Preservation of Ovarian Function in Young Age Breast Cancer

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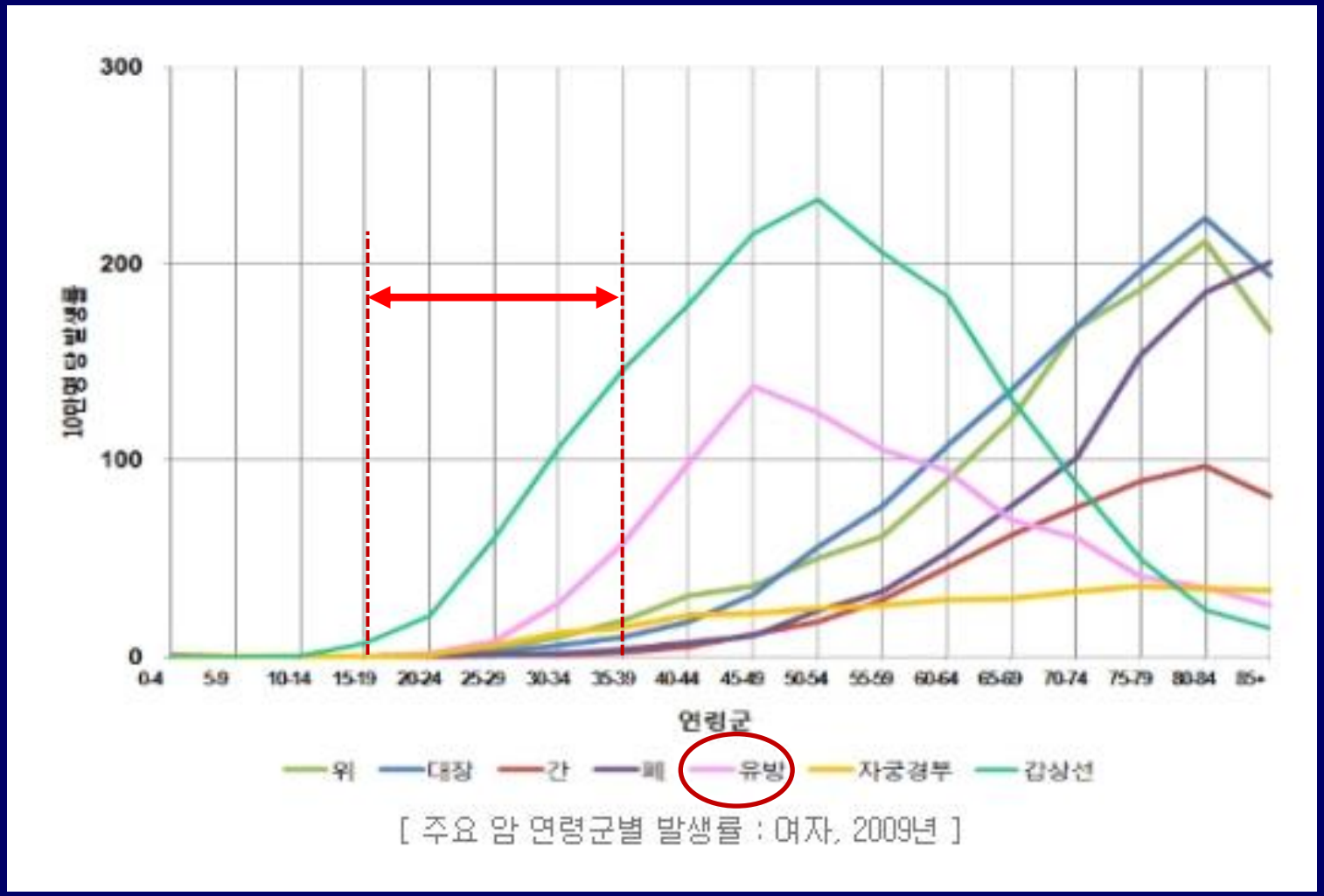
Incidence of breast cancer according to age

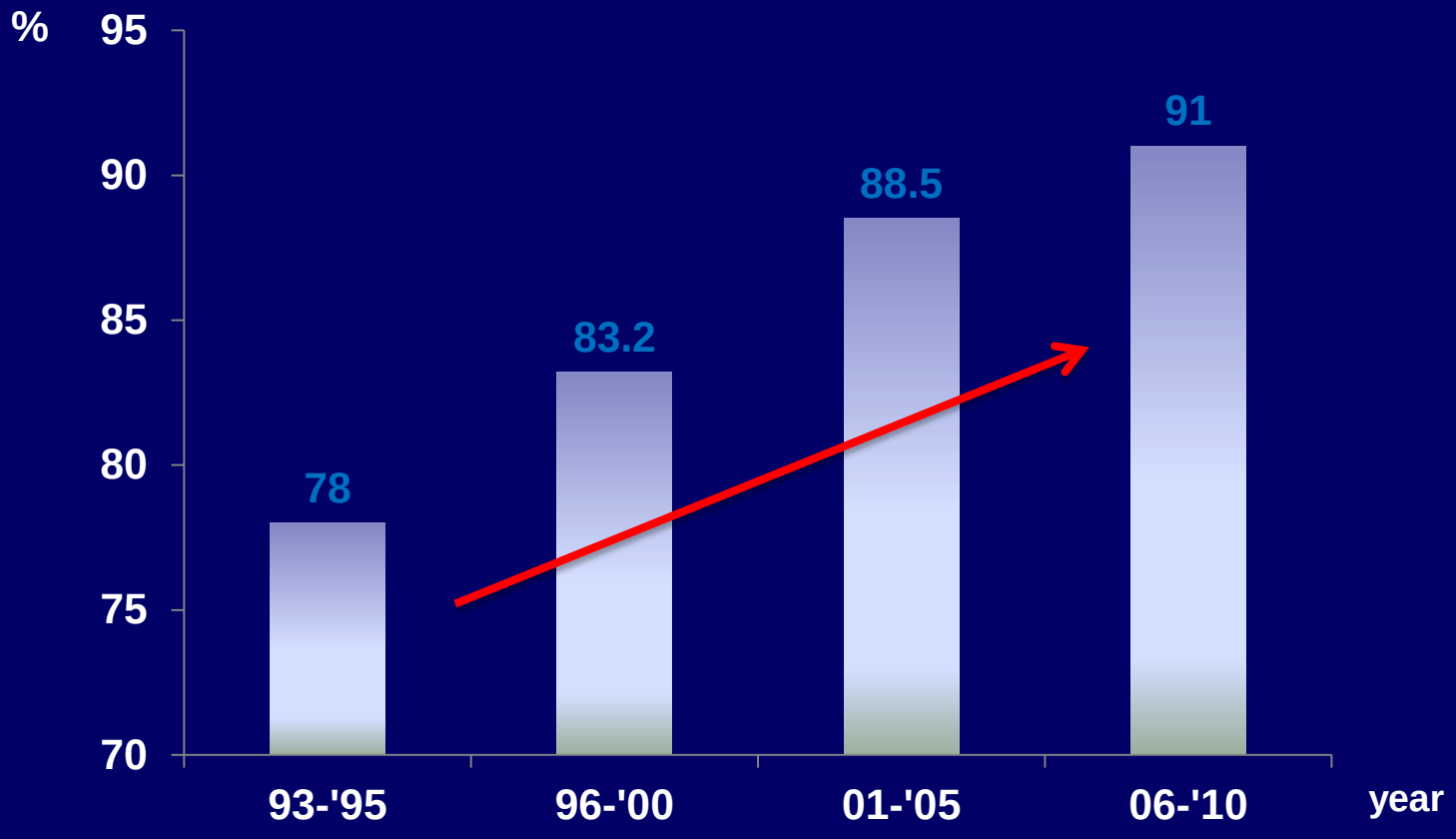


[주요 암 연령군별 발생률 : 여자, 2009년]

Korean national data

Outcomes of breast cancer treatment

5-yr survival rate of breast cancer in Korea by year at diagnosis



Korea national data

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Cancer in reproductive age

- **Survival rates for many of the malignancies affecting reproductive-aged women have been improved significantly.**

- **Quality of life in survivals should be considered**

  ➡ **Among them, Preservation of fertility potential against cancer therapy assumes high priority.**

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

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

Recommendations

As part of education and informed consent before cancer therapy, health care providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation. The discussion should be documented. Sperm and embryo cryopreservation as well as oocyte cryopreservation are considered standard practice and are widely available. Other fertility preservation methods should be considered investigational and should be performed by providers with the necessary expertise.

