GnRH given before and during CT to protect ovaries	? Normal pregnancies reported (3-8%)	yes

Modified from Lee; JCO

Fig 1. Flow diagram



Lee, S. J. et al. J Clin Oncol; 24:2917-2931 2006



Embryo cryopreservation. Can it be considered standard in BC patients? Main limits and concerns

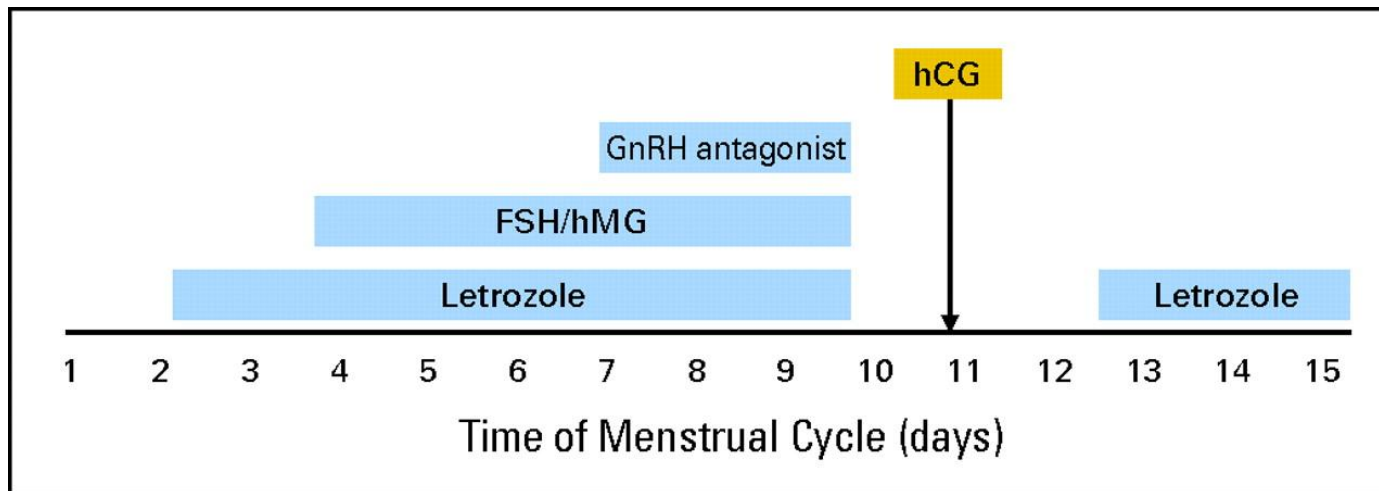
- Limited availability
- Requires partner or donor sperm
- Delay of anticancer treatment (2-6 weeks): 10-14 d of ovarian stimulation from the beginning of menstrual cycle
- Exposure to high estradiol level in HR+ pts
 - Risk of cancer recurrence?? ²

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 pts: controlled ovarian stimulation (COS) with letrozole
- 136 pts: no fertility-preserving strategies -> controls
- Time between surgery and CT longer for IVF pts (45.08 vs 33.46 days, $p < .01$)
- Mean Peak E2 level in COS pts:
 - 405.94 ± 256.64 pg/mL

Fig 1. Protocol for ovarian stimulation with letrozole and gonadotropins in patients diagnosed with breast carcinoma



