Guidelines Breast
Version 2024.1E

Gynecological Issues in Breast Cancer Patients

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Gynecologic Issues in Breast Cancer Patients

- **Versions 2015–2023:**
  Albert / Bauerfeind / Blohmer / Fehm / Fersis / Gerber / Hanf / Huober/ Loibl / Maas / Mundhenke/ Reimer / Rody / Scharl / Stickeler / Thill / Thomssen / Witzel
- **Version 2024:**
  Huober / Mundhenke

Screened data bases:

Pubmed	2009 –2023
ASCO	2009 - 2023
SABCS	2009 - 2023

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

	Oxford LoE	GR	AGO
Systemic hormone (replacement-) therapy			
▪ **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	- -
Topical vaginal application of			
▪ **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. Paggio F, Del Mastro L, Bruzzone M et al. Safety of systemic hormone replacemt therapy in breast cancer survivors: a systematic review and meta-analysis. Breast Cancer Res Treat. 2022 191(2):269-72.
2. 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.
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5. Mudhune GH, Armour M, McBride KA: Safety of menopausal hormone therapy in breast cancer survivors older than fifty at diagnosis: A systematic review and meta-analysis. Breast 2019, 47:43-55.
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7. Luo J, Cochrane B B, Wactawski-Wende J. Effects of menopausal hormone therapy on ductal carcinoma in situ of the breast. Breast Cancer Res Treat. 2013;137:915–925.

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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3. Bundred NJ: Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. Breast Cancer Res. 2012 Jan 17;14(1):R13.

Ospemifeme

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.
3. Portman DJ, Gass ML; Vulvovaginal Athrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause:

new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. Climacteric 2014 Oct;17(5):557-63
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6. Mazzarello S1, Hutton B, Ibrahim MF et al.: Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials. Breast Cancer Res Treat. 2015 Jul;152(1):1-8.
7. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Farrell R. ACOG Committee Opinion No. 659: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. Obstet Gynecol. 2016 Mar;127(3):e93-6
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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.
10. Simon JA, Goldstein I, Kim NN et al. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. Menopause. 2018 Jul;25(7):837-847.
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inhibitors: a phase II, randomized, double-blind, placebo-controlled trial. Menopause. 2020 May;27(5):526-534.

15. Hussain I, Sinai V, Talaulikar S. A systematic review of randomised clinical trials – The safety of vaginal hormones and selective estrogen receptor modulators for the treatment of genitourinary menopausal symptoms in breast cancer survivors. Post Reproductive Health 2023, Vol. 29(4) 222–231
16. Fallah P, Wolfe D, Hutton P et al. Management of genitourinary symptoms in patients with breast cancer: an updated systematic review of available evidence from randomized trials. Supportive Care in Cancer 2023 31:131
17. Merlino L, D`Matys V et al. Ovidio G, Therapeutic Choices for Genitourinary Syndrome of Menopause (GSM) in Breast Cancer Survivors: A Systematic Review and Update. Pharmaceuticals 2023, 16, 550.

Further Medical Approaches to Reduce Menopausal Symptoms I

Medical approaches* (reduction of hot flushes)	Oxford LoE	Oxford GR	Oxford AGO
▪ **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 uasing 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 +

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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4. Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ. 2010;340:c693.
5. Bordeleau L: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52.
6. Wiśniewska I, Jochymek B, Lenart-Lipińska M et al.: The pharmacological and hormonal therapy of hot flushes in breast cancer survivors. Breast Cancer. 2016 Mar;23(2):178-82.
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.
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3. Bordeleau L, Pritchard KI, Loprinzi CL et al: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52.

Desvenlafaxine
1. Archer DF, Dupont CM, Constantine GD et al.: Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety. Am J Obstet Gynecol. 2009;200(3):238 e231–238 e210.
2. Speroff L, Gass M, Constantine G et al.: Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstet Gynecol. 2008;111(1):77–87.
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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
1. Loprinzi CL, Sloan J, Stearns V et al.: Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol. 2009;27(17):2831–2837.

Citalopram
1. Barton DL, LaVasseur B, Sloan JA et al.: A phase III trial evaluating three doses of citalopram for hot flashes: NCCTG trial N05C9. J Clin Oncol. 2008;26(20):9538.
2. Kalay AE, Demir B, Haberal A et al.: Efficacy of citalopram on climacteric symptoms. Menopause. 2007;14(2):223–229.

