DANA-FARBER CANCER INSTITUTE

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HARVARD MEDICAL SCHOOL

Fertility Preservation for Early Breast Cancer: Medical Oncologist's Perspectives

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LIVESTRONG SURVIVORSHIP CENTER OF EXCELLENCE NETWORK

Fertility Preservation in Breast Cancer

- Why is this important?
- Who is at risk?
- What are options for fertility preservation?
- What are the risks?
- How can we help our patients?

Why is this important?

Breast Cancer in Younger Women: Reproductive and Late Health Effects of Treatment

- 577 women ages 25-51 at diagnosis (N=42 age 25-34; N=93 age 35-40)
- Surveyed ~ 6 years later
- Majority of women pre- or peri-menopausal at diagnosis
- Majority received adjuvant therapy

(Ganz et al., JCO, 2003)

Reproductive and Late Health Effects of Treatment (2)

- Overall, high levels of physical functioning
- However, social and emotional functioning, and vitality were lowest in the youngest women
- More depression symptoms, more negative affect in youngest women

(Ganz et al., JCO, 2003)

Reproductive and Late Health Effects of Treatment (3)

- Experience of menopausal transition with treatment was associated with lower mental health among youngest women

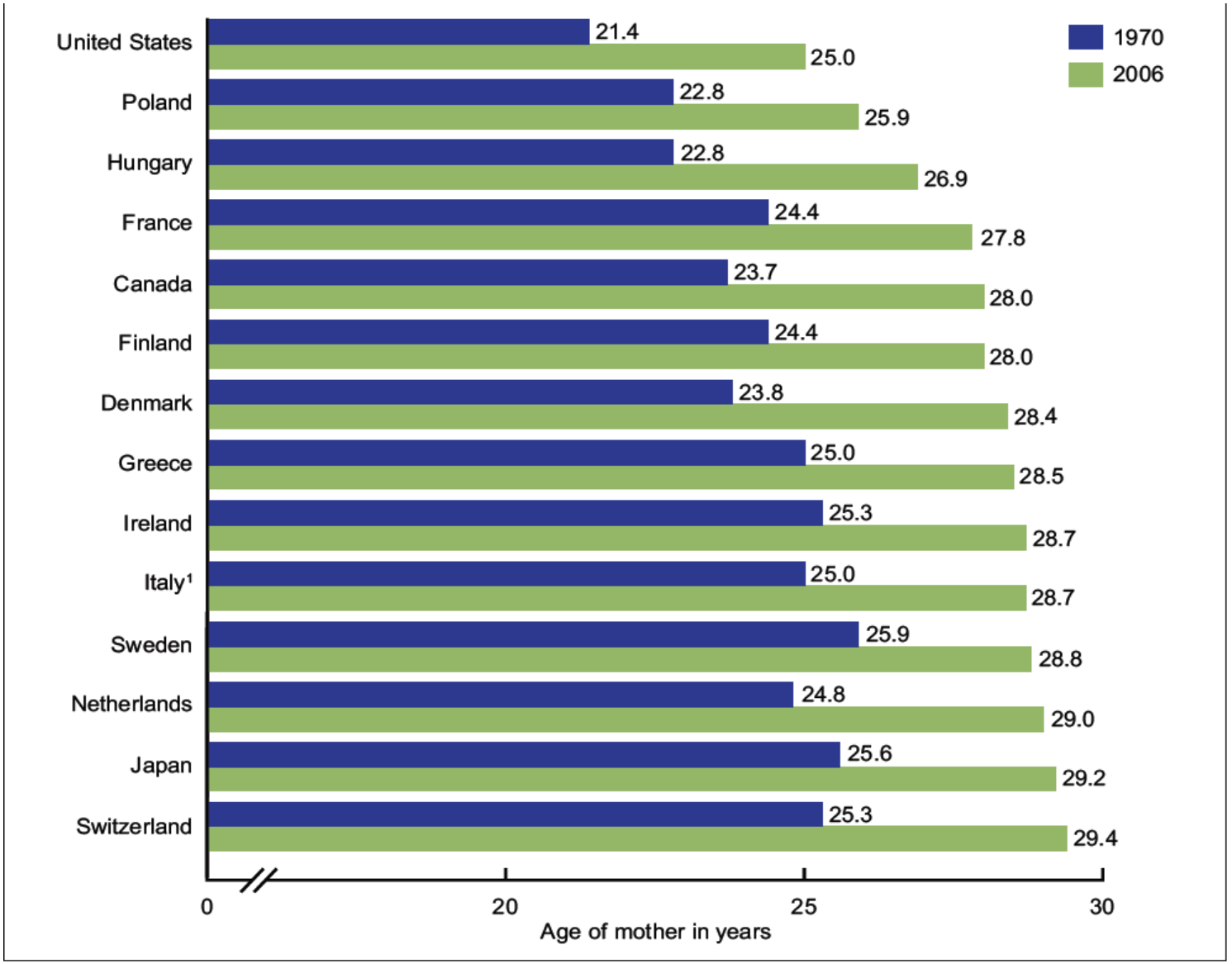
(Ganz et al., JCO, 2003)

Web-Based Survey of Fertility Issues in Young Women with Breast Cancer

- 657 women median age 33 at diagnosis of breast cancer
- 57% of women recalled substantial concern at diagnosis about fertility after treatment
- 29% reported that fertility concerns influenced treatment decisions

(Partridge et al., J Clin Oncol, 2004)

