BJOG: An International Journal of Obstetrics & Gynaecology

WILEY

BJOG An International Journal of Obstetrics and Gynaecology

RCOG GUIDELINES

Pregnancy and Breast Cancer

Green-top Guideline No. 12

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Accepted: 17 June 2025

Funding: All those involved in the development of the Green-top Guidelines, including the Guidelines Committee, Guidelines Committee co- chairs, guideline developers, peer reviewers and other reviewers, are unpaid volunteers and receive no direct funding for their work in producing the guideline. The exceptions to this are the RCOG staff involved who are salaried employees of the College, and Guidelines Committee members who receive reimbursement for expenses for attending Guidelines Committee meetings. Please see more information on travel expense rules on the RCOG website.

KEY RECOMMENDATIONS

- Any suspicious breast lesion or lump which is present for more than 7 days should be investigated by a specialist unit. [Good Practice Point (GPP)]
- Suspicious breast lesions should be investigated by ultrasonography with mammography reserved for investigation of extent of a known cancer. [Grade B]
- Breast surgery can be performed throughout pregnancy with appropriate fetal monitoring prior to and following surgery. [Grade C]
- Chemotherapy is contraindicated during the first trimester of pregnancy but can be administered during the second and third trimesters. [Grade B]
- Choose the treatment strategy according to local guidelines for a non-pregnant woman according to the pathology and tumour characteristics wherever possible. [GPP]
- Dosing of chemotherapy should be based on the woman's actual weight, not the pre-pregnancy weight. The woman should be reweighed and doses recalculated at each cycle of treatment. [GPP]
- Where possible the administration of HER2-directed therapy should be delayed until after birth. If HER2-directed therapy is required for the management of life-threatening metastatic disease individualised monitoring of the woman and fetus is recommended. [Grade B]
- Methylprednisolone or hydrocortisone should be used in place of dexamethasone. [GPP]
- Granulocyte-colony stimulating factor should be used as indicated in line with standard protocols. [Grade C]
- Where a delay in radiotherapy is not expected to adversely impact maternal outcome, it is recommended that adjuvant breast or chest wall radiotherapy is postponed until after the birth of the baby. [Grade B]

Abbreviations: CINV, chemotherapy induced nausea and vomiting; COS, controlled ovarian stimulation; ER, oestrogen receptor; GnRHa, gonadotrophin-releasing hormone agonist; HER2, human epidermal growth factor receptor 2; FGR, fetal growth restriction; FN, febrile neutropenia; Gy, gray; INCIP, International Network on Cancer, Infertility and Pregnancy; MDT, multidisciplinary team; NICE, National Institute for Health and Care Excellence; mGy, milligray; PABC, pregnancy associated breast cancer; PrBC, breast cancer that occurs during pregnancy; PPBC, postpartum breast cancer; PGT-M, preimplantation genetic testing for monogenic disorders; POI, premature ovarian insufficiency; SACT, systemic anti-cancer therapy; TNBC, triple negative breast cancer (cancers that lack receptors for oestrogen, progesterone and HER2); UKTIS, UK Teratology Information Service.

This is the third edition of this guideline. It replaces the previous editions published in March 2011 and January 2004, with earlier advice published in 1997.

- Adjuvant radiotherapy can be considered in specific circumstances (i.e., if risk from omission or delay outweighs harm to the fetus) provided that this is achievable within safe limits of radiation exposure to the fetus (i.e., below the deterministic threshold). Referral to a specialist centre with suitable expertise should be considered. [Grade D]
- In the metastatic setting, palliative radiotherapy may be indicated for local control of symptomatic disease or to preserve function (e.g., metastatic spinal cord compression). [Grade D]
- Women with breast cancer during pregnancy can be reassured that their breast cancer can be treated during pregnancy without long-term harm to their unborn child. [Grade A]
- Iatrogenic preterm birth should be avoided unless there are clear maternal or fetal indications. [Grade A]
- Women receiving chemotherapy should be advised not to breastfeed. [Grade B]
- Women of childbearing potential with a new diagnosis of breast cancer should be counselled, at diagnosis, about the potential impact of systemic therapy on their future fertility. [Grade B]
- Women of reproductive age who are being considered for medical treatment for breast cancer that may cause premature ovarian insufficiency should be offered oocyte or embryo cryopreservation as appropriate. [Grade C]
- Premenopausal women undergoing (neo)adjuvant chemotherapy for breast cancer and who are interested in fertility preservation should be offered temporary ovarian suppression with a gonadotrophin-releasing hormone agonist during their chemotherapy. [Grade A]
- Women with a history of early breast cancer who wish to become pregnant should be advised that pregnancy does not increase their risk of breast cancer recurrence. [Grade B]

1 | Purpose and Scope

The purpose of this guideline is to describe the diagnosis, management and treatment of breast cancer during and immediately after pregnancy. It also provides advice on future fertility considerations after a breast cancer diagnosis.

This guideline is for healthcare professionals who care for women, non-binary and trans people who experience pregnancy associated breast cancer (PABC). Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2 | Introduction and Background

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2017–19) [1]. There are around 56 800 new breast cancer cases in the UK every year (2017–19) [1]. Of these, 9% occur in women at or under 44 years of age [1]. Survival rates have improved significantly in recent decades. In women diagnosed under the age of 39 years, 85% are alive more than 5 years after their diagnosis [1] leading many women to now consider pregnancy as an option after cancer.

A new breast cancer diagnosis complicates about 1 in 3000 pregnancies [2]. With advancing maternal age at pregnancy [3] it is likely that the incidence of breast cancer during pregnancy will increase.

Clinical care of people who are pregnant with breast cancer should follow the principles of care for all pregnant women with medical disorders: the clinician's duty of care is first towards the woman and then to the fetus. This principle was outlined in the 2021 MBRRACE report which states that clinicians should 'Treat women who may become pregnant, are pregnant, or who have recently been pregnant the same as a non-pregnant person unless there is a very clear reason not to' [4]. For pregnant women with breast cancer a care plan should first be established by surgeons and oncologists, as if the woman was not pregnant. This plan can then be adapted with a multidisciplinary team (MDT) that should also include obstetricians, fetal and neonatal specialists. This team should balance potential treatment for the woman and her fetus with potential compromise for pregnancy outcome. These treatment options must be discussed with the woman.

As breast cancer during pregnancy is relatively rare and heterogeneous in its presentation, recommendations for care are guided by international registries rather than clinical trials. Treatment decisions are therefore limited to the best available evidence, which is often not definitive. In the absence of evidence of harm or safety in pregnancy, MDTs may need to consider treatment which is in the best interest for the woman. Pregnancy is not, however, an exception to the principle that an informed patient has the right to refuse treatment, even treatment needed to maintain life and a pregnant woman's informed decision to refuse recommended medical or surgical interventions for breast cancer should be respected [5].

3 | Identification and Assessment of the Evidence

The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews

of Effects [DARE] and the Cochrane Central Register of Controlled Trials [CENTRAL]), EMBASE, Trip, MEDLINE and International HTA database were searched for relevant papers. Databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search. Search terms included: 'pregnancy', 'breast cancer', 'inflammatory breast neoplasm', 'pregnancy complications' and 'breastfeeding'. The search was limited to studies on humans and papers in the English language and included all relevant studies 2010 until December 2023. Relevant guidelines were also searched for using the same criteria in the ECRI Guidelines Trust (replaces National Guideline Clearinghouse), Guidelines International Network and the National Institute for Health and Care Excellence (NICE) Evidence Search.

This guideline was developed using the methodology described in the Royal College of Obstetricians and Gynaecologists (RCOG) handbook *Developing a Green-top Guideline: Guidance for developers*. Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix A.

4 | How Should Women Who Have Breast Cancer Diagnosed During Pregnancy Be Cared for?

4.1 | Prognosis of Breast Cancer Diagnosed During Pregnancy and Postpartum

Historically, the prognosis of women diagnosed with breast cancer during pregnancy or up to 12 months postpartum has been reported as being worse than non-pregnant women of childbearing potential diagnosed outside of this timeframe [6, 7]. However, previous studies addressing PABC outcomes have conflated two separate but clearly related cohorts of women—those diagnosed with breast cancer while pregnant (a breast cancer that occurs during pregnancy, PrBC) and those diagnosed in the months postpartum (postpartum breast cancer; PPBC). There is increasing evidence that breast cancer prognosis differs between these two groups [8] and that if outcomes of the two groups are combined this distinction may be lost [9]. [*Evidence level 2+*]

4.1.1 | Breast Cancer Diagnosed During Pregnancy

Three meta-analyses [10–12] and a retrospective national registry review [13] meta-analysis have described a worse prognosis in women with PABC than their non-pregnant counterparts. However, these meta-analyses either included studies from the 1960s and 70s when diagnosis and treatment were radically different, had inconsistent definitions of PABC, and/or were poorly age and staged matched. Therefore, the applicability to modern day practice of the findings from these reports is limited.