Gabapentin
1. Bordeleau L, Pritchard KI, Loprinzi CL et al: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52
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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
1. Drewe J, Bucher KA, Zahner CA.: systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015 Feb 10;4:65. doi: 10.1186/s40064-015-0808-y. eCollection 2015.
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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.
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3. Ertz-Archambault NM, Rogoff LB, Kosiorek HE et al.: Depomedroxyprogesterone acetate therapy for hot flashes in survivors of breast cancer: no unfavorable impact on recurrence and survival. Support Care Cancer. 2019 Aug 11. doi: 10.1007/s00520-019-05013-7. [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.
3. Biglia N, Sgandurra P, Peano E et al.: Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric. 2009 Aug;12(4):310-8.

Omega 3-Fettsäuren

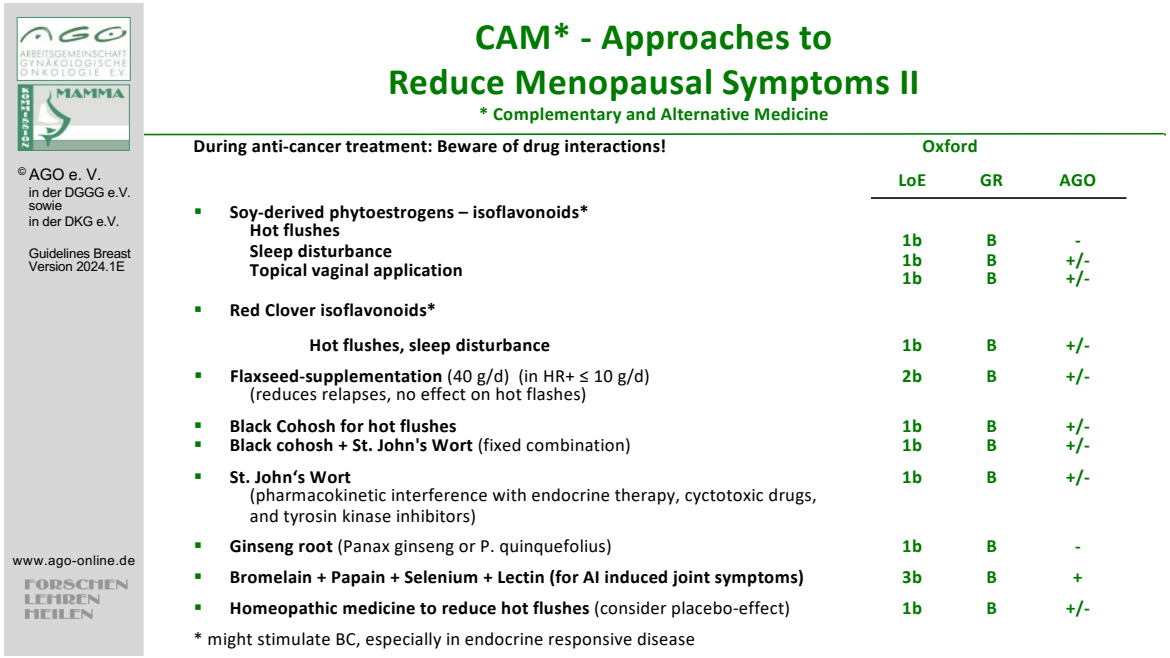
1. Lustberg M´B, Orchard TS, Reinbolt R et al. Randomized placebo-controlled pilot trial of omega 3 fatty acids for prevention of aromatase inhibitor-induced musculoskeletal pain. Breast Cancer Res Treat. 2018 Feb;167(3) 709-718. doi: 10.1007/s10549-017-4559-z. Epub 2017 Nov 3.

