Διατήρηση Γονιμότητας σε γυναίκες;;;; με καρκίνο;;;;;;

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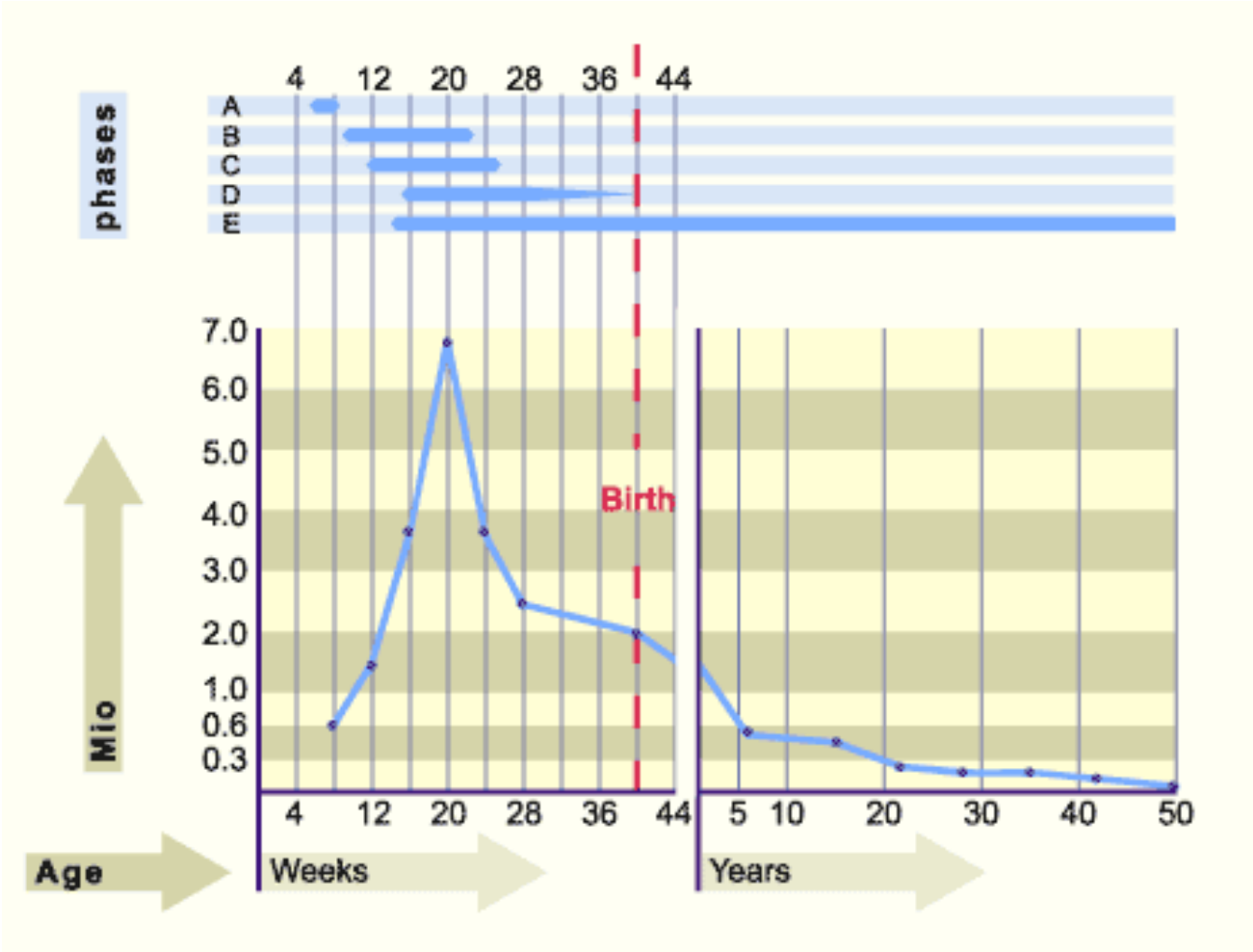
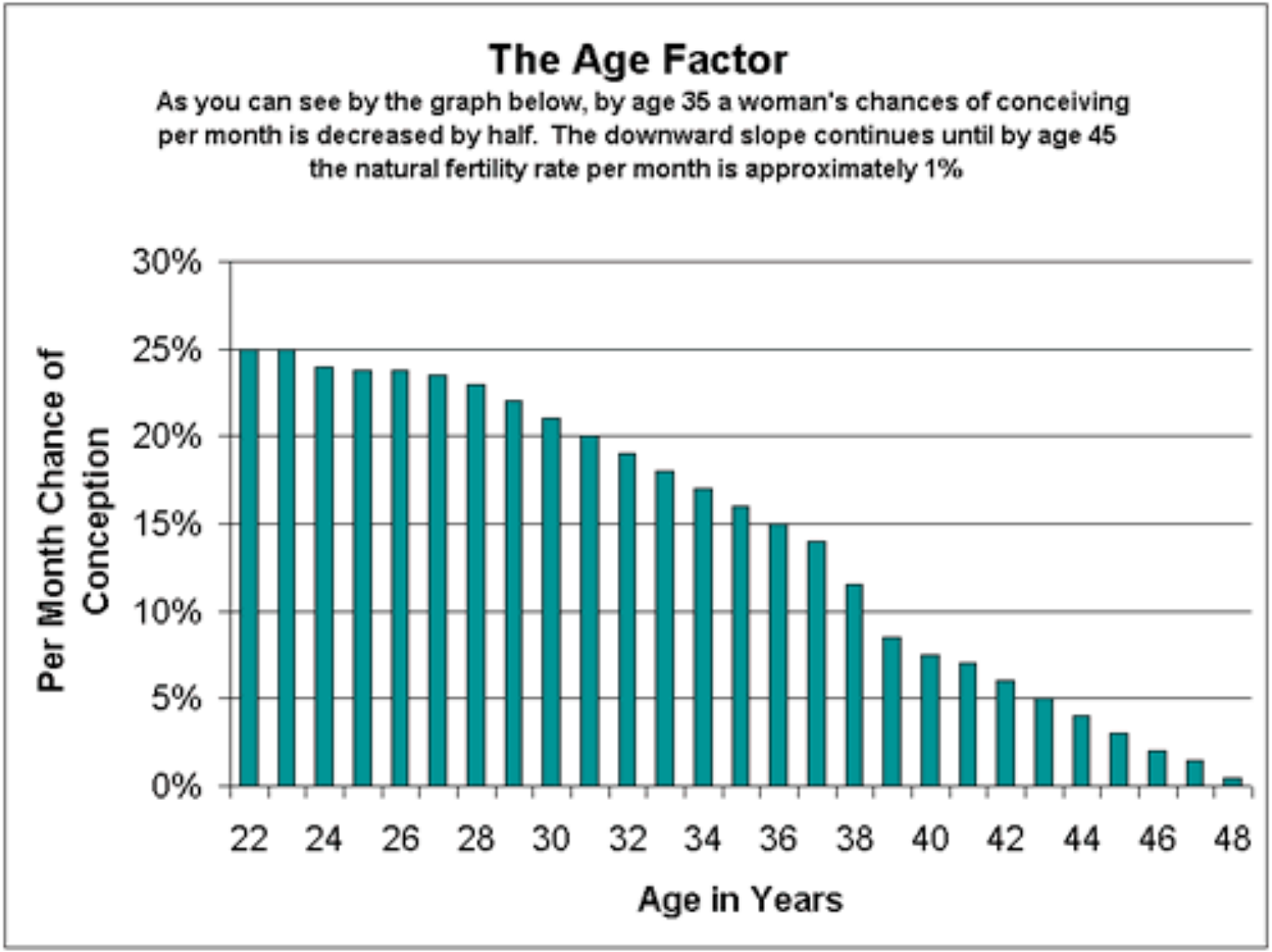
AUSTIN POWERS
"I'VE BEEN FROZEN FOR 30 YEARS.
I'VE GOT TO SEE IF MY BITS AND
PIECES ARE STILL WORKING"

Ovarian reserve



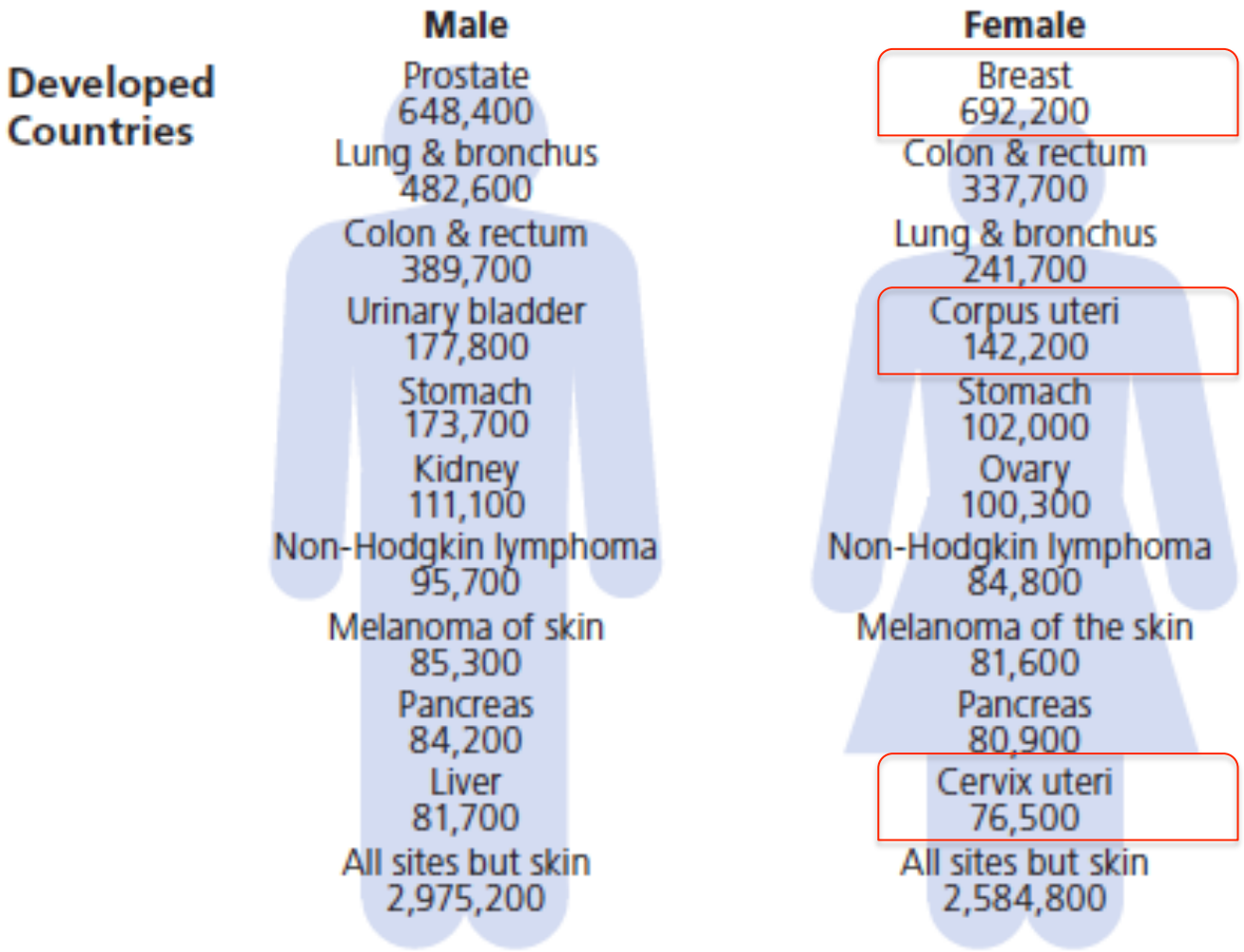
Age and Fertility



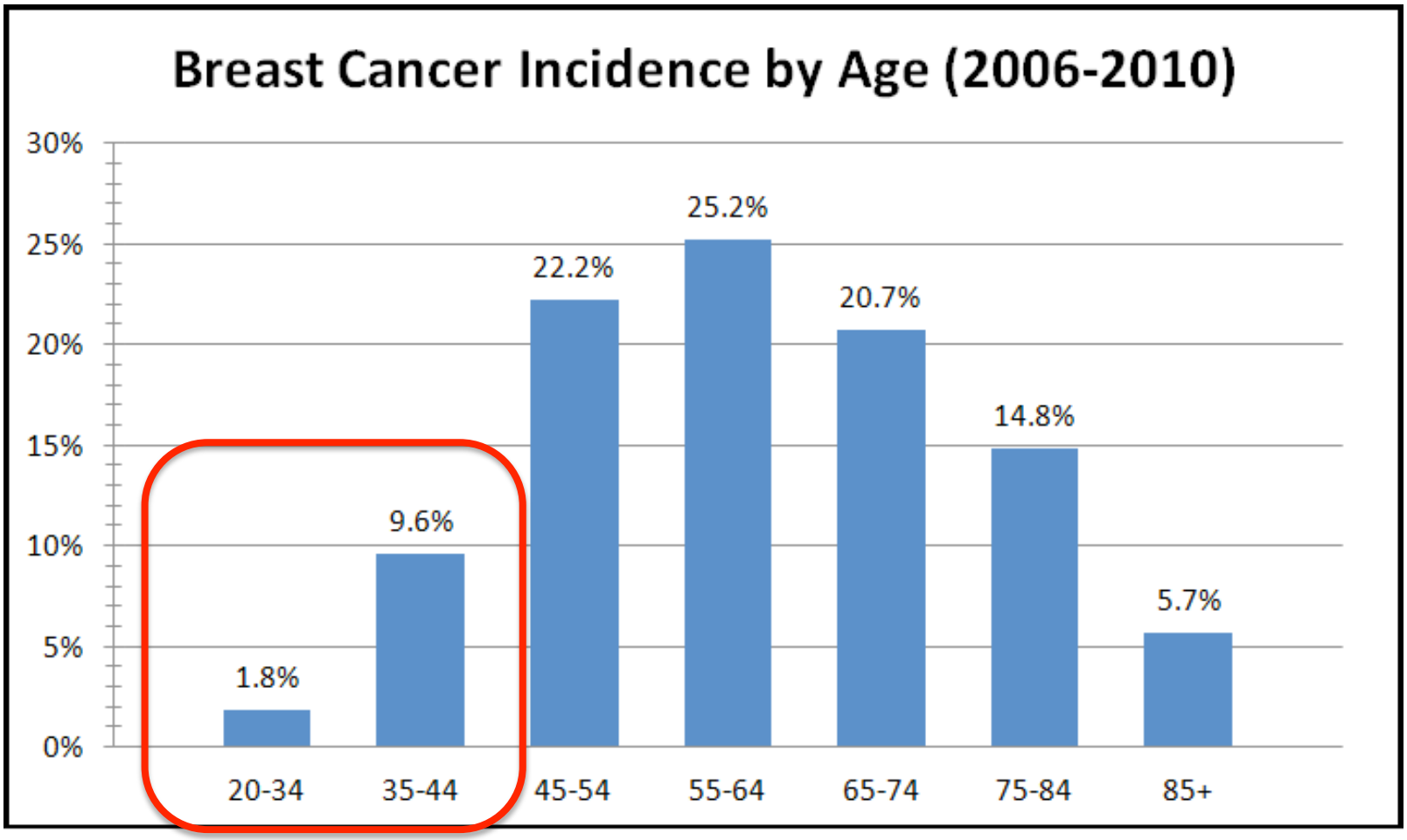

Bloomberg Businessweek
FREEZE YOUR EGGS, FREE YOUR CAREER
A new fertility procedure gives women more choices in the quest to have it all


Let's stop rushing to find husbands
and start rushing to freeze our eggs.
someecards

Estimated New Cancer Cases for Leading Cancer Sites



Breast cancer age distribution.



National Cancer Institute

Five-year Relative Survival Rates*(%) for Selected Cancers among Individuals† Aged 15 and Older in Select Countries

	United States (1999-2006)	England (1995-1999)	Demark (1995-1999)	Austria (1995-1999)	Poland (1995-1999)	Belgium (1995-1999)	Germany (1995-1999)
Brain	26.1	17.6	18.1	20.8	19.8	22.7	22.6
Breast (female)	89.0	77.3	77.5	80.0	73.7	77.3	78.3
Colorectal	65.0	50.5	49.3	58.1	38.8	57.4	57.5
Esophagus	17.0	9.9	5.2	10.6	7.6	19.0	19.2
Hodgkin lymphoma	84.2	78.6	79.6	79.6	78.4	83.5	—
Kidney	68.4	45.6	45.1	68.1	53.8	58.8	64.9
Larynx	61.3	63.9	59.1	63.6	47.9	58.7	58.5
Leukemia	50.1	42.3	45.1	32.7	32.6	42.1	46.7
Liver	13.8	7.7	—	9.1	7.9	11.5	8.1
Lung, bronchus, and trachea	15.8	8.4	7.9	14.4	9.2	16.5	13.2
Melanoma of the skin	91.4	84.6	85.1	82.7	63.0	77.9	83.4
Multiple myeloma	38.2	30.6	28.4	30.1	23.1	46.7	28.8
Non-Hodgkin lymphoma	67.1	50.7	49.4	50.6	40.2	56.5	56.6
Oral cavity	60.8	53.6	45.9	40.3	36.7	41.5	60.7
Ovary	45.2	30.2	32.3	44.9	31.0	40.5	36.9
Pancreas	5.6	4.4	2.9	6.8	5.2	9.6	5.7
Prostate	99.1	69.7	47.7	86.7	60.5	83.3	81.6
Stomach	25.9	16.1	14.4	30.3	14.4	31.5	27.5
Testis	95.4	89.7	90.2	88.2	—	92.7	—
Thyroid	97.3	77.6	76.0	84.9	82.3	72.9	84.3
Urinary bladder	79.3	72.4	68.9	77.8	61.2	69.6	78.2
Uterine cervix	70.2	59.1	64.0	63.7	51.5	65.1	60.5
Uterine corpus	83.8	75.2	82.5	78.4	72.7	76.9	76.8
All sites	65.9	46.2	—	56.1	38.6	54.2	52.3

FERTILITY/ENDOCRINE CONSIDERATIONS

Fertility and endocrine considerations

- Fertility preservation as well as sexual health and function should be an essential part in the management of AYAs with cancer who are at any risk for infertility due to cancer treatments[i]
- Discuss risks for infertility due to cancer and its therapy, fertility preservation, and contraception prior to the start of therapy[j]
  - Men are at risk for azoospermia following therapy, which may or may not resolve over time
  - Women are at risk for premature ovarian failure following therapy

Initiate referral for fertility preservation clinics within 24 hours for all patients who choose the option of fertility preservation
Refer to a mental health professional to assist with complex decision making if needed.
See Psychosocial/ Behavioral Considerations (AYAO-7)

Males

- Discuss the possibility of sperm banking
- Suggest a local sperm bank, or available online sperm banking kit

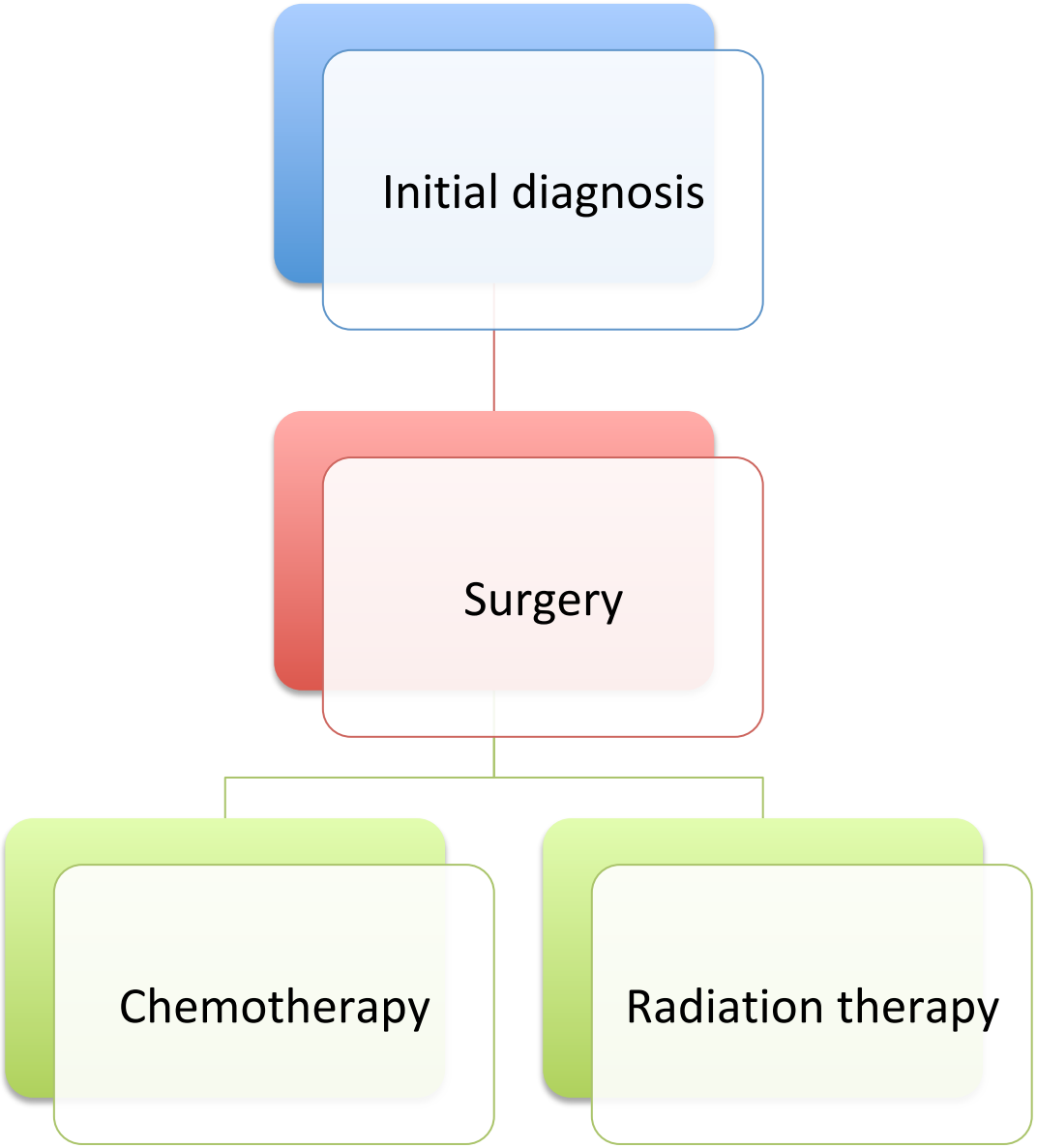
Females

- Discuss the possibility of embryo cryopreservation or oocyte cryopreservation
  - Initiate if provider deems that therapy can be delayed long enough for a cycle of oocyte stimulation (for low- and intermediate-risk Hodgkin's lymphoma, low-grade sarcomas, and breast cancer)
- Oophoropexy
  - Ovaries may be surgically moved away from the planned radiation field, either during cancer surgery or in a separate procedure
- Menstrual suppression
  - Medroxyprogesterone, oral contraceptives, or gonadotropin-releasing hormone (GnRH) agonists may be used in protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia
  - It is controversial whether menstrual suppression would protect the ovaries, but emerging data suggest that menstrual suppression with GnRH agonists may protect ovaries in young women with breast cancer before the initiation of chemotherapy.[k]

[i] Levine J, Canada A, Stern CJ. Fertility preservation in adolescents and young adults with cancer. J Clin Oncol 2010;28:4831-4841.

[j] The impact of cancer therapy on fertility is related to the age of the patient at the time of treatment and is dependent on the duration, dose intensity, and type of treatment. See NCCN Guidelines for

Cancer Treatment



Chemotherapy and Reproductive Function

High risk of prolonged azoospermia in men or amenorrhea in women

- Cyclophosphamide
- Ifosphamide
- Melphalan
- Busulfan
- Nitrogen mustard
- Procarbazine
- Chlorambucil

Intermediate risk

Cisplatin with low cumulative dose
Carboplatin with low cumulative dose
Adriamycin

Low risk

Treatment protocols for Hodgkin lymphoma without alkylating agents
Bleomycin
Actinomycin D
Vincristine
Methotrexate

Rodriguez-Wallberg and Oktay, *J Ped Hematol Oncol, 2010,*

Radiation and Reproductive Function

High risk of prolonged azoospermia in men or amenorrhea in women

- Total Body Irradiation (TBI) for bone marrow transplant/stem cell transplant
- Testicular radiation dose "/>2.5 Gy in adult men
- Testicular radiation dose ≥ 6 Gy in pre-pubertal boys
- **Pelvic or whole abdominal radiation dose ≥ 6 Gy in adult women**
- **Pelvic or whole abdominal radiation dose ≥ 10 Gy in post-pubertal girls**
- **Pelvic radiation or whole abdominal dose ≥ 15 Gy in pre-pubertal girls**

Intermediate risk

- Testicular radiation dose 1-6 Gy from scattered pelvic or abdominal radiation
- Pelvic or whole abdominal radiation dose 5-10 Gy in post-pubertal girls
- Pelvic or whole abdominal radiation dose 10-15 Gy in pre-pubertal girls
- Craniospinal radiotherapy dose ≥ 25 Gy

Rodriguez-Wallberg and Oktay, *J Ped Hematol Oncol, 2010,*

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1,2,3,4]

Regimens for HER2-negative disease (all category 1)[5]

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

FERTILITY AND BIRTH CONTROL

- See NCCN Guidelines for Adolescent and Young Adult Oncology.
- All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy
- Although amenorrhea frequently occurs during or after chemotherapy, it appears that the majority of women younger than 35 y resume menses within 2 y of finishing adjuvant chemotherapy.
- Menses and fertility are not necessarily linked. Absence of regular menses, particularly if the patient is taking tamoxifen, does not necessarily imply lack of fertility. Conversely, the presence of menses does not guarantee fertility. There are limited data regarding continued fertility after chemotherapy.
- Patients should not become pregnant during treatment with radiation therapy, chemotherapy, or endocrine therapy.
- Although data are limited, hormone-based birth control is discouraged regardless of the hormone receptor status of the patient's cancer.
- Alternative methods of birth control include intrauterine devices (IUDs), barrier methods, or, for patients with no intent of future pregnancies, tubal ligation or vasectomy for the partner.
- No therapy has been shown to preserve fertility in patients receiving chemotherapy.
- Breast feeding following breast-conserving cancer treatment is not contraindicated. However, the quantity and quality of breast milk produced by the breast conserved may not be sufficient or may be lacking some of the nutrients needed. Breast feeding during active treatment with chemotherapy and endocrine therapy is not recommended.