Low expression of oestrogen receptors (ER) and increased expression of human epidermal growth factor-2 (HER2) have been reported in women with PABC, with both factors known to be associated with a relatively worse prognosis [14–16]. A large nationwide study, published in 2021, comparing histopathological profiles of 741 women with PrBC with age matched non-PrBC women, confirmed that women with PrBC have tumours with a more aggressive phenotype than non-pregnant counterparts [17], a finding also noted in other national databases [18, 19]. However, when matched for tumour stage the outcome for women with PrBC is similar to non-pregnant controls [20–22]. [*Evidence level 2+*]

By using diagnostic and treatment pathways for women with PrBC which are as close as possible to women with non-PrBC, similar outcomes can be achieved [20, 21, 23, 24]. [*Evidence level 2+*]

4.1.2 | Breast Cancer Diagnosed in the Postpartum Period

Historically breast cancers diagnosed during pregnancy or in the first few postpartum years following birth have been combined under the heading of PABC [25]. Definitions of the length of the postpartum period have varied from 6 to 60 months [12].

Data published in 2021/22 suggest that breast cancer diagnosed during pregnancy has differing tumour biology and clinical outcomes when compared with breast cancer diagnosed in the postpartum period, and that this distinction can last for 5–10 years following birth [8, 26–28]. Therefore, there are calls to consider PrBC as a distinct entity from breast cancer diagnosed in the 5–10 years following birth (PPBC) [8, 29].

Compared with women diagnosed with breast cancer during pregnancy or nulliparous women, PPBC is associated with worse survival rates and more than double the risk of metastatic disease [15, 25, 28], findings that persist despite correcting for clinical and pathological factors [30]. Compared with women with PrBC, those with PPBC are noted to have higher rates of lymph node positivity and higher grade disease [25]. In a cohort of women with oestrogen receptor-positive (ER+) PPBC metastasis-free survival was similar to that seen in oestrogen receptor-negative (ER–) nulliparous women [30]. [*Evidence level 2–*]

The pathogenesis for this worsened prognosis is currently the topic of much investigation but is thought to be linked to the shift of mammary gland epithelium, from a state of proliferation and differentiation (in preparation for lactation), to involution (following cessation of, or in the absence of, lactation). Involutional changes specific to the immediate postpartum breast and seen again on cessation of lactation are noted to share numerous stromal attributes with putative pro-malignant states [29, 31, 32]. Furthermore, pro-malignant cytokines and altered immune infiltration may persist for several years following birth [27, 33, 34], which may explain the relatively worse clinical outcomes seen in women with PPBC compared with PrBC or controls.

4.2 | What Is the Optimal Care of Women With Breast Cancer Diagnosed During Pregnancy?

4.2.1 | Diagnosis and Radiological Investigations

Recommendation	Evidence level	Strength	Rationale for the recommendation
Any suspicious breast lesion or lump which is present for more than 7 days should be urgently referred to a specialist unit with the patient seen and diagnosed within the national "Faster Diagnosis Standard" 28 day timeframe	4	GPP	Rapid assessment of breast lumps will lead to most favourable clinical outcomes
Suspicious breast lesions should be investigated by ultrasonography to allow a targeted biopsy. Mammography should be reserved for investigation of extent of a known cancer	2++	B	Ultrasound assessment with targeted biopsy where indicated will permit rapid differentiation between benign and malignant lesions
Suspicious breast lesions (clinically or on imaging) should be investigated by image guided core biopsy and not solely fine needle aspirate cytology	2++	B	Core biopsy is more accurate, informative and can help treatment planning if malignant
Suspicious axillary lesions (clinically or on imaging) should be investigated by image guided core biopsy or fine needle aspirate cytology	2++	B	Preoperative axillary staging is essential for treatment planning
Non-contrast or diffusion-weighted imaging magnetic resonance imaging (MRI) scans are safe during pregnancy and can be used when indicated	2+	B	MRI scanning may contribute to surgical planning and staging information
Contrast enhanced MRI scanning should be avoided with the exception of situations where the benefits will clearly outweigh the risks	2−	C	Contrast enhanced MRI scanning may contribute to surgical planning and staging information
Positron emission tomography-computed tomography (PET-CT) can be used with caution if the MDT feels that information gained may change management and providing this information cannot be obtained by non-ionising imaging modalities	3	C	Case reports and national registry data show that in appropriately chosen patients PET CT may result in changes in management

Pregnant women with breast symptoms persisting over 7 days, such as a breast lump, skin distortion or nipple discharge not clearly because of pregnancy-related galactorrhoea should be referred to a diagnostic breast clinic for urgent assessment. Blocked milk ducts are a common problem encountered by lactating women and can present as a breast lump [35]. Any lump perceived to be a blocked milk duct that does not resolve within 7 days should be referred for urgent assessment. [*Evidence level 4*]

Diagnostic assessment of symptoms will include clinical evaluation with imaging and biopsy as indicated. Breast density and nodularity increase during pregnancy which can complicate clinical examination [36].

4.2.1.1 | Ultrasound Scanning. Breast ultrasound has the highest sensitivity for the diagnosis of PrBC and is the first line imaging examination in pregnant and lactating women [37]. [*Evidence level 2+*]

4.2.1.2 | Mammography. Mammography is not used routinely in women below the age of 40 as it has reduced sensitivity and specificity in this age group [38]. This is further affected by pregnancy-induced changes within the breast. However, it may be indicated in people who are pregnant in the presence of suspected false negative ultrasound scan or suggestion of malignancy on the ultrasound scan [37]. Fetal radiation exposure during two-view mammography is between 0.001 and 0.01 milligray (mGy), well below the 50 mGy limit of acceptable fetal exposure [36, 39]. Lead apron shielding will further reduce fetal exposure by 50% [39]. Once an underlying malignancy is proven, mammography with percutaneous biopsy will characterise tumour extent and presence or absence of associated malignant microcalcification [39]. This will be essential for surgical planning [40]. [*Evidence level 2+*]

4.2.1.3 | Digital Breast Tomosynthesis. Digital breast tomosynthesis acquires a series of images by passage of the X-ray tube across a limited arc above the breast. Multiple exposures are obtained and reconstructed to produce a set of parallel image planes through the whole breast, typically with 1 mm spacing [41]. Although digital breast tomosynthesis incurs a very slightly higher radiation dose to the fetus [42, 43], it offers

superior sensitivity and specificity in the dense breast tissue of pregnant women, and therefore is considered to provide clinically useful information in this setting with minimal risk to the fetus [37]. [*Evidence level 2+*]

4.2.1.4 | Percutaneous Core Biopsy. Imaging suspicion of the presence of a breast malignancy should be followed by image-guided biopsy of the lesion [44, 45] as the development of fistulae in this scenario is rare [36, 46]. Concerns regarding development of a milk fistula following percutaneous core biopsy are largely theoretical. Ultrasound guided core needle biopsy is sensitive and specific in diagnosing potential axillary lymph node metastasis [47]. [*Evidence level 2+*]

4.2.1.5 | Magnetic Resonance Imaging. Non-contrast MRI scanning is considered to be safe throughout pregnancy with no specific precautions or contraindications [48–50]. Available evidence indicates no acoustic injuries to the fetus, no evidence of teratogenesis or tissue heating with 3 Tesla MRI scanning [51, 52]. A study examined long-term safety of MRI scanning in the first trimester and found no increased harm to the fetus or in early childhood [53]. [*Evidence level 2+*]

Contrast-enhanced MRI is contraindicated during pregnancy as chelated gadolinium is known to cross the placenta and enter the fetal circulation where it may theoretically dissociate into the non-chelated form, which is neurotoxic. While several small retrospective studies in women have not shown adverse fetal effects, animal studies show fetal malformation and death following supraclinical doses [54]. A large study examined outcomes in children exposed to gadolinium in utero with follow-up to a median of 2.4 years. Exposure to gadolinium during MRI scanning at any stage of pregnancy was not associated with an increase in congenital anomalies [53]. A small increase in rheumatological, inflammatory or infiltrative skin conditions was noted in gadolinium-exposed infants, together with an increased relative risk for stillbirth or neonatal death (adjusted relative risk [RR] 3.70; 95% CI 1.55–8.85), although the study was not powered to definitively establish this association [53]. [*Evidence level 2–*]

European guidelines state that use of gadolinium-enhanced MRI scanning should only be used if "there is strong clinical indication" and then "at the lowest dose to achieve a diagnostic result" [55]. American guidance is similar, advising that gadolinium use should be limited to situations where the benefits would clearly outweigh the risks [56]. However, the use of diffusion-weighted imaging sequences will often add diagnostic accuracy to allow an avoidance of contrast imaging [57, 58]. [*Evidence level 4*]

4.2.1.6 | CT Scanning. CT scanning is uncommonly used for the diagnosis and management of early breast cancer. However, its use may potentially be considered in the presence of suspected metastatic disease. In practice, this can generally be achieved by modern MRI techniques. The radiation dose to the fetus is critical in deciding the appropriateness of CT scans in the pregnant woman. Scanning of the head, chest or abdomen/pelvis results in markedly differing fetal radiation doses; below 0.005–0.05, 0.001–0.66 and 8–25 mGy respectively [59]. [*Evidence level 3*]

Shielding of the abdomen with lead aprons does not substantially reduce fetal exposure to ionising radiation [60–62]. CT scanning of the abdomen/pelvis in pregnancy should be avoided if possible but if it is considered necessary for the clinical management of the pregnant woman, discussing the benefit of the information to be derived versus the risks with the mother is important; there may be a very low chance of complications [59]. [*Evidence level 3*]