Melatonin

1. Chen WY, Giobbie-Hurder A, Gantman K et al.: A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. Breast Cancer Res Treat 2014. 145(2):381–388, doi:10.1007/s10549-014-2944-4

Duloxetin

1. Henry NL, Unger JM, Schott AF et al. Randomized, Multicenter, Placebo-Controlled Clinical Trial of Duloxetine Versus Placebo for Aromatase Inhibitor-Associated Arthralgias in Early-Stage Breast Cancer: SWOG S1202. J Clin Oncol. 2018 Feb 1;36(4):326-332. doi: 10.1200/JCO.2017.74.6651. Epub 2017 Nov 14



CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

During anti-cancer treatment: Beware of drug interactions!	Oxford LoE	GR	AGO
▪ **Soy-derived phytoestrogens – isoflavonoids***			
Hot flushes	1b	B	-
Sleep disturbance	1b	B	+/-
Topical vaginal application	1b	B	+/-
▪ **Red Clover isoflavonoids***			
Hot flushes, sleep disturbance	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** (fixed combination)	1b	B	+/-
▪ **St. John's Wort** (pharmacokinetic interference with endocrine therapy, cyctotoxic drugs, and tyrosin kinase inhibitors)	1b	B	+/-
▪ **Ginseng root** (Panax ginseng or P. quinquefolius)	1b	B	-
▪ **Bromelain + Papain + Selenium + Lectin (for AI induced joint symptoms)**	3b	B	+
▪ **Homeopathic medicine to reduce hot flushes** (consider placebo-effect)	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.
4. Lethaby A, Marjoribanks J, Kronenberg F et al.: Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev. 2013 Dec 10;(12):CD001395. doi: 10.1002/14651858.CD001395.pub4.

<u>Soy- derieved isoflavonoids</u>
<u>Red clover-derived isoflavonoids</u>

1. Chen MN: Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric. 2015 Apr;18(2):260-9.
2. Lethaby A: Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev. 2013 Dec 10;12:CD001395.
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.
4. Ghazanfarpour M, Sadeghi R, Latifnejad Roudsari R et al.: Effects of red clover on hot flash and circulating hormone

concentrations in menopausal women: a systematic review and meta-analysis. Avicenna J Phytomed. 2015 Nov-Dec;5(6):498-511.
5. Shakeri F: Effectiveness of red clover in alleviating of menopausal symptoms: A 12-week randomized, controlled trial. Climacteric. 2015;18(4):568-73.
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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.
3. Kim MS: Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials. J Ginseng Res. 2013 Mar;37(1):30-6.
4. Mehrpooya M1, Rabiee S2, Larki-Harchegani A3, Fallahian AM1, Moradi A4, Ataei S1, Javad MT5. A comparative study on the effect of "black cohosh" and "evening primrose oil" on menopausal hot flashes. J Educ Health Promot. 2018 Mar 1;7:36. doi: 10.4103/jehp.jehp_81_17. eCollection 2018.
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 (bromelaine 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.

General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects

General approaches:	Oxford LoE	GR	AGO
▪ Physical exercise	1a	A	++
▪ Cognitive behavioral therapy (CBT), hypnosis	1a	A	++
▪ Mind body-medicine (yoga, education, counselling, mindfulness training)	1b	B	+
▪ Short interruption of endocrine therapy in case of unacceptable side effects	5	D	+
(Electro) Acupuncture			
▪ Aromatase-inhibitor treatment induced arthralgia	1a	B	+
▪ Hot flushes	2a	B	+
▪ Anxiety, Depression	2b	B	+
▪ Sleep	2a	C	+

* as in SOLE Trial

1. Duncan M, Moschopoulou E, Herrington E et al.: Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. BMJ Open. 2017 Nov 28;7(11):e015860.
2. Tran S, Hickey M, Saunders C et al. Nonpharmacological therapies for the management of menopausal vasomotor symptoms in breast cancer survivors. Support Care Cancer. 2020 Sep 17. doi: 10.1007/s00520-020-05754-w. Epub ahead of print. PMID: 32940768.
3. 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/ll/015-062.html

Physical exercise

1. Duijts SF: Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. J Clin Oncol. 2012 Nov 20;30(33):4124-33.
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3. Lahart IM, Metsios GS, Nevill AM et al.: Physical activity for women with breast cancer after adjuvant therapy. Cochrane

Database Syst Rev 2018, 1:Cd011292.

