Preserving Fertility and Ovulation Induction in Breast Cancer

Murat Sönmezer
Ankara University School of Medicine
Breast Cancer

- The most common cancer in women (1/3 all cancers)
- A woman has a 12.3%, or a 1-in-8, lifetime risk of being diagnosed with breast cancer
- Worldwide, around 1.4 million women are diagnosed with breast cancer annually
- In 2011, 13,110 new cases diagnosed in women of «reproductive age» in the US

DeSantis, CA Cancer J Clin, 2014
GLOBOCAN, 2008
Breast Cancer Incidence

DeSantis, CA Cancer J Clin, 2014
Breast Cancer Deaths

DeSantis, CA Cancer J Clin, 2014
Incidence rates increased for estrogen receptor-positive breast cancers in the youngest white women

*DeSantis, CA Cancer J Clin, 2014*
Chemotherapy / Gonadal Damage

<table>
<thead>
<tr>
<th>High risk agents</th>
<th>Medium risk agents</th>
<th>Low risk agents</th>
<th>New agents / risk?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Cholarambucil</td>
<td>Cholarambucil</td>
<td>5-Fluorouracil</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Melphalan</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>Busulfan</td>
<td>Actinomycin D</td>
<td></td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>Nitrogen mustard</td>
<td>Bleomycin</td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Procarbazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sonmez & Oktay, Uptodate, 2014
Fertility preservation for breast cancer

Critical points

- Fertility/ovarian function is preserved
- Positive impact on QoL and on coping with the disease
- Safety of COH in ER dependent tumors
- Time constraints
Options for Fertility Preservation

- Embryo cryopreservation
- Mature/immature oocyte cryopreservation
- In vitro maturation
- Ovarian transposition
- Donor oocyte
- Ovarian tissue cryopreservation
- Xenografting
- GnRHα pretreatment
- Antiapoptotic treatments $\Rightarrow$ SP1P

Sonmezer&Oktay, Hum Reprod Update, 2004
## Ovarian cryo. vs. oocyte/embryo cryo.

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cryo.</th>
<th>Oocyte /embryo cryo.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Chemo. not delayed</td>
<td>• Technique standard</td>
</tr>
<tr>
<td></td>
<td>• Only option for prepubertal girls</td>
<td>• High success rates</td>
</tr>
<tr>
<td></td>
<td>• Resumption of endocrine functions</td>
<td>• Widespread use</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• L/S upfront</td>
<td>• 2-3 W required</td>
</tr>
<tr>
<td></td>
<td>• Limited number of pregnancies</td>
<td>• Limited number of oocyte/embryo</td>
</tr>
<tr>
<td></td>
<td>• Cancer reseeding ?</td>
<td>• Not easily applicable in children</td>
</tr>
</tbody>
</table>
Positive impact on QoL and on coping with the disease

n=85

Graph 4: Motivational morale contribution of ovarian cryopreservation to patients' struggle with a malignancy. (1-5, 1; no effect, 5; maximum boosting morale)

Sonmezer&Ozkavukcu, ASRM, 2013
Letrozole / TMX Stimulation - IVF

29 women aged 24-43 years, 33 COH cycles

- TMX 60mg/d alone → 12 patients, 13 cycles
- TMX-FSH → 7 patients 9 cycles
- Letrozole (5mg/d)-FSH → 11 patients 11 cycles

Oktay, JCO, 2005
<table>
<thead>
<tr>
<th>Variable</th>
<th>Tam-IVF (a)</th>
<th>TamFSH-IVF (b)</th>
<th>Letrozole-IVF (c)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>36.6 ± 1.6</td>
<td>38.3 ± 1.9</td>
<td>38.5 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline FSH, mU/mL</td>
<td>9.4 ± 1.5</td>
<td>9.4 ± 1.5</td>
<td>6.2 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>PeakE₂, pg/mL†</td>
<td>419 ± 39</td>
<td>1,182 ± 271</td>
<td>380 ± 57</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Total follicles, No.</td>
<td>2 ± 0.3</td>
<td>6 ± 1</td>
<td>7.8 ± 0.9</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Follicle &gt; 17 mm, No.</td>
<td>1.2 ± 0.1</td>
<td>2.6 ± 0.4</td>
<td>3.2 ± 0.4</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Total oocytes, No.</td>
<td>1.7 ± 0.3</td>
<td>6.9 ± 1.1</td>
<td>12.3 ± 2.5</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Mature oocytes, No.</td>
<td>1.5 ± 0.3</td>
<td>5.1 ± 1.1</td>
<td>8.5 ± 1.6</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Total embryos, No.</td>
<td>1.3 ± 0.2</td>
<td>3.8 ± 0.8</td>
<td>5.3 ± 0.8</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

