Lebanese International Fertility Summit

2 – 3 October 2015
Hilton Beirut Habtoor Grand
VF protocols in women with breast cancer & BRCA 1-2 mutations

JN Hugues, M.D., Ph.D.
Department of Reproductive Medicine
In the US

Siegel et al., CA Cancer J Clin 2014

810,000 new cases of cancer in 2014

Breast cancer: 29% (235,000)

5% in females on reproductive age

5,250 women 30-40 yrs are diagnosed each year.

In France

0 new cases of breast cancer each year in women < 35 yrs
Breast cancer survival rate

Desantis 2013 US

The 5-year relative survival rate

- 74% to 82% in France, Italy, and The Netherlands
- 66% to 76% in Spain, Estonia, and the U.K.

Differences in stage at diagnosis and treatment.

Sant 2004 Europe

The overall 5-year relative survival rate improved from 74.8% (1975-1977) to 90.3% (2003-2009).

Death decrease: 1.9% per year from 2001 to 2010.

Improvement of treatment & Earlier diagnosis

Desantis 2013 US

The 10-year relative survival: 83.1%

The 15-year relative survival: 77.8%

Mortality
Age of first pregnancy ↑ 30 years in France

Survivors more concerned about future fertility than age and gravidity matched women

30% less toxic chemotherapy to help preserve fertility even at risk of increased cancer recurrence
General population: no risk of recurrence or death

Largillier et al., Cancer.2009

General population: even a protective effect

Rajkumar et al., PNAS 2001
Coll Study et al., Lancet 2002
Sankila et al., Cancer.2009
Pagani et al., Breast Cancer Res 2001

In patients with BRCA mutations: risk of developing a cancer

• Protective effect
  
Coll Study et al., Lancet 2002
Andrieu et al., J Natl Cancer Inst 1999

• Unprotective effect
  
Jernstrom et al., Lancet 1999
Cullinane et al., IJ Cancer 2006

• Reassuring data on the use of medications
  
Milne et al., Breast Cancer Res 2010
Dramatic decline of fecundity per cycle after 35 years

Diagnosis of breast cancer

Broekmans et al., Endocrine Reviews 2009

ASCO guidelines: Tamox for 10 yrs
Diminished ovarian reserve and response to FSH in women with BRCA 1 mutations

- Low ovarian response (33.3 % vs 3.3%)
- Lower level of AMH
- Higher doses of gonadotrophins
- Lower yield of oocytes (7.4 vs 12.4)

Earlier menopause

Some women with BRCA 1 mutations with reproductive life span 2 – 4 yrs shorter
The « Telomer theory of reproductive senescence »

BRCA genes involved in telomere repair and determinants of reproductive lifespan (Apoptosis IId to telomere shortening, spindle disruption, decreased formation of chiasmata, aneuploidy)

Survey of 2.254 BRCA + vs 764 controls

Pal et al., Fertil Steril 2010

The fertility experience of BRCA mutation carriers is similar to that of noncarriers.

There were no differences in age at first birth, age at last birth
Gonadal toxicity of treatments

Vascular damage

Ovarian tissue fibrosis

Follicular activation: burn-out

Follicular activation: burn-out

Direct ovarian toxicity

Vascular toxicity

Alkylation agents
Platinum compounds
Anthracyclins

Anthracyclins
Platinum compounds?
Bevacizumab?

Cellular effects

Cytoskeleton
DNA
Oxidative stress

Taxanes?
Anthracyclins
Platinum
Anthracyclins
Platinum compounds
Alkylation agents

Imatinib
Predicting ovarian function after cancer treatments remains a challenge.

- **Age**
- **Type of cancer**
- **Ovarian follicular status**
- **Sensitivity / chemo**
- **Chemotherapy regimens**
- **Doses of chemo**
All women with AMH < 1.9 ng/ml became amenorrheic.

