

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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## Gynecological Issues in Breast Cancer Patients

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- **Versions 2015–2021:**  
**Albert / Bauerfeind / Blohmer/ Fersis / Gerber / Hanf / Huober/  
Loibl / Maas / Reimer / Rody / Scharl / Thill / Thomssen / Witzel**
- **Version 2022:**  
**Loibl / Mundhenke**

# Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

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	Oxford LoE	GR	AGO
<b>Systemic hormone (replacement-) therapy</b>			
■ Endocrine responsive disease (ER pos.)	<b>1b</b>	<b>B</b>	-
■ Combined treatment TAM plus low dose HT	<b>2b</b>	<b>B</b>	+/-
■ Endocrine non-responsive disease (ER neg.)	<b>2b</b>	<b>D</b>	+/-
■ Tibolone	<b>1b</b>	<b>A</b>	--
<b>Topical vaginal application of</b>			
■ Estriol (E3 0.03 mg as treatment course*)	<b>2b</b>	<b>B</b>	+/-
■ DHEA locally	<b>2b</b>	<b>B</b>	-
■ Testosterone locally	<b>2b</b>	<b>B</b>	-
■ Estradiol (E2) during AI therapy	<b>4</b>	<b>C</b>	-

\* **4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week** – Note:.. Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred, see slide „Sexual Health“

# Further Medical Approaches to Reduce Menopausal Symptoms I

	Oxford		
	LoE	GR	AGO
<b>Medical approaches* (reduction of hot flashes)</b>			
▪ <b>Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients</b>			
▪ Venlafaxine	1a	A	+
▪ Desvenlafaxine	1b	A	+/-
▪ Sertraline, escitalopram	1b	A	+/-
▪ <b>Gabapentin (patients using TAM)</b>	1a	A	+
▪ <b>Oxybutynine (2.5 mg / 5 mg)</b>	1b	A	+/-
▪ <b>Pregabalin</b>	1b	A	+/-
▪ <b>Clonidine 0.05-0.15 mg/die (patients using TAM)</b>	2a	B	+/-
▪ <b>MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!)</b>	1b	A	+/-
▪ <b>Vitamin E</b>	1b	A	-
▪ <b>Omega-3 fatty acids</b>	1b	A	+/-
<b>Medical approaches (other treatment goals)</b>			
▪ <b>Melatonin (improvement in sleep quality)</b>	2b	C	+
▪ <b>Duloxetine (treating arthralgia while on AI)</b>	1b	B	+

## Medical approaches\* (reduction of hot flashes)

- **Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients**
  - Venlafaxine
  - Desvenlafaxine
  - Sertraline, escitalopram
- **Gabapentin (patients using TAM)**
- **Oxybutynine (2.5 mg / 5 mg)**
- **Pregabalin**
- **Clonidine 0.05-0.15 mg/die (patients using TAM)**
- **MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!)**
- **Vitamin E**
- **Omega-3 fatty acids**

## Medical approaches (other treatment goals)

- **Melatonin (improvement in sleep quality)**
- **Duloxetine (treating arthralgia while on AI)**

\* Note: Substantial placebo-effect has been proven (23-57%) **LoE 1b A +**

# CAM\* - Approaches to Reduce Menopausal Symptoms II

\* Complementary and Alternative Medicine

During anti-cancer treatment: Beware of drug interactions!

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li> <b>Soy-derived phytoestrogens – isoflavonoids*</b> <ul style="list-style-type: none"> <li>Hot flushes</li> <li>Sleep disturbance</li> <li>Topical vaginal application</li> </ul> </li> </ul>	1b 1b 1b	B B B	- +/- +/-
<ul style="list-style-type: none"> <li> <b>Red Clover isoflavonoids*</b> <ul style="list-style-type: none"> <li>Hot flushes, sleep disturbance</li> </ul> </li> </ul>	1b	B	+/-
<ul style="list-style-type: none"> <li> <b>Flaxseed-supplementation</b> (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses, no effect on hot flushes)         </li> </ul>	2b	B	+/-
<ul style="list-style-type: none"> <li> <b>Black Cohosh for hot flushes</b> </li> </ul>	1b	B	+/-
<ul style="list-style-type: none"> <li> <b>Black cohosh + St. John's Wort</b> (fixed combination)         </li> </ul>	1b	B	+/-
<ul style="list-style-type: none"> <li> <b>St. John's Wort</b> (pharmacokinetic interference with endocrine therapy, cytotoxic drugs, and tyrosin kinase inhibitors)         </li> </ul>	1b	B	+/-
<ul style="list-style-type: none"> <li> <b>Ginseng root</b> (Panax ginseng or P. quinquefolius)         </li> </ul>	1b	B	-
<ul style="list-style-type: none"> <li> <b>Bromelain + Papain + Selenium + Lectin</b> (for AI induced joint symptoms)         </li> </ul>	3b	B	+
<ul style="list-style-type: none"> <li> <b>Homeopathic medicine to reduce hot flushes</b> (consider placebo-effect)         </li> </ul>	1b	B	+/-

