Gynecological Issues in Breast Cancer Patients
Gynaecologic Issues in Breast Cancer Patients

Version 2015: Loibl / Gerber
(with contribution from Hanf / Kümmel und Stickeler / Scharl)
Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

- **Endocrine responsive disease**
  (HT may increase risk)

- **Endocrine non-responsive disease**
  (apparently no risk increase)

- **Endocrine responsive disease: combined treatment TAM plus low-dose-HT**

- **Tibolone**

- **Topical vaginal application of**
  - Estriol
  - Estradiol during AI therapy

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
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<tbody>
<tr>
<td>1b B -</td>
<td></td>
</tr>
<tr>
<td>2a B +/-</td>
<td></td>
</tr>
<tr>
<td>2b B +/-*</td>
<td></td>
</tr>
<tr>
<td>1b A - -</td>
<td></td>
</tr>
<tr>
<td>4 D +/-</td>
<td></td>
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<tr>
<td>4 C -</td>
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*Study participation recommended*
### Alternative Medical Approaches to Reduce Menopausal Symptoms

**Medical approaches:**

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

- **Gabapentin (BC and TAM-use)**

- **Pregabalin**

- **Clonidin (BC and TAM-use)**

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

- **Vitamine E**

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**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Medical approach</th>
<th>LoE</th>
<th>Grade</th>
<th>Notes</th>
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</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</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>Clonidin</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>MPA</td>
<td>1b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>1b</td>
<td>A</td>
<td>-</td>
</tr>
</tbody>
</table>
**“Herbal” Approaches to Reduce Menopausal Symptoms**

While anti-cancer treatment: Beware of drug interactions!

<table>
<thead>
<tr>
<th><strong>Herbal</strong> Approaches to Reduce Menopausal Symptoms</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy-derived phytoestrogens – isoflavonoids (might stimulate BC especially in endocrine responsive disease)</td>
<td>1b A -</td>
</tr>
<tr>
<td>Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses no effect on hot flashes)</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Black Cohosh for hot flushes</td>
<td>1b A -</td>
</tr>
<tr>
<td>Black cohosh + St.John´s Worth</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>St. John’s Wort (in combination-therap)y (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)</td>
<td>1b B --</td>
</tr>
<tr>
<td>Kava-Kava (Piper methysticum)</td>
<td>5 D --</td>
</tr>
<tr>
<td>Red Clover leaf (Trifolium pratense)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Dong Quai root (Angelica sinensis)</td>
<td>5 D --</td>
</tr>
<tr>
<td>Ginseng root (Panax ginseng or P. quinquefolius)</td>
<td>1b B -</td>
</tr>
<tr>
<td>Bromelain + Papain + Selen + Lektin (for, AI induced joint symptoms)</td>
<td>3b B +/-</td>
</tr>
</tbody>
</table>
Alternative General Approaches to Reduce Menopausal Symptoms after BC I

General approaches:

- Physical exercise
- Mind Body-medicine (yoga, hypnosis, education, counselling)
- Cognitive behavioral therapy (CBT)
- Acupuncture
  - Aromatase-inhibitor treatment induced arthralgia
  - Hot flashes
  - Depression
  - Anxiety, Sleep

(take note: no acupuncture in tumor bearing region, possibility of cell seeding)
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

- **Ovarian Function Protection**
- **CT + GnRHa** (Interaction with CT unclear)  
  (GnRHa application > 2 weeks prior to chemotherapy)  
  Oxford / AGO LoE / GR  
  | 1b | B | +/- |

Impairment of CT – effect cannot be excluded!

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

- **Fertility preservation with assisted reproduction therapy**  
  Oxford / AGO LoE / GR  
  | 4 | C | + |
# Ovarian Function Preservation – Comparison of Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>ZORO</th>
<th>PROMISE</th>
<th>Munster et al. - US</th>
<th>POEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>60 (60 HR-)</td>
<td>281 (50 HR-)</td>
<td>49 (13 HR-) of 124</td>
<td>218 (218 HR-)</td>
</tr>
<tr>
<td>Age median</td>
<td>38 years</td>
<td>39 years</td>
<td>39 years</td>
<td>Premenop. &lt; 50 years</td>
</tr>
<tr>
<td>Treatment</td>
<td>goserelin</td>
<td>triptorelin</td>
<td>triptorelin</td>
<td>goserelin</td>
</tr>
<tr>
<td>Start of treatment</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>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>menstruation at month 6 after chemotherapy</td>
<td>rate of early menopause at month 12 after chemotherapy</td>
<td>menstruation rate within 2 years after cht</td>
<td>Ovarian failure at 2 yrs after cht</td>
</tr>
<tr>
<td>Primary objective</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></td>
</tr>
<tr>
<td>Multivar. analysis</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>
</tr>
<tr>
<td>Resumption of menses at month 12 in HR- cohort</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>
</tr>
<tr>
<td>Median time to restoration of menses (months)</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>
</tr>
<tr>
<td>Cyclophosph. dose</td>
<td>4600 vs. 4700mg</td>
<td>4080 vs. 4008 mg</td>
<td>n.r.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

Vorteil GnRHa / Vorteil Kontrolle

nach Del Mastro et al. Cancer Treat Rev 2014
Assessment of ovarian reserve in infertile patients (>6-12 mths without conception)*

