



Fertility and Breast Cancer: Educational Opportunities and Preservation Options

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Patient Navigator

Disclosures

I have no disclosures to report.

I will not discuss any “off-label” use of medications.

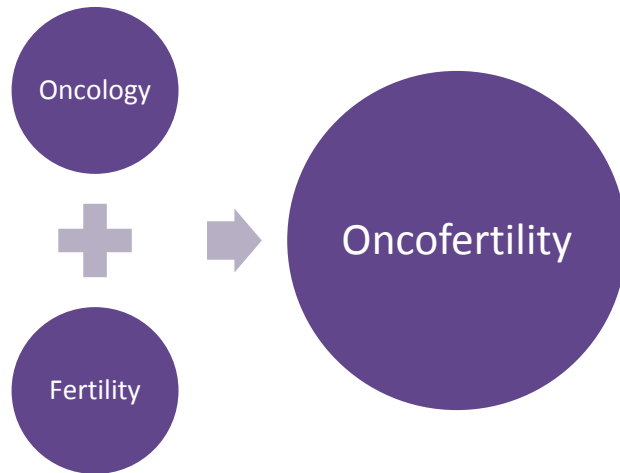
Objectives

- Describe the state of the science of fertility preservation
- Discuss experimental and standard fertility preservation options available
- Identify challenges and opportunities for fertility preservation and methods for fertility preservation
- Illustrate programmatic processes for establishing a fertility preservation service and educational opportunities

The History

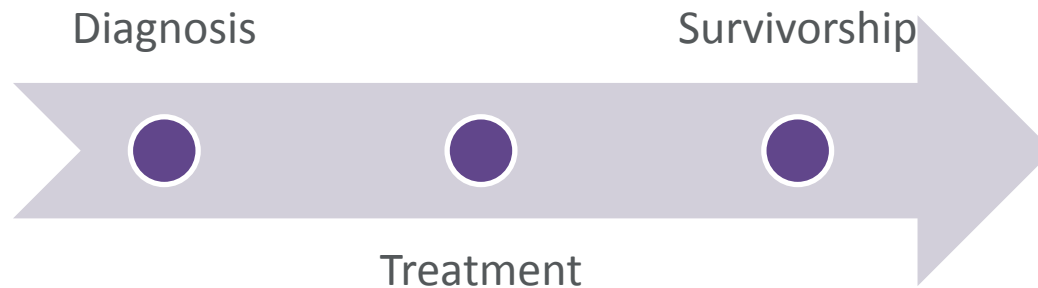
Of Northwestern's Program

- Oncofertility Consortium
 - A national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors. It was supported by the National Institutes of Health through the NIH Roadmap for Medical Research/Common Fund. The Consortium is now supported by a U54 grant.
 - Patient Navigation: Full time navigator hired in 2006



Patient Navigation

- Process by which an individual – a Patient Navigator – guides patients through and around barriers in a complex healthcare environment to help ensure diagnosis and treatment.



*Freeman HP. A model patient navigation program. *Oncol Issues*. September/October 2004:44-46.

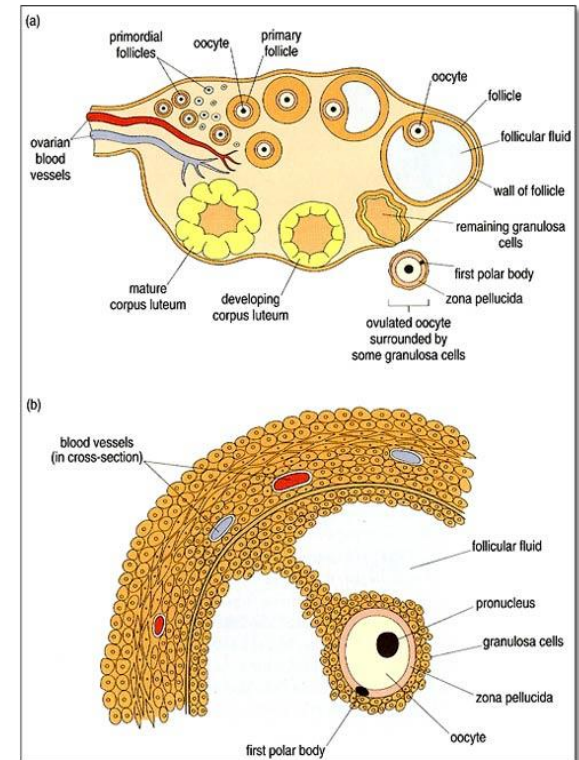
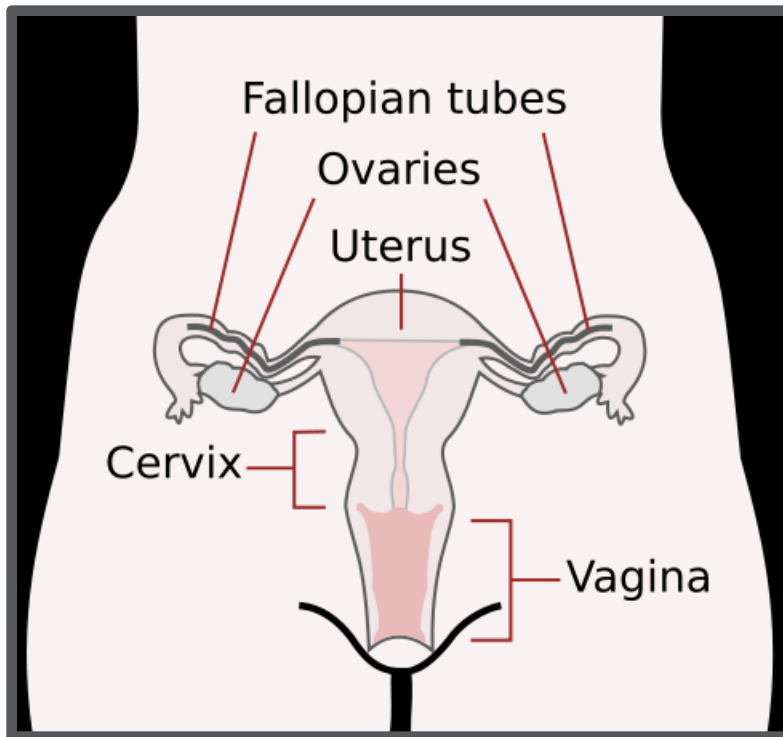
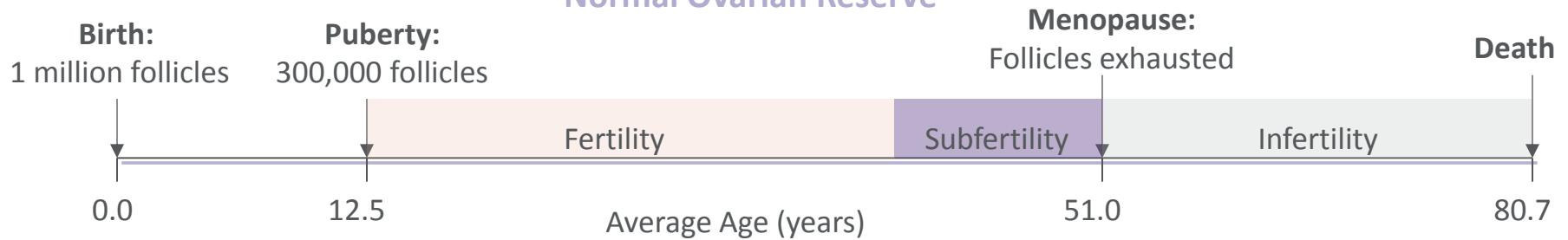
Risks of Infertility