Time is important!!!

Cancer diagnosis → Fertility preservation → Treatment

Fertility preservation for women with cancer

Fertility preserving surgery

Protection from radiation therapy

- Transposition of the ovaries
- Shield during treatment

Protection from chemotherapy

- GnRH analogs
- Oral Contraceptives

Assisted Reproduction

Gynecological cancer/fertility preserving surgery

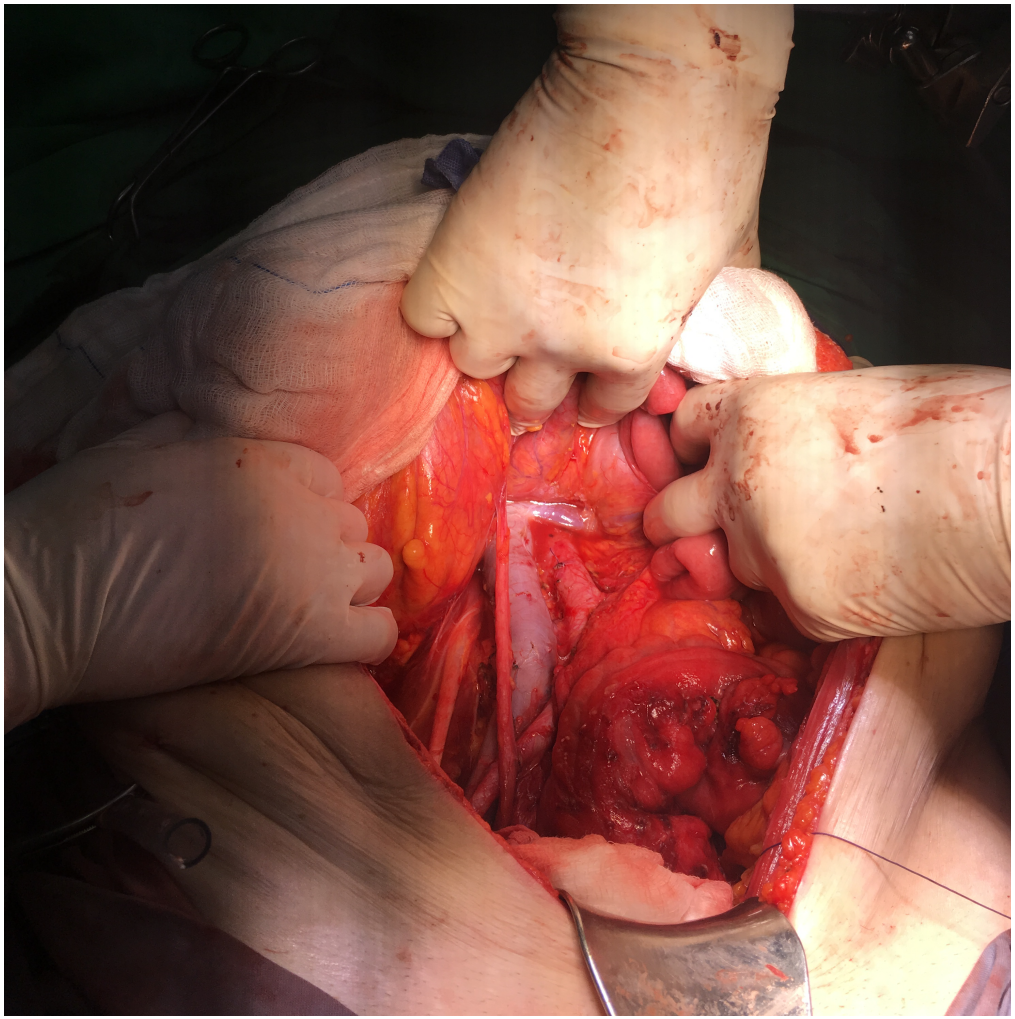
Diagnosis	Type of surgery	Description	Obstetric outcome	Oncologic outcome
Cervical cancer stage IA1,1A2,1B1	Radical vaginal trachelectomy	Laparoscopic pelvic lymphadenectomy. Vaginal resection of the cervix and surrounding parametria keeping the corpus of the uterus and the ovaries intact	Spontaneous pregnancies described in up to 70%. Risk of second trimester pregnancy loss and preterm delivery	Rates of recurrence and mortality are comparable to those described for similar cases treated by means of radical hysterectomy or radiation therapy
Borderline ovarian tumors FIGO stage I	Unilateral oophorectomy	Removal of the affected ovary only, keeping in place the unaffected one and the uterus	Pregnancies have been reported and favorable obstetric outcome	Oncologic outcome is comparable with the more radical approach of removing both ovaries and the uterus. Recurrence 0-20% vs 12-58% when only cystectomy was performed

Fertility-sparing interventions in female patients.
Rodriguez-Macias Wallberg et al, *J Pediatric Blood & Cancer, 2009,*

Gynecological cancer/fertility preserving surgery

Ovarian epithelial cancer stage I, grade 1	Unilateral oophorectomy	Removal of the affected ovary only, keeping in place the unaffected one and the uterus	Pregnancies have been reported and favorable obstetric outcome	7% recurrence of the ovarian malignancy and 5% deaths
Malignant ovarian germ cell tumors/sex cord stromal tumors	Unilateral oophorectomy	Removal of the affected ovary only	Pregnancies have been reported and favorable obstetric outcome	Risk of recurrence similar to historical controls
Endometrial adenocarcinoma Grade 1, stage 1A (without myometrial or cervical invasion)	Hormonal treatment with progestational agents for 6 months	Follow-up with endometrial biopsies every 3 months	Pregnancies have been reported	Recurrence rate 30-40%. Five percent recurrence during progesterone treatment

Fertility-sparing interventions in female patients.
Rodriguez-Macias Wallberg et al, *J Pediatric Blood & Cancer, 2009,*



Fertility sparing surgery in early stage epithelial ovarian cancer

Antonino Ditto[1], Fabio Martinelli[1], Domenica Lorusso[1], Edward Haeusler[2], Marialuisa Carcangiu[3], Francesco Raspagliesi[1]

Departments of [1]Gynecologic Oncology, [2]Anesthesiology, and [3]Pathology, IRCCS National Cancer Institute, Milan, Italy

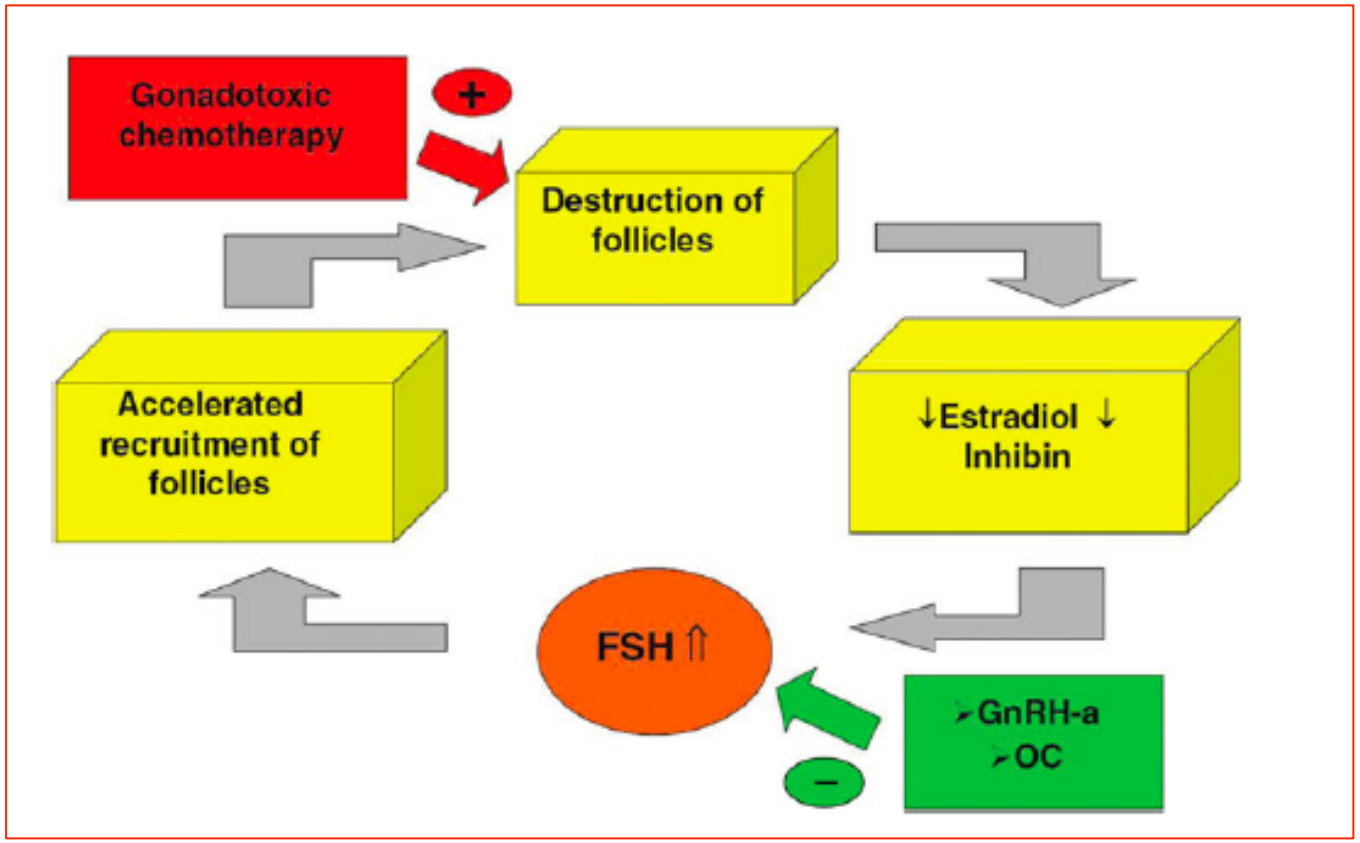
See accompanying editorial by Kajiyama on page 270.

Table 3. Obstetrical outcome, literature review*

Author (year)	No. of patients	No. of patients having pregnancies	No. of patients with term deliveries	No. of patients with abortion
Zanetta et al. (1997) [17]	56	20	17 babies	4 (2 ectopic preg)
Raspagliesi et al. (1997) [14]	10	3	3	–
Morice et al. (2005) [12]	34	9 (10 preg)	7	1
Colombo et al. (2005) [20]	24	7	6	–
Park et al. (2008) [7]	62	–	22	2
Anchezar et al. (2009) [18]	18	6 (7 preg)	6	–
Kajiyama et al. (2010) [19]	60	13	10	3
Satoh et al. (2010) [10]	211	55 (76 preg)	53 (66 babies)	–
Fruscio et al. (2013) [11]	240	84	68 (93 babies)	16
Current study	18	7	5 (5 babies)	2

*More recent case series may include previously published data from the same group.

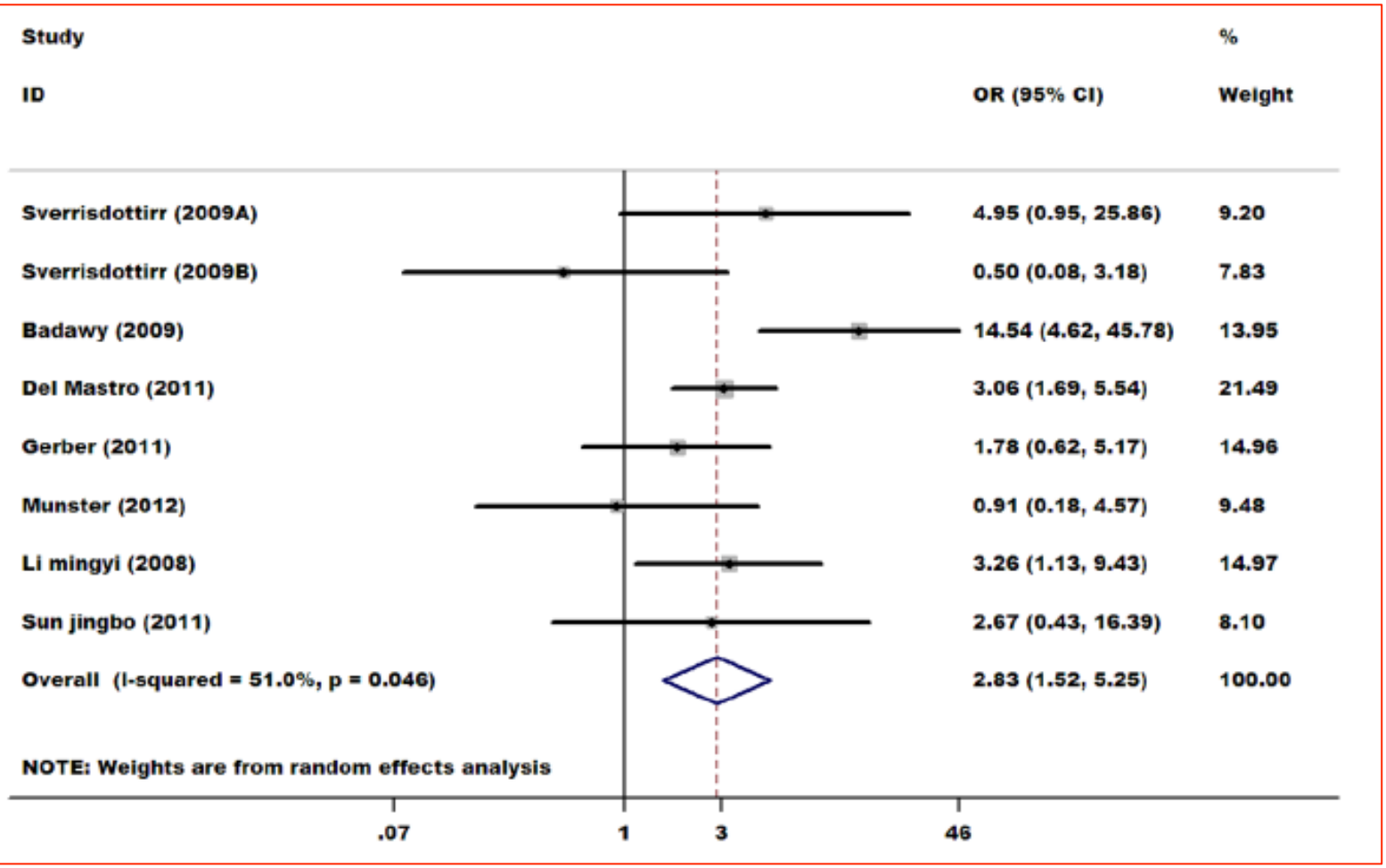
Gynecological cancer/ prophylaxis from radiation or chemotherapy



Human Reproduction Update, Vol.14, No.6 pp. 543–552, 2008

PLOS ONE

Gonadotropin-Releasing Hormone Analog Cotreatment for the Preservation of Ovarian Function during Gonadotoxic Chemotherapy for Breast Cancer: A Meta-Analysis

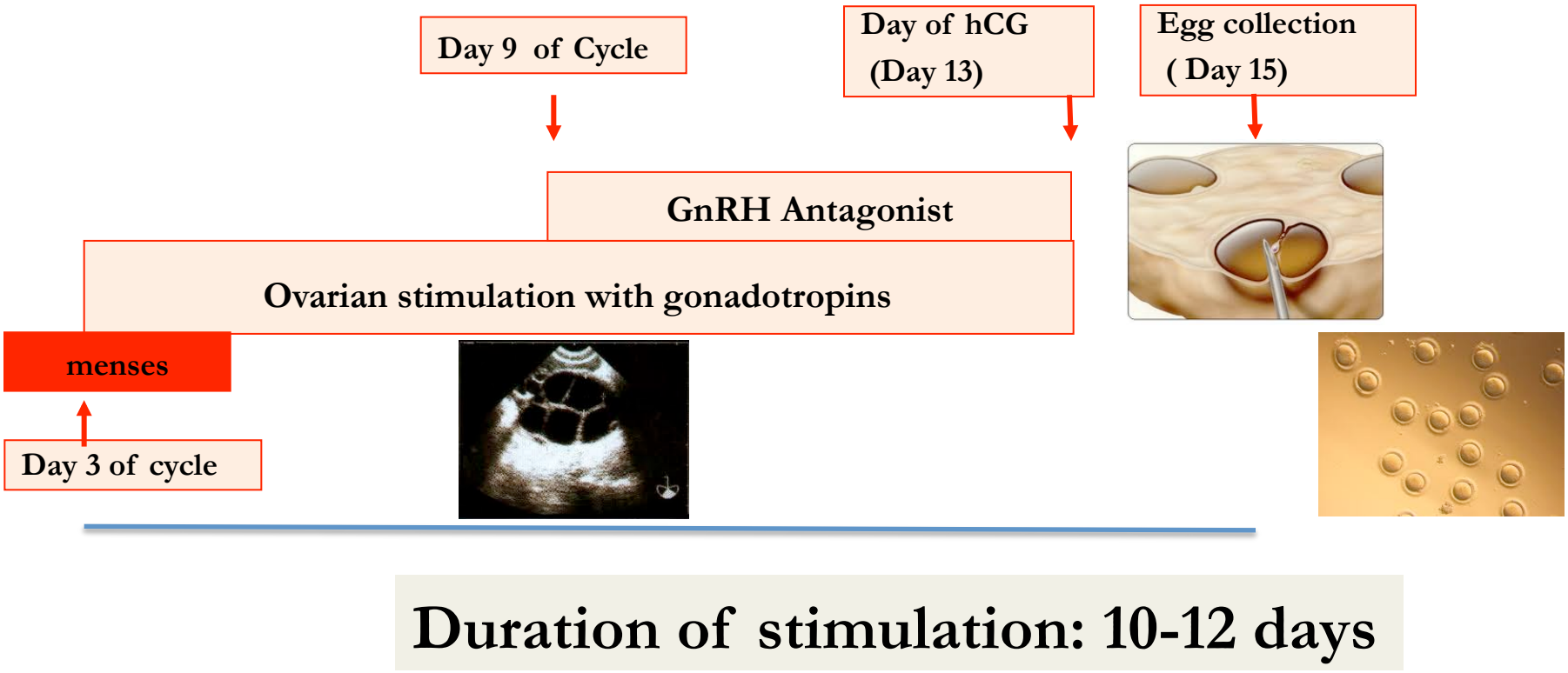


Assisted Reproduction for women with cancer

Assisted reproductive technologies

- Oocyte or embryo freezing
- Ovarian tissue cryopreservation
- Oocyte donation
- Surrogacy

Ovarian stimulation



Duration of stimulation: 10-12 days

Few years ago

Embryo cryopreservation represent the most efficacious method for fertility preservation in women with cancer

But.....

- Requires ovarian stimulation to harvest oocytes,
  - Sperm is also required!!!!!
  - Requires time?????
  - Associated with high E2 levels

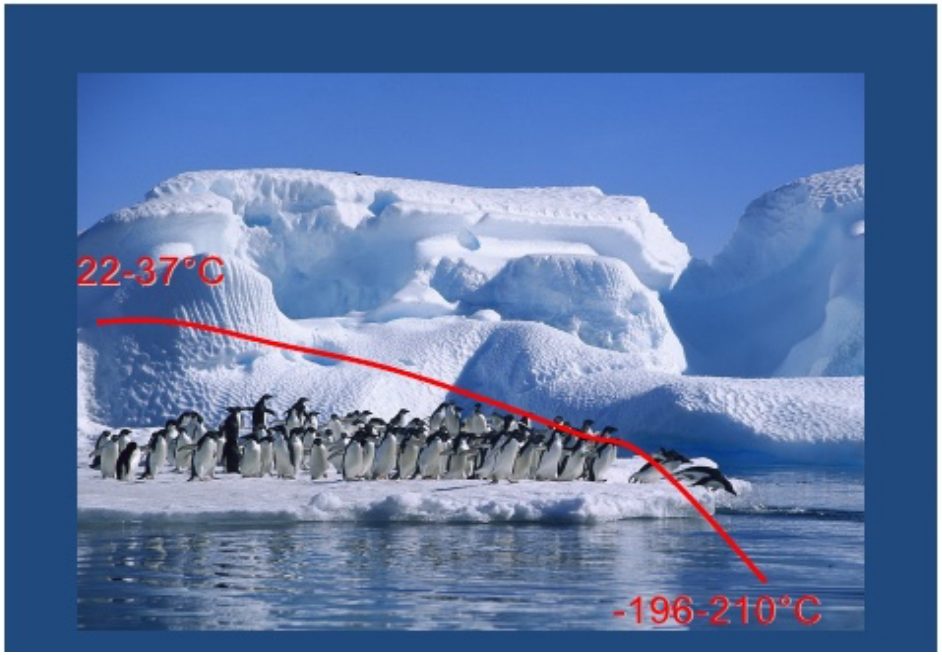
Now

Oocyte cryopreservation equally successful to embryo cryopreservation

Cryopreservation of eggs and embryos

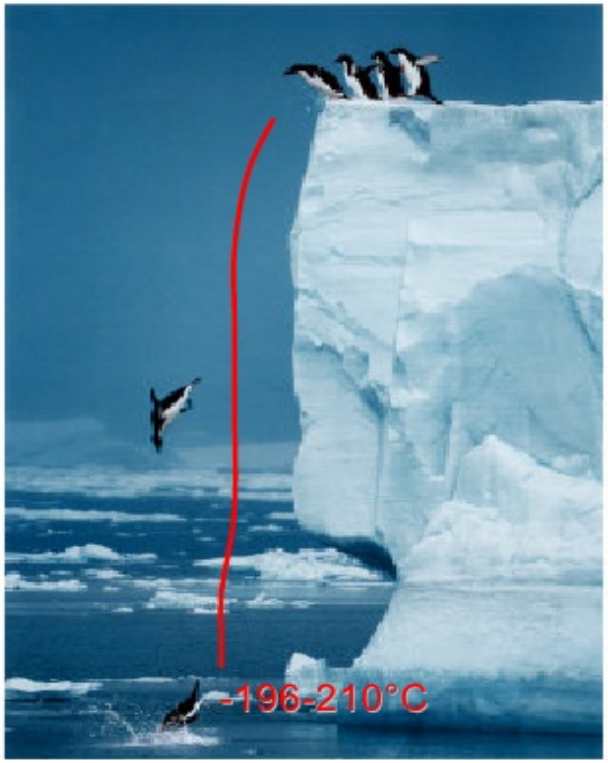
Techniques

Slow freezing



Vitrification

22-37°C



Cryopreservation procedures

Slow Freezing

Transformation of a liquid in solid with formation of ice. It is essential that the ice does not form inside the cell:

- Use of CPAs at low concentration (1,5M).
- Cooling rate (0,3ºC/min).
- Programmable freezers.

