Fertility Preservation for Breast Cancer

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Brigham & Women’s Hospital
Learning Objectives

• To be able to list and describe processes of ovulation induction and oocyte cryopreservation

• To be able to counsel patients about the meaning of serum AMH level

• To be able to discuss the evidence surrounding ovarian suppression during chemotherapy
Disclosures

• Royalties – Up to Date, Biomed Central

• Investigator- initiated study, Serono financial support

• Advance medical – consultant
American Society of Clinical Oncology Guidelines

- As part of informed consent process reproductive age men and women with cancer should have potential impact of cancer and its treatment discussed
- Fertility preservation options should be presented and referral to fertility specialist should be offered


- Breast cancer survivors who discuss fertility preservation have better well-being

Assisted Reproduction Outcomes in Female Cancer Survivors

- IVF outcomes compared to other infertility patients in 2 comparison groups.
- Pregnancy and live birth rates significantly lower
- Risk of cancelation of egg retrieval due to poor response significantly higher

Barton SE, et al. Female Cancer Survivors are Low Responders and have Reduced Success compared with Other Patients Undergoing Assisted Reproductive Technologies. Fertil Steril, 2012.
Breast Cancer Treatment

• Chemotherapy (cyclophosphamide, adriamycin ± taxotere ± herceptin)
  ➢ Various administration regimens

• Tamoxifen: 10 year delay prior to conception attempts if completed

• Increasing maternal age

• 30-57% of young women who try to conceive after breast cancer are successful

Impact of Chemotherapy on Ovarian Reserve

• Alkylation agents particularly accelerate follicular depletion

• Mechanisms:
  - Mediated by sphingomyelinase gene- produces ceramide which stimulates apoptosis
  - Blocking sphingomyelinase gene prevents chemotherapy induced follicular apoptosis

Fertility Preservation Options

- Oocyte (egg) freezing
- Embryo freezing
- Ovarian suppression
- Ovarian tissue cryopreservation (experimental)
- Research on ovarian protecting agents
Ovarian Reserve Testing

- Normal AMH > 0.9 ng/ml
- Antral follicle count
  - Number of follicles 2 - 9 mm in both ovaries: normal > 6
- Both are predictive of egg and embryo number, not quality
- Dose gonadotropins higher if AMH < 1.2, AFC ≤ 6
- AMH poorly predictive of pregnancy in young women
- Can be abnormal in fertile women


- Complex factors including AMH, age and chemotherapy agents predict post treatment menses

AMH Over Lifetime

Ovarian Function During the Recovery Period- after Chemo (mean ± SEM)

Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age

Oocyte / Embryo Cryopreservation
Ovulation Induction

• Goal: obtain good number of eggs/embryos in women who will be unable to conceive without them

• 15 eggs optimizes pregnancy rates in non-cancer scenario

• Some recommend low FSH dosing, but egg number will be lower

Dilemma

• Whenever possible, perform fertility preservation procedures before chemotherapy
  ➢ Not always possible with neoadjuvant chemotherapy

• Mouse data suggest that IVF performed soon after cyclophosphamide chemotherapy may result in chromosomally abnormal offspring.

Estrogen Receptor Positive Cancers

- Letrozole daily during stimulation 2.5 or 5.0mg if ER+
  - Usually maintains physiologic estradiol levels
  - Unclear if elevated estradiol levels are harmful
  - Unclear if any impact of letrozole has on egg quality
    - Given utility in PCO, probably not harmful
Stimulation for estrogen sensitive tumors: letrozole

1. Start letrozole on cycle day 2-3 or random
2. Start gonadotropins
3. Add GnRH antagonist when lead follicle reaches 14 mm.
4. Trigger when lead follicles reach 19-21 mm 36 h prior to retrieval
5. Some check estradiol 3 days after retrieval. If >250 pg/mL restart letrozole.