- Variety of factors influence fertility after treatment:
 - Treatment and Dose
 - Chemotherapy (alkylating, platinum agents)
 - Radiation (cranial, spinal, pelvic)
 - Surgery
 - Previous treatment(s)
 - Age

Back to Biology Basics

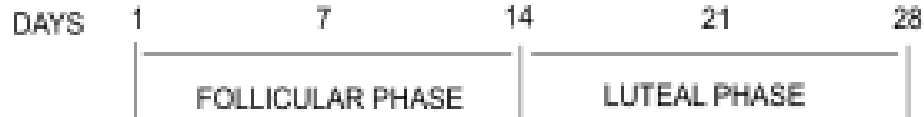
Females

Normal Ovarian Reserve

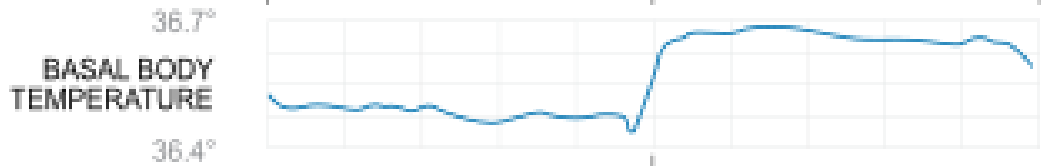


Back to Biology Basics

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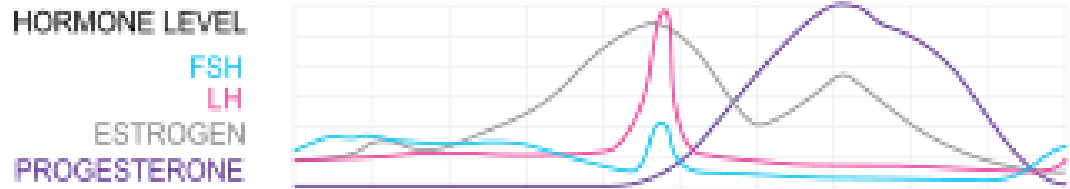


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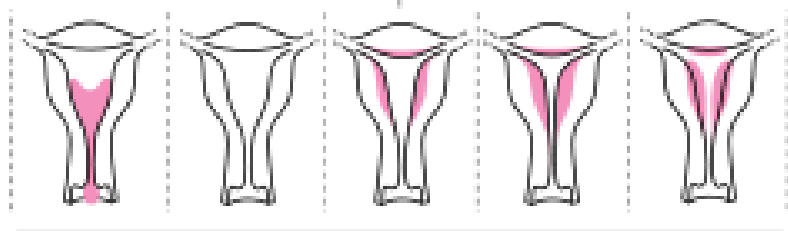
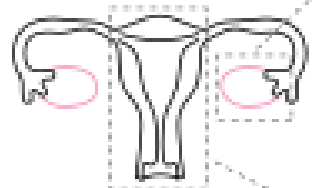
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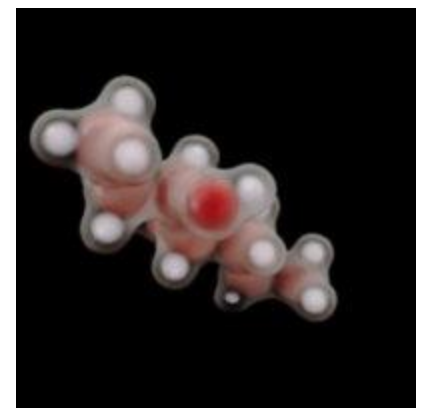
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or ovulation to



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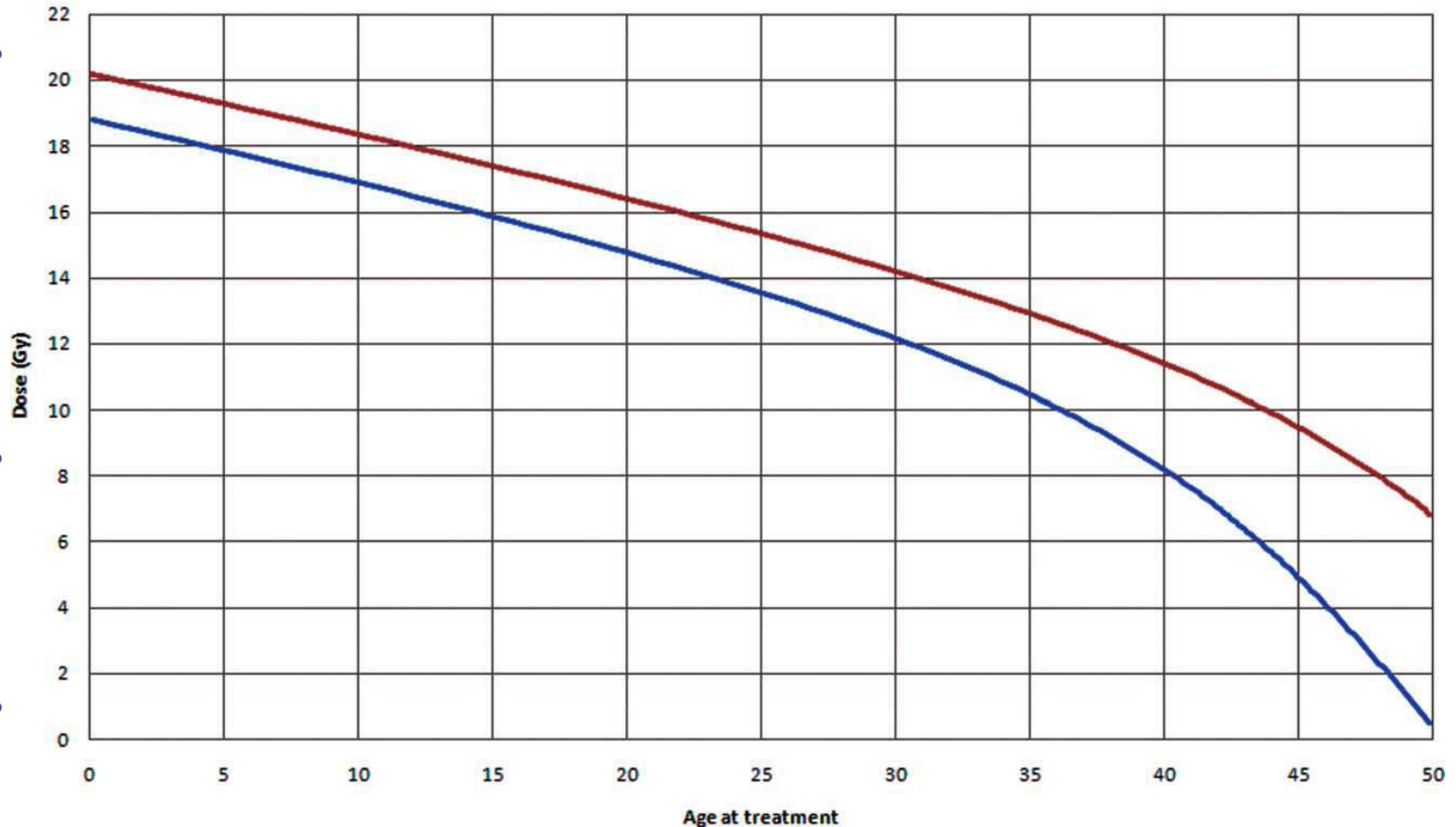


New Biology

- Anti-mullerian hormone (AMH)
 - In females
 - Secreted by granulosa cells in ovaries
 - Peaks at age 24, declines with age
 - Does not fluctuate with menstrual cycles
 - More accurate measurement of a woman's fertility

How Does Cancer Therapy Affect Female Fertility?

