

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 2015–2023:**
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- **Version 2024:**
Huober / Mundhenke

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

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

* **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

Medical approaches* (reduction of hot flashes)

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▪ Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients

▪ Venlafaxine	1a	A	+
▪ Desvenlafaxine, Sertraline, Escitalopram	1b	A	+/-
▪ Gabapentin (patients using TAM)	1a	A	+
▪ Oxybutynine (2.5 mg / 5 mg)	1b	A	+/-
▪ Pregabalin	1b	A	+/-
▪ Clonidine 0.05-0.15 mg/die (patients using TAM)	2a	B	+/-
▪ MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!)	1b	A	+/-
▪ Omega-3 fatty acids	1b	A	+/-
▪ Vitamin E	1b	A	-

Medical approaches (other treatment goals)

▪ Melatonin (improvement in sleep quality)	2b	C	+
▪ Duloxetine (treating arthralgias while on AI)	1b	B	+

* 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!

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

* might stimulate BC, especially in endocrine responsive disease

General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects

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

* as in SOLE Trial

Oxford

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

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

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- **CTx + GnRHa**
(preservation of ovarian function)
(GnRHa application > 2 weeks prior to chemo-therapy,
independent of hormone receptor status)
- **CTx + GnRHa**
(preservation of fertility)
- **Fertility preservation counselling including
referral of all potential patients to appropriate
reproductive specialists (further information
<https://fertiprotekt.com/english>; S2K Guideline Fertility
preservation in oncology)**

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LoE	GR	AGO
1a	A	+
2a	B	+/-
		++

Fertility preservation and assisted reproductive therapy (ART) - *Oncological safety*¹-

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Pretreatment approaches to preserve fertility <ul style="list-style-type: none"> GnRHa 1a A ++ Cryopreservation of ovarian tissue with subsequent transplantation² 4 D + Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation 2a C + ART after diagnosis of breast cancer 4 C +/- 			

¹Evidence is limited due to studies with poor quality e.g. (prospective randomized trials are not feasible)

² Risk of relapse caused by transplantation of ovarian tissue containing tumor cells from the original malignancy; Removal of transplanted ovarian tissue is necessary in patients with BRCA1/2 mutations due to increased risk of ovarian cancer

Oncological Safety of controlled ovarian stimulation (COS) or assisted reproductive therapy (ART)

N = 15 studies including 4643 patients undergoing COS or ART (assisted reproductive therapy)

COS before starting treatment (n=11 studies):

Reduced risk of recurrence RR 0.58, 95% CI 0,46-0,73

Reduced risk of mortality RR 0.54, 95% CI 0,38-0,76

No detrimental effect on EFS 0,76, 95% CI 0,55-1,06

- Subgroup of HR positive pts. HR 0.36, 95% CI 0.20–0.65

ART after treatment (n=4 studies):

Reduced risk of recurrence (RR 0.34, 95% CI 0.17-0.70)

No detrimental effect EFS (HR 0.43, 95% CI 0.17-1.11).

Conclusion: COS at diagnosis or ART following breast cancer treatment completion does not appear to be associated with any detrimental prognostic effect in young women

Arecco et al. Human Reprod 2022

Ovarian Protection – Synopsis of Randomized Trials

	ZORO	PROMISE	Munster et al. - US	POEMS	Option
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)	227 (126 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years	premenopausal
Treatment	goserelin	triptorelin	triptorelin	goserelin	goserelin
Start of treatment	> 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
Primary Endpoint	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
Primary objective	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
Multivar. analysis	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
Resumption of menses at month 12	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% amnorrhea rate between month 12 and 24
Median time to restoration of menses (months)	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.
Cyclophosph. dose	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*

Decreased ovarian reserve in BRCAmt carriers

	Oxford		
	LoE	GR	AGO
Anti-Mullerian Hormone	1b	B	+
Antral follicle count	3b	B	+
FSH	2b ^a	B	+
Combined test procedures for assessment of ovarian reserve*	5	C	+
Decreased ovarian reserve in BRCAmt carriers	2b	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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▪ Barrier methods	5	D	+
▪ Sterilization (tubal ligation / salpingectomy / vasectomy)	5	D	+
▪ Non-hormonal intrauterine devices (IUDs)	3b	D	+
▪ Levonorgestrel-releasing IUDs	2b	C	-
▪ Removal in newly diagnosed patients	4	D	+/-
▪ Timing methods	5	D	-
▪ Injectable progestin-only contraceptives	5	D	-
▪ Progestin-only oral contraceptives	5	D	-
▪ Combined oral contraceptives	5	D	-
▪ Options of emergency contraception			
▪ 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 CO2-Laser / Vaginal Erbium:YAG-Laser**

	LoE	GR	AGO
Assessment of sexual dysfunction	5	D	+
Use of patient-reported questionnaires	4	C	+
Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy	1b	B	+
Non-hormonal lubricants / moisturizers (also with physiotherapy)	1b	B	+
Estriol (E3 0.03 mg as treatment course*)	2b	B	+/-
DHEA local application	2b	B	-
Testosterone local application	2b	B	-
Estradiol (E2) during AI therapy	4	C	-
Fractionated microablative CO2-Laser / Vaginal Erbium:YAG-Laser	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.



Einschätzung der sexuellen Gesundheit¹

- Kurze Checkliste Sexueller Symptome für Frauen (BSSC-W)²
- Screening-Fragebogen zur Sexualfunktion insgesamt

1. Sind Sie zufrieden mit Ihrem Sexualeben? Ja – Nein

Wenn nein, dann beantworten Sie bitte die nächsten Fragen:

2. Seit wann/wie lange sind Sie mit Ihrem Sexualeben unzufrieden?

3a. Ihr Problem im Sexualeben ist: (eins oder mehrere markieren)

1. Problem mit weniger oder gar kein Interesse bzw. Lust	0
2. Problem mit reduzierter Empfindlichkeit / Sensibilität im Genitalbereich (Gefühl)	0
3. Problem mit verringerter vaginaler Lubrikation (Trockenheit der Scheide)	0
4. Problem, einen Orgasmus zu erreichen	0
5. Probleme mit Schmerzen beim Geschlechtsverkehr	0
6. Andere Probleme oder Sorgen

3b. Welche Probleme stören Sie am meisten? Bitte ankreuzen: 1 – 2 – 3 – 4 – 5 – 6

4. Wollen Sie über diese Probleme mit Ihrem Arzt/Ihrer Ärztin reden? Ja – Nein

- Sexual Complaints Screener For Women (SCS-W)^{3,4}
- FSFI-19, FSFI-6^{5,6}

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