Iodinated contrast material is known to cross the placenta, but animal studies have not shown any teratogenic effects [63]. Human studies have not shown any negative effect of contrast material on fetal thyroid gland development [64, 65]. Notwithstanding any concrete proof of fetal harm from iodinated contrast material, it is recommended that contrast be used where potential benefits outweigh risks [59]. [*Evidence level 3*]

4.2.1.7 | Positron Emission Tomography-Computed Tomography. A PET-CT scan is an important modality that is increasingly used in clinical practice to aid the staging of early and advanced breast cancer [66]. Historically, hesitation regarding the use of PET-CT as a staging tool in women with PrBC have centred on concerns of fetal exposure to ^{18}Fludeoxyglucose-DG (^{18}FDG) as a result of accumulation within maternal tissue and by traversing the placenta. Comprehensive testing has, however, shown that the actual levels of fetal exposure from ^{18}FDG is very low. Following maternal administration of a typical PET-CT dose of 250 MBq, fetal exposure is between 10 and 20 mGy [67], significantly below the 100 mGy level accepted to have deterministic effects; adoption of low dose, long axial field of view protocols may reduce fetal exposure further. The maternal urinary bladder is the primary contributor to fetal radiation dose and good maternal hydration with encouragement of early voiding (or catherisation) can help minimise radiation exposure. Micturition 1 hour post administration reduces fetal exposure by up to 45%, compared with emptying the bladder at 2.5 hours [68]. Data from the French national registry have shown that PET-CT investigation changed management strategies in 38 of 63 patients (60.3%) with pregnancy-associated cancer (46 had PABC) [69]. The International Atomic Energy Agency states that pregnancy is not a contraindication to nuclear medicine procedures provided there is clinical justification for the procedure and alternative imaging using non-ionising radiation has been explored [70]. [*Evidence level 4*]

4.2.2 | Surgery: Approach and Considerations

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women diagnosed with breast cancer during pregnancy should be under the care of a dedicated MDT which has the expertise and experience to manage all aspects of maternal and fetal health	4	GPP	Care of women with breast cancer by specialist MDTs has been shown to improve outcomes

Recommendation	Evidence level	Strength	Rationale for the recommendation
Breast surgery can be performed throughout pregnancy with appropriate fetal monitoring prior to and following surgery	2+	C	Any decision to delay surgery until the second trimester should be balanced against the risk of leaving the cancer in situ, as well as any consequent delays to chemotherapy
Breast surgical choices should be the same as for non-pregnant women, with the exception that reconstructive procedures, where required, should be performed postpartum	1++	A	Breast cancer surgery should be guided by tumour biology and the woman's choice
Sentinel node localisation should be performed with 99mTc-labelled radiocolloid, injected on the day of surgery. Isosulfan blue, Patent Blue or methylene blue dye should not be used during pregnancy for axillary staging	2++	B	Axillary staging is an essential component of treatment planning. Blue dye may cause allergic/anaphylactic reactions

Care is best facilitated by a specialised PrBC MDT which, in addition to the oncology team members, also includes an obstetrician, an obstetric physician (where available), an anaesthetist and, where necessary, a neonatologist [71–74]. [*Evidence level 4*]

4.2.2.1 | Timing of Surgery. Surgery can be performed in any trimester of pregnancy. There are no established teratogenic effects of modern anaesthetic agents in any trimester, including the first [75, 76]. A large observational study across NHS hospitals of 47 628 non-obstetric surgeries in 6 486 280 pregnancies found that pregnant women who underwent non-obstetric surgery had a slight excess of spontaneous miscarriage compared with non-pregnant women (RR 1.13; 95% CI 1.09–1.17), but it was not possible to separate risks of surgery and anaesthesia from the effects of the underlying condition [77]. Surgical outcomes do not differ between pregnant and non-pregnant women undergoing breast surgery [78]. [*Evidence level 2+*]

For an individual diagnosed with cancer in pregnancy, any decision to delay surgery until the second trimester should be balanced against the risk of leaving the cancer in situ, as well as any consequent delays to chemotherapy—which is contraindicated in the first trimester.

4.2.2.2 | Perioperative Care. Breast cancer, surgery and pregnancy itself are all risk factors for thrombosis. Thromboprophylaxis with low-molecular-weight heparin or equivalent should be administered in accordance with RCOG Green-top Guideline No. 37a [79]. [*Evidence level 2++*]

In the third trimester, positioning of the woman on the operating table in the left lateral tilt position will reduce aortocaval compression by the gravid uterus, allowing maintenance of cardiac preload and output [80]. Fetal heart-rate monitoring perioperatively should be guided by obstetricians [81]. [*Evidence level 4*]

4.2.2.3 | Choice of Surgical Operation. Surgical recommendations for women with PrBC (mastectomy versus breast conserving surgery) follow the same principles to those available to all women and are guided by clinical stage, tumour biology, trimester and the individual preferences of the woman [82, 83]. [*Evidence level 1++*]

For breast cancers requiring localisation to permit breast conserving surgery, localisation techniques should follow the same principles as in non-pregnant women [84]. [*Evidence level 1++*]

For early stage breast cancer, breast conserving surgery with a wide local excision followed by radiotherapy is as effective as mastectomy, provided the margins of the resected specimen are free of tumour [85]. [*Evidence level 1+*]

However, radiotherapy is challenging to deliver during pregnancy (see Section 4.2.4). Women diagnosed during the first and second trimesters who are considering breast conserving surgery and who are unlikely to require chemotherapy should have early input from a clinical oncologist. This is to advise on the possibility of radiotherapy during pregnancy, and the implications of any delay to radiotherapy if this is not given during pregnancy. Some women may choose to undergo a mastectomy to avoid these issues. For the vast majority of women diagnosed in pregnancy (neo)adjuvant chemotherapy will be indicated and radiotherapy can be safely delayed until postpartum. [*Evidence level 4*]

4.2.2.4 | Axillary Staging. Women with PrBC should undergo the same diagnostic assessment of the axillary lymph nodes as non-pregnant women. Abnormal appearing lymph nodes (using established criteria from The Royal College of Radiologists [86]) should be subject to ultrasound guided biopsy and those women with biopsy-proven axillary metastases should, similar to non-pregnant women, receive a recommendation for axillary node clearance [87]. [*Evidence level 1++*]

Sentinel node surgery has been extensively studied in pregnancy and is now the standard of care for women with clinically node-negative (cN0) PrBC [81, 88]. In pregnancy, the sentinel node should be identified using 99mTc-labelled radiocolloid. Measurement of radiation exposure to the fetus (approximately 4.3 mGy) indicates that levels are well below the safety threshold (50 mGy) for adverse effects on the fetus [89]. Fetal exposure can be further minimised by deploying same day radioactive tracer injection, thereby reducing time between injection and surgery. Accuracy of, and local recurrence rates following, sentinel node surgery in PrBC are similar to those seen in non-pregnant women [90]. Patent Blue, isosulfan blue and methylene blue use is not recommended because of concerns regarding maternal allergy or anaphylaxis [91–93]. [*Evidence level 2++*]

4.2.2.5 | Breast Reconstruction. There are very limited data upon which to base recommendations regarding immediate breast reconstruction in women with PrBC who undergo mastectomy. The three available publications are single institution case series describing outcomes in a total of 24 women [94–96]. Each describes tissue expander reconstruction with successful aesthetic, maternal and fetal outcomes. Operative time is increased when immediate reconstruction is undertaken [95]. Wound complications following breast surgery in pregnant women are not well reported. One study examining this parameter reported complications in five of 25 cases (20%) following mastectomy [97]. Such complications following reconstruction can be expected to be higher and could potentially delay commencement of systemic therapy for the pregnant woman.

Personalised decision making is clearly important. People who are pregnant contemplating immediate reconstruction following mastectomy should be fully informed of the lack of data available to provide evidence-based recommendations. Furthermore, physical changes in the breasts during the shift from pregnant to postpartum state may significantly exaggerate any asymmetry between the reconstruction and contralateral breast, leading to poorer long term cosmetic outcomes. [*Evidence level 4*]

4.2.3 | Systemic Therapy During Pregnancy

When discussing the potential impact of any medication administered during pregnancy it is important to discuss this within the context of a background incidence of major congenital malformations (2%–3%), miscarriage (10%–20%) and stillbirth (0.5%), irrespective of any drug or chemical exposure [98]. Evidence-based data exist on the use of systemic anti-cancer therapy (SACT) during pregnancy. [*Evidence level 2++*]

4.2.3.1 | Chemotherapy.