Effective and Mean Sterilising Doses



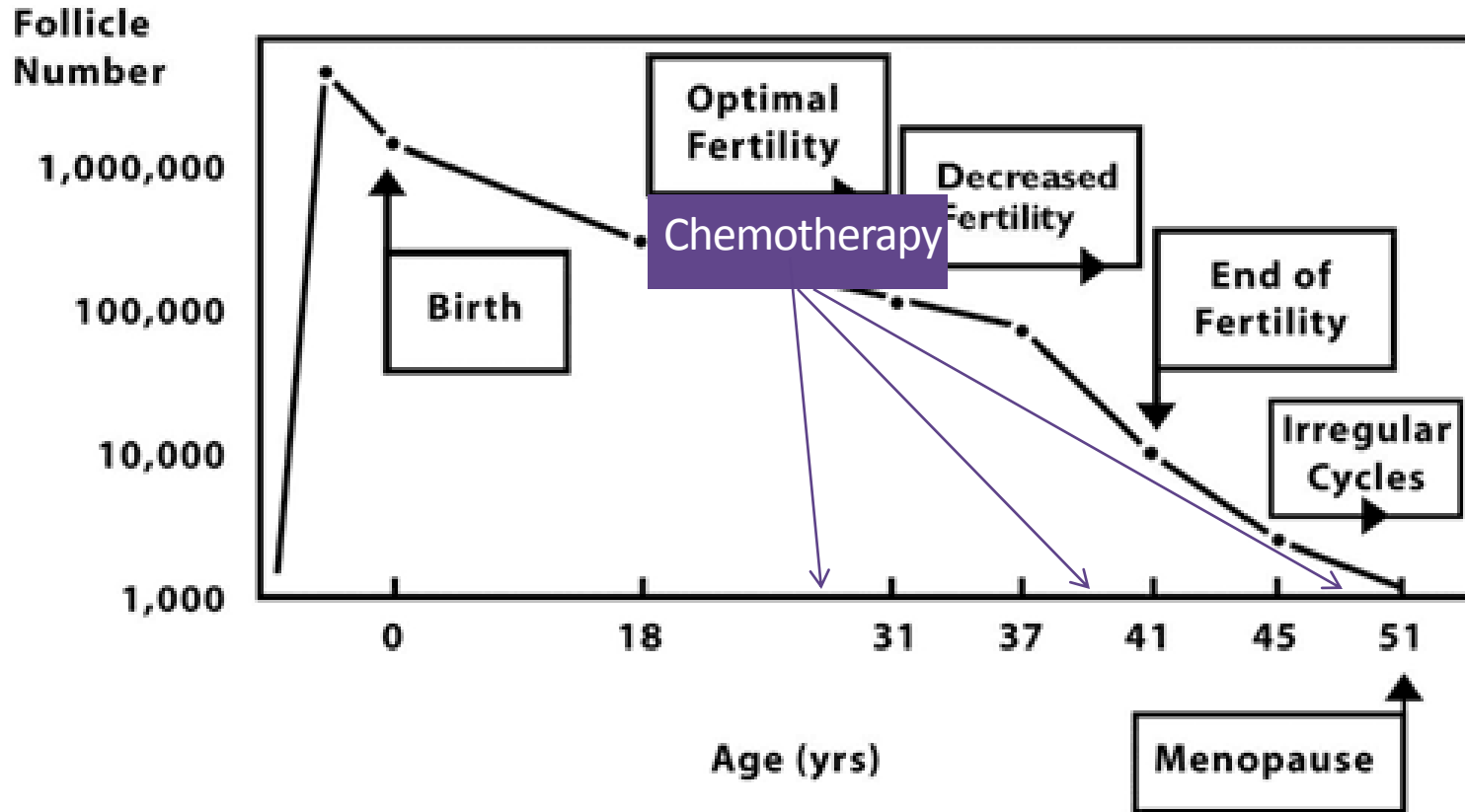
Wallace, *Cancer*, 2011

Meirow D, et al, *Human Reproduction*, 2007

Familiari G, et al *Human Reproduction*, 1993

Desmeules P, et al *Toxicology Science*, 2006.