<table>
<thead>
<tr>
<th>Cycle Day</th>
<th>Start</th>
<th>Gonadotropins</th>
<th>Letrozole</th>
<th>+/- Letrozole</th>
<th>Trigger</th>
<th>Antagonist</th>
<th>Oocyte Retrieval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Start or Cycle Day 2</td>
<td>Letrozole</td>
<td>+/− Letrozole</td>
<td>Antagonist</td>
<td>Trigger</td>
<td>Oocyte Retrieval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oocyte Retrieval

Retrieval: Transabdominal Approach (Oophoropexy/ Obesity)

Barton SE, et al. Female Cancer Survivors are Low Responders and have Reduced Success compared with Other Patients Undergoing Assisted Reproductive Technologies. Fertil Steril, 2012.
Short Stimulation/ Natural Cycle
(not recommended)

• Can give hCG without stimulation or only 2-3 days of stimulation, retrieve immature oocytes, in-vitro mature, and then freeze
  ➢ Must use 19 G needle and curette follicles extensively
  ➢ Much lower numbers of oocytes (1-5)

Maman E, et al. Luteal Phase Oocyte Retrieval and In Vitro Maturation is an Optional Procedure for Urgent Fertility Preservation. Fertil Steril, 2011

• If patient is stable and fertility is important waiting additional week to start chemotherapy is reasonable to get higher numbers of eggs/embryos
Ovarian Response in Breast Cancer Patients

Table I  Demographic and cycle characteristics.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Elective cryopreservation (n = 398)</th>
<th>Cryopreservation for Breast Cancer (n = 191)</th>
<th>P-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.4 ± 3.0</td>
<td>34.9 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>22.8 ± 3.4</td>
<td>23.6 ± 4.6</td>
<td>0.019</td>
</tr>
<tr>
<td>AFC</td>
<td>15.4 ± 10.0</td>
<td>15.4 ± 10.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^a$t-test.
Data presented as mean ± SD.
AFC: Antral follicle count.

Table IV  Outcomes by group for those who proceeded to retrieval.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Elective cryopreservation (n = 361)$^a$</th>
<th>Breast Cancer with letrozole (n = 144)$^b$</th>
<th>Breast Cancer without letrozole (n = 38)$^a$</th>
<th>P-value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes retrieved</td>
<td>17.0 ± 0.5</td>
<td>20.1 ± 1.1</td>
<td>16.6 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MII oocytes retrieved</td>
<td>13.2 ± 0.4</td>
<td>14.1 ± 0.8</td>
<td>12.2 ± 1.0</td>
<td>0.019$^c$</td>
</tr>
<tr>
<td>MII/total oocytes</td>
<td>0.77 ± 0.01</td>
<td>0.71 ± 0.01</td>
<td>0.74 ± 0.02</td>
<td>0.050</td>
</tr>
<tr>
<td>MII/AFC</td>
<td>0.93 ± 0.03</td>
<td>1.01 ± 0.06</td>
<td>1.10 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>MII/follicle ≥ 13 mm</td>
<td>1.03 ± 0.02</td>
<td>0.94 ± 0.03</td>
<td>0.96 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>≤6 oocytes retrieved (n, %)</td>
<td>45, 12.5%</td>
<td>15, 10.4%</td>
<td>6, 15.8%</td>
<td>NS$^*$</td>
</tr>
<tr>
<td>2PN/MII (ICSI, n = 84)</td>
<td>--</td>
<td>0.76 ± 0.02</td>
<td>0.82 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

$n =$ total number of subjects who proceeded to retrieval for each group.
$^a$ANCOVA: age, BMI and total gonadotropin dose as co-variates unless otherwise indicated.
$^b$P < 0.001 for comparison with elective cryopreservation.
$^c$Pairwise comparisons between groups: NS.
$^d$Chi-squared.
Data presented as mean (estimate) ± SE.
AFC: Antral Follicle Count, MII: Metaphase II (mature).

Molly MQ, et al. Response to Ovarian Stimulation is not Impacted by a Breast Cancer Diagnosis. Hum Reprod, 2017
### Table 4: Ovarian stimulation cycle outcomes among women with no cancer, women with breast cancer with and without BRCA mutations, or other cancer

<table>
<thead>
<tr>
<th>Cycle characteristics</th>
<th>No Cancer (n=664)</th>
<th>BRCA+ Breast Cancer (n=49)</th>
<th>BRCA+ Breast Cancer (n=11)</th>
<th>Other Cancer (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>34.6±4.2</td>
<td>35.2±4.7</td>
<td>35.5±4.0</td>
<td>34.9±4.4</td>
</tr>
<tr>
<td>Baseline AFC (n)</td>
<td>9.4±7.2</td>
<td>11.5±7.7</td>
<td>7.2±6.3</td>
<td>8.2±7.8</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>1.22 (0.59,1.50)</td>
<td>0.76 (0.50,1.15)</td>
<td>0.70 (0.54,0.90)*</td>
</tr>
<tr>
<td>Starting FSH dose (IU)</td>
<td>282.0±121.3</td>
<td>342.3±159.6</td>
<td>395.2±236.5</td>
<td>375.5±174.5</td>
</tr>
<tr>
<td>(Ref)</td>
<td>0.00</td>
<td>53.5 (21.1,185.9)*</td>
<td>142.8 (81.5,294.1)*</td>
<td>183.2 (153.3,213.1)*</td>
</tr>
<tr>
<td>Total FSH dose (IU)</td>
<td>1839.2±1294.7</td>
<td>2498.0±1570.9</td>
<td>4326.9±3046.6</td>
<td>2994.5±1715.8</td>
</tr>
<tr>
<td>(Ref)</td>
<td>0.00</td>
<td>637.7 (302.4,1944.9)*</td>
<td>2775.0 (2072.0,3478.0)*</td>
<td>1916.5 (1573.7,2259.4)*</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>11±2.0</td>
<td>11.3±2.4</td>
<td>13.0±3.0</td>
<td>12.1±2.0</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>1.09 (0.91,1.22)</td>
<td>1.12 (0.98,1.28)</td>
<td>1.05 (1.00,1.10)*</td>
</tr>
<tr>
<td>Total follicle number at hCG trigger (n)</td>
<td>12.9±6.6</td>
<td>12.1±5.8</td>
<td>12.1±5.5</td>
<td>13.3±5.9</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.95 (0.83,1.09)</td>
<td>0.87 (0.68,1.12)</td>
<td>0.85 (0.70,0.97)*</td>
</tr>
<tr>
<td>Number of oocytes retrieved (n)</td>
<td>15±8.6</td>
<td>14±9.6</td>
<td>15±7.1</td>
<td>20±10.7</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.94 (0.78,1.12)</td>
<td>0.86 (0.67,1.12)</td>
<td>1.11 (0.84,1.45)</td>
</tr>
<tr>
<td>Number of mature oocytes retrieved (n)</td>
<td>12±8.1</td>
<td>10±5.9</td>
<td>11±5.6</td>
<td>15±12.4</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.85 (0.72,0.99)*</td>
<td>0.90 (0.69,1.16)</td>
<td>1.08 (0.82,1.38)</td>
</tr>
<tr>
<td>Proportion of mature oocytes (n/n)</td>
<td>0.76±0.19</td>
<td>0.78±0.21</td>
<td>0.79±0.07</td>
<td>0.86±0.16</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.97 (0.78,1.19)</td>
<td>1.23 (0.94,1.60)</td>
<td>0.94 (0.69,1.26)</td>
</tr>
<tr>
<td>Oocytes/AFC ratio (n/n)</td>
<td>2.28±2.87</td>
<td>1.85±2.15</td>
<td>2.29±1.25</td>
<td>3.19±5.71</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.73 (0.46,1.18)</td>
<td>1.37 (0.66,2.82)</td>
<td>1.69 (0.95,2.98)</td>
</tr>
<tr>
<td>Mature oocytes/AFC ratio (n/n)</td>
<td>1.76±2.33</td>
<td>1.92±1.43</td>
<td>1.77±0.94</td>
<td>2.39±3.53</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.66 (0.41,1.10)</td>
<td>1.37 (0.66,2.80)</td>
<td>1.62 (0.94,2.80)</td>
</tr>
<tr>
<td>Number of embryos (n)</td>
<td>8.5±6.3</td>
<td>8.0±10.0</td>
<td>6.4±5.7</td>
<td>6.2±6.7</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>0.84 (0.74,0.97)*</td>
<td>0.90 (0.67,1.21)</td>
<td>1.09 (0.98,1.23)</td>
</tr>
<tr>
<td>Cycle cancelled (%)</td>
<td>14 (21.4)</td>
<td>0 (0)</td>
<td>2 (15.4)</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>(Ref)</td>
<td>1.00</td>
<td>8.55 (1.70,42.88)*</td>
<td>6.06 (2.12,17.35)*</td>
<td></td>
</tr>
</tbody>
</table>