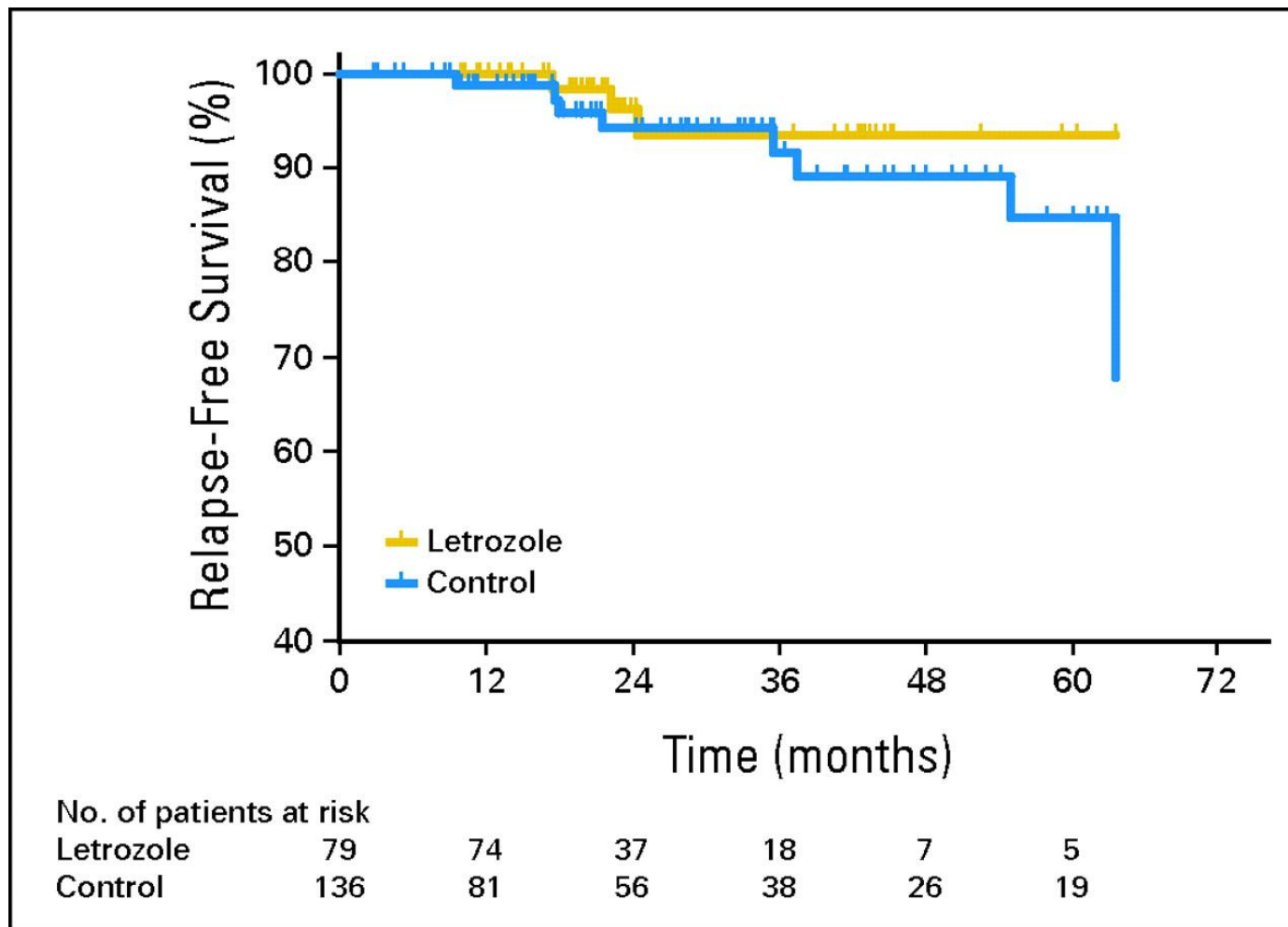
Azim, A. A. et al. J Clin Oncol; 26:2630-2635 2008

Mean oocytes retrieved: 10.3 ± 7.75

Mean oocytes or embryos cryopreserved per patient: 5.97 ± 4.97

No. Deliveries: 5 (3.9%)

Fig 2. Relapse-free survival in ovarian stimulation and control groups




Median FU (months)
 COS group 23.4
 Cntrl group 33.0

Azim, A. A. et al. J Clin Oncol; 26:2630-2635 2008



Safety concerns of ovarian function /fertility preservation options in HR + breast cancer patients