In Other Words



E.R. TE VELDE ET AL., 1998

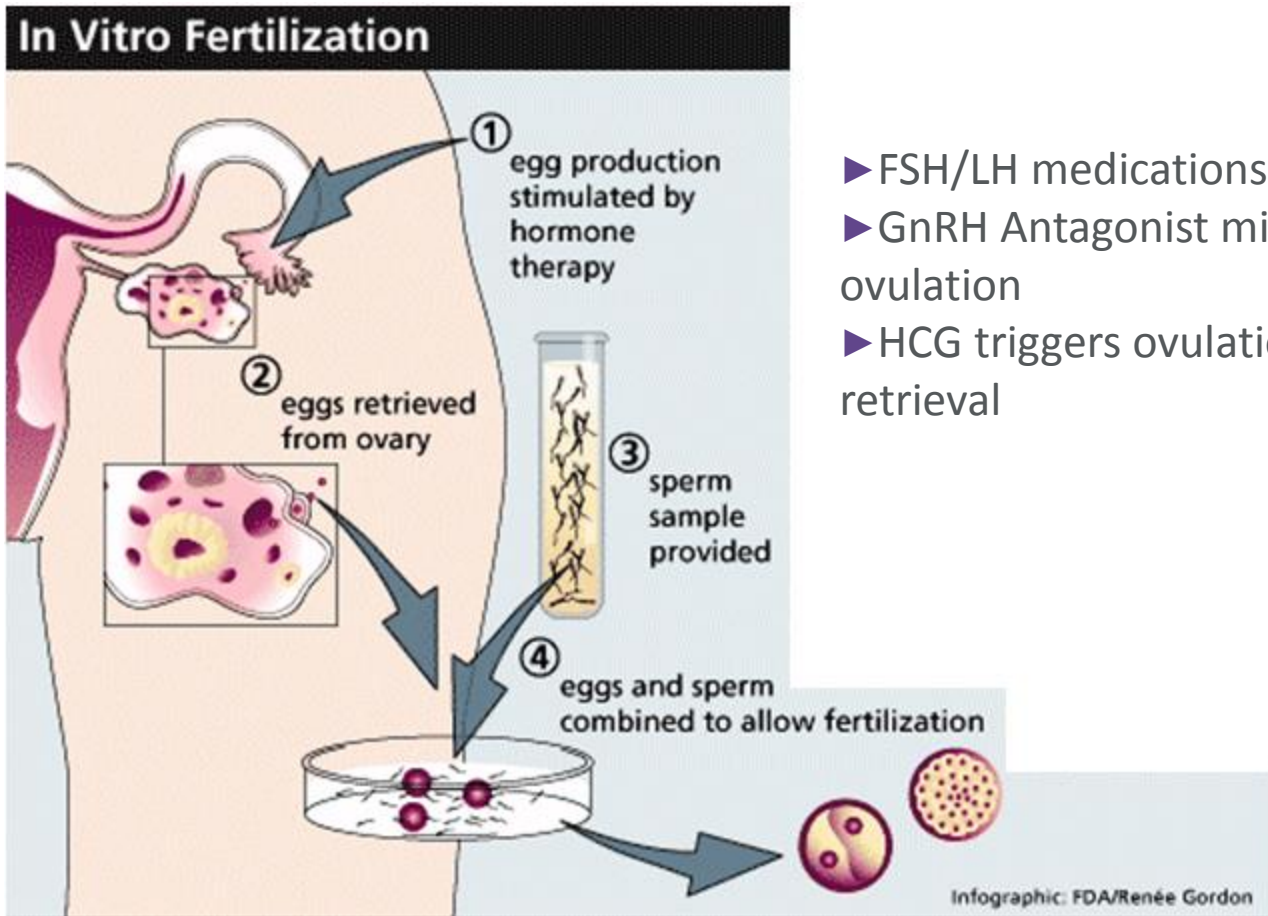
Fertility Preservation Options

- Embryo/Oocyte cryopreservation
- Hormone suppression
 - Conflicting data regarding usefulness
- Ovarian Tissue cryopreservation
- Ovarian shielding
- Surgical interventions

Embryo/Oocyte Cryopreservation

- Most commonly used fertility preservation techniques but there are some caveats:
 - Patient must be post pubertal
 - Patient must be emotionally/psychologically ready for multiple transvaginal ultrasounds, blood draws, etc
 - Patient/physician must be able to delay cancer treatment for at least 2 weeks
 - Patient must be healthy enough to undergo oocyte retrieval
 - Will require hormonal stimulation – daily injections
 - Oncology must be ok with hormonal stimulation

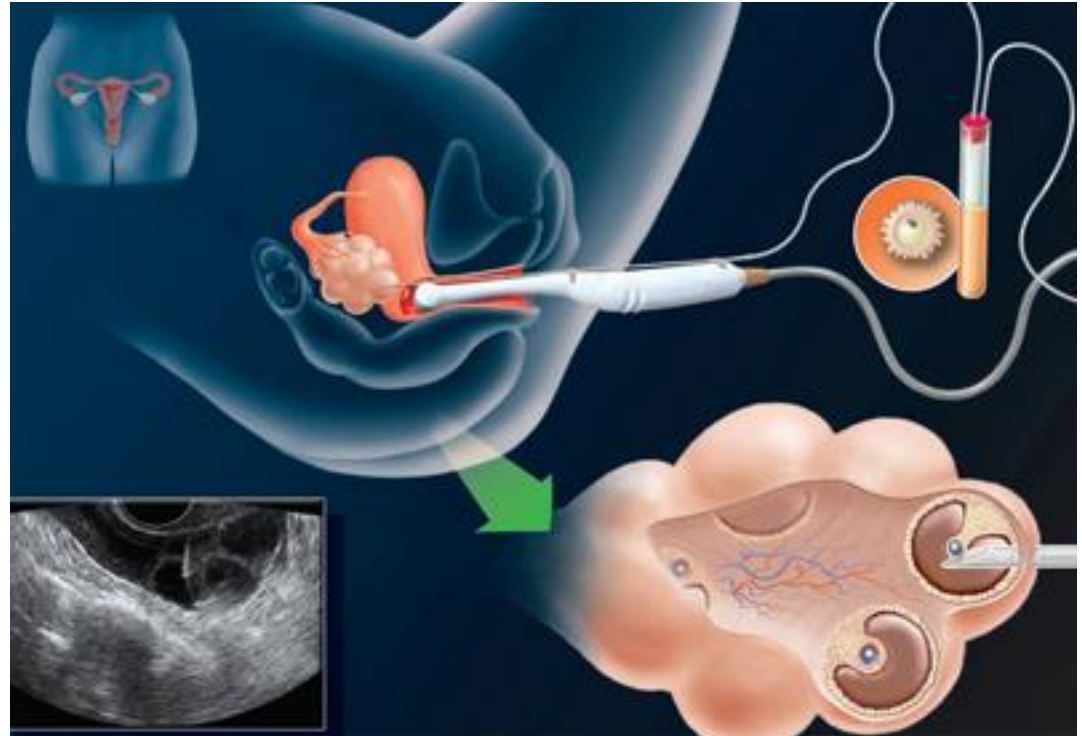
Embryo Cryopreservation



- ▶ FSH/LH medications for 8-13 days
- ▶ GnRH Antagonist midcycle to prevent ovulation
- ▶ HCG triggers ovulation 36 hours prior to retrieval

The Retrieval

- ▶ Retrieval done under conscious sedation with TVUS and needle guide
- ▶ Patient will know immediately how many eggs were retrieved
- ▶ Patient will find out how many eggs successfully fertilized usually the following day – frozen at various stages



Cryopreservation Techniques

- Slow Freeze

- Pioneered in the 70's – first human embryo frozen birth (1984)
- Programmable steps are used to “freeze down” a sample
- Sample treated with cryoprotectants
- Temperature dropped at 1°C/min

- Vitrification

- New technique to prevent ice crystal formation
- Cryoprotectants are added to protect the sample and to act like antifreeze and increase viscosity
- No phase change from liquid to solid, the amorphous state is like a “solid liquid”

Pregnancy After Egg/Embryo Cryopreservation

- Embryo
 - Patient undergoes uterine preparation – estrogen/progesterone
 - Controlled thaw
 - Zygotes mature if necessary
 - Preimplimentation genetic diagnosis (PGD) can be done at blastocyst
- Success Rates:
 - < 35 : 44.4%
 - 35-37 : 40.6%
 - 38 – 40: 36.1%
 - 41 – 42 : 31.6%
 - > 42 : 21.2%
- Oocyte
 - Patient undergoes uterine preparation – estrogen/progesterone
 - Controlled thaw
 - Intracytoplasmic sperm injection (ICSI)
 - Maturation
 - PGD
- Success Rates:
 - Live birth rates per egg (before 2005)
 - Slow freeze: 2%
 - Vitrification: 4%
 - Live birth rates from egg donors (43.2%)

What about hormone sensitive tumors?

- Each year, more than 200,000 women are diagnosed with breast cancer. Estimated that 11,000 of those are under 40.