J Clin Oncol 2013

ASRM PAGES

Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Patients preparing to undergo gonadotoxic medical therapy or radiation therapy or gonadectomy should be provided with prompt counseling regarding available options for fertility preservation. Fertility preservation can best be provided by comprehensive programs designed and equipped to confront the unique challenges facing these patients. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)

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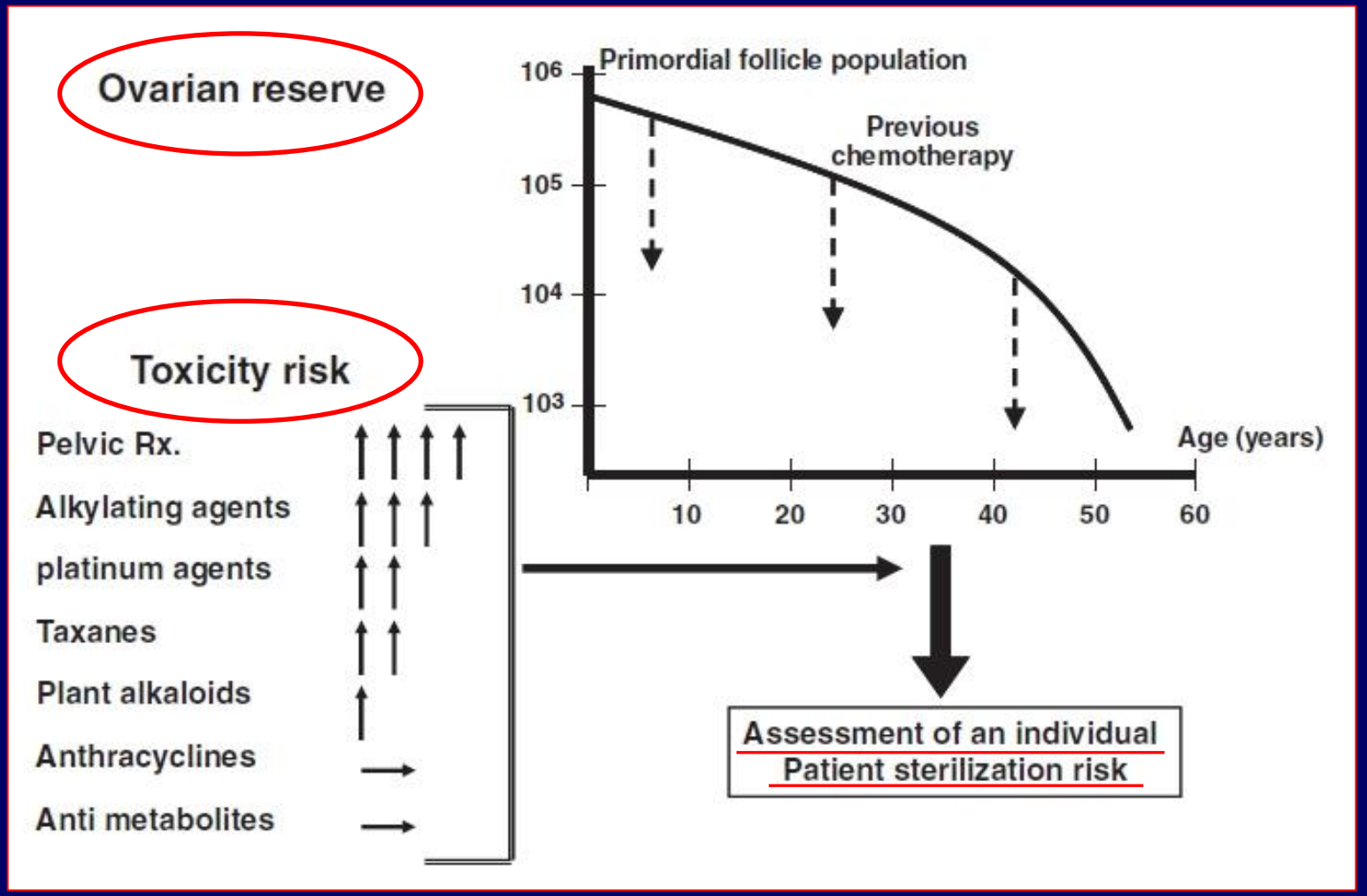
Impact factors on ovarian damage



Meirow D, Clin Obstet Gynecol 2010

Chemotherapeutic agents according to risk of gonadotoxicity

High risk	Medium risk	Low risk
Alkylating agents: cyclophosphamide ifosfamide busulphan chlorambucil melphalan chlormethine procarbazine	Platinum agents: cisplatin, carboplatin Anthracyclic antibiotics*: doxorubicin(adriamycin) Taxoids: paclitaxel, docetaxel	Vinca alkaloids: vincristine, vinblastine Anthracyclic antibiotics*: bleomycin Antimetabolites: methotrexate 5-fluorouracil mercaptopurine

* Anthracyclic antibiotics do not have a strict group effect and therefore the effect depends on the particular antibiotic used.

Fleischer RT, Obstet Gynecol Surv 2011

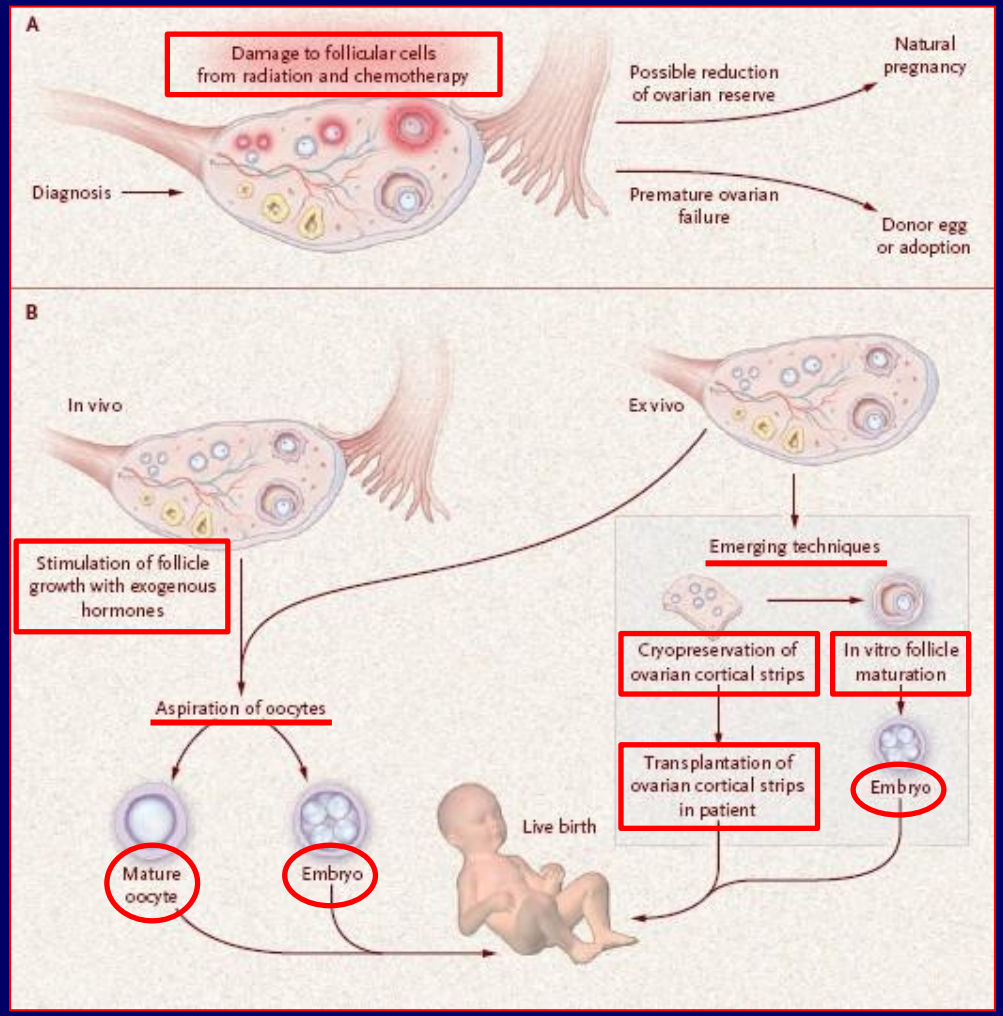
Risk of chemotherapy-induced amenorrhea in breast cancer

Regimen	Age	Degree of risk
AC ×4 cycles - docetaxel ×4 cycles	40-49	35%
	31-39	12%
	<31	6%
AC, EC	>40	30-70%
	30-39	<20%
CMF, CEF or CAF ×6 cycles	>40	>80%
	30-39	30-70%
	<30	<20%
FEC ×6 cycles	>40	73%
	<40	38%
Methotrexate + fluorouracil		very low
Monoclonal antibodies		little evidence
Taxanes		little evidence

AC, doxorubicin, cyclophosphamide; CAF, cyclophosphamide, doxorubicin, fluorouracil; CEF, cyclophosphamide, epirubicin, fluorouracil; CMF, cyclophosphamide, Methotrexate, fluorouracil; EC, epirubicin, cyclophosphamide.