*P* values indicate statistical significance:
- NS: Not significant
- < .05: Significant
- > .05: Not significant
A prospective case series of women with estrogen receptor-positive breast cancer: levels of tamoxifen metabolites in controlled ovarian stimulation with high-dose tamoxifen

E.M.E. Balkenende¹, T. Dahhan¹,*; S.C. Linn²; N.G.L. Jager³; J.H. Beijnen³; and M. Goddijn¹

- TMX 60mg/day+FSH
- 4 patients
- 5-11 oocytes vitrified
- Endoxifen >7ng/ml (ER inhibition)

Balkenende, Hum Reprod, 2012
Physiology of Ovarian Follicular Development
Physiology of Ovarian Follicular Development
A new model for ovarian follicular development during the human menstrual cycle

Angela R. Baerwald, B.Sc. Hon., Gregg P. Adams, D.V.M., M.S., Ph.D., and Roger A. Pierson, M.S., Ph.D.

University of Saskatchewan, Saskatoon, Saskatchewan, Canada

• Is there only one major follicular wave in a single menstrual cycle?
• n=50 healthy ovulating women

Barewald, Fertil Steril, 2003
32%
Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles

Murat Sönmez, M.D., Ilgin Türkçüoğlu, M.D., Uğur Coşkun, M.D., and Kutluk Oktay, M.D.

### TABLE 1

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Stage</td>
<td>I</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal</td>
<td>Mixed invasive ductal + lobular</td>
<td>Invasive ductal</td>
</tr>
<tr>
<td>COH start day</td>
<td>14</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>6.2</td>
<td>2.8</td>
<td>4.6</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>5.8</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>E₂ (ng/mL)</td>
<td>62</td>
<td>269</td>
<td>50</td>
</tr>
<tr>
<td>P (pg/mL)</td>
<td>1.2</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>7</td>
<td>6.5</td>
<td>9</td>
</tr>
<tr>
<td>Antral follicle count (n)</td>
<td>11</td>
<td>20(^a)</td>
<td>20(^b)</td>
</tr>
<tr>
<td>GnRH antagonist start day</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Peak E₂ (pg/mL)</td>
<td>499</td>
<td>988</td>
<td>478</td>
</tr>
<tr>
<td>Duration of COH (d)</td>
<td>9</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Oocytes retrieved (n)</td>
<td>9</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Metaphase II, no. (%)</td>
<td>7 (77.7)</td>
<td>10 (58.8)</td>
<td>11 (68.75)</td>
</tr>
<tr>
<td>Metaphase I + germinal vesicle, no. (%)</td>
<td>2 (22.3)</td>
<td>7 (41.2)</td>
<td>5 (31.25)</td>
</tr>
<tr>
<td>Fertilization rate, no. (%)</td>
<td>7/8 (87.5)</td>
<td>10/12 (83.3)</td>
<td>9/13 (69.2)</td>
</tr>
<tr>
<td>Cleavage rate (%)</td>
<td>7/7 (100)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Embryos frozen (n)</td>
<td>7</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>
### Random Start COH

- **Random start**  \( n = 35 \)
- **Conventional start**  \( n = 93 \)

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

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

*NS = not significant*

Cakmak, Fertil Steril, 2014
Luteal phase GnRHa trigger in random start fertility preservation cycles

Enis Ozkaya • Gabriel San Roman • Kutluk Oktay

Ozkaya, Oktay, JARG, 2012
# hCG vs GnRHa for ovulation trigger
## Letrozole + FSH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>hCG (n = 47)</th>
<th>GnRHa (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.0 ± 4.3</td>
<td>33.6 ± 4.4</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>23.3 ± 4.2$^a$</td>
<td>21.5 ± 2.5$^a$</td>
</tr>
<tr>
<td>Baseline FSH (mIU/ml)</td>
<td>6.8 ± 2.7</td>
<td>8.2 ± 2.9</td>
</tr>
<tr>
<td>FSH stimulation duration (day)</td>
<td>9.6 ± 1.6</td>
<td>9.9 ± 1.6</td>
</tr>
<tr>
<td>Total gonadotrophin dose (IU)</td>
<td>2012.8 ± 603.5</td>
<td>1994.4 ± 549.1</td>
</tr>
</tbody>
</table>