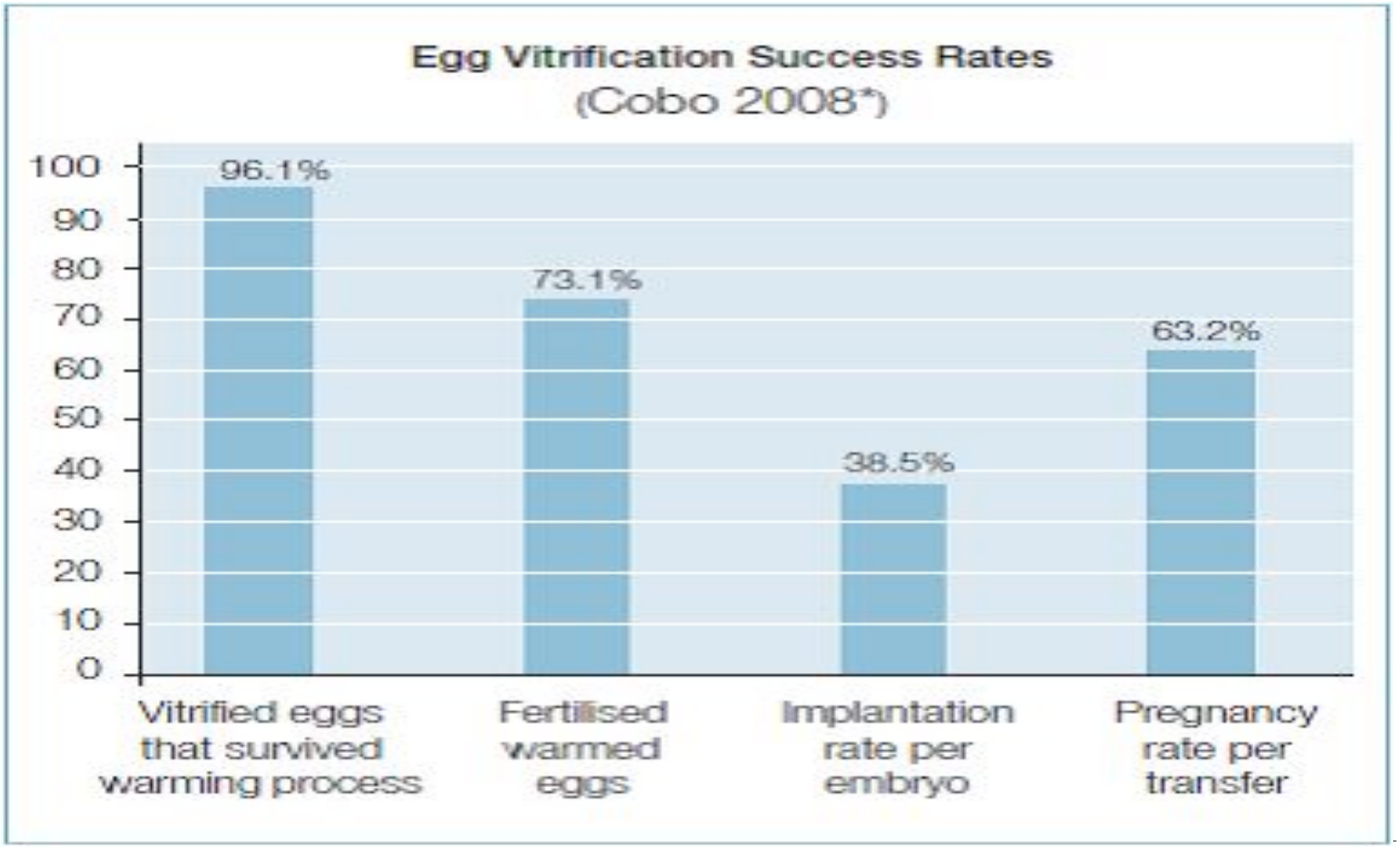
Vitrification

Transformation of a liquid in very viscous solid with no ice:

- High CPAs concentration (3-6M).
- Very high cooling rates: 15.000 a 30.000 ºC/min.
- Direct immersion into liquid Nitrogen.


Frozen
Kidney
Vitrified
Kidney

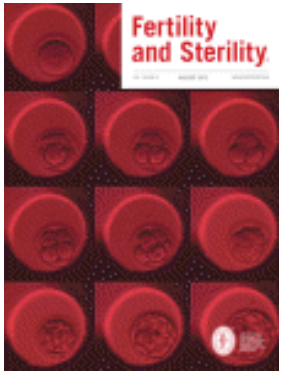
Oocyte Vitrification



Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama



Summary of randomized controlled trials comparing fresh versus vitrified oocytes.

	Cobo 2008 (24)	Cobo 2010 (26)	Rienzi 2010 (25)	Parmegiani 2011 (19)
Patient population	Oocyte donors	Oocyte donors	Infertile patients <43 years of age requiring ICSI with >6 mature oocytes	Infertile patients <42 years of age requiring ICSI with >5 mature oocytes
No. patients	30 vitrification 30 fresh	295 vitrification 289 fresh	40 vitrification 40 fresh	31 vitrification 31 fresh
Mean age at retrieval	26	26	35	35
No. oocytes	231 vitrification 219 fresh	3286 vitrification 3185 fresh	124 vitrification 120 fresh	168 vitrification NA fresh
No. oocytes per retrieval	18.2	11	13	NA
Survival	96.9%	92.5%	96.8%	89.9%
Fertilization rate	76.3 vitrification 82.2 fresh	74% vitrification 73% fresh	79.2% vitrification 83.3% fresh	71% vitrification 72.6% fresh
No. transferred vitrification vs. fresh	3.8 vitrification 3.9 fresh	1.7 vitrification 1.7 fresh	2.3 vitrification 2.5 fresh	2.5 vitrification 2.6 fresh
Day of transfer	3	3	2	2–3
Implantation rate	40.8% vitrification 100% fresh	39.9% vitrification 40.9% fresh	20.4% vitrification 21.7% fresh	17.1% vitrification NA fresh
CPR/transfer vitrification vs. fresh	60.8% (23 vitrification transfers) 100% (1 fresh transfer)	55.4% vitrification 55.6% fresh	38.5% vitrification 43.5% fresh	35.5% vitrification 13.3% fresh
CPR/oocyte thawed	6.1%	4.5%	12%	6.5%

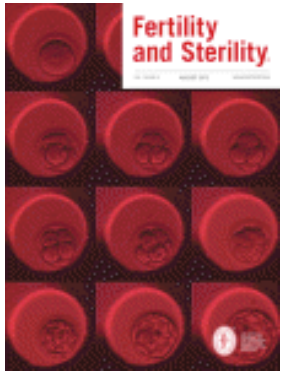
Note: All used vitrification with Cryotop, 15% EG + 15% DMSO + 0.5M sucrose. CPR = clinical pregnancy rate.

Practice Committee. Oocyte cryopreservation. Fertil Steril 2013.

Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama



Oocyte vitrification and warming should no longer be considered experimental.

This document replaces the document last published in 2008 titled, ‘‘Ovarian Tissue and Oocyte Cryopreservation,’’
Fertil Steril 2008;90:S241-6.

Fertil Steril 2013;99:37–43.

VOLUME 31 · NUMBER 19 · JULY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

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

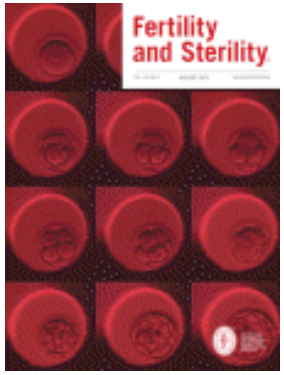
Alison W. Loren, Pamela B. Mangu, Lindsay Nohr Beck, Lawrence Brennan, Anthony J. Magdalinski, Ann H. Partridge, Gwendolyn Quinn, W. Hamish Wallace, and Kutluk Oktay

THE BOTTOM LINE

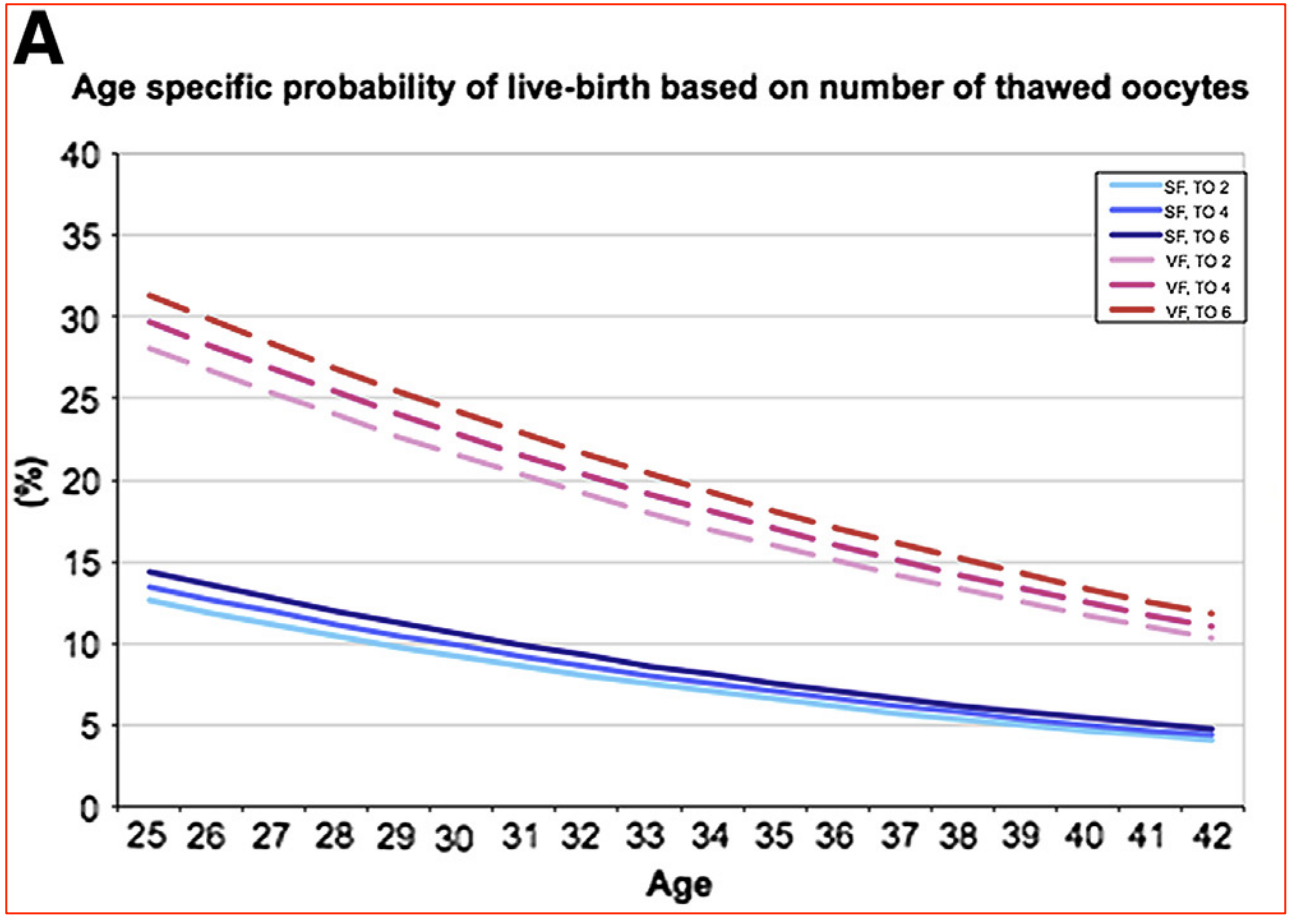
Adult Females

- Present both embryo and oocyte cryopreservation as established fertility preservation methods
- Discuss the option of ovarian transposition (oophoropexy) when pelvic radiation therapy is performed as cancer treatment
- Inform patients of conservative gynecologic surgery and radiation therapy options
- Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method, and these agents should not be relied on to preserve fertility
- Inform patients that other methods (eg, ovarian tissue cryopreservation, which does not require sexual maturity, for the purpose of future transplantation) are still experimental

Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis



Aylin Pelin Cil, M.D.,[a,b] Heejung Bang, Ph.D.,[c] and Kutluk Oktay, M.D., F.A.C.O.G.[a]



How many eggs should I store to achieve a pregnancy?

Surgival rates after thawing 75% and
fertilization rates of 75% are anticipated in women up to 38 years of age.

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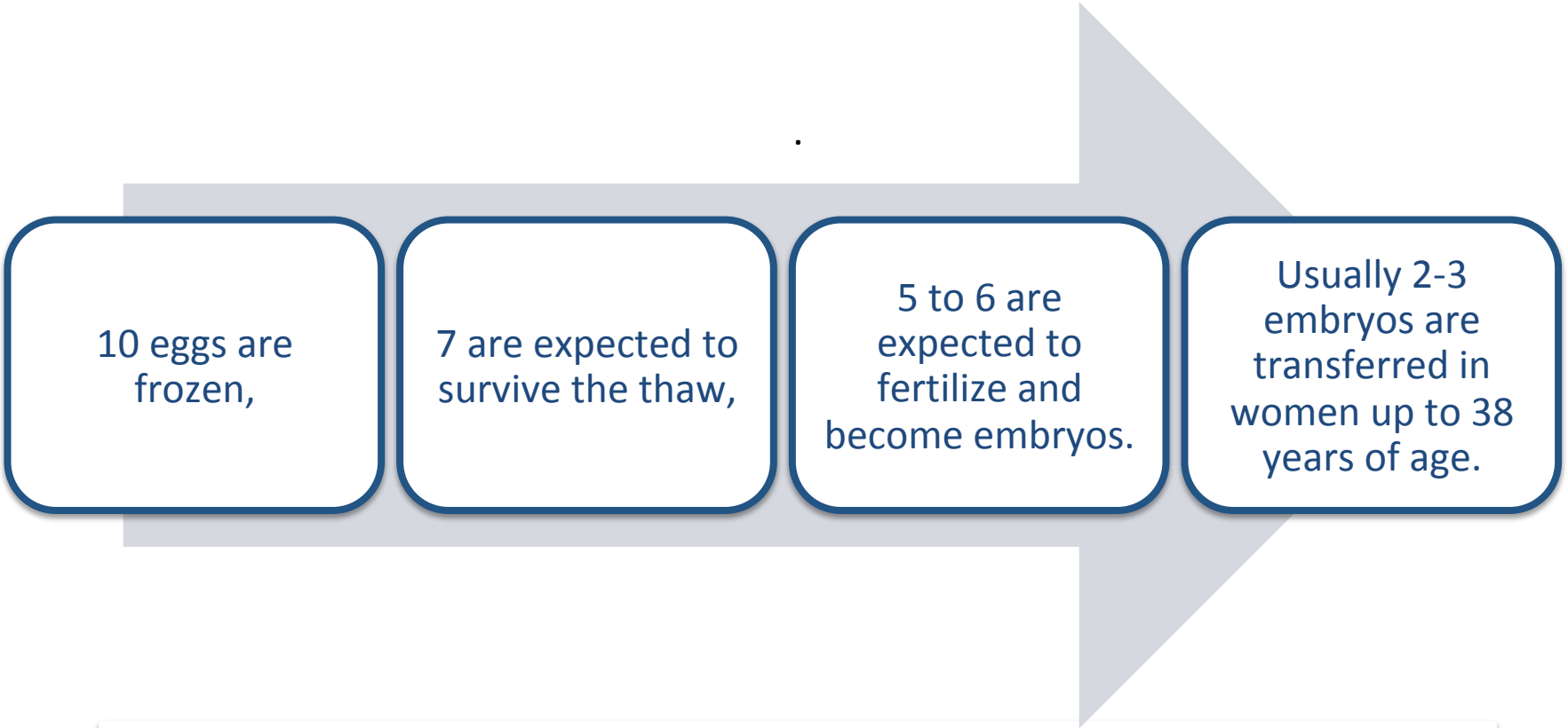


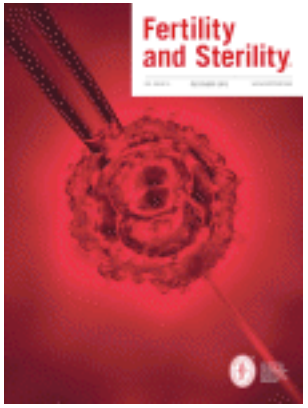
10 eggs should be stored for each pregnancy attempt.

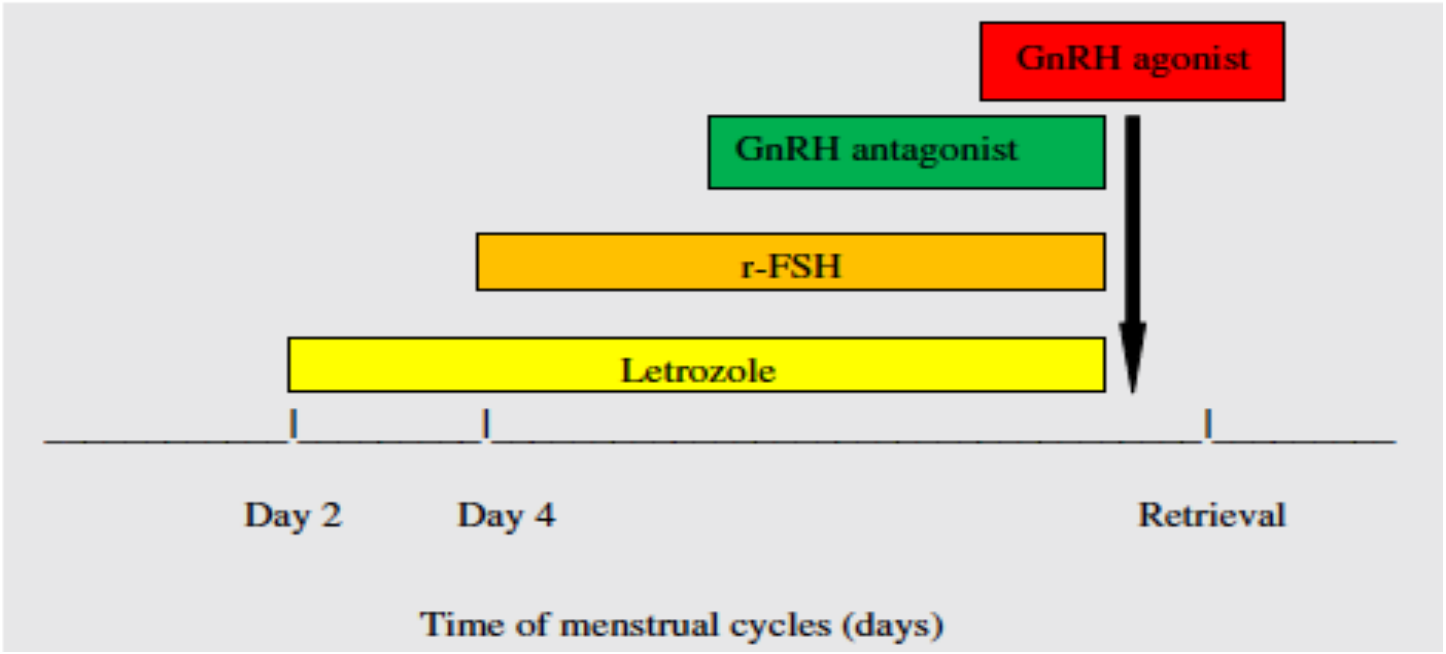
Problem#1

Ovarian stimulation increases estrogen levels

Ovarian stimulation and fertility preservation with the use of aromatase inhibitors in women with breast cancer

Jhansi Reddy, M.D.,[a,b] and Kutluk Oktay, M.D.[a,b]

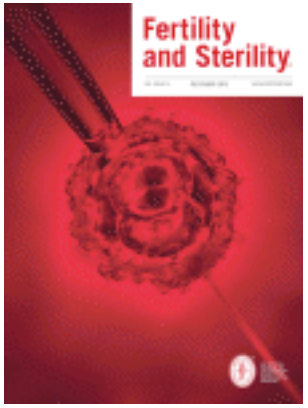


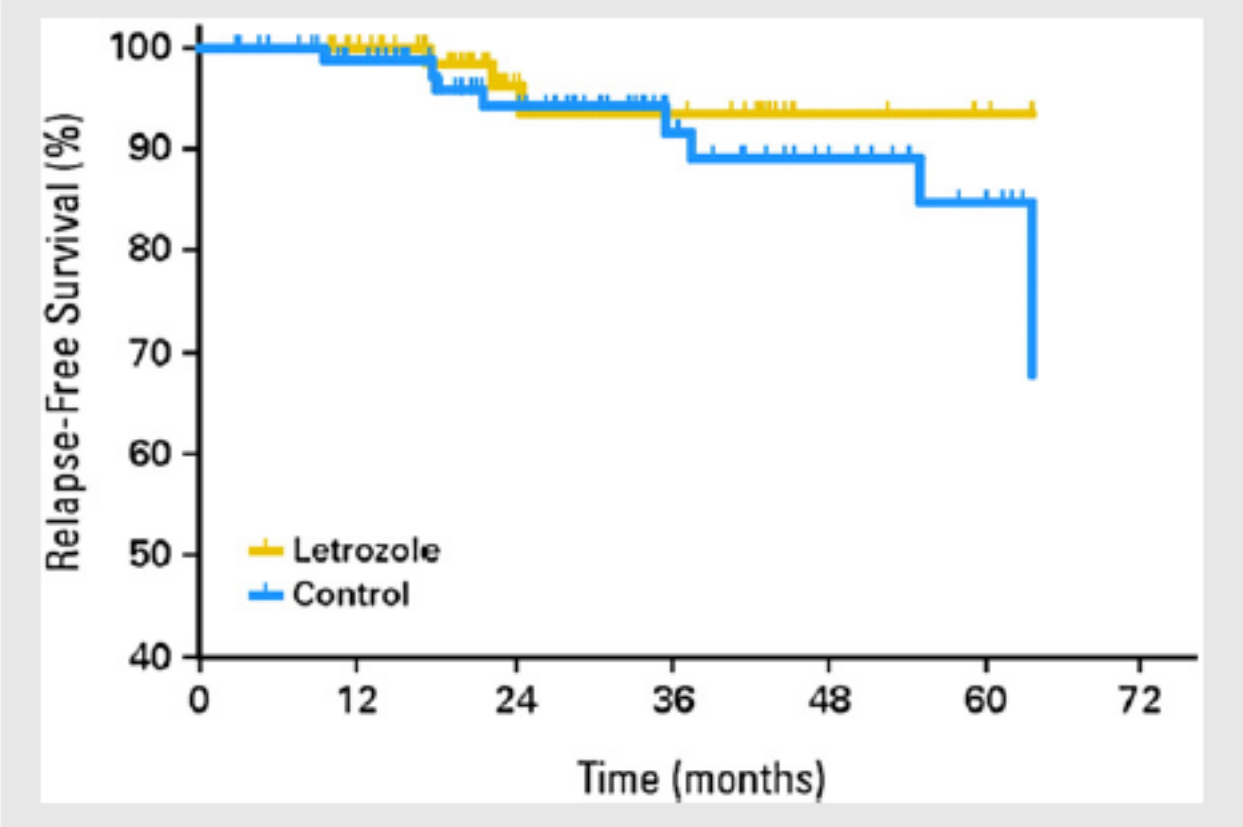


Fertil Steril 2012;98:1363–9.

Ovarian stimulation and fertility preservation with the use of aromatase inhibitors in women with breast cancer

Jhansi Reddy, M.D.,[a,b] and Kutluk Oktay, M.D.[a,b]





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Ovarian stimulation and fertility preservation with the use of aromatase inhibitors in women with breast cancer

Jhansi Reddy, M.D.,[a,b] and Kutluk Oktay, M.D.[a,b]

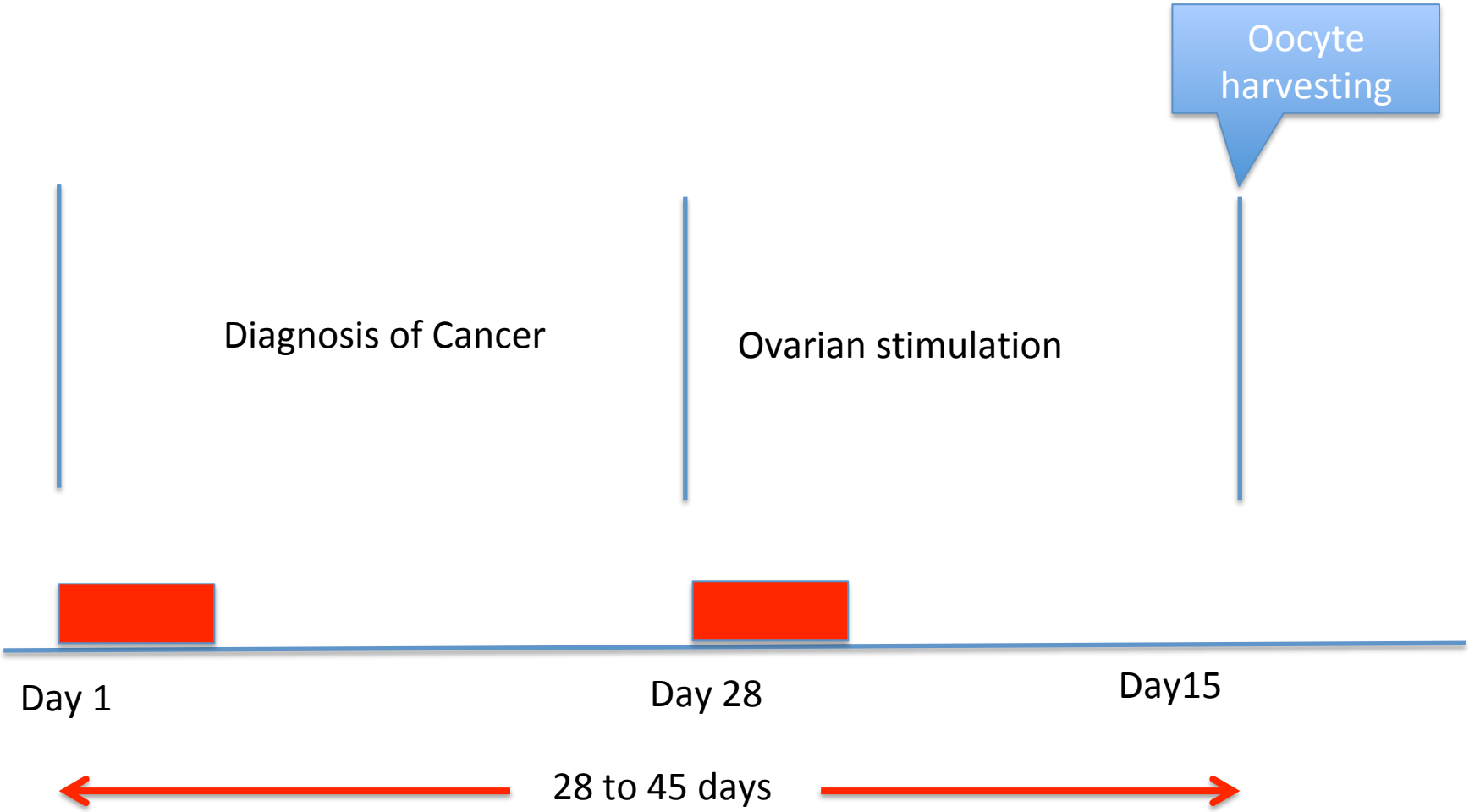
- Does not compromise number or oocytes retrieved
- Associated with decreased estradiol levels
- Triggerring with GnRH agonists resulted in more eggs and diminished risk of OHSS
- Women with BRCA mutation had decreased response
- No difference in disease free interval

Fertil Steril 2012;98:1363–9.

