

Pregnancy-associated breast cancer: Management of the mother, fetus and tumour

Andrea Tan¹ MBBS, Weining Wang² MD, Cheryl Long¹ MBBS, Zewen Zhang² MMed, Joanne Ngeow^{*2} FAMS, Citra Mattar^{*1} PhD

ABSTRACT

Introduction: Pregnancy-associated breast cancer (PABC) is described as breast cancer diagnosed within pregnancy or within 1 year postpartum. PABC is becoming more common due to delayed childbearing, with older maternal age increasing the likelihood of tumorigenesis coinciding with pregnancy. Our review aims to outline the important principles of managing PABC, and discusses future fertility implications, genetic testing and postnatal considerations that are not often considered in other existing reviews.

Method: A literature search was conducted using PubMed, Cochrane and Google Scholar databases.

Results: A persistent breast mass in pregnant women should be evaluated with a breast ultrasound. Total mastectomy is the standard treatment in the first trimester. Chemotherapy is contraindicated in the first trimesters, but can be given in the second and third trimester, and stopped before 35 weeks. Radiotherapy should be delayed until delivery, and hormone receptor therapy is contraindicated in pregnancy. A multidisciplinary team involving an obstetrician, medical oncologist and other allied health professionals is crucial. Delivery should be planned as close to 37 weeks as possible, and at least 3 weeks after the last chemotherapy cycle. Vaginal delivery is preferred, and breastfeeding can resume 14 days after the last chemotherapy regime.

Conclusion: A breast mass in a pregnant woman should not be dismissed. PABC must be managed by multidisciplinary teams at tertiary medical centres with access to surgery and chemoradiation therapies. Management strategies must include safe management and delivery of the fetus, contraception and future fertility planning.

Ann Acad Med Singap 2024;54:235-46

Keywords: antenatal, breast surgery, cancer, general surgery, neonatology, obstetrics and gynaecology, oncology, pathology

CLINICAL IMPACT

What is New

- Delayed childbearing and older maternal age, which increases the likelihood of tumorigenesis coinciding with pregnancy, leads to increased incidence of pregnancy-associated breast cancer (PABC).
- PABC is associated with higher recurrence and poorer survival rate compared to breast cancer outside of pregnancy, and is often diagnosed late.

Clinical Implications

- Our review summarises the current literature on diagnosis, staging prognosis and management.
- Future fertility implications, genetic testing and postnatal considerations in PABC should be considered.

INTRODUCTION

Breast cancer (BC) is the most common cancer affecting females worldwide, accounting for more than 50% of cancers in young females.¹ It occurs in 1 in 3000–10,000 pregnancies, with reported incidence rising with delayed childbearing.² The age standardised incidence rate in Singapore increased by 24.2% from 1993 to 2002.³ The rising incidence in Asian countries has also been attributed to obesity and the adaptation of less traditional lifestyles that include reduced parity and breastfeeding.³ Pregnancy-associated breast cancer (PABC) is described as BC diagnosed during pregnancy or within the first postpartum year.⁴ Median maternal age at diagnosis is 33–34 years while the median gestation at diagnosis ranges from 17–25 weeks.⁵

The Annals is an open access journal, allowing non-commercial use under CC BY-NC-SA 4.0.

¹ Department of Obstetrics & Gynaecology, National University Hospital, Singapore

² Division of Medical Oncology, National Cancer Centre Singapore, Singapore

* Joint last authors

Correspondence: Dr Citra Mattar, Department of Obstetrics & Gynaecology, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074. Email: citramattar@nus.edu.sg; Dr Joanne Ngeow, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive Singapore 169610. Email: joanne.ngeow@ntu.edu.sg

Accepted: 3 February 2025

Published: 10 April 2025

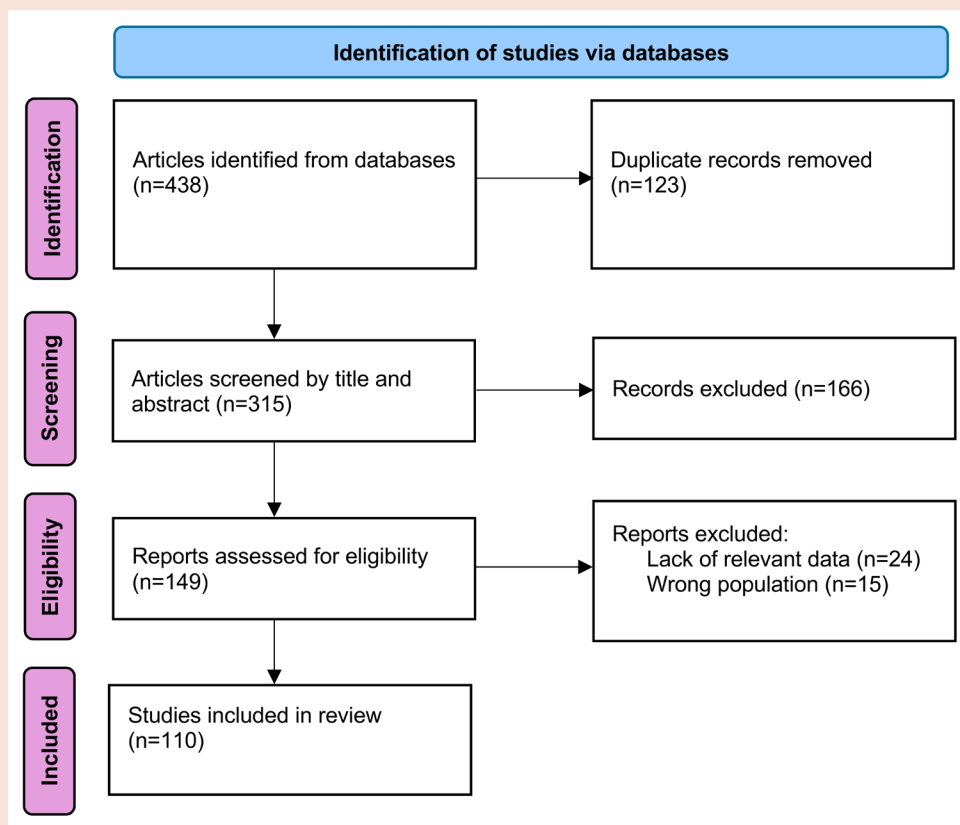
PABC is associated with worse prognosis compared to non-pregnancy associated BC. Prognostic factors include stage of cancer at diagnosis, histologically aggressive tumours, over-expression of the human epidermal growth factor receptor 2 (HER2), and negative status of progesterone (PR) and estrogen receptors (ER).⁶ PABC causes higher mortality and recurrence compared to non-pregnancy-related cancers, is associated with poorer survival if diagnosed postpartum,^{2,7} and late diagnosis comes at a more advanced stage of the disease where tumours are more aggressive.⁸ Physiological changes in pregnancy may delay diagnosis by masking symptoms, and imaging and invasive diagnostic procedures are often delayed due to concerns of fetal harm.

