

Diagnosis and Treatment of Patients with early and advanced Breast Cancer



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Gynecological Issues, Pregnancy and Reproduction in Breast Cancer Patients

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LEHREN
HEILEN

Gynecologic Issues, Pregnancy and Reproduction in Breast Cancer Patients



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- **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

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

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Systemic hormone (replacement-) therapy

- Endocrine responsive disease (ER pos.)
 - Combined treatment TAM plus low dose HT
- Endocrine non-responsive disease (ER neg.)
- Tibolone

Topical vaginal application of

- Estriol (E3 0.03 mg*)
- DHEA locally
- Testosterone locally
- Estradiol (E2) during AI therapy

	Oxford		
	LoE	GR	AGO
Endocrine responsive disease (ER pos.)			
Combined treatment TAM plus low dose HT	1a	B	-
Endocrine non-responsive disease (ER neg.)			
Tibolone	2b	B	+/-
Tibolone	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“

Further Medical Approaches to Reduce Menopausal Symptoms I

Medical approaches* (reduction of hot flashes)

Oxford

LoE GR AGO

	LoE	GR	AGO
<ul style="list-style-type: none"> Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients <ul style="list-style-type: none"> Venlafaxine Desvenlafaxine, Sertraline, Escitalopram 	1a	A	+
	2b	B	+/-
<ul style="list-style-type: none"> Gabapentin (patients using TAN) 	2b	B	+
<ul style="list-style-type: none"> Neurokinin-3 receptor antagonists (fezolinetant) (note: oncological endpoints were not studied) 	5	D	+/-
<ul style="list-style-type: none"> Pregabalin 	1b	A	+/-
<ul style="list-style-type: none"> Clonidin 0,05-0,15 mg/die (patients using TAM) 	2a	B	+/-
<ul style="list-style-type: none"> Oxybutynin (2,5 mg / 5 mg) 	1b	A	+/-
<ul style="list-style-type: none"> MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!) 	1b	B	+/-
<ul style="list-style-type: none"> Vitamin E 	1b	A	-

Medical approaches (other treatment goals)

<ul style="list-style-type: none"> Melatonin (improvement of sleep quality) 	2b	C	+
<ul style="list-style-type: none"> Duloxetine (treating arthralgias while on AI) 	1b	B	+
<ul style="list-style-type: none"> Omega 3 fatty acids (treating arthralgias while on AI) 	1b	B	+/-

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

CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

During anti-cancer treatment: Beware of drug interactions!

Oxford

	LoE	GR	AGO
<ul style="list-style-type: none"> Soy-derived phytoestrogens – isoflavonoids* <ul style="list-style-type: none"> Hot flushes Sleep disturbance Topical vaginal application 	<p>1b</p> <p>1b</p> <p>1b</p>	<p>B</p> <p>B</p> <p>B</p>	<p>-</p> <p>-</p> <p>+/-</p>
<ul style="list-style-type: none"> Red Clover isoflavonoids* <ul style="list-style-type: none"> Hot flushes, sleep disturbance 	<p>1b</p>	<p>B</p>	<p>+/-</p>
<ul style="list-style-type: none"> Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses, no effect on hot flashes) 	<p>2b</p>	<p>B</p>	<p>+/-</p>
<ul style="list-style-type: none"> Black Cohosh for hot flushes 	<p>1b</p>	<p>B</p>	<p>+/-</p>
<ul style="list-style-type: none"> Black cohosh + St. John's Wort (fixed combination) 	<p>1b</p>	<p>B</p>	<p>+/-</p>
<ul style="list-style-type: none"> St. John's Wort (pharmacokinetic interference with endocrine therapy, cytotoxic drugs, and tyrosin kinase inhibitors) 	<p>1b</p>	<p>B</p>	<p>+/-</p>
<ul style="list-style-type: none"> Ginseng root (Panax ginseng or P. quinquefolius) 	<p>1b</p>	<p>B</p>	<p>-</p>
<ul style="list-style-type: none"> Bromelain + Papain + Selenium + Lectin (for AI induced joint symptoms) 	<p>3b</p>	<p>B</p>	<p>+</p>
<ul style="list-style-type: none"> Homeopathic medicine to reduce hot flushes (consider placebo-effect) 	<p>1b</p>	<p>B</p>	<p>+/-</p>

* might stimulate BC, especially in endocrine responsive disease

General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects

General approaches:

- Physical exercise
- Cognitive behavioral therapy (CBT), hypnosis
- Mind body-medicine
(yoga, education, counselling, mindfulness training)
- Short interruption of endocrine therapy in case of unacceptable side effects

(Electro) Acupuncture

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

* as in SOLE Trial

Oxford

LoE	GR	AGO
1a	A	++
1a	A	++
1b	B	+
5	D	+
1a	B	+
2a	B	+
2b	B	+
2a	C	+

Sexual Health / Vaginal Dryness

Oxford

Evaluation

- **Assessment of sexual dysfunction**
- **Use of patient-reported questionnaires**

Therapy of dyspareunia and vaginal dryness

- **Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy**
- **Topical vaginal treatment**
 - **Non-hormonal lubricants / moisturizers (also with physiotherapy)**
 - **Estriol (E3 0.03 mg*)**
 - **DHEA local application**
 - **Testosterone local application**
 - **Estradiol (E2) during AI therapy**
 - **Fractionated microablative CO₂-Laser / Vaginal Erbium:YAG-Laser**

	LoE	GR	AGO
Assessment of sexual dysfunction	5	D	+
Use of patient-reported questionnaires	4	C	+
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.