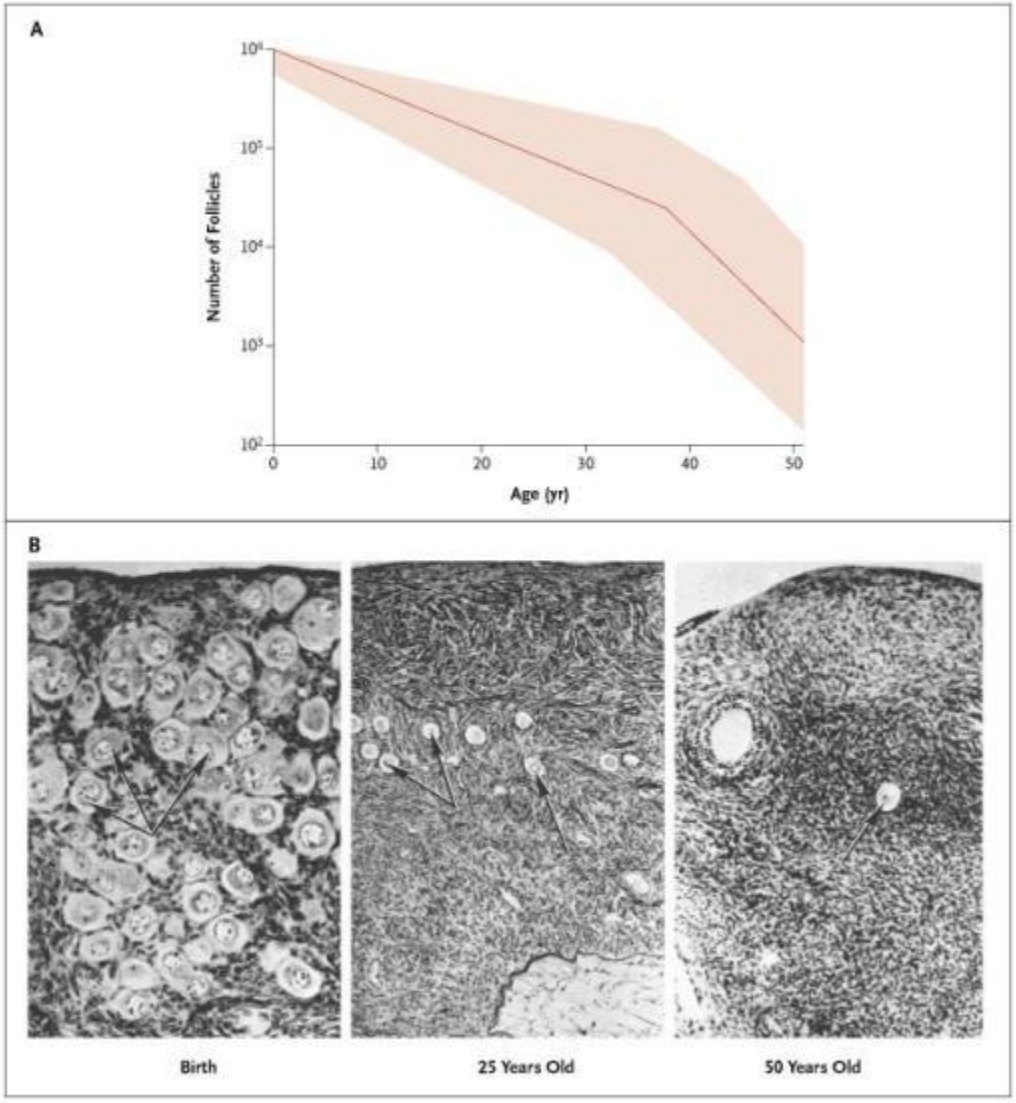
Average Age of First Birth



SOURCES: CDC/NCHS, National Vital Statistics System, Council of Europe, Vienna Institute of Demography, Statistics Canada, and Japanese Ministry of Health,Labour and Welfare. (Slide courtesy of D. Meirow)

Who is at risk?

Natural Decline of Oocytes with Increasing Age



(Lobo, NEJM 2005)

Risk of Amenorrhea is Related to Age and Treatment

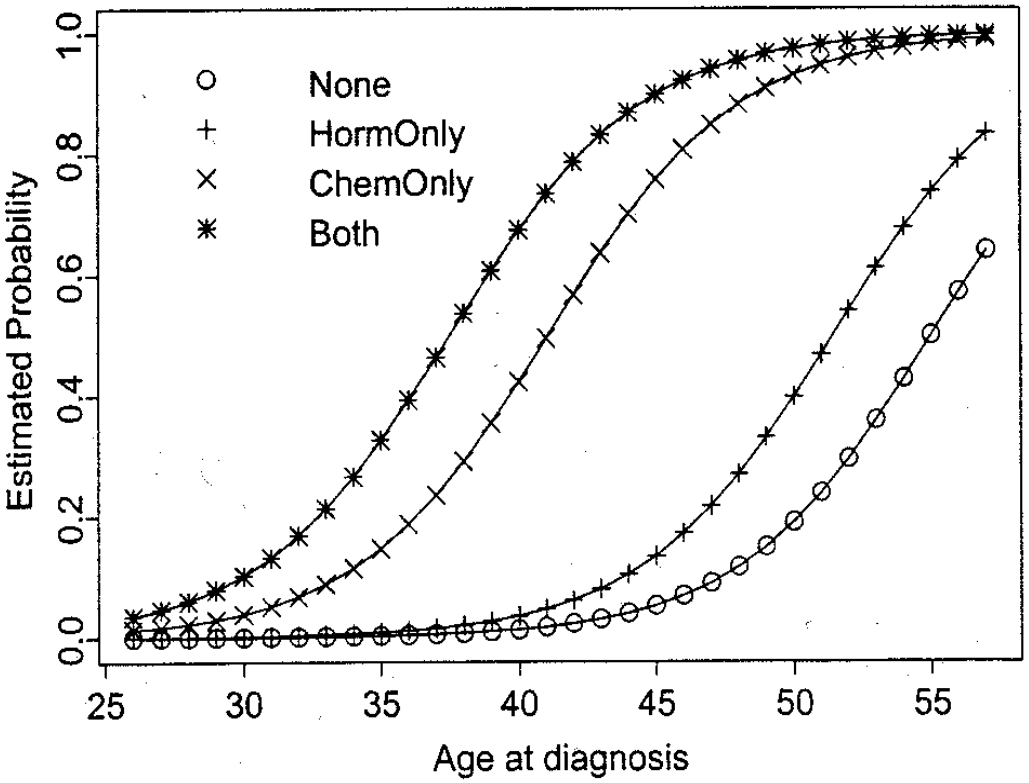


Fig 1. Probability of menopause during the first year after diagnosis (from model shown in Table 3).

Chemotherapy has substantial effect, but tamoxifen contributes to CRA.

(Goodwin et al., J Clin Oncol 1999)

Chemotherapy-related Amenorrhea

- CRA may be permanent or temporary
- CRA is an imperfect surrogate for menopause and infertility
- Accurate assessment of ovarian function has implications for
  - family planning, contraception
  - breast cancer treatment
  - other survivorship concerns

Risk of Chemotherapy-Related Amenorrhea with Common Breast Cancer Regimens

% Women With Amenorrhea

Treatment	Age <30	Age 30-40	Age>40
None	~0	<5	20-25
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. and Winer E.P. NEJM 2000; Nabholtz et al., ASCO 2002; Parulekar et al., JCO 2005; Fornier et al., Cancer 2005; Petrek et al, JCO 2006)

Effects of Paclitaxel, Dose Density, and Trastuzumab on CRA

DFCI Retrospective Study (n=451)
Mean age at 42, mean f/u 34 months

REGIMEN	CRA (%)	
AC-T	61.9%	
AC	57.9%	
Dose dense	66.7%	*No Difference*
Q3wk	57.4%	
Trastuzumab Use	59.1%	
No Trastuzumab	60.0%	
Tamoxifen	65.4%	
No Tamoxifen	46.6%	

Abusief et al., Cancer, 2010, 116(4), 791-8

Importance of Age and Regimen:
DFCI/MGH Patients ’97-’05

Table 5. The Proportion of Patients With Treatment-Related Amenorrhea by Age and Chemotherapy[a]

Treatment[b]	No. of Amenorrheic Women/Total No. (%)		
	Aged <40 Years, N=18/135 (13.3%)	Ages 40-49 Years, N=172/246 (69.9%)	Aged ≥50 Years, N=49/50 (98%)
AC	10/72 (13.9)	88/129 (68.2)	27/27 (100)
AC and paclitaxel			
4 Doses	7/52 (13.5)	72/98 (73.5)	20/21 (95.2)
12 Doses	1/11 (9.1)	13/20 (65)	2/2 (100)
AC, paclitaxel, and trastuzumab			
12 Doses	0/6 (0)	5/9 (55.6)	0 (0)
52 Doses	1/7 (14.3)	10/15 (66.7)	2/2 (100)
Dose-dense regimen	5/36 (13.9)	49/67 (73.1)	17/18 (94.4)
Tamoxifen	13/80 (16.3)	135/183 (73.8)	40/41 (97.6)

AC indicates doxorubicin and cyclophosphamide.

[a]Overall, there were 239 amenorrheic women among 431 participants.

[b]The majority of women in each chemotherapy treatment group also received tamoxifen.