Problem # 2

Ovarian stimulation could potentially delay treatment (Chemotherapy)

Time from diagnosis to egg harvesting



Facts and Fiction in ovarian physiology
Tradition and Innovation in Assisted Reproduction

Common belief

- Ovarian stimulation should start the first 2-3 days of the cycle
- The presence of a corpus luteum may compromise oocyte quality
- The presence of a dominant follicle precludes gonadotropin stimulation

Reality

- Ovarian stimulation can start any time in the cycle

Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase

Michael von Wolff, M.D.,[a] *Christian J. Thaler, M.D.,*[b] *Torsten Frambach, M.D.,*[c] *Cosima Zeeb, M.D.,*[e] *Barbara Lawrenz, M.D.,*[d] *Roxana M. Popovici, M.D.,*[a] *and Thomas Strowitzki, M.D.*[a]

TABLE 2

Outcome of study groups.

	Follicular phase group	Luteal phase group
Age of patients (yrs)	27.6 ± 4.9	31.2 ± 5.7
Aspirated oocytes, average (n)	13.1 ± 6.8	10.0 ± 5.7
Aspirated oocytes, median (n)	11.5	8.5
Days of stimulation	10.6 ± 2.5	11.4 ± 2.6
Total dosage (IU)	2,255 ± 928	2,720 ± 964
Oocytes further processed for ICSI treatment (n)	92	51
Viable metaphase II oocytes (%)[a]	83.7	80.4
Fertilization rate/ICSI treatment (%)	61.0	75.6
Fertilization rate/aspirated oocytes (%)[a]	51.1	60.8

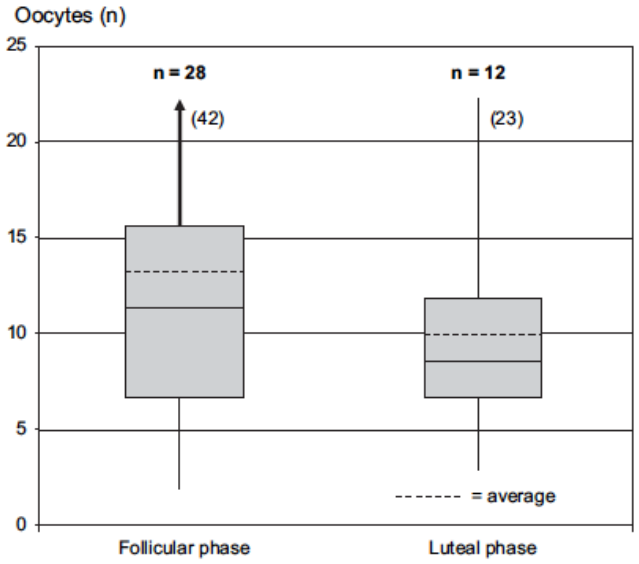
Note: ICSI = intracytoplasmic sperm injection.

[a] Data are limited to oocytes which were further processed for fertilization by ICSI.

von Wolff. Luteal phase stimulation. Fertil Steril 2009.

von Wolff. Luteal phase stimulation. Fertil Steril 2009.

Number of oocytes collected after initiation of ovarian stimulation in the follicular (n = 28) versus the luteal (n =12) phase.



von Wolff. Luteal phase stimulation. Fertil Steril 2009.

Effective method for emergency fertility preservation: random-start controlled ovarian stimulation

Hakan Cakmak, M.D., Audra Katz, R.N., Marcelle I. Cedars, M.D., and Mitchell P. Rosen, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California

TABLE 2

Comparison of outcomes of conventional-and random-start controlled ovarian stimulation cycles.

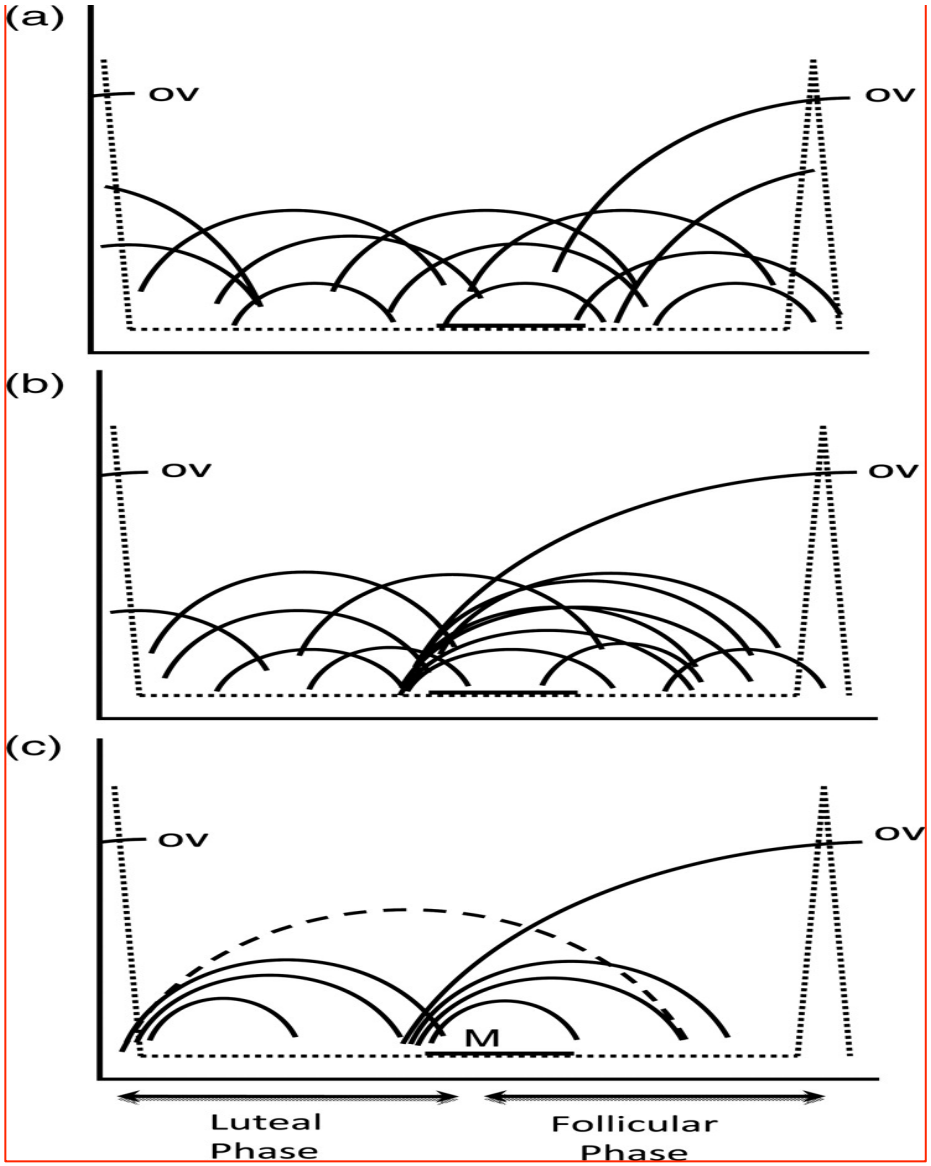
	Conventional start (n = 88; 103 cycles)	Random start (n = 35; 35 cycles)	*P* value	Late follicular phase start (n = 13; 13 cycles)	Luteal phase start (n = 22; 22 cycles)	*P* value[a]
Antral follicle count (AFC)	13.0 (11.7–14.5)	11.5 (9.6–13.8)	NS	10.5 (7.8–14.2)	12.1 (9.6–15.2)	NS
Days of ovarian stimulation	9.3 (9.0–9.5)	10.9 (10.4–11.5)	<.001	10.5 (9.6–11.4)[b]	11.2 (10.5–12.0)[c]	<.001
Total dose of gonadotropins (IU)[d]	3,404 (3,180–3,628)	4,158 (3,774–4,542)	.001	3,842 (3,213–4,472)	4,344 (3,860–4,827)[e]	.005
Gonadotropin daily dose (IU/d)[d]	361 (345–378)	372 (343–400)	NS	371 (324–418)	373 (337–409)	NS
Follicles ≥13 mm	10.5 (9.3–11.9)	11.8 (9.6–14.5)	NS	10.9 (7.8–15.4)	12.3 (9.5–16.0)	NS
Oocytes retrieved	14.4 (12.8–16.2)	14.5 (11.8–17.8)	NS	13.0 (9.3–18.2)	15.5 (11.9–20.1)	NS
Mature oocytes (MII) retrieved	9.7 (8.4–11.2)	9.9 (7.7–12.7)	NS	9.1 (6.0–13.7)	10.3 (7.5–14.2)	NS
MII oocytes/total oocytes ratio	0.66 (0.62–0.71)	0.67 (0.59–0.76)	NS	0.68 (0.56–0.82)	0.67 (0.58–0.78)	NS
Oocytes/AFC ratio	1.09 (0.99–1.19)	1.26 (1.07–1.49)	NS	1.24 (0.95–1.62)	1.28 (1.04–1.57)	NS
Mature oocytes/AFC	0.73 (0.65–0.82)	0.85 (0.70–1.04)	NS	0.84 (0.61–1.17)	0.86 (0.67–1.10)	NS
Fertilization rate after ICSI (2PN/MII)	0.72 (0.65–0.80)	0.87 (0.72–1.00)	NS	0.85 (0.67–1.00)	0.88 (0.70–1.00)	NS

Cakmak. Random-start ovarian stimulation. Fertil Steril 2013.

Human Reproduction Update, Vol.18, No.1 pp. 73–91, 2012
Advanced Access publication on November 8, 2011 doi:10.1093/humupd/dmr039

human reproduction update

Angela R. Baerwald[1,*], Gregg P. Adams[2], and Roger A. Pierson[3]



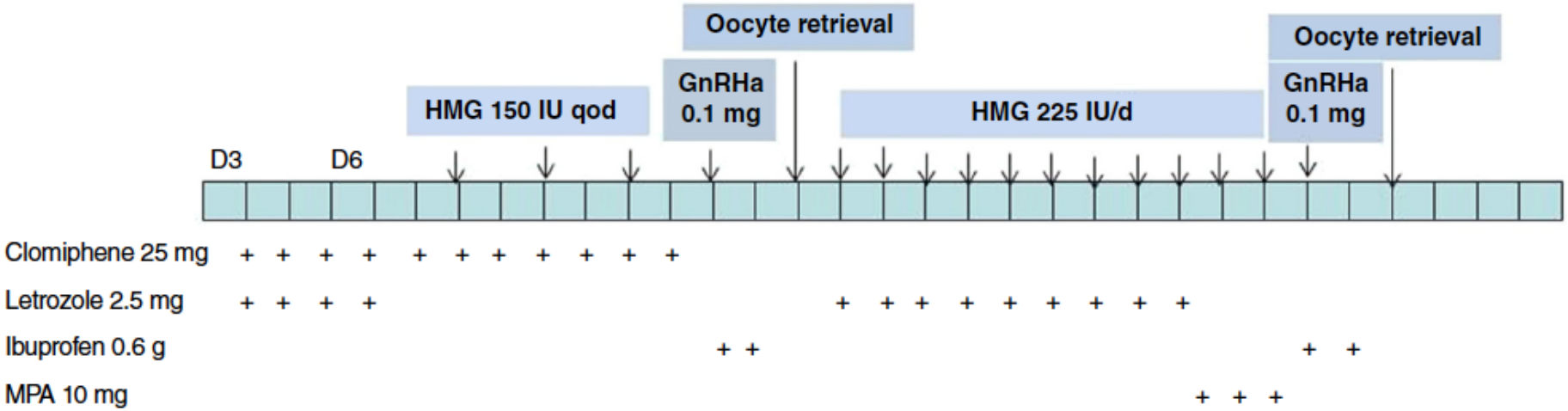
Continuous recruitment

Single recruitment episode

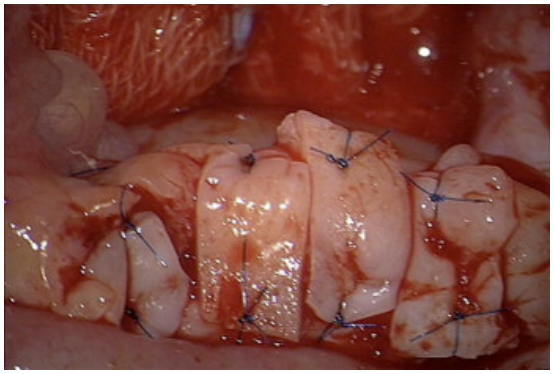
Wave theory of recruitment

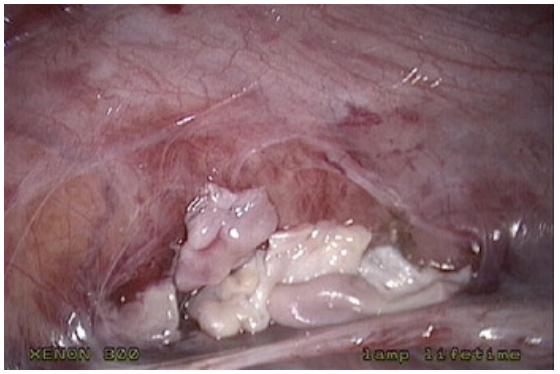
Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol)

Yanping Kuang [a,b,*], Qiuju Chen [a,b], Qingqing Hong [a,b], Qifeng Lyu [a,b], Ai Ai [a,b], Yonglun Fu [a,b], Zeev Shoham [c]



Ovarian cryopreservation for subsequent re-implantation





Advantages and disadvantages of heterotopic and orthotopic sites for ovarian tissue reimplantation.

	Heterotopic (subcutaneous)	Orthotopic
Advantages	No limitation of number 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. Transplantation of ovarian tissue. Fertil Steril 2013.

Donnez. Transplantation of ovarian tissue. Fertil Steril 2013.

Ovarian cryopreservation for subsequent re-implantation

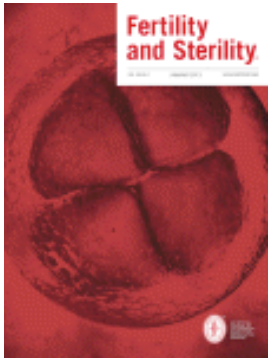
Cryopreservation of ovarian tissue is the only option available for prepubertal girls and for women who cannot delay the start of chemotherapy

The most common reasons given for not discussing fertility preservation options in a pediatric cancer population
‘‘not at significant risk’’ in 29% of cases,
‘‘too young’’ in 27%,
‘‘techniques unproven’’ in 22%,
‘‘no facilities’’ in 10%,
and ‘‘no funding’’ in 8% .

Donnez. Transplantation of ovarian tissue. Fertil Steril 2013.

Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation

Jacques Donnez, M.D., Ph.D.,[a] Marie-Madeleine Dolmans, M.D., Ph.D.,[b] Antonio Pellicer, M.D., Ph.D.,[c] Cesar Diaz-Garcia, M.D.,[c] Maria Sanchez Serrano, M.D.,[c] Kristen Tryde Schmidt, M.D., Ph.D.,[d] Erik Ernst, M.D., Ph.D.,[f] Valérie Luyckx, M.D.,[b] and Claus Yding Andersen, M.Sc., D.M.Sc.[e]



Pregnancy after ovarian transplantation

Series of 24 live births after transplantation of frozen-thawed ovarian cortex.

References	Cryopreservation procedure	Graft site	Live birth: Spont.	Live birth: IVF
Donnez et al. (1, 3, 26, 30, 31)	SF	Peritoneal window (2 steps)	+	
		Peritoneal window (1 step)		++
		Ovarian medulla	+++	
Meirow et al. (58)	SF	Beneath the ovarian cortex	–	+
Demeestere et al. (33)	SF	Ovarian and peritoneal windows (2 steps)	++	–
Andersen et al. (40, 41, 76, 77)	SF	Subcortical ovarian pocket	+	+
		Ovarian medulla	+	+
Silber et al. (37, 75)	SF	Ovarian medulla	++	–
Piver et al. (34)	SF	Ovarian and peritoneal windows (1 and 2 steps)	+	–
Roux et al. (35)			+	
Sanchez et al. (28)	SF	Ovarian medulla	–	++ (twins)
Revel et al. (78)[a]	SF	Peritoneal window (slice)	–	+
				+
Dittrich et al. (79)	SF	Peritoneal window	+	–
Revelli et al. (80)	SF	Ovarian medulla	+	
García Rada (81)	SF	Peritoneal pocket		+

Note: Four ongoing pregnancies at the present time: two in Spain, one in South Africa, and one in Australia.

[a] Personal communication, 2012.

Donnez. Transplantation of ovarian tissue. Fertil Steril 2013.

Human Reproduction, Vol.29, No.2 pp. 276–278, 2014
Advanced Access publication on December 9, 2013 doi:10.1093/humrep/det420

human reproduction

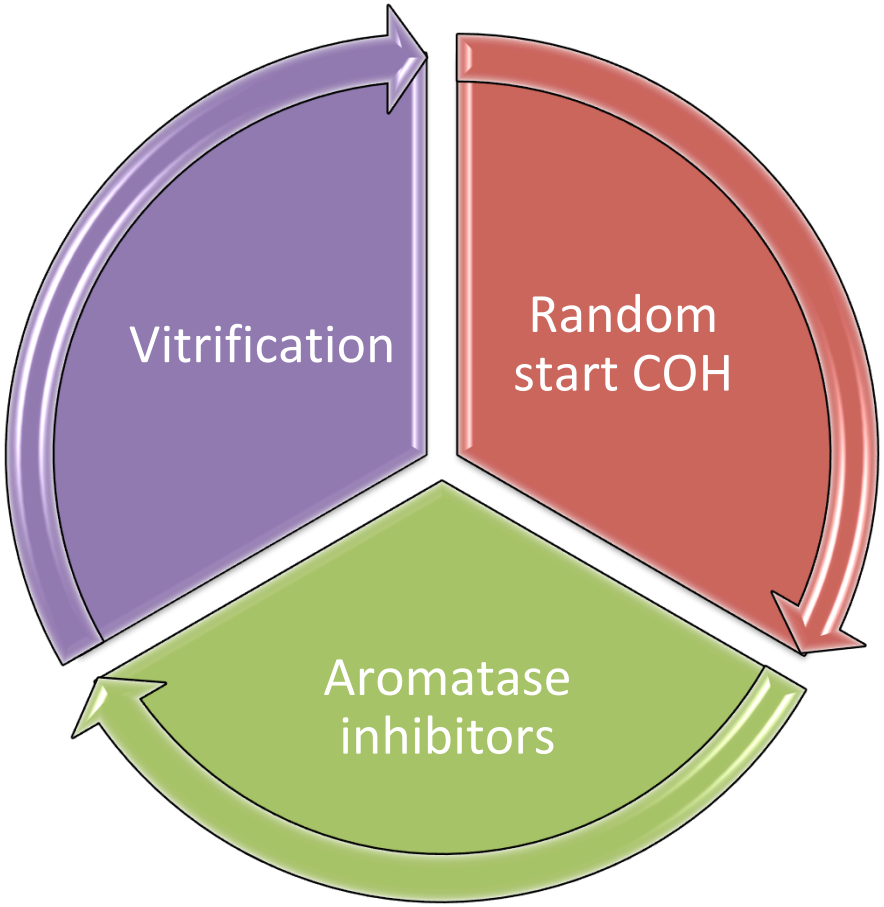
CASE REPORT *Infertility*

First pregnancy and live birth resulting from cryopreserved embryos obtained from *in vitro* matured oocytes after oophorectomy in an ovarian cancer patient

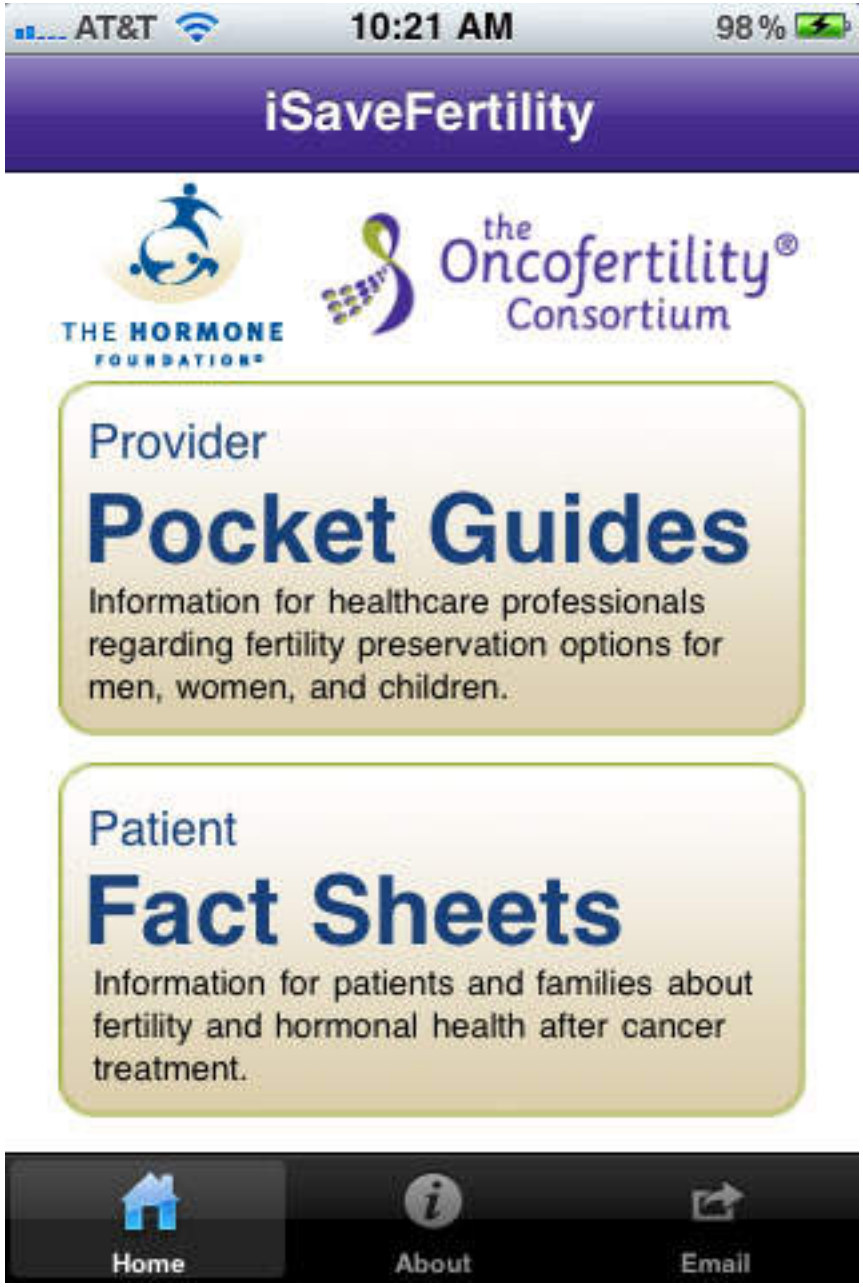
E.B. Prasath[1,4,*], M.L.H. Chan[1], W.H.W. Wong[1], C.J.W. Lim[1], M.D. Tharmalingam[1], M. Hendricks[1,4,5], S.F. Loh[1,2,4,5], and Y.N. Chia[3,6]

[1] Department of Reproductive Medicine, KKIVF Centre, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore [2]Duke-NUS Graduate Medical School, Singapore [3]Department of Gynaecological Oncology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore

Fertility preservation in women with cancer is feasible and successful because…….