Tests for fertility assessment

- Anti-Müllerian Factor
- Antral follicle count

* Tests are suggested for women > 35 yrs and infertility for 6-12 months; the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated and infertility treatment may be considered.
Assessment of Ovarian Reserve

Tests recommended to assess ovarian reserved (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 |

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.
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

No trial included women after diagnosis of breast cancer, non-estrogen containing devices do not increase the risk to develop primary breast cancer.
No further information

No references
No further information

References:

- Endocrine responsive disease
  (HT may increase risk)
- Endocrine non-responsive disease
  (apparently no risk increase)
- Endocrine responsive disease: combined
treatment TAM plus low-dose-HT


- Tibolone:

Topical Vaginal Application:

**Alternative Medical Approaches to Reduce Menopausal Symptoms (4/12)**

**Further information:**

Menopausal symptoms are bothersome for breast cancer survivors and affect quality of life. Since hormonal replacement therapy should be avoided in ER positive breast cancer patients alternatives are important. In breast cancer patients treated with tamoxifen and menopausal symptoms the use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin is considered effective in treating hot flashes.(L'Espérance S, 2013) The use of paroxetine and fluoxetine should be avoided because the may reduce the efficacy of tamoxifen. Patients not being treated with tamoxifen the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes. Breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes.( Bordeleau L, 2010) For urogenital problems vaginal moisturizers or topical estrogens can be used (Loibl S, 2011). Sertraline, phytoestrogens, black cohosh and St. John's wort should not be used to treat hot flashes.( L'Espérance S, 2013; Kontos M, 2010)

**References:**

SSRI:

Venlafaxine


Desvenlafaxine


**Paroxetine**


**Fluoxetine**


**Citalopram**

 Gabapentin


 Pregabalin


**Clonidin**


**D) MPA (depo-) (Medroxyprogesterone acetate)**


**Vitamine E**


“Herbal” Approaches to Reduce Menopausal Symptoms (5/12)

Further information and references:

The majority of studies, regarding the efficacy of herbal treatments for menopausal symptoms – mostly hot flushes – have not been conducted in women with breast cancer and many are of short duration. (Roberts H, 2010) Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating. (Ma H, 2011)


Soy-derived isoflavonoids are potent phytoestrogens, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated.


Flaxseed has no effect on reducing hot flashes based on randomized phase III trial where it failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi S, 2012).

Taken together neither Black cohosh (Cimicifuga racemosa) (Leach MJ, 2012) nor St John’s Wort (Caraci F, 2011) nor Dong Quai (Zhuang SR) nor Ginseng root (Kim MS. 2013) showed a benefit regarding improvement of menopausal symptoms. In a Phase III trial the fixed combination of Red Clover and St. John's Wort were significantly better in reducing menopausal symptoms than placebo.


In a recent randomised placebo controlled trial in 72 non breast cancer women suffering from hot flashes 40mg red clover leaves showed a significant reduction in hot flashes based on the menopausal rating scale compared to placebo.(Shakeri F, 2015)


A combination of sodium selenite, proteolytic plant enzymes (bromelaine and papain), and Lens culinaris lectin as a complementary treatment was effective in reducing hormonal treatment related athralgia and mucosal dryness. (Uhlenbrock B, 2010) But there were no reduction in other menopausal symptoms

Alternative General Approaches to Reduce Menopausal Symptoms after BC I (6/12)

Further information:

Physical exercises (PE) and cognitive behavioral therapy (CBT; this is one form of psychotherapy) have positive effects on menopausal symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. (Duijts SF, 2012; Pachman DR, 2010; Mann E, 2012) Mind-Body-Medicine (MBM; Relaxation training, Yoga, Hypnosis) resulted in a moderate up to a significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation. (Buffart LM, 2012; Cramer H, 2014) However these effects are seen even after a longer period of application and avoid after some months stopping MBM. Acupuncture can also be used but the results from RCT are conflicting. A meta-analysis showed significant effects of acupuncture compared with sham acupuncture, but marked heterogeneity was observed in this model. (Lee MS, 2009)

References:

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/12)

Further information:

Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

References:

Randomised Controlled Trials and Metaanalysis


Ovarian Function Preservation Comparison of Randomized Trials (8/12)

No further information

No references
Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure (9/12)

No further information

No references
Testing Ovarian Reserve (10/12)

Further information:

The menstruation history is reliable only in women < 45 years of age. A more precise evaluation, especially in perimenopausal patients is possible with the measurement of FSH and E2 levels in peripheral blood. Hormonal replacement should be stopped at least 6 weeks before measurement. In perimenopausal women undergoing treatment for breast cancer, it can be difficult to determine true menopausal status because adjuvant chemotherapy, tamoxifen, and gonadotropin-releasing hormone analogues can induce transient (or permanent) ovarian suppression [1,2]. Low AMH (antimuellerian hormone) levels seem to be indicative for reduced ovarian reserve and chemotherapy-related amenorrhea (CRA) in chemotherapy-treated breast cancer patients [3, 4,5,6].

Antral follicle count, defined as the sum of follicle diameters of all follicles of 10mm in both ovaries. [7]

References:

amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008 Apr-May;26(3):286-95


Assessment of Ovarian Reserve (11/12)

No further information

No references
Contraceptive Options for Women after Diagnosis of Breast Cancer (12/12)

No further information

References:

