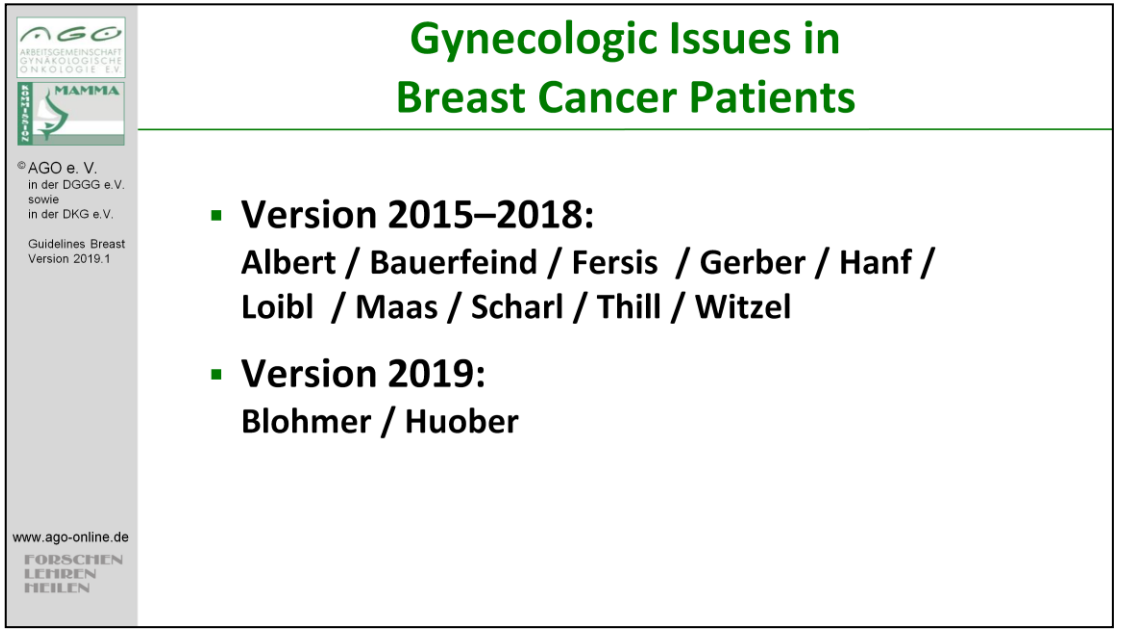
Guidelines Breast
Version 2019.1

Gynecological Issues in Breast Cancer Patients

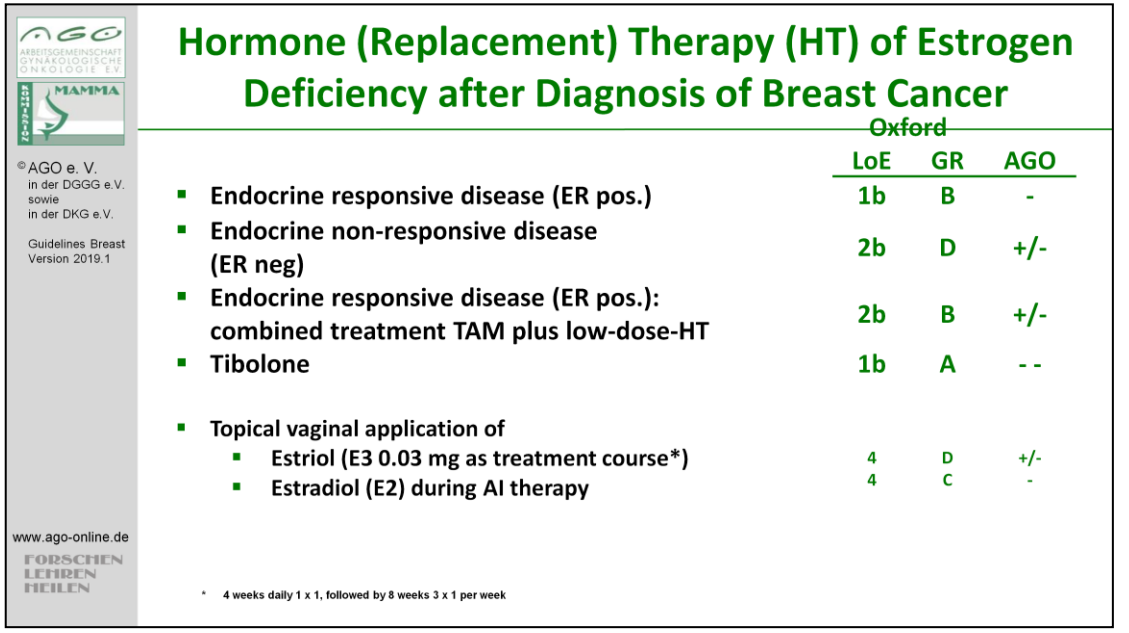
www.ago-online.de
FORSCHEN
LEHREN
HEILEN



Screened data bases:

Pubmed	2009 –2018
ASCO	2009 - 2018
Cochrane	2009 - 2018
Medline	2009 - 2018

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies



Endocrine 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 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

