

The background features a gradient from light green at the top to dark blue at the bottom. On the left side, there is a large, semi-circular scale with numerical markings from 140 to 260 in increments of 10. Several circular and semi-circular patterns, some solid and some dashed, are scattered across the background, some with arrows indicating direction. The overall aesthetic is clean and scientific.

# FERTILITY AND PREGNANCY AFTER BREAST CANCER

LISA KOLP, MD

JOHNS HOPKINS SCHOOL OF MEDICINE

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SPECIAL THANKS TO DR. MINDY CHRISTIANSON



# INTRODUCTION

- **About 6-7% of breast cancers are diagnosed in women <40 years old**
- **~11,000 women per year**
- **Estimated 400,000 breast cancer survivors <40 yo in 2010**



[www.seer.cancer.gov](http://www.seer.cancer.gov)

Jemal et al, CA Cancer j Clinic, 2009.

Brinton et al, 2008,

# OBJECTIVES

- 1. Is it safe to have a baby after breast cancer?
- 2. What are the risks to fertility from breast cancer treatment?
- 3. Fertility preservation options
- 4. Treatment of ovarian failure after breast cancer



## Is Pregnancy Safe after Diagnosis and Treatment of Breast Cancer?

# PREGNANCY AFTER BREAST CANCER

- Historically, physicians had assumed pregnancy after breast cancer was dangerous
  - High estrogen
  - High progesterone
  - Exposure to prolactin and placental lactogens

# AZIM META-ANALYSIS 2010

- Included 14 case-control, population-based and hospital-based studies published between 1970 and 2009
  - 18,145 breast cancer patients
  - 1417 pregnancies (1244 patients)

# AZIM META-ANALYSIS

- Patients who became pregnant had a 41% reduced risk of death compared with breast cancer patients who did not (hazard ratio 0.59, 95% CI 0.5-0.7)
- Protective effect mostly seen in patients under 35 years of age with lymph node negative disease



# HEALTHY MOTHER EFFECT??

- Must be considered
- Women with breast cancer who subsequently conceive are a self-selected healthier group with a better prognosis

# BREAST FEEDING AFTER BREAST CANCER

- Milk production compromised by surgery and radiation in treated breast
- No increase in recurrences in women who breast fed
- Azim 2009
  - 1/10 breast feeders
  - 1/10 bottle feeders
- Gelber 2001
  - 1/27 breast feeders
  - 6/25 bottle feeders



# NO ADVERSE FETAL OUTCOMES

- Danish study: 216 women who became pregnant after breast cancer compared with 10,453 women without breast cancer
- Similar risks of preterm delivery, low birth weight, congenital anomalies

## SWEDISH STUDY: SLIGHTLY HIGHER RISK?

- 331 women with a history of breast cancer compared to 2.8 million women without cancer
- Slightly higher risk
  - Delivery complications
  - Cesarean section
  - Preterm birth
  - Low birth weight
- Slightly higher risk of birth defects



# Is Pregnancy Safe after Diagnosis and Treatment of Breast Cancer?

**Probably yes, with caveats**

**At least 2 years after treatment**

**Complete treatment (not all hormonal treatment)**

# WHAT IS THE RISK TO FERTILITY FROM CANCER TREATMENT?

The background features a gradient from light green at the top to dark blue at the bottom. It is decorated with faint, semi-transparent circular patterns, including a large circular gauge on the right side with numerical markings (90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200) and arrows. There are also smaller circular motifs and dashed lines scattered throughout the design.

# CANCER TREATMENT

- Younger age, higher stage
  - 1/3 of women less than 50 have Stage 1 disease at diagnosis
  - 2/3 have tumor > 2cm or nodes + (Stage 2 or higher)
- Who undergoes chemotherapy?
  - Stage 1 greater than 1 cm
  - Stage 2 or higher

Who undergoes hormonal therapy?