(Abusief et al., Cancer, 2010, 116(4), 791-8)

Ovarian Reserve in Women Who Remain Premenopausal After Chemotherapy For Early Stage Breast Cancer

- 20 breast cancer survivors who remained premenopausal after chemotherapy
- 20 age, gravidity-matched controls
- Day 2-4 of cycle, measured ovarian reserve

(Partridge et al., Fertility and Sterility 2010)

Ovarian Reserve in Survivors Compared to Controls

	Survivors (n=20)	Controls (n=20)	P-value
Antral Follicle Count (AFC)	5.2	11.3	0.0042
Anti-Mullerian Hormone (AMH)	0.57	1.77	0.0004
Follicle Stimulating Hormone	11.56	8.04	0.02
Inhibin B (InB)	24.3	46.6	0.02
Estradiol (E2)	126.0	38.8	0.14

Prospective studies are needed to determine the predictive value of these tests for pregnancy after chemotherapy

(Partridge et al., Fertility and Sterility 2010)

Effects of Endocrine Therapy

The Passage of Time is Major Issue

- Adjuvant endocrine therapy for breast cancer does not appear to cause permanent amenorrhea or infertility
- BUT endocrine therapy usually entails years of treatment AND…
- Aging clearly compromises fertility
- Women often consider shortening course of endocrine therapy to conceive, but must weigh pros and cons

What are the options for fertility preservation?

Options for Preserving Fertility for Women with Breast Cancer

- Ovarian suppression (LHRH agonists) during treatment
- Cryopreservation of ovarian tissue
- Cryopreservation of oocytes
- Cryopreservation of embryos

Ovarian Suppression through treatment

- GnRH agonist mimics pre-pubescent state and theoretically could result in less damage from cytotoxic therapy
- In phase 2 trials, GnRH agonist administration with chemotherapy is associated with high rates of resumption of menses after chemotherapy

RCTs of Ovarian Suppression Through Treatment

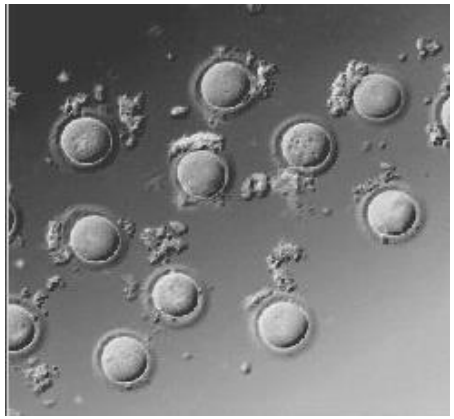
Investigator	Bawady	Sverrisdottir	Del Mastro	Leonard	Gerber	Munster	Elgindy	SWOG 0230
Year	2009	2009	2011	2010	2011	2012	2013	Pending
Patients (n)	80	285	281	227	60	49	100	416 planned
Study type	Phase II RCT	Substudy from combined analysis of 4 RCTs using core protocol	Phase III RCT	Phase III RCT (abstract only)	Phase II RCT	Phase III RCT	Phase II RCT	Phase III RCT
Treatment arms	CT + goserelin vs CT	TAM^ +/-CT Goserelin +/-CT Goserelin/TAM +/-CT TAM +/-CT	CT + triptorelin vs. CT	CT + goserelin vs. CT	CT + goserelin vs. CT	CT + triptorelin vs. CT	*'Delayed CT'*: CT + triptorelin vs. CT *'Early CT'*: CT + triptorelin + cetrorelix[β] vs. CT	CT + goserelin vs. CT
Median age [range]	30 [26-33]	45 [29-55][†]	39 [24-45]	NR	37 [26-47]	39 [21-43]	33 [18-40]	Pending
Premenopausal definition	Regular menstruation FSH <10 IU/L	LMP <6 months prior to study entry, including irregular cycles	Actively menstruation during 6 weeks pre-CT	Regular menses in 12 months preceding surgery	Regular menstruation FSH <15 in follicular phase	Regular menstruation (≥3 periods in 6 months, lasting ≥2 days, 21-35 days apart FSH <40 IU/L	Regular menstruation (≥3 consecutive periods within 21-35 days)	LMP < 6 weeks pre-randomisation or FSH & E2 in premenopausal range
%ER+	NR	45%	81%	NR[∞]	0%	73%	0%	0%
Marker of 'fertility preservation'	Resumption of menstruation or spontaneous ovulation	Resumption of menstruation	Resumption of menstruation	Resumption of menstruation	Resumption of menstruation	Resumption of menstruation	Resumption of menstruation	Resumption of menstruation
Primary endpoint	Rate of POF (no menstruation/ spontaneous ovulation) 3 months post-CT	Recovery of menstruation	Rate of CIA (no menstruation and post-menopausal FSH/E2 levels) for 12 months post-CT	Rate of amenorrhea 12 months after start of CT	Rate of normal ovarian function at 6 months post-CT	Uninterrupted or restored menstruation during f/u of at least 2 years post CT	Rate of regular menstruation at 12 months after completion of CT	Rate of ovarian failure (amenorrhea) at 2 years
Median f/u [range]	NR [3-8 months]	NR	12 months post-CT	NR	6, 12, 24, 48 months post-CT	18 months [5-43 months] after CT	NR All patients followed for at least 12 months	Planned f/u at 1,2 and 5 years
Rate of recovery of menstruation:	90% (goserelin) vs. 33% (control), p<0.001	At 6 months post ET cessation : 36% (goserelin) vs. 10% (control), 13% (TAM), 7% goserelin + TAM), p= 0.006	91.1% (triptorelin) vs. 74.1% (control) p<0.001	NR No statistically significant difference between treatment arms (further details not published)	70% (goserelin) vs. 56.7% (control)	88.5% (triptorelin) vs. 90.5% (control) Trial stopped early for futility	At 12 months post-CT *Delayed CT:* 72% (triptorelin) vs. 52% (control), p=0.15 *Early CT:* 60% (triptorelin + cetrorelix) vs 48% (control), p=0.39	Pending
Pregnancies	No data on pregnancies	No data on pregnancies	3 pregnancies in triptorelin arm, 1 in control arm	No data on pregnancies	1 pregnancy in each group	2 pregnancies in control arm	3 pregnancies, one in early CT + triptorelin + cetrorelix arm, 1 in early CT control arm	Pending

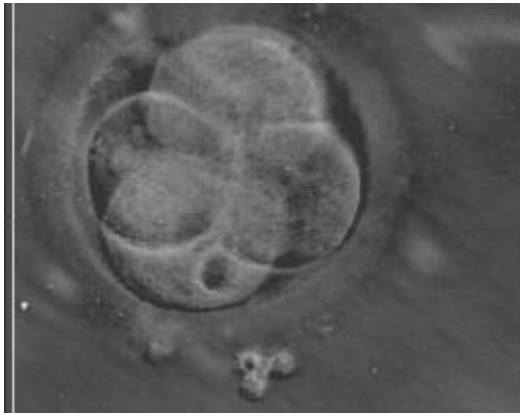
Summary of Data for GnRH Agonists

- **Successful pregnancies have occurred following chemotherapy with GnRHa**
- **Randomized data mixed to date- JURY IS OUT!**
- **Can consider if other options not feasible in motivated patient**

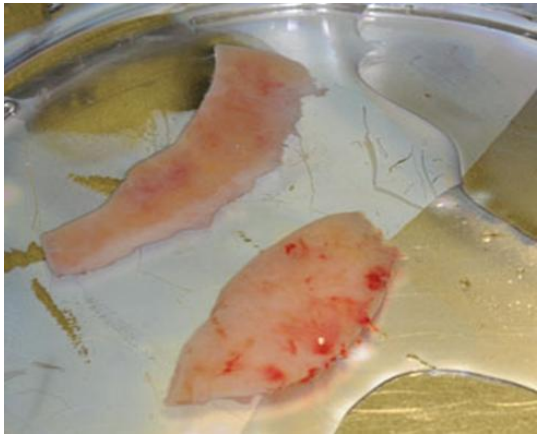
More bona fide options for fertility preservation in breast cancer patients