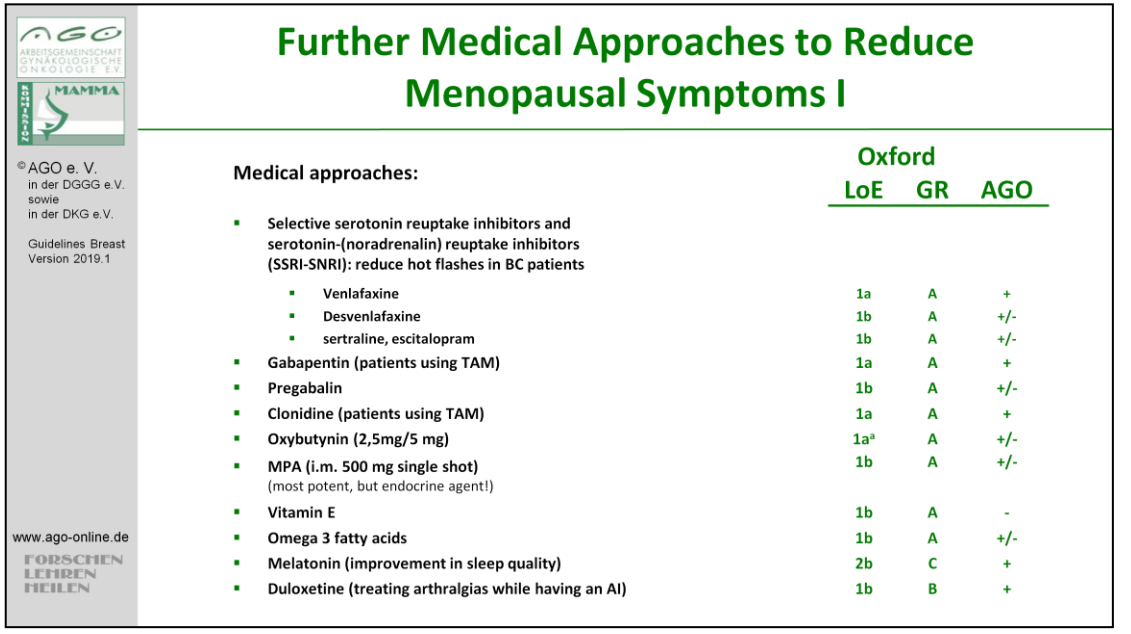
1. Holmberg L: Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst 100:475-82, 2008.
2. Fahlén M: Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. Eur J Cancer. 2013 Jan;49(1):52-9.
3. Lupo M, Dains JE, Madsen LT. Hormone Replacement Therapy: An Increased Risk of Recurrence and Mortality for Breast Cancer

Patients? J Adv Pract Oncol. 2015 Jul-Aug;6(4):322-30. Epub 2015 Jul

4. 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. Sismondi P., Kimmig R., Kubista E. et al.: Effects of Tibolone on climacteric symptoms and quality of life in breast cancer patients—Data from LIBERATE trial. Maturitas. 2011;70:365–372.
2. 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.



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).
3. L'Espérance S: Pharmacological and non-hormonal treatment of hot flashes in breast cancer survivors: CEPO review and recommendations. Support Care Cancer. 2013 May;21(5):1461-74
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.

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.

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.
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.
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

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

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.
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
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)

Oxybutynin

1. Roberto A. Leon-Ferre, Paul J. Novotny, Stephanie S. Faubion et al. A randomized, double-blind, placebo-controlled trial of oxybutynin for hot flashes : ACCRU study SC-1603. SABCS 2018, abstract GS6_2

(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.

Vitamine E

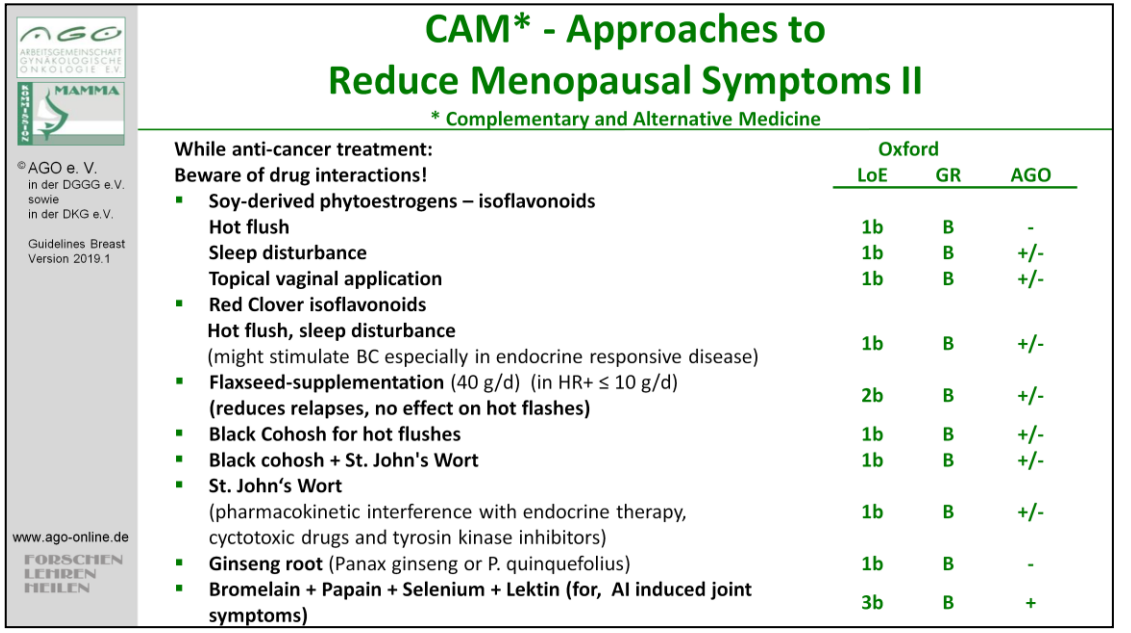
1. Rada G: Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review). The Cochrane Library 2010, Issue 9.
2. Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat. 2009 Jun;115(3):437-52.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



