Keynote Address:
Fertility Preservation in the
21st Century and Beyond

Clarisa Gracia, MD MSCE
Associate Professor
Director, Fertility Preservation Program
Penn Fertility Care
University of Pennsylvania
Disclosures

• Nothing to Disclose
Cancer
Better Dx/Rx → >130,000 reproductive age patients diagnosed annually

Improved Survival:
77% Dx’d @ <45 y
Live ≥ 5 y

Fertility Threatening Treatments
Major QOL issue in survivors

Reproductive Medicine:
Improved FP Options

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

As part of informed consent prior to therapy, oncologists should address the possibility of infertility with patients as early in treatment planning as possible

1 Lee SJ, Schover LR, et al., Journal of Clinical Oncology, 2006
Updated 2013
Artificial Reproductive Techniques

**Females**

- **Freeze Embryos**
  - **Mature Oocyte**
  - **Sperm**

**Established Methods**

- **Freeze Mature Oocytes**
- **In Vitro Maturation**
- **Collect Immature Eggs (Germinal Vesicle & MI)**
- **Freeze Tissue**
“Oocyte cryopreservation should no longer be considered experimental”

“In patients facing infertility due to chemotherapy, oocyte cryopreservation is recommended with appropriate counseling” (Level B)
RCTs of vitrified vs fresh oocytes

Mean Age = 26 years

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Fertilization Rates</td>
<td>76.3% vitrification</td>
<td>74% vitrification</td>
<td>79.2% vitrification</td>
<td>71% vitrification</td>
</tr>
<tr>
<td>Rate</td>
<td>82.2 fresh</td>
<td>73% fresh</td>
<td>83.3% fresh</td>
<td>72.6% fresh</td>
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<tr>
<td>No. transferred</td>
<td>3.8 vitrification</td>
<td>1.7 vitrification</td>
<td>2.3 vitrification</td>
<td>2.5 vitrification</td>
</tr>
<tr>
<td>Vitrification vs.</td>
<td>3.9 fresh</td>
<td>1.7 fresh</td>
<td>2.5 fresh</td>
<td>2.6 fresh</td>
</tr>
<tr>
<td>fresh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of Transfer</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2-3</td>
</tr>
<tr>
<td>Implantation Rate</td>
<td>40.8% vitrification 100% fresh</td>
<td>39.9% vitrification 40.9% fresh</td>
<td>20.4% vitrification 21.7% fresh</td>
<td>17.1% vitrification NA fresh</td>
</tr>
<tr>
<td>CPR/transfer</td>
<td>60.8% (23) vitrification transfers 100% (1 fresh transfer)</td>
<td>55.4% vitrification 55.6% fresh</td>
<td>38.5% vitrification 43.5% fresh</td>
<td>35.5% vitrification 13.3% fresh</td>
</tr>
<tr>
<td>CPR/oocyte thawed</td>
<td>6.1%</td>
<td>4.5%</td>
<td>12%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>
What is the process?
Embryo and Mature Oocyte Banking Require Ovarian Stimulation

2 week process:
Injectable FSH, frequent monitoring, egg retrieval

Risks:
Delay in cancer therapy
Ovarian Hyperstimulation
High estrogen levels
Thrombosis Risk
Bleeding Risk

Only possible in pubertal females
Benefits of Freezing Oocytes/Embryos

• Established technique

• Gestational Carrier may be option
  • Cancer therapies have toxicities
  • After hysterectomy

• Preimplantation genetic diagnosis (PGD) may be an option for genetic disorders
  • BRCA1, BRCA2, Lynch syndrome/HNPCC, Li-Fraumeni syndrome, MEN, neurofibromatosis
  • Sickle cell, thalassemia
In Vitro Maturation (IVM) of Immature Oocytes

...an emerging technology

• Retrieval of immature oocytes after no or limited gonadotropin stimulation, then freeze mature oocytes
  – 3-6 days of FSH priming
  – hCG only
  – FSH + hCG

• Advantages
  – Shorter duration of stimulation, but still start with menses
  – Less exposure to hyper-estrogenism
  – Less cost
  – Lower risk of OHSS

• Disadvantages
  – Lower success rates overall
  – Long-term safety unknown

Ovarian Tissue Banking

• No ovarian stimulation, minimal delay in treatment, no partner needed, may perform after recent chemo exposure, 
  only option in prepubertal girls