Intervention	Ovarian stimulation required
Embryo cryopreservation	YES
Oocyte cryopreservation	YES
Ovarian cryopreservation and transplantation	NO
Ovarian suppression with GnRH analogs or antagonists	NO



Combining ovarian tissue cryobanking with retrieval of immature oocytes followed by in vitro maturation and vitrification: an additional strategy for fertility preservation

Huang JY, Fertil Steril 2007, Jun 1



Gonadotropin releasing hormone (GnRH) analogs or antagonists

Role in preventing chemotherapy-
induced menopause in breast
cancer patients



Rationale for Gn-RHa use to protect ovarian function

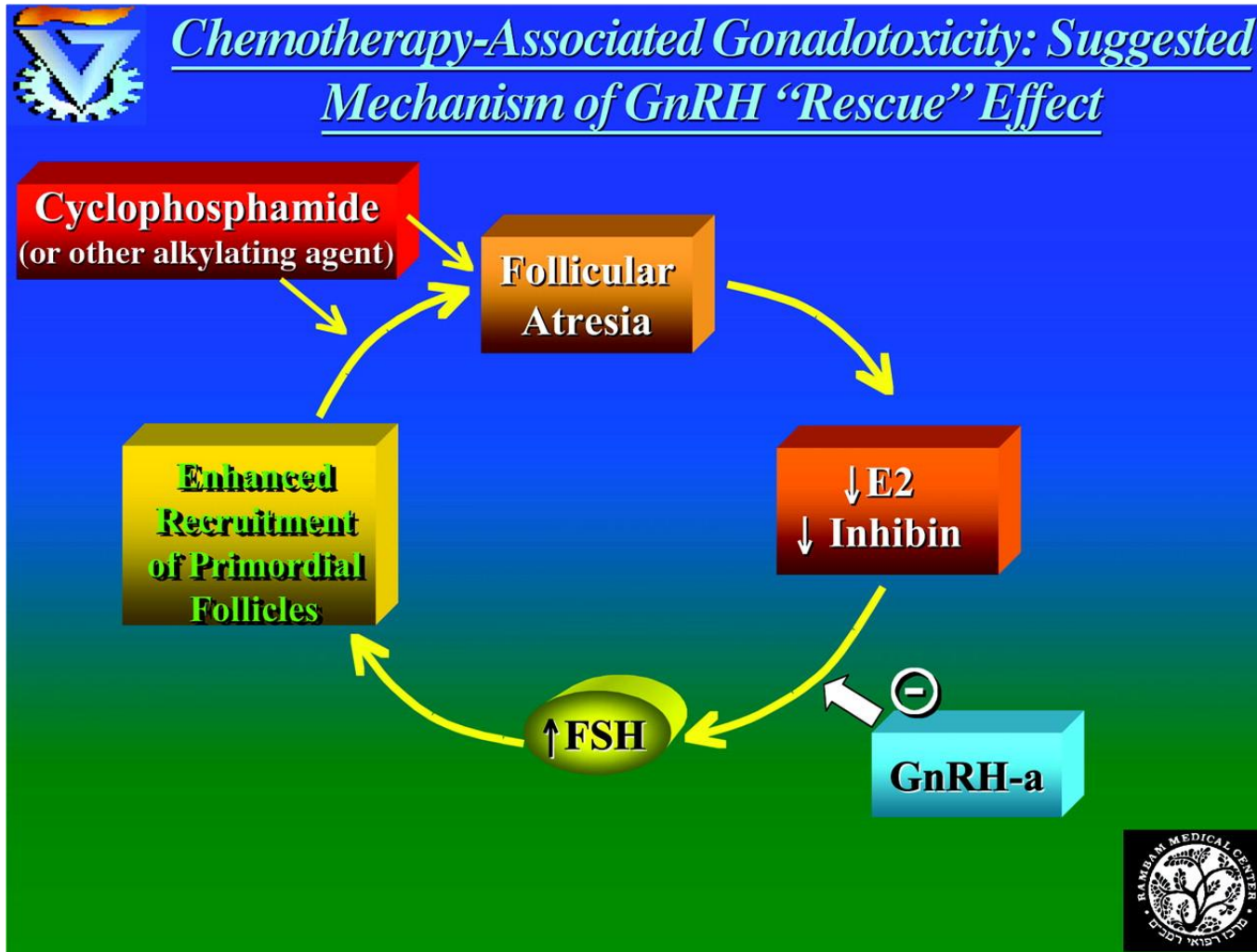
- CT affects more tissues with rapid cellular turn-over
 - A state of induced gonadal inhibition during CT may protect gonads
 - Chronic administration of LH-RHa decreases FSH secretion and suppress gonadal function