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.

Soy- derieved 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.
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.
6. Ghazanfarpour M, Latifnejad Roudsari R, Treglia G et al.: Topical administration of isoflavones for treatment of vaginal symptoms in postmenopausal women: A systematic review of randomised controlled trials. J Obstet Gynaecol. 2015 Nov;35(8):783-7.
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

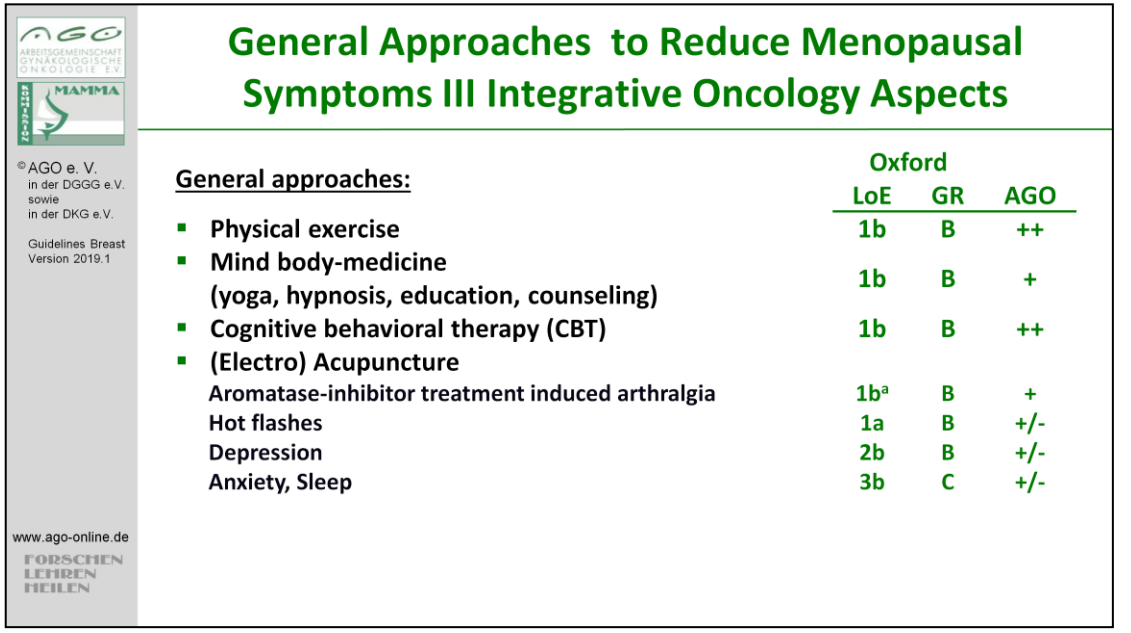
1. Leach MJ: Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012; 9:CD007244.
2. Caraci F: Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metab. 2011 Jul 1;12(6):570-7.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

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.



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. doi: 10.1136/bmjopen-2017-015860.

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.
2. Hartman SJ, Nelson SH, Myers E et al.: Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study. Cancer. 2018 Jan 1;124(1):192-202. doi: 10.1002/cncr.30987. Epub 2017 Sep 19.

