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Guidelines Breast
Version 2025.1E

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**FORSCHEN
LEHREN
HEILEN**

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Gynecological Issues, Pregnancy and Reproduction in Breast Cancer Patients



Gynecologic Issues, Pregnancy and Reproduction in Breast Cancer Patients

- **Versions 2015–2024:**
Albert / Bauerfeind / Blohmer / Fehm / Fersis / Gerber / Hanf /
Hooper/ Loibl / Maas / Mundhenke /Reimer / Rody / Scharl /
Stickeler/ Thill / Thomssen / Witzel
- **Version 2025:**
Park-Simon / Witzel

Screened data bases:

Pubmed	2009 –2024
ASCO	2009 - 2024
SABCS	2009 - 2024

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*)	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, then 1-2 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.
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. 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.
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6. Paggio F, Del Mastro L, Bruzzone M et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. Breast Cancer Res Treat. 2022 191(2):269-72.
7. 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. van Barele M, Heemskerk-Gerritsen BAM, Louwers YV, et al. Estrogens and Progestogens in Triple Negative Breast Cancer: Do They Harm? *Cancers (Basel)*. 2021 May 21;13(11):2506. doi: 10.3390/cancers13112506. PMID: 34063736; PMCID: PMC8196589.
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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. 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.
2. 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.
3. 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.

Ospemifeme

1. 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.
2. 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.
3. Meriggiola MC, Villa P, Maffei S, et al; PEONY Study Group. Vulvovaginal atrophy in women with and without a history of breast cancer: Baseline data from the PatiEnt satisfactiON studY (PEONY) in Italy. *Maturitas*. 2024 May;183:107950. doi: 10.1016/j.maturitas.2024.107950. Epub 2024 Mar 5. PMID: 38462385.

Topical Vaginal Application:

1. 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.
2. 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
3. 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.
4. Cold S, Cold F, Jensen MB, et al. Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. *J Natl Cancer Inst*. 2022 Oct 6;114(10):1347-1354. doi: 10.1093/jnci/djac112. PMID: 35854422; PMCID: PMC9552278.
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. 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
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8. 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) 222–23
9. Jain AL, Jamy O, Mullins J et al. Usefulness of patient-reported outcomes to assess the effectiveness of topical hormonal therapy for gynecologic symptoms after antihormonal treatment for breast cancer. *Proc (Bayl Univ Med Cent)*. 2020 Apr 7;33(3):331-335.
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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Further Medical Approaches to Reduce Menopausal Symptoms I

	Oxford		
	LoE	GR	AGO
Medical approaches* (reduction of hot flushes)			
▪ Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flushes in BC patients			
▪ Venlafaxine	1a	A	+
▪ Desvenlafaxine, Sertraline, Escitalopram	2b	B	+/-
▪ Gabapentin (patients using TAN)	2b	B	+
	5	D	+/-
▪ Neurokinin-3 receptor antagonists (fezolinetant) (note: oncological endpoints were not studied)			
▪ Pregabalin	1b	A	+/-
▪ Clonidin 0,05-0,15 mg/die (patients using TAM)	2a	B	+/-
▪ Oxybutynin (2,5 mg / 5 mg)	1b	A	+/-
▪ MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!)	1b	B	+/-
▪ Vitamin E	1b	A	-
Medical approaches (other treatment goals)			
▪ Melatonin (improvement of sleep quality)	2b	C	+
▪ Duloxetine (treating arthralgias while on AI)	1b	B	+
▪ Omega 3 fatty acids (treating arthralgias while on AI)	1b	B	+/-

* Note: Substantial placebo-effect has been proven (23-57%) *LoE 1b A +*

- Gallagher S, Johnstone A, De Livera A, et al. A survey of women diagnosed with breast cancer experiencing oncology treatment-induced hot flushes: identification of specific characteristics as predictors of hot flush occurrence, frequency, and severity. *J Cancer Surviv.* 2024 Jul 31. doi: 10.1007/s11764-024-01647-7. Epub ahead of print. PMID: 39085555.
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Venlafaxine

- 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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- 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.
- Taleghani SY, Etesam F, Esfandbod M. Evaluation and Comparison of Citalopram and Venlafaxine for Management of Hot Flashes in Women with Breast Cancer. *Drug Res (Stuttg).* 2023 Oct;73(8):465-472. doi: 10.1055/a-2061-7020. Epub 2023 Aug 30. PMID:

37647930.