All results reported as mean ± standard deviation, unless otherwise noted. * indicates statistical significance (p-value < 0.05)

• Poisson regression estimate, RR (95% CI), Adjusted for age and BMI at cycle start
• Linear regression estimate, β (95% CI), Adjusted for age and BMI at cycle start
• Poisson regression estimate, β (95% CI), Adjusted for age and BMI at cycle start, and ICSI use
• Logistic regression estimate, OR (95% CI), Adjusted for age and BMI at cycle start

Safety of Controlled Ovarian Stimulation in Estrogen Sensitive Tumors

- Compared 79 breast cancer patients (81% ER positive) undergoing letrozole stimulation with 136 controls who did not undergo ovarian stimulation

- No difference in relapse-free survival over study follow up period (median 2 years)

- Non-randomized study and long-term follow up not yet available

Embryo/ Oocyte Cryopreservation

• We vitrify embryos at 2 PN stage
  ➢ >90% survival
    • No concern about loss of embryos from poor cleavage or blastocyst development
    • Will find out about embryo development in future
    • We typically thaw 2-4 depending on age at cryopreservation

• Oocyte cryopreservation
  ➢ Vitrification provides >90% survival
    • Most deliveries from MII oocytes
    • We freeze all oocytes
    • In vitro maturation likely to improve
Using Oocytes/Embryos after Cancer

- Assess health of survivor
  - Cancer therapies may have significant toxicities
  - Maternal-fetal medicine (MFM) consultation recommended
    - Cardio-pulmonary assessment
    - Uterine evaluation

- Gestational surrogacy may be an option
  - Sexually transmitted disease screening tests
  - Legal consultation
  - Very costly

- Preimplantation genetic diagnosis (PGD) an option for genetic cancers
  - Need a large number of embryos
Embryo Cryo Outcome

- 10 patients returned for 16 transfers
- 6 pregnancies, 4 using a gestational carrier
- 4 singletons, 1 twin, 1 ectopic
- Gestational ages at delivery 36-39 weeks
  - 50% of patients returning had delivery from their embryos
- One patient spontaneously conceived after failed Ets
- 2 patients had failed ETs, then delivered with donor eggs

Pregnancy in Cancer Survivors

• Delivery rates in older patients unclear
  ➢ Likely c/w pregnancy rates with embryo cryopreservation

• No evidence of increased risk of birth defects or chromosome abnormalities in babies born from a parent with current cancer or history of cancer
  ➢ Some chemotherapeutic agents are teratogenic

• Insufficient numbers of live births after fertility preservation published to confirm this.