Mind Body Medicine

1. Mann E: Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. Lancet Oncol. 2012 Mar;13(3):309-18.

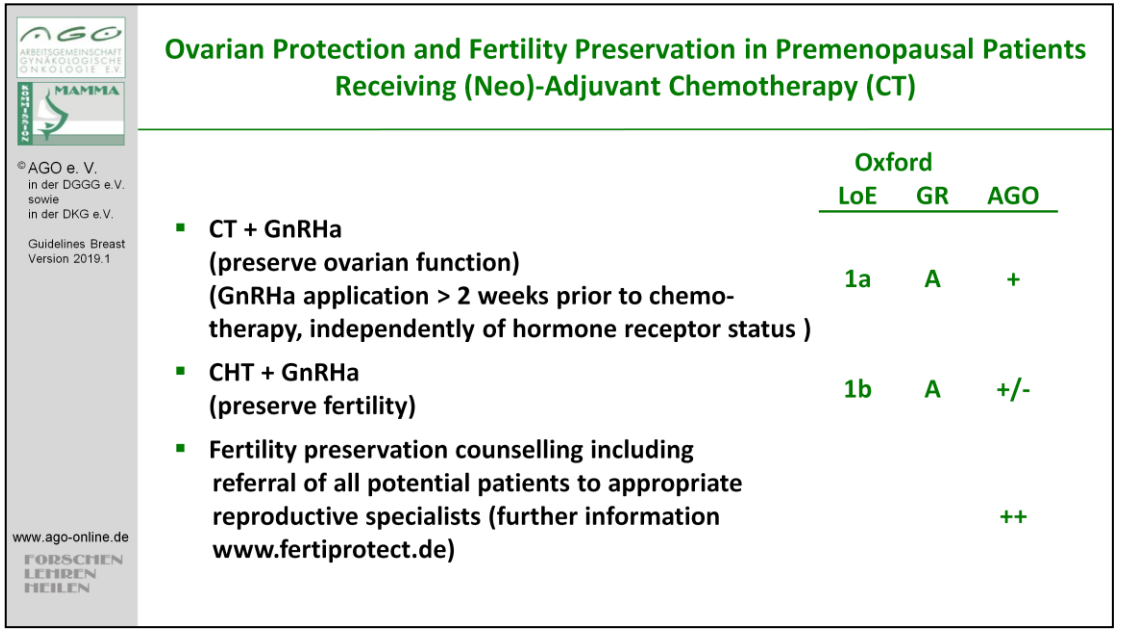
2. Buffart LM: Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC Cancer. 2012 Nov 27;12:559.
3. Cramer H: Characteristics of randomized controlled trials of yoga: a bibliometric analysis. BMC Complement Altern Med. 2014 Sep 2;14:328.
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.
6. Stefanopoulou E, Grunfeld EA. Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review. J Psychosom Obstet Gynaecol. 2017;38(3):210-25
7. Tao WW, Tao XM, Song CL. Effects of non-pharmacological supportive care for hot flushes in breast cancer: a meta-analysis. Support Care Cancer. 2017;25(7):2335-47
8. van Driel CM, Stuursma A, Schroevers MJ et al. Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis. BJOG. 2019 Feb;126(3):330-339. doi: 10.1111/1471-0528.15153. Epub 2018 Mar 15.

Cognitive behavioral therapy

1. Mewes JC, Steuten LM, Duijts SF et al.: Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients. J Cancer Surviv. 2015 Mar;9(1):126-35. doi: 10.1007/s11764-014-0396-9. Epub 2014 Sep 2.
2. Desautels C, Savard J, Ivers H et al.: Treatment of Depressive Symptoms in Patients with Breast Cancer: A Randomized Controlled Trial Comparing Cognitive Therapy and Bright Light Therapy. Health Psychol. 2017 Nov 27. doi: 10.1037/hea0000539. [Epub ahead of print]

Acupuncture

1. Chiu HY1, Shyu YK, Chang PC et al.: Effects of Acupuncture on Menopause-Related Symptoms in Breast Cancer Survivors: A Meta-analysis of Randomized Controlled Trials. Cancer Nurs. 2016 May-Jun;39(3):228-37.
2. Garland SN1, Xie SX, Li Q et al.: Comparative effectiveness of electro-acupuncture versus gabapentin for sleep disturbances in breast cancer survivors with hot flashes: a randomized trial. Menopause. 2017 May;24(5):517-523. doi: 10.1097/GME.0000000000000779.
3. Chen L, Lin CC, Huang TW et al.: Effect of acupuncture on aromatase inhibitor-induced arthralgia in patients with breast cancer: A meta-analysis of randomized controlled trials. Breast. 2017;33:132-8.
4. Chien TJ, Hsu CH, Liu CY et al.: Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis. PLoS One. 2017;12(8):e0180918.
5. Hershman DL, Unger JM, Greenlee H et al.: Randomized blinded sham- and waitlist-controlled trial of acupuncture for joint symptoms related to aromatase inhibitors in women with early stage breast cancer (S1200). San Antonio Breast Cancer Conference 2017; Abstract GS4-04.
6. Hershman DL, Unger JM, Greenlee H et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA. 2018 Jul 10;320(2):167-176. doi: 10.1001/jama.2018.8907.
7. Wang W, Liu Y, Sun S et al. Electroacupuncture for postmenopausal women with stress urinary incontinence: secondary analysis of a randomized controlled trial. World J Urol. 2018 Oct 13. doi: 10.1007/s00345-018-2521-2. [Epub ahead of print]
8. Befus D, Coeytaux RR, Goldstein KM et al. Management of Menopause Symptoms with Acupuncture: An Umbrella Systematic Review and Meta-Analysis. J Altern Complement Med. 2018 Apr;24(4):314-323. doi: 10.1089/acm.2016.0408. Epub 2018 Jan 3.