Mind Body Medicine

1. Buffart LM: Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC Cancer. 2012 Nov 27;12:559.
2. Cramer H: Characteristics of randomized controlled trials of yoga: a bibliometric analysis. BMC Complement Altern Med. 2014 Sep 2;14:328.
3. Haller H, Winkler MM, Klose P et al.: Mindfulness-based interventions for women with breast cancer: an updated systematic review and meta-analysis. Acta Oncol 2017, 56:1665-76.
4. Koch AK, Rabsilber S, Lauche R et al.: The effects of yoga and self-esteem on menopausal symptoms and quality of life in breast cancer survivors-A secondary analysis of a randomized controlled trial. Maturitas 2017 Nov;105:95-99. doi: 10.1016/j.maturitas.2017.05.008. Epub 2017 May 13.
5. Goldstein KM, Shepherd-Banigan M, Coeytaux RR et al.: Use of mindfulness, meditation and relaxation to treat vasomotor symptoms. Climacteric. 2017;20(2):178-82.
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Ovarian Protection with GnRHa and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

	Oxford		
	LoE	GR	AGO
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-
▪ **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*)**			++

Ovarian function protection

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4. Lambertini M, Moore HCF, Leonard RCF et al.: Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. J Clin Oncol 2018, 36:1981-90
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1. Loren AW, Mangu PB, Beck LN et al. Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2013;31(19):2500–10.
2. Peccatori FA, Azim Jr HA, Orecchia R et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–70.
3. Abe A, Kuwahara A, Iwasa T et al.: A survey on fertility management in young women of reproductive age treated with chemotherapy. Int J Clin Oncol. 2016 Dec;21(6):1183-1190.
4. Marklund A, et al. Reproductive Outcomes After Breast Cancer in Women With vs Without Fertility Preservation. JAMA Oncol. 2021 Jan 1;7(1):86-91.
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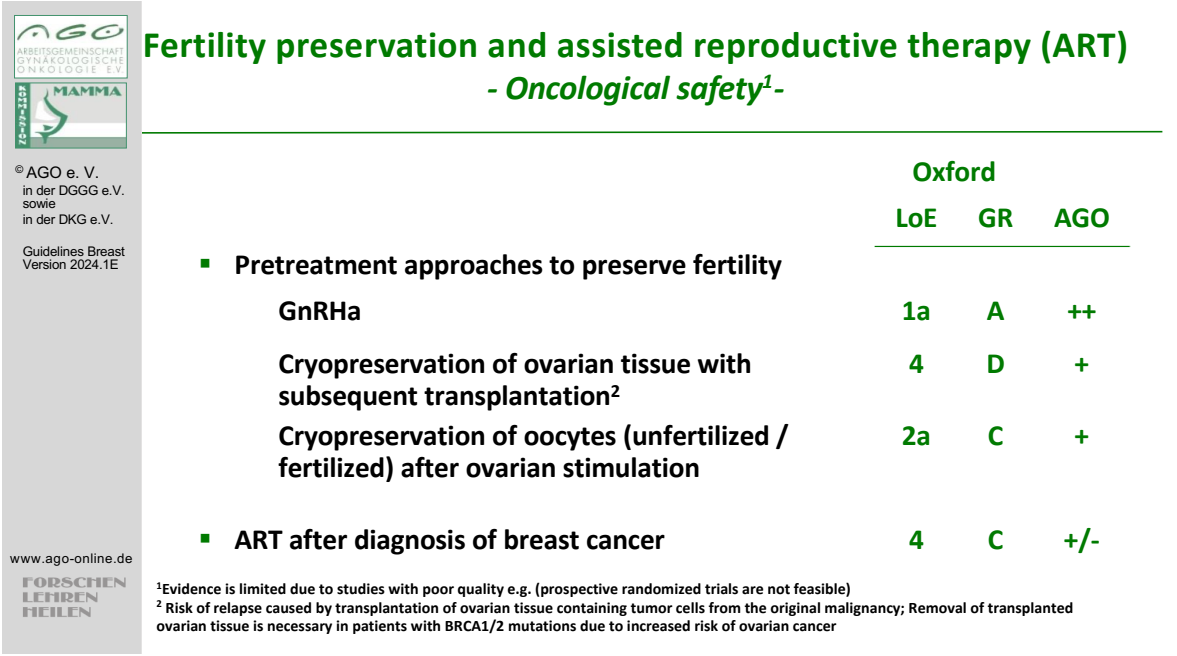

