

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer



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Gynecological Issues in Breast Cancer Patients

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**FORSCHEN
LEHREN
HEILEN**

Gynecologic Issues in Breast Cancer Patients

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- **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



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	Oxford		
	LoE	GR	AGO
■ Endocrine responsive disease (receptor pos.)	1b	B	-
■ Endocrine non-responsive disease (receptor neg.)	3b	D	+/-
■ Endocrine responsive disease (receptor pos.): combined treatment TAM plus low-dose-HT	2b	B	+/-
■ Tibolone	1b	A	--
■ Topical vaginal application of			
■ Estriol (E3 0.03 mg as treatment course*)	4	D	+/-
■ Estradiol (E2) during AI therapy	4	C	-

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* course: 4 weeks daily 1x1, further 8 weeks: 3 x 1 per week

Further Medical Approaches to Reduce Menopausal Symptoms I

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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 (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)

Oxford		
LoE	GR	AGO
1a	A	+
1b	A	+/-
1b	A	+/-
1a	A	+
1b	A	+/-
1a	A	+
1b	A	+/-
1b	A	-
2b	C	+

CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

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While anti-cancer treatment:

Beware of drug interactions!

- **Soy-derived phytoestrogens – isoflavonoids**

Hot flush

Sleep disturbance

Topical vaginal application

- **Red Clover isoflavonoids**

Hot flush, sleep disturbance

(might stimulate BC especially in endocrine responsive disease)

- **Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d)**

(reduces relapses, no effect on hot flashes)

- **Black Cohosh for hot flushes**

- **Black cohosh + St. John's Wort**

- **St. John's Wort**

(pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)

- **Ginseng root (Panax ginseng or P. quinquefolius)**

- **Bromelain + Papain + Selenium + Lektin (for, AI induced joint symptoms)**

	Oxford		
	LoE	GR	AGO
Hot flush	1b	B	-
Sleep disturbance	1b	B	+/-
Topical vaginal application	1b	B	+/-
Hot flush, sleep disturbance (might stimulate BC especially in endocrine responsive disease)	1b	B	+/-
Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses, no effect on hot flashes)	2b	B	+/-
Black Cohosh for hot flushes	1b	B	-
Black cohosh + St. John's Wort	1b	B	+/-
St. John's Wort (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)	1b	B	+/-
Ginseng root (Panax ginseng or P. quinquefolius)	1b	B	-
Bromelain + Papain + Selenium + Lektin (for, AI induced joint symptoms)	3b	B	+

General Approaches to Reduce Menopausal Symptoms III

Integrative Oncology Aspects



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General approaches:

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

Oxford		
LoE	GR	AGO
1b	B	++
1b	B	+
1b	B	++
1b ^a	B	+
1a	B	+/-
2b	B	+/-
3b	C	+/-

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"> CT + GnRHa (preserve ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status) 	1a	B	+
<ul style="list-style-type: none"> CHT + GnRHa (preserve fertility) 	2a	B	+/-
<ul style="list-style-type: none"> Fertility preservation counselling 	4	C	++
<ul style="list-style-type: none"> Fertility preservation using assisted reproduction therapy (ART) (further information www.fertiprotect.de) 	4	C	+

Ovarieller Funktionserhalt – Synopsis der randomisierten Studien

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	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	Amenorrhoea 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 amenorrhoea 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% amnorrhoea 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. 4700mg	4080 vs. 4008 mg	n.r.	n.a.	5940 vs. 5940mg

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Testing Ovarian Reserve

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

Tests for fertility assessment

- **Anti-Müllerian Hormone**
- **Antral follicle count**

	Oxford		
	LoE	GR	AGO
Assessment of ovarian reserve in infertile patients (> 6-12 months without conception)*	5	C	+
Anti-Müllerian Hormone	1b	B	+
Antral follicle count	3b	B	+

- * 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

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

Test	Details
FSH (follicle stimulating hormone) plus estradiol	<ul style="list-style-type: none"> ▪ 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)	<ul style="list-style-type: none"> ▪ 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)	<ul style="list-style-type: none"> ▪ 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

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- **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**
- Options after Diagnosis of Breast Cancer**

Oxford		
LoE	GR	AGO
5	D	+
5	D	+
3b	D	+
2b	C	-
4	D	+/-
5	D	-
5	D	-
5	D	-
5	D	+
5	D	+

- **Copper intrauterine device (Cu-IUD)**

- **Levonorgestrel, Ulipristal orally**

Sexual Health

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- **Assessment of sexual dysfunction**
- **Use of patient-reported questionnaires**
- **Vaginal dryness:
Non-hormonal lubricants / moisturizers**
- **Fractionated microablative CO2-Laser/
Vaginal Erbium:YAG-Laser**
- **Psychoeducational support, group therapy,
sexual counseling, marital counseling,
psychotherapy**

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

Assessment of Sexual Health

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- **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?

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* Hatzichristou D, Rosen RC, Denogatis LR, Low WY, Sadovsky R, Symonds T. Recommendations for the clinical evaluation of men and women with sexual dysfunction.
J Sex Med 2010;7:337-348