Desvenlafaxine

1. Kim Y, Yeom CW, Lee HJ, et al. Differential effects of desvenlafaxine on hot flashes in women with breast cancer taking tamoxifen: a randomized controlled trial. NPJ Breast Cancer. 2024 Jul 17;10(1):59. doi: 10.1038/s41523-024-00668-w. PMID: 39019875; PMCID: PMC11255222.

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

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Gabapentin

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2. Garland SN, 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. PMID: 27875389; PMCID: PMC5403590.
3. Shan D, Zou L, Liu X, et al. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020 Jun;222(6):564-579.e12.

Neurokinin-3. Rezeptor Antagonisten:

1. Fraser GL, Lederman S, Waldbaum A, et al. A phase 2b, randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. *Menopause*. 2020;27(4):382-392.
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Pregabalin

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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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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.

(D) MPA (depo-) (Medroxyprogesterone acetate)

1. 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. 2020 May;28(5):2139-2143. doi: 10.1007/s00520-019-05013-7. Epub 2019 Aug 11. PMID: 31402403.
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Vitamine E

1. Rada G: Non-hormonal interventions for hot flashes 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 flashes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric. 2009 Aug;12(4):310-8.

Sleep disturbances

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

Aromatase-inhibitor induced arthralgia

1. Bae K, Lamoury G, Carroll S, et al. Comparison of the clinical effectiveness of treatments for aromatase inhibitor-induced arthralgia in breast cancer patients: A systematic review with network meta-analysis. Crit Rev Oncol Hematol. 2023 Jan;181:103898. doi: 10.1016/j.critrevonc.2022.103898. Epub 2022 Dec 16. PMID: 36535489.

Duloxetine

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. PMID: 29136387; PMCID: PMC5805479.

Omega fatty acid

1. Hershman DL, Unger JM, Crew KD, et al. Randomized Multicenter Placebo-Controlled Trial of Omega-3 Fatty Acids for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain: SWOG S0927. *J Clin Oncol*. 2015 Jun 10;33(17):1910-7. doi: 10.1200/JCO.2014.59.5595. Epub 2015 May 4. PMID: 25940724; PMCID: PMC4451174
2. 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.

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, cytotoxic 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.
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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. 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.
3. 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.

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7. Rowe IJ, Baber RJ. The effects of phytoestrogens on postmenopausal health. *Climacteric*. 2021 Feb;24(1):57-63. doi: 10.1080/13697137.2020.1863356. Epub 2021 Jan 4. PMID: 33395316.
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9. Shakeri F: Effectiveness of red clover in alleviating of menopausal symptoms: A 12-week randomized, controlled trial. *Climacteric*. 2015;18(4):568-73.

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. Castelo-Branco C, Gambacciani M, Cano A, et al. Review & meta-analysis: isopropanolic black cohosh extract iCR for menopausal symptoms - an update on the evidence. *Climacteric*. 2021 Apr;24(2):109-119. doi: 10.1080/13697137.2020.1820477. Epub 2020 Oct 6. PMID: 33021111.
2. Fritz H, Seely D, McGowan J, et al. Black cohosh and breast cancer: a systematic review. *Integr Cancer Ther*. 2014;13:12-29
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4. Kim MS: Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials. *J Ginseng Res*. 2013

Mar;37(1):30-6.

5. Mehrpooya M, Rabiee S, Larki-Harchegani A, et al. 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.
6. Ruan X, Mueck AO, Beer AM, et al. Benefit-risk profile of black cohosh (isopropanolic *Cimicifuga racemosa* extract) with and without St John's wort in breast cancer patients. *Climacteric*. 2019 Aug;22(4):339-347. doi: 10.1080/13697137.2018.1551346. Epub 2019 Jan 10. PMID: 30626212.
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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.
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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			

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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*)	2b	B	+/-
▪ DHEA local application	2b	B	-
▪ Testosterone local application	2b	B	-
▪ Estradiol (E2) during AI therapy	4	C	-
▪ Fractionated microablative CO ₂ -Laser / Vaginal Erbium:YAG-Laser	1b	B	+/-