Recommendation	Evidence level	Strength	Rationale for the recommendation
Chemotherapy is contraindicated during the first trimester of pregnancy but can be administered during the second and third trimesters	2++	B	Chemotherapy administered during the first trimester is associated with a significantly increased risk of fetal malformation
Chemotherapy should not be given beyond 35 weeks of pregnancy, or within 2 weeks of anticipated birth if this is earlier, with the exception of less myelosuppressive weekly regimens that can be continued longer at the discretion of the treating oncologist	4	GPP	Chemotherapy has a myelosuppressive effect on both the woman and fetus and therefore adequate time for bone marrow recovery prior to birth is advisable to reduce the risk of infection
Choose the treatment strategy according to local guidelines for a non-pregnant woman according to the pathology and tumour characteristics wherever possible	4	GPP	The majority of chemotherapy agents used in the management of breast cancer can be safely given adjuvantly or neoadjuvantly in the second and third trimesters of pregnancy and the regime which offers the best maternal outcome should be used
Anthracyclines, cyclophosphamide, taxanes and carboplatin are the preferred chemotherapy agents in the treatment of pregnant women with breast cancer	2++	B	These agents are considered as optimal in the treatment of breast cancer, especially in stage I–III disease, and have been demonstrated to be safe to administer during pregnancy
Dosing of chemotherapy should be based on the woman's actual weight, not the pre-pregnancy weight. The woman should be reweighed and doses recalculated at each cycle of treatment	4	GPP	Pharmacokinetics of chemotherapeutic agents are altered in pregnancy. Dosing on pre-pregnancy weight may lead to underdosing and reduced efficacy

4.2.3.1.1 | Timing of Chemotherapy. In the first trimester from implantation to organogenesis, chemotherapy is contraindicated owing to the teratogenic effects [99–103]. The period of organogenesis is characterised by the growth and differentiation of tissues into organs and is the stage of development most susceptible to teratogenic agents. Data from the International Network on Cancer, Infertility and Pregnancy (INCIP) database confirmed the risks from chemotherapy exposure prior to 12 weeks of pregnancy, with major malformations seen in 21.7% (95% CI 7.5–43.7; odds ratio, 9.24 [95% CI, 3.13–27.30]) of exposed pregnancies ($n = 29$) [104]. Chemotherapy administered after 12 weeks of pregnancy was associated with a major congenital malformation rate of 3.0% (95% CI 1.9–4.6), similar to the expected rates in the general population. [*Evidence level 2+*]

Pregnant women with breast cancer should follow the treatment plan for non-pregnant women as far as is possible, while taking into account gestational age at diagnosis and the expected date of birth. However, at times a more tailored approach may be needed [105]. [*Evidence level 4*]

Chemotherapy should be discontinued 2–3 weeks prior to birth to allow sufficient time for both maternal and fetal bone marrow recovery to minimise the risk of complications postpartum [106]. In general this means no chemotherapy after 35 weeks of pregnancy although weekly chemotherapy regimens, which are less myelosuppressive, could be cautiously continued for another week or two if this would allow completion of the chemotherapy course. [*Evidence level 4*]

4.2.3.1.2 | Choice of Regime. The choice of chemotherapy regime should be selected, as far as possible, according to tumour biology and tumour stage, based on local practice in non-pregnant women. The standard (neo)adjuvant breast cancer chemotherapy regimes consist of an anthracycline/cyclophosphamide doublet in combination or in sequence with a taxane, with or without a platinum agent [87]. [*Evidence level 1+*]

The majority of data on the use of chemotherapy in women and people who are pregnant with breast cancer involves the use of anthracycline (doxorubicin or epirubcin) and cyclophosphamide containing regimes. There are a number of studies reporting that anthracycline-based chemotherapy does not increase rates of fetal harm [20, 107, 108]. [*Evidence level 2+*]

Taxanes (docetaxel and paclitaxel) have less reported use in pregnancy than anthracycline/cyclophosphamide combinations, although the body of evidence supporting their safety in the second and third trimesters is increasing, with studies failing to highlight any major concerns regarding perinatal outcomes [108–111]. Taxane based chemotherapy is now considered as safe to administer during the second and third trimesters of pregnancy [106]. Weekly paclitaxel has equivalent efficacy to three-weekly docetaxel in the population of non-pregnant women with breast cancer [112], and may be the preferable taxane regimen in pregnancy as it is less myelosuppressive, with a lower risk of complications should unexpected early birth occur. Nab-paclitaxel is a nano-particle albumin-bound formulation of paclitaxel that is predominantly used in women who have had hypersensitivity reactions to taxanes. While there are currently no data regarding the use of this agent in pregnancy, the drug is essentially an alternative formulation of paclitaxel, and there is no reason to suspect it could not be used in pregnant women where indicated. [*Evidence level 2+*]

In recent years carboplatin has been added to the regimes in the neoadjuvant treatment of triple negative breast cancer (TNBC) (tumours that lack receptors for oestrogen, progesterone and HER2), with demonstrated improvements in pathological complete response rate [113, 114]. Carboplatin is the backbone of many treatment regimes for gynaecological cancers and therefore much of the evidence regarding its safety in pregnancy can be extrapolated from that cohort [115, 116], where carboplatin is deemed safe. As with paclitaxel the benefit of reduced myelosuppression would make the use of weekly carboplatin preferential over three-weekly carboplatin. [*Evidence level 2+*]

5-Fluorouracil has also been demonstrated to be safe to administer during the second and third trimesters of pregnancy [117], but is no longer felt to add any additional disease-free survival advantage [118] when added into anthracycline/cyclophosphamide regimes and therefore should be omitted in early breast cancer. Capecitabine, the oral prodrug of 5-fluorouracil, is still extensively used in the treatment of advanced disease and, although there are very little data regarding its use in pregnancy, could be considered for the treatment of advanced disease. [*Evidence level 4*]

Older regimes such as cyclophosphamide/methotrexate/fluorouracil (CMF) have inferior efficacy compared with anthracycline/taxane combinations. CMF should be avoided in pregnancy as there is a risk of prolonged fetal exposure with methotrexate owing to amniotic fluid accumulation of the drug [119]. [*Evidence level 4*]

4.2.3.1.3 | Dosing. Chemotherapy is usually dosed on body surface area or body weight, with the exception of carboplatin that is dosed on renal function, either calculated or measured.

Pharmacokinetic profiles of drugs differ between pregnant and non-pregnant women, and there is limited evidence from human studies and animal preclinical models that the pharmacokinetics of chemotherapy agents are also altered in the pregnancy. These differences are mostly because of the altered physiology of pregnancy, with haemodynamic changes and an increase in plasma volume and glomerular filtration rate, together with hormonal changes to hepatic function, and changes in albumin concentrations affecting protein-bound drugs such as taxanes. These changes may result in decreased plasma exposure to chemotherapy drugs [120, 121]. There is, however, insufficient evidence to make altered dosing recommendations in the context of pregnancy. Available outcome data do not show a worse outcome for pregnant compared with non-pregnant women and the same drug doses should be used. Chemotherapy dosing in pregnant women, as for non-pregnant women, should therefore be based on the woman's actual weight at each cycle to account for pregnancy-related weight changes [81, 88, 122]. Dosing based on pre-pregnancy weight is likely to lead to under dosing with potentially reduced efficacy. [*Evidence level 4*]

The use of dose dense (dd) (where the interval between successive treatments is reduced compared with a standard regimen) chemotherapy regimens is increasing in the treatment of early breast cancer, particularly for women with a higher risk of recurrence [123, 124]. This involves reducing the interval between chemotherapy regimes with the use of granulocyte-colony stimulating factor (G-CSF) support, and could be a useful strategy to ensure completion of chemotherapy prior to birth. A cohort of ten women undergoing dd chemotherapy for breast cancer experienced an increased risk of fetal or maternal toxicity [108]. [*Evidence level 2–*]

Intensified dd regimens (using a higher dose over a shorter period of time) is not a common approach in non-pregnant women, is associated with higher rates of toxicity, and is not recommended in pregnancy.

While maternal drug exposure is relevant for breast cancer related outcomes, transplacental drug transfer is relevant for fetal outcomes, but few studies exist. In a preclinical model of non-human primates, involving simultaneous collection of fetal and maternal plasma samples [120], transplacental transfer of anthracyclines and taxanes demonstrated marked variability but, when a drug was detected, levels were low. Transfer of carboplatin was greater (at 57% of maternal levels) [120], although the clinical impact of this remains uncertain [115]. It does appear that the

fetus may be relatively protected from exposure to some chemotherapy agents because the placenta acts as a protective barrier. However, even when drugs are not efficiently transferred across the placenta, fetal development can be indirectly affected by drug effects on placental function. Exposure to chemotherapy in utero may be associated with fetal growth restriction (FGR), as shown in a cohort study of 1170 women treated over a 20-year period in all cancer subtypes, where 500 had received chemotherapy [125]. The highest rates of FGR were with platinum-based chemotherapy exposure (OR 3.12; 95% CI 1.45–6.7). Breast cancer specific studies, involving the use of anthracyclines and alkylating-based chemotherapy, with or without a taxane, identified only an association of chemotherapy with low birthweight [23, 126] but not with the incidence of small-for-gestational-age infants [23, 122, 126]. Data from INCIP confirmed FGR is common after chemotherapy in pregnancy, with duration of chemotherapy having a negative impact on growth [127]. [*Evidence level 2+*]

Because of potential adverse effects on fetal growth, women undergoing chemotherapy should receive additional monitoring for fetal growth. [*Evidence level 4*]

4.2.3.2 | Endocrine Therapy.