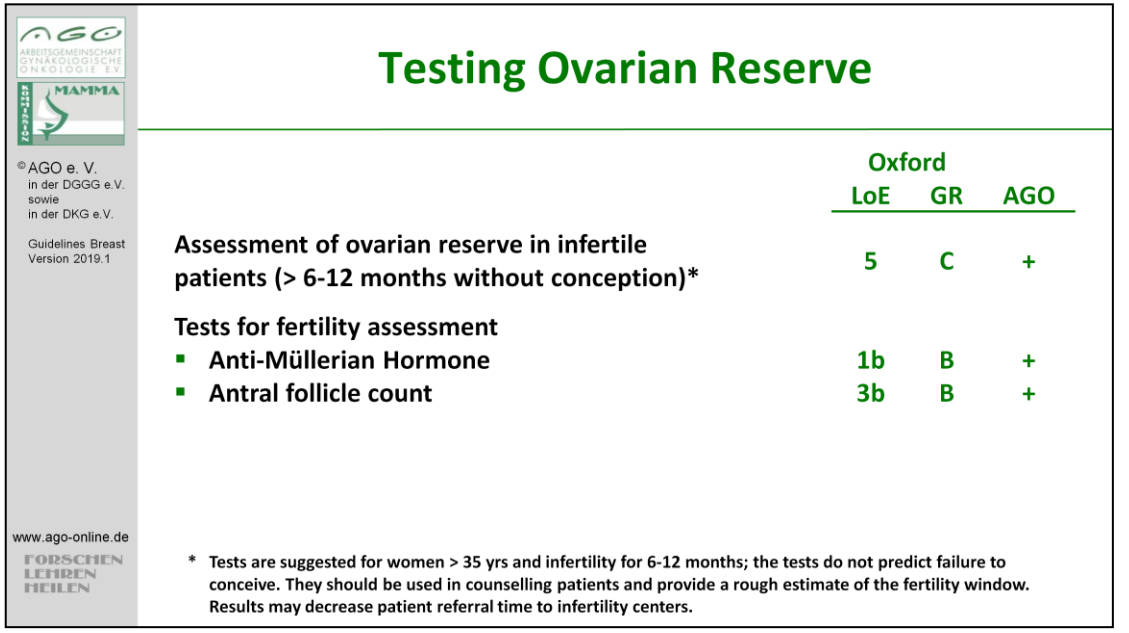
1. Munholz RR, Pereira AA, Sasse AD et al. Gonadotropin-releasing hormone agonists for ovarian preservation in premenopuasal women undergoing chemotherapy for early-stage breast cancer. JAMA Oncol 2016;2(1): 65-73.
2. Shandley LM, Spencer JB, Fothergill A et al. Impact of tamoxifen on fertility in breast cancer survivors. Fertil Steril 2017;107(1):243-2523.
3. https://www.awmf.org/uploads/tx_szleitlinien/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12.pdf
4. Shen YW, Zhang XM, Lv M et al. Utility of gonadotropin-releasing hormone agonists for prevention of chemotherapyinduced ovarian damage in premenopausal women with breast cancer: a systematic review and meta-analysis. OncoTargets and Therapy 2015; 8: 3349-3359.
5. Lambertini M, Ceppi M, Poggio F et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol 2015; 26: 2408-2419.
6. 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(19):1981-1990. doi: 10.1200/JCO.2018.78.0858.

7. Paluch-Shimon S, Pagani O, Partridge AH, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast 2017;35: 203 – 217.
8. Oktay K, Harvey BE, Partridge AH et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36:1994–2001. 10.1200/JCO.2018.78.1914
9. Moore HCF, Unger JM, Phillips KA et al. Final Analysis of the Prevention of Early Menopause Study (POEMS)/SWOG Intergroup S0230. J Natl Cancer Inst. 2018 Oct 27. doi: 10.1093/jnci/djy185. [Epub ahead of print]