There is no excuse not to offer this option to our patients


AT&T
10:21 AM
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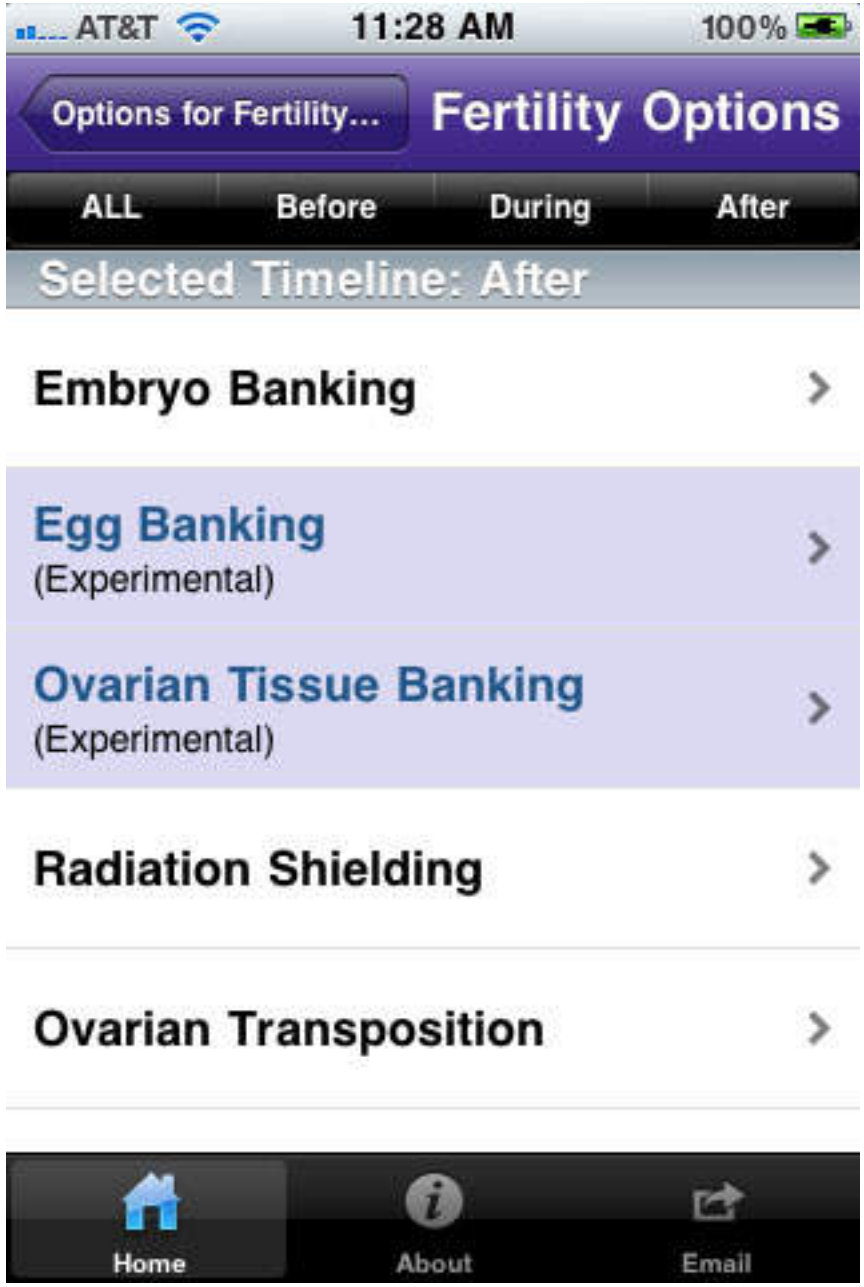
iSaveFertility
THE HORMONE FOUNDATION
the Oncofertility® Consortium
Provider
Pocket Guides
Information for healthcare professionals regarding fertility preservation options for men, women, and children.
Patient
Fact Sheets
Information for patients and families about fertility and hormonal health after cancer treatment.
Home
About
Email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Options for Fertility...
Fertility Options
ALL
Before
During
After
Selected Timeline: After
Embryo Banking
Egg Banking
(Experimental)
Ovarian Tissue Banking
(Experimental)
Radiation Shielding
Ovarian Transposition
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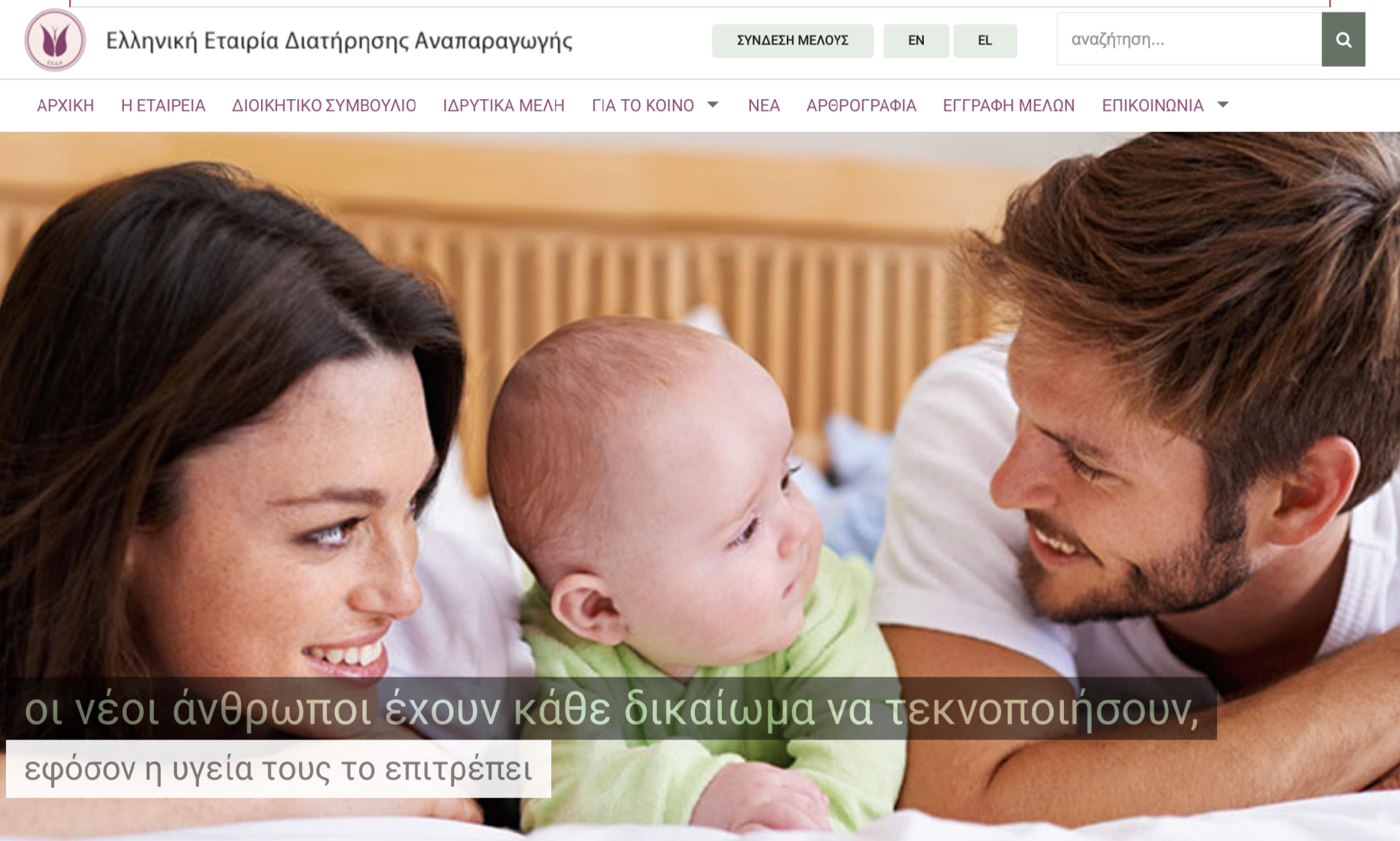
About
Email

Ελληνική Εταιρία Διατήρησης Αναπαραγωγής

Hellenic Society for Fertility Preservation

(www. hsfp.gr)



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Σας Ευχαριστώ

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Χημειοθεραπεία και Αναπαραγωγή

High risk of amenorrhea in women

- Pelvic or whole abdominal radiation dose ≥ 6 Gy in adult women
- Pelvic or whole abdominal radiation dose ≥ 10 Gy in post-pubertal girls
- Pelvic radiation or whole abdominal dose ≥ 15 Gy in pre-pubertal girls

Intermediate risk

- Testicular radiation dose 1-6 Gy from scattered pelvic or abdominal radiation
- Pelvic or whole abdominal radiation dose 5-10 Gy in post-pubertal girls
- Pelvic or whole abdominal radiation dose 10-15 Gy in pre-pubertal girls
- Craniospinal radiotherapy dose ≥ 25 Gy

Rodriguez-Wallberg and Oktay, *J Ped Hematol Oncol, 2010,*

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

CLINICAL STAGE	WORKUP
Stage I T1, N0, M0 or Stage IIA T0, N1, M0 T1, N1, M0 T2, N0, M0 or Stage IIB T2, N1, M0 T3, N0, M0 or Stage IIIA T3, N1, M0	• History and physical exam • CBC, platelets • Liver function tests and alkaline phosphatase • Diagnostic bilateral mammogram; ultrasound as necessary • Pathology review[a] • Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status[b] • Genetic counseling if patient is high risk for hereditary breast cancer[c] • Breast MRI[d] (optional), with special consideration for mammographically occult tumors • Fertility counseling if premenopausal[e] For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:[f] • Bone scan indicated if localized bone pain or elevated alkaline phosphatase • Abdominal ± pelvic diagnostic CT or MRI indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis • Chest diagnostic CT (if pulmonary symptoms present) If clinical stage IIIA (T3, N1, M0) consider: • Chest diagnostic CT • Abdominal ± pelvic diagnostic CT or MRI • Bone scan or sodium fluoride PET/CT[g] (category 2B) • FDG PET/CT[h,i] (optional, category 2B)

See Locoregional Treatment (BINV-2)

GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy

Zeev Blumenfeld[1,3] and Michael von Wolff[2]

Table I. Rate of POF following GnRH-a as co-treatment during chemotherapy (peer-reviewed papers with control groups only, abstracts not included).

	Age (year) (GnRH-a)	GnRH-a	Control	Age(year) (Control)
Waxman *et al.* (1987) (Lymphoma)	NA	50.0% (4/8)	66.7% (6/9)	
Blumenfeld *et al.* (2000) (Systemic lupus erythematosus)	18–35	0% (0/8)	55.6% (5/9)	20–35
Pereyra Pacheco *et al.* (2001) (Lymhoma, leukaemia, thymoma)	15–20	0% (0/12)	100% (4/4)	16–20
Dann *et al.* (2005) (Non-Hodgkin Lymphoma)	18–40	0% (0/7)	17% (1/6)	21–40
Somers *et al.* (2005) (Systemic lupus erythematosus)	24–28	5.0% (1/20)	30.0% (6/20)	25–28
Elis *et al.* (2006) (Non-Hodgkin Lymphoma)	17–40	0% (0/3)	8.7% (2/24)	17–40
Castelo-Branco *et al.* (2007) (Lymphoma)	14–45	10.0% (3/30)	76.9% (20/26)	14–45
Blumenfeld *et al.* (2008) (Hodgkin Lymphoma	14–40	3.1% (2/65)	63.0% (29/46)	14–40
Huser *et al.* (2008) (Hodgkin Lymphoma)	18–35 median=32.5	20.8% (15/72)	71.1% (32/45)	18–35 median = 29
Total		11.1% (25/225)	55.5% (105/189)	

Table II. Rate of POF following OC as co-treatment during chemotherapy (peer-reviewed papers with control groups only, abstracts not included).

	Age (year)	OC	Control
Whitehead *et al.* (1983) (Lymphoma)	23 (median)	44.4% (4/9)	37.1% (13/35)
Longhi *et al.* (2003) (Osteosarcoma)	NA	15.8% (3/19)	4.2% (3/71)
Behringer *et al.* (2005) (Hodgkin Lymphoma)	15–40	10.1% (7/69)	44.1% (64/145)
Elis *et al.* (2006) (Non-Hodgkin Lymphoma)	17–40	0% (0/9)	8.7% (2/24)
Total		13.2% (14/106)	29.8% (82/275)

Human Reproduction Update, Vol.14, No.6 pp. 543–552, 2008

Vitrification

Solidification of water or water based solutions without ice crystal formation.

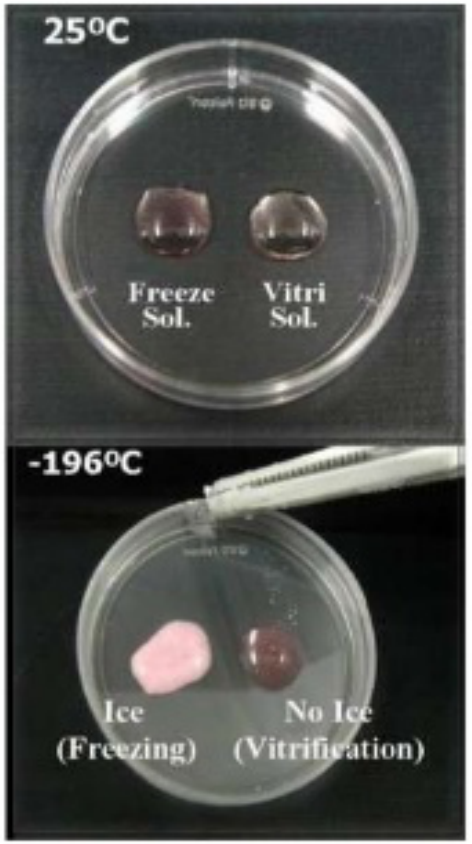
It is facilitated by:

- High CPA concentration (3-6M)

- High cooling rates:
  15.000 to 30.000 ºC/min

↓

Direct immersion into LN



VOLUME 31 · NUMBER 19 · JULY 1 2013

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

THE BOTTOM LINE

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

Intervention

- Discuss the risk of infertility and fertility preservation options with patients with cancer anticipating treatment

Target Audience

- Medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons, as well as nurses, social workers, psychologists, and other nonphysician providers

Key Recommendations

- Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy
- Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists
- Address fertility preservation as early as possible, before treatment starts
- Document fertility preservation discussions in the medical record
- Answer basic questions about whether fertility preservation may have an impact on successful cancer treatment
- Refer patients to psychosocial providers if they experience distress about potential infertility
- Encourage patients to participate in registries and clinical studies

CURRENT OPINION

Random-start ovarian stimulation in patients with cancer

Volume 27 • Number 3 • June 2015

Hakan Cakmak and Mitchell P. Rosen

Table 1. Comparison between conventional, late follicular and luteal start IVF cycles; median (interquartile range)

	Conventional start (n = 136)	Late follicular start (n = 32)	Luteal start (n = 44)	*P* Value
Follicles ≥ 13 mm	12.5 (6.5–17)	14.0 (9.0–19.75)	13.0 (8.25–16.75)	NS
Mature oocytes (MII) retrieved	11 (6.5–16)	12.0 (7.0–16.75)	10.0 (5.25–15)	NS
MII oocyte/total oocyte ratio	0.71 (0.60–0.82)	0.75 (0.63–0.83)	0.72 (0.60–0.84)	NS
Mature oocyte/AFC ratio	0.83 (0.46–1.12)	0.91 (0.64–1.27)	0.86 (0.58–1.17)	NS
Fertilization rate (2PN/MII)	0.79 (0.67–0.85)	0.86 (0.78–1.00)	0.87 (0.76–1.00)	NS
High-quality day 3 embryos/2PN ratio	0.92 (0.76–1.00)	0.91 (0.81–1.00)	0.88 (0.83–1.00)	NS

AFC, antral follicle count; NS, not significant.

RANDOM-START (LATE FOLLICULAR OR LUTEAL PHASE START) CONTROLLED OVARIAN STIMULATION PROTOCOLS

Three patients with breast cancer

- ovarian stimulation at the time of patient presentation (menstrual cycle day 11, 14 and 17) rather than waiting for spontaneous menses.
- GnRH antagonist was started to prevent premature LH surge when the lead follicle measured over 13mm.
- Seven to 10 embryos cryopreserved per patient

Sonmezer M, et al. Fertil Steril 2011; 95:2125.e9–2125.e11.

Two patients with cancer had successful COS initiated during the luteal phase

- 12 MII oocytes in both the cases .
- One of the patients had oocyte cryopreservation
- the other had ICSI with 83.3% fertilization rate .

Bedoschi GM, et al. J Assist Reprod Genet 2010; 27:491–494.

Ovarian stimulation and fertility preservation with the use of aromatase inhibitors in women with breast cancer

Jhansi Reddy, M.D.,[a,b] and Kutluk Oktay, M.D.[a,b]

Fertil Steril 2012;98:1363–9.

Summary of included studies.

Study ID	Study design	Population (n)	Main outcome(s)	Findings
Oktay et al., 2005	Prospective cohort	7 tamoxifen + FSH 11 letrozole + FSH 12 tamoxifen	Mature oocytes Embryos Peak E_2 levels	Tamoxifen + FSH and letrozole + FSH had significantly greater number of mature oocytes and embryos compared with tamoxifen alone. Letrozole + FSH had the lowest peak E_2 levels.
Oktay et al., 2006	Retrospective, age-matched cohort	47 letrozole + FSH 56 GnRHa + gonadotropins (control group)	Mature oocytes Embryos	No difference in mature oocytes or embryos. Peak E_2 levels were significantly lower in the letrozole + FSH group.
Azim et al., 2008	Prospective cohort	79 letrozole + FSH 136 declined IVF (control group)	Risk of cancer recurrence	No difference in relapse-free survival.
Lee et al., 2010	Prospective cohort	35 fertility preservation (FP) before surgery 58 FP after surgery	Mature oocytes Embryos Number of cycles	Women referred before surgery had significantly more oocytes and embryos and had 2 cycles of FP.
Lee et al., 2012	Prospective cohort	34 Low-dose FSH + letrozole 117 higher-dose FSH + letrozole	Mature oocytes Embryos	No difference.
Oktay et al., 2010	Retrospective cohort	27 GnRHa trigger 47 hCG trigger	Mature oocytes Embryos OHSS rate	GnRHa trigger had significantly greater number of mature oocytes and embryos while reducing the risk of OHSS.
Domingo et al., 2012	Retrospective, age-matched cohort	66 nonhormonally dependent cancer 142 hormonally dependent cancer 97 standard IVF (control group)	Retrieved oocytes	Hormonally dependent group had a significantly poorer response to stimulation.
Oktay et al., 2009	Prospective cohort	14 *BRCA* mutation positive 33 *BRCA* mutation negative	Retrieved oocytes	BRCA mutation–positive women were significantly more likely to have fewer retrieved oocytes.
Oktay et al., 2010	Prospective cohort	32 letrozole + FSH	Maturation of immature oocytes	Mature oocyte yield was increased by 45% using in vitro maturation.

Note: GnRHa = GnRH agonist; OHSS = ovarian hyperstimulation syndrome.

Reddy. Aromatase inhibitor and preserving fertility. Fertil Steril 2012.

Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles

Murat Sönmezer, M.D.,[a,b] *Ilgın Türkçüoğlu, M.D.,*[c] *Uğur Coşkun, M.D.,*[d] *and Kutluk Oktay, M.D.*[e]

TABLE 1

Baseline characteristics and COH outcome of the patients with breast cancer undergoing emergency fertility preservation.

Characteristic	Case 1	Case 2	Case 3
Age (y)	29	26	26
Stage	I	II	II
Histology	Invasive ductal	Mixed invasive ductal + lobular	Invasive ductal
COH start day	14	11	17
FSH (mIU/mL)	6.2	2.8	4.6
LH (mIU/mL)	5.8	2.8	1.2
E_2 (ng/mL)	62	269	50
P (pg/mL)	1.2	0.4	2.5
Endometrial thickness (mm)	7	6.5	9
Antral follicle count (n)	11	20[a]	20[b]
GnRH antagonist start day	5	1	5
Peak E_2 (pg/mL)	499	988	478
Duration of COH (d)	9	12	9
Oocytes retrieved (n)	9	17	16
Metaphase II, no. (%)	7 (77.7)	10 (58.8)	11 (68.75)
Metaphase I + germinal vesicle, no. (%)	2 (22.3)	7 (41.2)	5 (31.25)
Fertilization rate, no. (%)	7/8 (87.5)	10/12 (83.3)	9/13 (69.2)
Cleavage rate (%)	7/7 (100)	NA	NA
Embryos frozen (n)	7	10	9

CURRENT OPINION

Random-start ovarian stimulation in patients with cancer

Volume 27 • Number 3 • June 2015

Hakan Cakmak and Mitchell P. Rosen

KEY POINTS

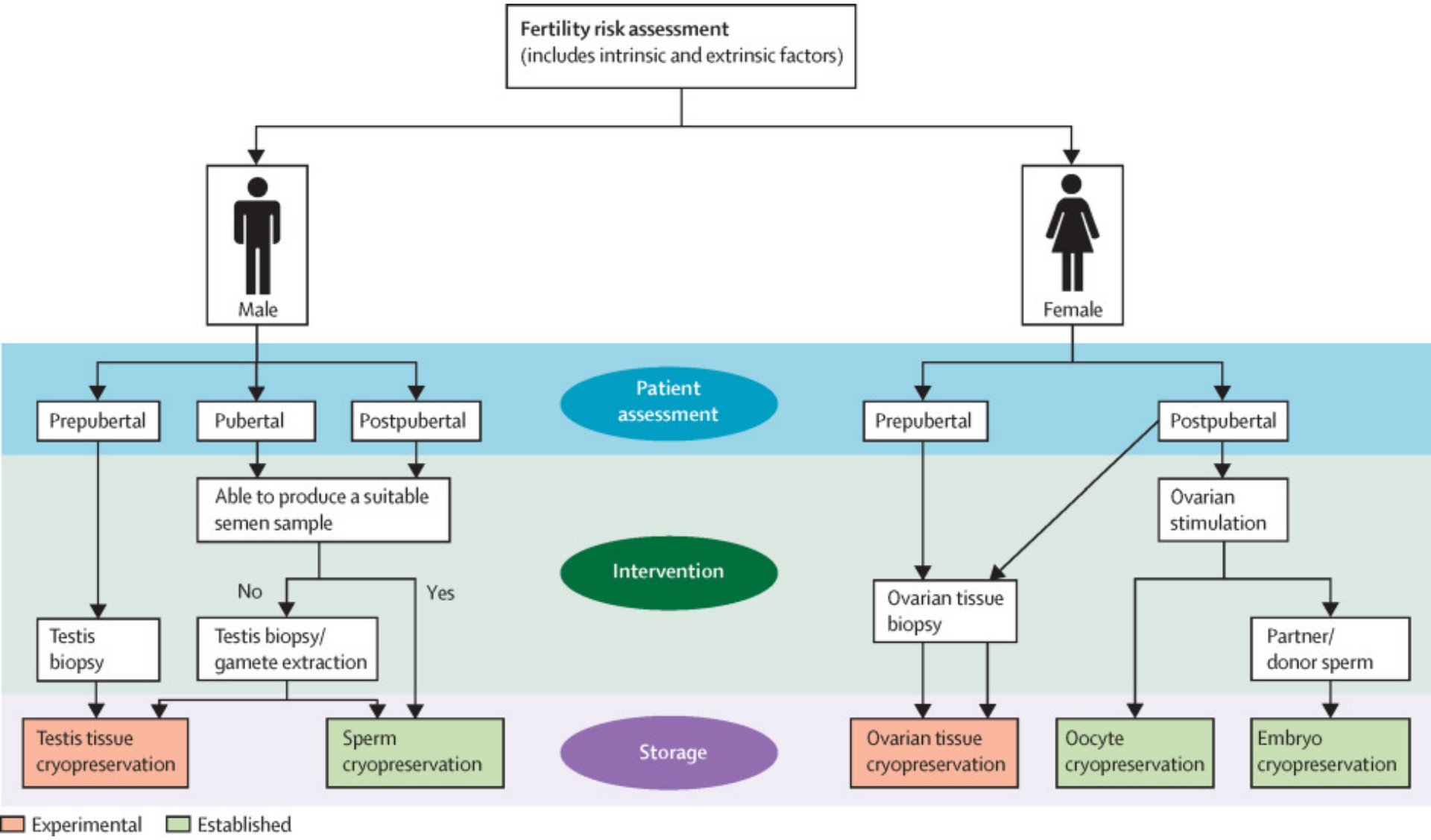
- Random-start ovarian stimulation provides a significant advantage by decreasing total time for the IVF cycle without compromising oocyte yield and maturity.
- Starting ovarian stimulation in the late follicular or luteal phase did not show any superiority against the other.
- The presence of corpus luteum or luteal phase progesterone levels do not adversely affect synchronized follicular development, number of mature oocytes retrieved, and/or fertilization rates.
- Random-start ovarian stimulation with letrozole along with gonadotropins in patients with estrogen-sensitive cancers is well tolerated, and yields similar number of oocytes and embryos compared with standard protocols while minimizing the risk of high estrogen exposure.