METHOD

A systematic search was conducted in PubMed, Cochrane Library and Google Scholar using the terms “pregnancy associated breast cancer” or “pregnancy-related breast cancer”, “breast cancer in pregnancy”, “breast cancer during pregnancy” and “management of breast cancer in

pregnancy”. English-language narrative reviews, practice guidelines, clinical studies, systemic reviews, meta-analyses, cohort and case control studies, observational studies focusing on women diagnosed with BC during pregnancy or within 1 year postpartum, and published within the last 5 years were included. Non-pregnant populations, editorials and conference abstracts were excluded. Of 438 initial articles, 315 articles remained after removing duplicates. A total of 110 articles were selected for final review after screening abstracts and reviewing full texts (Fig. 1). A qualitative analysis was performed to summarise data and a narrative review was performed. Due to study heterogeneity, meta-analysis was not performed. Key themes included diagnosis and staging, treatment strategies, prognosis and prevention, fertility preservation, breastfeeding and contraception, and management challenges. Comparisons were made between treatment strategies for surgery, chemotherapy, radiotherapy, and hormonal and endocrine therapy—highlighting the consensus and discrepancies.

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram showing the study selection process.



Adapted from PRISMA 2020 flow diagram. Source: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

Genetic mutations and screening

Approximately 23% of BC in women are linked to pathogenic germline mutations in cancer predisposition genes *BRCA1/2*, *CHEK2*, *ATM* and *PALB2*; approx. 35% carry *BRCA1* and *CHEK2* mutations with 15% harbouring variants of uncertain significance (VUS) in *CHEK2*, *BRCA2* and *BRIP1*.^{9,10} *BRCA1* germline mutation carries a higher risk of PABC than *BRCA2* mutations.

Genetic testing in PABC is indicated in women with diagnosis at <40 years old with a strong family history of breast, ovarian and related cancers, *BRCA1/2*, and triple-negative BC.¹⁰⁻¹³ Identifying cancer predisposition syndromes such as Hereditary Breast and Ovarian Cancer (HBOC) is important for appropriate management. *BRCA1/2* repair deoxyribonucleic acid (DNA) double-strand breaks, and mutations can lead to genomic instability and increased oncogenesis. Germline pathogenic variants (PV) in *BRCA1/2*, inherited in an autosomal dominant pattern, increase the lifetime risk of breast and ovarian cancer via HBOC. Other genes are involved in aberrant homologous recombination of DNA that increases the lifetime BC risk.⁹ The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) recommend genetic testing focused on *BRCA1/2* mutations, especially in patients with a strong family history for breast cancer and early-onset disease.^{10,11} Additional multigene panel testing can be used to screen a broader range of cancer predisposition genes.¹⁰ All patients should undergo genetic counselling before and after testing, to help women understand the implications of their results. In PABC, genetic counselling is crucial to address concerns regarding the impact of inherited mutations on current and future children.

Genetic risk evaluation in women with PABC can influence oncological management and surveillance, while facilitating family screening.¹⁴ PV of high penetrance genes such as *BRCA1/2* and *PALB2* can guide surgical decisions to reduce contralateral BC risk and enable use of targeted therapeutics such as poly(ADP-ribose) polymerase inhibitors (olaparib).^{15,16}

Genetic testing can identify low to moderate penetrance genes, like *RAD51C*, aiding risk assessment and counselling. However, VUS results, which are typically not actionable, may not explain early-onset PABC. Nonetheless, such patients, particularly those with a strong family history of cancer, should remain under cancer surveillance, as 6% of VUS may be reclassified into potentially actionable PVs.^{9,17,18}

Pathology

Invasive ductal carcinoma is the most prevalent histological subtype among PABCs, often presenting with a more aggressive immune-histological profile, with higher rates of ER or PR negativity and HER2 positivity.^{19,20} These tumours are larger, more aggressive, diagnosed at more advanced stages with lymphovascular invasion, and more resistant to hormonal treatment.²⁰⁻²²

Breast cancer during pregnancy

Diagnosis

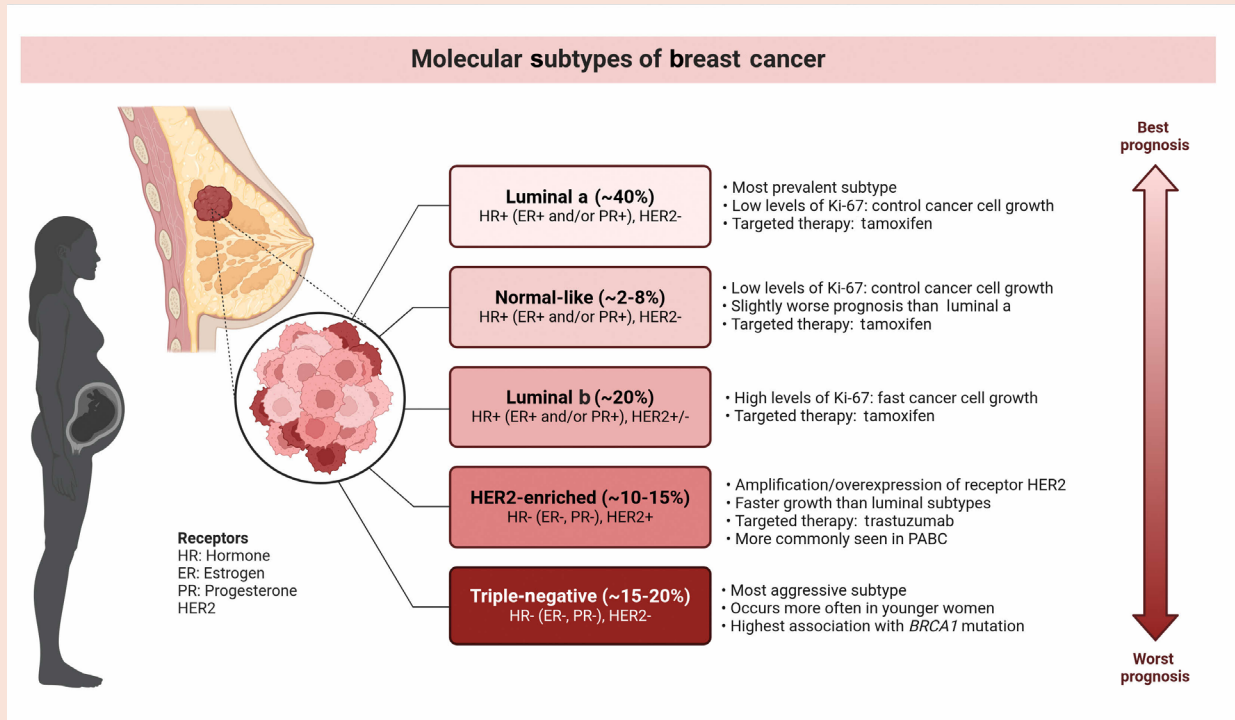
Triple assessment of breast lesions includes physical examination, imaging and histology.¹⁶ Most women present with a painless palpable mass and rarely, with blood-stained nipple discharge.