Christinat A, J Thorac Dis 2013

Fertility preservation strategies



Jeruss JS, NEJM 2009

Options for fertility preservation

- **Non-surgical**
  - Cryopreservation of embryos & oocytes
  - Administration of gonadotropin-releasing hormone analogues (GnRHa)

- **Surgical**
  - Cryopreservation of ovarian tissue

Oocyte cryopreservation

- First human live birth in 1987
  - Initially low live-birth rates of 1.9~2%/oocyte thawed (2006)
- Damage during freeze-thaw procedure
  - Meiotic spindle depolymerization, zona pellucida hardening, cytoplasmic and cytoskeleton damage, polar body degeneration/fusion..
- Vitrification
  - High cryoprotectant concentrations & extremely fast cooling
    : more effectively avoids ice crystal formation
  - ⇨ Yields higher LBR (5%/thawed oocyte & 29~39%/transfer)[1,2]

cf. Currently offered by >50% of ART clinics in US[3]

[1]Oktay K, Fertil Steril 2006; [2]Rienzi L, Hum Reprod 2012; [3]Rudick B, Fertil Steril 2010

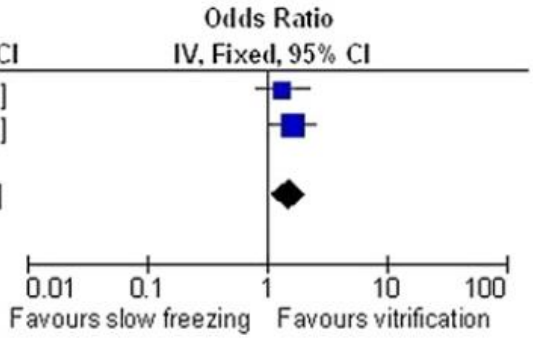
Oocyte cryopreservation

Odds ratio of fertilization from meta-analysis

A Vitrification vs. Slow freezing. Fixed effects model

Study or Subgroup	Vitrification Events	Vitrification Total	Slow Freezing Events	Slow Freezing Total	Weight	Odds Ratio IV, Fixed, 95% CI
Cao 2009	182	268	46	75	41.0%	1.33 [0.78, 2.27]
Smith 2010	200	260	104	155	59.0%	1.63 [1.05, 2.54]
Total (95% CI)		528		230	100.0%	**1.50 [1.07, 2.11]**
Total events	382		150			

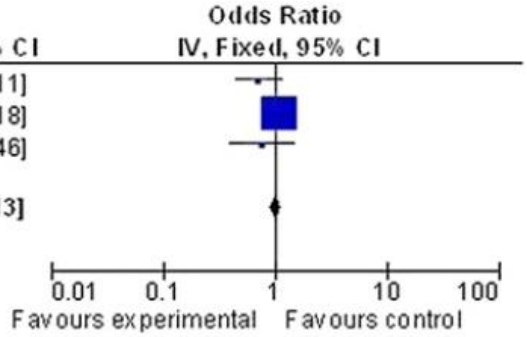
Heterogeneity: $Chi^2 = 0.33$, $df = 1$; $I^2 = 0\%$
Test for overall effect: $Z = 2.36$



B Vitrification vs. Fresh oocytes. Fixed effects model

Study or Subgroup	Vitrification Events	Vitrification Total	Fresh Events	Fresh Total	Weight	Odds Ratio IV, Fixed, 95% CI
Cobo 2008	171	224	180	219	5.5%	0.70 [0.44, 1.11]
Cobo 2010	2256	3039	2334	3185	91.8%	1.05 [0.94, 1.18]
Rienzi 2010	95	120	100	120	2.8%	0.76 [0.40, 1.46]
Total (95% CI)		3383		3524	100.0%	**1.02 [0.91, 1.13]**
Total events	2522		2614			

Heterogeneity: $Chi^2 = 3.60$, $df = 2$; $I^2 = 44\%$
Test for overall effect: $Z = 0.33$



Cobo A, Fertil Steril 2012

Oocyte cryopreservation

ASRM Practice Committee (2013)

- **Recommended with appropriate counseling in patients facing infertility due to cancer treatments**
- **Not yet sufficient data to recommend for sole purpose of circumventing reproductive aging in healthy women**
- **More data are needed before this should be used routinely in lieu of embryo cryopreservation**

⇨ **Should no longer be considered experimental**

Fertil Steril 2013

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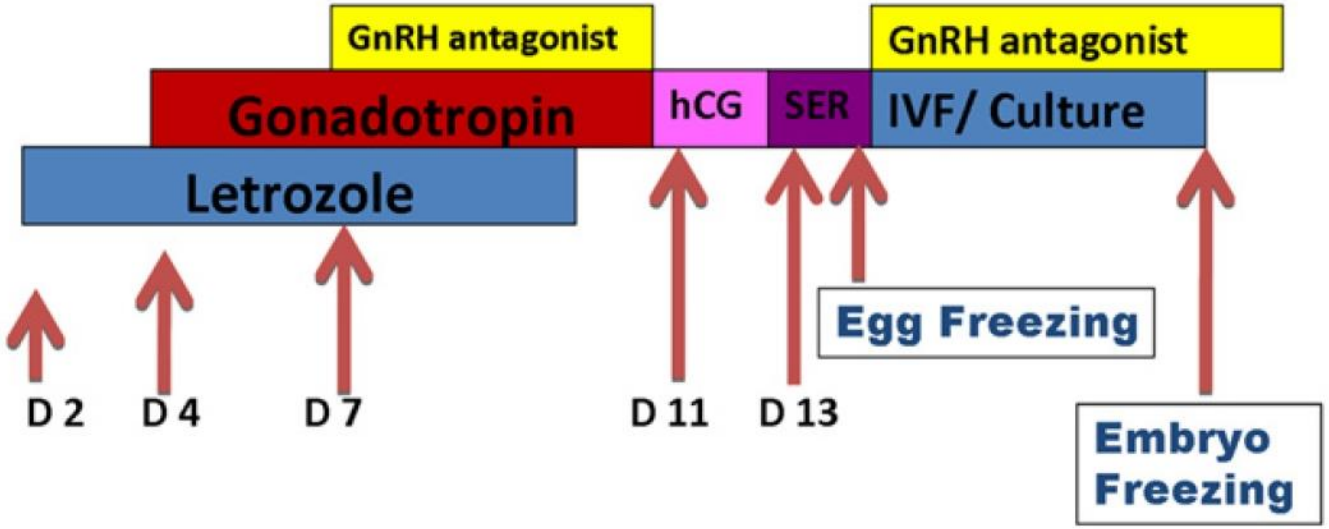
COS Protocol for Breast Cancer Patients

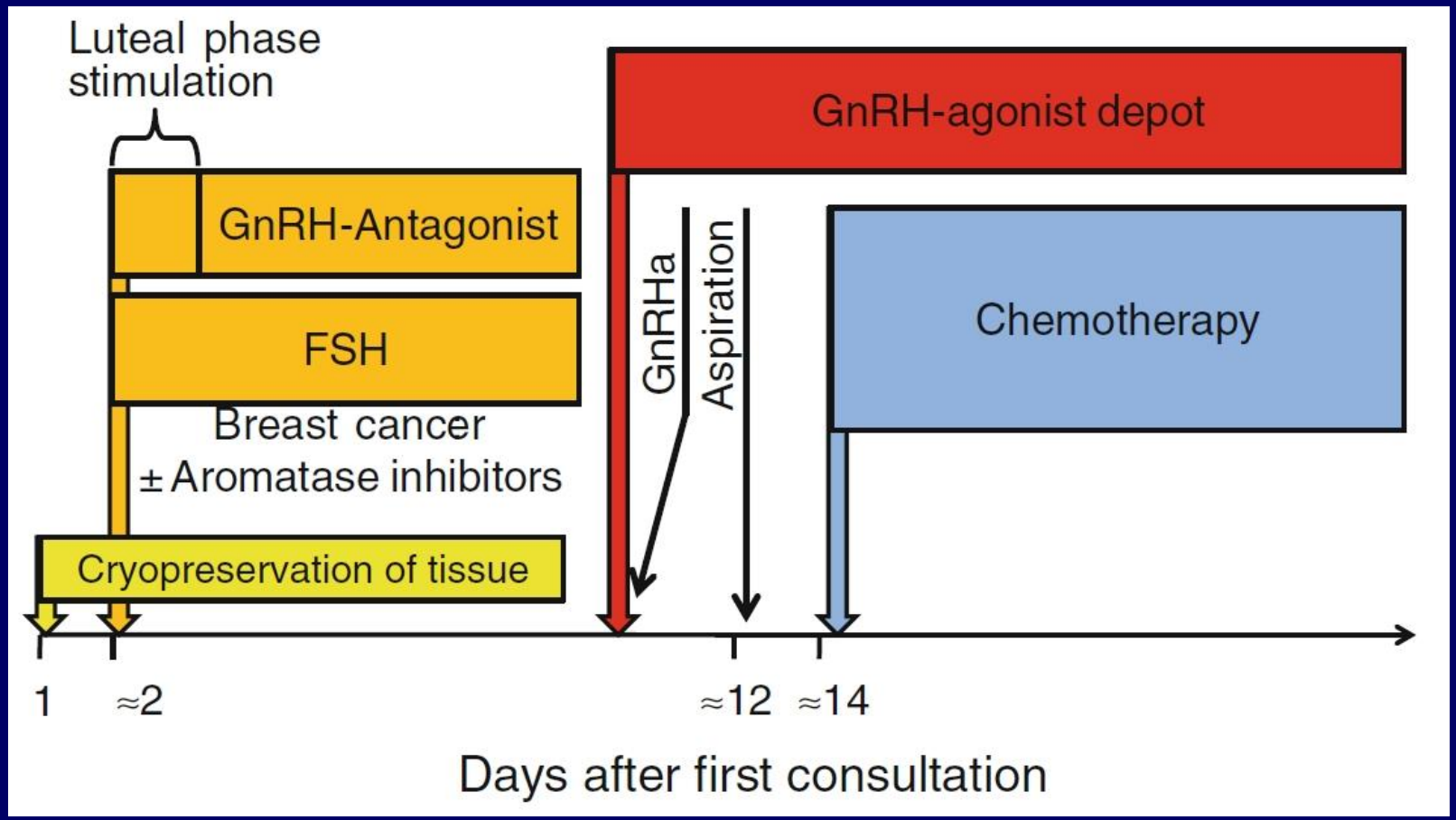
Protocol for COS for embryo/oocyte cryopreservation in breast cancer patients (d: cycle day; SER: ultrasound-guided egg retrieval).



Kim. Breast cancer and fertility preservation. Fertil Steril 2011.

Kim SS, Fertil Steril 2011

Cryopreservation of oocytes & embryos



Von Wolff M et al., Arch Gynecol Obstet 2011

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In vitro maturation (IVM)

- **In vitro maturation of immature oocytes and fertilization**
  - **Does not require standard ovarian stimulation**
    : **possibility of retrieval, regardless of phase of menstrual cycle**
- **Recent development of culture system**
  - **Maturation rate: up to 72.5%[1]**
  - **Pregnancy rates: 20~54%[2]**
- **Optimal option for fertility preservation[3]**
  or investigational d/t unknown efficacy and safety[4]

[1]Huang J, Am J Surg 2010; [2]Suikkary AM, Curr Opin Ob Gyn 2008;
[3]Chian RC, Fertil Steril 2013; [4]ASRM Practice Committee 2013

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Cryopreservation of oocytes & IVM

Advantages

No male partner/gamete donor needed
Avoid risk of cancer re-transmission

IVM
Immediate harvesting (can start treatment without delay)
Suitable for prepubertal girls

Disadvantages

Oocytes sensitive to cryoinjury
Requires invasive procedure for tissue harvesting or follicle aspiration
Oocyte retrieval requires 2~3 weeks for multiple follicular maturation
Risk of ovarian hyperstimulation
Oocyte retrieval not suitable for prepubertal girls
IVM, especially, has low success rate

Embryo cryopreservation

- **Routinely performed in patients undergoing IVF!**
  - First child birth after embryo freezing in 1984
  - Outcome of children after cryopreservation: reassuring
  - Most established & reliable method for female fertility preservation
- **Concerns**
  - Requires a source of sperm
  - Could not be offered to prepubertal patients who have an underdeveloped reproductive endocrine axis
  - Concerns related to oncogenic potential of supraphysiological levels of gonadotropins and E2
  - Maybe a delay in the timing of chemotherapy
  - Legal, ethical, religious issues

Embryo cryopreservation

Data from 2010 SART statistics (146,693 cycles)

	Oocyte Donors	<35	35-37	38-40	41-42	>42
Fresh cycle: Live birth/ET	55.6	47.8	38.4	28.1	16.8	6.3
Thawed: Live birth/ET	34.8	38.7	35.1	28.5	21.4	15.3
Avg No. ET	2.0	1.9	1.9	2.1	2.2	2.1

Fertil Steril 2013

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GnRH agonist

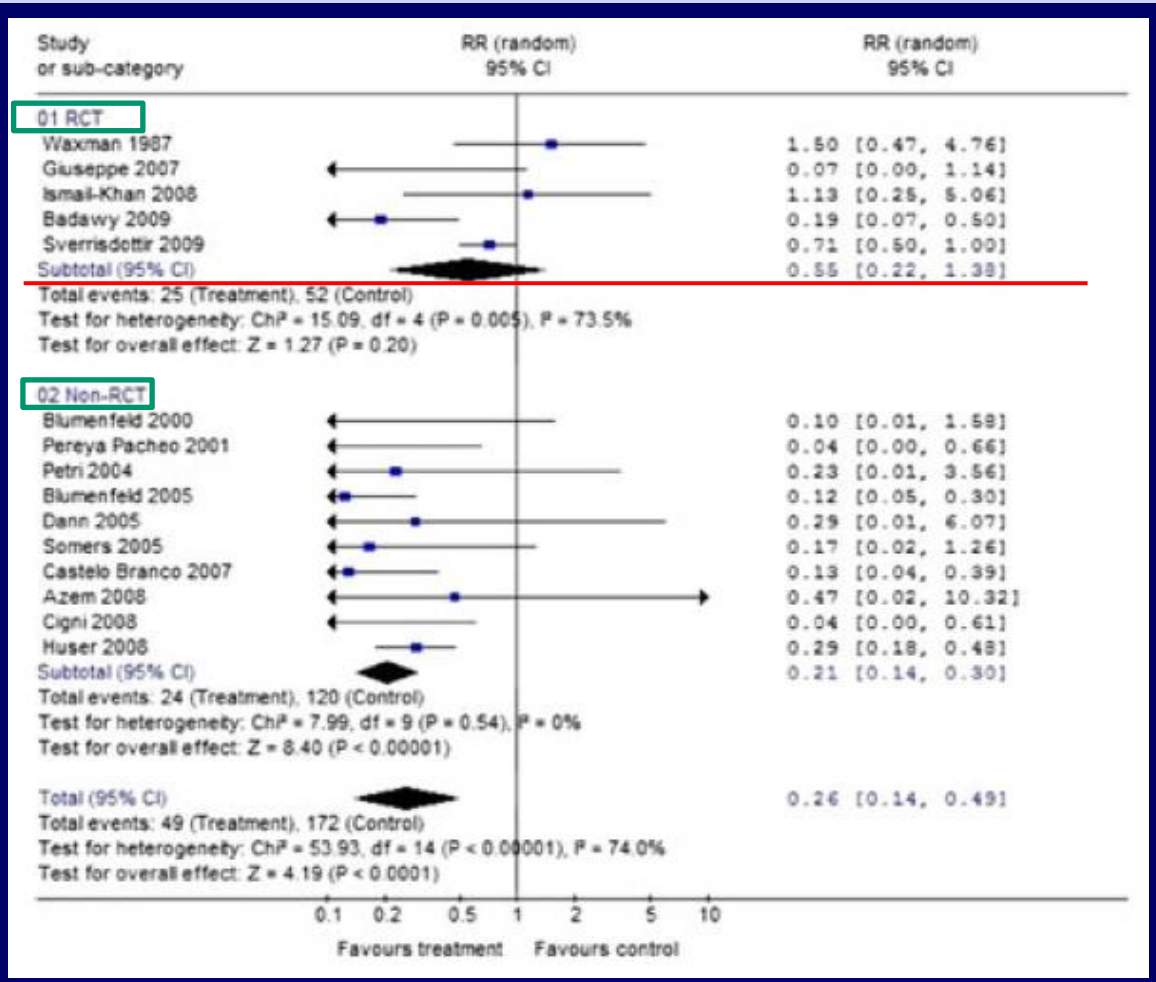
Possible Mechanism for Ovarian Protection

- **Not fully understood but may include,**
  - **Interruption of FSH secretion**
  - **Decrease in utero-ovarian perfusion**
  - **Activation of GnRH receptors**
  - **Up-regulation of intra-gonadal anti-apoptotic molecules such as sphingosine-1-phosphate**
  - **Protection of undifferentiated germline stem cells**

Blumenfeld Z, Oncologist 2007

GnRH agonist

Rate ratio for patients resuming menstruation in cancers by study design



Ben-Aharon I, Breast Cancer Res Treat 2010

GnRH agonist

GnRH Agonist Therapy to Protect Ovarian Function in Young Korean Breast Cancer Patients

The increased survival of patients with breast cancer has given rise to other problems associated with the complications of chemotherapy. One major complication is premature ovarian failure, an especially harmful outcome for women of reproductive age. This study was performed to evaluate the efficacy of GnRH agonist (GnRHa) treatment on protecting ovarian function in young breast cancer patients (30.59±5.1 yr) receiving chemotherapy after surgery. Twenty-two women were enrolled and given subcutaneous injections of leuprolide acetate (3.75 mg) every 4 weeks during chemotherapy. Follow-up laboratory tests (luteinizing hormone [LH], follicle stimulating hormone [FSH], and estradiol) were performed 1, 3, and 6 months after chemotherapy. Menstruation patterns and clinical symptoms were followed up for a mean duration of 35.6±1.7 months. FSH and LH levels were normal in all patients 6 months after completing chemotherapy (8.0±5.3, 4.4±2.7 mIU/mL, respectively). During follow-up, none of the patients complained of menopausal symptoms and 81.8% experienced recovery of menstruation. This report is the first trial of GnRHa as a treatment modality to protect ovarian function during adjuvant chemotherapy in young Korean breast cancer patients.