Ovarian Suppression
Meta-analysis of Menses with Ovarian Suppression

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chemotherapy + GnRH Events</th>
<th>Total</th>
<th>Chemotherapy alone Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds ratio M–H, random, 95% CI</th>
<th>Odds ratio M–H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badawy et al²⁵</td>
<td>35</td>
<td>39</td>
<td>13</td>
<td>39</td>
<td>8.6%</td>
<td>17.50 (5.11, 59.88)</td>
<td></td>
</tr>
<tr>
<td>Del Mastro et al⁰⁸</td>
<td>88</td>
<td>139</td>
<td>60</td>
<td>121</td>
<td>19.2%</td>
<td>1.75 (1.07, 2.88)</td>
<td></td>
</tr>
<tr>
<td>Eligdoy et al⁰⁸</td>
<td>41</td>
<td>50</td>
<td>40</td>
<td>50</td>
<td>11.1%</td>
<td>1.14 (0.42, 3.10)</td>
<td></td>
</tr>
<tr>
<td>Gerber et al⁰⁵</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>29</td>
<td>1.8%</td>
<td>3.00 (0.12, 76.79)</td>
<td></td>
</tr>
<tr>
<td>Jiang et al⁰⁸</td>
<td>9</td>
<td>10</td>
<td>6</td>
<td>11</td>
<td>3.1%</td>
<td>7.50 (0.69, 81.25)</td>
<td></td>
</tr>
<tr>
<td>Li et al¹⁰</td>
<td>23</td>
<td>31</td>
<td>15</td>
<td>32</td>
<td>10.3%</td>
<td>3.26 (1.13, 9.43)</td>
<td></td>
</tr>
<tr>
<td>Moore et al³⁵</td>
<td>61</td>
<td>66</td>
<td>54</td>
<td>69</td>
<td>10.2%</td>
<td>3.39 (1.16, 9.94)</td>
<td></td>
</tr>
<tr>
<td>Munster et al⁰⁵</td>
<td>23</td>
<td>26</td>
<td>19</td>
<td>21</td>
<td>4.5%</td>
<td>0.81 (0.12, 5.34)</td>
<td></td>
</tr>
<tr>
<td>Song et al²⁷</td>
<td>53</td>
<td>89</td>
<td>39</td>
<td>94</td>
<td>17.5%</td>
<td>2.08 (1.15, 3.74)</td>
<td></td>
</tr>
<tr>
<td>Sun et al²⁷</td>
<td>10</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>4.5%</td>
<td>5.00 (0.75, 33.21)</td>
<td></td>
</tr>
<tr>
<td>Svenssdottir et al²⁷</td>
<td>10</td>
<td>51</td>
<td>5</td>
<td>43</td>
<td>9.3%</td>
<td>1.96 (0.58, 6.92)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>541</td>
<td>521</td>
<td>100%</td>
<td></td>
<td>2.57 (1.65, 4.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events 381 285

Heterogeneity: $\chi^2=17.51, df=10 (P=0.06); I^2=43%$
Test for overall effect: $Z=4.16 (P=0.0001)$

Figure 2: Forest plot of the rate of resumed menses for GnRH agonists plus chemotherapy versus chemotherapy alone in a random-effect model.

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone; M–H, Mantel–Haenszel.

Meta-analysis of Pregnancy with Ovarian Suppression

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chemotherapy + GnRH</th>
<th>Chemotherapy alone</th>
<th>Weight</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M-H</td>
</tr>
</tbody>
</table>
| Del Mastro et al
| 3 | 139 | 1 | 121 | 7.6% | 2.65 (0.27, 25.79) |
| Gerber et al
| 1 | 28 | 1 | 29 | 6.8% | 1.04 (0.06, 17.43) |
| Moore et al
| 22 | 105 | 12 | 113 | 66.0% | 2.23 (1.04, 4.77) |
| Munsier et al
| 0 | 28 | 2 | 21 | 19.5% | 0.15 (0.01, 3.24) |
| Total (95% CI) | 298 | 284 | 100% | 1.77 (0.92, 3.40) |

Total events: 26, 16
Heterogeneity: $\chi^2=3.10$, df=3 ($P=0.38$); $I^2=3\%$
Test for overall effect: $Z=1.72$ ($P=0.09$)

Figure 3 Forest plot of the rate of spontaneous pregnancy for GnRH agonists plus chemotherapy versus chemotherapy alone in a fixed-effect model.

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone; M-H, Mantel–Haenszel.

Goserelin For Ovarian Suppression

257 randomized
218 evaluable
135 with complete data

Ovarian failure:
8% Goserelin
22% chemo alone
OR 0.30(0.09,0.97)

Pregnancy:
21% Goserelin
11% chemo
(P=0.03)
Delivery rates similar

Ovarian Tissue Banking

- Laparoscopic oophorectomy or ovarian biopsies

- No ovarian stimulation, minimal delay in treatment (only option in prepubertal girls)

- Autologous transplantation – human births
  - All births after orthotopic transplant
  - Risk of seeding cancer cells in cancer that involve the ovaries
  - Repeat surgery required

- Grafts function hormonally for 3-8 years but AMH levels are low

- In vitro maturation of eggs from tissue – no deliveries yet
Ovarian Cortical Tissue