2/3 of women under 40 have hormone receptor + tumors



# CHEMOTHERAPY JEOPARDIZES OVARIAN FUNCTION

- Loss of oocytes (eggs) due to age

AGE	NUMBER OF OOCYTES
5 months gestation	6-7 million
Birth	1-2 million
37 years old	25,000
51 years old	1000

# CHEMOTHERAPY JEOPARDIZES OVARIAN FUNCTION

- Chemotherapy causes depletion of follicles (eggs) in a drug/dose/age dependent fashion
- Cyclophosphamide is the most gonadotoxic
  - 20-70% of women less than 40 have ovarian failure
- AC regimens
  - 0% of women less than 30, up to 96% of women over 30
- Taxanes
  - Increase the risk in regimens including docetaxel, doxorubicin and cyclophosphamide but not paclitaxel

# FERTILITY PRESERVATION IMPORTANT

- American Society of Clinical Oncology (ASCO) encourages prioritizing healthy survivorship
- Recognizes fertility preservation as integral part of cancer patient care

VOLUME 24 · NUMBER 18 · JUNE 20 2006

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

## American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

*Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Karen Hagerly, Lindsay N. Beck, Lawrence V. Brennan, and Kutluk Oktay*

**A B S T R A C T**

**Purpose**  
To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer.

**Methods**  
An expert panel and a writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature from 1987 to 2005 was performed, and included a search of online databases and consultation with content experts.

**Results**  
The literature review found many cohort studies, case series, and case reports, but relatively few randomized or definitive trials examining the success and impact of fertility preservation methods in people with cancer. Fertility preservation methods are used infrequently in people with cancer.

**Recommendations**  
As part of education and informed consent before cancer therapy, oncologists should address the

From the Dana-Farber Cancer Institute, Boston, MA; Fertility Preservation Program, Center for Reproductive Medicine and Fertility, Weill Medical College, Cornell University; Fertility Hope, New York, NY; Oncology/Hematology Care, Crestview Hills, KY; American Society of Clinical Oncology, Alexandria, VA; Yale University Fertility Center, New Haven, CT; M.D. Anderson Cancer Center, Houston, TX; and the Royal Hospital for Sick Children, Edinburgh, Scotland, UK.

Submitted March 14, 2006; accepted March 24, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this