Ovarieller Funktionserhalt – Synopse der randomisierten Studien

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

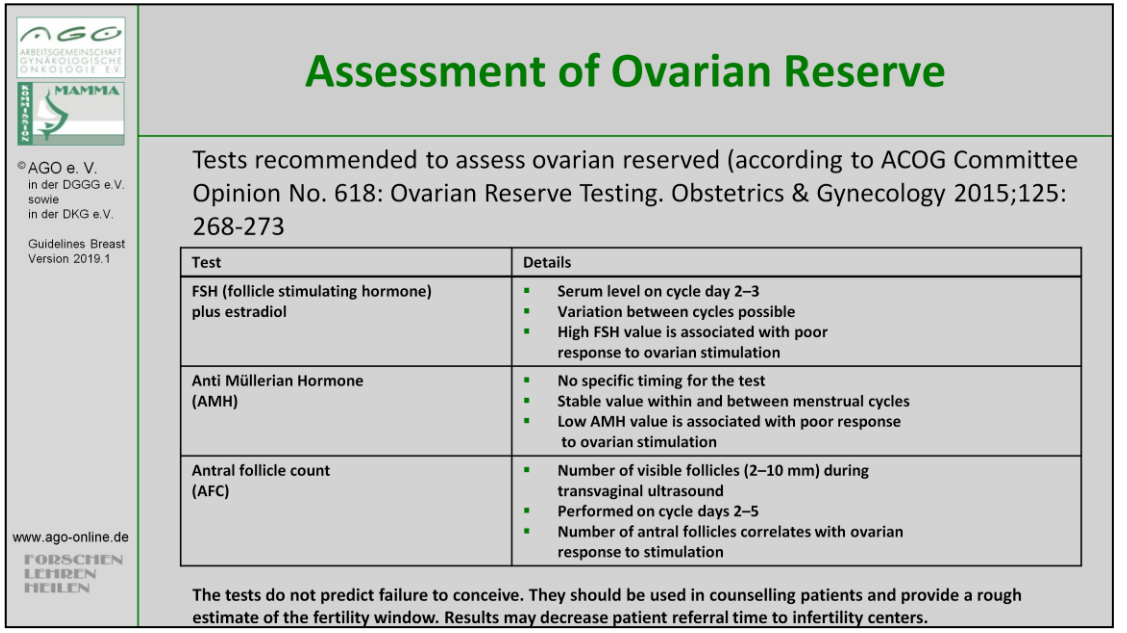
1. Munhoz RR, Pereira AA, Sasse AD et al.: Gonadotropin-Releasing Hormone Agonists for Ovarian Function Preservation in Premenopausal Women Undergoing Chemotherapy for Early-Stage Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Jan 1;2(1):65-73.
2. Gerber B, von Minckwitz G, Stehle H et al.: Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011 Jun 10;29(17):2334-41.
3. Del Mastro L, Boni L, Michelotti A et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. JAMA. 2011 Jul 20;306(3):269-76.
4. Munster PN, Moore AP, Ismail-Khan R et al.: Randomized Trial Using Gonadotropin-Releasing Hormone Agonist Triptorelin for the Preservation of Ovarian Function During (Neo)Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol. 2012;30(5):533–8.
5. Moore HCF, Unger JM, Phillips K-A et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372(10):923–32.
6. Leonard RCF, Adamson DJA, Bertelli G et al.: GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: the Anglo Celtic Group OPTION trial. Ann Oncol. 2017 Aug 1;28(8):1811-1816. doi: 10.1093/annonc/mdx184.



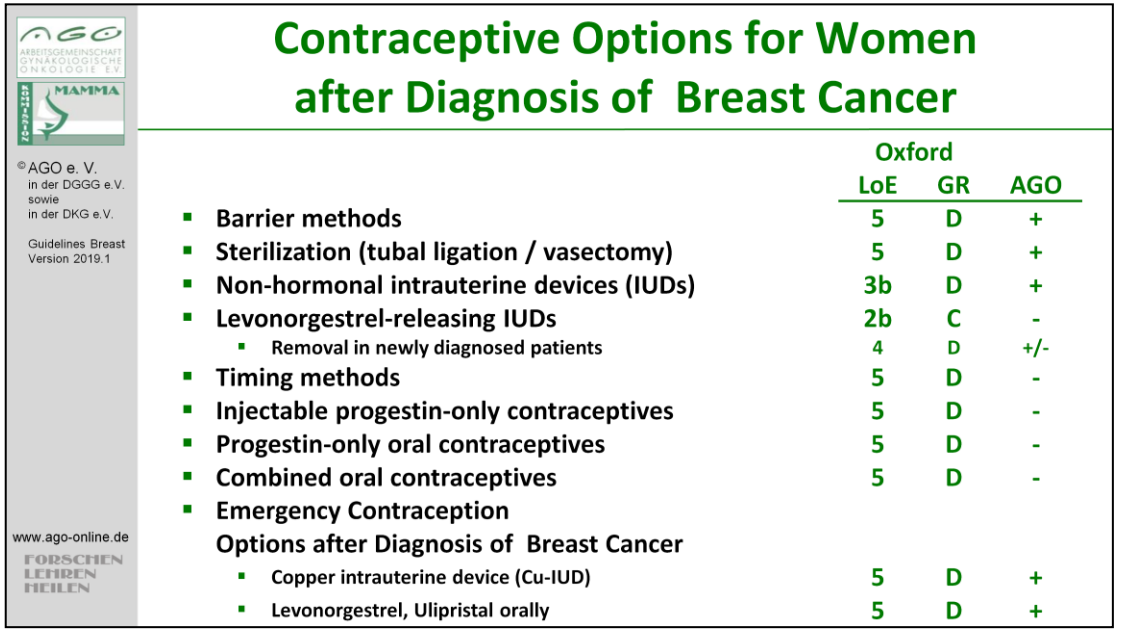
1. Anderson RA, Rosendahl M, Kelsey TW et al.: Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer. Eur J Cancer. 2013 Nov;49(16):3404-11.
2. Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. J Clin Endocrinol Metab. 2011 May;96(5):1336-43.
3. 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.
4. Miyoshi Y, Yasuda K, Tachibana M et al.: Longitudinal observation of serum anti-Müllerian hormone in three girls after cancer treatment. Clin Pediatr Endocrinol. 2016 Oct;25(4):119-126.
5. 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.
6. 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.
7. Anderson RA, Mansi J, Coleman RE et al.: The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian

function following chemotherapy for early breast cancer. Eur J Cancer. 2017 Dec;87:58-64. doi: 10.1016/j.ejca.2017.10.001. Epub 2017 Nov 5.

