Gynecological Issues in Breast Cancer Patients
Gynecologic Issues in Breast Cancer Patients

- **Versions 2015-2017:**
  Loibl / Gerber / Albert / Bauerfeind / Fersis / Thill / Hanf / Scharl

- **Version 2018:**
  Maass/Witzel
Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

- **Endocrine responsive disease (receptor pos.)**
  - Oxford: 1b
  - LoE: B
  - GR: -

- **Endocrine non-responsive disease (receptor neg.)**
  - Oxford: 3b
  - LoE: D
  - GR: +/-

- **Endocrine responsive disease (receptor pos.): combined treatment TAM plus low-dose-HT**
  - Oxford: 2b
  - LoE: B
  - GR: +/-

- **Tibolone**
  - Oxford: 1b
  - LoE: A
  - GR: -

- **Topical vaginal application of**
  - Estriol (E3 0.03 mg as treatment course*)
    - Oxford: 4
    - LoE: D
    - GR: +/-
  - Estradiol (E2) during AI therapy
    - Oxford: 4
    - LoE: C
    - GR: -

* course: 4 weeks daily 1x1, further 8 weeks: 3 x 1 per week
Further Medical Approaches to Reduce Menopausal Symptoms I

### Medical approaches:

- **Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients**
  - 1<sup>st</sup> choice: venlafaxine
  - 2<sup>nd</sup> choice: desvenlafaxine
  - 3<sup>rd</sup> choice: sertraline, escitalopram

- **Gabapentin (patients using TAM)**

- **Pregabalin**

- **Clonidine (patients using TAM)**

- **MPA (i.m. 500 mg single shot)**
  (most potent, but endocrine agent!)

- **Vitamin E**

- **Melatonin (improvement in sleep quality)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>1b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>Sertraline, escitalopram</td>
<td>1b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>Gabapentin (TAM)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>1b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>Clonidine (TAM)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>MPA (500 mg single shot)</td>
<td>1b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>1b</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>Melatonin</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>
While anti-cancer treatment:
Beware of drug interactions!

- **Soy-derived phytoestrogens – isoflavonoids**
  - Hot flush
  - Sleep disturbance
  - Topical vaginal application
  - LoE: 1b, GR: B, AGO: -

- **Red Clover isoflavonoids**
  - Hot flush, sleep disturbance
    (might stimulate BC especially in endocrine responsive disease)
  - LoE: 1b, GR: B, AGO: +/-

- **Flaxseed-supplementation** (40 g/d) (in HR+ ≤ 10 g/d)
  - (reduces relapses, no effect on hot flashes)
  - LoE: 2b, GR: B, AGO: +/-

- **Black Cohosh for hot flushes**
  - LoE: 1b, GR: B, AGO: -

- **Black cohosh + St. John's Wort**
  - LoE: 1b, GR: B, AGO: +/-

- **St. John’s Wort**
  - (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)
  - LoE: 1b, GR: B, AGO: +/-

- **Ginseng root** (Panax ginseng or P. quinquefolius)
  - LoE: 1b, GR: B, AGO: -

- **Bromelain + Papain + Selenium + Lektin** (for AI induced joint symptoms)
  - LoE: 3b, GR: B, AGO: +
## General Approaches to Reduce Menopausal Symptoms III
### Integrative Oncology Aspects

### General approaches:

- **Physical exercise**
  - Oxford LoE: 1b
  - Oxford GR: B
  - AGO: ++

- **Mind body-medicine**
  - (yoga, hypnosis, education, counseling)
  - Oxford LoE: 1b
  - Oxford GR: B
  - AGO: +

- **Cognitive behavioral therapy (CBT)**
  - Oxford LoE: 1b
  - Oxford GR: B
  - AGO: ++

- **Acupuncture**
  - Aromatase-inhibitor treatment induced arthralgia
  - Oxford LoE: 1b
  - Oxford GR: B
  - AGO: +
  - Hot flashes
    - Oxford LoE: 1a
    - Oxford GR: B
    - AGO: +/-
  - Depression
    - Oxford LoE: 2b
    - Oxford GR: B
    - AGO: +/-
  - Anxiety, Sleep
    - Oxford LoE: 3b
    - Oxford GR: C
    - AGO: +/-
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (neo)-Adjuvant Chemotherapy (CT)

- **CT + GnRHa**  
  (preserve ovarian function)  
  (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status)  
  **Oxford**  
  LoE: 1a  
  GR: B  
  AGO: +

- **CHT + GnRHa**  
  (preserve fertility)  
  **Oxford**  
  LoE: 2a  
  GR: B  
  AGO: +/-

- **Fertility preservation counselling**  
  **Oxford**  
  LoE: 4  
  GR: C  
  AGO: ++

- **Fertility preservation using assisted reproduction therapy (ART)**  
  (further information www.fertiprotect.de)  
  **Oxford**  
  LoE: 4  
  GR: C  
  AGO: +
### Ovarieller Funktionserhalt –
**Synopse der randomisierten Studien**