*Oktay, RBM Online, 2010*
<table>
<thead>
<tr>
<th>Parameter</th>
<th>hCG trigger (n = 47)</th>
<th>GnRHa trigger (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak estradiol (pg/ml)</td>
<td>472.6 ± 345.5</td>
<td>695.5 ± 539.0</td>
<td>0.044</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>8.8 ± 1.8</td>
<td>8.4 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total oocytes</td>
<td>12.8 ± 7.7</td>
<td>16.4 ± 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mature oocytes</td>
<td>7.4 ± 4.9</td>
<td>11.9 ± 6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oocyte maturation rate (%)</td>
<td>68.5 ± 23.3</td>
<td>77.3 ± 21.1</td>
<td>0.049</td>
</tr>
<tr>
<td>Two-pronuclei embryo^a</td>
<td>6.3 ± 4.6</td>
<td>9.3 ± 5.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>74.0 ± 24.9</td>
<td>84.1 ± 11.1</td>
<td>0.027</td>
</tr>
<tr>
<td>Drop in E2 from day 0 to 4 (%)</td>
<td>79.0 ± 13.4</td>
<td>89.5 ± 6.3</td>
<td>0.013</td>
</tr>
<tr>
<td>Mild or moderate OHSS (%)</td>
<td>10 (21.3)</td>
<td>1 (3.7)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Oktay, RBM Online, 2010
Consecutive COH Cycles with Letrozole

- Single cycle stimulation  n=61
- Two cycle stimulation  n=17

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Single cycle (n = 61)</th>
<th>Two cycles (n = 17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes (n)</td>
<td>9.1 ± 5.2</td>
<td>16.1 ± 13.2</td>
<td>.008</td>
</tr>
<tr>
<td>Mature oocytes (n)</td>
<td>6.2 ± 3.0</td>
<td>10.3 ± 7.7</td>
<td>.004</td>
</tr>
<tr>
<td>Inseminated oocytes (n)</td>
<td>6.0 ± 3.9</td>
<td>9.8 ± 5.5</td>
<td>.002</td>
</tr>
<tr>
<td>Fertilized oocytes (n)</td>
<td>5.4 ± 2.3</td>
<td>7.4 ± 3.9</td>
<td>.040</td>
</tr>
<tr>
<td>Embryos (n)</td>
<td>3.7 ± 3.1</td>
<td>6.4 ± 2.9</td>
<td>.019</td>
</tr>
</tbody>
</table>
Consecutive COH Cycles with Letrozole

![Graph showing time from surgery to chemotherapy with single and two cycle groups.](image)

*Note: Image description is not provided, but it includes a graph titled "Time from Surgery to Chemotherapy" showing cumulative rate over time with groups labeled 'Single Cycle' and 'Two Cycles'.*

Turan, Fertil Steril, 2013
Luteal phase immature oocyte retrieval and IVM

- Single patients aged 21, 30, and 40 years seeking fertility preservation before chemo
- 7, 5, and 7 immature oocytes retrieved
- Following IVM 5, 3, and 5 MII oocytes vitrified

Demirtas, RBM Online, 2008
Immature Oocyte Cryopreservation
Which comes first? IVM vs. Cryopreservation

- Donated oocytes following standard GnRH-ant protocol
  - n=71 patients, 96 oocytes

Fresh IVM oocytes
- n=69
  - GV: 38
  - M1: 31

Post thaw IVM oocytes
- N=27
  - GV: 12
  - M1: 15

Lee JA, Fertil Steril. 2013
IMMATURE OOCYTES OVERALL

Fresh IVM Oocytes 69 (72%) (38 GV (56%) + 31 MI (44%))

Oocytes Matured (IVM-MII) 53 (77%)

CRYOPRESERVED – SLOW FREEZE

THAWED

Oocytes Survival Rate 44 (83%)

Oocytes Matured/Survived 44 (64%)*

Post-Thaw IVM 27 (GV+MI) (28%) (12 GV (56%) + 15 MI (44%))

CRYOPRESERVED – SLOW FREEZE

THAWED

Oocytes Survival Rate 23 (85%)

Oocytes Matured (IVM-MII) 9 (39%)

Oocytes Matured/Survived 9 (33%)*
• Oocytes from small antral follicle COC with «multiple cumulus layers» (42%) were more likely to resume meiosis and progress to metaphase II (MII) than oocytes with a «single layer of cumulus cells» or less (23% vs. 3%, respectively).
• MII oocytes- ICSI →Morula (25%)
Ovarian Tissue Cryopreservation in Breast Cancer
**Early stage breast cancer**