• Requires surgical removal of ovarian tissue
  – Autologous transplantation - ortho topic/ heterotopic
  – Maturation in vitro

• Emerging technology
Ovarian Tissue Excision, Processing and Transplantation

Gracia

36 year old Lymphoma Treated with 1 cycle RCHOP prior to OTC

OTT 3 years Post treatment

Vitrification
Hormone changes after transplant

FSH = 130

- Estradiol

- Ovulation

- Improved symptoms

- Menstrual periods
## Summary of 25+ Births from Orthotopic Transplants

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>AGE at CRYO</th>
<th>SURGICAL METHOD</th>
<th>PREGNANCY</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin</td>
<td>25</td>
<td>Biopsy</td>
<td>Spontaneous <em>live birth</em></td>
<td>Donnez, 2004</td>
</tr>
<tr>
<td>Neuro ectodermic tumor</td>
<td>19</td>
<td>Biopsy</td>
<td>Spontaneous <em>live birth</em></td>
<td>Donnez, 2011</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>20</td>
<td>Biopsy</td>
<td>Spontaneous <em>live birth</em></td>
<td>Donnez, 2011</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>24</td>
<td>USO</td>
<td>2 spontaneous <em>live births</em></td>
<td>Donnez, 2011</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>27</td>
<td>USO</td>
<td>IVF after reimplantaion with follicle development, <em>live birth</em></td>
<td>Donnez, 2011</td>
</tr>
<tr>
<td>Ovarian Failure</td>
<td>24</td>
<td>Biopsy</td>
<td>Spontaneous <em>live birth</em></td>
<td>Silber, 2008</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>36</td>
<td>USO</td>
<td>IVF 2 <em>live birth (twins)</em></td>
<td>Sanchez-serrano 2010</td>
</tr>
</tbody>
</table>

Efficiency not known
Gaps In Knowledge

• What is the actual pregnancy rate per transplant?
  – Dolmans reports 582 OTC cases
  – 6 pregnancies/11 transplants

• Should we individualize cases?
  – How much tissue should be removed/transplanted?

• What is the best way to freeze the tissue?

• How safe is it in terms of reseeding cancer?

• What to do when a patient does not have a uterus or is not a good surgical candidate?

Dolmans JARG 2012
Dolmans et al. Blood 2013
Bastings Hum Repr Up 2013
Can very Immature Eggs from Tissue be Matured in Vitro?

• Advantages
  – Eliminates risk of transplanting cancer cells
  – Eliminates need for surgical transplantation
  – Could use eggs for IVF and place in gestational carrier

• Disadvantages
  – Complicated process that is poorly understood
The Mission of the Oncofertility Consortium

To focus on the fertility threat posed by cancer treatment and serve as an authoritative voice for patients while creating corridors of discovery between research disciplines, clinical practice and training that can be created at the intersection of oncology, pediatrics, reproductive science, policy research, reproductive health law, bioethics, communication science, and cognitive and learning science.

...exploring and expanding options for the reproductive future of cancer survivors
Research themes

- Discover and study the hormones that control reproduction function
- Determine how ovarian follicles are selected each cycle
- Develop and exploit \textit{in vitro} follicle systems to discover governing mechanisms of development
Follicle development in 3D alginate culture: Births in mice and maturation to MII/fertilization in primates

FSH

Secondary follicle
Day 0

Multilayer follicle
Week 1

Antral follicle, ≤ 0.5 mm
Week 3

Antral follicle, 0.8 - 1 mm
Week 5

AMH

VEGF

P4, E2

hCG bolus

Fast-grow follicle

MII oocyte

GV oocyte

Zelinski
Careful examination of sample volume, CPA concentrations, cooling and warming rates

Vitrification of ovarian tissue using glycerol, EG and polymers in a sealed straw preserved stromal structure, and morphology & cellular proliferation in preantral follicles.

- Additional benefit for tissue transplantation?
…or can we cryopreserve ovarian germ cells?

Oocyte formation by mitotically active germ cells purified from ovaries of reproductive-age women

Yvonne A R White¹,²,⁴, Dori C Woods¹,²,⁴, Yasushi Takai³, Osamu Ishihara³, Hiroyuki Seki³ & Jonathan L Tilly¹,²
Clinical Application of Fertility Preservation Technologies

- ALL patients should be informed of the potential risk and options available.