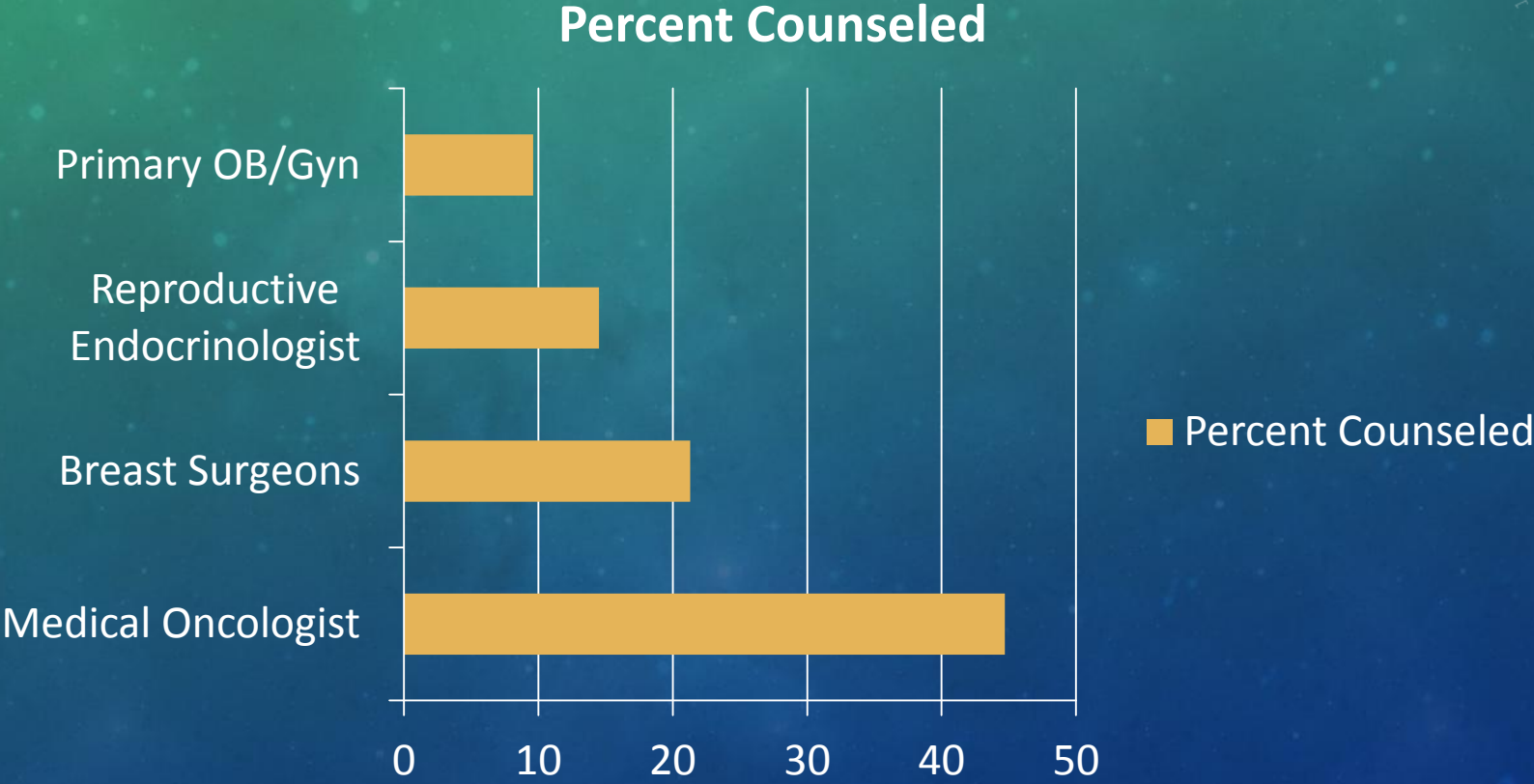
# FERTILITY IS IMPORTANT TO YOUNG BREAST CANCER PATIENTS

- **Interviews with breast cancer survivors 10 years after diagnosis:**
  - **Women desiring a child when diagnosed but who became infertile after treatment experienced significantly higher levels of distress than those who didn't become infertile**