**Ovarian metastasis (histology and IHC)**

**IHC**

![IHC images](A, B, C, D)

**Standard histology**

![Standard histology images](A, B, C, D)

**Ovarian involvement:** 0/63 patients (100 cortical pieces) undergoing ovarian cryopreservation

*Sanches M, Hum Reprod, 2009*
Early stage breast cancer
Ovarian metastasis (histology and IHC)

Ovarian cortex from one of the 51 women with breast cancer. Histologic and immunohistochemical analysis shows no signs of metastatic infiltration. (A) H&E. (B) WT-1. (C) CK-7. Magnification, x10.

Ovarian involvement: 0/51

Rosendahl, Fertil Steril, 2011
Non gynecoogic ovarian metastasis
Analysis of 150 cases

- Colon: 30%
- Stomach: 16%
- Appendix: 13%
- Breast: 13%
- Pancreas: 12%
- Biliary tract: 15%
- Liver: 4%

Alvarado-Cabrero I, Anal Quant Cytol Histol. 2013
Ovarian Tissue Cryopreservation + IVM
Ovarian tissue cryopreservation and IVM

- 57 patients undergoing ovarian tissue cryo., aged 8-35 years
- Antral fluid was collected from removed ovary
- 266 oocytes retrieved
  - Degenerated: 28
  - GV: 200
  - MI: 35
  - MII: 3
- 24-28h IVM before cryopreservation (maturation rate 31%)

*Fasano, Reprod Biol Endocrinol. 2011*
Combining ovarian tissue cryobanking with retrieval of immature oocytes followed by in vitro maturation and vitrification: an additional strategy of fertility preservation

Jack Y. J. Huang, M.D., Togas Tulandi, M.D., M.H.C.M., Hananel Holzer, M.D., Seang Lin Tan, M.D., M.B.A., and Ri-Cheng Chian, Ph.D.

Department of Obstetrics and Gynecology, McGill University Health Center, McGill University, Montreal, Quebec, Canada

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Cancer type</th>
<th>Day of menstrual cycle</th>
<th>Surgical procedure</th>
<th>No. of GV oocytes retrieved from ovarian tissue</th>
<th>No. of MII oocytes following IVM</th>
<th>Maturation rate (%)</th>
<th>No. of MII oocytes vitrified</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>Hodgkin lymphoma</td>
<td>2</td>
<td>Ovarian wedge resection</td>
<td>3</td>
<td>3</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>Breast</td>
<td>19</td>
<td>Oophorectomy</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>Hodgkin lymphoma</td>
<td>5</td>
<td>Ovarian wedge resection</td>
<td>4</td>
<td>2</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>Rectal cancer</td>
<td>14</td>
<td>Ovarian wedge resection and oophoropexy</td>
<td>3</td>
<td>2</td>
<td>67</td>
<td>2</td>
</tr>
</tbody>
</table>
Improving fertility preservation in cancer: ovarian tissue cryobanking followed by ovarian stimulation can be efficiently combined

- **Study group**: n=12 patients
- **Control group**: n=28 patients
- In the study group, half ovarian tissue was removed

*Hueber Zeeb, Fertil Steril, 2011*
### Main characteristics and stimulation outcome of patients with (study group) and without (control group) ovarian biopsy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group (n = 12)</th>
<th>Control group (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patients (y), mean ± SD</td>
<td>31.1 ± 6.2</td>
<td>27.6 ± 5.0</td>
</tr>
<tr>
<td>Days of stimulation, mean ± SD</td>
<td>10.2 ± 2.6</td>
<td>10.6 ± 2.5</td>
</tr>
<tr>
<td>Dosage of stimulation (IU), mean ± SD</td>
<td>2527 ± 942</td>
<td>2255 ± 945</td>
</tr>
<tr>
<td>Total no. of aspirated oocytes</td>
<td>145</td>
<td>367</td>
</tr>
<tr>
<td>Aspirated oocytes per patient, n</td>
<td>12.1</td>
<td>13.1</td>
</tr>
<tr>
<td>MII-oocytes/aspirated oocytes, %</td>
<td>65.5</td>
<td>83.8</td>
</tr>
<tr>
<td>No. of MII oocytes (processed for ICSI)</td>
<td>44</td>
<td>66</td>
</tr>
<tr>
<td>Fertilization rate/MII oocytes, %</td>
<td>75.0</td>
<td>60.6</td>
</tr>
</tbody>
</table>