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Defer the administration of endocrine therapy until after birth	2–	B	Fetal malformations have been reported following tamoxifen and aromatase inhibitor exposure in utero

Tamoxifen is indicated in the treatment of ER+ breast cancer for both early and advanced disease [87]. Fetotoxicity has been reported in some animal studies. A literature review of 167 pregnancies reported anomalous fetal development in 12.6%, which exceeds the baseline rate of fetal anomalies in the general population of around 4% [128]. The reported malformations were varied including facial malformations and anomalies in the infant female external genitalia, and were not confined to first trimester exposure. There is also a theoretical concern of potential malignancies in female offspring in later life as has been observed following exposure to diethylstilboestrol in utero [128], although the small numbers mean that a definitive causal relationship has not been established. The UK Teratology Information Service (UKTIS) advise that there is insufficient evidence to support the use of tamoxifen in pregnancy. [*Evidence level 2+*]

4.2.3.3 | Targeted Therapies.

Recommendation	Evidence level	Strength	Rationale for the recommendation
Where possible the administration of HER2-directed therapy should be delayed until after birth. If HER2-directed therapy is required for the management of life-threatening metastatic disease individualised monitoring of the woman and fetus is recommended	2+	B	Trastuzumab administration is associated with a significant risk of oligohydramnios and anhydramnios and consequently fetal toxicity
Inadvertent trastuzumab exposure during the first trimester is not an indication for termination	2	B	The risk of fetal harm with short duration of exposure in the first trimester is low
If HER2-directed therapy is required for the management of life-threatening metastatic disease, twice-weekly fetal scans to assess amniotic fluid volume and fetal wellbeing with umbilical artery Doppler measurements should be arranged	4	GPP	To maximise clinical benefit in a life-threatening situation, while minimising the risk of fetal harm, additional monitoring in line with other high risk pregnancies is appropriate

4.2.3.3.1 | Trastuzumab. Trastuzumab is a monoclonal antibody (MAB) directed against the HER2 receptor that is indicated in HER2 positive disease, both in early breast cancer to reduce the risk of recurrence [87] and in advanced breast cancer to prolong survival [129]. [*Evidence level 1+*]

Oligohydramnios (OR 17.68; 95% CI 12.26–25.52; $p < 0.01$), congenital respiratory disorders (OR 9.98; 95% CI 2.28–34.67; $p < 0.01$) and neonatal kidney failure (OR 9.15; 95% CI 4.62–18.12; $p < 0.01$) were reported in a case–control study of 328 individuals exposed to anti-HER2 agents during pregnancy and registered in the WHO international pharmacovigilance database [130]. Neonatal deaths have been reported because of renal and respiratory failure [131, 132]. Gestation of exposure may be relevant, with a smaller study documenting oligohydramnios and anhydramnios in 17 of 24 (70.8%) cases through second and third trimester exposure, but only 1 of 6 (16.7%) cases through first trimester exposure [127]. In the Herceptin Adjuvant (HERA) trial which investigated the use of adjuvant trastuzumab, 16 pregnancies occurred during and up to 3 months after trastuzumab exposure [133], with no cases of oligohydramnios or anhydramnios reported, but 25% of the pregnancies ended in spontaneous miscarriage, numerically higher than the general population risk of around 15% [134]. The risk of oligo/anhydramnios is potentially linked to duration of trastuzumab exposure, although statistical significance has not been proven [132]. There is some evidence that oligohydramnios induced by trastuzumab is reversible upon discontinuation of treatment [132]. [*Evidence level 3*]

The effects of trastuzumab on amniotic fluid production and renal development are likely to be attributable to blockade of feto-renal epidermal growth factor receptors and downregulation of vascular endothelial growth factor expression. MABs are transported across the placenta by active transport in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. The placental Fc receptor responsible for this is not effective until the 14th week of pregnancy.

Despite the fact that treatment with trastuzumab is associated with cardiotoxicity in adults this has not been reported in infants exposed in utero [131]. [*Evidence level 2+*]

A study describing 51 pregnant women case-matched with non-pregnant HER2 positive women found that the pregnant women had poorer breast cancer survival with statistically significant earlier recurrence [135], perhaps owing to delayed HER2-directed therapy. More reassuring data came from a much larger study of 2749 (non-pregnant) women with early breast cancer that found delays in initiation of trastuzumab of less than 6 months after diagnosis did not appear to worsen prognosis [136]. [*Evidence level 2+*]

Treatment with trastuzumab is not recommended in pregnancy and should be delayed until postpartum wherever possible. However, short duration of therapy (less than one trimester) could be considered, with careful monitoring for complications, in women who present with imminently life-threatening metastatic disease in pregnancy. Furthermore, available data suggest that women who accidentally become pregnant while receiving, or soon after completion of HER2-directed treatment, can be reassured that inadvertent exposure to limited cycles of trastuzumab is not a reason for a pregnancy termination. [*Evidence level 3*]

More recently, the therapeutic options for the treatment of HER2 positive breast cancer have been expanded with pertuzumab, a MAB directed against a different subdomain of the HER2 receptor, trastuzumab-based antibody-drug conjugates (ADCs), and small molecule inhibitors that hinder tyrosine kinase activity. Fetal toxicity has also been reported following maternal exposure during pregnancy to the ADC, trastuzumab emantansine (cardiovascular malformations; two of 20 cases [10%]), and the tyrosine kinase inhibitor, lapatinib (intrauterine growth retardation; eight of 18 cases [44.4%]) [130].

4.2.3.3.2 | Other Targeted Therapies. There are numerous other targeted therapies employed in the treatment of breast cancer including: mechanistic target of rapamycin (mTOR) inhibitors; cyclin-dependent kinase (CDK) 4 and 6 inhibitors; poly-ADP ribose polymerase (PARP) inhibitors; and immunotherapy. These agents are usually used in addition to endocrine therapy or chemotherapy. There are little or no data to support the use of these newer targeted agents in the treatment of PABC, and their use is not currently recommended. [*Evidence level 4*]

4.2.3.4 | Bone-Modifying Therapy.

Recommendation	Evidence level	Strength	Rationale for the recommendation
Consider bone-modifying treatment to pregnant women with metastatic disease only where the maternal need outweighs the risk to the fetus, for example, uncontrolled hypercalcaemia, or significant bone pain	2–	B	There is only a small body of evidence supporting the safe use of bisphosphonates in pregnancy and caution is advised
Where exposure to bisphosphonates has occurred, either prior to or during pregnancy, fetal growth and skeletal development should be monitored. Mother and infant should also be monitored for hypocalcaemia	3	D	Limited clinical data but low birthweight and hypocalcaemia have been reported following exposure

Bisphosphonates and denosumab are routinely used in the treatment of women with secondary breast cancer, to reduce the risk of skeletal-related events from bone metastases [129, 137], and in the management of hypercalcaemia of malignancy. Bisphosphonates (zoledronic acid and sodium clodronate), when delivered as adjuvant therapy, have also produced improvements in survival in women with early breast cancer [138]. [*Evidence level 1+*]

Preclinical animal studies have demonstrated the potential for fetal and maternal toxicity arising from bisphosphonate administration in pregnancy [139, 140]. The majority of the data regarding bisphosphonates in pregnancy in humans relates to alendronic acid exposure and includes instances where bisphosphonates were taken prior to conception owing to the long half-life of these agents. Bisphosphonate exposure has not resulted in any major fetal malformations [141–143]; however, there have been possible associations with increased risk of spontaneous miscarriage, decreased infant birthweight, and earlier gestational age at birth [142]. Bisphosphonates are known to cause hypocalcaemia which can affect the contractility of the uterus [81] and there are reports of neonatal hypocalcaemia following in utero exposure [144]. UKTIS advise that there are currently insufficient data to support the use of bisphosphonates in pregnancy [144]. [*Evidence level 2–*]

For the management of imminently life-threatening hypercalcaemia the available data, predominantly gleaned from the management of hyperparathyroidism in pregnancy, indicates that bisphosphonates can safely be administered in this situation [145]. [*Evidence level 3*]

In postmenopausal women with early breast cancer, bisphosphonates reduce the risk of breast cancer recurrence and can, therefore, be given with adjuvant endocrine therapy in conjunction with ovarian function suppression in premenopausal women. After administration bisphosphonates remain in bone for a long period of time, potentially years, which is an important consideration for those women planning a pregnancy following treatment. During this time they are slowly released from bone and excreted by the kidneys. UKTIS advise that, where exposure to bisphosphonates has occurred, either prior to or during pregnancy, monitoring of fetal growth, skeletal development and neonatal calcium levels may be warranted. [*Evidence level 4*]

Denosumab is a MAB that is only used in metastatic breast cancer. However, there are no data regarding the use of denosumab in pregnancy and it cannot be recommended.

4.2.3.5 | Supportive Therapy.