Breast ultrasound is the firstline imaging modality for pregnant women due to the absence of ionising radiation, with a near 100% negative predictive value and good sensitivity for malignancy detection despite increased breast nodularity during pregnancy.²³ Further diagnostic imaging may be needed to characterise suspicious lesions. Although long-term cancer predisposition and genetic damage on the fetus are uncertain, radiation dose should be minimised.²⁴ No teratogenic effects have been documented at radiation exposures <50 mGy,²³ but risk of fetal organ malformation and mental retardation is approx. 1% with exposure >100 mGy.²⁵ Mammography produces radiation <3 mGy, which is generally safe during pregnancy and lactation, and should be implemented if there is high BC likelihood.¹⁶ This is further reduced with abdominal lead apron shielding. With its detection rate of 78%, it is useful in assessing micro-calcifications, multifocality, multicentricity and contralateral lesions.¹⁶

Iodinated X-ray contrast may affect the neonatal thyroid gland, necessitating thyroid function monitoring in the first week after birth.²⁶ Magnetic resonance imaging (MRI) of the breast without contrast is safe but of limited use. Gadolinium crosses the placenta, enters the fetal circulation and amniotic fluid, and is associated with nephrogenic systemic fibrosis and renal impairment, making it relatively contraindicated in pregnancy.²⁶⁻²⁸ Breast mass biopsy, required for histopathological diagnosis, is safe in pregnancy.¹⁶ The sensitivity of core needle biopsy is approx. 90% and is the technique of choice.²⁹ It is important to inform the pathologist about the patient's pregnancy to avoid misdiagnosis due to gestational hyperproliferative changes.²⁴

BC diagnosis in pregnant women is challenging and often delayed due to physiological changes

Fig. 2. Molecular subtypes of pregnancy-associated breast cancer.



ER: estrogen; HER2: human epidermal growth factor receptor 2; HR: hormone; PABC: pregnancy-associated breast cancer; PR: progesterone

Table 1. Radiation exposure dose and risk of detrimental effects on the fetus.

Absorbed radiation dose	Effects on fetus
1 mGy	Background
<50 mGy	Threshold of acceptable fetal exposure
60–200 mGy	Threshold of congenital fetal loss, congenital anomalies, intellectual effects
100 mGy at conception or >500 mGy after 25 weeks	Embryological/fetal death
50–500 mGy at 8–15 weeks	Growth restriction, intellectual effects
50–100 mGy (after first trimester)	0.3–1% childhood cancers
50–500 mGy (after first trimester)	1–6% childhood cancers
Absorbed radiation dose	Imaging modality
0.0005–0.001 mGy	Chest X-ray
0.001–0.001 mGy	Mammogram 2 views
0.1 mGy	Pelvis/Abdomen X-ray
0.01–1 mGy	Chest CT or pulmonary angiography
4–5 mGy	Bone scan Tc-99m
1.3–3.5 mGy	Abdominal CT
10–50 mGy	Pelvic CT
10–50 mGy	PET-CT whole body
Nil	MRI

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; Tc-99m: technetium-99m

and atypical symptoms.³⁰ Patients are more likely to present at advanced stages with the average presentation-to-diagnosis interval being 1–2 months.²⁸ This delay has been reported to increase the risk of nodal involvement by 0.9%.³¹ Hence, breast masses persisting for >2–4 weeks should be carefully evaluated. Atypical symptoms like bloody nipple discharge should be evaluated with ultrasound or mammography. Cytology, ductogram and ductoscopy have poor sensitivity and specificity, and should not be used. It is common to misdiagnose a new breast mass as an infected or blocked milk duct in pregnancy or puerperium. If the mass or inflammatory skin changes persist after antibiotic treatment, a biopsy is recommended.

Staging

Further staging imaging should be performed to guide therapy decisions. Multidisciplinary discussions involving radiologists and oncologists are important to ensure careful planning to minimise cumulative toxicity exposure.²⁴ The most common metastatic sites are the lungs, liver and bone. For T1–2 tumours (≤50 mm) with no lymph node involvement and low metastatic risk, staging can be delayed until after delivery.¹⁶ Chest X-ray, full blood count, and liver and renal function tests are sufficient.¹⁶ For T3 tumours (>50 mm) or with lymph node involvement, staging should include chest X-ray, hepatic ultrasonography and MRI of spine as these carry minimal radiation and contrast exposure.¹⁶

Management

Timely intervention is important given the variable treatment effects at different stages of pregnancy. Treatment should be carefully planned and coordinated by a multidisciplinary team including maternal-fetal medicine specialists and oncologists. The NCCN recommends following the treatment protocols for non-pregnant BC as closely as possible,¹⁶ and not to delay therapy unless delivery has been planned within the next 2–4 weeks.³² However, treatment of PABC diagnosed in the first trimester is particularly challenging as chemotherapy, endocrine therapy, anti-HER2 therapy and radiotherapy are contraindicated.

Chemotherapy

Almost all chemotherapeutic agents cross the placenta, and first trimester exposure is associated with the greatest risks of fetal loss, growth restriction and congenital abnormalities, such as cardiac septal defects, neural tube defects, limb deformities and cleft palate.^{16,33} Its use should be avoided in

the first trimester as recommended by NCCN.³³ In the second trimester, chemotherapy with taxanes, anthracyclines and cyclophosphamides may be considered with 3 weekly fetal weight and amniotic fluid monitoring.^{24,34} Chemotherapy in the second and third trimesters carries a 1.3% risk of fetal malformation, similar to the baseline risk without exposure.¹⁶ Chemotherapy should also be stopped after 35 gestational weeks or within 3 weeks of planned delivery to minimise risks of maternal myelosuppression in the peripartum period.^{16,35,36} It takes at least 3 weeks for the placenta to metabolise and excrete the chemotherapy agents, and spontaneous labour is more likely to occur after 37 weeks.³⁷

ESMO and NCCN recommend that chemotherapy regimens used in PABC should follow those for non-pregnant BC.^{10,16,34} Anthracycline and alkylating agents are most widely used in pregnancy, but there is limited safety data on taxanes,^{16,38} which are associated with fetal growth restriction and increased neonatal intensive care unit admissions, and should be avoided.³⁸ The safety profile is summarised in Fig. 4.