### Subgroup analysis of biopsied and nonbiopsied ovaries in the study group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biopsied ovaries</th>
<th>Nonbiopsied ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of aspirated oocytes</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Aspirated oocytes per patient, n&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.8</td>
<td>7.5</td>
</tr>
<tr>
<td>MII oocytes/aspirated oocytes, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70.0</td>
<td>61.3</td>
</tr>
<tr>
<td>No. of MII oocytes (processed for ICSI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Fertilization rate/MII oocytes, %</td>
<td>80.0</td>
<td>68.4</td>
</tr>
</tbody>
</table>

*Hueber Zeeb, Fertil Steril, 2011*
Oocyte retrieval from removed ovary

<table>
<thead>
<tr>
<th>Characteristic of the patient’s menstrual cycle</th>
<th>Patients n</th>
<th>Mean age ± SEM</th>
<th>Mean fragments of ovarian tissue (range)</th>
<th>Oocytes retrieved n (range)</th>
<th>Mean oocytes retrieved /fragment</th>
<th>Mean oocytes retrieved /patients</th>
<th>Stage at collection (%)</th>
<th>IVM rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>11</td>
<td>23.1 ± 1.3</td>
<td>20.1 (10-29)</td>
<td>38 (0-9)</td>
<td>0.17 ± 0.07(^a)</td>
<td>3.4 ± 1.06(^a)</td>
<td>71%</td>
<td>42.1%</td>
</tr>
<tr>
<td>Natural cycle FP</td>
<td>19</td>
<td>26.3 ± 1.5</td>
<td>21.6 (7-32)</td>
<td>69 (0-15)</td>
<td>0.17 ± 0.06(^a)</td>
<td>3.6 ± 1.09(^a)</td>
<td>80%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Natural cycle LP</td>
<td>16</td>
<td>27.9 ± 1.1</td>
<td>18.1 (12-26)</td>
<td>44 (0-13)</td>
<td>0.15 ± 0.05(^a)</td>
<td>2.8 ± 0.83(^a)</td>
<td>84%</td>
<td>39.5%</td>
</tr>
<tr>
<td>Post-partum</td>
<td>5</td>
<td>31 ± 2.2</td>
<td>26.3 (16-36)</td>
<td>33 (1-12)</td>
<td>0.23 ± 0.12(^a)</td>
<td>6.6 ± 1.86</td>
<td>91%</td>
<td>28.1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>29.5 ± 0.5</td>
<td>20-32</td>
<td>8 (0-8)</td>
<td>0.15 ± 0.26</td>
<td>4</td>
<td>100%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>4</td>
<td>9.2 ± 1.4</td>
<td>31.7 (17-40)</td>
<td>46 (2-22)</td>
<td>0.36 ± 0.28(^b)</td>
<td>11.5 ± 4.27(^b)</td>
<td>93%</td>
<td>23.9%</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>26 ± 0.9</td>
<td>21.8 (7-40)</td>
<td>238 (0-22)</td>
<td>0.19</td>
<td>4</td>
<td>84%</td>
<td>31%</td>
</tr>
</tbody>
</table>

- Oocytes were retrieved regardless of menstrual cycle period or contraception

Fasano, Reprod Biol Endocrinol. 2011
Fertility preservation in BRCA1 positive breast cancer patients

• A possible negative impact of subsequent conception on breast cancer survivors – «not demonstrated»
• Coexistence of an ovarian cancer
• PGD to avoid transmitting BRCA mutations
• Decreased ovarian reserve !! Deficient DNA repair make oocytes more vulnerable
## GnRHa Cotreatment during Chemo