8. Morarji K, McArdle O, Hui K et al.: Ovarian function after chemotherapy in young breast cancer survivors. Curr Oncol. 2017 Dec;24(6):e494-e502. doi: 10.3747/co.24.3335. Epub 2017 Dec 20.



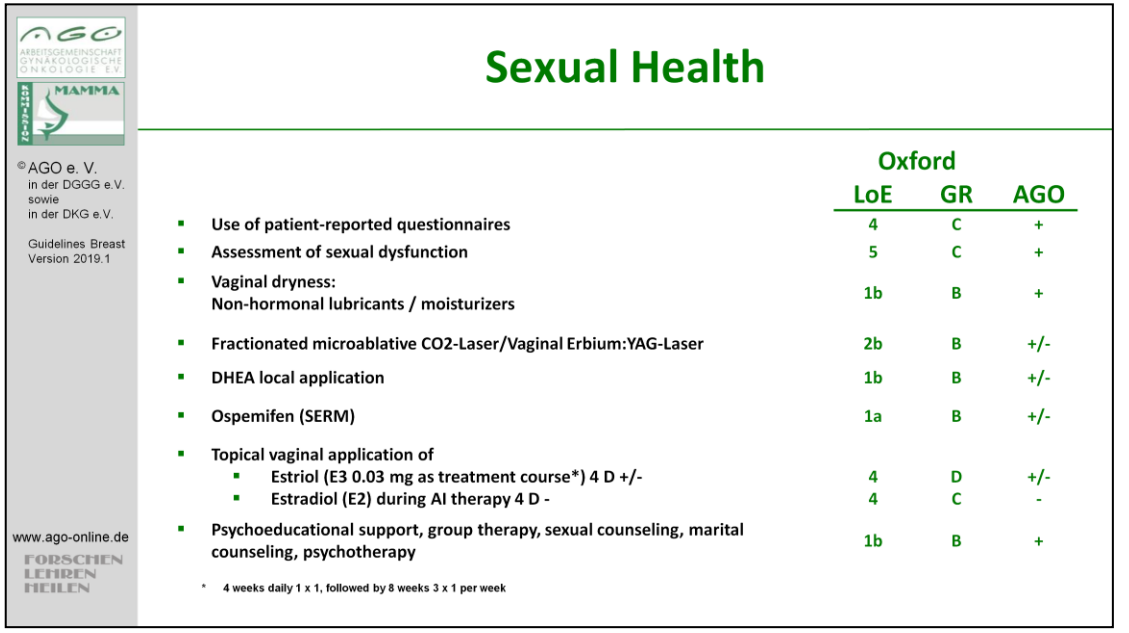
Tests recommended to assess ovarian reserved (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015 ;125 : 268–273



1. Lu, Y., Ma, H., Malone, K.E. et al. Oral contraceptive use and survival in women with invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20: 1391–1397
2. 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.
3. 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.
4. 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.
5. Yun Fu Zhigang Zhuang: Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis Int J Clin Exp Pathol 2014; 7 (10) 6419-6429
6. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis. Int J Clin Exp Pathol. 2014 Sep 15;7(10):6419-29. eCollection 2014. Review.

<u>Emergency Contraception - Options after Diagnosis of Breast Cancer</u>

1. Casay PM et al: Caring for breast cancer survivor‘s health and well beeing WJCO 2014;10: 5 (4): 693-704



Runowicz CD, Leach CR, Henry NL et al.: American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2015 Dec 7. pii: JCO.2015.64.3809

Vaginal dryness

1. 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. doi: 10.1007/s10549-015-3434-z. Epub 2015 May 24.
2. Advani P, Brewster AM, Baum GP et al.: A pilot randomized trial to prevent sexual dysfunction in postmenopausal breast cancer survivors starting adjuvant aromatase inhibitor therapy. J Cancer Surviv. 2017;11(4):477-85
3. Kim YH, Park S, Lee M et al.: Effect of a pH-Balanced Vaginal Gel on Dyspareunia and Sexual Function in Breast Cancer Survivors Who Were Premenopausal at Diagnosis: A Randomized Controlled Trial. Obstet Gynecol. 2017;129(5):870-6.
4. Mitchell CM, Reed SD, Diem S et al. Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. JAMA Intern Med. 2018 May 1;178(5):681-690. doi:

10.1001/jamainternmed.2018.0116.

Laser therapy

1. Salvatore S, Pitsouni E, Del Deo F et al.: Sexual Function in Women Suffering From Genitourinary Syndrome of Menopause Treated With Fractionated CO2 Laser. Sex Med Rev. 2017;5(4):486-94
2. Gambacciani M, Levancini M. Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. Menopause. 2017;24(3):316-9.
3. Arunkalaivanan A, Kaur H, Onuma O. Laser therapy as a treatment modality for genitourinary syndrome of menopause: a critical appraisal of evidence. Int Urogynecol J. 2017;28(5):681-5.
4. Rabley A, O'Shea T, Terry R et al. Laser Therapy for Genitourinary Syndrome of Menopause. Curr Urol Rep. 2018 Aug 17;19(10):83. doi: 10.1007/s11934-018-0831-y.
5. Gambacciani M, Levancini M, Russo E et al. Long-term effects of vaginal erbium laser in the treatment of genitourinary syndrome of menopause. Climacteric. 2018 Apr;21(2):148-152. doi: 10.1080/13697137.2018.1436538. Epub 2018 Feb 13.
6. Cruz VL, Steiner ML, Pompei LM et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. Menopause. 2018 Jan;25(1):21-28. doi: 10.1097/GME.0000000000000955.