Ovarian cryopreservation for subsequent re-implantation

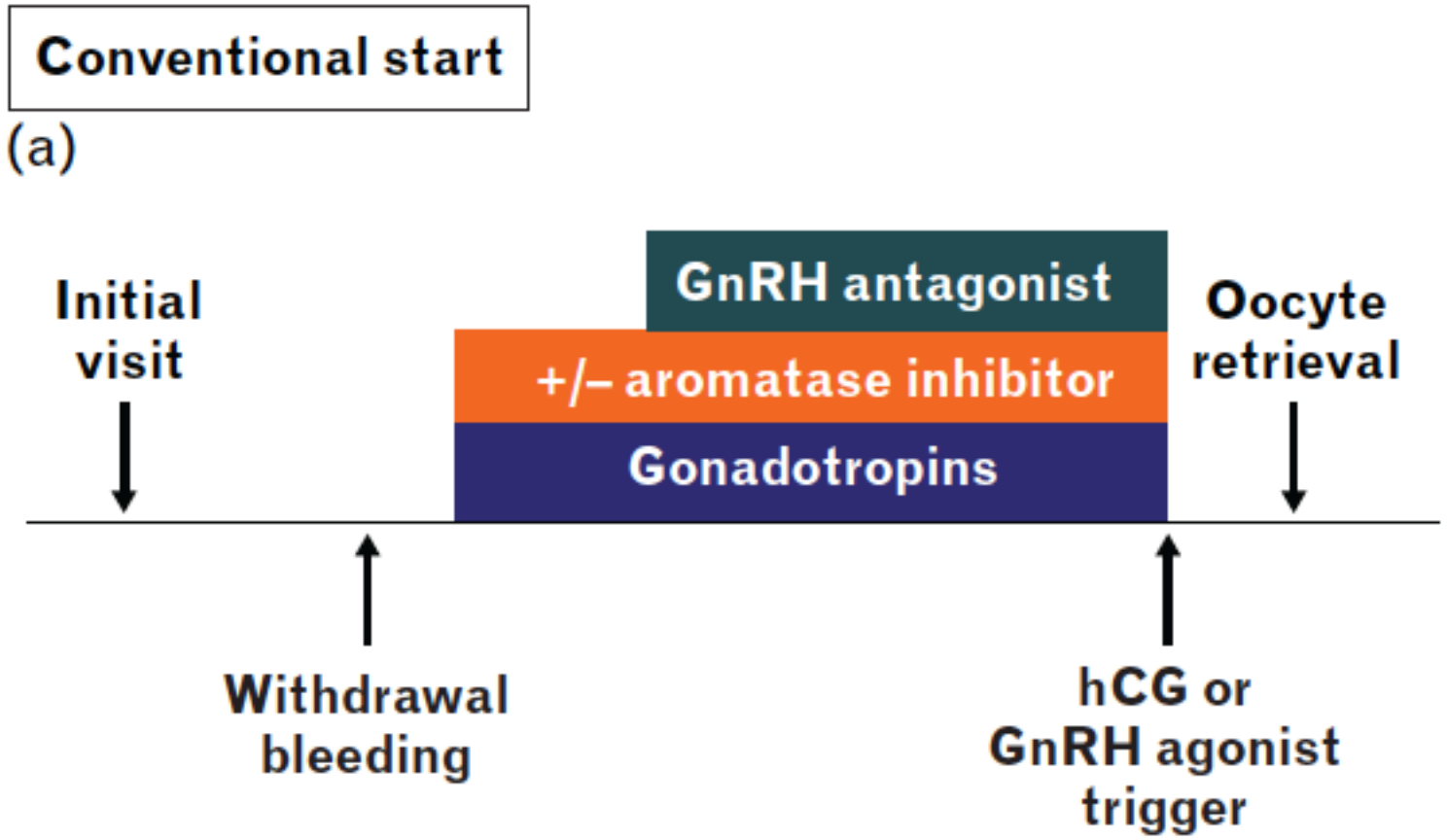
There is concern regarding the potential for reseeding tumor cells following ovarian transplantation procedures in cancers that can involve the ovary, such as leukemia

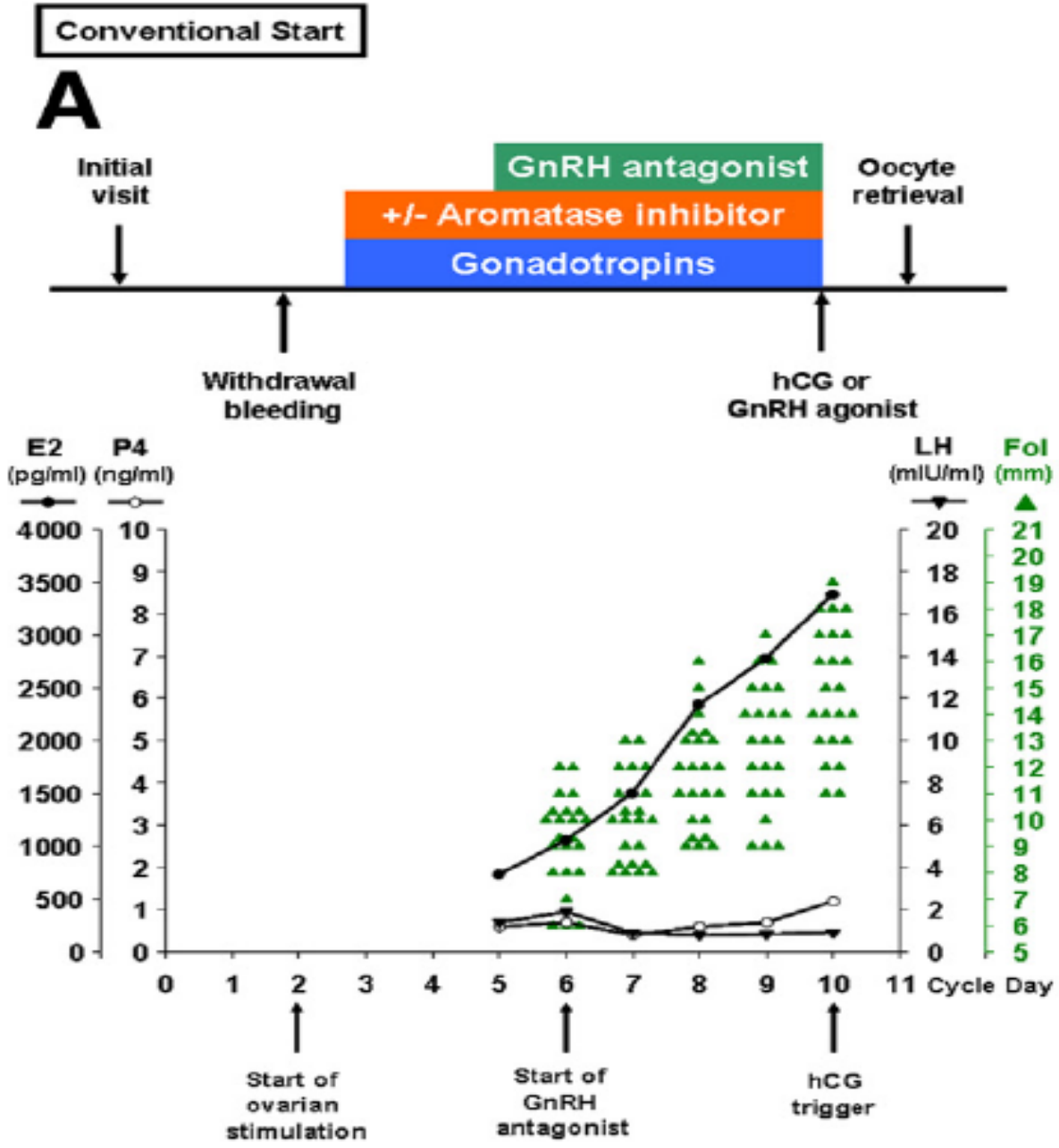
Therefore, transplantation of ovarian tissue is not recommended in patients with a history of leukemia

S Joshi et al. Fertility preservation in HCT recipients
Bone Marrow Transplantation (2014), 1–8


Fertility risk assessment
(includes intrinsic and extrinsic factors)
Male
Female
Patient assessment
Prepubertal
Pubertal
Postpubertal
Prepubertal
Postpubertal
Able to produce a suitable semen sample
Ovarian stimulation
Intervention
No
Yes
Testis biopsy
Testis biopsy/ gamete extraction
Ovarian tissue biopsy
Partner/ donor sperm
Storage
Testis tissue cryopreservation
Sperm cryopreservation
Ovarian tissue cryopreservation
Oocyte cryopreservation
Embryo cryopreservation
Experimental
Established

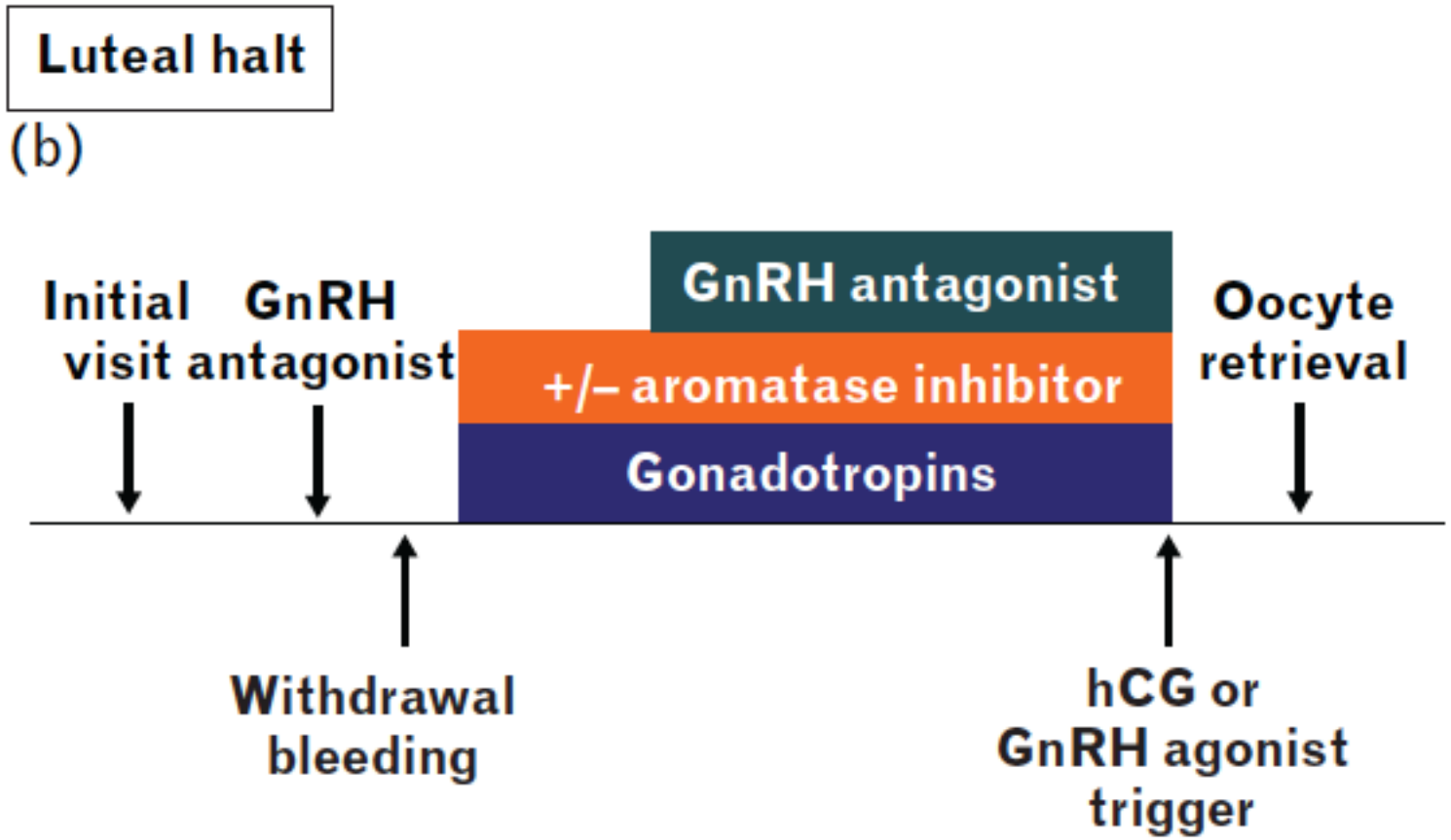
CONVENTIONAL (EARLY FOLLICULAR PHASE START) CONTROLLED OVARIAN STIMULATION PROTOCOLS





Cakmak. Random-start ovarian stimulation. Fertil Steril 2013.

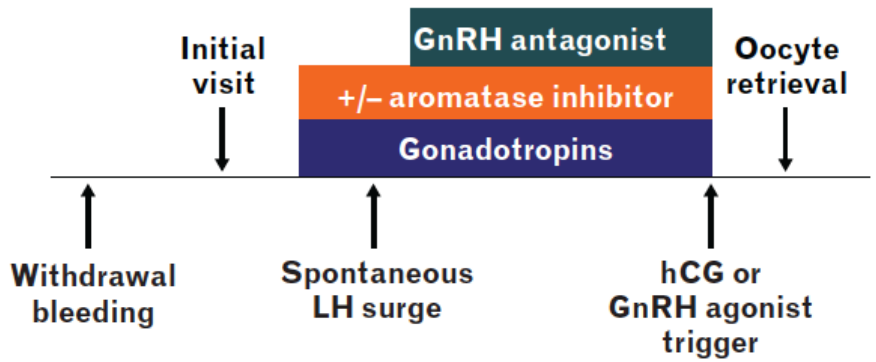
LUTEAL HALT PROTOCOLS



RANDOM-START CONTROLLED OVARIAN STIMULATION IN PATIENTS WITH ESTROGEN-SENSITIVE CANCERS

Late follicular phase start

(c)



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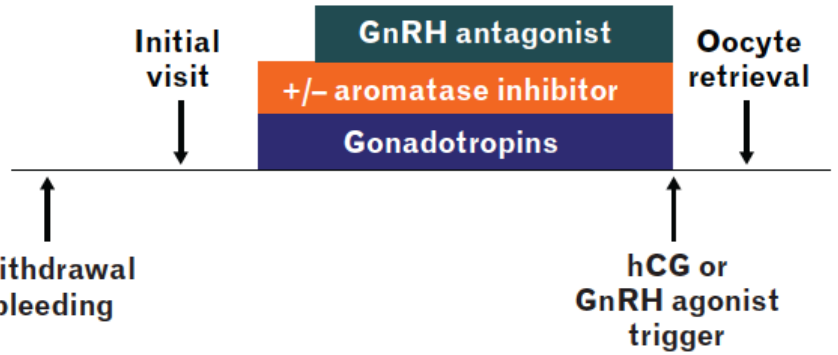
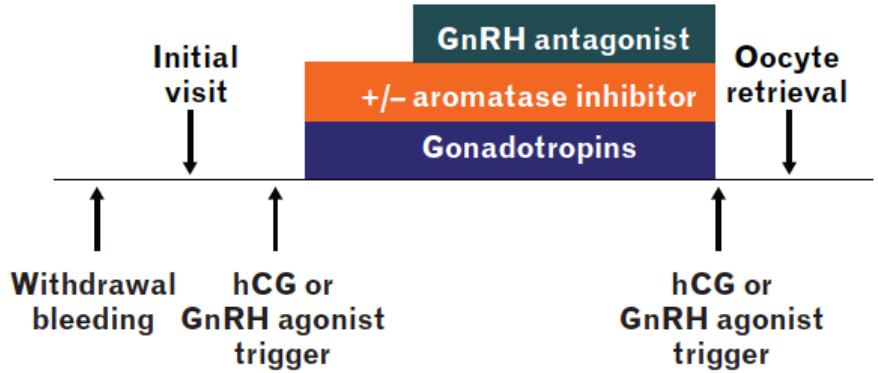
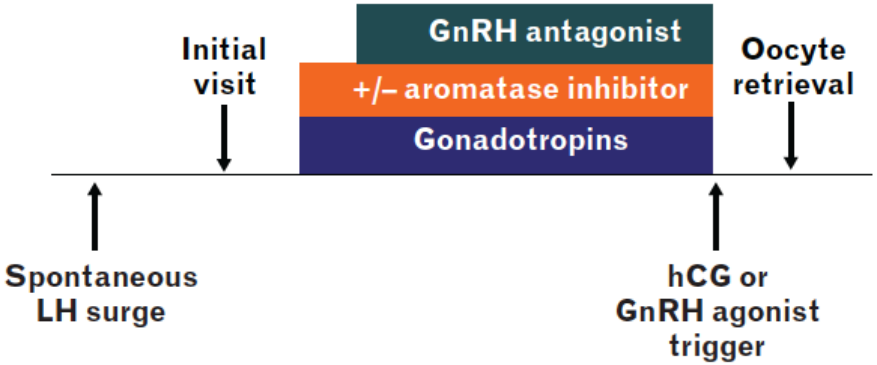


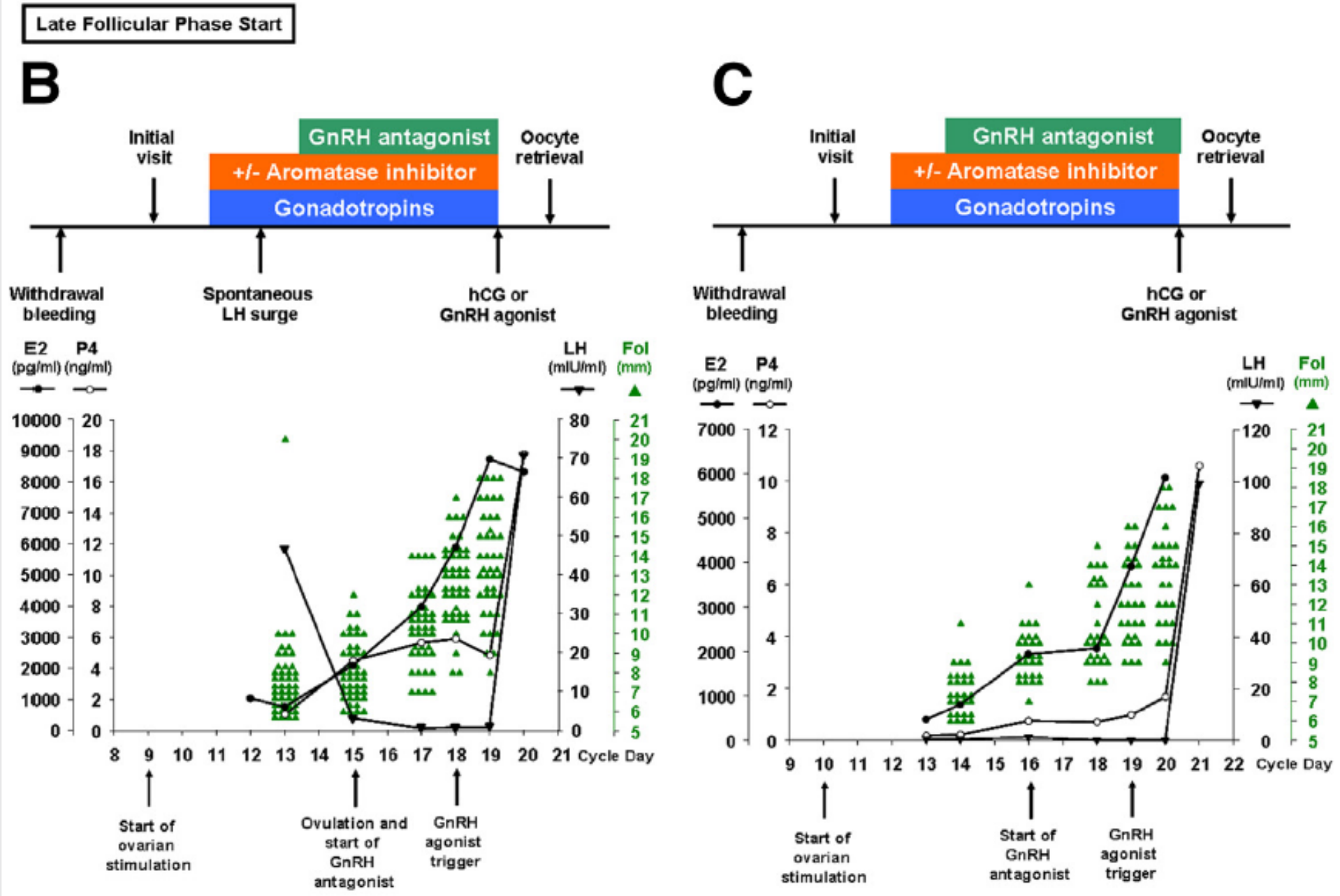
Luteal phase start

(e)

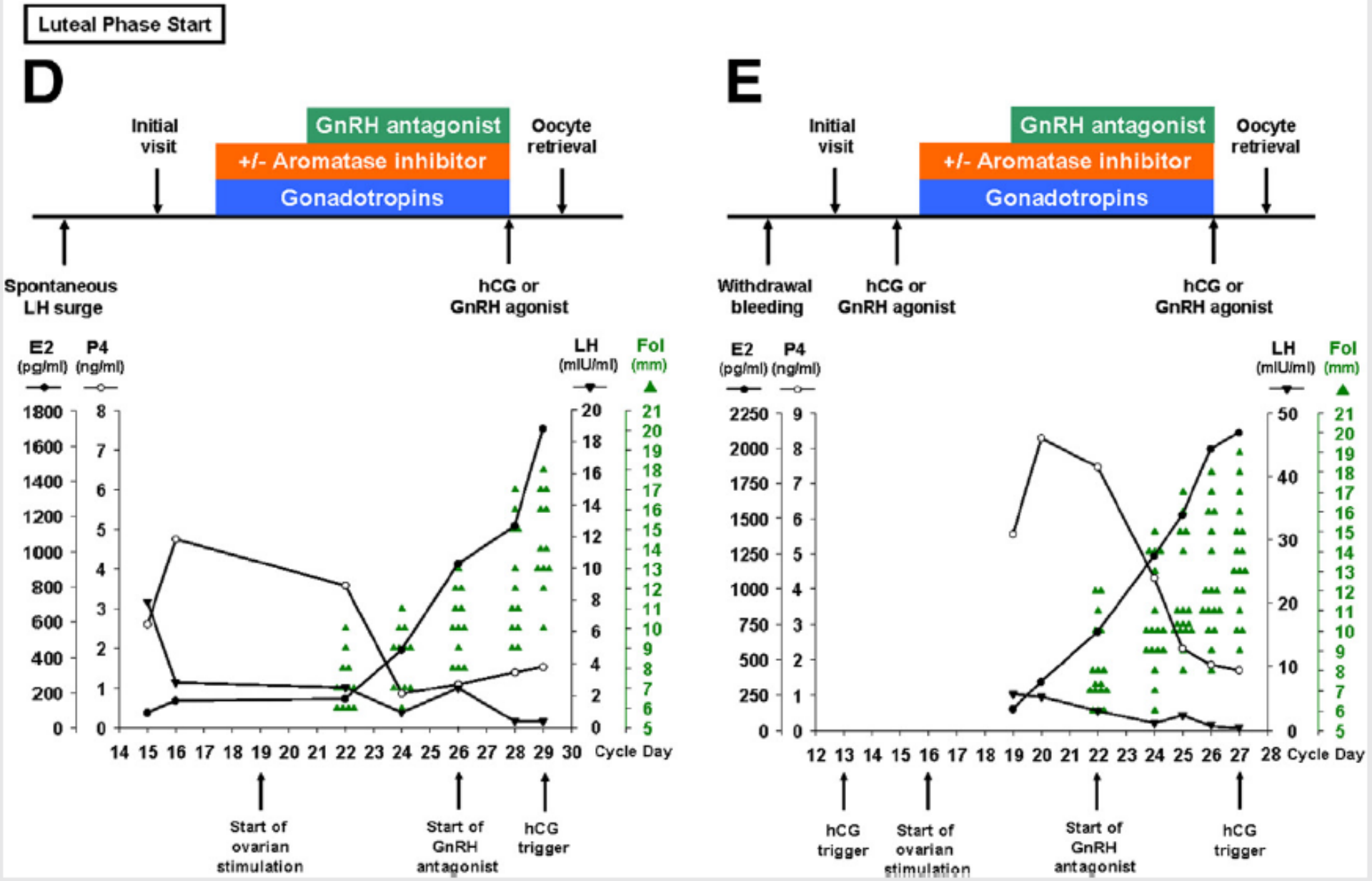


(f)





Cakmak. Random-start ovarian stimulation. Fertil Steril 2013.



Cakmak. Random-start ovarian stimulation. Fertil Steril 2013.