Hyun Jung Park[1], Young-Ah Koo[1], Young Hyuck Im[2], Byung-Koo Yoon[1], and DooSeok Choi[1]

Departments of Obstetrics & Gynecology[1], Hematology & Oncology[2], Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

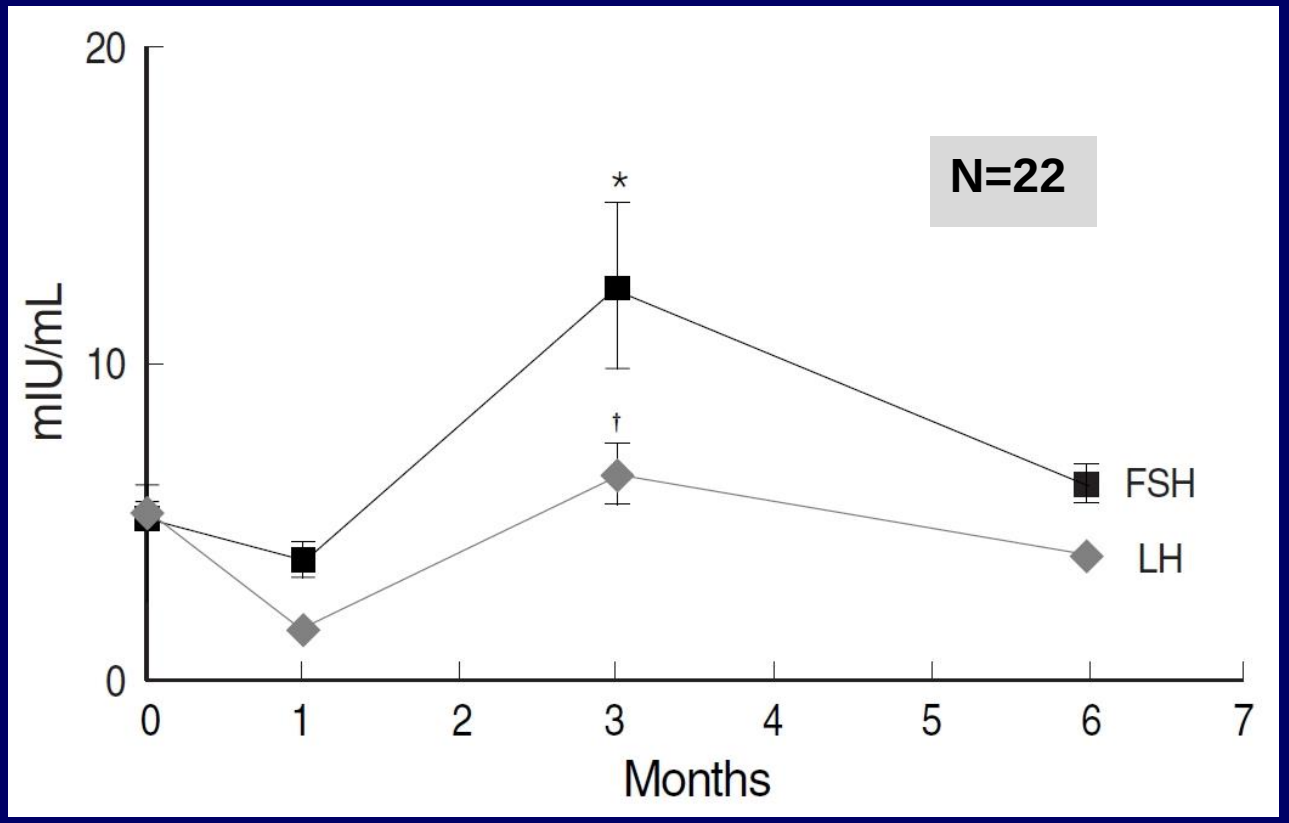
Received : 15 July 2008
Accepted : 25 February 2009

Address for Correspondence
DooSeok Choi, M.D.

Park HJ, JKMS 2010

GnRH agonist

Gonadotropin levels before and after chemotherapy



Park HJ, JKMS 2010

GnRH agonist

Experience at Samsung Medical Center

- From Jun. 2004 to Sep. 2012
  : by date of completion of GnRHa injection
- Total number=87
  : mean & median age=31 (range: 21-40)
  : follow-up duration for at least 12 months after chemotherapy
  cf. follow-up loss during the period: 25

Outcomes	N (percent)
Resume of menstruation	78 (89.7%)
Pregnancy with fetal viability	14
Treatment failure	9 (10.3%)
Total	87

Unpublished data

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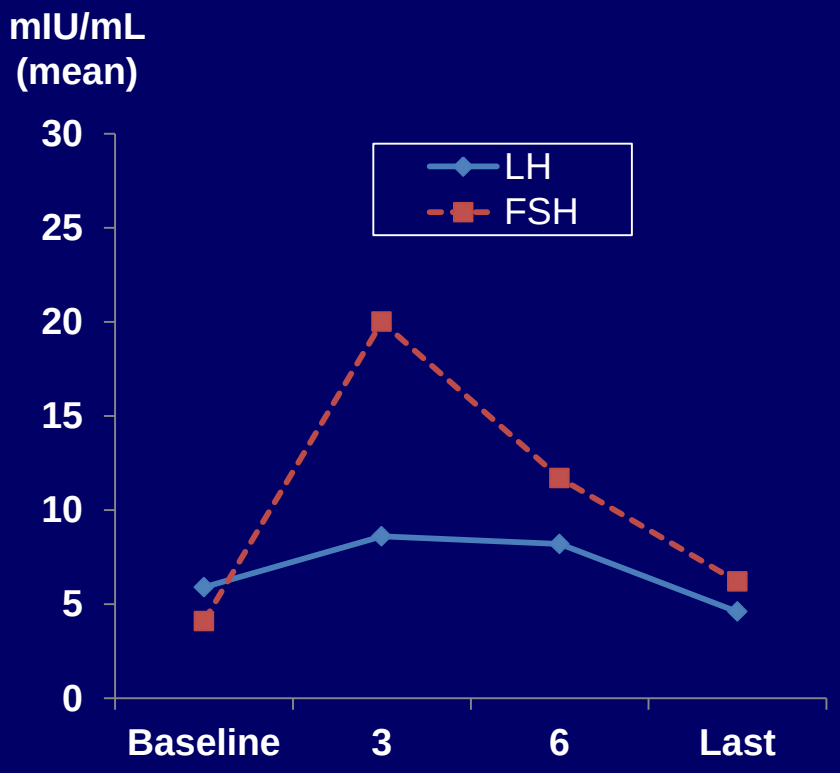
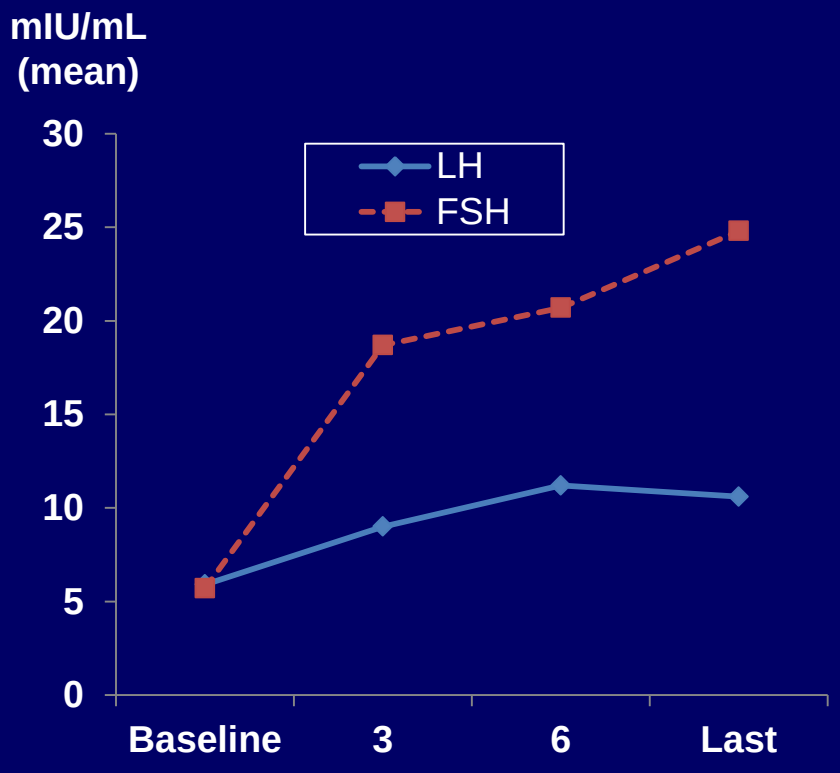
GnRH agonist