Lokal DHEAS

1. Barton DL, Sloan JA, Shuster LT et al. Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). Support Care Cancer. 2018 Feb;26(2):643-650. doi: 10.1007/s00520-017-3878-2. Epub 2017 Sep 18.
2. Labrie F, Archer DF, Koltun W et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause. 2018 Nov;25(11):1339-1353. doi: 10.1097/GME.0000000000001238.
3. 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. doi: 10.1097/GME.0000000000001138.

Ospemifen

1. Lee A, Kim TH, Lee HH et al. Therapeutic Approaches to Atrophic Vaginitis in Postmenopausal Women: A Systematic Review with a Network Meta-analysis of Randomized Controlled Trials. J Menopausal Med. 2018 Apr;24(1):1-10. doi: 10.6118/jmm.2018.24.1.1. Epub 2018 Apr 30.
2. Di Donato V, Schiavi MC, Iacobelli V et al. Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part I: Evaluation of efficacy. Maturitas. 2018 Nov 24. pii: S0378-5122(18)30742-4. doi: 10.1016/j.maturitas.2018.11.016. [Epub ahead of print]

Topical Vaginal Application:

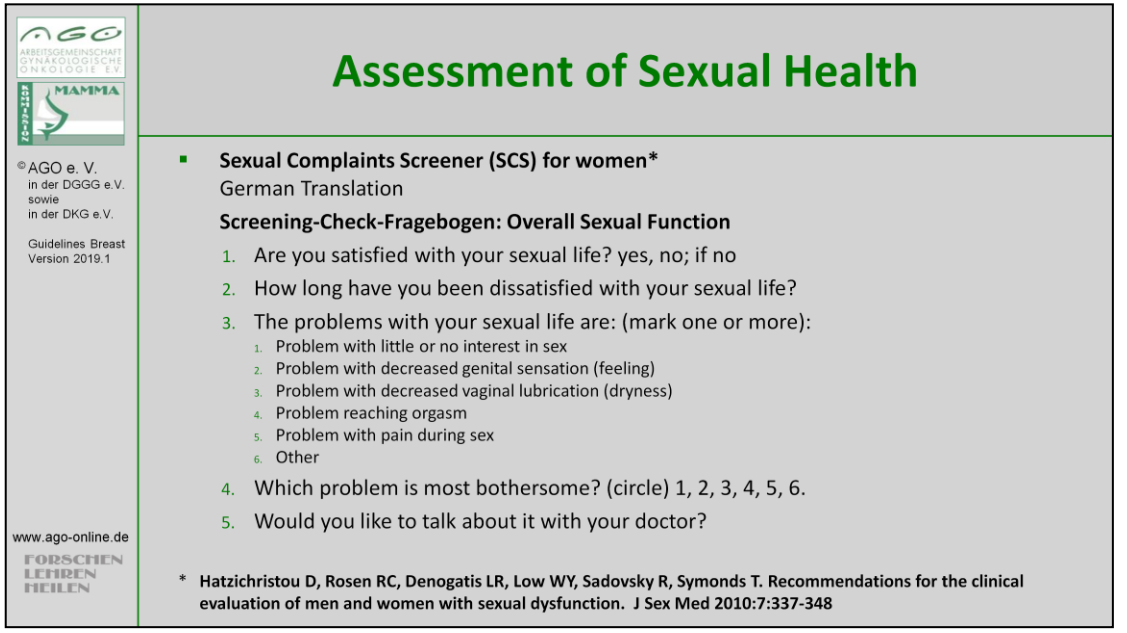
1. Biglia N, Peano E, Sgandurra P, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrinol 2010;26(6):404–12
2. Le Ray I., Dell'Aniello S., Bonnetain F. et al.: Local estrogen therapy and risk of breast cancer 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
4. Buchholz S, Mögele M, Lintermans A et al.: Vaginal estriol-lactobacilli combination and quality of life in endocrine-treated breast cancer. Climacteric. 2015;18(2):252-9.
5. 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
6. Cold S et al. Vaginal estrogens and risk of recurrence or death in women treated for estrogen receptor positive breast cancer,

European Journal of Cancer 2015,51, S3 (Abstract)

7. 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. doi: 10.1007/s10549-015-3434-z. Epub 2015 May 24.
8. Melisko ME, Goldman ME, Hwang J et al. (2017): Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. JAMA Oncol. 3(3):313-319.
9. 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

Paartherapie

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. doi: 10.1007/s00520-016-3218-y. Epub 2016 May 6.



1. Hatzichristou D, Rosen RC, Denogatis LR et al.: Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010:7:337-348