* 4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week, then 1-2 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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Ovarian Protection and Fertility Preservation in Premenopausal Patients

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> CTx + GnRHα (preservation of ovarian function) (GnRHα application > 2 weeks prior to chemo-therapy, independent of hormone receptor status) 	1a	A	+
<ul style="list-style-type: none"> CTx + GnRHα (preservation of fertility) 	2a	B	+/-
<ul style="list-style-type: none"> 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) 			++
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation¹ 	2a	C	+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Cryopreservation of ovarian tissue with subsequent transplantation² 	4	D	+
<ul style="list-style-type: none"> ART after diagnosis of breast cancer¹ 	4	C	+/-

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

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

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Pregnancy rates

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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	Amenorrhoea with elevated FSH levels between 12 and 24 months
Primary objective	to detect 30% absolute increase of menstruation rate	to detect at least 20% absolute reduction in early menopause	to detect 20% difference in amenorrhoea rate – from 10% to 30%		To detect 20%-25% absolute reduction in early menopause
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only independent predictive factor	Age, total cyclophosphamide dose and baseline AMH
Resumption of menses at month 12	83% with LHRH vs. 80% w/o	93% with LHRHa vs. 74% w/o	74% with LHRH vs. 68% w/o	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%	78% with LHRHa vs. 62% amenorrhoea 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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Guidelines Breast
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FORSCHEN
LEHREN
HEILEN

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

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

COS before starting treatment (n=11 studies):

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

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

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

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

ART after treatment (n=4 studies):

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

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

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

Arecco et al. Human Reprod 2022

1. 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.

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:

1. 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;87:58-64
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.
4. 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.
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, Niu J, 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.

Breast Cancer During Pregnancy or Breast Feeding* - Diagnostics and Surgery -

	Oxford		
	LoE	GR	AGO
▪ Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)	4	C	++
▪ Staging if indicated (bone scan after delivery)	5	D	+
▪ Full body MRI (without contrast agent)	4	C	+/-
▪ Surgery like in non-pregnant patients	4	C	++
▪ Sentinel node excision (technetium only)	2a	B	+
▪ SLNE during 1 st trimester	5	D	+/-
▪ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
▪ Blue dye (not tested in pregnant animals or humans)	4	C	--

* Participation in register study recommended

Study link: <http://germanbreastgroup.de/studien/adjutant/brustkrebs-in-der-schwangerschaft.html>

1. Loibl S, Azim HA Jr, Bachelot T et al. ESMO Expert Consensus Statements on the management of breast cancer during pregnancy (PrBC). Ann Oncol. 2023 Oct;34(10):849-866.
2. Peccatori FA 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. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

Outcome information (e.g. GBG registry)

1. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol. 2013 Jul 10;31(20):2532-9.
2. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012 Sep;13(9):887-96.
3. Raphael J, Trudeau ME, Chan K. Outcome of patients with pregnancy during or after breast cancer: a review of the recent literature. Curr Oncol. 2015 Mar;22(Suppl 1):S8-S18

Statement: Breast imaging & biopsy like in non-pregnant

1. Athanasiou A, Appelman L, Pijnappel RM, et al. ESR Essentials: diagnostic work-up in patients with symptomatic breast disease-practice recommendations by the European Society of Breast Imaging. Eur Radiol. 2024 Jul 31. doi: 10.1007/s00330-024-10980-5.
2. Di Florio-Alexander RM, Slanetz PJ, Moy L et al. ACR Appropriateness Criteria((R)) Breast Imaging of Pregnant and Lactating Women. Journal of the American College of Radiology : JACR 2018;15(11s):S263-s75.
3. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70
4. Zafrakas M, Papasozomenou P, Gereade A, et al. Screening and Diagnostic Mammography During Pregnancy and Lactation: A Systematic Review of the Literature. Cureus. 2024 Aug 8;16(8):e66465. doi: 10.7759/cureus.66465.

Statement: Staging: ultrasound, chest X-ray if indicated

1. Wang PI, et al. Imaging of pregnant and lactating patients: part 2, evidence-based review and recommendations. AJR Am J Roentgenol 2012;198:785-792.