Egg or Embryo freezing





Ovarian tissue freezing

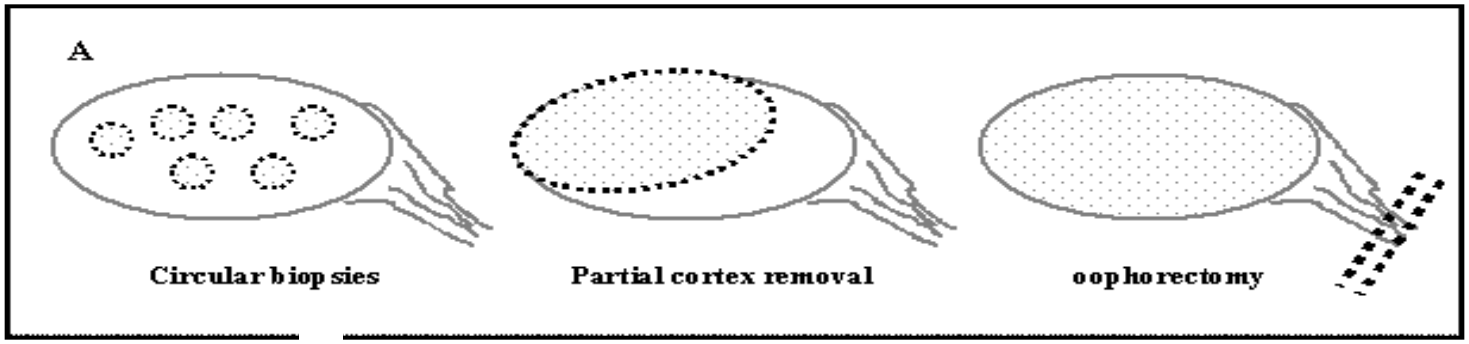


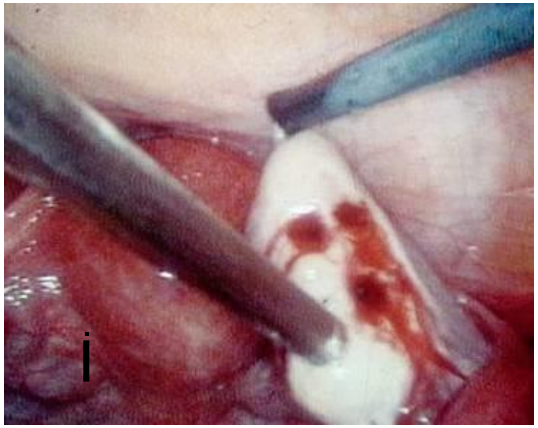
(Slide courtesy of D. Meirow)

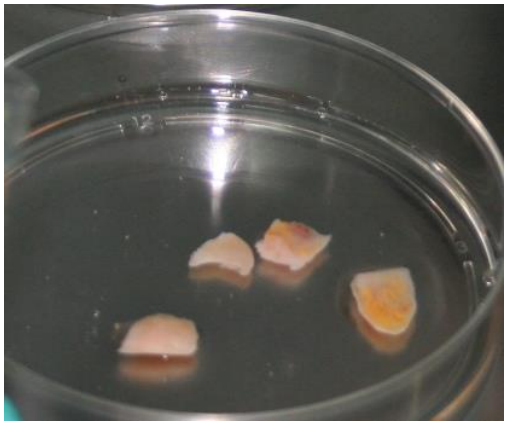
Cryopreservation of Ovarian Tissue

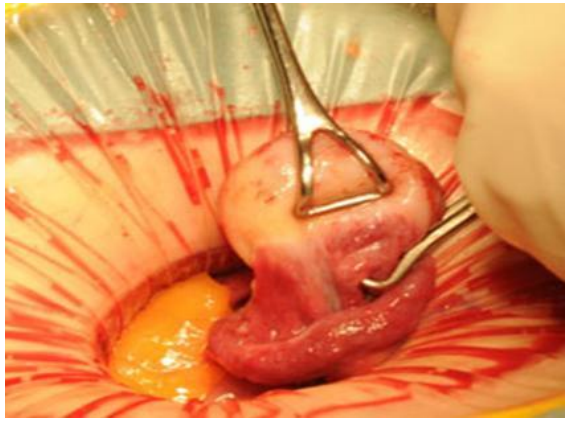
- Requires surgical procedure and time to remove ovary or piece of ovary
- No requirement for sperm
- Technically complex
- May increase risk of infertility in low risk situation
- Potential for reintroduction of malignant cells at reimplantation, complex in BRCA carrier
- *Highly experimental- relatively few babies born to date*