Several studies have addressed the safety of anthracycline-based regimens in PABC.³⁸ Hahn et al. reported congenital abnormalities including talipes equinovarus, bilateral ureteric reflux and trisomy 21 in 3 infants among 57 pregnant women treated with 5-fluorouracil, doxorubicin and cyclophosphamide.³⁹ Peccatori et al. reported no congenital anomalies among 20 patients treated with single agent epirubicin weekly (median 14 weeks) with a mean total dose of 420 mg/m².⁴⁰ Chemotherapy drugs cross the placenta via passive diffusion, with the degree and rate of transfer dependent on the concentration gradient between maternal, fetal and placental blood. In pregnancy, increased blood volume and cardiac output enhances drug delivery to tissues. An increased glomerular filtration rate, enhanced liver metabolic enzyme activity and altered hepatic function influence therapeutic levels at different gestational stages.⁴¹ As there are no robust studies examining optimal doses in pregnancy, non-pregnant dosing regimens are used.²⁴

Mastectomy, breast conservation and breast reconstruction

NCCN and ESMO recommend total mastectomy as the standard local treatment for first trimester PABC.^{7,12,16} Breast conservation surgery (BCS) requires concomitant radiotherapy and is possible if radiotherapy can be safely delayed until postpartum.¹⁶ Survival rate after mastectomy is similar to BCS, but comparative studies are

Fig. 3. Effects of chemotherapy on the fetus in the first trimester.

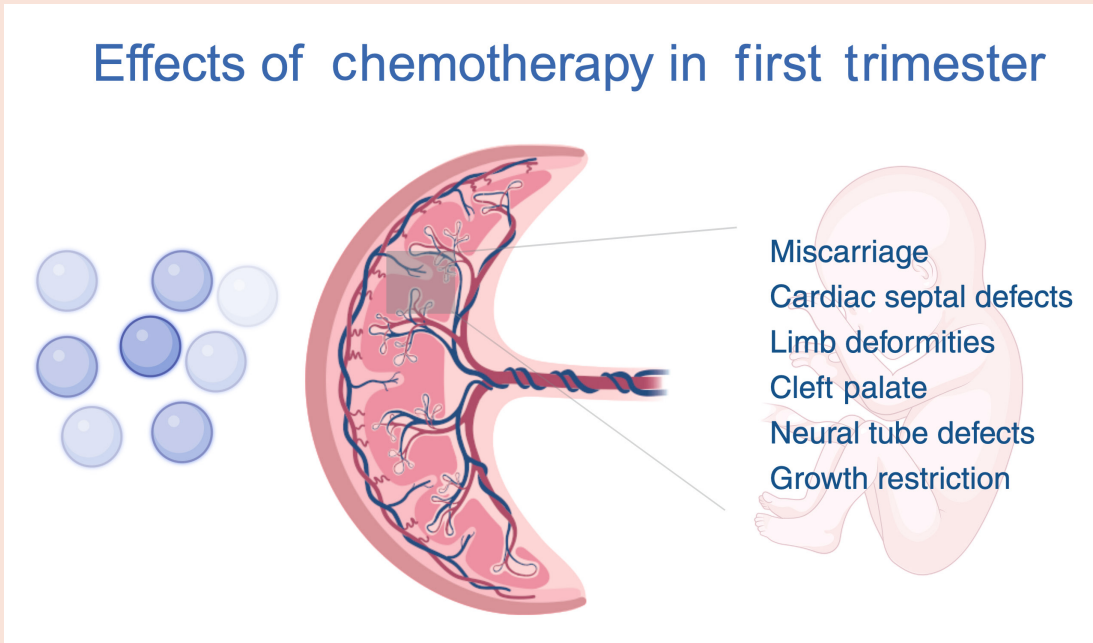


Fig. 4. Chemotherapy agents and their adverse effects in pregnancy.

	Anthracyclines	Alkylating agents	Platinum-based compounds	Antimetabolites	Vinca alkaloids
					
Examples	Daunorubicin Bleomycin Doxorubicin	Cyclophosphamide Chlorambucil Melphalan Busulfan	Cisplatin Carboplatin	Methotrexate 5-fluorouracil	Vincristine Vinblastine
Mode of action	Inhibits DNA synthesis and function by poisoning topoisomerase, a critical enzyme for unwinding of the DNA for replication and synthesis, thereby causing growth arrest and programmed cell death	Inhibits tumour growth by introducing alkyl groups into DNA, leading to cross-linking of DNA strands that prevents DNA separation, which is essential for replication and transcription	Covalently binds to DNA to form DNA cross-links, thereby inhibiting DNA replication and transcription	Inhibits DNA, RNA, thymidylate and purine synthesis which hampers cell division and function	Disrupts microtubule formation and inhibits microtubule polymerisation to cause mitotic arrest during metaphase and apoptosis
Maternal effects	Cardiotoxicity	Myelosuppression	Nephrotoxicity Neurotoxicity Myelosuppression	Myelosuppression Acute renal failure	Neurotoxicity
Fetal effects	Congenital malformations Miscarriage Prematurity Intrauterine demise (40, 41)	Congenital malformations growth restriction Neonatal pancytopenia (39, 41)	Limited information (41)	Fetal teratogenicity (41)	Fetal teratogenicity (41)

DNA: deoxyribonucleic acid; RNA: ribonucleic acid
Numbers in brackets: refer to REFERENCES

small.^{16,42,43} Women with PABC in China were more likely to undergo mastectomy than BCS due to smaller breast sizes.⁴⁴ Multidisciplinary input from maternal-fetal medicine specialists, breast surgeons and obstetric anaesthetists is important to optimise maternal and fetal benefit-to-risk ratio. If surgery occurs between 24–30 gestational weeks, the risk of intraoperative fetal compromise and preterm delivery must be discussed, with obstetric and neonatal specialists on standby.¹⁶ Common anaesthetic agents are not teratogenic when used at standard concentrations and for <3 hours. However, caution is required when administering the inhalational agents propofol and midazolam. Intraoperative changes like maternal hypoxaemia, hypercapnia and hypotension can cause utero-placental hypoperfusion from uterine artery vasoconstriction, and reduced placental perfusion, fetal asphyxia and acidosis, and eventual intra-uterine demise.⁴⁵ Interpretation of fetal heart rate patterns should include consideration of anaesthetic effects on fetal heart rate and variability.⁴⁶ Post-operative thromboprophylaxis is recommended due to immobility and pregnancy-related hypercoagulability.⁴⁷

