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HEILEN

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

## Gynecological Issues in Breast Cancer Patients



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## Gynecologic Issues in Breast Cancer Patients

- **Versions 2015–2020:**  
Albert / Bauerfeind / Blohmer/ Fersis / Gerber / Hanf / Huober/  
Loibl / Maas / Rody / Scharl / Thill / Witzel
  
- **Version 2021:**  
Reimer / Thomssen

### Screened data bases:

Pubmed	2009 –2020
ASCO	2009 - 2020
SABCS	2009 - 2020

### Übersichten:

1. Marsh S, Borges VF, Coons HL, Afghahi A. Sexual health after a breast cancer diagnosis in young women: clinical implications for patients and providers. Breast Cancer Res Treat. 2020 Dec;184(3):655-663.
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3. Lambertini M, Peccatori FA, Demeestere I et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines<sup>†</sup>. Ann Oncol. 2020 Dec;31(12):1664-1678. S3

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5. S3-Leitlinie: Peri- and Postmenopause. Diagnosis and Interventions. Guideline of the DGGG, SGGG and OEGGG (S3 Level, AWMF Registry No.015-062, January 2020). <http://www.awmf.org/leitlinien/detail/II/015-062.html>

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer			
	Oxford		
	LoE	GR	AGO
<b>Systemic hormone (replacement-) therapy</b>			
▪ Endocrine responsive disease (ER pos.)	1b	B	-
▪ Combined treatment TAM plus low dose HT	2b	B	+/-
▪ Endocrine non-responsive disease (ER neg.)	2b	D	+/-
▪ Tibolone	1b	A	--
<b>Topical vaginal application of</b>			
▪ 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“

### Endocrine responsive disease

1. Fahlén M: Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. Eur J Cancer. 2013 Jan;49(1):52-9.
2. Holmberg L: Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst 100:475-82, 2008.
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5. Wang Y, Lewin N, Qaoud Y et al. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. Breast. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002. Epub 2018 May 12.

### Endocrine non-responsive disease

1. Wang Y, Lewin N, Qaoud Y et al. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. *Breast*. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002. Epub 2018 May 12.

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

1. Kuhle CL, Kapoor E, Sood R et al.: Menopausal hormone therapy in cancer survivors: A narrative review of the literature. *Maturitas*. 2016 Oct;92:86-96.

#### Tibolone

1. Kenemans P, Bundred NJ, Foidart J et al.; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol*. 2009 Feb;10(2):135-46.
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#### Ospemifene

1. Goldstein SR, Bachmann GA, Koninckx P et al.; Ospemifene Study Group. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. *Climacteric*. 2014 Apr;17(2):173-82.
2. Cagnacci A, Xholli A, Venier M. Ospemifene in the Management of Vulvar and Vaginal Atrophy: Focus on the Assessment of Patient Acceptability and Ease of Use. *Patient Prefer Adherence*. 2020 Jan 10;14:55-62.

#### Topical Vaginal Application:

1. Biglia N, Peano E, Sgandurra P, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. *Gynecol Endocrinol* 2010;26(6):404–12

2. Le Ray I., Dell’Aniello S., Bonnetain F. et al.: Local estrogen therapy and risk of breast cancer recurrence among hormone treated patients: A nested case-control study. *Breast Cancer Res. Treat.* 2012;135:603–609.
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9. Barton DL, Shuster LT, Dockter T et al. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). *Support Care Cancer.* 2018 Apr;26(4):1335-1343.
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Further Medical Approaches to Reduce Menopausal Symptoms I			
	Oxford		
	LoE	GR	AGO
<b>Medical approaches* (reduction of hot flashes)</b>			
▪ Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients			
▪ Venlafaxine	1a	A	+
▪ Desvenlafaxine	1b	A	+/-
▪ 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	+/-
▪ Vitamin E	1b	A	-
▪ Omega-3 fatty acids	1b	A	+/-
<b>Medical approaches (other treatment goals)</b>			
▪ 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 +			

1. Chubak J, Bowles EJ, Yu O, Buist DS et al.: Breast cancer recurrence in relation to antidepressant use. Cancer Causes Control. 2016 Jan;27(1):125-36.
2. Haque R, Shi J, Schottinger JE et al.: Tamoxifen and Antidepressant Drug Interaction in a Cohort of 16 887 Breast Cancer Survivors. J Natl Cancer Inst. 2015 Dec 1;108(3).
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7. Antoine C, Ameye L, Paesmans M et al.: Treatment of climacteric symptoms in breast cancer patients: a retrospective study from a medication databank. Maturitas. 2014 Jul;78(3):228-32.



8. Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015;10;4:65.
9. Leon-Ferre RA, Majithia N, Loprinzi CL. Management of hot flashes in women with breast cancer receiving ovarian function suppression. Cancer Treat Rev. 2017 Jan;52:82-90.

### SSRI

1. Shams T1, Firwana B, Habib F et al.: SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. J Gen Intern Med. 2014 Jan;29(1):204-13.

### Venlafaxine

1. Ramaswami R, Villarreal MD, Pitta DM et al.: Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2015 Jul;152(2):231-7.
2. Boekhout AH, Vincent AD, Dalesio OB et al: Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2011 Oct 10;29(29):3862-8.
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### Desvenlafaxine

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3. Deecher DC, Alf inito PD, Leventhal L et al.: Alleviation of thermoregulatory dysfunction with the new serotonin and

norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized rodent models. *Endocrinology*. 2007;148(3):1376–1383.

#### Paroxetine

1. Simon JA, Portman DJ, Kaunitz AM et al.: Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause*. 2013 Oct;20(10):1027-35. doi: 10.1097/GME.0b013e3182a66aa7.

#### Fluoxetine

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#### Citalopram

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#### Gabapentin

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#### Pregabalin

1. Loprinzi CL, Qin R, Baclueva EP et al.: Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for

alleviating hot flashes, N07C1. J Clin Oncol. 2010;28(4):641–647.

#### Clonidin

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3. Friedman GD, Udaltsova N, Habel LA: Norepinephrine antagonists and cancer risk. Int J Cancer 2011. 128(3):737–738, doi:10.1002/ijc.25351 (Clonidin)
4. Burbos N, Morris EP. Menopausal symptoms. BMJ Clin Evid. 2011 Jun 15;2011:0804.

#### Oxybutynin

1. Leon-Ferre RA, Novotny PJ, Wolfe EG et al. Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603). JNCI Cancer Spectr. 2019 Oct 21;4(1):pkz088.
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#### (D) MPA (depo-) (Medroxyprogesterone acetate)

1. Prior JC, Nielsen JD, Hitchcock CL et al.: Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy. Clin Sci (Lond). 2007;112(10):517–525.
2. Loprinzi CL, Levitt R, Barton D et al.: Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol. 2006 Mar 20;24(9):1409-14. Epub 2006 Feb 27.
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05013-7. [Epub ahead of print]

### Vitamine E

1. Rada G: Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review). The Cochrane Library 2010, Issue 9.
2. Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat. 2009 Jun;115(3):437-52.
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### Omega 3-Fettsäuren


1. Lustberg MB, Orchard TS, Reinbolt R et al. Randomized placebo-controlled pilot trial of omega 3 fatty acids for prevention of aromatase inhibitor-induced musculoskeletal pain. Breast Cancer Res Treat. 2018 Feb;167(3) 709-718. doi: 10.1007/s10549-017-4559-z. Epub 2017 Nov 3.

### Melatonin

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### Duloxetine

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# CAM\* - Approaches to Reduce Menopausal Symptoms II

\* Complementary and Alternative Medicine

## During anti-cancer treatment: Beware of drug interactions!

### ▪ Soy-derived phytoestrogens – isoflavonoids\*

Hot flushes

Sleep disturbance

Topical vaginal application

### ▪ Red Clover isoflavonoids\*

Hot flushes, sleep disturbance

### ▪ 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 (fixed combination)

### ▪ 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 + Lectin (for AI induced joint symptoms)

### ▪ Homeopathic medicine to reduce hot flushes (consider placebo-effect)

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

\* might stimulate BC, especially in endocrine responsive disease

1. Roberts H. Safety of herbal medicinal products in women with breast cancer. *Maturitas*. 2010;66(4):363-9.
2. Ma H: Estrogenic botanical supplements, health-related quality of life, fatigue, and hormone-related symptoms in breast cancer survivors: a HEAL study report. *BMC Complement Altern Med*. 2011;11:109.
3. Kim W, Lee WB, Lee JW et al.: Traditional herbal medicine as adjunctive therapy for breast cancer: A systematic review. *Complement Ther Med*. 2015 Aug;23(4):626-32. doi: 10.1016/j.ctim.2015.03.011.
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### Soy- derieived isoflavonoids