Operation – laparoscopy/ Lap





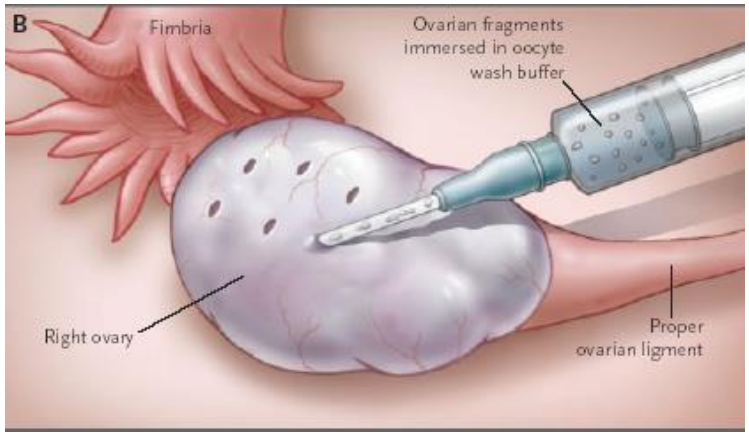


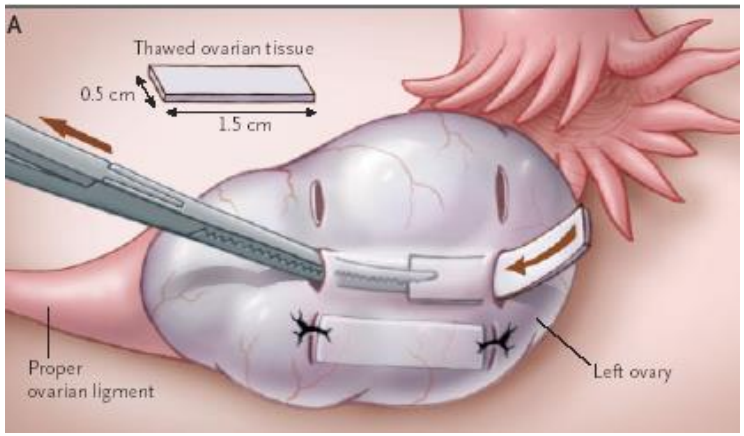


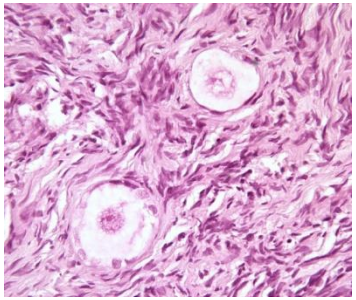
Transplantation of Ovarian Tissue

A patient with Non Hodgkin's lymphoma

Ovarian failure post bone marrow transplantation







Follicles from thawed ovarian tissue

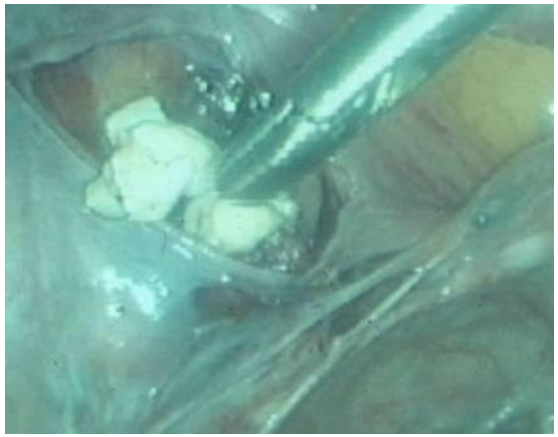
The NEW ENGLAND JOURNAL of MEDICINE

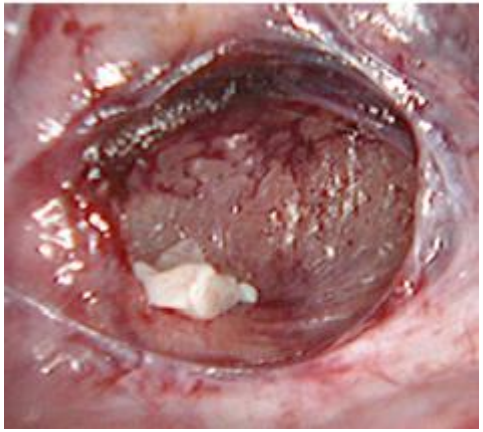
Meirow, Dor *et al*
2005

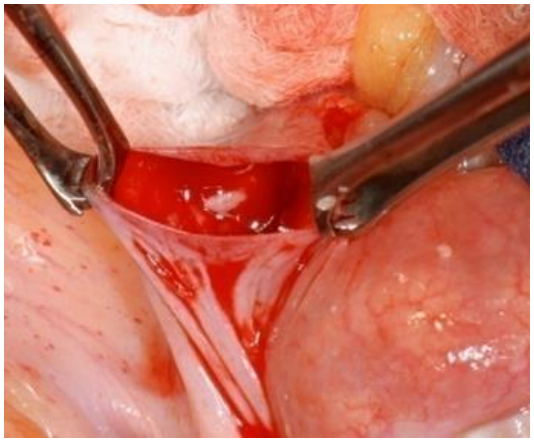
Orthotopic Surgical grafting of ovarian tissue

Publications: Radford, Oktay, Donnez, Demeestere, Azem

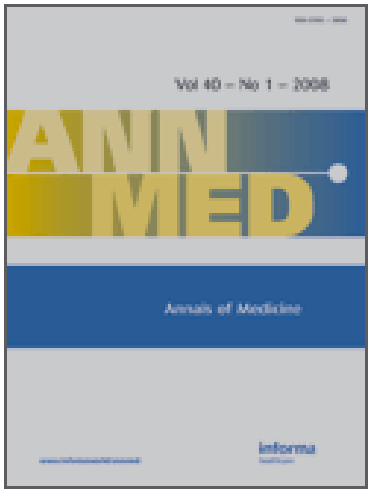
- **Additional space**
- **No ovary**
- **Fibrosis of vascular bed**







Children born after ovarian transplantation. A review of 13 live births.



- Age at tissue collection 19-36
- Previous chemotherapy 40%
- Endocrine results
- IVF / Spontaneous pregnancy 50%
- Pregnancy results- normal babies 100%

Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, Pellicer A, Dolmans MM. **Ann Med 2011 .Jan 13**

Many centers, sporadic cases, different conditions.

Success rate unknown.

Cryopreservation of *Eggs*

- Available at select centers
- Requires time and money, not partner
- Requires ovarian stimulation prior to systemic breast cancer treatment- concerning in patients with hormone-sensitive breast cancer

(Porcu et al., Curr Opin Endocrinol Diabetes Obes, 2008)

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Fertility Experts Issue New Report on Egg Freezing; ASRM Lifts Experimental Label from Technique

October 22 , 2012
by: ASRM Office of Public Affairs
Published in ASRM Press Release

Note: All information is embargoed until the time of presentation at the meeting, unless otherwise indicated.

HIGHLIGHTS FROM THE 68th ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Embargoed for Release: Monday, October 22, 2012 – 12:01 AM Eastern Daylight Time

Fertility Experts Issue New Report on Egg Freezing; ASRM Lifts "Experimental" Label from Technique

San Diego, CA - The Practice Committee of the American Society for Reproductive Medicine (ASRM) issued a new report today stating that in young patients egg freezing techniques have been shown to produce pregnancy rates, leading to the birth of healthy babies, comparable to IVF cycles using fresh eggs.

The report entitled "Mature Oocyte Cyryopreservation" replaces a report released in 2008 which had stated that the technique was experimental and should only be offered in that context. The current report examined nearly 1000 published papers on the topic. While randomized controlled studies were rare, the Committee found sufficient evidence to "demonstrate acceptable success rates in young highly selected populations."

The report does urge caution, however. The Committee points out that the age of the woman at the time of egg freezing is a very important factor. "Success rates with oocyte cryopreservation appear to decline with maternal age consistent with the clinical experience with fresh oocytes."

The report proposes that egg freezing could provide a viable alternative source of tissues for couples needing donor eggs to build their families. In addition, among the medical indications for its use are fertility preservation for patients who may be left infertile following medical treatments for other diseases, some genetic conditions, or IVF treatment interrupted by the unexpected inability to obtain sperm.

The ASRM Practice Committee is not yet ready to endorse widespread use of egg freezing for elective use. Citing a lack of data on safety, efficacy, cost-effectiveness, and potential emotional risks, the report states, "Marketing this technology for the purpose of deferring childbearing may give women false hope and encourage women to delay childbearing. Patients who wish to pursue this technology should be carefully counseled."

"Oocyte cryopreservation is an exciting and improving technology, and should no longer be considered experimental. Pregnancy rates and health outcomes of the resulting children are now comparable to those of IVF with fresh eggs," said Eric Widra, MD, Chair of the Society for Assisted Reproductive Technology (SART) Practice Committee.
Samantha Pfeifer, MD, Chair of the ASRM Practice Committee said, "While a careful review of the literature indicates

Cryopreservation of *Embryos*

- Widely available
- Highly successful
- Requires time and partner/sperm, money
- Requires ovarian stimulation prior to systemic breast cancer treatment with high hormonal levels (Natural cycle IVF has low yield)

(Oktay et al, JCO, 2005; Partridge & Winer, JCO 2005)