Fertility preservation and assisted reproductive therapy (ART)

- Oncological safety[1] -

	Oxford		
	LoE	GR	AGO
▪ **Pretreatment approaches to preserve fertility**			
GnRHa	1a	A	++
Cryopreservation of ovarian tissue with subsequent transplantation[2]	4	D	+
Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation	2a	C	+
▪ **ART after diagnosis of breast cancer**	4	C	+/-

[1]Evidence 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

GnRH-Analogon:

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1. Luke B, Brown MB, Missmer SA et al.: Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016 ;31(1):183-9.
2. Oktay K, Turan V, Bedoschi G et al.: Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. J Clin Oncol. 2015;33(22):2424–9.
3. Arecco L, Blondeaux E, Bruzzone M, et al.. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022; 37(5):954-968. doi: 10.1093/humrep/deac035. PMID: 35220429; PMCID: PMC9071231.
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5. Beebeejaun Y, Athithan A, Copeland TP, et al. Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis. Fertil Steril. 2021; 116(1):198-207. doi: 10.1016/j.fertnstert.2021.01.044. PMID: 34148584.

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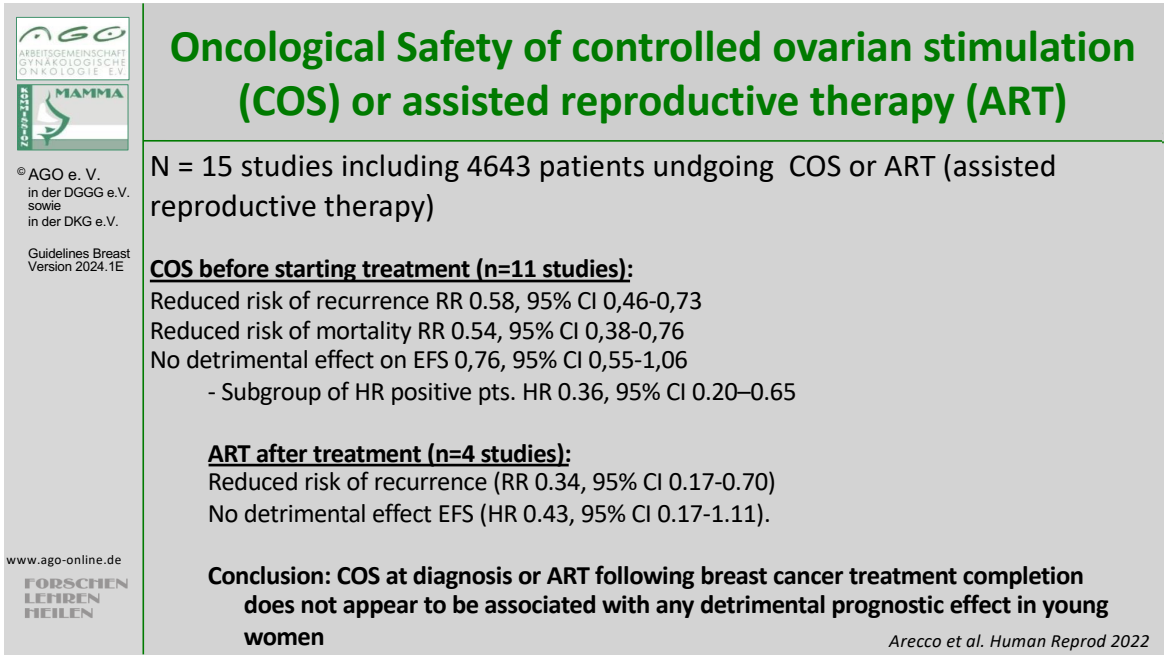