Resumed menstruation (N=78)



Treatment failure (N=9)

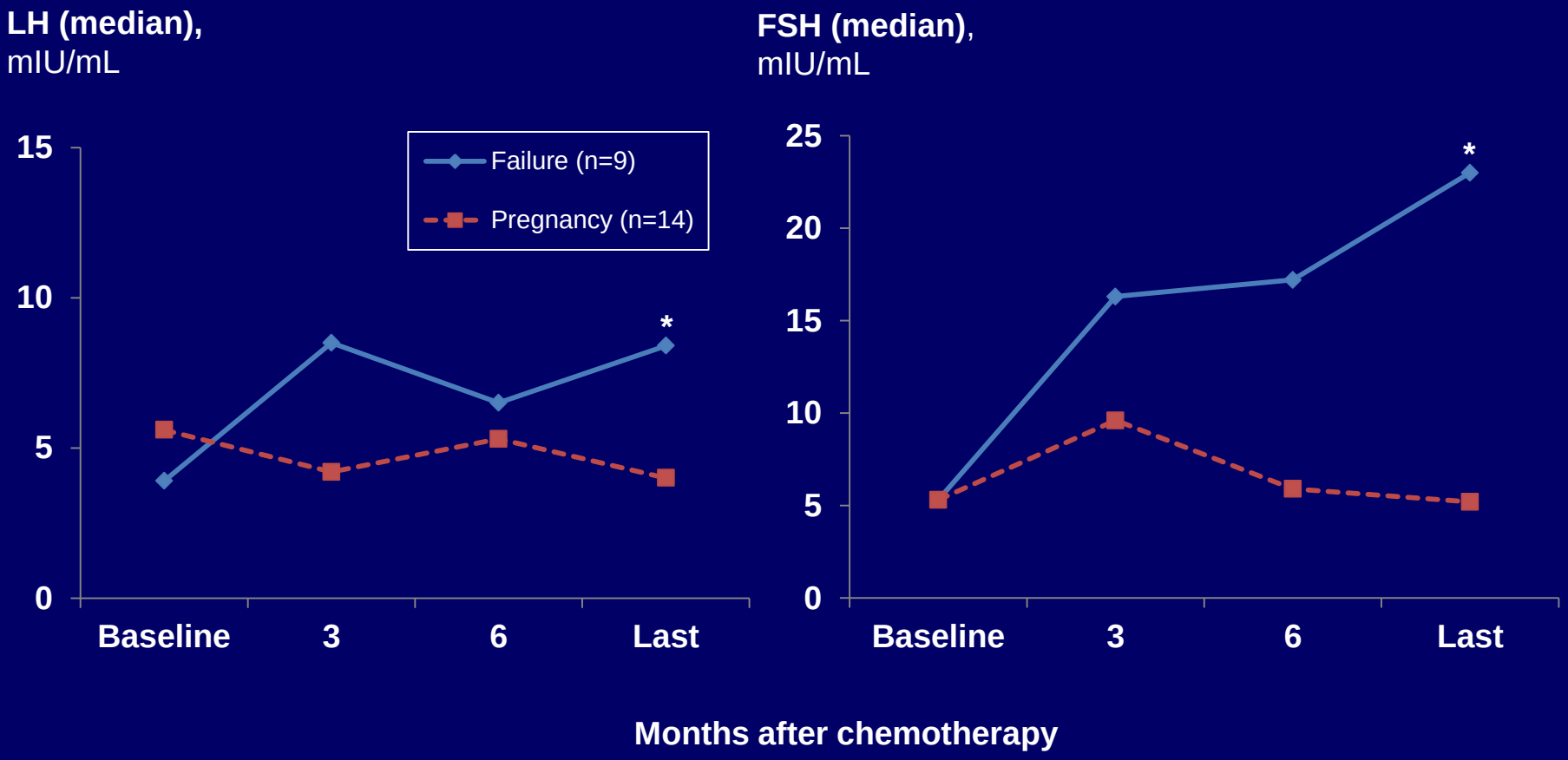


Months after chemotherapy

Unpublished data

GnRH agonist

Comparisons of gonadotropin levels: pregnancy vs. ovarian failure



Unpublished data

GnRH agonist in Breast cancer

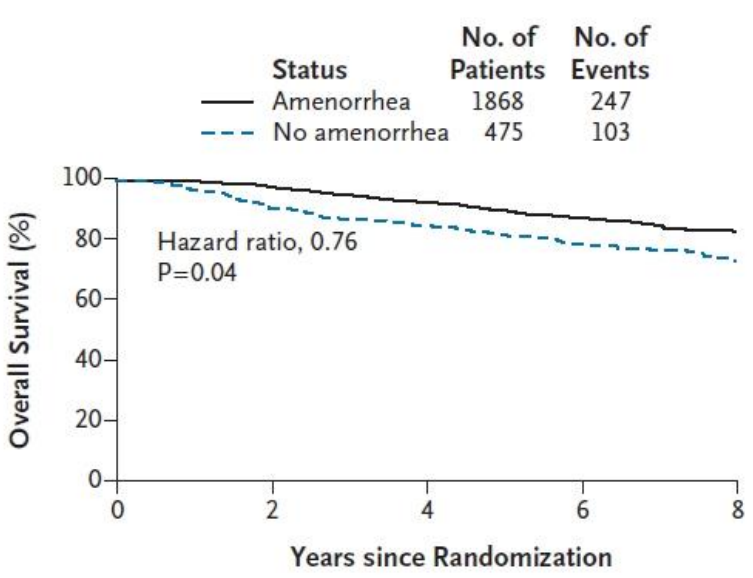
Trial	Subjects	Intervention	Regimen	F/U	Results
Sverrisdottir (2009)	n=260 A: 45	Goserelin (n=22) Control (n=20)	CMF	36m	Amenorrhea rates -XGOSE: 64% -Control: 90%
Badawy (2009)	n=80 A: 30/29.2	Goserelin (n=39) Control (n=39)	FAC	8m	Amenorrhea rates -XGOSE: 10% -Control: 67%
Gerber B (2011)	n=60 A: 35/38.5	Goserelin (n=28) Control (n=28)	FEC, EC, FAC, TAC, others	24m	Regular menses at 6m -XGOSE: 63% -Control: 57%
del Mastro (2011)	n=281 A: 39/39	Triptorelin (n=148) Control (n=133)	Various	12m	Early MP rates -XTRIP: 9% -Control: 26%
Munster (2012)	n=49 A: 39/38	Triptorelin (n=27) Control (n=22)	ACT, AC, FEC, FAC	18m	Amenorrhea rates -XTRIP: 12% -Control: 10%
Elgindy (2013)	n=100 A: 33.3/32.3	GnRH anta+ago Control	FAC	12m	Resumption of mens : No diff (about 80%)

Limitation of GnRHa use

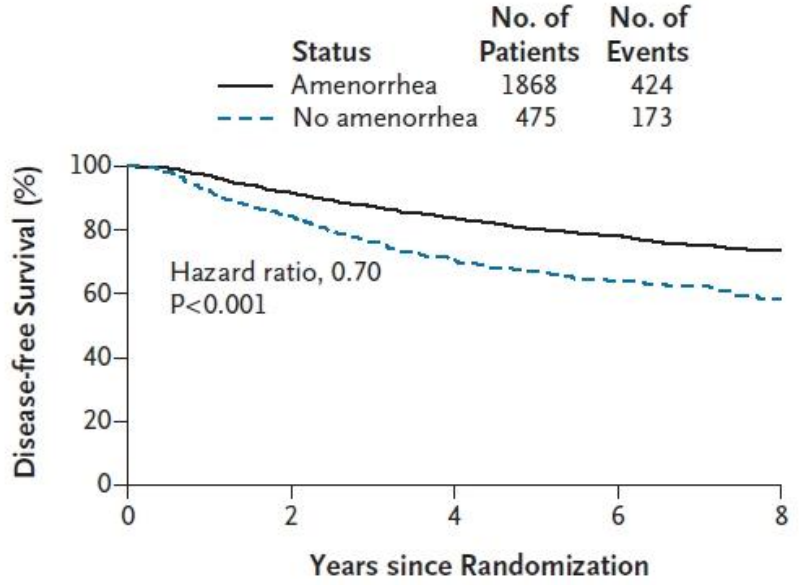
- Benefits in terms of fertility outcomes are lacking
- Studies have been limited by inadequate follow-up and the assessment of surrogate measures of fertility rater than pregnancy rates
- While GnRH analogs are not currently FDA approved for fertility preservation, these medication may be used “off label”
- Further studies are required to establish the efficacy of this treatment and determine which patients are the best candidates

GnRH agonist

Improvement of survival in patients with amenorrhea for > 6 months



No. at Risk					
Total	2343	2251	2067	1111	373
Amenorrhea	1868	1825	1685	897	284
No amenorrhea	475	426	382	214	89



No. at Risk					
Total	2343	2101	1838	974	323
Amenorrhea	1868	1705	1519	797	250
No amenorrhea	475	396	319	177	73

Amenorrhea was associated with improved survival regardless of the treatment and estrogen-receptor status.