Hormone sensitive- Breast cancer protocols

Cancer cells

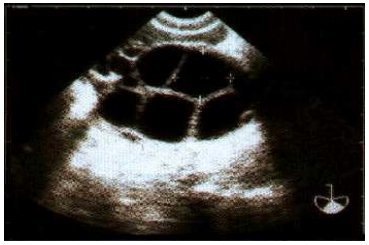
TAMOXIFEN

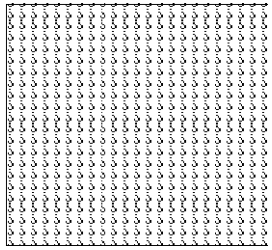
High E2

Low E2

Aromatase Inhibitor

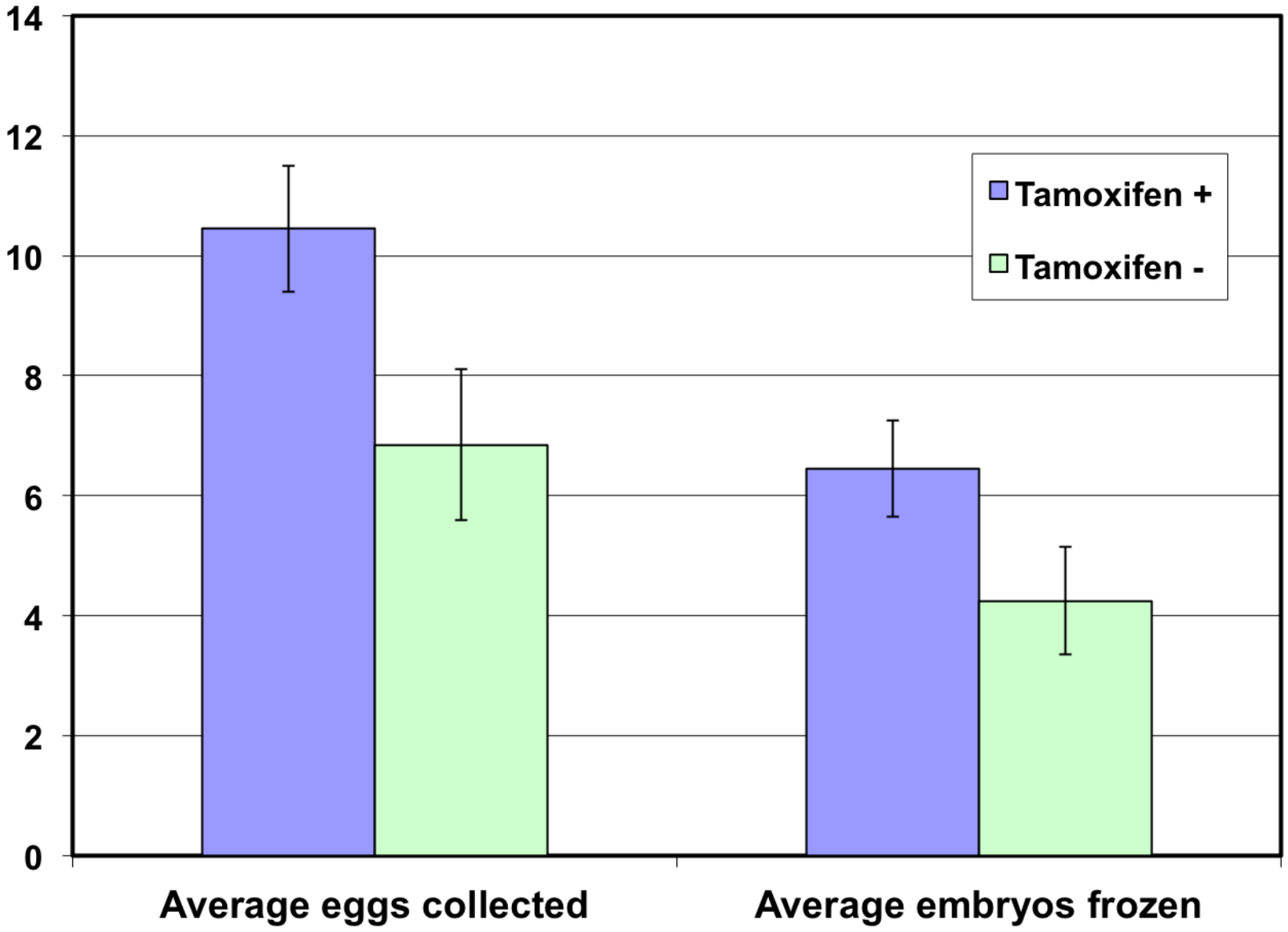
Ovarian Stimulation FSH





Good No. of eggs

Tamoxifen co-administration during ovarian stimulation for IVF

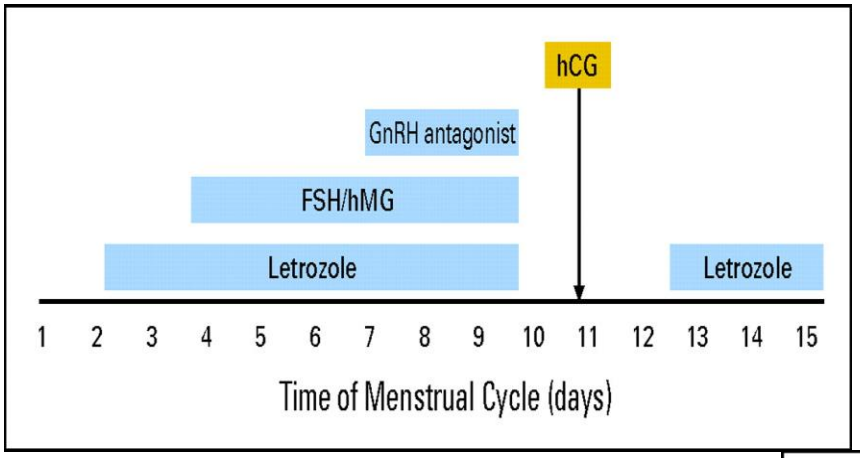


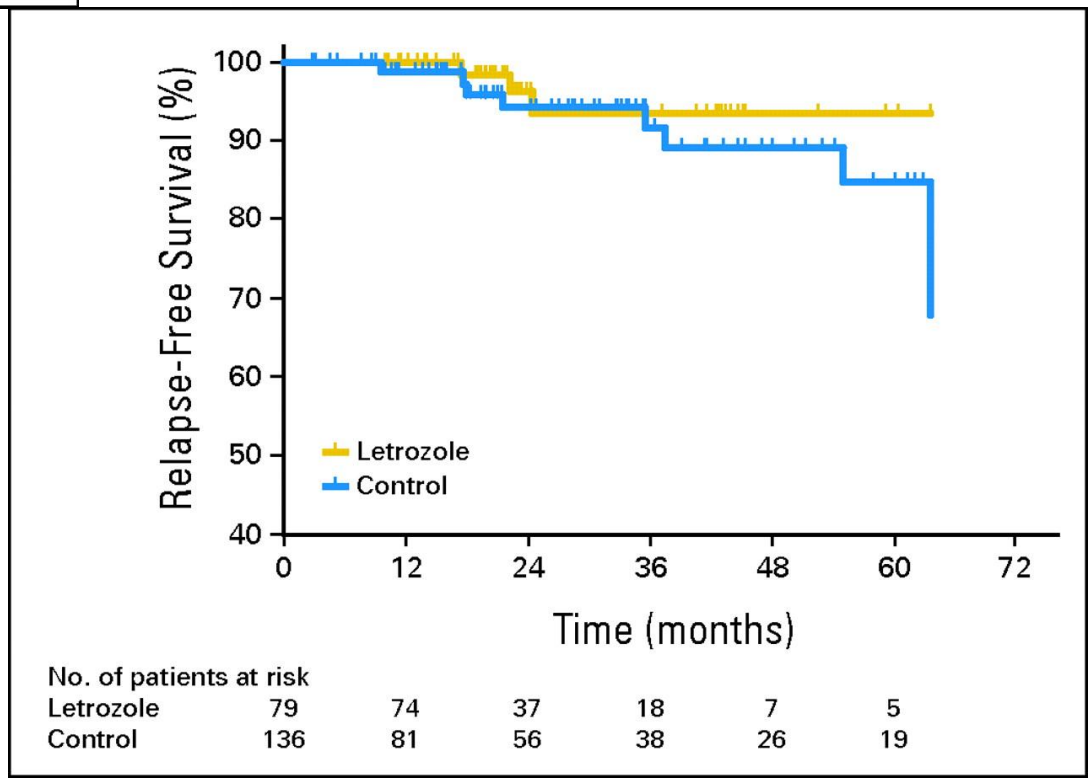
What are the risks?