20 yo, acute leukemia; urgent TBI, chemo, stem cell transplant

11 yo acute leukemia; TBI, chemo, stem cell transplant

18 mo, pelvic sarcoma; pelvic radiation and chemotherapy
Serum AMH Decrease Prevented by Everolimus

Fig. 4. Serum AMH decreases after CY treatment whereas mTOR inhibitor cotreatment maintains AMH concentration. (A) AMH serum concentrations were measured in untreated 8-wk-old C57BL/6 mice, mice exposed to three weekly doses of 75 mg/kg CY, and mice exposed to three weekly doses of 150 mg/kg CY. Mice treated with 75 mg/kg CY had significantly lower serum AMH levels compared with control (\(*P < 0.005\)), as did mice treated with 150 mg/kg CY (\(*P < 0.05\)). (B and C) AMH serum concentrations were measured in 8-wk-old mice that underwent long-term treatment (3 wk) with polyvinylpyrrolidone (PVP) alone daily, 75 mg/kg CY weekly for 3 wk, RAD daily, RAD daily plus 75 mg/kg CY weekly, INK daily, or INK plus 75 mg/kg CY weekly. There were no differences in AMH concentrations in mice treated with RAD or INK alone compared with untreated controls. Mean \(\pm\) SEM. Mice cotreated for 3 wk with weekly 75 mg/kg CY and daily RAD and killed 1 wk after the final CY treatment had a significantly higher AMH compared with CY alone (12.5 vs. 11.1, \(*P < 0.05\)). Mice cotreated for 3 wk with weekly 75 mg/kg CY and daily INK and killed 1 wk after the final CY treatment had a higher AMH level compared with CY alone but this did not reach significance (12.6 vs. 11.1, n.s., \(P > 0.05\)). Results are derived from five mice per treatment group with SEM shown.

Goldman KN, et al. mTORC1/2 Inhibition Preserves Ovarian Function and Fertility During Genotoxic Chemotherapy. PNAS 2017
Conclusions

• All breast cancer patients should be informed of the potential impact on fertility of chemotherapy and delay to conception

• Fertility preserving options should be discussed
  ➢ Technologies pose some risk
  ➢ Delay cancer therapy, costly
  ➢ Ovarian tissue cryo still experimental

• Live birth rates with banked eggs and embryos are still unclear

• We should target those at highest risk of infertility
  ➢ But we can’t predict this with accuracy

• Available options must be weighed against time, risk of infertility and cost
Goldman KN, et al. mTORC1/2 Inhibition Preserves Ovarian Function and Fertility During Genotoxic Chemotherapy. PNAS 2017
### CUNICAL INSTRUCTIONS

**PRE-CHMO CYCLE:** Start Gynecology when E2 expected to be 390. Lives in CT, to do E2 and US on day 7. AMI= 6-8 (0.6-0.8) Prin Letrozole, ignore E2 levels.
## Letrozole Simulation: Data

<table>
<thead>
<tr>
<th></th>
<th>Cases- Letrozole</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.4 + 3.6</td>
<td>36.9 + 3.9</td>
<td>0.44</td>
</tr>
<tr>
<td>Baseline FSH</td>
<td>7.1 + 3.1</td>
<td>4.2 + 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak estradiol</td>
<td>483.4 + 278.9</td>
<td>1464 + 644.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>11.7 + 2.3</td>
<td>12.2 + 1.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>12.4 + 7.0</td>
<td>11.1 + 5.5</td>
<td>0.43</td>
</tr>
<tr>
<td># 2PN zygotes</td>
<td>6.6 + 4.0</td>
<td>6.9 + 4.1</td>
<td>0.73</td>
</tr>
</tbody>
</table>

- Compared 47 breast cancer patients (86% ER positive) undergoing letrozole stimulation to 56 age-matched controls undergoing IVF with downregulation protocol
- Breast cancer patients had higher baseline FSH but similar response to stimulation and lower peak estradiol levels