Although some studies suggest that sentinel lymph node biopsy (SLNB) can be performed safely in pregnancy, the data is limited.^{16,40,48} Gentilini et al. estimated that the standard SLNB procedure exposes the fetus to <50 mGy radiation and does not significantly elevate the risk of fetal malformation, intellectual impairment or death.⁴⁹ Technicium-99m-labelled colloid is a method used for SLNB that is 99% effective at identifying positive lymph nodes. During surgery, it is injected into the peri-tumour subdermis and a gamma probe is used to identify radiotracer activity.⁴⁸ Its short half-life of 6 hours and ability to remain at the injection site minimises fetal radiation exposure.⁵⁰ Methylene blue and isosulfan blue dye should be avoided due to potential teratogenic effects and maternal anaphylaxis. The ESMO, NCCN and European Society of Mastology recommend that the decision to perform SLNB should be individualised, and avoided <30 weeks gestation as the specificity and sensitivity is not established in PABC.^{16,51}

The postoperative appearance of the affected breast can leave a long-lasting emotional impact, affecting sexuality and body confidence.⁵² Immediate reconstruction following mastectomy proffers superior cosmetic results, but increases operating time, blood loss and anaesthesia exposure. Moreover, lactogenesis, glandular hypertrophy and breast tissue expansion may hinder wound healing, making it more challenging

to achieve aesthetic results. After breast involution, the changing shape and contour may result in permanent deformation.^{24,37} Hence, the European Consensus advises against immediate reconstruction during pregnancy.

Radiotherapy

Radiotherapy should be postponed until after delivery due to potential fetal malformations, mental retardation, growth restriction and fetal loss arising from exposure during pregnancy,^{2,16,37} the severity of which depends on gestational age, radiation field and total dose.⁵³ Radiation exposure during fetal organogenesis (weeks 2–8) may lead to structural malformations when doses exceed 0.1–0.2 Gy.⁵³ Lower intelligence quotient results from exposure >0.1 Gy (week 8–25), and severe mental retardation may result from exposure >1 Gy.⁵³ Any fetal radiation exposure may increase the likelihood of childhood cancers.²⁵ Mazonakis et al. studied total fetal radiation dose after breast irradiation at various trimesters and estimated dose thresholds to be between 2.1–7.6 cGy (first trimester), 2.2–24.6 cGy (second trimester) and 2.2–58.6 cGy (third trimester), depending on the field of exposure. Internal scatter and leakage radiation contribute to these doses, with the degree of scatter affected by the source, treatment field size and proximity to the fetus.²⁵ With the addition of abdominal lead shielding that reduces radiation exposure by 50–70%, radiotherapy is considered sufficiently safe in the first and second trimesters (2010 international consensus meeting).²⁴

The first consideration in treatment planning is whether radiotherapy can be delayed. The risk of local recurrence is approx. 1% for every month of delayed radiotherapy, and a delay of <3 months is considered acceptable. Delaying radiotherapy until after delivery may promote local recurrence, unless the diagnosis is made in the late second or third trimesters, in which case radiotherapy may be postponed without significantly increasing maternal risk. If antepartum radiotherapy is necessary, the dose to the fetus should be calculated prior to the treatment and include modifications to field size, radiation energy, usage of photon energies <25 MV and the use of a lead shield with 4–5 half-value layers.⁵⁴

Endocrine therapy

Tamoxifen selectively inhibits the hormones responsible for promoting tumour growth. Hormone-sensitive BC are stimulated by estrogen and progesterone, and inhibition of these hormones by tamoxifen (a selective estrogen receptor modulator) slows tumorigenesis. Its use

is restricted in pregnancy due to associations with ambiguous genitalia, Pierre Robin sequence and oculo-auriculo-vertebral dysplasia (Goldenhar syndrome) in the fetus.^{2,55} Initiation of hormone-receptor modulators should only be used after childbirth and following completion of chemotherapy.^{16,50}

Biological agents

The HER2 pathway promotes cell growth and division, but with overexpression, cell growth is accelerated beyond normal limits resulting in tumour formation. Trastuzumab is a monoclonal antibody that targets the HER2 receptors, inhibiting overexpression and limiting tumour growth. HER2 receptors are strongly expressed in fetal renal epithelium, and trastuzumab use reduces fetal urine output resulting in oligohydramnios, which predisposes to fetal limb malformations and pulmonary hypoplasia.² The NCCN and ESMO guidelines advise against using biological agents like trastuzumab in all trimesters.^{12,16}

Considerations for the fetus

Systemic medications used in pregnancy can be sequestered in amniotic fluid due to maternal water retention, increased plasma volume and hepato-renal perfusion, cytochrome P450 activity and serum albumin levels.² To reduce miscarriage, congenital malformation and fetal cardiotoxicity risks in the first trimester, chemotherapy should be commenced after 14 gestational weeks.^{2,24} Other gestation-dependent risks include fetal myelosuppression, growth restriction and sepsis. Dose-dense chemotherapy, where standard doses are given with shorter intervals between treatment cycles, may be considered (e.g. every 2 instead of the conventional 3 weeks), although this is supported by limited evidence.^{36,56-58}

The care of both fetal and maternal health requires multidisciplinary coordination, involving the obstetrician, medical oncologist and other allied health specialists. Fetal morphology, growth and well-being should be evaluated by ultrasound screening prior to every chemotherapy cycle as per NCCN guidelines.^{16,24} Most studies recommend intraoperative fetal monitoring after 22–24 gestational weeks when viability is attained.⁵⁹ Maternal haemodynamic stability, oxygenation and temperature control must be optimised to support fetal perfusion. Fetal cardiotocography is advised after each chemotherapy cycle to monitor for preterm contractions.⁴⁵ Serial fetal growth surveillance is required following chemotherapy.⁵⁰

Delivery should be planned as close to 37 weeks as possible.^{12,16} Fetal maturation and urgency of

maternal therapy are both important considerations, as prematurity remains a major risk factor for impaired cognitive development. Vaginal delivery is preferred especially if treatment is incomplete as recovery is faster and there is less delay to recommencing therapy.⁶⁰ Caesarean delivery is reserved for obstetric indications. Delivery should ideally be planned at least 3 weeks after the last anthracycline-based chemotherapy for bone marrow recovery and to reduce likelihood of maternal and fetal neutropenia.^{36,50,61,62} After 35 gestational weeks, chemotherapy should be avoided as labour may occur spontaneously; neonatal review for intrauterine chemotherapy exposure and placental histopathology (to exclude rare metastases) should be arranged following delivery.^{12,24} It is safe to resume chemotherapy 1 week after an uncomplicated vaginal or caesarean delivery.