Risks inherent in fertility preservation procedures

- Risk of procedures themselves
- Unclear if letrozole or tamoxifen stimulation protocols actually mitigate risks particularly in women with HR+ disease

Stimulation With Letrozole To Harvest Oocytes



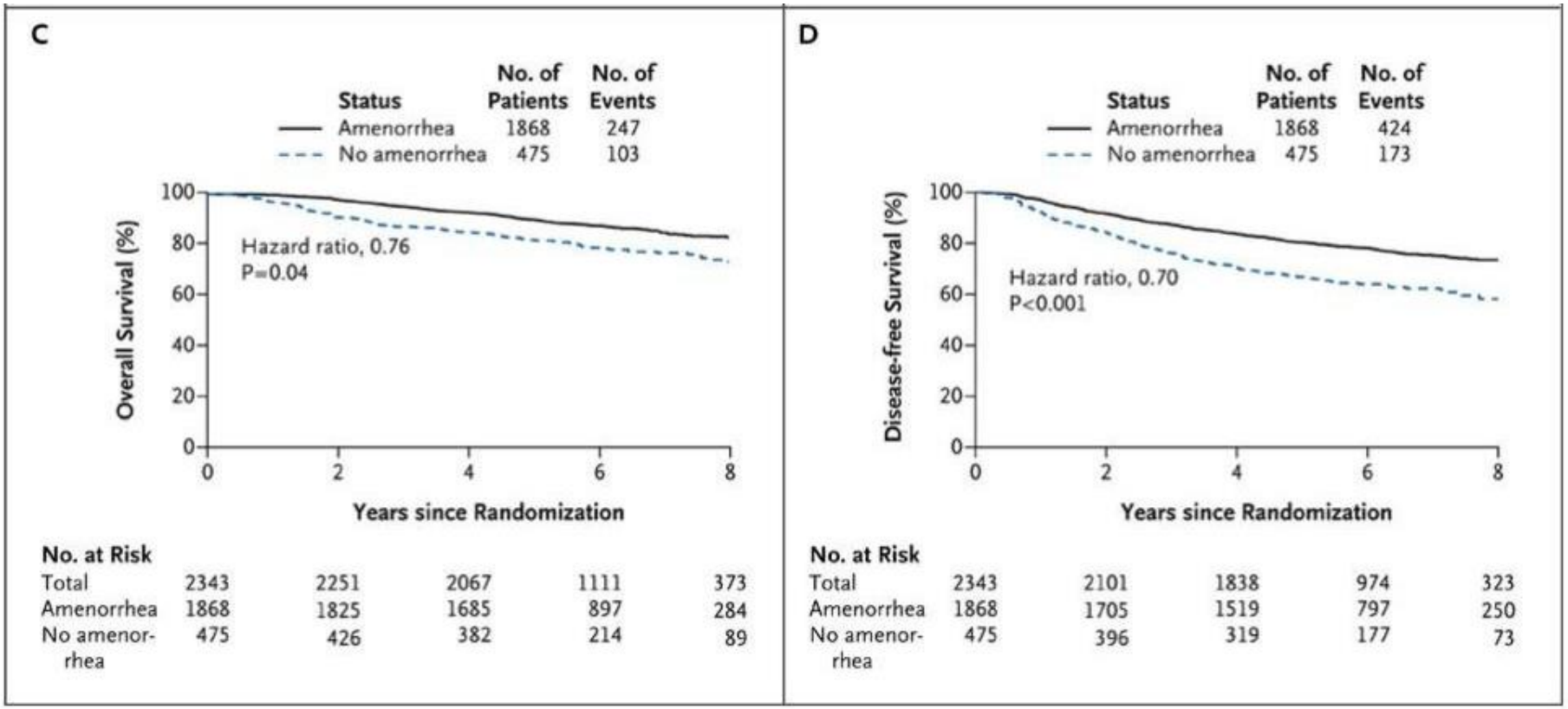


JOURNAL OF CLINICAL ONCOLOGY

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

Does “protecting” women from going into menopause lead to worse outcomes?

Amenorrhea associated with improved DFS and OS in NSABP-30



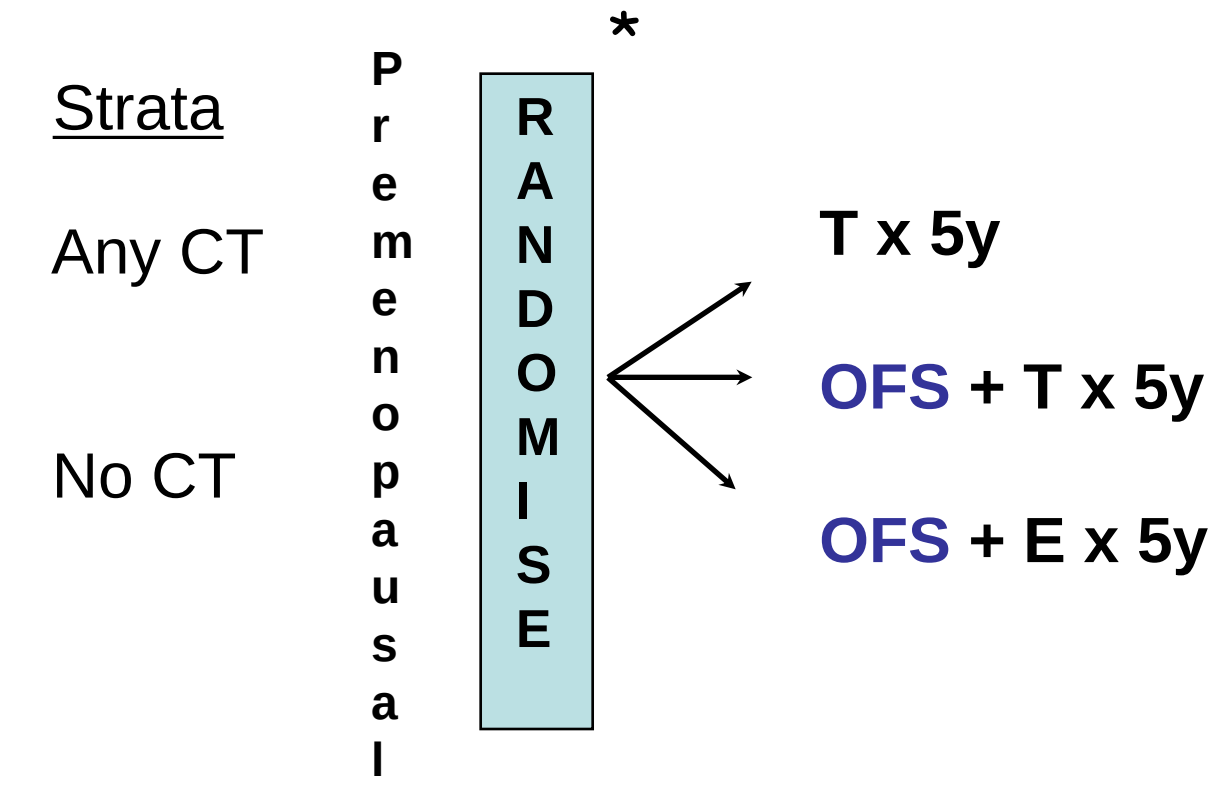
(Swain SM *et al. N Engl J Med* 2010)

SOFT [BIG 2-02, IBCSG 24-02]

Premeno.

ER ³ 10% and/or
PgR ³ 10%

Patients with estradiol (E_2) in the premenopausal range either after CT or without CT



*Randomization within a 6-month evaluation period after end of CT, or within 12 weeks after definitive surgery for patients with no CT

CT=chemotherapy; T=tamoxifen; E=exemestane; OFS=ovarian function suppression using GnRH analogue x 5 years or bilateral oophorectomy or radiation

Is Pregnancy After Breast Cancer Safe?