<table>
<thead>
<tr>
<th></th>
<th>ZORO</th>
<th>PROMISE</th>
<th>Munster et al. - US</th>
<th>POEMS</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient number</strong></td>
<td>60 (60 HR-)</td>
<td>281 (50 HR-)</td>
<td>49 (13 HR-) of 124</td>
<td>218 (218 HR-)</td>
<td>227 (126 HR-)</td>
</tr>
<tr>
<td><strong>Age median</strong></td>
<td>38 years</td>
<td>39 years</td>
<td>39 years</td>
<td>Premenop. &lt; 50 years</td>
<td>premenopausal</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>goserelin</td>
<td>triptorelin</td>
<td>triptorelin</td>
<td>goserelin</td>
<td>goserelin</td>
</tr>
<tr>
<td><strong>Start of treatment</strong></td>
<td>&gt;2 weeks prior to cht</td>
<td>&gt;1 week prior to cht</td>
<td>&gt; 1 week prior to cht</td>
<td>&gt; 1 week prior to cht</td>
<td>&gt; 1 week prior to cht</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>menstruation at month 6 after chemotherapy</td>
<td>rate of early menopause at month 12 after cht</td>
<td>menstruation rate within 2 years after cht</td>
<td>Ovarian failure at 2 yrs after cht</td>
<td>Amenorrhea with elevated FSH levels between 12 and 24 months</td>
</tr>
<tr>
<td><strong>Primary objective</strong></td>
<td>to detect 30% absolute increase of menstruation rate</td>
<td>to detect at least 20% absolute reduction in early menopause</td>
<td>to detect 20% difference in amenorrhea rate – from 10% to 30%</td>
<td>To detect 20%-25% absolute reduction in early menopause</td>
<td></td>
</tr>
<tr>
<td><strong>Multivar. analysis</strong></td>
<td>age as only independent predictive factor</td>
<td>treatment as only independent predictive factor</td>
<td>n.d.</td>
<td>Treatment as only Independent predictive factor</td>
<td>Age, total cyclophosphamide dose and baseline AMH</td>
</tr>
<tr>
<td><strong>Resumption of menses at month 12</strong></td>
<td>83% with LHRH vs. 80% w/o</td>
<td>93% with LHRHa vs. 74% w/o</td>
<td>74% with LHRH vs. 68% w/o</td>
<td>78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%</td>
<td>78% with LHRHa vs. 62% amnorrhea rate between month 12 and 24</td>
</tr>
<tr>
<td><strong>Median time to restoration of menses (months)</strong></td>
<td>6.1 with LHRHa vs. 6.8 w/o; p=0.30</td>
<td>not reached with LHRH vs. 6.7 w/o; p=0.07</td>
<td>5.8 with LHRH vs. 5.0 w/o; p=0.58</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Cyclophosph. dose</strong></td>
<td>4600 vs. 4700mg</td>
<td>4080 vs. 4008 mg</td>
<td>n.r.</td>
<td>n.a.</td>
<td>5940 vs. 5940mg</td>
</tr>
</tbody>
</table>
Testing Ovarian Reserve

Assessment of ovarian reserve in infertile patients (> 6-12 months without conception)*

Tests for fertility assessment

- Anti-Müllerian Hormone
- Antral follicle count

Oxford

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* Tests are suggested for women > 35 yrs and infertility for 6-12 months; the tests do not predict failure to conceive. They should be used in counselling patients and provide a rough estimate of the fertility window. Results may decrease patient referral time to infertility centers.
Assessment of Ovarian Reserve

Tests recommended to assess ovarian reserve (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015;125:268-273)

<table>
<thead>
<tr>
<th>Test</th>
<th>Details</th>
</tr>
</thead>
</table>
| FSH (follicle stimulating hormone) plus estradiol | ▪ Serum level on cycle day 2–3  
▪ Variation between cycles possible  
▪ High FSH value is associated with poor response to ovarian stimulation |
| Anti Müllerian Hormone (AMH)                    | ▪ No specific timing for the test  
▪ Stable value within and between menstrual cycles  
▪ Low AMH value is associated with poor response to ovarian stimulation |
| Antral follicle count (AFC)                      | ▪ Number of visible follicles (2–10 mm) during transvaginal ultrasound  
▪ Performed on cycle days 2–5  
▪ Number of antral follicles correlates with ovarian response to stimulation |

The tests do not predict failure to conceive. They should be used in counselling patients and provide a rough estimate of the fertility window. Results may decrease patient referral time to infertility centers.
Contraceptive Options for Women after Diagnosis of Breast Cancer

- **Barrier methods**
- **Sterilization (tubal ligation / vasectomy)**
- **Non-hormonal intrauterine devices (IUDs)**
- **Levonorgestrel-releasing IUDs**
  - Removal in newly diagnosed patients
- **Timing methods**
- **Injectable progestin-only contraceptives**
- **Progestin-only oral contraceptives**
- **Combined oral contraceptives**
- **Emergency Contraception**
  - Copper intrauterine device (Cu-IUD)
  - Levonorgestrel, Ulipristal orally

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>
## Sexual Health

### Assessment of sexual dysfunction
- Oxford: LoE 5, GR C, AGO +

### Use of patient-reported questionnaires
- Oxford: LoE 4, GR C, AGO +

### Vaginal dryness:
- Non-hormonal lubricants / moisturizers
  - Oxford: LoE 1b, GR B, AGO +

### Fractionated microablative CO2-Laser / Vaginal Erbium:YAG-Laser
- Oxford: LoE 2b, GR B, AGO +/-

### Psychoeducational support, group therapy, sexual counseling, marital counseling, psychotherapy
- Oxford: LoE 1b, GR B, AGO +
Assessment of Sexual Health

- **Sexual Complaints Screener (SCS) for women**
  German Translation

**Screening-Check-Fragebogen: Overall Sexual Function**

1. Are you satisfied with your sexual life? yes, no; if no
2. How long have you been dissatisfied with your sexual life?
3. The problems with your sexual life are: (mark one or more):
   1. Problem with little or no interest in sex
   2. Problem with decreased genital sensation (feeling)
   3. Problem with decreased vaginal lubrication (dryness)
   4. Problem reaching orgasm
   5. Problem with pain during sex
   6. Other
4. Which problem is most bothersome? (circle) 1, 2, 3, 4, 5, 6.
5. Would you like to talk about it with your doctor?