Rationale for Gn-RHa use to protect ovarian function

- Results in rats (Ataya, Cancer Res 1985) and rhesus monkeys (Ataya Biol Reprod 1995) showed that LH-RH a reduce the ovarian toxicity of CT

Figure 1. A suggested pathophysiologic mechanism of chemotherapy-induced gonadotoxicity



2. Decrease in utero Ovarian perfusion

3. Activation of GnRH Receptors-> decreased Apoptosis

4. Protection of undifferentiated germ line Stem Cells

Blumenfeld, Z. Oncologist 2007;12:1044-1054



GnRH agonist therapy as ovarian protectants in female patients undergoing chemotherapy: a review of the clinical data

T R. Beck-Fruchter¹, A. Weiss¹ and E. Shalev^{1,2,3}

	Disease	The GnRH agonist used
Waxman <i>et al.</i> (1987)	HL	Buserelin
Pereyra Pacheco <i>et al.</i> (2001)	Hematological oncologic pathology	Leuprolide acetate
Blumenfeld and Eckman (2005)	HL, NHL	Tryptorelin acetate
Franke <i>et al.</i> (2005)	HL	Goserelin acetate
Dann <i>et al.</i> (2005)	NHL-aggressive	Tryptorelin acetate
Somers <i>et al.</i> (2005)	SLE	Leuprolide acetate
Del Mastro <i>et al.</i> (2006)	Breast cancer	Goserelin
Recchia <i>et al.</i> (2006)	breast cancer	Goserelin
Castelo-Branco <i>et al.</i> (2007)	HL	Tryptorelin
Giuseppe <i>et al.</i> (2007)	HL	Tryptorelin
Blumenfeld <i>et al.</i> (2008)	HL	Tryptorelin acetate
Huser <i>et al.</i> (2008)	HL	Tryptorelin

GnRH agonist therapy as ovarian protectants in female patients undergoing chemotherapy: a review of the clinical data

R. Beck-Fruchter¹, A. Weiss¹ and E. Shalev^{1,2,3}

Table IV. Ovarian function in the 12 studies reviewed.

	Preserved Ovarian function <i>N</i> (%)		Amenorrhea/POF <i>N</i> (%)		No. of pregnant patients (No. of pregnancies)	
	Study	Control	Study	Control	Study	Control
Waxman <i>et al.</i> (1987)	4 (50)	3 (33)	4 (50)	6 (66)	0	1
Pereyra Pacheco <i>et al.</i> (2001)	12 (100)	0	0	4 (100)	2 (3)	
Blumenfeld and Eckman (2005)	70 (93)	38 (46)	5 (7)	44 (54)	21 (31)	13 (18)
Franke <i>et al.</i> (2005)	4 (80)		1 (20)		1 (1)	
Dann <i>et al.</i> (2005)	7 (100)	5 (83)	0	1 (17)	5	3
Somers <i>et al.</i> (2005)	19 (95)	14 (70)	1 (5)	6 (30)	7	3
Del Mastro <i>et al.</i> (2006)	27 (97)		1 (3)			
Recchia <i>et al.</i> (2006)	67 (67)				3 (3)	
Giuseppe <i>et al.</i> (2007)	14 (100)	8 (53)	0	7 (47)	0	(2)
Castelo-Branco <i>et al.</i> (2007)	27 (90)		2 (7)	20 (77)	1 (1)	
Blumenfeld <i>et al.</i> (2008)	63 (70)	29 (63)	2 (3)	17 (37)	19 (26)	12 (20)
Huser <i>et al.</i> (2008)			15 (21)	32 (71)		
Total	314 (91)	97 (41)	31 (9)	137 (59)	59	33

POF, premature ovarian failure.