Ovarian Protection and Fertility Preservation in Premenopausal Patients

Oxford

LoE GR AGO

- **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**
- **CTx + GnRHa (preservation of fertility)**
- **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)**
 - **Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation¹**
 - **Cryopreservation of ovarian tissue with subsequent transplantation²**
- **ART after diagnosis of breast cancer¹**

LoE	GR	AGO
1a	A	+
2a	B	+/-
		++
2a	C	+
4	D	+
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

Ovarian Protection – Synopsis of Randomized Trials

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	ZORO	PROMISE	Munster et al. - US	POEMS	Option
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)	227 (126 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years	premenopausal
Treatment	goserelin	triptorelin	triptorelin	goserelin	goserelin
Start of treatment	> 2 weeks prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht
Primary Endpoint	menstruation at month 6 after chemotherapy	rate of early menopause at month 12 after cht	menstruation rate within 2 years after cht	Ovarian failure at 2 yrs after cht	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

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

Assessment of Ovarian Reserve

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	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.

Breast Cancer During Pregnancy or Breast Feeding*

- Diagnostics and Surgery -

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	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

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

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

- Radiation therapy during pregnancy
- (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)
 - Anthracyclines: AC
 - Dose-dense regimens with short-acting G-CSF
 - Taxanes
 - Platinum salts (carboplatin, cisplatinum)
 - MTX (e.g. CMF)
- Endocrine treatment
- HER2-targeted treatment
- Checkpoint inhibitors
- Bisphosphonates, denosumab

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.

Breast Cancer During Pregnancy or Breast Feeding*

- Delivery and Breast-Feeding -

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- **Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)**
- **Termination of pregnancy does not improve maternal outcome**
- **Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir**
- **If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities**

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

* Participation in register study recommended

Breast Cancer During Pregnancy and Breast Feeding*

- Outcome -

Oxford
LoE

- **BC during pregnancy**
 - Prognosis is not worse if adequately treated **3a**
- **BC during lactation and within the first year after pregnancy**
 - Prognosis worse than in BCP and if unrelated to pregnancy **3a**
- **Pregnancy / lactation after BC**
 - Outcome not compromised **3a**

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Breast Cancer and Pregnancy*

- Family Planning -

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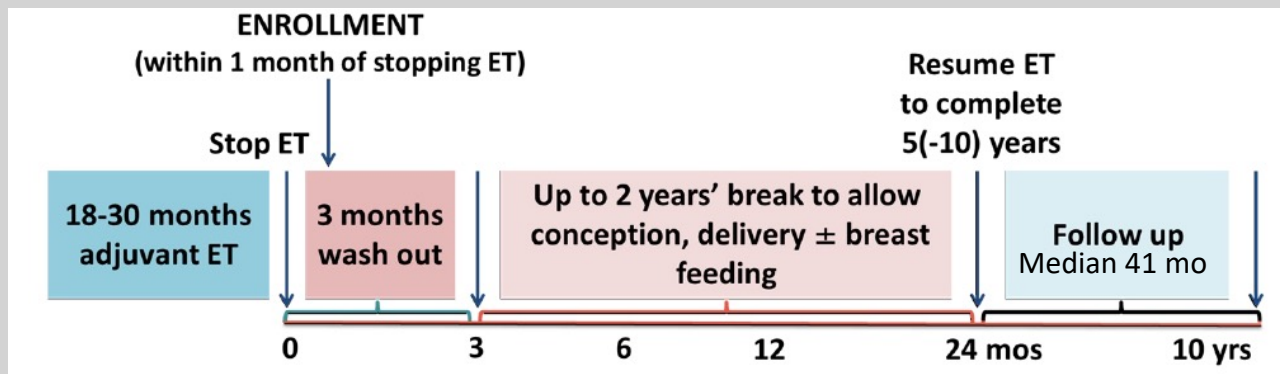
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	Oxford		
	LoE	GR	AGO
▪ Breast cancer patients of reproductive age should be offered fertility counseling before starting any kind of treatment	5	D	++
▪ Assisted reproductive treatment after breast cancer	4	D	+/-
▪ Success rates for getting pregnant 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 <i>gBRCA</i> status	2a	B	
▪ Interruption of endocrine treatment (maximum 2 years after at least 18 months of prior therapy) in case of desire to get pregnant without short-term survival disadvantage	2b	B	+

* Participation in register study recommended

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

N=516



AGO +

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.

Contraceptive Options for Women after Diagnosis of Breast Cancer

Oxford

LoE GR AGO

	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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