Breastfeeding reduces BC risk in the general population by 4–5% for every year of lactation.⁶³ There is a lack of data surrounding women with PABC whose challenges include reduced lactogenesis, breast and nipple scarring, fibrosis and atrophy following breast-conserving surgery, ipsilateral mastectomy or radiotherapy.^{64,65} Breastfeeding is not contraindicated after breast conservation therapy, but milk quality and quantity are likely to be affected.¹⁶ Chemotherapeutic toxins are excreted in breastmilk, causing neutropaenia in breastfed neonates.⁶⁶ The Academy of Breastfeeding Medicine recommends waiting 7–10 days after doxorubicin and paclitaxel, and 1–3 days for cyclophosphamides before breastfeeding.⁴¹ The Royal College of Obstetrics and Gynaecology recommends waiting 14 days from the last chemotherapy administration before commencing breastfeeding.⁴ The NCCN advises against breastfeeding with endocrine therapy, and recommends waiting at least 6 months after completing trastuzumab.^{16,66,67} Nevertheless breastfeeding support is critical. Alternative feeding strategies include breastfeeding from the contralateral breast, milk expression without feeding during systemic therapy to maintain production, utilising donor milk, and restricted breastfeeding between chemotherapy cycles.⁴¹

Postnatal considerations

The postnatal implications of PABC have not been widely studied. Conservative treatment strategies prioritising fetal well-being and causing deferred treatment carry poorer prognosis. An underestimated prognostic factor is the mother's desire to postpone treatment until after delivery, which is more commonly observed among Asian women.⁴⁴ Affected women have higher rates of

mental health problems like depression, anxiety, social isolation and self-blame.^{68,69} Not being able to breastfeed while coping with the side effects of chemo- or radiotherapy exacerbates these disorders and may impair mother-baby bonding. A small proportion of younger women may resume ovulation after chemoradiation.^{70,71} Effective contraception is a critical component of management. Non-hormonal contraceptives like the copper intrauterine device, barriers and tubal ligation are recommended by the NCCN and ESMO.⁶⁸ Oral hormonal contraceptive use in women with current or treated BC is contraindicated and is deemed a UK Medical Eligibility Criteria category 4—an unacceptable health risk.⁷² Some studies showed that the levonorgestrel-releasing intrauterine system does not increase recurrence risk and may offer endometrial protection in tamoxifen users. However, due to limited definitive data, the NCCN advises against its use.^{15,16,73} The Faculty of Sexual and Reproductive Healthcare guidelines state that progesterone-only contraception (POC) can be considered on a case-by-case basis if the woman understands potential recurrence, and in consultation with a specialist, if non-hormonal alternatives are unacceptable or if the non-contraceptive benefits are desired.⁷⁴ POC has no adverse effects on lactation for patients who wish to breastfeed.^{74,75}

Conception and fertility preservation

The average age of women with PABC is 28–32 years, hence fertility preservation is an important consideration.⁷⁶ Amenorrhea occurs in approx. 18–60% of women on cyclophosphamide or anthracycline regimes.⁷⁷ Chemotherapy-induced infertility is age-dependent and reflects ovarian reserve and the specific agent used.⁷⁸ Older women are at higher risk of infertility and secondary ovarian failure due to diminished ovarian reserve. Chemotherapy further accelerates this by inhibiting DNA synthesis, accelerating primordial follicular apoptosis, decreasing primordial follicle quantity, while indirectly damaging ovarian stroma tissue via vascular spasm, reduced ovarian circulation, and (particularly with doxorubicin) microvascular damage and acute ischaemia.¹⁹ Anti-metabolites and vinca alkaloids do not cause DNA damage and present a lower risk of follicular depletion.⁶

Prior to chemotherapy, women desiring future childbearing should be referred to fertility specialists to discuss ovarian tissue cryopreservation, or oocyte or embryo freezing.⁷⁹ Unlike embryo freezing, oocyte or ovarian tissue freezing does not require fertilisation or a sperm-donor at the point of time of the procedure, making it suitable for patients without partners.⁷⁹ Ovarian

tissue collection and transplantation are laparoscopic procedures with low surgical complications rates of 0.2–1.4%,⁷⁹ and is preferred for women ≤ 36 years or requiring urgent treatment with insufficient time for ovarian stimulation.⁷⁹ There is little data regarding appropriate intervals between treatment, cryopreservation and reproductive outcomes.⁷⁹ Oocyte preservation involves approx. 2 weeks of ovarian stimulation and reproductive outcomes are dependent on ovarian reserve.⁷⁹ Risks include ovarian hyperstimulation syndrome and an increased risk of bleeding and infection.⁷⁹ Oocyte preservation using estrogen-ovarian stimulation was conventionally expected to accelerate growth of ER positive tumours.^{80,81} Recent studies however demonstrate equivalence in survival and recurrence rates between PABC women with and without ovulation induction.⁸² Alternative stimulation protocols employ tamoxifen or aromatase inhibitors like letrozole.⁸⁰ Women also have the option of natural ovulation cycles for oocyte preservation. In vitro maturation of immature oocytes is a quicker alternative and may benefit women who are unable to undergo ovarian stimulation.⁸³ It eliminates risks associated with ovarian stimulation but results in poorer embryo quality and reproductive success rates.⁸³

Prognosis and outcomes

As most recurrences occur within 2 years of diagnosis, pregnancy avoidance is recommended until >2 years from remission.⁸⁴ The effects of a future pregnancy on the risk of PABC relapse is uncertain, as $<10\%$ of women continue to have subsequent pregnancies.² A meta-analysis of 30 studies and 3628 women with PABC reported poorer prognosis and higher recurrence risks than non-pregnant and non-puerperal BC patients,⁴⁰ attributed to delayed diagnosis and longer duration for tumour growth and metastasis.^{24,67} A study of 1174 women demonstrated higher survival rates with increasing intervals between pregnancy and cancer diagnosis, at 38%, 51% and 60% for the intervals of ≤ 12 , 12–48 and >48 months postpartum, respectively. A comparison with age-matched controls found that the survival rate of non-PABC women was 65%.⁸⁵

It is uncertain if pregnancy itself influences BC biology. During the remodelling phase of breast involution, the pro-inflammatory wound healing microenvironment together with rapid collagen deposition and extracellular matrix remodelling is believed to drive tumour growth.⁸⁶ Pregnancy appears to result in short-term increases in BC risk within 5 to 10 years postpartum.⁸⁷ A Swedish nationwide cohort study of 12,666 patients with BC and 61,121 age-matched controls reported

higher odds of developing BC in parous women 15 years after childbirth than in nulliparous women.⁸⁷

Future research

There is a lack of consensus on optimal chemotherapy regimens in PABC due to tertiary centres using varying protocols and a dearth long-term longitudinal studies. More research is needed to fully characterise the psychological impact of PABC on the mother. Existing data mainly comes from high-income countries, and research involving women in minority populations and low-to-middle-income countries is urgently required.