↓
(19%)



Menstrual activity resumption by age

Age	Menstrual activity resumption %
<40 y	94-100
>= 40 y	42-56

CLINICAL ARTICLE

Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study

Ahmed Badawy, M.D.,^a Aboubakr Elnashar, M.D.,^a Mohamed El-Ashry, M.D.,^b and May Shahat, M.D.

Fertil Steril 2008

TABLE 2

Outcome 8 months after therapy.

	Study group (chemotherapy + GnRHa) (n = 39)	Control group (chemotherapy) (n = 39)	P value
Menstruating	35 (89.6%)	13 (33.3%)	< .001 ^a
Ovulating	27 (69.2%)	10 (25.6%)	< .001 ^a
POF	4 (11.4%)	21 (66.6%)	< .001 ^a
Serum FSH (mIU/mL)	8.3 ± 2.10	15.2 ± 5.31	< .009 ^a
Serum LH (mIU/mL)	7.6 ± 2.34	16.3 ± 2.43	< .004 ^a
Serum E ₂ (pg/mL)	279 ± 23.32	75.43 ± 18.98	< .001 ^a
Serum P (ng/mL)	6.3 ± 1.01	3.7 ± 1.21	< .004 ^a

Note: POF = premature ovarian failure.

^aP value < .05 was significant.

Badawy. GnRHa/chemotherapy cotreatment. Fertil Steril 2008.

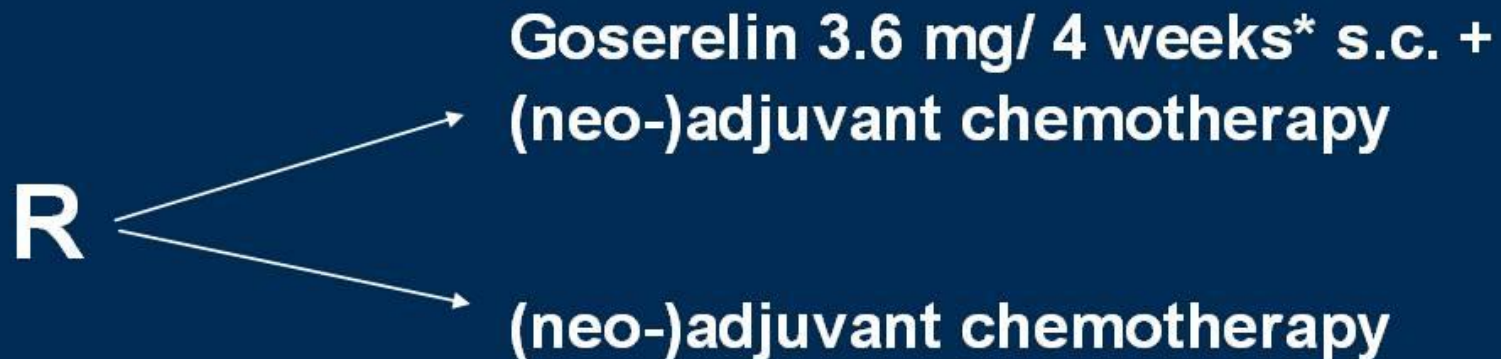
ZORO-Study (Zoladex Rescue of Ovarian Function):

**A prospective randomized multicenter study
to prevent chemotherapy induced ovarian failure
with the GnRH-Agonist Goserelin in young hormone
insensitive breast cancer patients receiving
anthracycline containing (neo-)adjuvant chemotherapy**

