Physicians Attitudes and Knowledge about Fertility Preservation

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Disclosure Information
Relationship Relevant to this Session

Lambertini, Matteo:

• Consultant or advisor: Teva
• Honoraria: Theramex
Outline

• Introduction

• Attitudes and knowledge about:
  - Embryo/oocyte cryopreservation
  - Cryopreservation of ovarian tissue
  - Temporary ovarian suppression with GnRHa during chemotherapy

• Attitudes and knowledge about fertility preservation in advanced breast cancer

• Conclusions
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Fertility and Pregnancy-related Issues: Young Women Advocates Statement

“Fertility and pregnancy-related issues are one of the five priority areas of concern for young women with breast cancer”
Oncofertility Counseling is Mandatory As soon as Possible after Diagnosis

**ESMO GUIDELINES 2013**

Young women desiring future fertility should be counselled on available fertility preserving options before starting anticancer treatments. Counseling should be implemented soon after diagnosis, to allow prompt referral to fertility specialists [IV, B].

**ASCO GUIDELINES 2018**

Recommendation 1.1. People with cancer are interested in discussing fertility preservation. Health care providers caring for adult and pediatric patients with cancer (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons, and others) should address the possibility of infertility as early as possible before treatment starts.

Physicians Attitudes and Knowledge about Fertility Preservation

A BCY3/ BCC 2017 survey on physicians’ knowledge, attitudes and practice on fertility and pregnancy issues in young breast cancer patients

Fertility preservation

- 12.1% Yes
- 24.9% No, but I know where to find it
- 63.0% Not aware

Lambertini M et al, Breast 2018;42:41-9
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• Conclusions
Embryo/Oocyte Cryopreservation Available Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Year</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESMO</strong></td>
<td>2013</td>
<td>Embryo or oocyte cryopreservation is the main method to preserve female fertility. Ovarian stimulation should be carried out before commencing chemotherapy.</td>
</tr>
<tr>
<td><strong>ASCO</strong></td>
<td>2018</td>
<td>Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization. Cryopreservation of unfertilized oocytes is an option, and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing.</td>
</tr>
</tbody>
</table>

Embryo/Oocyte Cryopreservation: Efficacy Data

**Embryo cryopreservation**
Prospective single-center cohort study
n=131 breast cancer patients

- Women with breast cancer stage ≤ 3 who underwent ovarian stimulation and cryopreserved embryos for fertility preservation (N = 131)
- 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
  - Underwent FET twice (n = 7)
    - 3 deliveries

**Pregnancy rate = 20/33 (61%)**

**Oocyte cryopreservation**
Prospective multicenter cohort study
n=618 breast cancer patients

- Have not yet returned (n = 98)
- Returned to undergo 40 FETs (n = 33)
- Underwent FET (n = 38)
- 33/131 (25%)
- 38/618 (6%)

**Pregnancy rate = 13/38 (34%)**

Embryo/Oocyte Cryopreservation: Safety Concerns

A BCY3/ BCC 2017 survey on physicians’ knowledge, attitudes and practice on fertility and pregnancy issues in young breast cancer patients

Controlled ovarian stimulation should be considered safe in all patients

Controlled ovarian stimulation should not be considered safe in patients:

- With hormone receptor-positive disease
- Candidates to neoadjuvant chemotherapy

22% of respondents agreed
18% of respondents agreed

Lambertini M et al, Breast 2018;42:41-9
Embryo/Oocyte Cryopreservation: Safety Data

Prospective single-center cohort study
n=120 FP & n=217 no FP

Retrospective cohort study (Swedish registry)
n=188 FP & n=378 no FP

Retrospective single-center cohort study
n=114 FP & n=148 no FP

Relapse-free survival

Recurrence
Mortality

Kim J et al, J Clin Endocrinol Metab 2016;101(4):1364-71

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Embryo/Oocyte Cryopreservation: Safety Data

Hormone-receptor status

Timing of chemotherapy administration

Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies.

Fertility preservation success subsequent to concurrent aromatase inhibitor treatment and ovarian stimulation in women with breast cancer.

Fertility preservation with ovarian stimulation and time to treatment in women with stage II–III breast cancer receiving neoadjuvant therapy.
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Ovarian Tissue Cryopreservation
Updated Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Year</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO</td>
<td>2013</td>
<td>Ovarian tissue cryopreservation is still considered experimental, but remains a unique option for young girls with cancer</td>
</tr>
<tr>
<td>ASCO</td>
<td>2018</td>
<td>Ovarian tissue cryopreservation remains experimental. However, emerging data may prompt reconsideration of this designation in the future (this technique is already considered non-experimental in some countries, and its experimental status is undergoing evaluation in the United States)</td>
</tr>
</tbody>
</table>

Ovarian Tissue Cryopreservation

Knowledge

Prescription

Availability
### Ovarian Tissue Cryopreservation Efficacy Data

**Diagnosis of breast cancer**

- **Breast cancer treatment:**
- **16 ovarian transplants**
- **14 pregnancies**
- **3 failures**
- **11 births**

**2004**

- **2 recurrences**
- **0 metastasis**
- **0 death**

**2006**

![Diagram showing ovarian tissue cryopreservation efficacy data](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OV (n = 38)</th>
<th>OCT (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status of patient at reimplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea &gt;1 y</td>
<td>5 (13.2)</td>
<td>11 (35.5)</td>
<td>NS</td>
</tr>
<tr>
<td>POI without amenorrhea</td>
<td>30 (78.9)</td>
<td>19 (61.3)</td>
<td></td>
</tr>
<tr>
<td>Regular menstruations</td>
<td>3 (7.9)</td>
<td>1 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Age at retrieval, y</td>
<td>35.5 (3.1)</td>
<td>35.8 (3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at reimplantation, y</td>
<td>40.0 (3.3)</td>
<td>41.0 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>AMH before reimplantation, pM</td>
<td>0 [0–1.33]</td>
<td>0 [0–0]</td>
<td>NS</td>
</tr>
<tr>
<td>No. of pregnant patients</td>
<td>13 (34.2)</td>
<td>5 (16.1)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients with live births</td>
<td>11 (28.9)</td>
<td>2 (6.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Ovarian Tissue Cryopreservation Safety Data