Effective method for emergency fertility preservation: random-start controlled ovarian stimulation

Hakan Cakmak, M.D., Audra Katz, R.N., Marcelle I. Cedars, M.D., and Mitchell P. Rosen, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California

Objective: To determine whether random-start controlled ovarian stimulation (COS), in which a patient is stimulated on presentation regardless of her menstrual-cycle phase, has outcomes similar to conventional early follicular phase–start COS for fertility preservation in cancer patients.
Design: Retrospective cohort study.
Setting: Academic medical center.
Patient(s): Women recently diagnosed with cancer and in preparation for gonadotoxic therapy.
Intervention(s): Random- versus conventional-start COS.
Main Outcome Measure(s): Primary outcome: number of mature oocytes retrieved; secondary outcomes: pattern of follicular development, oocyte yield, and fertilization rate.
Result(s): The number of total and mature oocytes retrieved, oocyte maturity rate, mature oocyte yield, and fertilization rates were similar in random- (n = 35) and conventional-start (n = 93) COS cycles. No superiority was noted when comparing COS started in the late follicular (n = 13) or luteal phase (n = 22). The addition of letrozole, in the case of estrogen-sensitive cancers, did not adversely affect COS outcomes or oocyte maturity and competence in either random- or conventional-start protocols.
Conclusion(s): Random-start COS is as effective as conventional-start COS in fertility preservation. This protocol would minimize delays and allow more patients to undergo fertility preservation and still proceed with cancer treatment within 2–3 weeks. (Fertil Steril® 2013;100:1673–80. ©2013 by American Society for Reproductive Medicine.)
Key Words: Random start, fertility preservation, controlled ovarian stimulation

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/cakmakh-fertility-preservation-controlled-ovarian-stimulation/

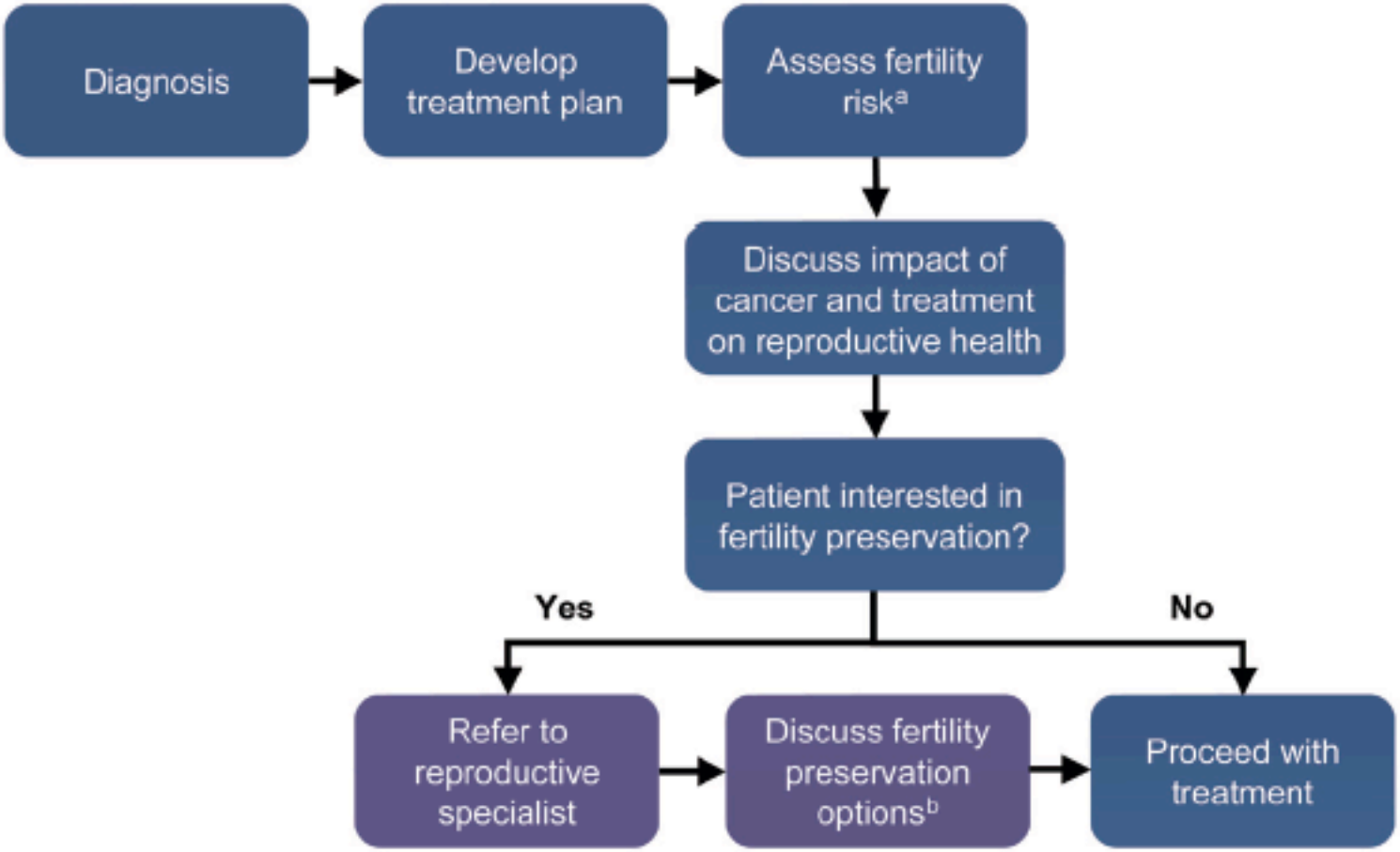
Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Access to Information

- American Fertility Association: http://www.theafa.org
- American Society of Clinical Oncology: http://www.asco.org/ guidelines/fertility
- American Society of Reproductive Medicine: http:// www.reproductivefacts.org
- Fertile Hope: http://www.fertilehope.org
- International Council on Infertility Information Dissemination: http://www.inciid.org
- Oncofertility Consortium: http://www.myoncofertility.org
- RESOLVE: the National Infertility Association: http://www.resolve.org

Fertility preservation for cancer patients



Published in final edited form as:
Curr Opin Obstet Gynecol. 2013 June ; 25(3): . doi:10.1097/GCO.0b013e32836091f4.

Current trends and progress in clinical applications of oocyte cryopreservation

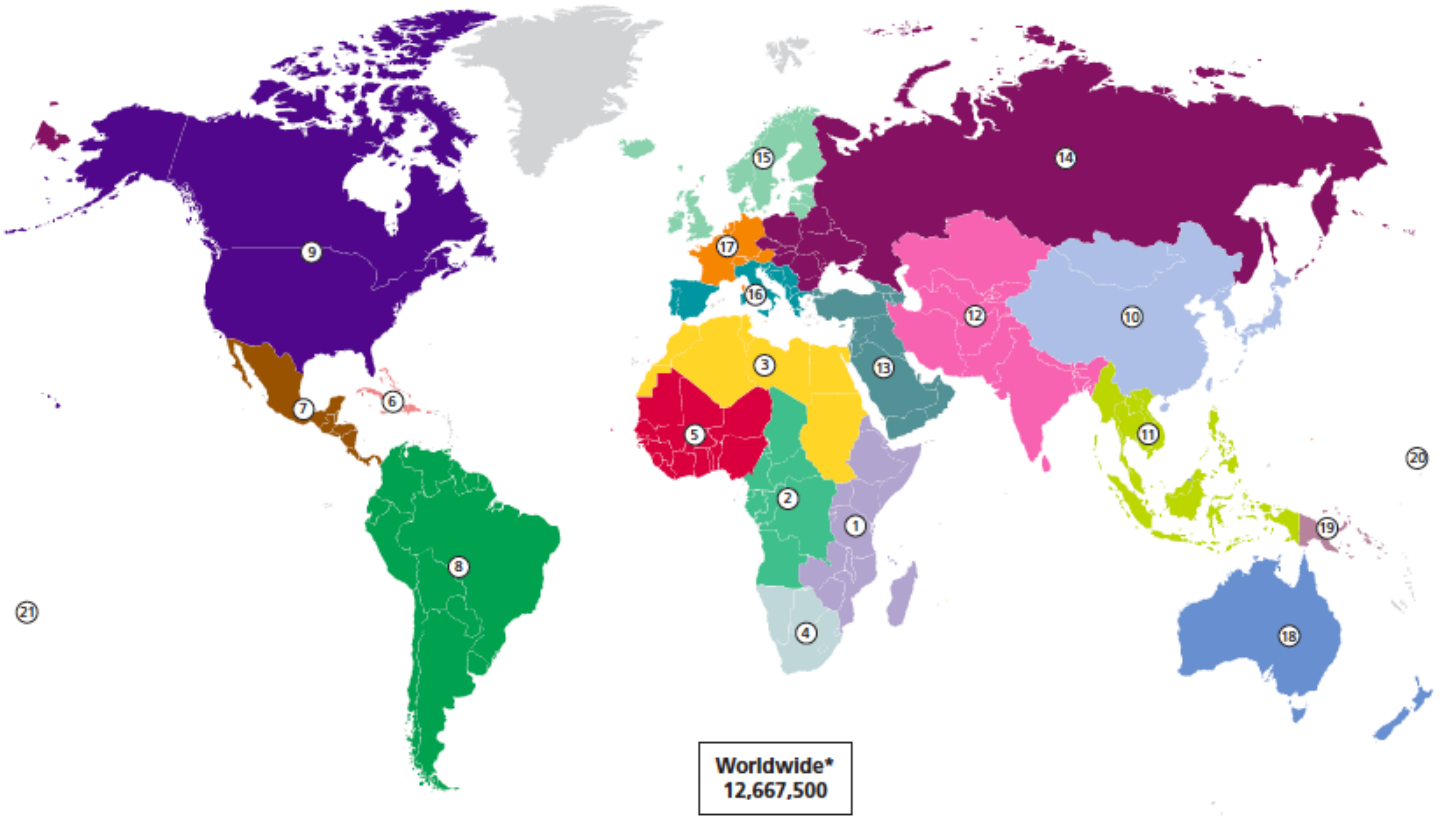
Aylin P. Cil[a] and **Emre Seli**[b]

Fertilization, in-vitro embryo development, and pregnancy rates using vitrified nondonor and donor oocytes are **similar** to those achieved with fresh oocytes; **success rates with slow-freezing are lower compared with vitrification.**

• As a result of significantly improved clinical outcomes reported for vitrified oocytes, **oocyte cryopreservation now represents the most applicable option** for single reproductive-age women in need of fertility preservation.

Curr Opin Obstet Gynecol. 2013 June

Estimated Number of New Cancer Cases by World Area, 2008*

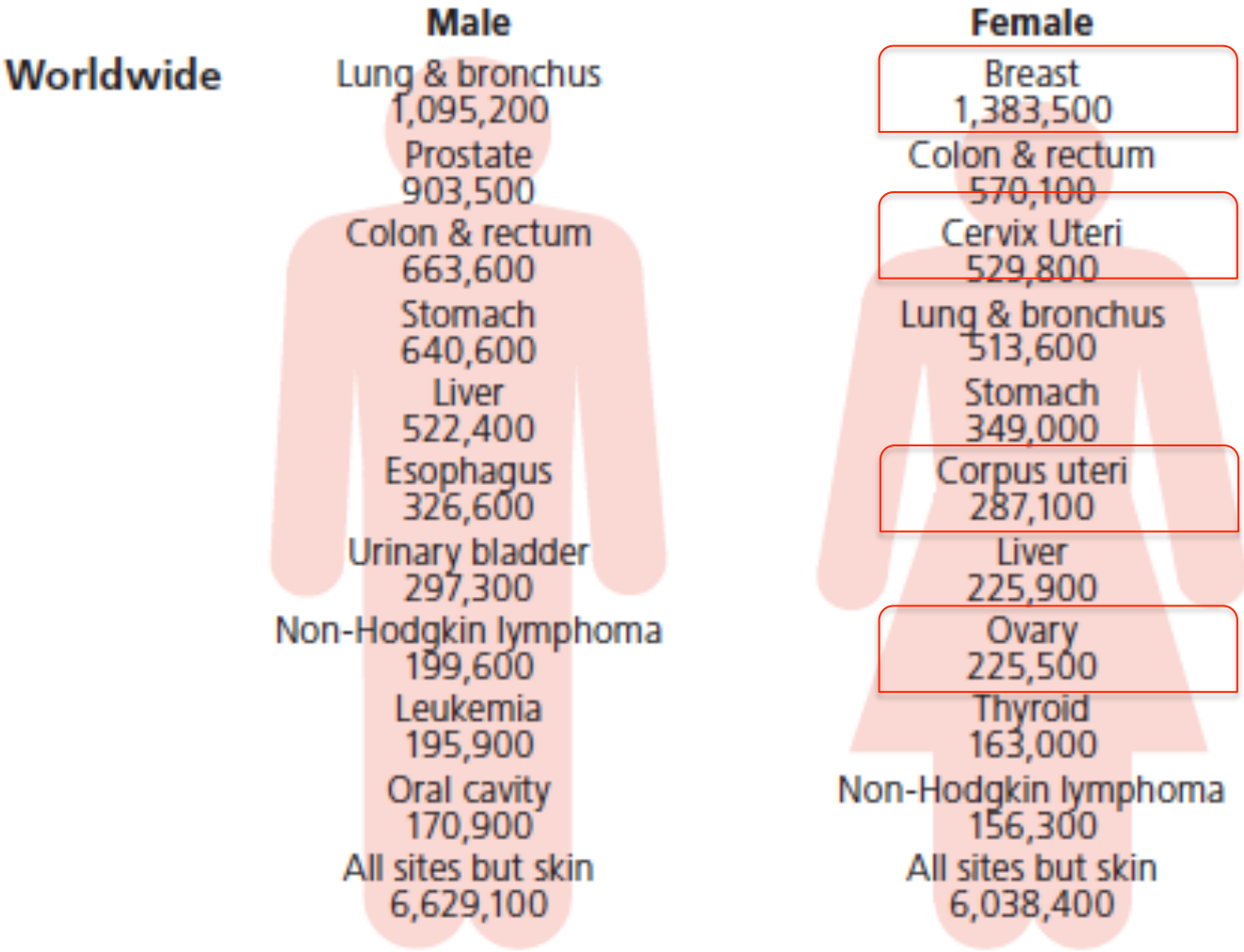


1 Eastern Africa (221,100)
2 Middle Africa (66,900)
3 Northern Africa (164,400)
4 Southern Africa (79,200)
5 Western Africa (184,100)
6 Caribbean (79,300)
7 Central America (176,600)
8 South America (650,100)
9 Northern America (1,603,900)
10 Eastern Asia (3,720,700)
11 South-Eastern Asia (725,600)
12 South-Central Asia (1,423,100)
13 Western Asia (223,300)
14 Central and Eastern Europe (985,200)
15 Northern Europe (480,200)
16 Southern Europe (713,900)
17 Western Europe (1,034,300)
18 Australia/New Zealand (127,000)
19 Melanesia (7,000)
20 Micronesia (700)
21 Polynesia (1,100)

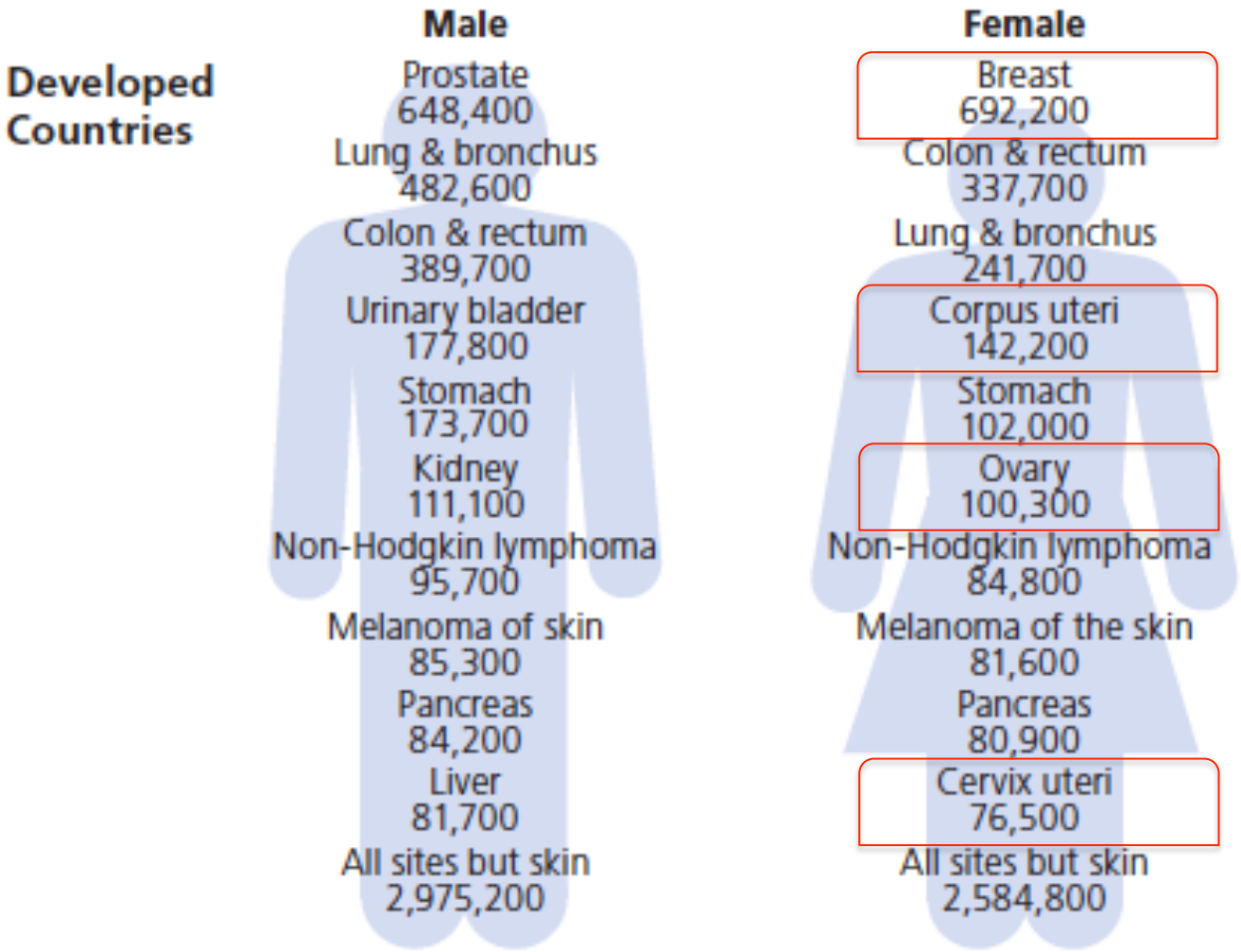
*Region estimates do not sum to the worldwide estimate due to calculation method.
Source: GLOBOCAN 2008.

Suggested citation: American Cancer Society. *Global Cancer Facts & Figures 2nd Edition.* Atlanta: American Cancer Society; 2011.

Estimated New Cancer Cases for Leading Cancer Sites

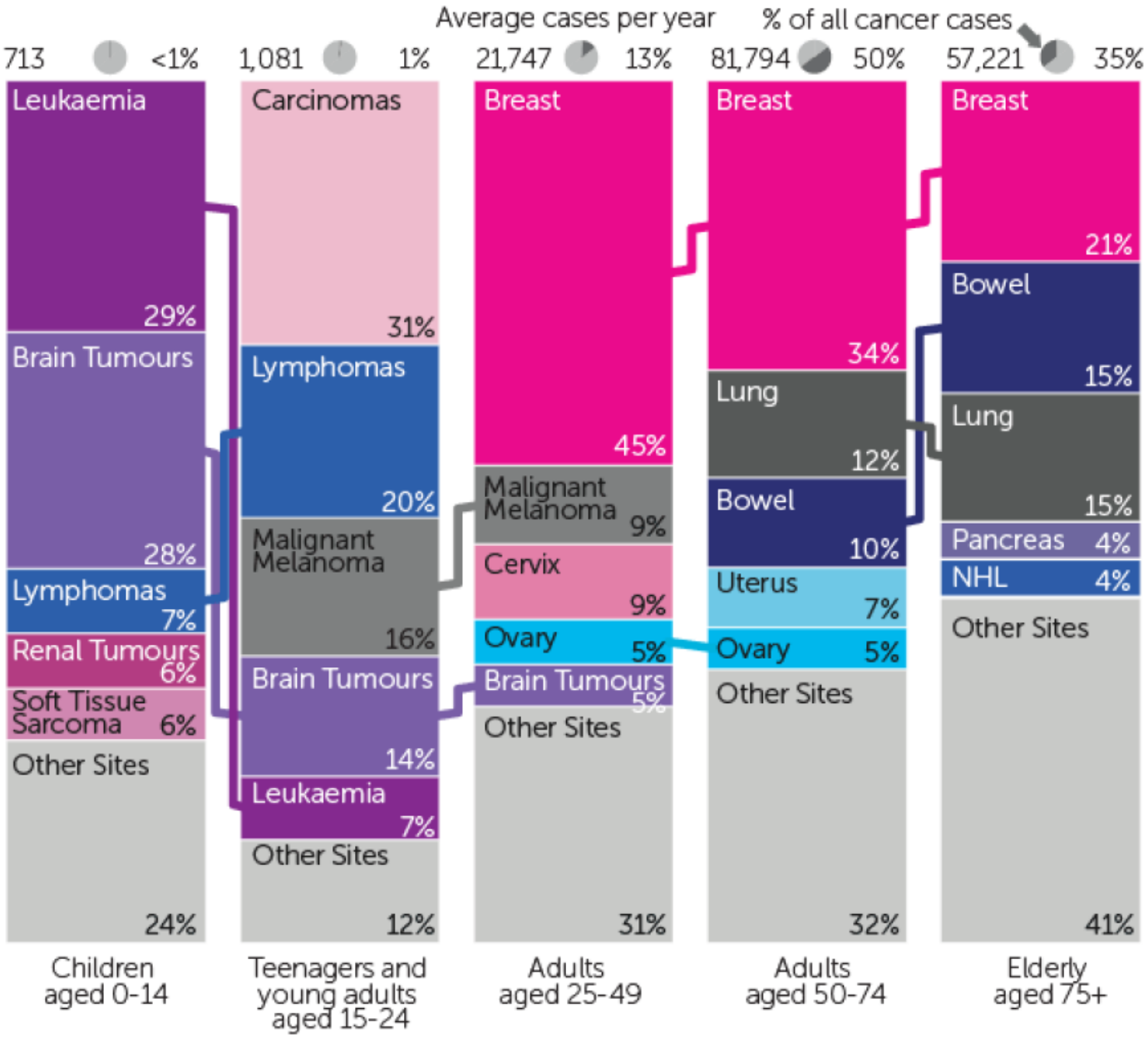


Estimated New Cancer Cases for Leading Cancer Sites



The 5 Most Commonly Diagnosed Cancers in Females

Average Percentages and Numbers of New Cases, by Age, UK, 2009-2011



Women with genetic risk for breast cancer

Approximately 20%-25% of breast cancer patients have a positive family history

5%-10% of breast cancer cases demonstrate an autosomal dominant inheritance.

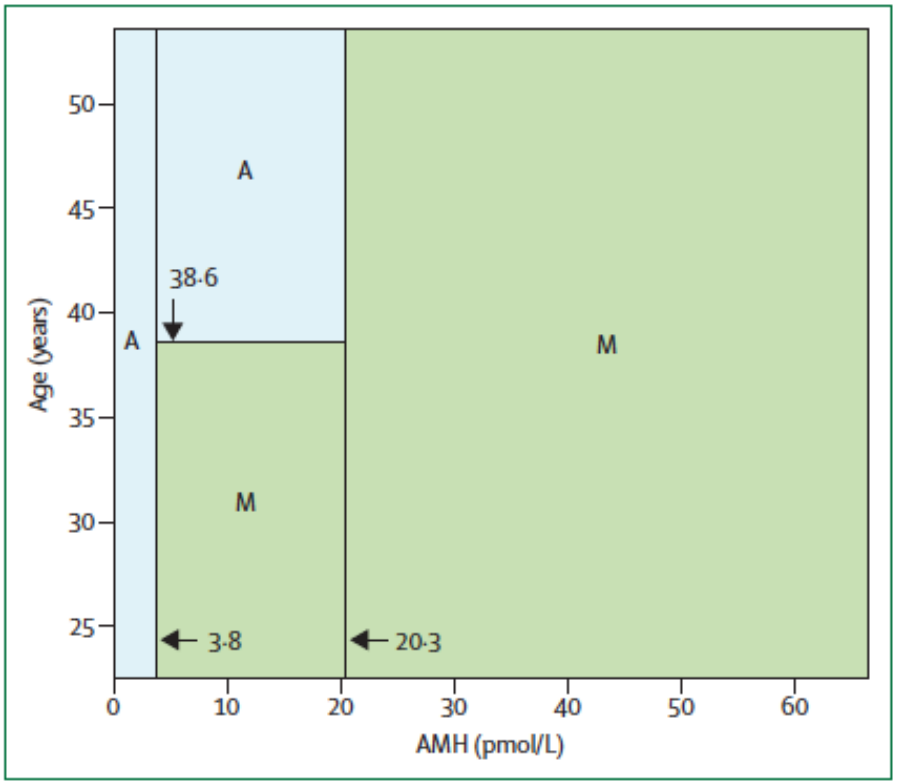
- Lifetime breast cancer risk ranges from 65% to 81% for BRCA1 mutation carriers and 45% to 85% for BRCA2 carriers.
- Moderate risk genes including homozygous ataxia-telangiectasia (ATM) mutations, somatic mutations in tumor suppressor gene CHEK2, and BRCA1 and BRCA2 modifier genes BRIP1 and PALB2 confer a 20%-40% lifetime risk of breast cancer.

Endocrine late-effects of cancer treatment 2

Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults

Richard A Anderson, Rod T Mitchell*, Thomas W Kelsey, Norah Spears, Evelyn E Telfer, W Hamish B Wallace*

Lancet Diabetes Endocrinol 2015



Panel 2: The Edinburgh Selection Criteria for gonadal tissue cryopreservation

These criteria were established with ethics committee review and approval because they refer to experimental procedures, and should be regarded as a starting point for future discussion, research, and refinement.

Female patients[112]

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy is acceptable if younger than 15 years
- A realistic chance of 5-year survival
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology
- Not pregnant and no existing children

Male patients

- Age 0–16 years
- A high risk of infertility (>80%)
- Unable to produce a semen sample by masturbation
- No clinically significant pre-existing testicular disease (eg, cryptorchidism)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology

KEY POINTS

- Random-start ovarian stimulation provides a significant advantage by decreasing total time for the IVF cycle without compromising oocyte yield and maturity.
- Starting ovarian stimulation in the late follicular or luteal phase did not show any superiority against the other.
- The presence of corpus luteum or luteal phase progesterone levels do not adversely affect synchronized follicular development, number of mature oocytes retrieved, and/or fertilization rates.
- Random-start ovarian stimulation with letrozole along with gonadotropins in patients with estrogen-sensitive cancers is well tolerated, and yields similar number of oocytes and embryos compared with standard protocols while minimizing the risk of high estrogen exposure.