CONCLUSION

Due to increasing maternal age and other socio-biological determinants, PABC is increasingly diagnosed, often at advanced stages as pregnancy-related physiological changes delay diagnostic processes. As a result, PABC carries an overall poorer prognosis compared to non-pregnant BC. Imaging modalities for diagnosis and staging are generally safe in pregnancy and minimal delay in instituting therapy should be the goal. PABC must be managed by multidisciplinary teams at tertiary medical centres with access to surgery and chemoradiation therapies. Protocols must include safe management and delivery of the fetus, contraception and future fertility planning, and consider the psychosocial ramifications of this diagnosis.

Ethics statement

Not applicable.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

REFERENCES

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002;360:187-95.
2. Macdonald HR. Pregnancy associated breast cancer. *Breast J* 2020;26:81-5.
3. Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. *Asian Pac J Cancer Prev* 2015;16:2857-70.
4. Royal College of Obstetricians & Gynaecologists. Pregnancy and breast cancer (Green-top Guideline No. 12). <https://rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/pregnancy-and-breast-cancer-green-top-guideline-no-12/>. Accessed 3 February 2025.
5. Ring AE, Smith IE, Jones A, et al. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. *J Clin Oncol* 2005;23:4192-7.
6. Genin AS, Lesieur B, Gligorov J, et al. Pregnancy-associated breast cancers: do they differ from other breast cancers in young women? *Breast* 2012;21:550-5.
7. Molckovsky A, Madarnas Y. Breast cancer in pregnancy: a literature review. *Breast Cancer Res Treat* 2008;108:333-8.
8. Keyser EA, Staat BC, Fausett MB, et al. Pregnancy-associated breast cancer. *Rev Obstet Gynecol* 2012;5:94-9.
9. Zografos E, Korakiti AM, Andrikopoulou A, et al. Germline mutations in a clinic-based series of pregnancy associated breast cancer patients. *BMC Cancer* 2021;21:572.
10. Paluch-Shimon S, Pagani O, Partridge AH, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). *Breast* 2017;35:203-17.
11. Daly MB, Pilarski R, Yurgelun MB, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020. *J Natl Compr Canc Netw* 2020;18:380-91.
12. Peccatori FA, Azim HA Jr., Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6: vi160-70.
13. Partridge AH, Niman SM, Ruggeri M, et al. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. *N Engl J Med* 2023;388:1645-56.
14. Hall MJ, Forman AD, Pilarski R, et al. Gene panel testing for inherited cancer risk. *J Natl Compr Canc Netw* 2014;12: 1339-46.
15. Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. *Proc Natl Acad Sci U S A* 2011;108:3406-11.
16. National Comprehensive Cancer Network. Breast cancer version 1. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 3 February 2025.
17. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer — a multicenter validation study. *N Engl J Med* 1998;339:941-6.
18. Chiang J, Chia TH, Yuen J, et al. Impact of Variant Reclassification in Cancer Predisposition Genes on Clinical Care. *JCO Precis Oncol* 2021;5:577-84.
19. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. *Future Oncol* 2016;12:2333-44.
20. Muñoz E, González N, Muñoz L, et al. Ovarian stimulation in patients with breast cancer. *Ecancermedicalscience* 2015;9:504.
21. Jones AL. Fertility and pregnancy after breast cancer. *Breast* 2006;15 Suppl 2:S41-6.
22. Halaska MJ, Pentheroudakis G, Strnad P, et al. Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: a matched controlled study. *Breast J* 2009;15:461-7.
23. Vashi R, Hooley R, Butler R, et al. Breast imaging of the pregnant and lactating patient: imaging modalities and pregnancy-associated breast cancer. *AJR Am J Roentgenol* 2013;200:321-8.
24. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur J Cancer* 2010;46:3158-68.
25. Mazonakis M, Varveris H, Damilakis J, et al. Radiation dose to conceptus resulting from tangential breast irradiation. *Int J Radiat Oncol Biol Phys* 2003;55:386-91.