- Concerns
  - Stimulation of breast cancer growth from high estrogen state of pregnancy
  - Increased disease recurrence, decreased survival

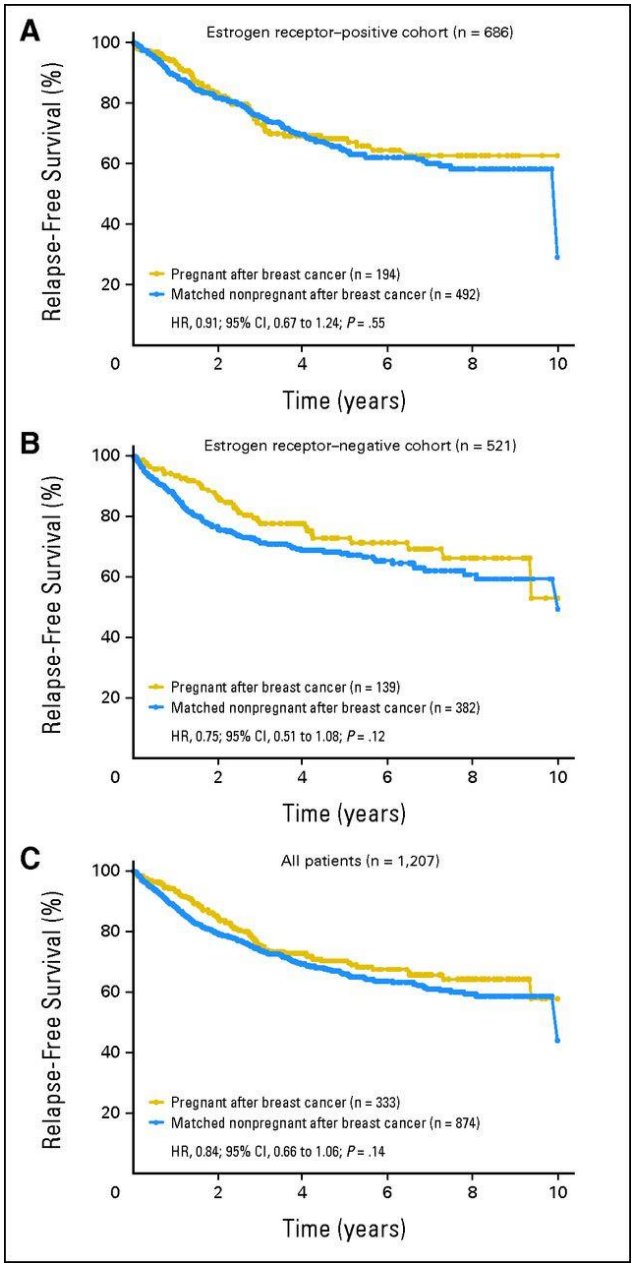
- Methods of analysis of available studies
  - Case-control studies
  - Retrospective cohort studies

Recent Studies Evaluating Safety of Pregnancy after Breast Cancer

Study	Cases	Controls	RR (95% CI)
Sankila (1994)	91	471	0.20 (0.10-0.50)
Von Schoultz (1995)	50	2119	0.48 (0.18-1.29)
Kroman (1997)	173	5514	0.55 (0.28-1.06)
Valentgas (1999)	53	265	0.80 (0.30-2.30)
Gelber (2001)	94	188	0.44 (0.21-0.46)
Mueller (2003)	438	2775	0.54 (0.41-0.71)
Blakely (2004)	47	323	0.70 (0.25-1.95)
Ives (2007)	123	2416	0.59 (0.37-0.95)

All show protective effect, but limited by case-control and retrospective cohort methodology. "Healthy mother" cannot be eliminated.

No differences in disease-free survival between pregnant group and matched nonpregnant group.

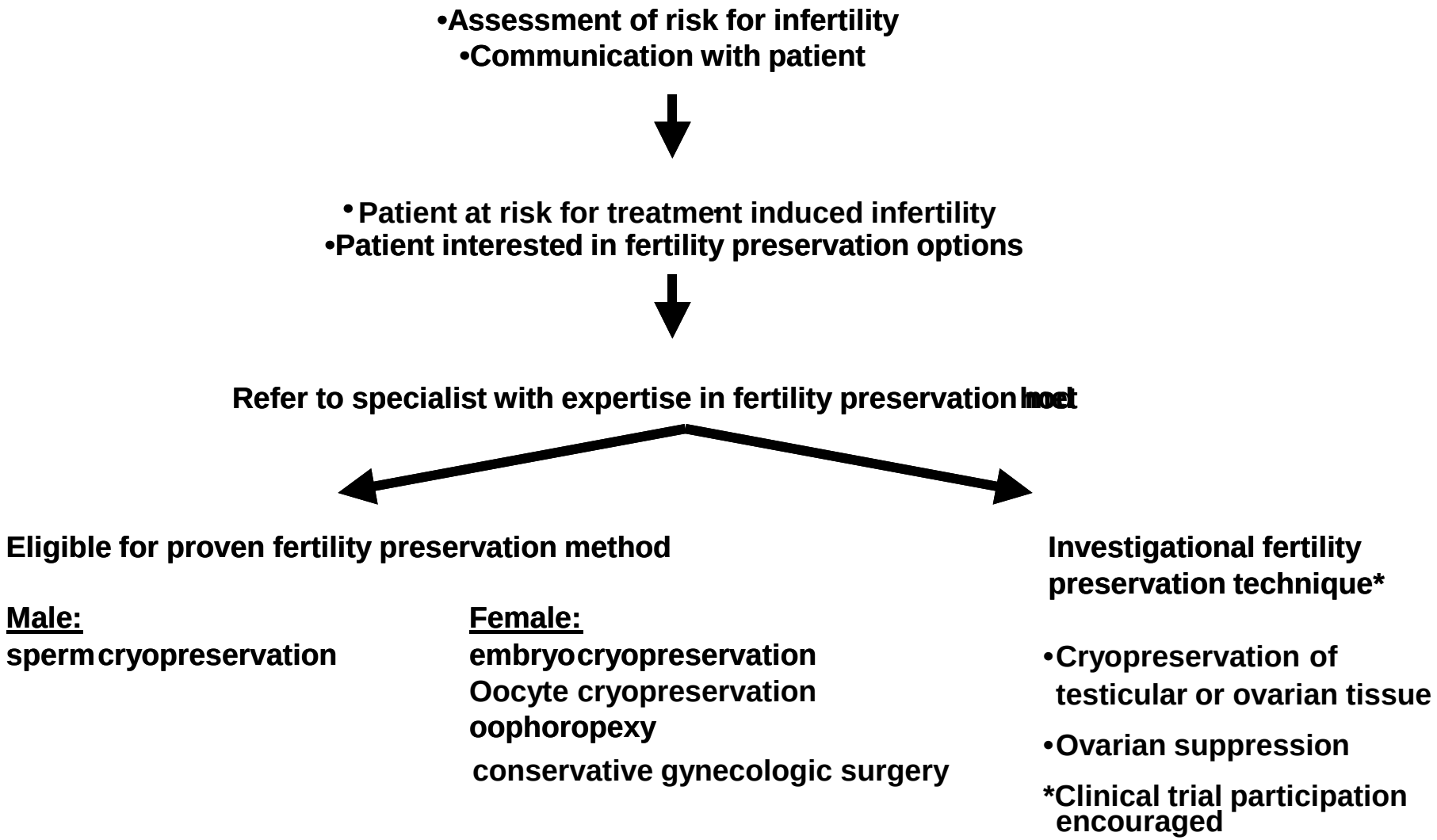


Azim H A et al. JCO 2013;31:73-79

JOURNAL OF CLINICAL ONCOLOGY

How can we help our patients?

American Society of Clinical Oncology Recommendations on Fertility Preservation in People Treated for Cancer



www.asco.org

(Modified from Lee et al., J Clin Onc; 2006)

Fertility After Breast Cancer

- Very difficult issue for many young women when facing a breast cancer diagnosis and treatment
- Much is known and much still unknown- support research in this area
- Patient preferences critical factor
  - frank discussions necessary
  - help with grieving losses sometimes

Fertility After Breast Cancer

- Imperative to discuss this with our young patients early and refer early as needed
- Know your local resources
- International resources:
  - Fertilehope.org
  - Youngsurvival.org

Thank you!