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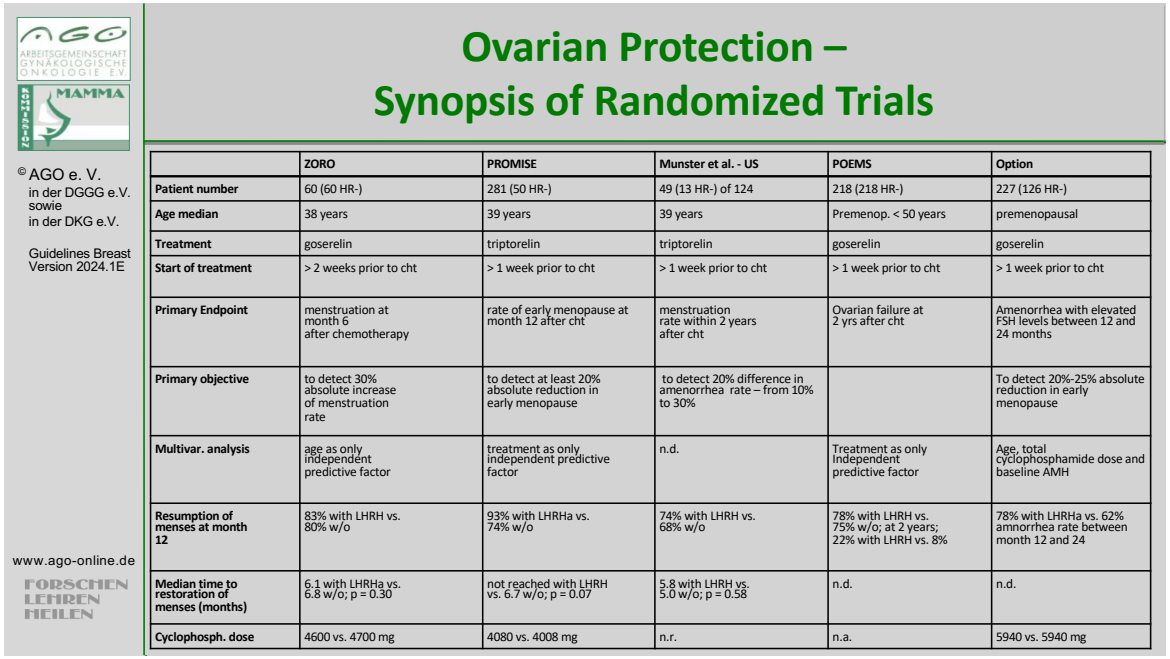

Ovarian Protection – Synopsis of Randomized Trials

	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

	Oxford		
	LoE	GR	AGO
Tests for fertility assessment			
▪ **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.**

AMH:

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2. Fréour T, Barrière P, Masson D. Anti-müllerian hormone levels and evolution in women of reproductive age with breast cancer treated with chemotherapy. Eur J Cancer. 2017 Mar;74:1-8. doi: 10.1016/j.ejca.2016.12.008. Epub 2017 Jan 28.
3. Trapp E, Steidl J, Rack B et al.: Anti-Müllerian hormone (AMH) levels in premenopausal breast cancer patients treated with taxane-based adjuvant chemotherapy - A translational research project of the SUCCESS A study. Breast. 2017 Oct;35:130-135. doi: 10.1016/j.breast.2017.07.007. Epub 2017 Jul 18.
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5. Zong X, Yu Y, Chen W, Zong W, Yang H, Chen X. Ovarian reserve in premenopausal women with breast cancer. Breast. 2022:143-150. doi: 10.1016/j.breast.2022.05.009.

Antrale Follicle Count:

1. Sinha N, Letourneau JM, Wald K et al: Antral follicle count recovery in women with menses after treatment with and without

gonadotropin-releasing hormone agonist use during chemotherapy for breast cancer. J Assist Reprod Genet 2018, 35:1861-8.

2. Su HI, Chung K, Sammel MD et al.: Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. Fertil Steril. 2011 Apr;95(5):1857-9.

FSH:

1. Furlanetto J, Thode C, Huober J. et al. Changes in hormone levels (E2, FSH, AMH) and fertility of young women treated with neoadjuvant chemotherapy (CT) for early breast cancer (EBC). SABCS 2017, # 754, PD 7-09
2. Furlanetto J, Marmé F, Seiler S, et al. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials. Eur J Cancer. 2021;152:193-203. doi: 10.1016/j.ejca.2021.04.038.

Combined tests:

1. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2020;114(6):1151-1157

Ovarian reserve BRCA mt:

1. Zhang X, NiuJ, Che T et al. Fertility preservation in BRCA mutation carriers—efficacy and safety issues: a review
2. Reproductive Biology and Endocrinology 2020 18:11
3. Oktay KH, Volkan T, Bedoschi G et al. A prospective longitudinal analysis of the predictors of amenorrhea after breast cancer chemotherapy: Impact of *BRCA* pathogenic variants. *Cancer Medicine.* 2023;12:19225–19233.