- Fertility preserving technologies pose some risk
  - Delay cancer therapy, are costly and invasive
  - Experimental
  - Ethical questions in children
  - Most likely to pursue FP: older, wealthier, early stage disease*

- Who should we target for fertility preservation?
  - What factors determine the degree and duration of ovarian dysfunction after gonadotoxic threats?

ORACLE Study
48 women ages 15-35 undergoing chemotherapy for cancer

Trends over study period demonstrate acute impact + recovery
Recovery depends on baseline ovarian reserve and treatment.

**Predicted Rate of Change in log AMH by Pre-Treatment AMH Values**

- **Pre-Tx AMH > 2**
  - 11.9% per month

- **Pre-Tx AMH < 2**
  - 2.6% per month

**Predicted Rate of Change in log AMH by Alkylator Use**

- **No Alkylator Tx**
  - 21% per month

- **Alkylator Tx**
  - 5.4% per month

(P= 0.043) (P= 0.056)

Fertil Steril 2013
Measures of Ovarian Reserve in Cancer Survivors Remote from Therapy

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n =71)</th>
<th>Controls (n =67)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25.67 (24.17-27.17)</td>
<td>27.26 (26.10-28.43)</td>
<td>0.10</td>
</tr>
<tr>
<td>FSH (MIU/ml)</td>
<td>11.12 (9.47-13.06)</td>
<td>7.25 (6.00-8.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>0.81 (0.61-1.07)</td>
<td>2.85 (2.06-3.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AFC</td>
<td>14.55 (10.80-18.30)</td>
<td>27.20 (23.05-31.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, BMI
Geometric hormone means presented

Associations persist when restricted to regularly menstruating women
Measures of ovarian reserve associated with treatment parameters
What do these measures tell us?

• High risk survivors in Mid-20’s have measures similar to naturally aging women in early 40’s

Risk of Pregnancy Over the Study

- 85 survivors and 98 controls were at risk for pregnancy during the study

- Pregnancy rates over the study were no different between groups

P = 0.33

Average follow-up time: 17.5 months
Longest follow-up time – 5 years

Pediatr Blood Cancer. 2013
Are Measures Predictive of Fertility?

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n=19)</th>
<th>Controls (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (range)</td>
<td>30.1 (20-38)</td>
<td>28.9 (21-39)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Marital status- single, % (n)</strong></td>
<td>21 (4)</td>
<td>61 (11)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>FSH</td>
<td>12.1 (8.0-18.4)</td>
<td>7.9 (6.2-10.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Estradiol</td>
<td>30.0 (23.3-38.8)</td>
<td>26.7 (23.0-31.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Inhibin</td>
<td>34.4 (18.8-62.9)</td>
<td>36.5 (23.5-56.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>AMH</td>
<td>0.6 (0.3-1.1)</td>
<td>1.8 (1.1-3.0)</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>AFC</td>
<td>10.2 (6.8-15.3)</td>
<td>20.7 (16.5-26.0)</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Unplanned conceptions, % (n)</td>
<td>16% (3/19)</td>
<td>44% (8/18)</td>
<td>0.06</td>
</tr>
<tr>
<td>Months to conceive, mean</td>
<td>8.6 (0-28)</td>
<td>3.1 (0-7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Infertility Treatment</td>
<td>3</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Compared to survivors who DID NOT conceive, those who did were **OLDER**, Married and cohabitating. **Measures reflect quantity NOT quality.**

Pediatr Blood Cancer. 2013
Measures of ovarian reserve may help to predict time to menopause after cancer.
Looking Ahead...

- More effective and available options for fertility preservation

- Better understanding of reproductive window after potentially gonadotoxic therapies
  - Counseling before and after

- Less gonadotoxic therapies
The Oncofertility Consortium

www.myoncofertility.org

oncofertility.northwestern.edu

FERTLINE
866-708-FERT (3378)

Numerous research papers and publications
Thank you!

NIH
RO1-HD062797-01 (Gracia)
KL1-CA-133839-01 (Gracia) NIH Roadmap Interdisciplinary Research Consortia
R03 (Gracia)

Collaborators
CHOP – Jill Ginsberg, MD
Abramson Cancer Center
Oncofertility Consortium – National Physicians Cooperative