SEER Database (2008)

Alterations in the ovarian hormonal milieu deregulate the centrosome cycle in mammary epithelial cells, leading to aneuploidy and cancer (in mice)

Oncogene (2008) 27, 1759–1766

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www.nature.com/onc



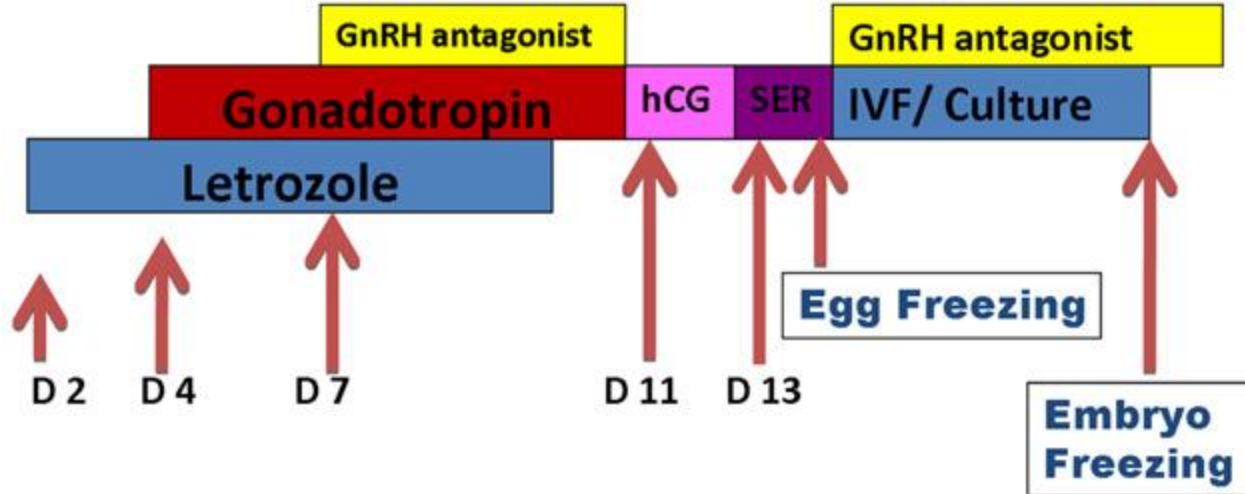
ORIGINAL ARTICLE

Ovarian hyperstimulation induces centrosome amplification and aneuploid mammary tumors independently of alterations in p53 in a transgenic mouse model of breast cancer

EL Milliken¹, KL Lozada¹, E Johnson¹, MD Landis¹, DD Seachrist¹, I Whitten¹, ALM Sutton¹, FW Abdul-Karim^{2,3} and RA Keri^{1,4}

The Proposal

- Using tamoxifen or letrozole with low-dose gonadotropin for ovarian stimulation
 - Letrozole – potent 3rd generation aromatase inhibitor that competitively inhibits the activity of aromatase enzyme in estrogen receptor positive cells and suppresses estrogen levels
 - Tamoxifen is a selective estrogen receptor modulator



The Data

- 2005 – Oktay – JCO – Fertility Preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation
 - Outcomes: **Recurrence rate** in the 29 women that did FP **was similar** to the 31 patients who did not undergo FP
- 2008 – Azim – JCO – Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study.
 - Outcomes: **no increase in recurrence or death** in 79 breast cancer patients who chose to have embryos stored before treatment using letrozole compared with 136 patients who were evaluated but declined FP
- 2012 – Westphal – Gyn Onc - Integration and safety of fertility preservation in a breast cancer program.
 - Outcomes: **2 local breast cancer recurrences out of the 44 breast cancer patients** who underwent ovarian stimulation with a mean follow up of 47 months

Additional Thoughts

- Is it as black and white as assumed?

RANDOMIZED STUDY COMPARING CHEMOTHERAPY WITH AND WITHOUT ESTROGEN PRIMING IN ADVANCED BREAST-CANCER

A randomized trial was performed to determine if combination chemotherapy (CT) with estrogen (E) priming (E+ study arm) was superior to CT alone (E- study arm) in patients with advanced breast cancer. CT for both arms included adriamycin + vincristine (AV) starting on day 7 alternating with cytoxan + methotrexate + fluorouracil (CMF) starting on day 28, the entire cycle repeated every 6 weeks. Estrogen priming consisting of 2 mg estradiol + 1 mg estriol (E+ arm) was given orally twice daily beginning on day 1 and continuously through CT until disease progression or unacceptable toxicity. Performance status (KPS) for all patients (n=19, E+ arm; n=22, E- arm) ranged between 70-100%. Mean age (53 y, E+ arm; 56 y, E- arm), menopausal and estrogen receptor status and treatment duration (approximately 38 weeks) were similar for both groups. **Estrogen priming did not alter or enhance CT toxicity.** Objective responses (CR,PR) were noted in 79% on the E+ arm (CR=11%, PR=68%) and in 73% on the E- arm (CR=9%, PR=64%). Thus, **estrogen priming in this cohort of patients with advanced breast cancer did not appear to add to the toxicity or palliative benefit of CT.**

GnRH Analogues

Gonadotropin Releasing Hormones

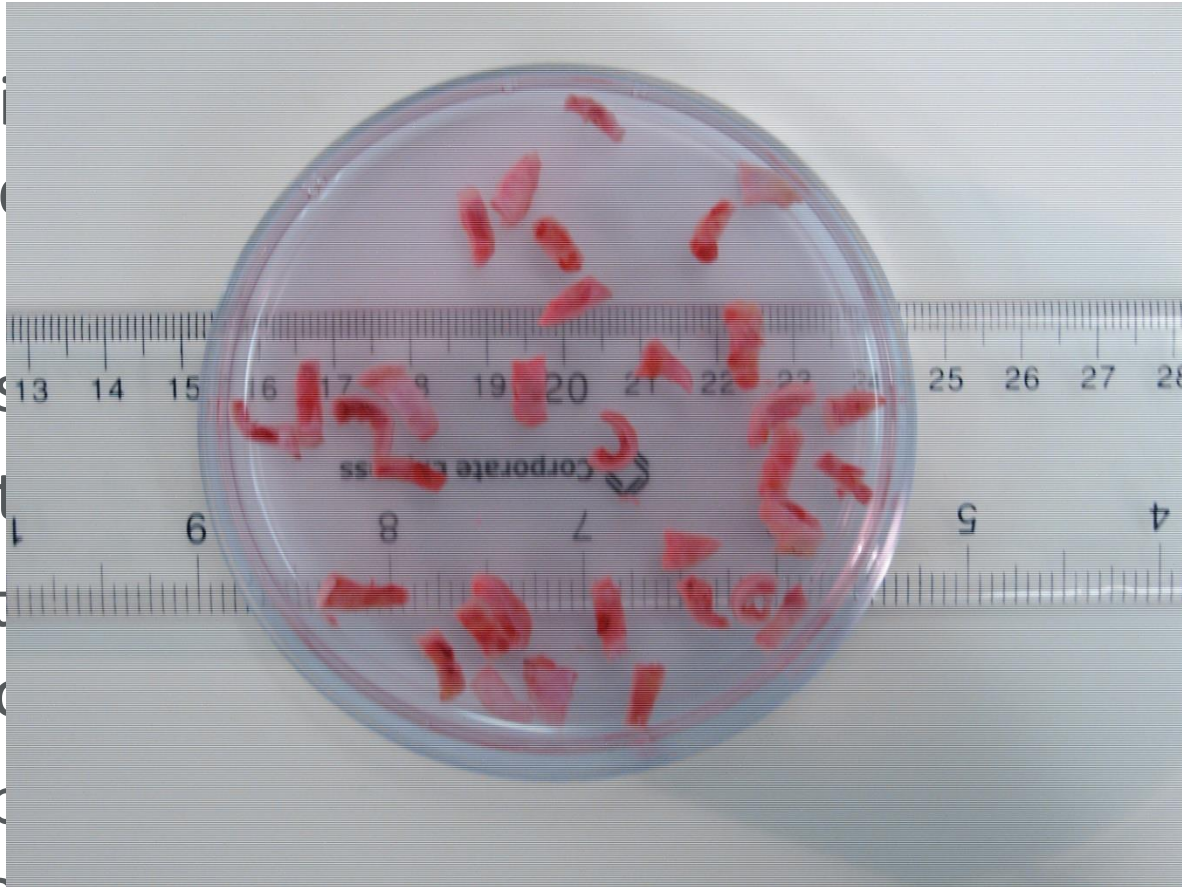
Moore HC, et al, *NEJM*, 2015 : 135 pre-menopausal hormone receptor negative breast cancer patients were randomized to chemotherapy alone or chemotherapy with gosarelin. Outcomes showed that 8 % of patients in the gosarelin group vs 22% of patients in the chemotherapy along group experienced ovarian failure. 21% vs 11% of the gosarelin vs chemotherapy alone were able to get pregnant .

Vitek WS, et al, *Fert Ster*, 2014: Meta-analysis of 131 patients who received gnRH agonist along with chemotherapy vs 121 patient who received chemotherapy alone showed no difference in the rate of the return of menses

Yang, et al, *Breast*, 2013: Meta-analysis of 274 patients who received GnRH agonist vs 254 patients who received chemotherapy alone showed that 'maybe' there is some benefit to patients in the GnRH agonist group in rates of premature ovarian failure in the 1st year after treatment but there was no significant effect on return of menses or pregnancy rates.

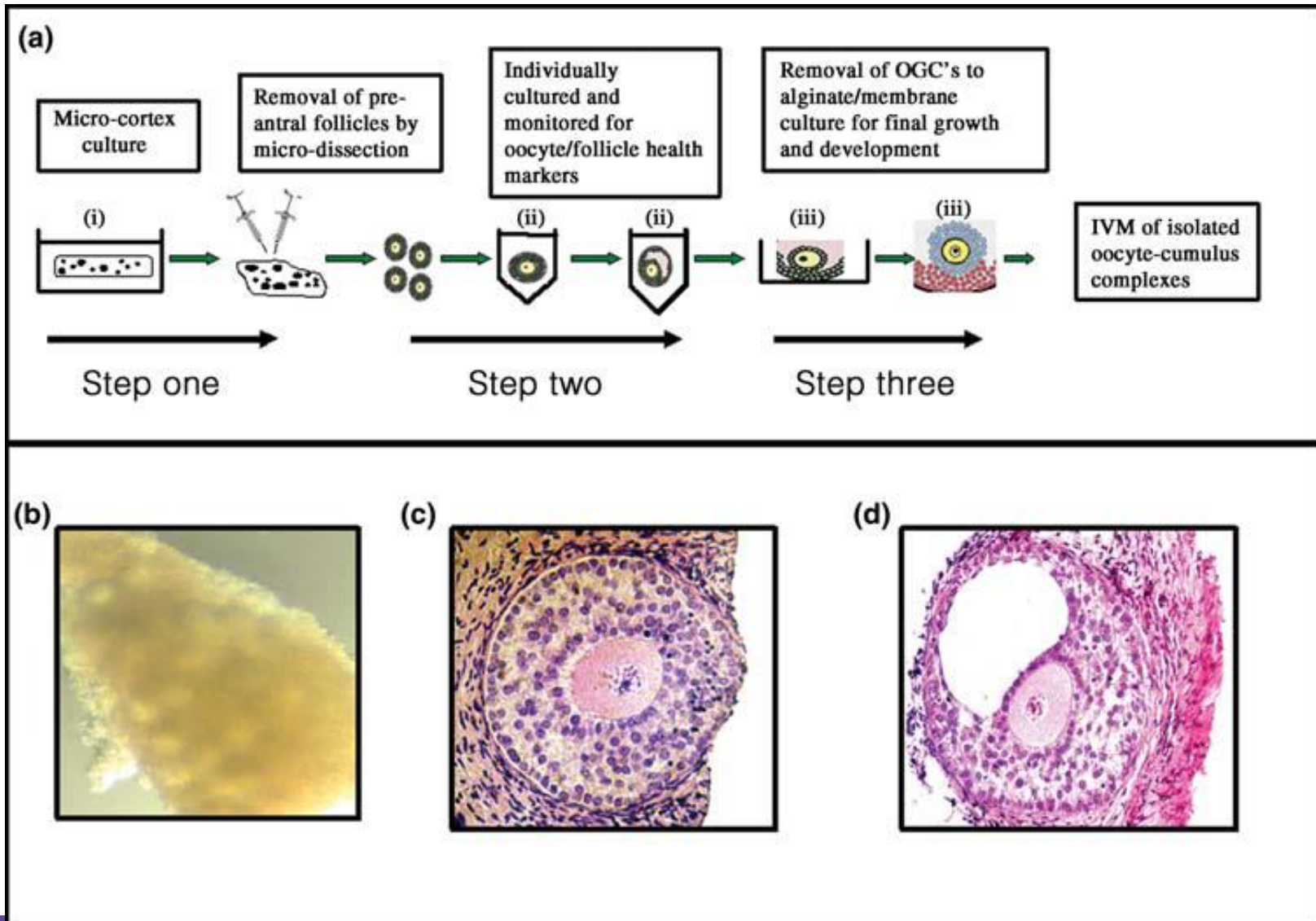
Ovarian Tissue Cryopreservation

- Ovarian tissue is cryopreserved and used
- Strips of ovarian tissue are not
- Most
- Sample



National Physicians Cooperative of

Use of Cryopreserved Tissue to Initiate a Pregnancy



Assembling the Team

'If you build it, they will come'

The Obvious

- Oncology Nurses
- Oncology LCSW
- Hem/Onc MD
- Urologist(s)
- Reproductive Endocrinologist(s)
- Laboratory Staff
- Navigator
- REI/Urology Nurses

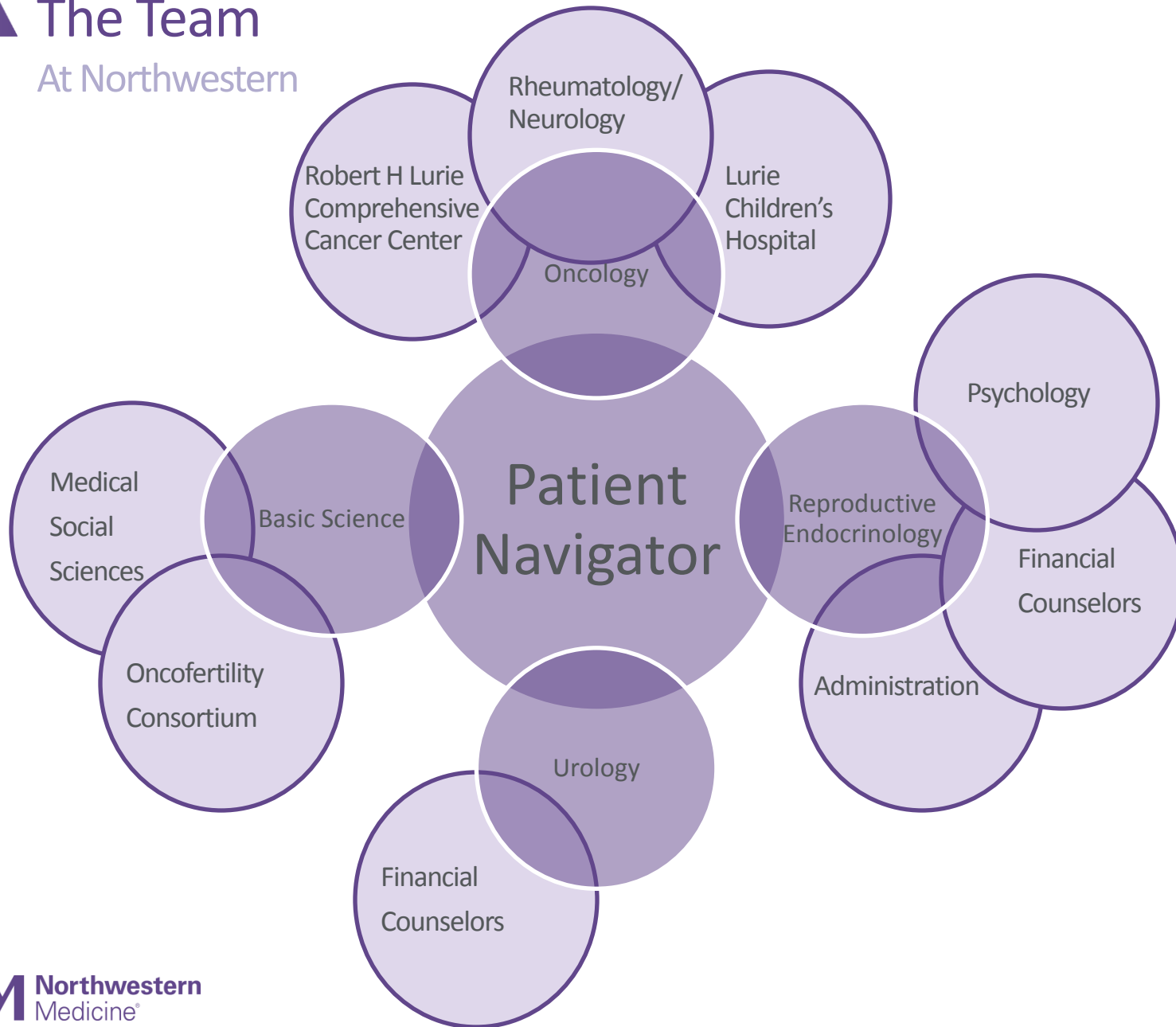
The Not So Obvious

- Phone Receptionists
- Inpatient Unit Clerks
- Billing Professionals
- Psychologists
- Chaplain services
- Fellows/Residents
- CRAs
- Administration



The Team

At Northwestern



EPIC Questionnaire

Epic NMFF Production - NMFF HEMATOLOGY/ONCOLOGY - JESSICA HERRON

Desktop Action Patient Care Charge Router Reg/ADT Reports Report Mgmt Tools Admin Help

Back Forward Home Schedule In Basket Chart Encounter Tel Enc Record Viewer Mgt Console Print Log Out

Epic Home Zztest,Jessezz EpicCare

Zztest, Jessezz MRN 0102374201 DOB: 2/14/1977 Age: 33y/o Sex F Flag (None) Code (None) Allergies(3/10/09) CHOCOLATE CON* Brandies, Juli* PCP Brandies, Juli* HM Alert* DUE INS MEDICARE AS* MyChart Active

Questionnaires ? Close X

Current Questionnaires

FERTILITY PRESERVATION OPTIONS [2100]

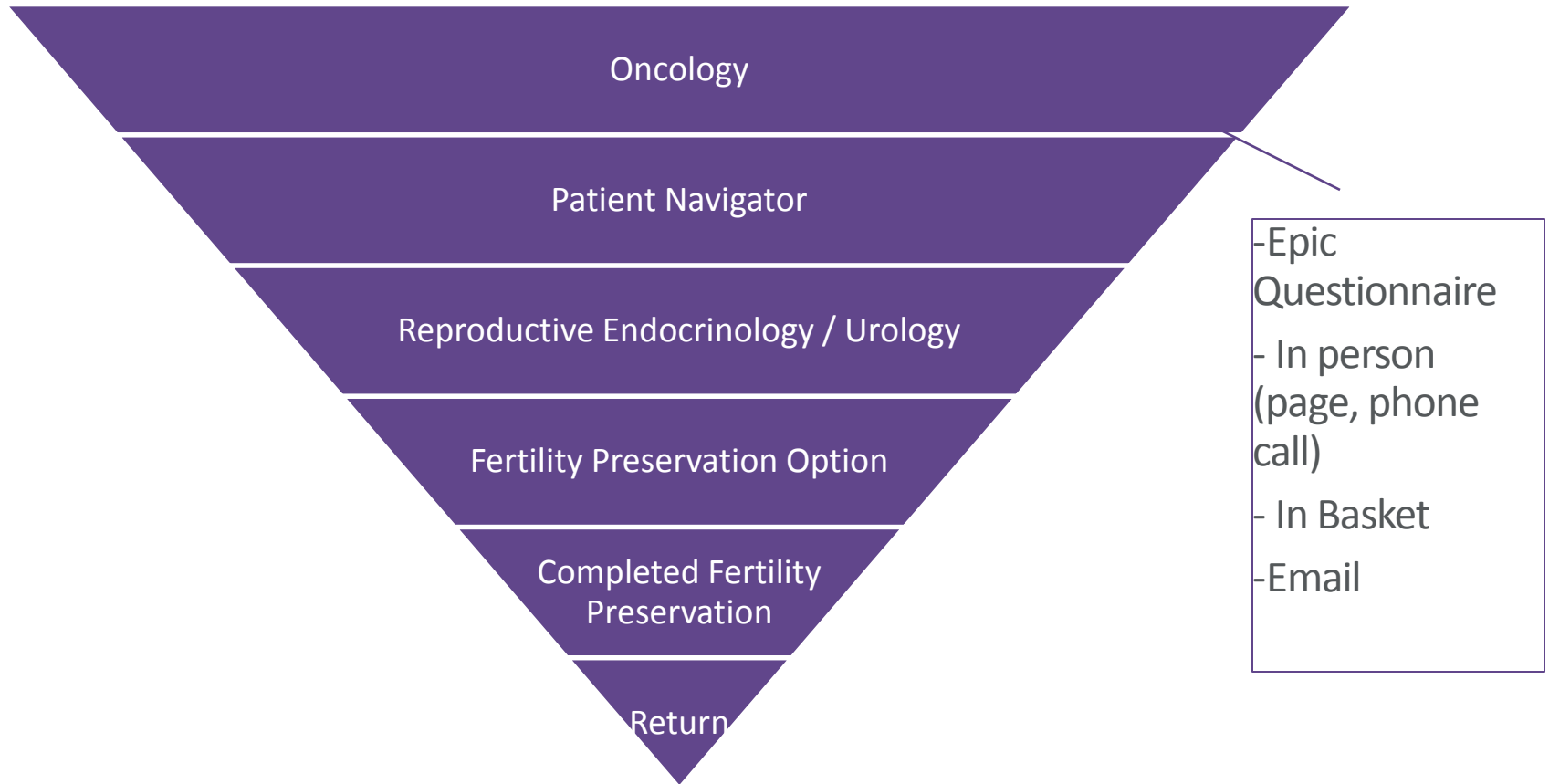
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Adv	Question	Answer	Comment
	FERTILITY PRESERVATION OPTIONS		
✓	Has the patient been informed about the impact their treatment may have on fertility?		
	Is the patient interested in fertility preservation?		
	Patient referred for fertility preservation consult		