Statement: Whole Body MRI

1. Han SN, Amant F, Michielsen K, et al. Feasibility of whole-body diffusion-weighted MRI for detection of primary tumor, nodal and distant metastases in women with cancer during pregnancy: a pilot study. Eur Radiol. 2017 Dec 7.
2. Peccatori FA, Codacci-Pisanelli G, Del Grande M, et al. Whole body MRI for systemic staging of breast cancer in pregnant women. Breast. 2017 Oct;35:177-181.

Statement: Surgery like in non-pregnant patients

1. Annane K et al. Infiltrative breast cancer during pregnancy and conservative surgery. Fetal Diagn Ther 2005, 20: 442-444
2. Kuerer H et al., Conservative surgery and chemotherapy for breast carcinoma during pregnancy. Surgery 2002, 131: 108-110
3. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861
4. Genin AS, De Rycke Y, Stevens D, et al. Association with pregnancy increases the risk of local recurrence but does not impact overall survival in breast cancer: A case-control study of 87 cases. Breast. 2015 Oct 8. pii: S0960-9776(15)00207-6.

Statement: „Sentinel node biopsy“ during pregnancy

1. Bothou A, Margioulas-Siarkou C, Petousis S, et al. Sentinel lymph node biopsy for breast cancer during pregnancy: A comprehensive

update. Eur J Clin Invest. 2024 Mar;54(3):e14134

2. Han SN, Amant F, Cardonick EH, et al. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. Breast Cancer Res Treat 2018;168(2):551-57.
3. Gropper AB, Calvillo KZ, Dominici L, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. Ann Surg Oncol. 2014 Aug;21(8):2506-11.

Reviews

1. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. Cancer. 2006 Jan 15;106(2):237-46.
2. Shachar SS, Gallagher K, McGuire K, et al. Multidisciplinary Management of Breast Cancer During Pregnancy. Oncologist 2017;22(3):324-34.
3. Lee GE, Mayer EL, Partridge A. Prognosis of pregnancy-associated breast cancer. Breast Cancer Res Treat 2017;163(3):417-21.
4. Ruiz R, Herrero C, Strasser-Weippl K, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review. Breast 2017;35:136-41.
5. Talele AC, Slanetz PJ, Edmister WB, et al. The lactating breast: MRI findings and literature review. Breast J 2003, 9: 237-240
6. Hachar SS, Gallagher K, McGuire K et al. Multidisciplinary Management of Breast Cancer During Pregnancy. Oncologist 2017;22(3):324-34.
7. Framarino-Dei-Malatesta M, Sammartino P, Napoli A. Does anthracycline-based chemotherapy in pregnant women with cancer offer safe cardiac and neurodevelopmental outcomes for the developing fetus? BMC Cancer 2017;17(1):777.
8. Ben Brahim E, Mrad K, Driss M, et al. Placental metastasis of breast cancer. Gynecol Obstet Fertil 2001, 29: 545-548
9. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. JCO 2001; 19: 1671-5
10. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70

Breast Cancer During Pregnancy or Breast Feeding * - (Neo-)adjuvant Therapy -

	Oxford		
	LoE	GR	AGO
▪ Radiation therapy during pregnancy	4	C	-
▪ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
▪ Anthracyclines: AC	2b	B	++
▪ Dose-dense regimens with short-acting G-CSF	4	C	+/-
▪ Taxanes	2a	B	++
▪ Platinum salts (carboplatin, cisplatinum)	4	C	+/-
▪ MTX (e.g. CMF)	4	D	--
▪ Endocrine treatment	4	D	--
▪ HER2-targeted treatment	3a	C	--
▪ Checkpoint inhibitors	4	D	--
▪ Bisphosphonates, denosumab	4	D	--

Treatment (Chemotherapy, surgical procedure and radiotherapy) of patients with breast cancer during pregnancy should be as similar as possible to standard treatment of young, not pregnant patients with breast cancer.

General principles

1. Amant F, Nekljudova V, Maggen C, et al: Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer 2022;170:54–63.
2. Loibl S, Azim HA Jr., Bachelot T, et al. ESMO Expert Consensus on the management of breast cancer during pregnancy (PrBC). Ann Oncol 2023; 34(10): 849-866.