### Red clover-derived isoflavonoids

1. Chen MN: Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric*. 2015 Apr;18(2):260-9.
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3. Fritz H, Seely D, Flower G et al.: red clover, and isoflavones and breast cancer: a systematic review. PLoS One. 2013 Nov 28;8(11):e81968.
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7. Ghazanfarpour M, Sadeghi R, Roudsari RL. The application of soy isoflavones for subjective symptoms and objective signs of vaginal atrophy in menopause: A systematic review of randomised controlled trials. J Obstet Gynaecol. 2016;36(2):160-71.
8. Ribeiro AE, Monteiro NES, Moraes AVG et al. Can the use of probiotics in association with isoflavone improve the symptoms of genitourinary syndrome of menopause? Results from a randomized controlled trial. Menopause. 2018 Dec 10. doi: 10.1097/GME.0000000000001279. [Epub ahead of print]

#### Flaxseed

1. Flower G: Flax and Breast Cancer: A Systematic Review. Integr Cancer Ther. 2013 8;13(3):181-192.
2. Pruthi S: A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. Menopause 2012; 19:48-53.

#### Black cohosh (Cimicifuga racemosa) nor St John's Wort nor Ginseng root

1. Leach MJ: Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012; 9:CD007244.
2. Caraci F: Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metab. 2011 Jul 1;12(6):570-7.
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Mar;37(1):30-6.


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5. Wobser RW, Takov V. Black Cohosh. 2020 Dec 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 29261886.

#### Sodium selenite, proteolytic plant enzymes (bromelain and papain), and Lens culinaris lectin

1. Beuth J, van Leendert R, Schneider B et al.: Complementary medicine on side-effects of adjuvant hormone therapy in patients with breast cancer. In Vivo. 2013 Nov-Dec;27(6):869-71.

#### Homeopathic medicine

1. Heudel PE, Van Praagh-Doreau I, Duvert B et al.: Does a homeopathic medicine reduce hot flushes induced by adjuvant endocrine therapy in localized breast cancer patients? A multicenter randomized placebo-controlled phase III trial. Support Care Cancer. 2019 May;27(5):1879-1889. doi: 10.1007/s00520-018-4449-x. Epub 2018 Sep 7.



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# 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)

## (Electro) Acupuncture

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

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

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### Physical exercise

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)			
	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>	1b	A	+/-

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# Ovarian Protection – Synopsis of Randomized Trials

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	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. 4700mg	4080 vs. 4008 mg	n.r.	n.a.	5940 vs. 5940mg

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	<h2>Assessment of Ovarian Reserve</h2>		
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2021.1E</p>	<b>Tests for fertility assessment</b>		
<ul style="list-style-type: none"> <li>■ <b>Anti-Müllerian Hormone</b></li> </ul>	<b>LoE</b>	<b>GR</b>	<b>AGO</b>
<ul style="list-style-type: none"> <li>■ <b>Antral follicle count</b></li> </ul>	<b>1b</b>	<b>B</b>	<b>+</b>
<ul style="list-style-type: none"> <li>■ <b>FSH</b></li> </ul>	<b>3b</b>	<b>B</b>	<b>+</b>
<ul style="list-style-type: none"> <li>■ <b>Combined test procedures for assessment of ovarian reserve*</b></li> </ul>	<b>2b<sup>a</sup></b>	<b>B</b>	<b>+</b>
	<b>5</b>	<b>C</b>	<b>+</b>
<p>www.ago-online.de <b>FORSCHEN LEHREN HEILEN</b></p>	<p>* Tests are suggested for women &gt; 35y 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.</p>		

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### Antrale Follicle Count

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### FSH

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Contraceptive Options for Women after Diagnosis of Breast Cancer			
	Oxford		
	LoE	GR	AGO
■ <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	+


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### Emergency Contraception - Options after Diagnosis of Breast Cancer

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# 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.

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## Evaluation

### Sexual Complaints Screener For Women (SCS-W) (Langversion und Kurzversion):

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#### Behandlung der Dyspareunie und der vaginalen Trockenheit

##### Psychoedukative Unterstützung, Gruppentherapie, Sexualberatung, Eheberatung, Psychotherapie

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##### Kombinationstherapie (Olivenöl, Beckenbodenentspannung und vaginale Feuchtigkeitsgele):

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#### Vaginal topische Behandlung

##### Medikamentös (nicht-hormonelle Vaginalgele, Östrogene, DHEA, Testosteron)

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## Assessment of Sexual Health

- **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>**

### General recommendations

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