Hotkey List

Exit Workspace

The Funnel Effect





Zen and the Art of the First FP visit

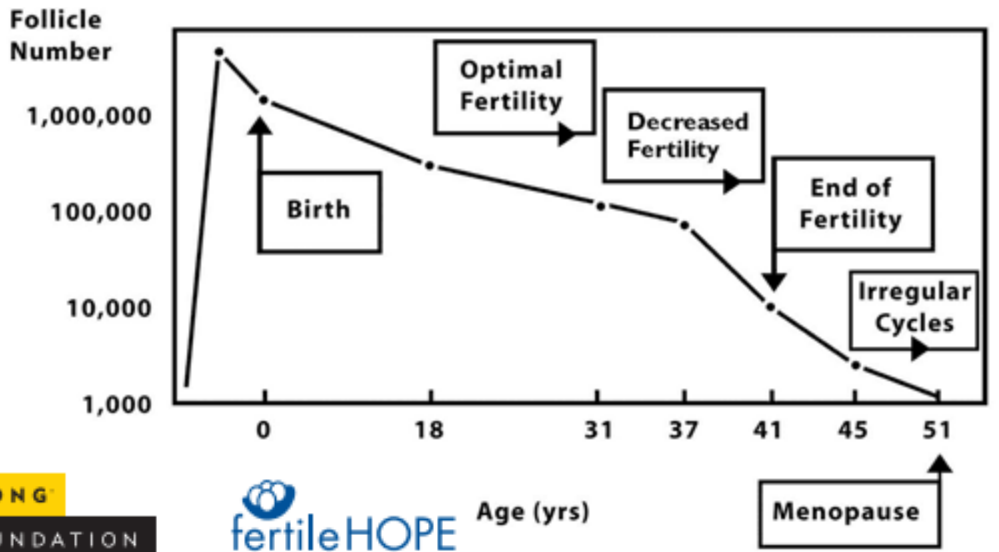


- The Challenge:
 - A patient who has just been told they have cancer now having to think/learn about fertility on the verge of information overload
- Our Goal
 - Make the patient feel comfortable
 - Get a decent health history
 - Learn about the short and long term treatment plans
 - Provide an understandable menu of options
 - Include disadvantages, risks and benefits
 - Discuss cost/insurance coverage
 - Offering mental health support/counseling
 - Be done talking in 20 minutes so there is plenty of time for questions w/out information overload
- The Key
 - Separating what is important from what is not important!!!

Intake Forms

- Patient Demographic
 - **Name, DOB, address, preferred phone, email**
- Disease
 - **Stage, location, treatment plan, treating physician**
- Menstrual history
 - **LMP, onset of menses, cycle length, OCP use**
- General Health History
 - Surgical hx, medical hx, alcohol & tobacco use, exercise, dietary restrictions, allergies
- Fertility Preservation Options
- Additional office visit
 - REI/Urology visits scheduled
- Financial Assistance/Insurance

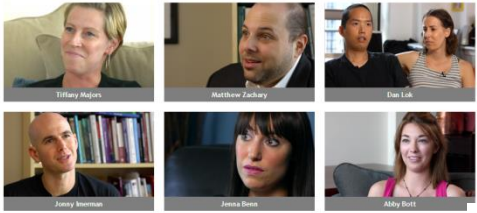
Tools



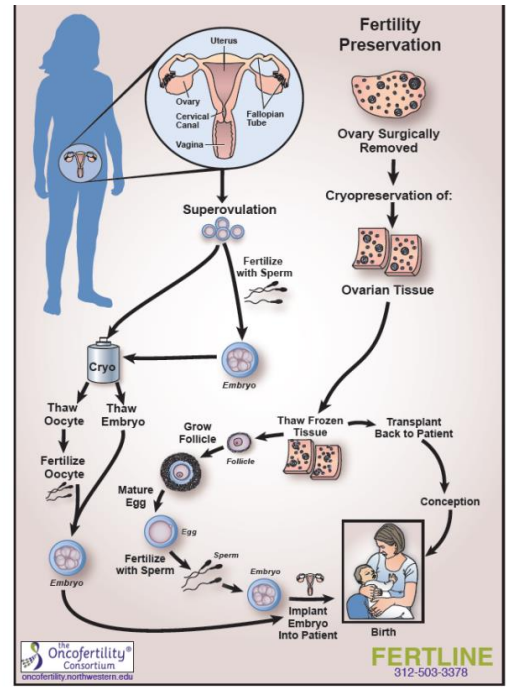
E.R. TE VELDE ET AL., 1998

PATIENT NAVIGATOR

for fertility preservation
 Meet Our Partners Contact Us Call Us 312-503-3378 (FERT)
 PERSONAL STORIES
 These stories shared here are from actual patients who underwent fertility preservation. Click on their videos to hear their stories.



SAVEMYFERTILITY



The Reproductive Endocrinology Office

NEEDS

- Offers embryo/oocyte cryopreservation
- Ability to see patients within 1 business day
- Does not 'batch' patients for hyperstimulation
- Understands cancer diagnoses, treatments
- Inpatient consults

WANTS

- Offers ovarian tissue cryopreservation
- Open 7 days/week
- Performs procedures in office
- Discounted services
- Psychology services
- Same facility

Insurance

- Insurance Verification
 - Each patient has “Fertility Preservation” benefits verified
- Insurance Billing
 - Despite response on verification, insurance is billed with appropriate cancer diagnosis as primary and fertility preservation (V26.42 or V26.82) as secondary
 - Appeals – 1st, 2nd and peer to peer discussions
- Package prices
 - \$5,000 – embryo cryopreservation
 - \$4,000 – oocyte cryopreservation
 - Subsequent discounts for thaw/fertilization and transfer
- Storage
 - \$75 - \$275 for eggs/sperm/ovarian tissue
 - \$106 - \$400 for embryos

Financial Assistance

- Clinic
 - Does the REI/Urology clinic offer a discount? Ask!
- Sharing Hope
 - If no insurance coverage and if patient meets income requirements, can obtain discounted services at certain providers, discounted storage and free EMD Serono fertility medications
- HeartBeat
 - Free Ferring fertility drugs through Walgreens
- Advocacy Funding
 - Location specific funding
- Social fundraising
 - Giveforward.com

stupidcancer[®].org



Barriers / Facilitators

- Many Moving Parts
 - Interdisciplinary clinic
- Provider outreach / education
 - Grand rounds, in-services, tumor board
- Patient outreach / education
 - Patient conferences, brochures
- Logistical challenges
 - FP Champion / ENRICH program for Oncology Nurses
- Institution buy-in
 - ASCO/ASRM/NCCN guidelines, AYA expectations

Additional Resources

SAVE MY FERTILITY



American Society of Clinical Oncology
Making a world of difference in cancer care



MyOncofertility.org



stupidcancer.org

Pearls of Wisdom

- It takes an interdisciplinary TEAM
 - REI/Urology office needs to be able to accommodate these patients first
 - Oncology healthcare professionals and patients need easy access to clinics
 - Be nice!!!
- Over communicate
 - Keep every provider in the loop with each step
- Patience is a virtue
 - Not every provider will be on board at first, not every patient is going to understand at first

Questions?

Thank You

Kristin N Smith

Patient Navigator for Fertility Preservation

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