26. Mattsson S, Leide-Svegborn S, Andersson M. X-RAY AND MOLECULAR IMAGING DURING PREGNANCY AND BREASTFEEDING-WHEN SHOULD WE BE WORRIED? *Radiat Prot Dosimetry* 2021;195:339-48.
27. Rimawi BH, Green V, Lindsay M. Fetal Implications of Diagnostic Radiation Exposure During Pregnancy: Evidence-based Recommendations. *Clin Obstet Gynecol* 2016; 59:412-8.
28. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. *Arch Surg* 2003;138:91-8; discussion 99.
29. Oyama T, Koibuchi Y, McKee G. Core needle biopsy (CNB) as a diagnostic method for breast lesions: comparison with fine needle aspiration cytology (FNA). *Breast Cancer* 2004; 11:339-42.
30. García-Manero M, Royo MP, Espinos J, et al. Pregnancy associated breast cancer. *Eur J Surg Oncol* 2009;35:215-8.
31. Nettleton J, Long J, Kuban D, et al. Breast cancer during pregnancy: quantifying the risk of treatment delay. *Obstet Gynecol* 1996;87:414-8.
32. Jones AL. Management of pregnancy-associated breast cancer. *Breast* 2006;15 Suppl 2:S47-52.
33. de Haan J, Verheeecke 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;19:337-46.
34. 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;1:1145-53.
35. Alfasi A, Ben-Aharon I. Breast Cancer during Pregnancy-Current Paradigms, Paths to Explore. *Cancers (Basel)* 2019;11.
36. Cardonick E. Pregnancy-associated breast cancer: optimal treatment options. *Int J Womens Health* 2014;6:935-43.
37. Lohsiriwat V, Peccatori FA, Martella S, et al. Immediate breast reconstruction with expander in pregnant breast cancer patients. *Breast* 2013;22:657-60.
38. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. *Ann Oncol* 2004;15:146-50.
39. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer* 2006;107:1219-26.
40. Peccatori FA, Azim HA, Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat* 2009;115:591-4.
41. Johnson HM, Mitchell KB. ABM Clinical Protocol #34: Breast Cancer and Breastfeeding. *Breastfeed Med* 2020;15:429-34.
42. Toesca A, Gentilini O, Peccatori F, et al. Locoregional treatment of breast cancer during pregnancy. *Gynecol Surg* 2014;11:279-84.
43. Rojas KE, Bilbro N, Manasseh DM, et al. A Review of Pregnancy-Associated Breast Cancer: Diagnosis, Local and Systemic Treatment, and Prognosis. *J Womens Health (Larchmt)* 2019;28:778-84.
44. Zhang R, Liu X, Huang W, et al. Clinicopathological features and prognosis of patients with pregnancy-associated breast cancer: A matched case control study. *Asia Pac J Clin Oncol* 2021;17:396-402.
45. Van De Velde M, De Buck F. Anesthesia for non-obstetric surgery in the pregnant patient. *Minerva Anestesiol* 2007; 73:235-40.
46. Cheek TG, Baird E. Anesthesia for nonobstetric surgery: maternal and fetal considerations. *Clin Obstet Gynecol* 2009;52:535-45.
47. Ní Mhuireachtaigh R, O’Gorman DA. Anesthesia in pregnant patients for nonobstetric surgery. *J Clin Anesth* 2006;18:60-6.
48. 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;168:551-7.
49. Gentilini O, Cremonesi M, Trifirò G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004;15:1348-51.
50. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer* 2006;106:237-46.
51. 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;54:e14134.
52. Srinivasa DR, Garvey PB, Qi J, et al. Direct-to-Implant versus Two-Stage Tissue Expander/Implant Reconstruction: 2-Year Risks and Patient-Reported Outcomes from a Prospective, Multicenter Study. *Plast Reconstr Surg* 2017;140:869-77.
53. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol* 2005;6:328-33.
54. Stovall M, Blackwell CR, Cundiff J, et al. Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36. *Med Phys* 1995; 22:63-82.
55. Braems G, Denys H, De Wever O, et al. Use of tamoxifen before and during pregnancy. *Oncologist* 2011;16:1547-51.
56. Citron ML. Dose-Dense Chemotherapy: Principles, Clinical Results and Future Perspectives. *Breast Care (Basel)* 2008; 3:251-5.
57. Del Mastro L, De Placido S, Bruzzi P, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. *Lancet* 2015;385:1863-72.
58. Gray R, Bradley R, Braybrooke J, et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet* 2019;393:1440-52.
59. Reitman E, Flood P. Anaesthetic considerations for non-obstetric surgery during pregnancy. *Br J Anaesth* 2011;107 Suppl 1:i72-8.
60. Lydon-Rochelle M, Holt VL, Martin DP, et al. Association between method of delivery and maternal rehospitalization. *JAMA* 2000;283:2411-6.
61. Berveiller P, Mir O, Degrelle SA, et al. Chemotherapy in pregnancy: exploratory study of the effects of paclitaxel on the expression of placental drug transporters. *Invest New Drugs* 2019;37:1075-85.
62. Azim HA Jr, Del Mastro L, Scarfone G, et al. Treatment of breast cancer during pregnancy: regimen selection, pregnancy monitoring and more. *Breast* 2011;20:1-6.
63. Scott AR, Stoltzfus KC, Tchelebi LT, et al. Trends in Cancer Incidence in US Adolescents and Young Adults, 1973-2015. *JAMA Netw Open* 2020;3:e2027738.
64. Stensheim H, Møller B, van Dijk T, et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009;27:45-51.
65. Cottreau CM, Dashevsky I, Andrade SE, et al. Pregnancy-Associated Cancer: A U.S. Population-Based Study. *J Womens Health (Larchmt)* 2019;28:250-7.
66. Andersson TM, Johansson ALV, Hsieh CC, et al. Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol* 2009;114:568-72.

67. Amant F, Loibl S, Neven P, et al. Breast cancer in pregnancy. *Lancet* 2012;379:570-9.
68. Shao C, Yu Z, Xiao J, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis. *BMC Cancer* 2020;20:746.
69. Korakiti AM, Moutafi M, Zografos E, et al. The Genomic Profile of Pregnancy-Associated Breast Cancer: A Systematic Review. *Front Oncol* 2020;10:1773.
70. Longway M, Matthews CA. Resumption of ovarian function 20 years after chemotherapy-induced ovarian failure: a case report. *Fertil Steril* 2009;92:392.e17-8.
71. Lammers SWM, Geurts SME, Hermans KEPE, et al. Ovarian function recovery in breast cancer patients receiving adjuvant anastrozole treatment: updated results from the phase 3 DATA trial. *Breast Cancer Res Treat* 2024;208:179-92.
72. The Faculty of Sexual & Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC). UK: Faculty of Sexual and Reproductive Healthcare; 2019.
73. Kesim MD, Aydin Y, Atis A, et al. Long-term effects of the levonorgestrel-releasing intrauterine system on serum lipids and the endometrium in breast cancer patients taking tamoxifen. *Climacteric* 2008;11:252-7.
74. Healthcare FoSR. Contraception After Pregnancy. <https://www.fsrh.org/standards-and-guidance/documents/contraception-after-pregnancy-guideline-january-2017/>. Accessed 3 February 2025.
75. Phillips SJ, Tepper NK, Kapp N, et al. Progestogen-only contraceptive use among breastfeeding women: a systematic review. *Contraception* 2016;94:226-52.
76. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. *Breast Cancer Res Treat* 2016;160:347-60.
77. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006;24:5769-79.
78. Beadle BM, Woodward WA, Middleton LP, et al. The impact of pregnancy on breast cancer outcomes in women ≤ 35 years. *Cancer* 2009;115:1174-84.
79. Lambertini M, Peccatori FA, Demeestere I, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines[†]. *Ann Oncol* 2020;31:1664-78.
80. Boutas I, Kontogeorgi A, Koufopoulos N, et al. Breast Cancer and Fertility Preservation in Young Female Patients: A Systematic Review of the Literature. *Clin Pract* 2023;13:1413-26.
81. Jahanbin B, Soleimani V. Histology of Pregnancy-Associated Breast Cancer. *Adv Exp Med Biol* 2020;1252:81-86.
82. Taheripanah R, Balash F, Anbiaee R, et al. Breast Cancer and Ovulation Induction Treatments. *Clin Breast Cancer* 2018;18:395-9.
83. Das M, Son WY. In vitro maturation (IVM) of human immature oocytes: is it still relevant? *Reprod Biol Endocrinol* 2023;21:110.
84. Wakeford R. The risk of childhood leukaemia following exposure to ionising radiation—a review. *J Radiol Prot* 2013;33:1-25.
85. Rummel SK, Lovejoy L, Shriver CD, et al. Contribution of germline mutations in cancer predisposition genes to tumor etiology in young women diagnosed with invasive breast cancer. *Breast Cancer Res Treat* 2017;164:593-601.
86. Slocum E, Germain D. Collagen and PAPP-A in the Etiology of Postpartum Breast Cancer. *Horm Cancer* 2019;10:137-44.
87. Lambe M, Hsieh C, Trichopoulos D, et al. Transient increase in the risk of breast cancer after giving birth. *N Engl J Med* 1994;331:5-9.