Recommendation	Evidence level	Strength	Rationale for the recommendation
Antiemetics including 5-HT3 antagonists, cyclizine, prochlorperazine, metoclopramide, domperidone and olanzapine may be used as indicated in line with standard protocols	2+	C	Optimal management of anticipated or actual treatment-related toxicity is essential to improve patient tolerability and adherence. These agents have been demonstrated as safe to use during pregnancy
Aprepitant may be used in line with standard protocols where a Neurokinin-1 (NK1) antagonist is indicated	3	C	Optimal management of anticipated or actual treatment-related toxicity is essential to improve patient tolerability and adherence. These agents have been demonstrated as safe to use during pregnancy
Methylprednisolone or hydrocortisone should be used in place of dexamethasone	4	GPP	Corticosteroids reduce chemotherapy-induced nausea and vomiting (CINV) and treatment associated hypersensitivity reactions. Corticosteroids generally have been demonstrated as safe to use during pregnancy. These specific agents are more extensively metabolised in the placenta than dexamethasone, thus minimising fetal exposure
G-CSF should be used as indicated in line with standard protocols	2+	C	Prevention of febrile neutropenia(FN) is paramount to minimise maternal toxicity and optimise treatment intensity. G-CSF has been demonstrated as safe to use during pregnancy
H2 receptor antagonists may be used where required to prevent administration associated hypersensitivity reactions	2+	C	Prevention of treatment associated hypersensitivity reactions is imperative to minimise maternal toxicity and optimise treatment intensity. H2 antagonists have been demonstrated as safe to use during pregnancy
Antihistamines may be administered where required	2+	C	Antihistamines have been demonstrated as safe to use during pregnancy
Seek pharmacist/ Medicines Information (MI) centre/UKTIS/ UK Medicines Information (UKMi) drugs in pregnancy special advisory service for advice on any other medication indicated that is not covered by this guideline	4	GPP	A variety of supportive medications may be required for the symptomatic management of SACT-associated toxicity which are beyond the scope of this guideline

Determining which supportive therapy to prescribe during pregnancy involves careful consideration of risks to the fetus and the woman, both from the supportive medication itself and also the likelihood and consequences of treatment-related toxicities should standard supportive medications be withheld. It is also worth considering that systemic therapy is only indicated from the second trimester onwards, that many of these supportive treatments will only be indicated for short courses with each cycle of chemotherapy and not for continuous dosing, thus minimising fetal exposure.

4.2.3.5.1 | Antiemetics. For women undergoing chemotherapy the recommended antiemetic prophylaxis will depend on the emetogenicity of the regime with 5-HT3 antagonists, corticosteroids and NK1 antagonists being routinely employed to prevent both acute and delayed chemotherapy-induced nausea and vomiting (CINV). Olanzapine is also now recommended for the prevention of CINV for highly emetogenic regimes [146], although this has not been widely adopted as routine practice in the UK. Agents such as metoclopramide, domperidone, cyclizine and prochlorperazine are generally reserved for breakthrough nausea and vomiting.

4.2.3.5.2 | 5-HT3 Antagonists. Ondansetron is the 5-HT3 antagonist that has been most extensively evaluated in pregnancy and is routinely used in the treatment of hyperemesis gravidarum that has failed to respond to first line therapy. There are some reports of malformations following fetal exposure to ondansetron during the first trimester [147, 148]. However, a large retrospective analysis of 1970 women receiving ondansetron during pregnancy did not identify a significantly increased risk of any adverse fetal outcome [149]. This finding was corroborated further by a large case–control study [150] and a separate cohort study [151] of birth defects following ondansetron exposure, with neither study showing an increase in the majority of birth defects. Both of these studies [150, 152] did suggest a small increased risk (0.03% absolute increase) of oral cleft palate following use in the first trimester [152], with a greater risk associated with intravenous administration compared with oral formulation [153]. Subsequent data from almost 1.9×10^6 pregnancies, of which almost 24000 women had at least one

ondansetron injection and after adjusting for potential confounding, showed no excess cleft palate risk with ondansetron dosing [151]. Regardless of any first trimester risk, ondansetron use in the second trimester and beyond, as a means to prevent chemotherapy-induced emesis, is considered safe. [*Evidence level 2++*]

There are fewer data on the use of granisetron and the longer acting 5-HT3 antagonist palonosetron in pregnancy. Anecdotally these agents have been used for the prevention of CINV in people who are pregnant with breast cancer, and preclinical animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development [154, 155]. In ex vivo modelling studies granisetron did not appear to cross the placenta [156].

5-HT3 antagonists, preferably ondansetron, should be administered to pregnant women undergoing treatment for breast cancer where indicated according to the emetogenicity of the SACT regime.

4.2.3.5.3 | Corticosteroids. The corticosteroid of choice in chemotherapy regimes for the prevention of CINV is usually dexamethasone, whereas hydrocortisone is often used to prevent or treat administration associated hypersensitivity reactions. Methylprednisolone or hydrocortisone are the steroids of choice for the management of treatment-related adverse effects in breast cancer in pregnancy, as they are extensively metabolised in the placenta thus minimising fetal exposure [157]. Both are widely available as oral and injectable preparations and therefore it would seem prudent to use these agents instead of dexamethasone; 4 mg methylprednisolone or 20 mg hydrocortisone are considered equivalent to 0.75 mg dexamethasone [158]. [*Evidence level 4*]

Animal studies and an early human study suggested an association between exposure to corticosteroids, predominantly in the first trimester, and cleft lip malformations, but this finding is not corroborated by the majority of pregnancy exposure data in humans [159]. Steroids are widely used throughout pregnancy for the management of a range of conditions. Corticosteroids, preferably methylprednisolone or hydrocortisone, should be used in the prevention of CINV and the prevention and management of acute hypersensitivity reactions in women with breast cancer receiving SACT. This is consistent with the advice of UKTIS that, where use of systemic corticosteroids is clinically indicated, treatment should not be withheld on account of pregnancy [159]. [*Evidence level 4*]

Screening for glucocorticoid-induced diabetes should be considered in all patients commencing steroids in line with national guidelines [160]. The use of steroids may exacerbate gestational diabetes which should be managed in accordance with the NICE guideline [NG3] [161].

4.2.3.5.4 | Neurokinin-1 Receptor Antagonists. There has been little published evidence regarding the use of NK1 antagonists during pregnancy, aprepitant being the agent that has most use in pregnancy. No fetal adverse effects have been observed in animal studies [162], however, the supraphysiological dosing above the exposure level in humans could not be attained in animal studies. Expert consensus advocates their use for the prevention of CINV [119] and aprepitant can be considered for pregnant women where necessary. [*Evidence level 3*]

4.2.3.5.5 | Olanzapine. Off-label use of the atypical antipsychotic olanzapine for the prevention of CINV is relatively new, with no data concerning its use for this indication in pregnancy. There is, however, experience regarding the use of olanzapine in pregnancy for psychiatric indications. A retrospective study of over 1300 women taking olanzapine during pregnancy found no increased incidence of fetal malformations [163]. Newborns exposed to prolonged olanzapine and other atypical antipsychotics during the third trimester have been reported to show withdrawal symptoms and other central nervous system (CNS) disorders and monitoring is recommended following birth [164]. Olanzapine use may also predispose the woman to gestational diabetes, therefore a glucose tolerance testing is advised [164, 165]. Olanzapine would only be indicated for short courses at low doses for CINV prevention and, therefore, may be considered for pregnant women following the failure of other antiemetics. [*Evidence level 4*]

4.2.3.5.6 | Other Antiemetics. Cyclizine and prochlorperazine are recommended as first-line agents in the management of hyperemesis gravidarum, with metoclopramide and domperidone reserved as second line because of their potential to cause extrapyramidal adverse effects in the woman [166]. These antiemetics have been extensively studied in pregnancy, are considered as safe to administer during pregnancy [167] and should be used for the management of breakthrough nausea and vomiting in the pregnant woman with breast cancer. [*Evidence level 3*]

4.2.3.5.7 | Granulocyte-Colony Stimulating Factors. The use of G-CSF is recommended to reduce the risk of FN for all chemotherapy regimes where the risk of FN is high (20% or higher) [168, 169], and in less myelosuppressive regimens in women who are at high risk of FN complications owing to co-morbidities. G-CSF is also used as secondary prevention in women who have previously experienced an episode of FN as a common strategy to maintain dose intensity. [*Evidence level 1++*]

G-CSF is known to cross the placenta, but no adverse effects are seen in animals with clinically relevant dosing [170].

Two studies, which reviewed the data from the Severe Chronic Neutropenia Internal Registry, reported the safe use of G-CSF in pregnancy outside of a cancer diagnosis [171, 172]. There are also small numbers of women included in retrospective studies treated with G-CSF in combination with chemotherapy for various cancers, predominantly breast cancer and lymphomas, where G-CSF has not been associated with fetal harm [173]. Furthermore, G-CSF has been studied, as part of a randomised placebo-controlled trial of 150 women, as a potential agent to prevent unexplained recurrent miscarriage. Although the proposed benefits of G-CSF in preventing miscarriage were not proven, there were no significant differences in pregnancy outcome or fetal harm between the G-CSF treated and placebo treated groups [174]. G-CSF should be used in pregnancy for the same indications as in a non-pregnant woman with breast cancer. [*Evidence level 2+*]

4.2.3.5.8 | H2 Antagonists. H2 antagonists are often recommended as premedication to reduce risk of hypersensitivity reactions, for example prior to the administration of paclitaxel. Following a UK national shortage of ranitidine in 2020, alternative H2 antagonists including cimetidine, famotidine and nizatidine have been used in premedication regimes. The UKTIS advises that the use of H2 antagonists in pregnancy appears to be safe with data from more than 4600 pregnancy exposures, albeit with the majority of this data relating to ranitidine administration. Increased risk of childhood asthma following maternal exposure to H2 antagonists has been reported; however, further research has been recommended as present data are not reliable [175]. [*Evidence level 2+*]

Where H2 antagonists are deemed necessary, especially for the premedication of women with known hypersensitivity reactions to SACT, they can be administered in pregnancy.