Random-start ovarian stimulation in patients with cancer.
Cakmak, Hakan; Rosen, Mitchell

Current Opinion in Obstetrics & Gynecology. 27(3): 215-221, June 2015.
DOI: 10.1097/GCO.0000000000000180

Box 1. no caption available

FIGURE 1

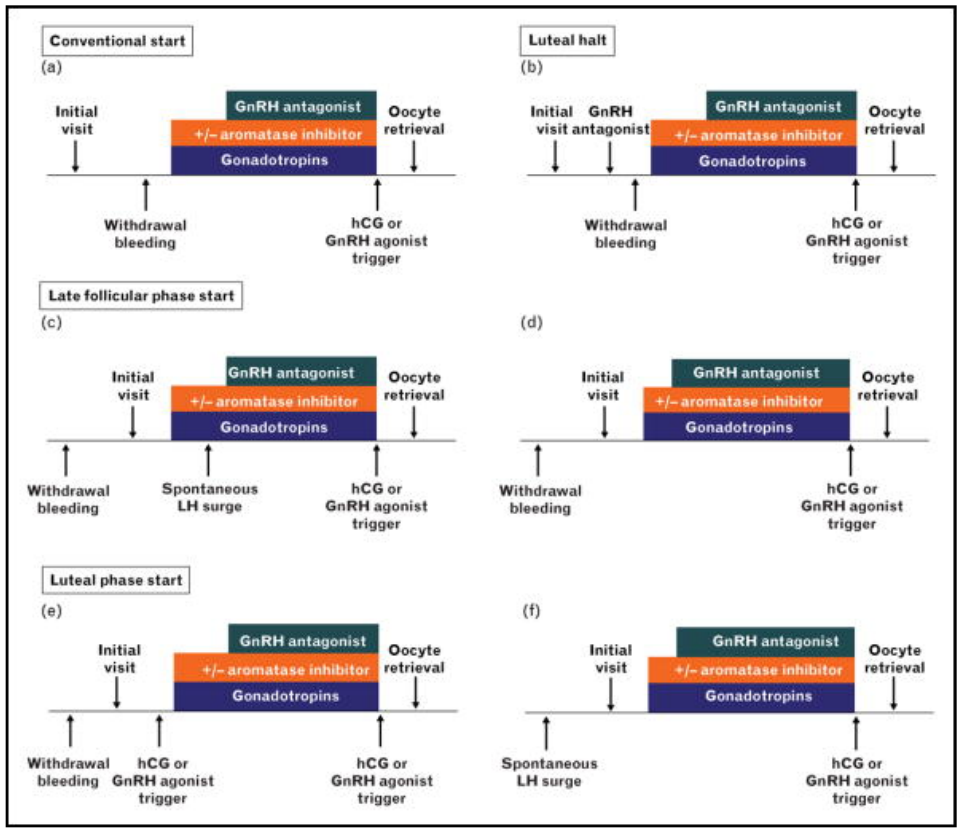
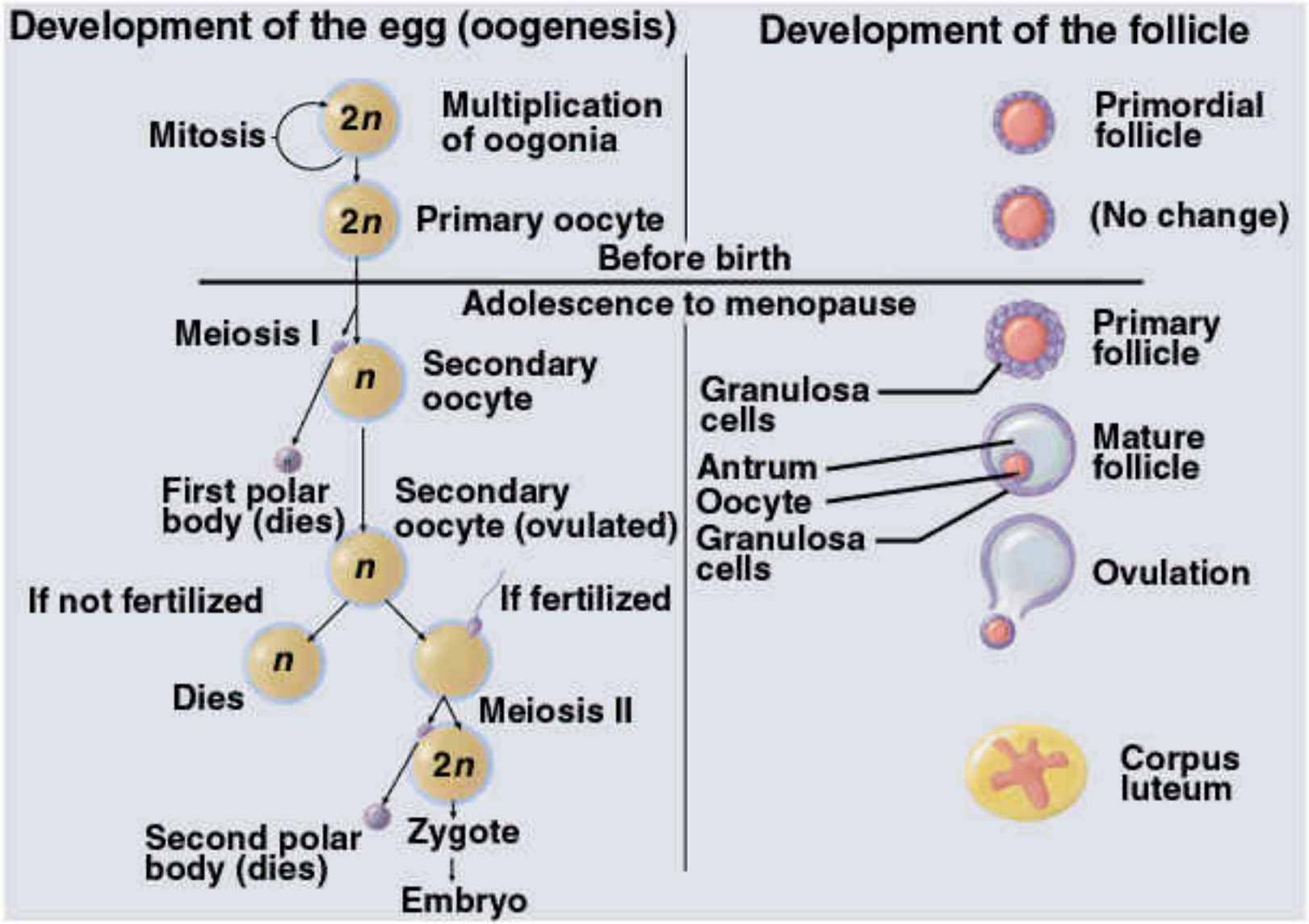


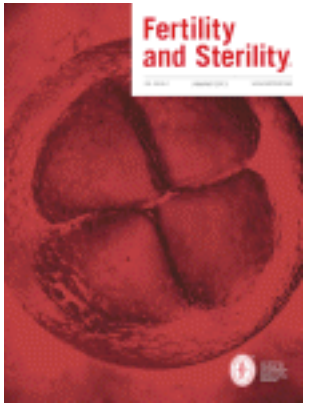
FIGURE 1 . Controlled ovarian stimulation protocols in patients with cancer. (A) In conventional (early follicular phase start) antagonist protocol, ovarian stimulation starts with menses and GnRH antagonist is initiated to prevent premature LH surge when the lead follicle reaches 12 mm. (B) In luteal halt protocol, administration of GnRH antagonist in the luteal phase induces corpus luteum regression, menses ensues 2-4 days later and ovarian stimulation is initiated earlier than awaiting spontaneous menses. If the patient with cancer presents in the late follicular phase, (C) ovarian stimulation without GnRH antagonist can be started if the follicle cohort following the lead follicle is smaller than 12 mm and stays smaller than 12 mm before a spontaneous LH surge. After the LH surge, GnRH antagonist is started when the secondary follicle cohort reaches 12 mm to prevent premature secondary LH surge. (D) If the follicle cohort following the lead follicle reaches 12 mm before the spontaneous LH surge, pituitary suppression with GnRH antagonist is initiated and continued until triggering final oocyte maturation. If the patient with cancer presents in the late follicular phase, (E) ovulation can be induced with hCG or GnRH agonist when the dominant follicle reaches 18 mm in diameter and ovarian stimulation is started in 2-3 days in luteal phase. If the patient with cancer presents in the luteal phase, (F) ovarian stimulation can be started in the absence of GnRH antagonist and GnRH antagonist administration is initiated later in the cycle, when the follicle cohort reached 12 mm to prevent premature secondary LH surge. GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

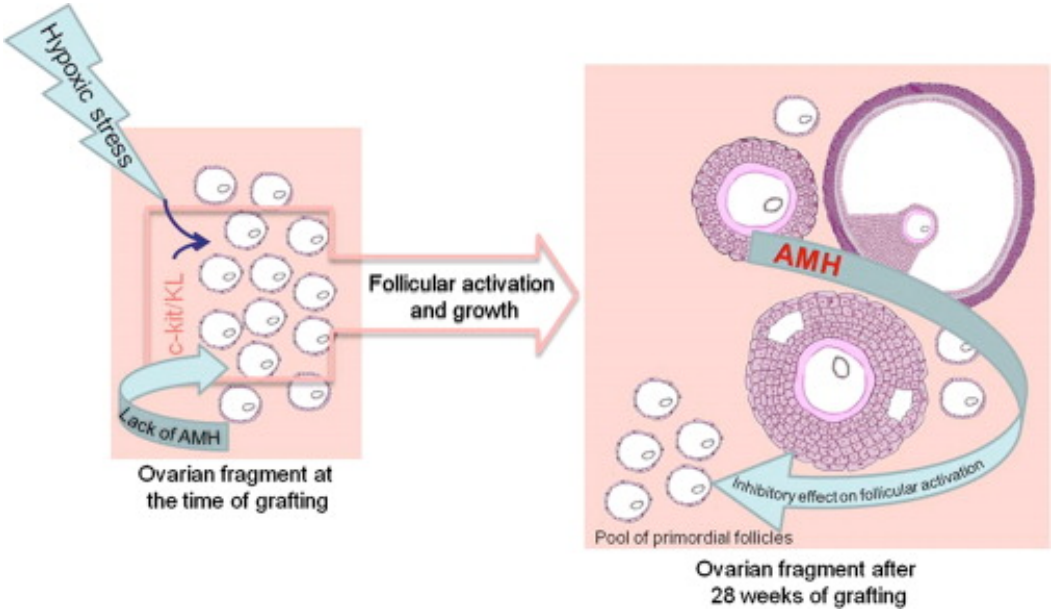
Oogenesis and Follicle Development



Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation

Jacques Donnez, M.D., Ph.D.,[a] Marie-Madeleine Dolmans, M.D., Ph.D.,[b] Antonio Pellicer, M.D., Ph.D.,[c] Cesar Diaz-Garcia, M.D.,[c] Maria Sanchez Serrano, M.D.,[c] Kristen Tryde Schmidt, M.D., Ph.D.,[d] Erik Ernst, M.D., Ph.D.,[f] Valérie Luyckx, M.D.,[b] and Claus Yding Andersen, M.Sc., D.M.Sc.[e]

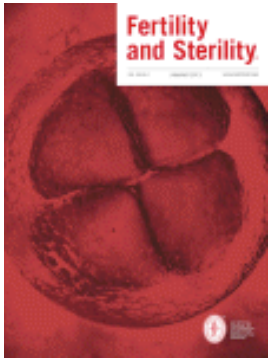




The amount of ovarian cortex to remove is influenced mainly by the estimated risk of ovarian failure related to the planned treatment and existing ovarian volume. For cases with pelvic irradiation, TBI, and high doses of alkylating agents, oophorectomy should be performed. It should also be performed in very young girls owing to the small size of the ovaries

Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation

Jacques Donnez, M.D., Ph.D.,[a] Marie-Madeleine Dolmans, M.D., Ph.D.,[b] Antonio Pellicer, M.D., Ph.D.,[c] Cesar Diaz-Garcia, M.D.,[c] Maria Sanchez Serrano, M.D.,[c] Kristen Tryde Schmidt, M.D., Ph.D.,[d] Erik Ernst, M.D., Ph.D.,[f] Valérie Luyckx, M.D.,[b] and Claus Yding Andersen, M.Sc., D.M.Sc.[e]



Pregnancy after ovarian transplantation

Series of 24 live births after transplantation of frozen-thawed ovarian cortex.

References	Cryopreservation procedure	Graft site	Live birth: Spont.	Live birth: IVF
Donnez et al. (1, 3, 26, 30, 31)	SF	Peritoneal window (2 steps)	+	
		Peritoneal window (1 step)		++
		Ovarian medulla	+++	
Meirow et al. (58)	SF	Beneath the ovarian cortex	–	+
Demeestere et al. (33)	SF	Ovarian and peritoneal windows (2 steps)	++	–
Andersen et al. (40, 41, 76, 77)	SF	Subcortical ovarian pocket	+	+
		Ovarian medulla	+	+
Silber et al. (37, 75)	SF	Ovarian medulla	++	–
Piver et al. (34)	SF	Ovarian and peritoneal windows (1 and 2 steps)	+	–
Roux et al. (35)			+	
Sanchez et al. (28)	SF	Ovarian medulla	–	++ (twins)
Revel et al. (78)[a]	SF	Peritoneal window (slice)	–	+
				+
Dittrich et al. (79)	SF	Peritoneal window	+	–
Revelli et al. (80)	SF	Ovarian medulla	+	
García Rada (81)	SF	Peritoneal pocket		+

Note: Four ongoing pregnancies at the present time: two in Spain, one in South Africa, and one in Australia.

[a] Personal communication, 2012.

Donnez. Transplantation of ovarian tissue. Fertil Steril 2013.

Chemo-radiation effect on Genetic cells

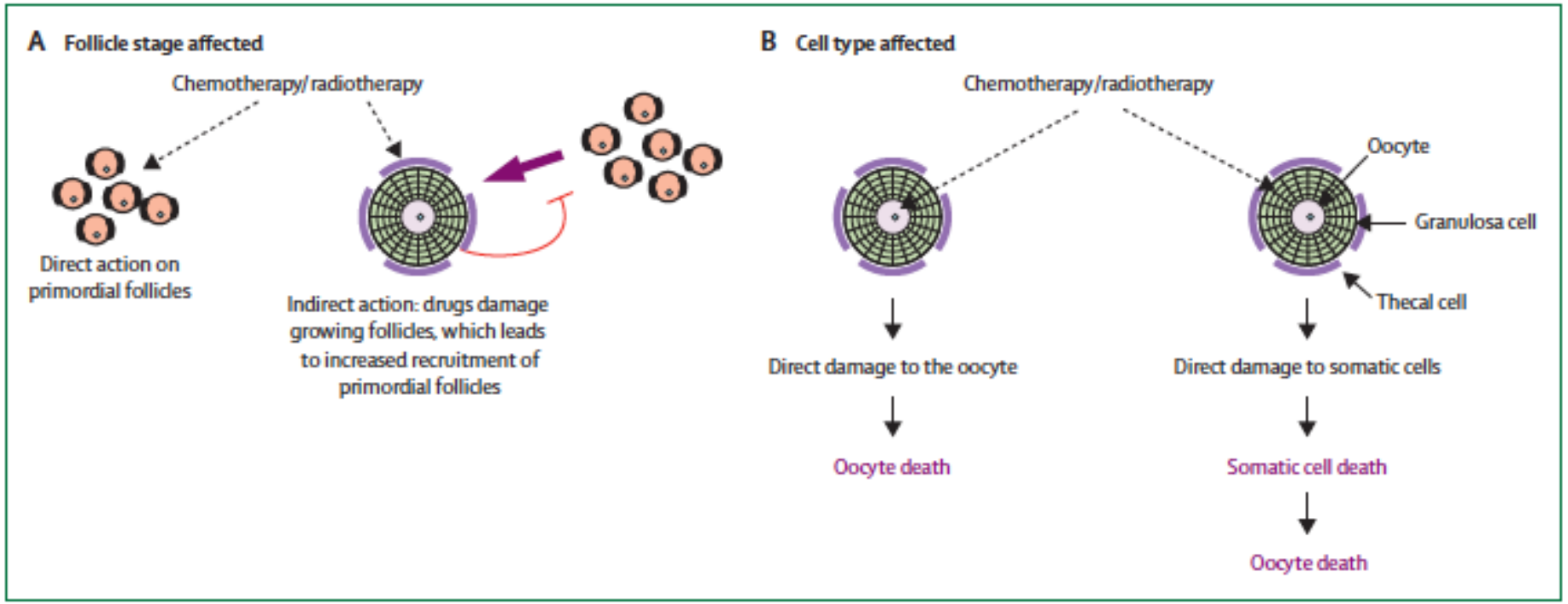


***Figure 3*: Follicle stage and cell types affected by chemotherapy and radiotherapy**
(A) Cancer treatments could directly affect the resting pool of primordial follicles or the growing follicle population. Since growing follicles inhibit recruitment of primordial follicles, loss of this growing population leads to increased activation of primordial follicles and so loss of that reserve. (B) Cancer treatments could directly target oocytes or somatic cells. Oocyte death would result from death of the follicular somatic cells, since oocytes are dependent on these for survival. Reproduced from Morgan and colleagues[30] by permission of the European Society of Human Reproduction and Embryology.

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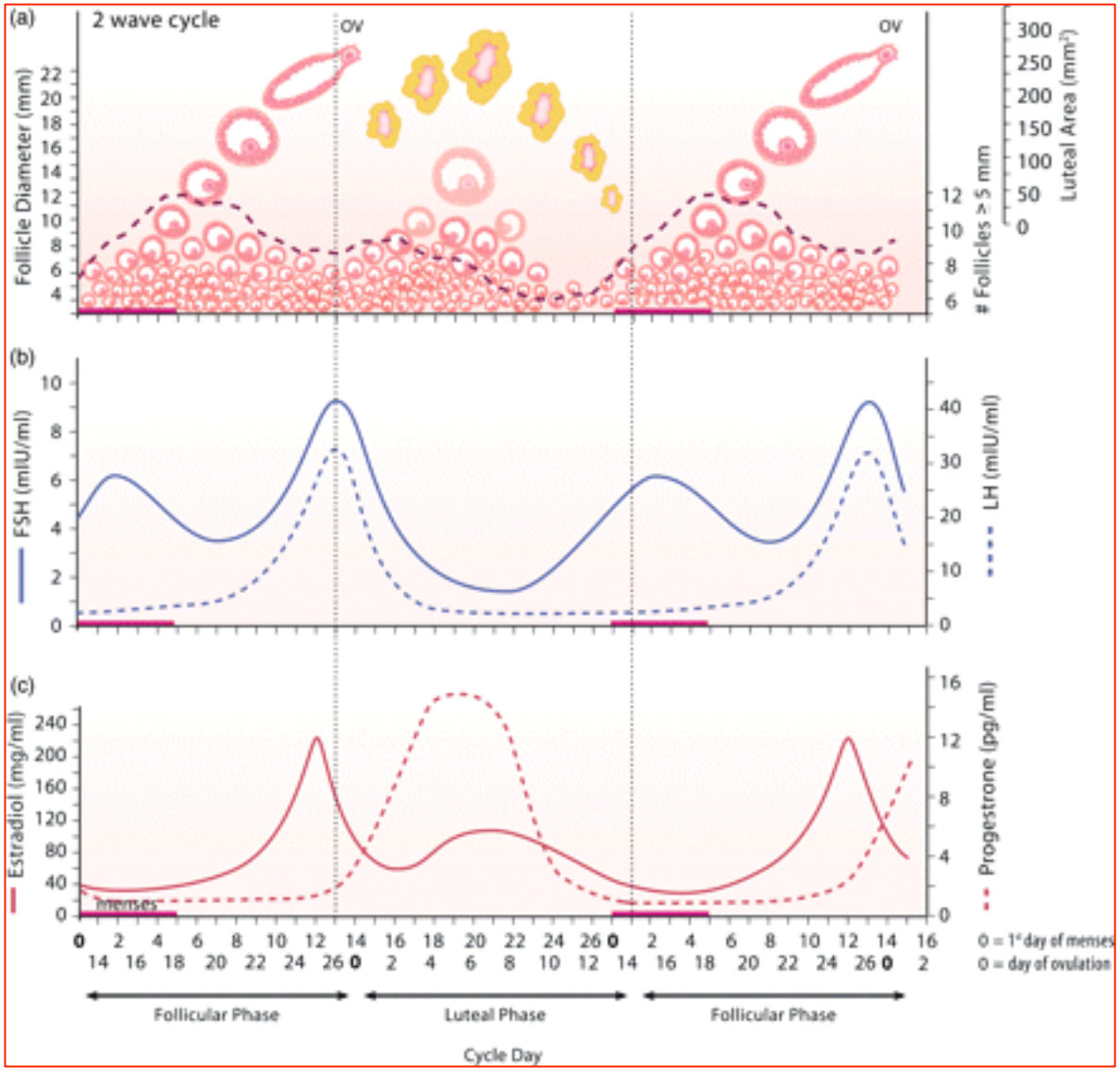
Advanced Access publication on November 8, 2011 doi:10.1093/humupd/dmr039

human reproduction update

Angela R. Baerwald[1,*], Gregg P. Adams[2], and Roger A. Pierson[3]

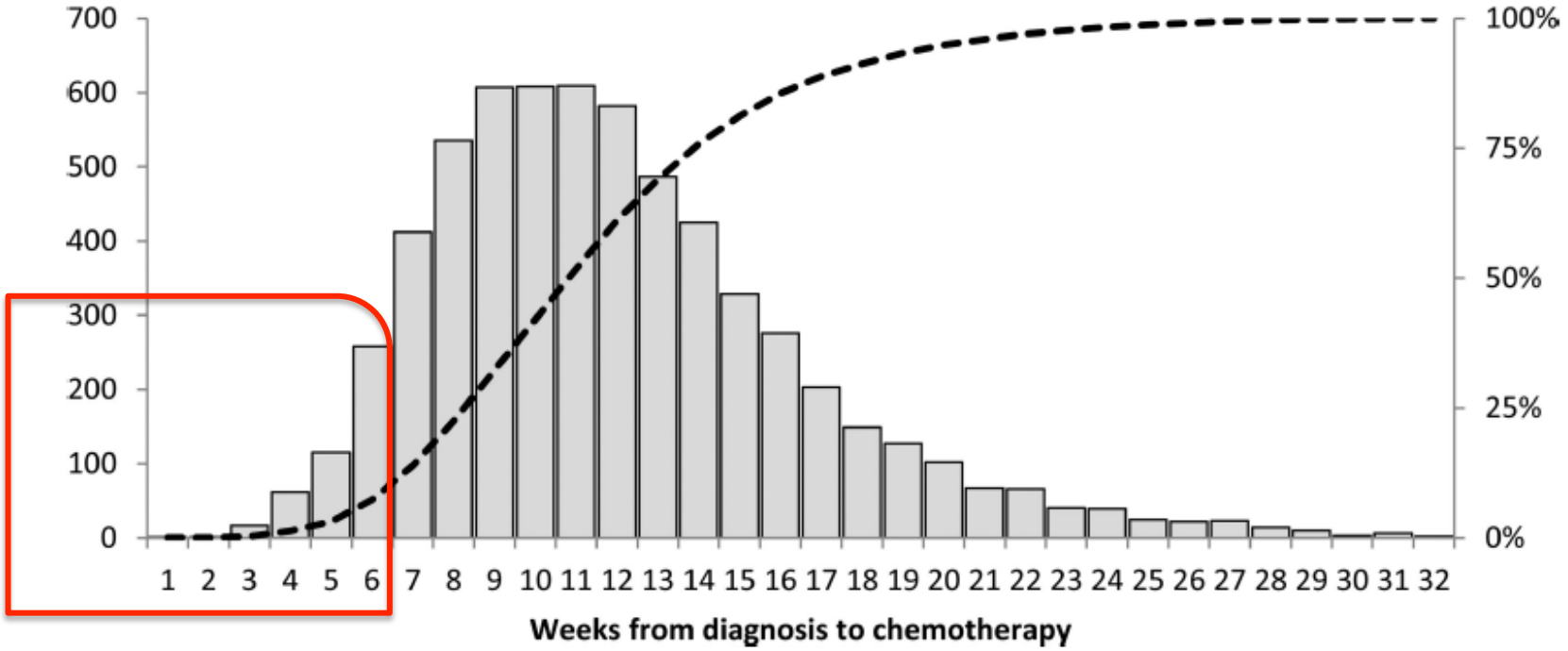


Time from diagnosis to chemotherapy

Time to Adjuvant Chemotherapy for Breast Cancer in National Comprehensive Cancer Network Institutions

Jonathan L. Vandergrift, Joyce C. Niland, Richard L. Theriault, Stephen B. Edge, Yu-Ning Wong, Loretta S. Loftus, Tara M. Breslin, Clifford A. Hudis, Sara H. Javid, Hope S. Rugo, Samuel M. Silver, Eva M. Lepisto, Jane C. Weeks

Manuscript received June 15, 2012; revised October 29, 2012; accepted October 31, 2012.



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Results

Mean TTC was 12.0 weeks overall and increased over the study period.

The largest effects were associated with therapeutic factors,

- immediate post-mastectomy reconstruction (2.7 weeks; $P < .001$),
- re-excision (2.1 weeks; $P < .001$), and
- use of the 21-gene RTPCR assay (2.2 weeks; $P < .001$).