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>Odds Ratio (95% CI)</th>
<th>Events, Treated</th>
<th>Events, Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilani^</td>
<td>2007</td>
<td>0.06 (0.00, 1.24)</td>
<td>0/15</td>
<td>5/15</td>
</tr>
<tr>
<td>Badawy</td>
<td>2009</td>
<td>0.06 (0.02, 0.20)</td>
<td>4/39</td>
<td>26/39</td>
</tr>
<tr>
<td>Sverrisdottir_1</td>
<td>2009</td>
<td>0.19 (0.04, 1.06)</td>
<td>14/22</td>
<td>18/20</td>
</tr>
<tr>
<td>Sverrisdottir_2</td>
<td>2009</td>
<td>2.03 (0.31, 13.27)</td>
<td>27/29</td>
<td>20/23</td>
</tr>
<tr>
<td>Behringer*</td>
<td>2010</td>
<td>0.67 (0.08, 5.30)</td>
<td>7/10</td>
<td>7/9</td>
</tr>
<tr>
<td>Del Mastro</td>
<td>2011</td>
<td>0.25 (0.12, 0.52)</td>
<td>11/139</td>
<td>31/121</td>
</tr>
<tr>
<td>Gerber</td>
<td>2011</td>
<td>0.56 (0.19, 1.62)</td>
<td>9/30</td>
<td>13/30</td>
</tr>
<tr>
<td>Demeestere*</td>
<td>2012</td>
<td>1.14 (0.38, 3.42)</td>
<td>9/45</td>
<td>7/39</td>
</tr>
<tr>
<td>Munster</td>
<td>2012</td>
<td>1.24 (0.19, 8.20)</td>
<td>3/26</td>
<td>2/21</td>
</tr>
<tr>
<td>Elgindy_1</td>
<td>2013</td>
<td>0.75 (0.15, 3.79)</td>
<td>3/23</td>
<td>4/24</td>
</tr>
<tr>
<td>Elgindy_2</td>
<td>2013</td>
<td>0.63 (0.10, 4.21)</td>
<td>2/23</td>
<td>3/23</td>
</tr>
<tr>
<td>M-H Overall</td>
<td></td>
<td>0.36 (0.25, 0.53)</td>
<td>89/401</td>
<td>136/364</td>
</tr>
<tr>
<td>Random Effect Pooled OR</td>
<td></td>
<td>0.43 (0.22, 0.84)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wang C, Plos One 2013
GnRHa Cotreatment during Chemo
Spontaneous menstruation

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sverrisdottir (2009A)</td>
<td>4.95 (0.95, 25.86)</td>
<td>9.20</td>
</tr>
<tr>
<td>Sverrisdottir (2009B)</td>
<td>0.50 (0.08, 3.18)</td>
<td>7.83</td>
</tr>
<tr>
<td>Badawy (2009)</td>
<td>14.54 (4.62, 45.78)</td>
<td>13.95</td>
</tr>
<tr>
<td>Del Mastro (2011)</td>
<td>3.06 (1.69, 5.54)</td>
<td>21.49</td>
</tr>
<tr>
<td>Gerber (2011)</td>
<td>1.78 (0.62, 5.17)</td>
<td>14.96</td>
</tr>
<tr>
<td>Munster (2012)</td>
<td>0.91 (0.18, 4.57)</td>
<td>9.48</td>
</tr>
<tr>
<td>Li mingyi (2008)</td>
<td>3.26 (1.13, 9.43)</td>
<td>14.97</td>
</tr>
<tr>
<td>Sun jingbo (2011)</td>
<td>2.67 (0.43, 16.39)</td>
<td>8.10</td>
</tr>
<tr>
<td>Overall (I-squared = 51.0%, p = 0.046)</td>
<td>2.83 (1.52, 5.25)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Del Mastro, Cancer Treat Reviews, 2014
GnRHa Cotreatment during Chemo
Ovarian reserve

- One trial showed higher anti-Müllerian hormone levels (improved ovarian reserve) after use of a GnRH agonist (1.4 ± 0.35 versus 0.5 ± 0.15 ng/mL in untreated controls)
- After 1 year follow up 20% of patients in each group developed POF, «showing no evidence of ovarian protection»
GnRHa Cotreatment during Chemo Concerns

- Normality of offspring – DNA breaks during chemo (Down Syndrome)
- Increased gonadodotoxicity by decreasing the effect of detoxifying enzymes – GST
- Extrapituitary GnRH receptors
  - Antigonadotropin, antiproliferative, antiapoptotic effects
  - Possible reduction of chemo effect on breast cancer
- Definition of ovarian failure is heterogeneous
- No study showed increased fertility

Sonmezer & Oktay, The Oncologist, 2007
Conclusions - I

- Patients should be referred as early as possible to increase the success rate of FP
- In an emergent setting, random start COH can be safely and effectively performed
- Breast cancer recurrence risk seems not increased following Letrozole-IVF
Conclusions - II

- Ovarian tissue cryopreservation appears safe in early stage breast cancer
- Ovarian tissue cryopreservation can be performed along with COH-embryo/oocyte cryopreservation
- The possibility of dormant tumor cell growth should be considered in ER dependent breast cancer following ovarian transplantation
- More data establishing the safety of ovarian suppression in cancer patients and its long-term efficacy in preserving fertility (not just resumption of menses) are needed.