4.2.3.5.9 | Antihistamines. Chlorphenamine is recommended as premedication to reduce the risk of associated hypersensitivity reactions, for example prior to the administration of paclitaxel. It may also be administered in the event of a hypersensitivity reaction to any agent. The available data do not indicate that chlorphenamine use in pregnancy is associated with increased rates of congenital malformation [176]. Chlorphenamine could be administered for the prevention and treatment of hypersensitivity reactions with SACT in pregnant women undergoing treatment for breast cancer in line with standard treatment protocols. [*Evidence level 2+*]

Antihistamines may be used in the management of treatment-related toxicity where the woman's preference is often for a non-sedating antihistamine. Both cetirizine and loratidine are widely used during pregnancy for the symptomatic relief of allergic conditions [177]. [*Evidence level 2+*]

The available evidence regarding the use of fexofenadine has not demonstrated cause for concern, but data are very limited and fexofenadine use should be reserved for cases where other antihistamines have proven ineffective. [*Evidence level 4*]

4.2.4 | Therapeutic Radiation During Pregnancy

Recommendation	Evidence level	Strength	Rationale for the recommendation
Where a delay in radiotherapy is not expected to adversely impact maternal outcome, it is recommended that adjuvant breast or chest wall radiotherapy is postponed until after the birth of the baby	2++	B	There are well-recognised risks associated with fetal exposure to radiation (data from animal studies, case reports, and survivors of nuclear incidents). The available information on long-term consequences of in utero exposure to radiotherapy is limited
Adjuvant radiotherapy can be considered in specific circumstances (i.e. if risk from omission or delay outweighs harm to the fetus) provided that this is achievable within safe limits of radiation exposure to the fetus (i.e. below the deterministic threshold). Referral to a specialist centre with suitable expertise should be considered	3	D	Successful radiotherapy of breast cancers during pregnancy and birth of healthy children has been reported in case reports/series. Radiotherapy of people who are pregnant with breast cancer is possible with fetal doses below the deterministic threshold
The option of mastectomy versus breast conserving surgery may be considered, if the former will allow omission of, or avoid, unacceptable delay in radiotherapy	4	GPP	Randomised studies have shown equivalent outcomes for breast cancer recurrence and survival with breast conserving surgery and radiotherapy versus mastectomy
If the woman is unexpectedly discovered to be pregnant during radiotherapy, they should be informed of the individual risks, so that they can make an informed choice regarding continuation of the pregnancy	4	D	There are well-recognised risks associated with fetal exposure to radiation (data from animal studies, case reports, and survivors of nuclear incidents). The possible effects of radiation include fetal death in the first 2 weeks post conception, congenital malformations up to 8 weeks, and the highest risk of neurodevelopmental delay between 8 and 15 weeks of pregnancy. The available information on long term consequences of in utero exposure to radiotherapy is limited
In the metastatic setting, palliative radiotherapy may be indicated for local control of symptomatic disease or to preserve function (e.g. metastatic spinal cord compression)	4	D	Careful discussion is required between the clinical oncologist and the woman regarding the risks and benefits of radiotherapy, with consideration given to the overall prognosis of the woman and the likelihood of the pregnancy reaching term

It is well-established that the human embryo and fetus are sensitive to ionising radiation at doses greater than 0.1 gray (Gy) (equivalent to more than 1000 chest X-rays) [178, 179]. This is derived from animal studies, and data from survivors of nuclear incidents such as occurred at Chernobyl. The risks are uncertain between 0.05 and 0.1 Gy and deemed negligible when below 0.05 Gy [180]. [*Evidence level 2++*]

Significant potential harmful effects of ionising radiation can be summarised into four main categories: pregnancy loss (miscarriage, stillbirth); malformation; growth disturbance; and carcinogenic effects [181]. The effect of exposure to radiation (for the same given dose) highly depends on the gestational age; the greatest risk for a lethal effect is in the preimplantation stage, whereas the risk of malformations is highest during organogenesis (weeks 3–8) and CNS damage most likely between 8 and 16 weeks of pregnancy [181, 182]. [*Evidence level 2++*]

Broadly, radiation effects are expressed as being either deterministic or stochastic. Deterministic effects have a cause and effect relationship, such that below a certain threshold the effect will not occur. However, once the threshold has been crossed, the effect of significance will increase linearly with dose. Stochastic effects represent the radiation effects that may occur by chance (i.e., no threshold dose) [183]. [*Evidence level 2++*]

Successful radiotherapy for breast cancers during pregnancy and birth of healthy offspring have been reported, but information on long-term sequelae of in utero exposure to radiotherapy is limited [88]. Advanced radiotherapy techniques may be less effective at minimising radiation dose to healthy maternal and fetal tissue. This is because of the low dose exposure to normal tissues outside the breast, generated by intensity-modulated radiotherapy or volumetric-modulated arc therapy. Therefore, conventional radiotherapy techniques are favoured. Additionally, imaging during radiotherapy is used to verify treatment position and can result in additional dose to the fetus [182]. Orthogonal kilovoltage instead of CT (megavoltage) imaging is preferred as this uses lower beam energies and provides the lowest additional peripheral dose [182, 183]. [*Evidence level 2+*]

During breast irradiation, the most critical factors determining the fetal dose are the field size and distance from the radiation field. Radiotherapy delivery during pregnancy requires input from the physicist to determine fetal dose and to achieve adequate shielding (a total of 4–5 half value layers. A half value layer is defined as the thickness of the material required to attenuate the radiation beam by half). This can reduce the dose to the fetus by 50%–75% [182]. Commercial planning systems are very precise in estimating dose within the treatment volume, but underestimate the peripheral dose. Therefore, additional measures such as the use of dedicated software, a phantom model and/or in vivo dosimetry using thermo-luminescent dosimeters (TLD) to monitor actual fetal exposure should be used [182]. [*Evidence level 3*]

It is important for a physicist to calculate the fetal radiation dose, and modifications to the treatment plan such as changing the field size, angle, and radiation energy should be considered where possible. Treatment plan documentation should include estimation of the fetal dose. The principle is that fetal dose should be "as low as reasonably achievable" as the effects of radiation are linearly cumulative. In practice, even though the fetus is excluded from the direct radiation field, exposure occurs via radiation leaking from the accelerator and collimator scatter. Planning treatment requires a close discussion between radiation oncologists, medical physicists, and dosimetrists. Maternal and fetal consequences of treatment with and without radiation should be carefully discussed with the woman to enable informed consent. [*Evidence level 3*]

Fetal exposure increases exponentially with gestational stage as the distance between the radiation field edge and uterine fundus narrows. Therefore, it is important to evaluate the expected change in fundal height during radiotherapy while calculating the fetal dose [184]. In the first 12 weeks of a singleton gestation, the uterine fundus remains within the pelvis, and by 20 weeks reaches the umbilicus. Therefore, there is a theoretical window in the first, or early part of the second trimester for breast radiotherapy to be delivered safely. For example, when giving breast or chest wall radiotherapy during early pregnancy, the fetus will be exposed to 0.1%–0.3% of the total dose (0.05–0.15 Gy with a prescription dose of 50 Gy equivalent) [180]. Hypofractionated radiotherapy (e.g., 26 Gy in five fractions as per FAST-FORWARD trial) [185] has been shown to be non-inferior to the standard 40 Gy in 15 fractions schedule, and is therefore applicable in these women. Towards the latter stages of pregnancy, the dose to the fetus could exceed 2 Gy. Hershman et al. [186] showed that it is safe to delay adjuvant radiotherapy for up to 12 weeks following breast conserving surgery, without impacting on overall or cancer-specific mortality. Therefore in the last trimester, it is reasonable to delay radiotherapy until after birth [180]. [*Evidence level 4*]

More recently, there has been interest on the role of proton therapy in reducing the out of field dose compared with traditional photon therapy, for which there is evidence of benefit in the management of CNS tumours. Furthermore, with the use of pencil beam scanning, a 30-fold decrease in dose to the fetus has been demonstrated compared with photon therapy with all shielding in place. An additional benefit of proton therapy in this respect is that no shielding is necessary when using pristine pencil beams [186, 187]. This is an area of research which can be used to model this more specifically in women with breast cancer.

4.2.5 | Termination of Pregnancy

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women diagnosed with breast cancer during pregnancy should have all treatment options discussed and the implications of terminating or continuing with their pregnancy to allow informed decision making	4	GPP	All treatment options must be fully discussed with the woman. Women should be supported in their decision making

It is important that women diagnosed with breast cancer during their pregnancy make informed decisions about all available options and are supported in their decision making. The decision to continue or end a pregnancy must be a personal one. Women should be reassured that the prognosis for women diagnosed with breast cancer during pregnancy is similar to that of a non-pregnant women (see Section 4.1), and that termination does not appear to improve outcomes [188]. [*Evidence level 3*]

Furthermore, for women with early breast cancer, surgery can be performed throughout pregnancy and chemotherapy from the second trimester. Where treatments cannot be given during pregnancy, such as trastuzumab and pertuzumab, the implications (or otherwise) of any delay in therapy should be discussed to allow informed decision making.