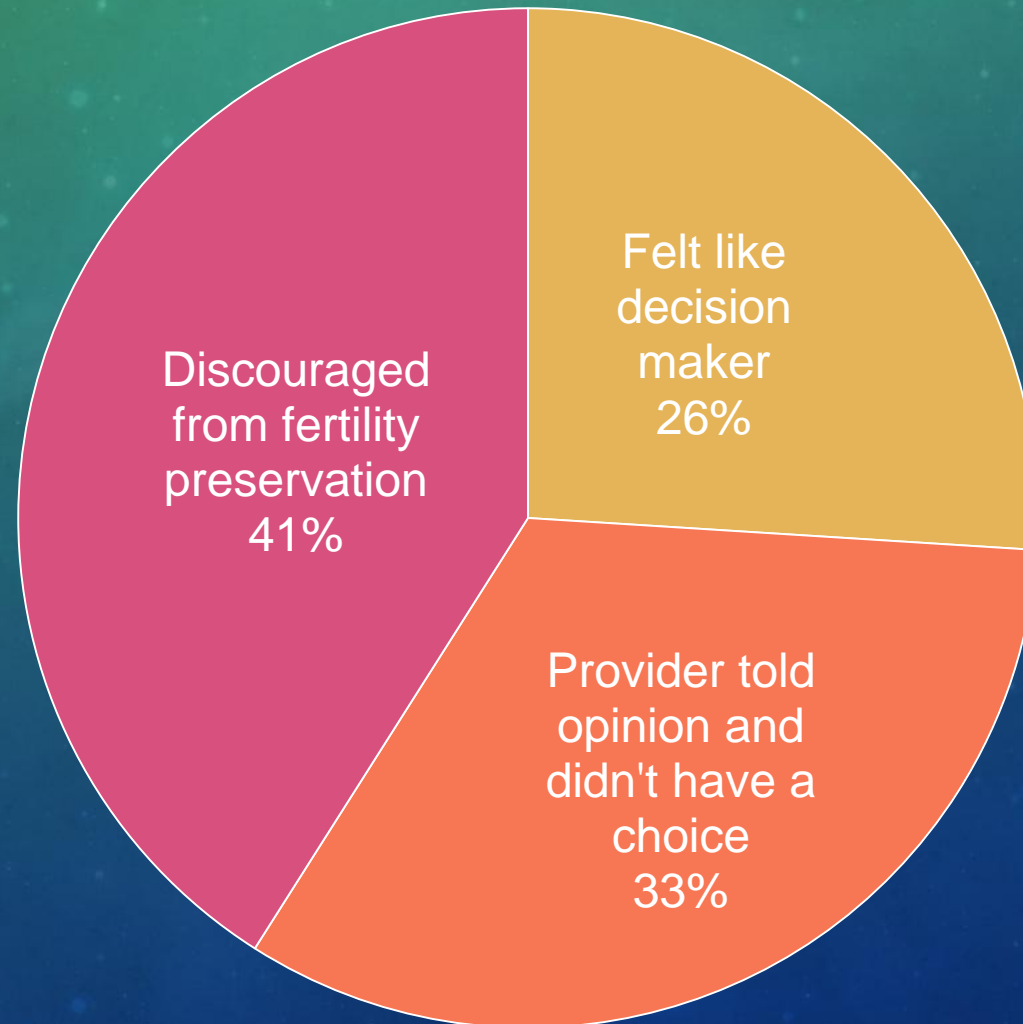
# EXPERIENCES OF YOUNG BREAST CANCER PATIENTS REGARDING FERTILITY PRESERVATION

- 88.4% received chemotherapy
- 87.2% did not receive fertility preservation (embryo cryopreservation or oocyte cryopreservation)
- 46.8% were not counseled regarding fertility preservation

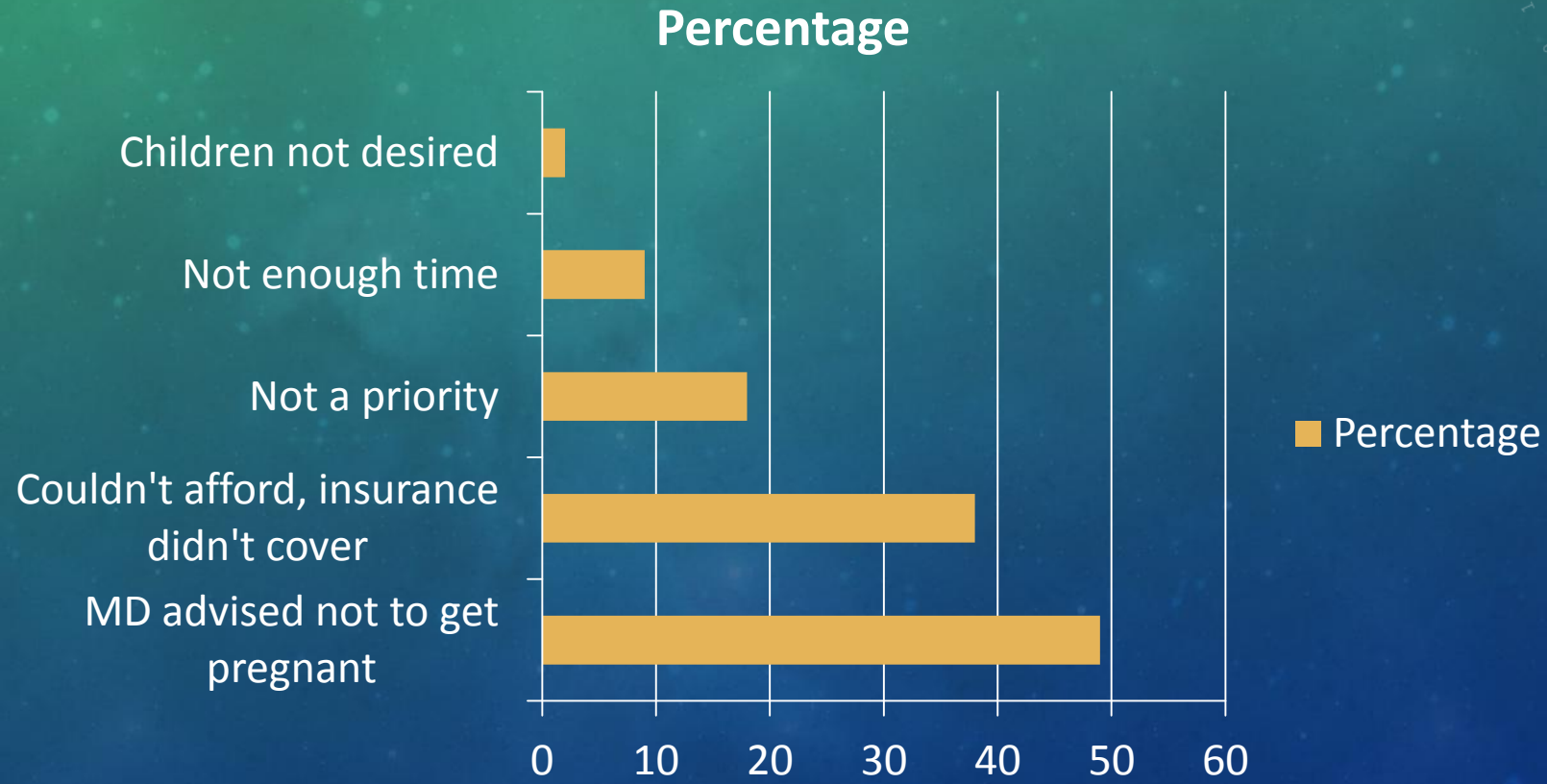
# WHO COUNSELED REGARDING FERTILITY PRESERVATION



# DESCRIPTION OF FERTILITY PRESERVATION DISCUSSION



# REASONS FERTILITY PRESERVATION NOT CHOSEN







## **Fertility Preservation:**

**What Options are Available for Women with Breast Cancer?**

# WINDOW OF OPPORTUNITY



**Assisted reproductive technologies (ART) for fertility preservation can be performed 2-4 weeks after surgery, prior to chemotherapy**

# EMBRYO CRYOPRESERVATION

- **Widely established**
- **Controlled ovarian hyperstimulation, oocyte retrieval, fertilization and then cryopreservation**
- **Embryos thawed and transferred to patient or gestational carrier**
- **Pregnancy rates can be  $\geq 40\%$  per transfer**
- **Requires 2-4 weeks**



# EMBRYO CRYOPRESERVATION

## Candidates:

Have partner or willing to use donor sperm

Can delay cancer treatment 2-4 wks

## Not Candidates:

No partner or decline donor sperm

Can't delay treatment

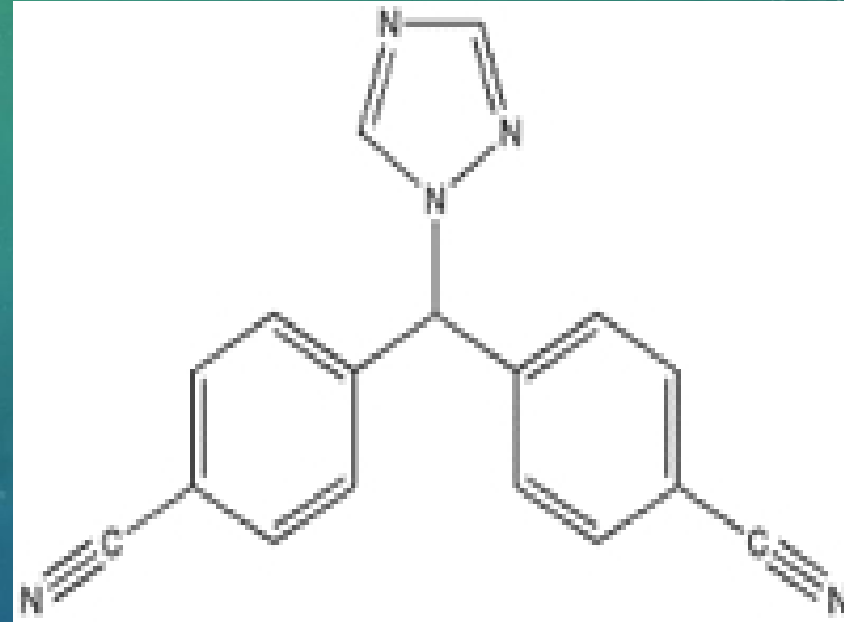
Moral or religious objections to freezing embryos (or live in country where illegal)

# CONTROLLED OVARIAN HYPERSTIMULATION – RISKY?

- **Results in supraphysiologic levels of estrogen, 10-20 times normal reproductive cycles**
- **Theoretical concern about stimulating receptors on estrogen-responsive cells**
- **Estrogen may have a mitogenic effect on hormone receptor negative tumors**

# LETROZOLE

- **3<sup>rd</sup> generation aromatase inhibitor**
- **Can be used for ovarian stimulation**
- **Competitively inhibits aromatase enzyme activity in ER+ cells and suppresses estrogen production**



# LETROZOLE OVULATION INDUCTION

- **No increased risk of recurrence in breast cancer patients with this protocol compared to those who declined ART**
  - **Mean follow-up 48 months**
- **Time-lapse between surgery and chemo longer (45 d vs 33 d, P=0.01)**

# OOCYTE CRYOPRESERVATION

- **Considered investigational**
- **Option for women who:**
  - **No partner or decline donor sperm**
  - **Understand success rate much lower than embryo cryopreservation**
- **ASRM advises live-birth rate of 2-4% per oocyte**





# OOCYTES EXTREMELY SENSITIVE

- **Largest cell in human body**
- **Largest water content**
- **Abundant cytoplasm**
- **Ice crystals can damage meiotic spindle**



# OVARIAN TISSUE CRYOPRESERVATION

- Ovarian tissue harvested at laparoscopy or laparotomy
  - Obtain by biopsy or oophorectomy
- Tissue then be transplanted upon completion of gonadotoxic therapy after patient is in remission

# TRANSPLANTATION OF OVARIAN TISSUE

- **Investigational approach with about 18 live births to date**
- **Option available for those who cannot delay treatment to harvest oocytes**
- **Rarely used for breast cancer patients**



## **Fertility Preservation:**

**Are GnRH Analogs Effective at Protecting the Ovaries from  
Gonadotoxic Chemotherapy?**

# THE PREMISE

- **Theorized that toxicity from chemotherapy reduced by diminishing ovarian function**
- **Gonadotropin-releasing hormone (GnRH) agonists diminish ovarian function**
  - **Since effect reversible, resumption of ovulation is possible when cytotoxic and GnRH therapies are discontinued**
- **Whether protective against gonadal damage is controversial**

# SUPPORT OF GNRH AGONISTS

- **Systematic review of 9 controlled, mainly non-randomized studies found GnRH agonists during chemotherapy protective**
  - **Resumed menstrual cycles, premenopausal FSH:**
    - 93% GnRH agonist
    - 48% No GnRH agonist
  - **Pregnancy rates:**
    - 22% GnRH agonist
    - 14% None GnRH agonist

# SUPPORT OF GNRH AGONISTS

- **Randomized trial: 285 breast cancer patients undergoing cyclophosphamide chemotherapy**
  - **GnRH agonist**
  - **GnRH agonist plus tamoxifen**
  - **Tamoxifen alone**
  - **Controls**
- **Menses up to 36 months out:**
  - **36% GnRH agonist**
  - **7% GnRH agonist plus tamoxifen**
  - **13% Tamoxifen alone**
  - **10% Controls**

# OTHER STUDIES DO NOT SUPPORT GNRH AGONISTS

- **3 small randomized trials reported GnRH agonist treatment ineffective in preserving fertility in patients receiving chemotherapy for lymphoma or breast cancer**
- **Protective role of GnRH analogues against cyclophosphamide induced ovarian damage was not demonstrated in human ovarian xenograft model**

Waxman et al, 2007. Giuseppe et al, 2007.

Ismail-Khan et al 2008. Maltaris et al 2007.





# DONOR OOCYTES

- IVF using donor oocytes is proven approach
- Success rates exceeding 60% per embryo transfer



# GESTATIONAL SURROGACY

- **Candidates include those who:**
  - **Underwent hysterectomy**
  - **High risk of recurrent breast cancer**
  - **Lifelong therapy with aromatase inhibitors**
  - **Do not want to wait until completion of aromatase inhibitors**



## **What Other Gynecologic Health Concerns Face Young Women with Breast Cancer?**

# CHEMOTHERAPY-INDUCED AMENORRHEA

- **Majority of patients will have amenorrhea**
- **Menses resume in 6 months for 60%**
- **Menses resume in 12 months for 90%**
- **For women younger than 40 yo, risk of permanent menopause is 15-45%**

Abusief et al, Cancer, 2010.  
Burstein et al, NEJM, 2000.  
Fornier et al, Cancer, 2005.  
Petrek et al, J Clin Oncol, 2006.

# MENOPAUSAL SYMPTOMS: HOT FLASHES

- Vasomotor symptoms most common
- 20% of breast cancer patients consider stopping endocrine therapy because of symptoms.
- Possible Treatments:
  - Venlafaxine
  - Paroxetine
  - Gabapentin
  - Clonidine

# MENOPAUSAL SYMPTOMS: VAGINAL ATROPHY

- **Atrophic vaginitis**
  - **Treatment options:**
    - **Replens**
    - **Vaginal 17 $\beta$  Estradiol (if oncologist approves)**
    - **Vaginal estriol**

# CONTRACEPTION

- **Hormonal contraceptives contraindicated (even in hormone negative tumors)**
- **Current recommendations:**
  - **Nonhormonal alternatives such as barrier methods, sterilization, non-hormonal IUD**
- **Mirena IUD - controversial**



# CONCLUSIONS

- **Early referral is key!**
  - **Preferably before or right after surgery to allow ovarian stimulation without delaying chemotherapy**
- **Young women with early stage breast cancer should not be discouraged from pregnancy in the future**