Contraceptive Options for Women after Diagnosis of Breast Cancer

	Oxford LoE	Oxford GR	AGO
▪ **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	+

Contraception (general)

1. Moormann PG, Havrilesky LJ, Giersch JM et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis.J Clin Oncol. 2013 Nov 20;31(33):4188-98.
2. Lambertini M, Massarotti C, Havas et al. Contraceptive Use in Premenopausal Women With Early Breast Cancer. JAMA Netw Open. 2022;5(9)
3. Fitzpatrick D, Pirie K, Reeves G, et al. (2023) Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case–control study and meta-analysis. PLoS Med 20(3): e1004188

LNG-IUDs

1. Dominick S et al: Levonogestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database syst Rev 2015; Dec 9; 12: CD007245.
2. Soini T, Hurskainen R, Grénman S et al.: Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. Acta Oncol. 2016 Feb;55(2):188-92.
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meta-analysis. Int J Clin Exp Pathol. 2014 Sep 15;7(10):6419-29. eCollection 2014. Review.

Emergency Contraception - Options after Diagnosis of Breast Cancer

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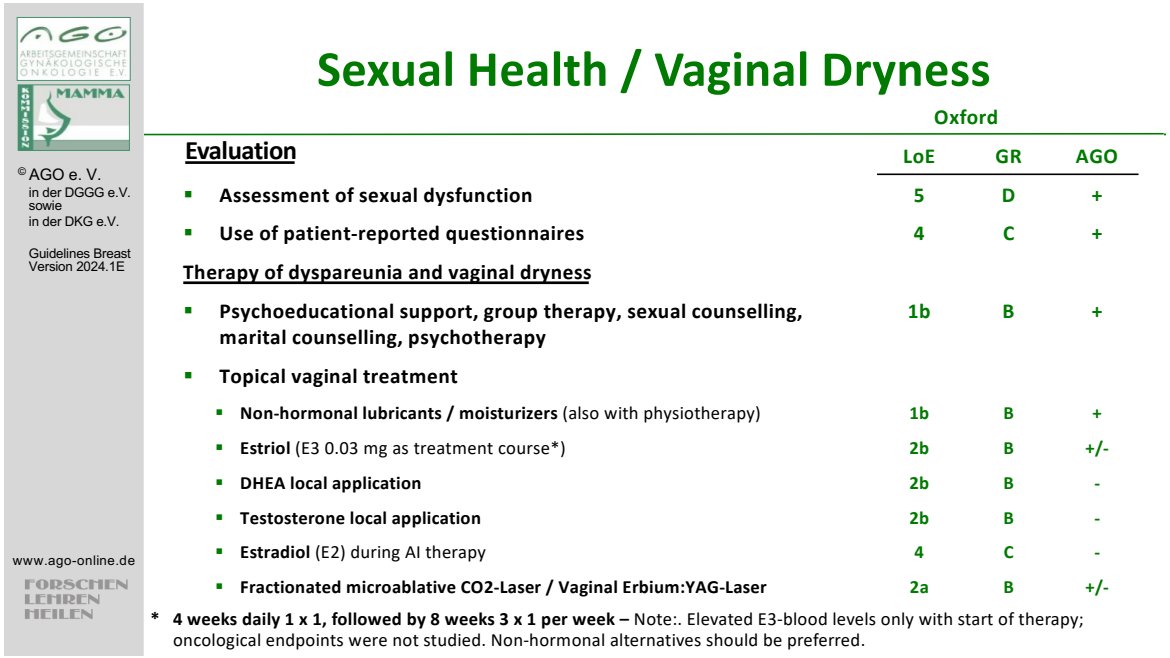

Sexual Health / Vaginal Dryness

Evaluation	Oxford LoE	GR	AGO
▪ **Assessment of sexual dysfunction**	5	D	+
▪ **Use of patient-reported questionnaires**	4	C	+
Therapy of dyspareunia and vaginal dryness			
▪ **Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy**	1b	B	+
▪ **Topical vaginal treatment**			
▪ **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.