**Gerber B, von Minckwitz G, Stehle H, Felberbaum R,
Maass N, Fischer D, Sommer HL, Conrad B,
Mehta K, Loibl S**

on behalf of the German Breast Group

ZORO Study Design



*** Anthracycline/taxane containing chemotherapy; goserelin starting at least 2 weeks before chemotherapy, then every 4 weeks (28 ± 3 days) until the end of the last chemotherapy cycle (EOC)**

Objectives

Primary objective:

Ovarian function at 6 months after EOC, defined as 2 consecutive menstrual periods within 21-35 days during a time frame of 5-8 months after last application of Goserelin.

Secondary objectives:

- time to recovery of regular menstrual period
- ovarian function at 0, 6, 12, 18 and 24 months by menstruation and endocrine function (estradiol, progesterone, FSH, LH, SHBG)
- pregnancy rate
- treatment compliance, toxicity, quality of life
- menopausal symptoms score

Baseline Characteristics

		Goserelin		Observation	
		n	%	n	%
Age [year]	Median (range)	35.0 (26-44)		38.5 (29-47)	
ER & PR	Negative	30	100.0	30	100.0
Premenopausal		30	100.0	30	100.0
Grade	II	8	27.6	6	20.7
	III	21	72.4	23	79.3
Lymph Node Status	negativ	19	65.5	15	57.7
	positiv	10	34.5	11	42.3

Results

- Recruitment period: 03/2005 – 08/2007
- 63 patients recruited
- 60 treated: 30 each arm

Chemotherapy:

n= 28 FEC/FAC

n= 13 TAC

n= 10 FEC - Doc

n= 9 EC - Doc

Patients with Regular Menses after End of Chemotherapy (EOC)

	Goserelin	Observation	p-value
Time after EOC			
around month 6 (5-8) (primary endpoint)	21 (70.0%)	17 (56.7%)	0.4219
at 12 months	4	7	
at 18 months	2	2	
at 24 months	1	2	
> 24 months	0	1	
Missing	2	1	

Is this Definitive?

- Well designed study, first randomized data
 - No data on fertility, ovarian reserve (difficult to measure)
 - ‘Modern’ chemotherapy regimens
- Preservation of fertility remains an important issue for many patients with breast cancer BUT
 - Use of GnRH agonists cannot be recommended for routine use in this setting without further data to suggest benefit
 - Theoretical disadvantage in HR+ disease
 - SWOG 0230: 173/478 pts accrued with HR neg early stage BC randomized to goserelin or not with adjuvant chemotherapy
 - Primary endpoint ovarian failure 2 yrs after starting chemotherapy

Promise-GIM6 Study Design

**Pts with stage I-II-III breast cancer candidate for CT
ER+ or ER-**



RANDOM



CT alone



CT + LH-RHa

No. Planned pts: 280

No. Enrolled pts: 282 (Jan 2008)



Conclusions

- All ovarian function/fertility preservation options for BC patients should be considered experimental
- Safety concerns arise for options (embryo/oocyte cryopreservation) requiring ovarian stimulation in HR+ patients and/or cancer treatment delay
- Immature oocyte retrieval and in-vitro maturation followed by embryo cryopreservation or oocyte vitrification may be a new strategy avoiding ovarian stimulation and cancer treatment delay
- GnRHa strategy is a promising approach to prevent CT-induced ovarian failure and ongoing phase III studies will give definitive evidence of its role
- Cryopreservation options and GnRHa strategy are not mutually exclusive. In the future combining the various modalities may increase the odds of ovarian function/fertility preservation in young breast cancer patients.



Mullan F. Seasons of survival: reflections of a physician with cancer. *NEJM* 313:270-3, 1985

- “The challenge in overcoming cancer is not only to find therapies that will prevent or arrest the disease quickly, but also to map the middle ground of survivorship and minimize medical and social hazards”