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Bawady</th>
<th>Sverrisdottir</th>
<th>Del Mastro</th>
<th>Leonard</th>
<th>Gerber</th>
<th>Munster</th>
<th>Elgindy</th>
<th>SWOG 0230</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>80</td>
<td>285</td>
<td>281</td>
<td>227</td>
<td>60</td>
<td>49</td>
<td>100</td>
<td>257</td>
</tr>
<tr>
<td>Study type</td>
<td>Phase II RCT</td>
<td>Substudy from combined analysis of 4 RCTs using core protocol</td>
<td>Phase III RCT</td>
<td>Phase III RCT (abstract only)</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>CT + goserelin vs CT</td>
<td>TAM^ +/- CT</td>
<td>CT + triptorelin vs. CT</td>
<td>CT + goserelin vs. CT</td>
<td>CT + triptorelin vs. CT</td>
<td>Delayed CT: CT + triptorelin vs. CT</td>
<td>Early CT: CT + triptorelin + cetrorelixβ vs. CT</td>
<td>CT + goserelin vs. CT</td>
</tr>
<tr>
<td>Premenopausal definition</td>
<td>Regular menstruation FSH &lt;10 IU/L</td>
<td>LMP &lt;6 months prior to study entry, including irregular cycles</td>
<td>Actively menstruation during 6 weeks pre-CT</td>
<td>Regular menses in 12 months preceding surgery</td>
<td>Regular menstruation FSH&lt;15 in follicular phase</td>
<td>Regular menstruation (2 periods in 6 months, lasting ≥2 days, 21-35 days apart FSH &lt;10 IU/L)</td>
<td>Regular menstruation in 12 consecutive periods within 21-35 days</td>
<td>LMP &lt;6 weeks pre-randomisation or FSH &amp; E2 in premenopausal range</td>
</tr>
<tr>
<td>%ER+</td>
<td>NR</td>
<td>45%</td>
<td>NR</td>
<td>9%</td>
<td>73%</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Marker of 'fertility preservation'</td>
<td>Resumption of menstruation or spontaneous ovulation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation, postmenopausal FSH, pregnancy</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Rate of POF (no menstruation/ spontaneous ovulation) 12 months post-CT</td>
<td>Rate of CIA (no menstruation and post-menopausal FSH/E2 levels) for 12 months post-CT</td>
<td>Rate of amenorrhea 12 months after start of CT</td>
<td>Rate of normal ovarian function at 6 months post-CT</td>
<td>Rate of amenorrhea during f/u of at least 2 years post CT</td>
<td>Rate of regular ovarian function at 12 months after completion of CT</td>
<td>Rate of ovarian failure (amenorrhea) at 2 years, FSH</td>
<td></td>
</tr>
<tr>
<td>Median f/u [range]</td>
<td>NR [3-8 months]</td>
<td>12 months post-CT</td>
<td>NR</td>
<td>6, 12, 24, 48 months post-CT</td>
<td>18 months [5-43 months] after CT</td>
<td>NR</td>
<td>All patients followed for at least 12 months</td>
<td>Planned f/u at 1.2 and 5 years</td>
</tr>
<tr>
<td>Rate of recovery of menstruation:</td>
<td>30% (goserelin) vs. 33% (control), p&lt;0.001</td>
<td>At 6 months post ET cessation : 36% (goserelin) vs. 10% (control), 13% (TAM), 7% (goserelin + TAM), p=0.006</td>
<td>91.1% (triptorelin) vs. 74.1% (control) p&lt;0.001</td>
<td>NR</td>
<td>88.5% (triptorelin) vs. 90.5% (control) Trial stopped early for futility</td>
<td>70% (goserelin) vs. 56.7% (control)</td>
<td>93% (goserelin) vs. 22% (control) 18% vs. 9% pregnancy success</td>
<td>0%</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>No data on pregnancies</td>
<td>No data on pregnancies</td>
<td>3 pregnancies in triptorelin arm, 1 in control arm</td>
<td>No data on pregnancies</td>
<td>1 pregnancy in each group</td>
<td>2 pregnancies in control arm</td>
<td>3 pregnancies, one in early CT + triptorelin + cetrorelix arm, 1 in early CT control arm and 1 in delayed CT + triptorelin arm</td>
<td>Pending</td>
</tr>
</tbody>
</table>