Reviews:

1. The North American Menopause Society (NAMS). The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020 Sep;27(9):976-992.
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Evaluation

Sexual Complaints Screener For Women:

1. Burri A, Porst H. Preliminary Validation of a German Version of the Sexual Complaints Screener for Women in a Female Population Sample. Sex Med. 2018 Jun;6(2):123-130.
2. Rosen R, Brown C, Heiman J et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000 Apr-Jun;26(2):191-208.
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Treatment of vaginal dryness:

Education, Group therapy, counselation:

1. Carroll AJ, Baron SR, Carroll RA. Couple-based treatment for sexual problems following breast cancer: A review and synthesis of the literature. Support Care Cancer. 2016 Aug;24(8):3651-9.
2. Huynh V, Vemuru S, Hampanda K, et al. No One-Size-Fits-All: Sexual Health Education Preferences in Patients with Breast Cancer. Ann Surg Oncol. 2022;29(10):6238-6251.

Non-hormonal treatment:

1. Juraskova I, Jarvis S, Mok K et al. The acceptability, feasibility, and efficacy (phase I/II study) of the OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR) intervention to improve dyspareunia and alleviate sexual problems in women with breast cancer. J Sex Med. 2013 Oct;10(10):2549-58.

Vaginal topic treatment

1. Donders G, Belle G, Neven P et al.: Effect of ultra-low-dose estriol and lactobacilli vaginal tablets (Gynoflor®) on inflammatory and infectious markers of the vaginal ecosystem in postmenopausal women with breast cancer on aromatase inhibitors. Eur J Clin Microbiol Infect Dis (2015) 34:2023–2028
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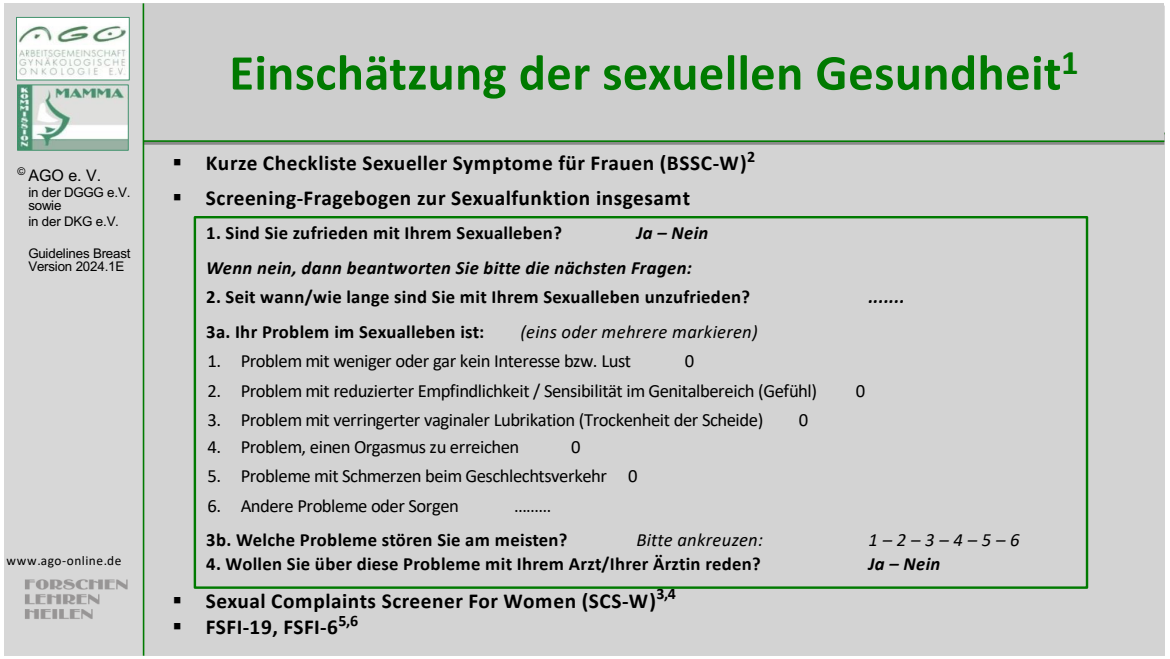

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