Statement: Radiotherapy during pregnancy

1. Kal HB et al., Radiotherapy during pregnancy: fact and fiction. Lancet Oncol 2005, 6: 328-333 (Review)

Statement: (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)

1. Auger N, Maniraho A, Ayoub A, Arbour L. Association of maternal cancer with congenital anomalies in offspring. Paediatr Perinat Epidemiol. 2023 Dec 19.
2. Ring et al, Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. J Clin Oncol 2005, 23: 4192-4197
3. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2008 Apr;19(4):607-13.
4. Del Gobbo A, et al. Chemotherapy for breast cancer during pregnancy induces vascular alterations and impaired development of

- placental villi: A preliminary histopathological study. Eur J Obstet Gynecol Reprod Biol. 2020;250:155–161 (11).
5. Vandenbroucke T, et al. Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. International Network on Cancer, Infertility and Pregnancy (INCIP). Eur J Cancer 2020;138:57–67

Statement: Anthracyclines: AC, EC

1. Amant F et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol 2012;13:256-264.
2. Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. Obstet Gynecol. 2012 Dec;120(6):1267-72.
3. Loibl S, Han SN, Amant F. Being Pregnant and Diagnosed with Breast Cancer. Breast Care (Basel). 2012 Jun;7(3):204-209. Epub 2012 Jun 27.
4. Loibl S et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012 13(9):887-96.
5. Peccatori FA, Azim HA Jr, Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast Cancer Res Treat. 2009 Jun;115(3):591-4.

Omission of 5FU based on the same evidence as in non-pregnant patients (GIM2 study) - see also chapter on adjuvant chemotherapy

1. Del Mastro L, De Placido S, Bruzzi P et al. Gruppo Italiano Mammella (GIM) investigators. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early stage breast cancer: an open-label, 2x2 factorial, randomised phase 3 trial. Lancet. 2015 May 9;385(9980):1863-72.

Statement: Taxanes

1. Aranda-Gutierrez A, Ferigno Guarjardo AS, Vaca-Cartagena BF, et al. Obstetric and neonatal outcomes following taxane use during pregnancy: a systematic review. BMC Cancer 2024; 24 (1): 9.
2. Ferrigno Guajardo AS, Vaca-Cartagena BF, et al. Taxanes for the treatment of breast cancer during pregnancy: an international cohort study. J Natl Cancer Inst. 2024 Feb 8;116(2):239-248.

Statement: Platinum salts

1. Calsteren KV, Verbesselt R, Devlieger R, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. Int J Gynecol Cancer 2010 Dec;20(9):1456-64.

2. Köhler C, Oppelt P, Favero G, et al. How much platinum passes through the placental barriers? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. *Am J Obstet Gynecol*. 2015 Aug;213(2):206.
3. Kong TW, Lee EJ, Lee Y, et al. Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy. *Obstet Gynecol Sci*. 2014 Nov;57(6):539-43.
4. Zheng X, Zhu Y, Zhao Y, et al. Taxanes in combination with platinum derivatives for the treatment of ovarian cancer during pregnancy: A literature review. *International journal of clinical pharmacology and therapeutics* 2017;55(9):753-60.

Statement: MTX (e.g. CMF)

1. Ring et al., Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. *J Clin Oncol* 2005, 23: 4192-4197

Statement: Endocrine treatment

1. Cunha GR, Taguchi O, Namikawa R, et al. Teratogenic effects of clomiphene, tamoxifen, and diethylstilbestrol on the developing human female genital tract *Hum Pathol*. 1987;18:1132–1143.
2. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy — case report and literature review. *Gynecol Oncol*. 2001;80:405-408.

Statement Trastuzumab during pregnancy

1. Andrikopoulou A, Apostolidou K, Chatzinikolaou S, et al.: an update. *BMC Cancer* 2021;21:463.
2. Azim HA Jr et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). *Breast Cancer Res Treat*. 2012;133(1):387-91.
3. Lambertini M, Martel S, Campbell C et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. *Cancer* 2018.
4. Paluch-Shimon S, Cardoso F, Partridge AH, et al.: ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). *Ann Oncol* 2022;33:1097–1118.
5. Yildirim N, Bahceci A. Use of pertuzumab and trastuzumab during pregnancy. *Anticancer Drugs* 2018;29(8):810-13.
6. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* 2013; 5(7):733-41.
7. Zagouri F et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat*.