Risk of malignant contamination appears to be low in breast cancer patients

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Type of studies</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Number of patients</td>
<td>13</td>
<td>69</td>
<td>51</td>
<td>9</td>
<td>94</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Average age</td>
<td>nk</td>
<td>32.8</td>
<td>31</td>
<td>nk</td>
<td>32.1</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>BRCA mutation</td>
<td>nk</td>
<td>0</td>
<td>nk</td>
<td>nk</td>
<td>nk</td>
<td>nk</td>
<td>nk</td>
</tr>
</tbody>
</table>

**Evaluation methods**

- Histology: yes, yes, yes, yes, yes, yes, yes
- Immunohistochemistry: yes, yes, no, no, no, yes, yes
- Molecular biology: no, no, no, no, no, yes, yes
- In vivo study: no, no, no, yes, yes, yes, no

**Results**

- Cancerous cells in the ovarian transplant: 0, 0, 0, 0, 0, 0, 0
- Local recurrence: na, na, na, 1, na, 0, na

Fleury A et al, J Gynecol Obstet Hum Reprod 2018; [Epub ahead of print]
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# Ovarian Suppression with GnRHa during CT

## Updated Guidelines

<table>
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</thead>
<tbody>
<tr>
<td>ESO-ESMO BCY3</td>
<td>2017</td>
<td>GnRHa <strong>should be discussed</strong> as an option with all patients interested in potentially preserving fertility and/or ovarian function who are candidates for chemotherapy, irrespective of tumor subtype</td>
</tr>
<tr>
<td>AIOM</td>
<td>2017</td>
<td>GnRHa during chemotherapy <strong>should be recommended</strong> to all pre-menopausal breast cancer patients undergoing chemotherapy who are interested in ovarian function and/or fertility preservation</td>
</tr>
<tr>
<td>ASCO</td>
<td>2018</td>
<td>When proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa <strong>may be offered</strong> to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. GnRHa <strong>should not</strong> be used in place of proven fertility preservation methods.</td>
</tr>
</tbody>
</table>

**Updated ESMO and ESHRE guidelines are upcoming**

Ovarian Suppression with GnRHa during CT

Knowledge

Prescription

Availability

Lambertini M et al, Breast 2018;42:41-9
Ovarian Suppression with GnRHa during CT Efficacy Data

Premature Ovarian Insufficiency (POI)

- OR* 0.38 (95% CI 0.26-0.57)
  p<0.001

- 14.1% in GnRHa group
- 30.9% in Control group

Post-Treatment Pregnancies

- GnRHa Group: 37/359 (10.3%)
- Control Group: 20/367 (5.5%)

- IRR* 1.83 (95% CI 1.06-3.15)
  p=0.030

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Ovarian Suppression with GnRHa during CT Safety Data

**ER+**

**Disease-Free Survival**
- HR 1.17; 95% CI 0.62-2.20

**Overall Survival**
- HR 0.79; 95% CI 0.24-2.59

**ER-**

**Disease-Free Survival**
- HR 0.95; 95% CI 0.64-1.42

**Overall Survival**
- HR 0.65; 95% CI 0.39-1.07

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Physicians Attitudes and Knowledge about Fertility Preservation in Advanced Breast Cancer

How often do you discuss the possible treatment-related loss of ovarian function and fertility in young breast cancer patients before starting anticancer therapies?

Stage I-III Patients (n=139)
- Always: 71%
- Usually: 21%
- Sometimes: 2%
- Rarely: 1%
- Never: 5%

Stage IV Patients (n=132)
- Always: 34%
- Usually: 23%
- Sometimes: 20%
- Rarely: 20%

Courtesy of S. Paluch-Shimon
Physicians Attitudes and Knowledge about Fertility Preservation in Advanced Breast Cancer

Reasons for NOT discussing fertility preservation with women with ABC?

I feel it irresponsible towards future children who may end up orphaned from their mother 45%

Future pregnancy is not safe in this clinical setting 42%

Fertility preservation and future pregnancy in this clinical setting is irrelevant therefore I have no obligation to discuss this with the patient 18%

Fertility preservation is not safe in this clinical setting 17%

Courtesy of S. Paluch-Shimon
**Fertility preservation in advanced breast cancer**

**Current recent guidelines**

<table>
<thead>
<tr>
<th>Guideline statement</th>
<th>LoE/GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fertility preservation:</strong> the impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).</td>
<td>Expert opinion/ B</td>
<td>100%</td>
</tr>
</tbody>
</table>

Cardoso F et al, Ann Oncol 2018;29(8):1634-57
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Conclusions

- Fertility preservation and pregnancy-related issues are priority areas of concern for young breast cancer patients
- As early as possible after diagnosis, a proper oncofertility counseling is mandatory to inform all women irrespectively of the stage of their disease
- Embryo/oocyte cryopreservation are standard options for fertility preservation
- Ovarian tissue cryopreservation remains experimental in most of the countries but may be discussed in specific circumstances
- Temporary ovarian suppression with GnRHa during chemotherapy should now be considered an available option to preserve ovarian function and potential fertility in young breast cancer patients (but not an alternative to cryopreservation techniques)
- Improving physicians awareness and education in this field is crucial as well as strengthening the collaboration between oncologists and fertility specialists