\* might stimulate BC, especially in endocrine responsive disease

# General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects



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## General approaches:

- **Physical exercise**
- **Cognitive behavioral therapy (CBT), hypnosis**
- **Mind body-medicine  
(yoga, education, counselling, mindfulness training)**
- **Short interruption of endocrine therapy in case of unacceptable side effects**

## **(Electro) Acupuncture**

- **Aromatase-inhibitor treatment induced arthralgia**
- **Hot flushes**
- **Anxiety, Depression**
- **Sleep**

	Oxford		
	LoE	GR	AGO
	1a	A	++
	1a	A	++
	1b	B	+
	5	D	+
	1a	B	+
	2a	B	+
	2b	B	+
	2a	C	+

\* as in SOLE Trial

# Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information <a href="https://fertiprotekt.com/english">https://fertiprotekt.com/english</a>)</li> </ul>			++
<ul style="list-style-type: none"> <li>CTx + GnRHa (preservation of ovarian function) (GnRHa application &gt; 2 weeks prior to chemotherapy, independent of hormone receptor status )</li> </ul>	1a	A	+
<ul style="list-style-type: none"> <li>CTx + GnRHa (preservation of fertility)</li> </ul>	2a	B	+/-

# Ovarian Protection – Synopsis of Randomized Trials

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

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# Assessment of Ovarian Reserve

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## Tests for fertility assessment

- **Anti-Mullerian Hormone**
- **Antral follicle count**
- **FSH**
- **Combined test procedures for assessment of ovarian reserve\***

	Oxford		
	LoE	GR	AGO
<b>1b</b>	<b>B</b>	<b>+</b>	
<b>3b</b>	<b>B</b>	<b>+</b>	
<b>2b<sup>a</sup></b>	<b>B</b>	<b>+</b>	
<b>5</b>	<b>C</b>	<b>+</b>	

\* Tests are suggested for women > 35 y and infertility for 6-12 months; the tests do not predict failure to conceive. They should be used in counselling patients and to 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



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	Oxford		
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■ <b>Barrier methods</b>	5	D	+
■ <b>Sterilization (tubal ligation / salpingectomy / vasectomy)</b>	5	D	+
■ <b>Non-hormonal intrauterine devices (IUDs)</b>	3b	D	+
■ <b>Levonorgestrel-releasing IUDs</b>	2b	C	-
■ Removal in newly diagnosed patients	4	D	+/-
■ <b>Timing methods</b>	5	D	-
■ <b>Injectable progestin-only contraceptives</b>	5	D	-
■ <b>Progestin-only oral contraceptives</b>	5	D	-
■ <b>Combined oral contraceptives</b>	5	D	-
■ <b>Options of emergency contraception</b>			
■ Copper intrauterine device (Copper-IUD)	5	D	+
■ Levonorgestrel, Ulipristal orally	5	D	+

# Sexual Health / Vaginal Dryness

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## Evaluation

- **Assessment of sexual dysfunction**
- **Use of patient-reported questionnaires**

## Therapy of dyspareunia and vaginal dryness

- **Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy**
- **Topical vaginal treatment**
  - **Non-hormonal lubricants / moisturizers** (also with physiotherapy)
  - **Estriol (E3 0.03 mg as treatment course\*)**
  - **DHEA local application**
  - **Testosterone local application**
  - **Estradiol (E2) during AI therapy**
  - **Fractionated microablative CO<sub>2</sub>-Laser / Vaginal Erbium:YAG-Laser**

	Oxford		
	LoE	GR	AGO
	5	D	+
	4	C	+
	1b	B	+
	1b	B	+
	2b	B	+/-
	2b	B	-
	2b	B	-
	4	C	-
	2a	B	+/-

\* **4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week** – Note: Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred.

# Assessment of Sexual Health

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- **Brief Sexual Symptom Checklist (BSSC-W)<sup>ref2</sup>**
  - **Screening-Questionnaire: Overall Sexual Function**

1. Are you satisfied with your sexual life? *Yes - No*  
*If NO, please continue to question 2*
2. How long have you been dissatisfied with your sexual life? .....
3. The problem(s) with your sexual life is: *(mark one or more)*
  1. Problem with little or no interest in sex *0*
  2. Problem with decreased genital sensation of clitoris or vagina (feeling) *0*
  3. Problem with decreased vaginal lubrication (dryness) *0*
  4. Problem reaching orgasm *0*
  5. Problem with pain and/or cramping during sex *0*
  6. Other .....
4. Which problem is most bothersome? *1 - 2 - 3 - 4 - 5 - 6 (circle)*
5. Would you like to talk about it with your doctor? *Yes - No*

- **Sexual Complaints Screener For Women (SCS-W)<sup>ref3</sup>**
- **FSFI-19, FSFI-6<sup>ref5</sup>**