*AMH can predict long-term ovarian activity after chemotherapy*

Women with ongoing menses had higher AFC.
Incidence of pregnancies

- 8% in women < 35 years (Blakely et al., Cancer 2004)
- 6% in women < 40 years (Oven Ustaalioglu et al., J BUON)
- 3% in women < 45 years (Mueller et al., Cancer 2004)
- 173 live births in 5725 women < 45 years (3%)
Ovarian tissue cryopreservation

Oocyte cryopreservation

Embryo cryopreservation

Medical treatments

Early referral for Fertility Preservation
**Primordial**

**Initial recruitment**

**Secondary**

**FSH**

**Cyclic recruitment**

**Antral**

**Preovulatory**

**Atretic**
Exogenous FSH administration

Serum E2 levels ↑↑

Preovulatory follicles

About 10 days

Controlled ovarian hyperstimulation
GnRH antagonists 0.25 mg/d

Exogenous FSH

From early follicular phase
Random start protocols

Principle: multiples waves of follicular development

Initiation of ovarian stimulation in luteal phase

- After luteolysis induced by GnRH antagonist, stimulation with FSH
GnRH antagonists 0.25 mg/d

Exogenous FSH

hCG

Number of oocytes collected after initiation of ovarian stimulation in the follicular (n = 28) and luteal (n = 12) phase.

**Issue of Estrogen exposure**

Increased E2 levels: at risk of proliferation & dissemination of breast cancer cells?

No evidence short-term E2 exposure is detrimental

Consensus to discourage traditional COH regimen

**Suggestions**

Natural cycles: low oocyte yield

*Tamoxifen*: Selective Estrogen Receptor Modulator (competitive estrogen antagonist)

*Letrozole*: Competitive Inhibitor of the Aromatase enzyme complex
Tamoxifen

Tamox is for women with ER (+) starting after stimulation when E2 levels rise at the time GnRH antagonist is used with long GnRH agonist (no short flare-up agonist).

- 8 cycles with ER (+): co-treatment Tamox 20 mg/J
- 8 cycles with ER (-): without Tamox
Tamoxifen

No significant difference in the oocyte and embryo number in Tamox (+) and (-) whatever the GnRH analog protocol used.

Higher E2 serum values in Tamox (+) treated women.
But long term (3-10 yrs): no increase in cancer recurrence or mortality.
Ovarian stimulation

Aromatase Inhibitors

Oktay et al., J. Clin. Oncol. 2005

Exogenous FSH

GnRH antagonists

Letrozole 5 mg

Start from early follicular phase

hCG
<table>
<thead>
<tr>
<th>Number&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Breast cancer patients&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>Oocytes (M2 oocytes)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>2PN Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cancer</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Oocyte yield</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jun et al. [36]</td>
<td>26</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Jun et al. [20]</td>
<td>22</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Jun et al. [37]</td>
<td>50</td>
<td>11.5 (9.6)</td>
<td>13 (9.7)</td>
</tr>
<tr>
<td>Jun et al. [21]</td>
<td>38</td>
<td>12 (9)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Jun et al. [19]</td>
<td>50</td>
<td>12.4 (9)</td>
<td>11.7 (8.9)</td>
</tr>
<tr>
<td>Jun et al. [22]</td>
<td>63</td>
<td>12.4</td>
<td>10.9</td>
</tr>
<tr>
<td><strong>A poorer yield of oocytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jun et al. [38]</td>
<td>28</td>
<td>10</td>
<td>13.9</td>
</tr>
<tr>
<td>Jun et al. [39]</td>
<td>208</td>
<td>10.5 (7.8)</td>
<td>12.4 (9.5)</td>
</tr>
</tbody>
</table>

- Domingo et al., FS 2012
- Friedler et al., FS 2012
- Chung et al., FS 2013
- Garcia-Velasco et al., FS 2013

- A poorer yield of oocytes
- A similar yield of oocytes
### IVF Results in Women with BRCA Mutations

**Superior reproductive performance in BRCA mutation carriers**

<table>
<thead>
<tr>
<th>Number</th>
<th>Patients diagnosis</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>2245</td>
<td>Breast cancer, non-cancer</td>
<td>Parity, Infertility, Age at first birth</td>
</tr>
<tr>
<td>181</td>
<td>Non-cancer</td>
<td>Parity</td>
</tr>
<tr>
<td>908</td>
<td>Non-cancer</td>
<td>Parity, Use of infertility drugs, Fertility problems</td>
</tr>
<tr>
<td>829</td>
<td>Non-cancer</td>
<td>Age at menopause</td>
</tr>
<tr>
<td>1426</td>
<td>Breast cancer</td>
<td>Risk for amenorrhea post chemotherapy</td>
</tr>
<tr>
<td>43</td>
<td>Non-cancer</td>
<td>AMH Levels</td>
</tr>
<tr>
<td>1236</td>
<td>Breast cancer, non-cancer</td>
<td>Age at menopause</td>
</tr>
<tr>
<td>13</td>
<td>Non-cancer</td>
<td>IVF performance</td>
</tr>
</tbody>
</table>

**Reproductive performance in BRCA mutation carriers**

<table>
<thead>
<tr>
<th>Number</th>
<th>Patients diagnosis</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>Breast cancer</td>
<td>Age at menopause</td>
</tr>
<tr>
<td>12</td>
<td>Breast cancer</td>
<td>IVF performance</td>
</tr>
<tr>
<td>382</td>
<td>Non-cancer</td>
<td>Age at menopause</td>
</tr>
<tr>
<td>908</td>
<td>Non-cancer</td>
<td>Age at menopause</td>
</tr>
<tr>
<td>24</td>
<td>Breast cancer</td>
<td>AMH levels</td>
</tr>
<tr>
<td>143</td>
<td>Non-cancer</td>
<td>AMH levels</td>
</tr>
<tr>
<td></td>
<td>BRCA(+) [n=20]</td>
<td>BRCA(−) [n=36]</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Age</td>
<td>32.40±3.86</td>
<td>33.94±5.48</td>
</tr>
<tr>
<td>Fertilization start on days</td>
<td>10.54±2.37</td>
<td>9.92±1.56</td>
</tr>
<tr>
<td>LH-assisted protocol (%)</td>
<td>52.94 %</td>
<td>61.76 %</td>
</tr>
<tr>
<td>HMG-antagonist protocol (%)</td>
<td>47.06 %</td>
<td>38.24 %</td>
</tr>
<tr>
<td>Peak LH (pmol/L)</td>
<td>6255±4875</td>
<td>6306±4150</td>
</tr>
<tr>
<td>Oocytes collected</td>
<td>11.50±6.63</td>
<td>11.69±7.23</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>8.4±6.39</td>
<td>7.19±5.21</td>
</tr>
<tr>
<td>Cervical mucus harvest rate (%)</td>
<td>70.6 %</td>
<td>59.66 %</td>
</tr>
</tbody>
</table>

Shapira et al., JARG 2015

The table above presents the fertilization rate & oocytes in BRCA (+) vs (-) women with breast cancer. Similar outcomes were observed.
Women with breast cancer stage ≤ 3 who underwent ovarian stimulation and cryopreserved embryos for fertility preservation (N = 131)

Have not yet returned (n = 98)

Returned to undergo 40 FETs (n = 33)

Underwent FET to self (18 FETs) (n = 18)
- 9 deliveries
- 11 children born

Underwent FET to gestational carrier (22 FETs) (n = 15)
- Underwent FET once (n = 8)
  - 6 deliveries
  - 10 children born
- Underwent FET twice (n = 7)
  - 3 deliveries
  - 4 children born
Succes of frozen embryo transfer in women with Breast Cancer

Oktay et al., J. Clin. Oncol. 2015

Mean age at cryopreservation: 36.6 +/- 4 yrs
Mean number of embryos cryopreserved: 6.5 +/- 4.9
Post thaw survival rate: 84.4%

Return for FET at a median 5.25 yrs
- Self transfer: 65.3 +/- 14.3 months
- Gestational carrier: 45.3 +/- 17.4 months

<table>
<thead>
<tr>
<th>Sex</th>
<th>FP Group</th>
<th>Infertility Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex transferred</td>
<td>40</td>
<td>1.97 ± 0.7</td>
</tr>
<tr>
<td>rate†</td>
<td>33 of 81 (40.7)</td>
<td>(26.1)</td>
</tr>
<tr>
<td>After embryo transfer</td>
<td>7 of 18 (38.8)</td>
<td>(27.4)</td>
</tr>
</tbody>
</table>

Success rate similar to classical COH in infertile population
**Triggering of ovulation**

GnRH agonist used to trigger in GnRH antagonist protocols

*Oktay et al., RBM 200*

**Pre-implantation Genetic Diagnosis**

Emotional support, during the decision-making process as well as afterwards, should be actively offered to all couples, including those refraining from PGD

*Derks-smeets et al., HRU 2014*
1. Breast cancer is frequent in the young population

2. Young breast cancer patients show concerns regarding future fertility and ask for fertility preservation

3. Pregnancy is safe after breast cancer

4. Due to gonadotoxicity of chemotherapy, fertility preservation should be offered to every women < 40 yrs

5. IVF treatment of breast cancer patients is experimental and should only be done under institutional review board-approved protocols

6. IVF stimulation for embryo cryopreservation is effective and safe. Aromatase inhibitors are promising to reduce high E2 exposure

7. Patients with BRCA mutations require specific counselling