Swain SM, NEJM 2010

Options for preserving fertility

- **Non-surgical**
  - Cryopreservation of embryos & oocytes
  - Administration of gonadotropin-releasing hormone analogues (GnRHa)

- **Surgical**
  - Cryopreservation of ovarian tissue

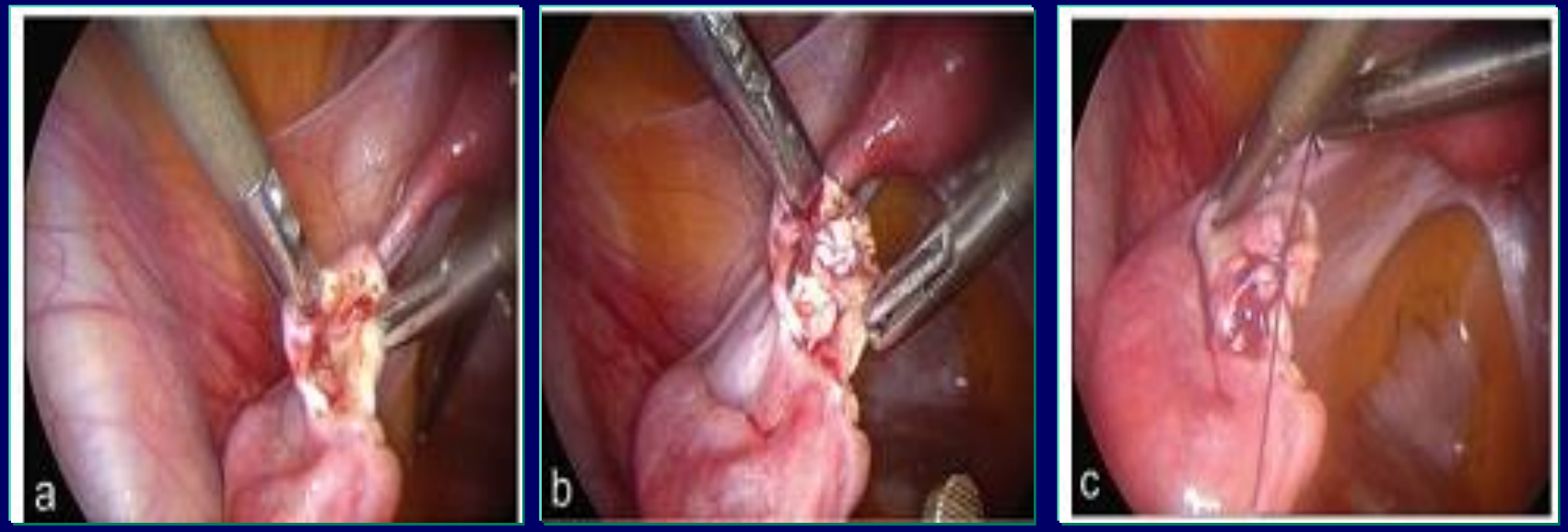
Ovarian tissue cryopreservation

- Ovarian cortex contains hundreds of primordial follicles
  - Large potential source of oocytes later
  - Less susceptible to cryo/thawing injury

- Limited numbers of reported successful pregnancies
  - A total of 29 live births from 12 patients[1]

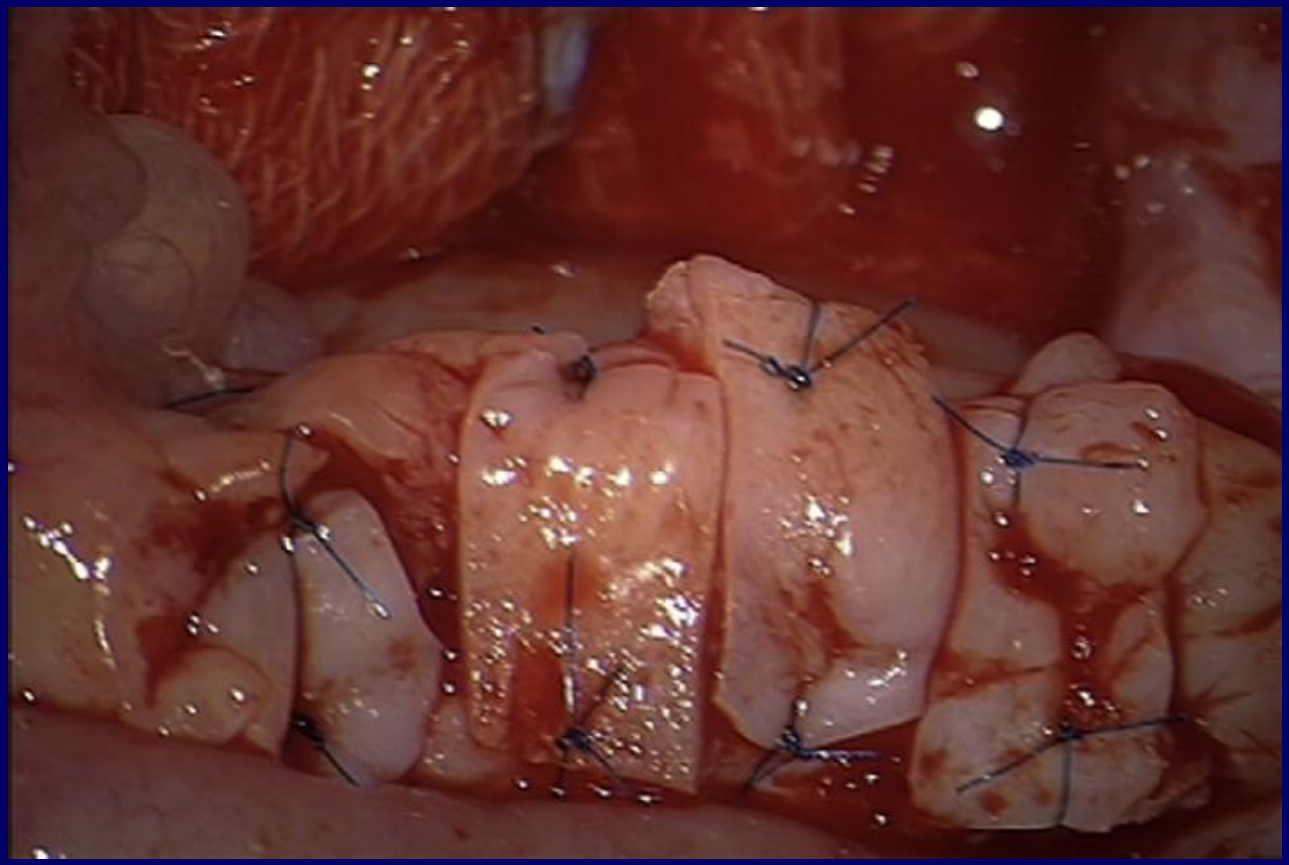
[1]McLaren JF, AJOG 2012

Orthotopic transplantation



Donnez J, Hum Reprod 2006

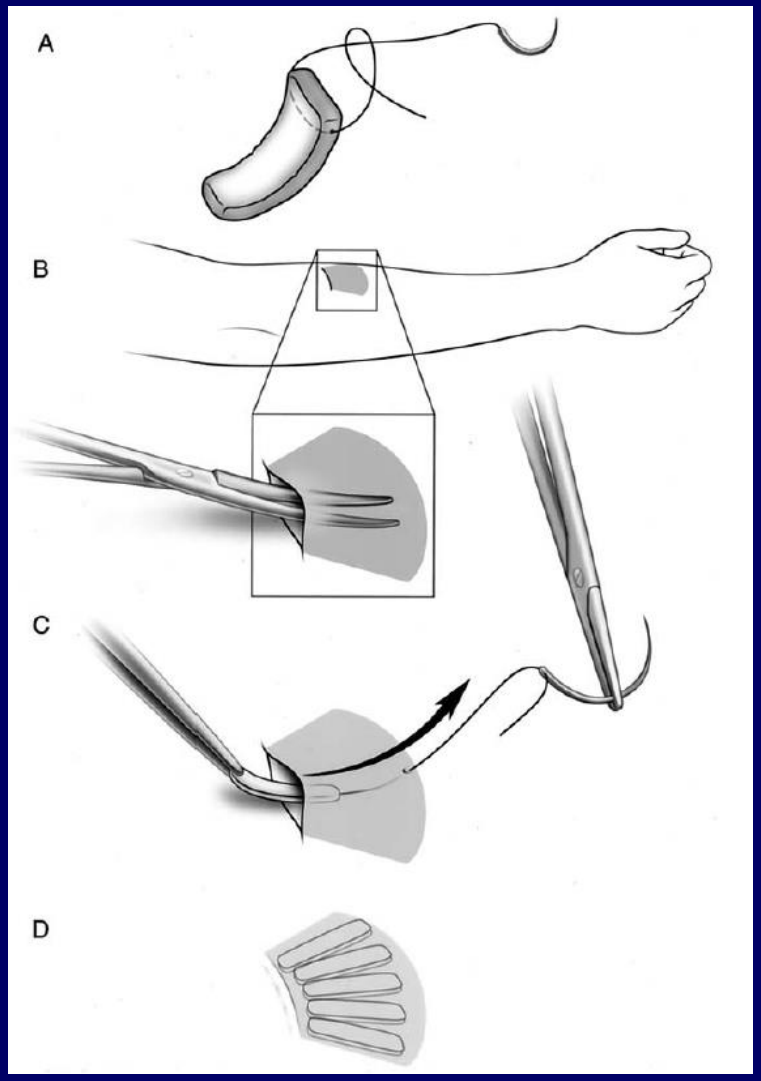
Orthotopic transplantation



Ovarian cortex reimplantation on the ovarian medulla

Donnez J, Fertil Steril 2013

Heterotopic transplantation



Oktay K, Fertil Steril 2003

Ovarian tissue cryopreservation

Advantages and disadvantages for reimplantation sites

	Heterotopic (subcutaneous)	Orthotopic
Advantages	- No limitation of numbers of fragments transplanted - Easy transplantation procedure - Easy access for follicular monitoring and oocyte collection	- Possibility of natural conception - Restoration of fertility demonstrated - Favorable environment for follicular development
Disadvantages	- Restoration of fertility not yet demonstrated - IVF procedure required - Effect of the local environment on oocyte quality is unknown	- Number of fragments transplanted limited by ovarian size - Invasive transplantation procedure

Donnez J, Fertil Steril 2013

Ovarian tissue cryopreservation

Limitations

- No live births have been reported who cryopreserved tissue before puberty
- 60% loss of primordial follicles & failure in 20% of grafts
- Ovarian function generally resumes between 60-130 days post-transplant, but lasts for up to 3 years
- Potential for reseeding tumor cells

McLaren JF, AJOG 2012; Martinez F, Gynecol Endocrinol 2013;
ASRM Practice Committee 2013

Ovarian tissue cryopreservation

Risk of transferring malignant cells in breast cancer

- Incidence of ovarian metastasis: 13.2~37.8%

  : most commonly in advanced-stage cancers

- Autotransplantation of frozen-thawed ovarian fragments appears to be safe in patients with low-stage cancers

- Further procedures, such as PCR & long-term xenografting, are necessary to prove the safety

Gagnon Y, Cancer 1989; Perrotin F, Gynecol Obstet Fertil 2001;
Li CI, JAMA 2003; Kyono K, Fertil Steril 2010; Donnez J, Ann Med 2011

Ovarian tissue cryopreservation

Advantages

Immediate harvesting (can start treatment without delay)
No male partner/gamete donor needed
Resume endocrine function
Resume and preserve reproductive function
Suitable for prepubertal girls (as well as adults)

Disadvantages

Requires surgical procedure for tissue harvesting and transfer
Possibility of reintroducing malignant cells
Low success rate

Summary

	Ovarian tissue freezing	Oocyte freezing	Embryo freezing	GnRH agonist
In prepubertal	Yes	Limited	No	No
In patients with low ovarian reserve	Limited	Limited	Limited	Limited
Ovarian stimulation	No	Yes	Yes	No
Delay in treatment	No	Yes	Yes	No
Surgery	Yes	No	No	No
Cancer seeding	Yes (theoretical)	No	No	No
Live birth	Yes	Yes	Yes	Yes
Restoration of endocrine function	Possible	No	No	Possible

Modified from Oktem O, 2010

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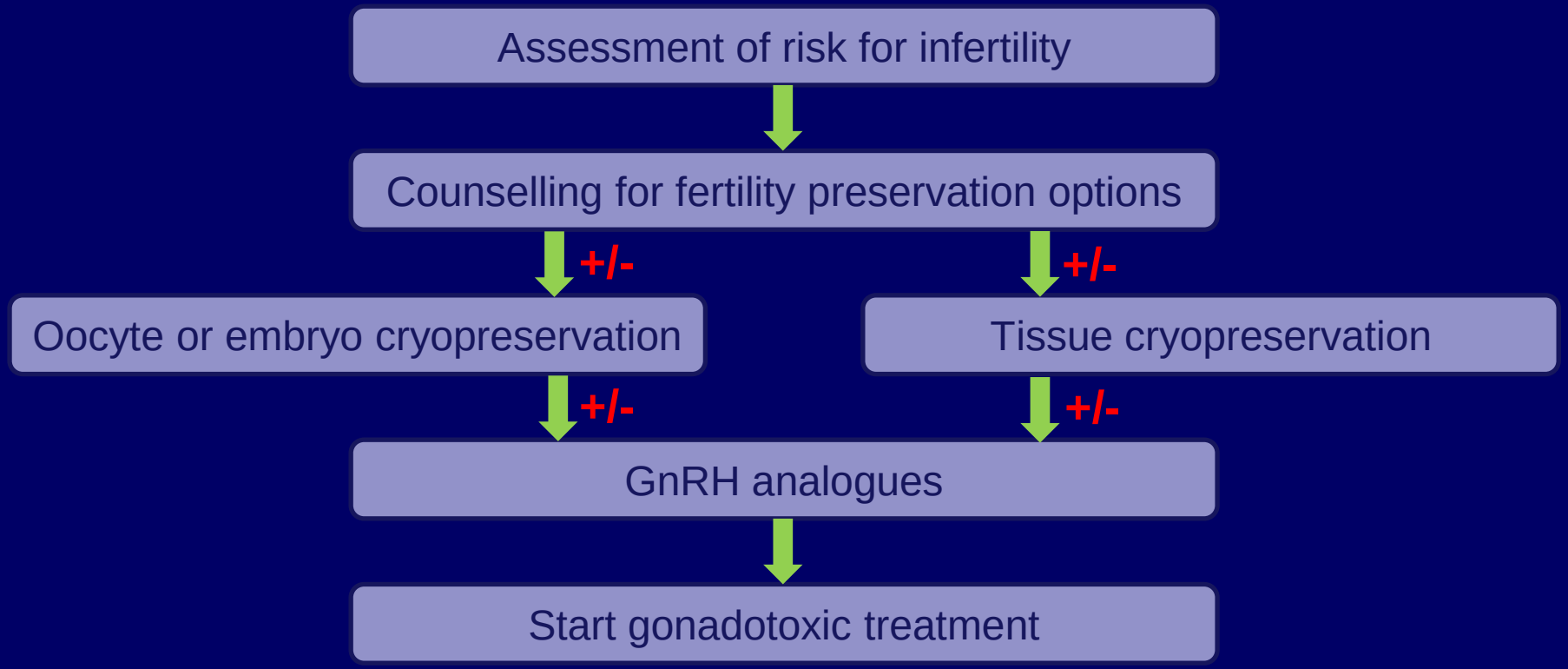
ASRM Practice Committee Guideline (2013)

- Fertility preservation technologies are rapidly evolving with hope that new and refined techniques will emerge.
- Patients facing treatments likely to impair reproductive function deserve prompt counseling regarding their options for fertility preservation and rapid referral to an appropriate program.
- At the present time, embryo and oocyte cryopreservation remain the principal established modalities for fertility preservation.
- Ovarian tissue cryopreservation and the use of GnRH analogs still should be viewed as investigational.

Fertil Steril 2013

Currently suggested algorithm for fertility preservation



Thanks for your attention!

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