2013 Jan;137(2):349-57.

Statement Immunotherapy during pregnancy

1. Garutti M, Lambertini M, Puglisi F: Checkpoint inhibitors, fertility, pregnancy, and sexual life: a systematic review. ESMO Open 2021;6:100276.
2. Borgers JSW, et al. Immunotherapy for cancer treatment during pregnancy. Lancet Oncol. 2021 Dec;22(12):e550-e561. doi: 10.1016/S1470-2045(21)00525-8..

Statement Bisphosphonate during pregnancy

1. Levy S, Fayed I, Taguchi N et al. Pregnancy outcome following in utero exposure to bisphosphonates. Bone. 2009 Mar;44(3):428-30.
2. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9. Review.

General information: Chemotherapy during pregnancy

1. Murthy RK, Theriault RL, Barnett CM, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. Breast Cancer Res. 2014 Dec 30;16(6):3414.

Breast Cancer During Pregnancy or Breast Feeding* - Delivery and Breast-Feeding -

	Oxford		
	LoE	GR	AGO
▪ Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)	2b	C	++
▪ Termination of pregnancy does not improve maternal outcome	3b	C	
▪ Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir	4	C	++
▪ If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities	5	D	++

* Participation in register study recommended

General principles

1. Paluch-Shimon S, Cardoso F, Partridge AH, et al.: ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol 2022;33:1097–1118.
2. Loibl S, Azim HA Jr., Bachelot T, et al. ESMO Expert Consensus on the management of breast cancer during pregnancy (PrBC). Ann Oncol 2023; 34(10): 849-866.

Statements: Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome

1. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.

Statements: Delivery mode like in non-pregnant; Avoid delivery in leucocyte nadir

1. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861

Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities

1. Williams Obstetrics lecture book

2. Pistilli B et al. Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: how should we counsel cancer patients about breastfeeding? *Cancer Treat Rev.* 2013;39(3):207-11.
3. Hays KE, Ryu RJ, Swisher EM et al. Duration of cisplatin excretion in breast milk. *Journal of human lactation : official journal of International Lactation Consultant Association* 2013;29(4):469-72.

Breast Cancer During Pregnancy and Breast Feeding* - Outcome -

	Oxford LoE
<ul style="list-style-type: none"> ▪ BC during pregnancy <ul style="list-style-type: none"> ▪ Prognosis is not worse if adequately treated 	3a
<ul style="list-style-type: none"> ▪ BC during lactation and within the first year after pregnancy <ul style="list-style-type: none"> ▪ Prognosis worse than in BCP and if unrelated to pregnancy 	3a
<ul style="list-style-type: none"> ▪ Pregnancy / lactation after BC <ul style="list-style-type: none"> ▪ Outcome not compromised 	3a

* Participation in register study recommended

General principles

1. Amant F, Lefrère H, Borges VF, et al.: The definition of pregnancy-associated breast cancer is outdated and should no longer be used. *Lancet Oncol* 2021;22:753–754.
2. Amant F, Nekljudova V, Maggen C, et al: Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. *Eur J Cancer* 2022;170:54–63.
3. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. *Lancet*. 2012 Feb 11;379(9815):570-9.
4. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012;13:887-896.
5. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. *Cancer biology & medicine* 2018;15(1):6-13.
6. Loibl S, Azim HA Jr., Bachelot T, et al. ESMO Expert Consensus on the management of breast cancer during pregnancy (PrBC). *Ann Oncol* 2023; 34(10): 849-866.

Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately

1. Azim HA Jr., Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev* 2012;38:834-842.

2. Amant F et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study J Clin Oncol. 2013;31(20):2532-9.
3. Gerstl B, Sullivan E, Ives A et al. Pregnancy Outcomes After a Breast Cancer Diagnosis: A Systematic Review and Meta-analysis. Clin Breast Cancer 2018;18(1):e79-e88.
4. de Haan J, Verheecke M, Van Calsteren K et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol 2018;19(3):337-46.
5. Iqbal J, Amir E, Rochon PA, et al. Association of the Timing of Pregnancy With Survival in Women With Breast Cancer JAMA Oncol 2017;3(5):659–665
6. Lefrère H, et al. Breast cancer diagnosed in the post-weaning period. Lancet Oncol. 2021: 22:1139-50
7. Lambertini M, Kroman N, Ameye L et al. Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status. J Natl Cancer Inst 2018;110(4):426-29.
8. Litton JK et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. Oncologist. 2013;18(4):369-76.
9. O’sullivan et al. Clinico-pathologic features, treatment and outcomes of breast cancer during pregnancy or the post-partum period. Breast Cancer Res Treat 2020;180(3):695–706
10. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. Cancer biology & medicine 2018;15(1):6-13.
11. Ploquin A, Pistilli B, Tresch E et al. 5-year overall survival after early breast cancer diagnosed during pregnancy: A retrospective case-control multicentre French study. Eur J Cancer 2018;95:30-37.
12. Peccatori FA, Lambertini M, Scarfone G et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. Cancer biology & medicine 2018;15(1):6-13.

Statement: Pregnancy and lactation after breast cancer: Outcome not compromised

1. Azim HA Jr et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol 2013;31:73-79.
2. Kroman N et al. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. Acta Oncol. 2008;47(4):545-9

Review articles

1. Del Mastro et al, Infertility and pregnancy after breast cancer: current knowledge and future perspectives. *Cancer Treat Rev.* 2006 Oct;32(6):417-22. Epub 2006 Jul 13. Review.
Kroman N, et al. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *Breast.* 2003 Dec;12(6):516-21.
2. Kroman N, et al. Should women be advised against pregnancy after breast-cancer treatment? *Lancet.* 1997 Aug 2;350(9074):319-22.
3. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer.* 2011 Jan;47(1):74-83. Epub 2010 Oct 11. Review.
4. Paganì O, Azim H Jr. Pregnancy after Breast Cancer: Myths and Facts. *Breast Care (Basel).* 2012 Jun;7(3):210-214. Epub 2012 Jun 27.
5. Valachis A, Tsali L, Pesce LL, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. *Obstet Gynecol Surv.* 2010 Dec;65(12):786-93.
6. Azim HA Jr, Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev.* 2012 Nov;38(7):834-42. Epub 2012 Jul 9. Review.
7. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. *Lancet.* 2012 Feb 11;379(9815):570-9.
8. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi160-70
9. Lambertini M, et al. Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis.. *J Clin Oncol.* 2021;39:3293-3305.

Breast Cancer and Pregnancy*

- Family Planning -

	Oxford		
	LoE	GR	AGO
▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
▪ Assisted reproductive treatment after breast cancer	4	D	+/-
▪ Success rates for getting pregnant and for delivering a child lower in breast cancer patients compared to non-cancer patients	3b	D	
▪ Breast cancer patients should not be advised against getting pregnant independent of their tumor's hormone receptor status and gBRCA status	2a	B	
▪ Interruption of endocrine treatment (maximum 2 years after at least 18months of prior therapy) in case of desire to get pregnant without short-term survival disadvantage	2b	B	+

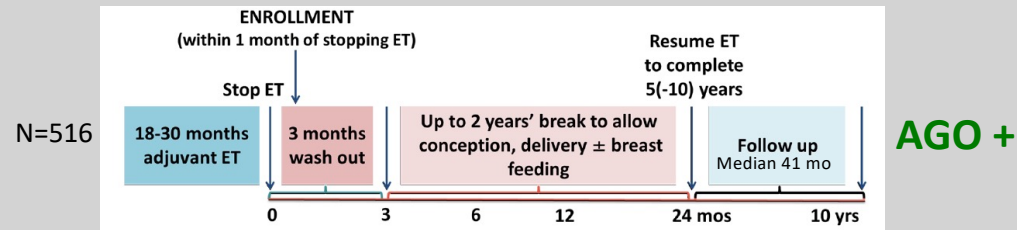
* Participation in register study recommended

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Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant



Women under 42 years were studied:

- Outcome: 64% live births; 62% of mothers breastfed; 2% birth defects.
- A time-limited interruption of endocrine therapy to pursue pregnancy does not result in prognostic disadvantages (BCFI).
- Interruption of ET (maximum 2 years after at least 18 months of prior therapy) for pregnancy desire does not lead to short-term survival disadvantages.

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Contraceptive Options for Women after Diagnosis of Breast Cancer

	Oxford		
	LoE	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	+

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