The diagnosis of metastatic breast cancer during pregnancy is uncommon. Treatments that may be urgently needed, such as radiotherapy for imminent spinal cord compression, can be challenging to deliver during pregnancy. As with early breast cancer, all treatment options and their implications should be discussed, including the impact of not administering the treatment on the woman's prognosis against the risk of fetal complications if generally contraindication treatments are administered. The option of termination (or preterm birth) to allow for optimal oncological treatment should also be part of these discussions.

4.2.6 | Care During Pregnancy

Recommendation	Evidence level	Strength	Rationale for recommendation
Women with PrBC can be reassured that their breast cancer can be treated during pregnancy without long-term harm to their unborn child	1+	A	A prospective assessment of children born to women with PrBC showed normal infant development until 36 months
Women with PrBC should have monitoring to identify FGR from 28^{+0} weeks of gestation and thereafter according to clinical need	2+	B	An international multicentre prospective assessment of children born to women with PrBC showed increased risk of FGR
Iatrogenic preterm birth should be avoided unless there are clear maternal or fetal indications	1+	A	An international multicentre prospective assessment of children born to women with PrBC showed that impaired cognitive development was associated with iatrogenic preterm childbirth, but not breast cancer or its treatment
In the absence of established lymphoedema, in women who have had any previous axillary surgery medical procedures (including blood tests, cannulation and blood pressure measurements) can be performed on the side of surgery if the contralateral arm is unsuitable for use	2+	C	There is no evidence that medical procedures on the surgical side increase the risk of lymphoedema

Women with PABC tend to be older and preterm births occur more commonly (OR 4.84; 95% CI 4.05–5.79) [122]. The risk of spontaneous preterm rupture of membranes was also increased and may have contributed to preterm birth (OR 1.79, 95% CI 1.06–3.05) [122]. Another cohort of 122 women with PABC showed that babies were more likely to be born of low birthweight (aOR 8.88; 95% CI 5.87–13.43) and preterm (aOR 12.93, 95% CI 8.97–18.64) [189]. Preterm birth was usually by induction of labour (aOR 4.40; 95% CI 2.63–7.38) or by caesarean (aOR 2.46; 95% CI 1.57–3.86) compared with women without cancer [189]. In this study, the indication for preterm birth was unclear. In a separate study, birthweight was below the 10th centile in 28/127 (22%) children from women with breast cancer compared with 19/125 (15%) of children from a control group [190]. Reassuringly, gestational hypertension and diabetes were no more common in women with PABC [189]. [*Evidence level 2–*]

Women who have had previous axillary lymph node surgery have a risk of subsequent lymphoedema. For women who do not have established lymphoedema there is not good evidence that medical procedures (including blood tests, cannulation and blood pressure testing) increase the risk of lymphoedema development [87]. Where the non-affected arm is unsuitable for use, medical procedures can be performed on the affected side. [*Evidence level 2+*]

Breast cancer, chemotherapy and pregnancy itself are all risk factors for venous thrombosis. Thromboprophylaxis with low-molecular-weight heparin or equivalent should be administered in accordance with RCOG Green-top Guideline No. 37a [79]. [*Evidence level 2++*]

Both pregnancy and immunosuppression from chemotherapy are deemed clinical risk factors for adverse outcomes from influenza and COVID-19, and immunisation is advised for the affected individual and their household contacts in accordance with the recommendations from the UK Health Security Agency Green Book [191]. [*Evidence level 2++*]

PrBC, with or without treatment, has shown no negative effects on infant cardiac or cognitive development in infants aged 18 and 36 months [190]. Only preterm birth, independently of cancer treatment, was correlated with impaired cognitive development [190]. [*Evidence level 2+*]

4.2.7 | Timing of Birth

Recommendation	Evidence level	Strength	Rationale for the recommendation
A date for birth should be jointly planned by the MDT and the woman. This date should be kept under review and adjusted according to maternal and fetal wellbeing	4	GPP	Pragmatic clinical management. The MDT should include, for example, a breast oncologist and surgeon, obstetrician/obstetric physician/fetal medicine specialist and neonatologist
Women with breast cancer should aim to give birth at term (after 37^{+0} weeks)	2+	B	This gives the best outcome for the fetus without compromising maternal wellbeing
If preterm birth is indicated, corticosteroids for fetal lung maturation can be given as usual in addition to previously administered steroids given with chemotherapy	4	GPP	This is a standard of care and additional steroids would not be considered harmful
Birth should be planned a minimum of 2–3 weeks after the last dose of chemotherapy to reduce the risk of fetal and maternal myelosuppression	4	GPP	Chemotherapy has a myelosuppressive effect on both the woman and fetus and therefore adequate time for bone marrow recovery prior to birth is advisable to reduce the risk of infection

The timing of birth for women with breast cancer must balance maternal benefits from optimal treatment following birth, with fetal toxicity from maternal treatment and neonatal harm from prematurity. Preterm birth causes short and long term neonatal morbidity directly correlated with gestational age at birth [190, 192], and birth after 37 weeks of pregnancy should be the aim where possible. Judicious treatment of breast cancer during the second and third trimesters usually makes this aim achievable (see Section 4.2.3). The decision for timing of birth in a woman with breast cancer must therefore consider multiple issues across different disciplines and exemplifies the need for a MDT, which should include a breast oncologist and surgeon, obstetrician/obstetric physician and neonatologist. [*Evidence level 4*]

Once a treatment plan during pregnancy has been implemented, an interval of 2–3 weeks between chemotherapy and planned birth is recommended to reduce the risk of peripartum haematological toxicity for woman and neonate [106] (see Section 4.2.3). [*Evidence level 4*]

4.2.8 | Metastatic Breast Cancer Diagnosed During Pregnancy

Recommendation	Evidence level	Strength	Rationale for the recommendation
For women with metastatic breast cancer requiring palliative care, late preterm birth (34–37 weeks) may be discussed	4	GPP	The pregnant woman is the clinician's primary patient and a decision on timing of childbirth should be in her best medical interest, while also considering the long term benefits of continued pregnancy for the healthy well-grown fetus

Most breast cancers diagnosed in pregnancy are localised to the breast and women will receive treatment intended to be curative. The diagnosis of metastatic breast cancer during pregnancy is rare. The aim of treatment in metastatic breast cancer is to prolong survival, maintain quality-of-life and to palliate symptoms. Median overall survival for a woman with newly-diagnosed metastatic breast cancer ranges from around 15 months for triple negative breast cancer to around 4 years for ER+/HER2 negative and HER2 positive cohorts [193]. For a pregnant woman with newly-diagnosed metastatic disease the stage of the pregnancy, the urgency of the indication for treatment for the maternal cancer, and modality of that treatment are important considerations, as well as the woman's desire to continue with, or to consider termination of, her pregnancy. A multidisciplinary approach is needed to plan and discuss all treatment options and their implications for both the woman and the fetus. Overall, although metastatic breast cancer is incurable and available data suggest that pregnancy itself does not appear to adversely influence breast cancer prognosis (see Section 4.1), some treatments are challenging to give in pregnancy, or at certain trimesters in pregnancy (see Section 4). As with early breast cancer, the optimal treatment for the woman should be determined, followed by consideration of what adaptations can be made to that therapeutic plan because of the pregnancy. Where the woman's health is of immediate concern, therapies that are normally advised against in pregnancy may need to be considered. These include consideration of short duration HER2-targeted therapy to maximise response rates in HER2 positive cancer, use of bisphosphonates in malignant hypercalcaemia, and radiotherapy to manage impending cord compression or fracture and brain metastases. [*Evidence level 4*]

4.3 | Long-Term Paediatric Outcomes After a Maternal Diagnosis of Breast Cancer During Pregnancy

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women undergoing treatment for breast cancer during pregnancy should be reassured that paediatric outcomes after maternal treatment for cancer in pregnancy are good	2+	B	Case–control studies have shown that exposure in utero to maternal cancer and its treatment does not impair development in childhood
Newborns exposed to platinum agents in utero should undergo the automated auditory brainstem response test in addition to the automated otoacoustic emission test	4	GPP	Children exposed to platinum agents risk ototoxicity which may not be identified by otoacoustic emission testing alone

Optimal fetal development is multifactorial. For women diagnosed with breast cancer during their pregnancy, factors such as diagnostic tests, cancer therapies, maternal illnesses and higher levels of maternal stress [194] all have the potential to impact on outcomes of children born to women with a diagnosis of breast cancer during their pregnancy [195].

A multicentre case–control study compared 129 children of women who were diagnosed with cancer during pregnancy with matched children of women without cancer [190]. The children were prospectively assessed for general and cardiac health measures, development using Bayley Scales of Infant Development and neurological function at 18, 36 months and subsequently every 3 years. The study found that, with a median follow-up of 22 months, prenatal exposure to maternal cancer, with or without treatment, did not impact general development, cardiac or cognitive function. Consistent with studies of children born to women without cancer [196, 197], prematurity across both exposed and control groups, did correlate with a worse cognitive outcome. Six-year follow-up of the cohort identified that children prenatally exposed to maternal cancer had lower verbal IQ and visuospatial long-term memory scores, and higher diastolic blood pressures than matched controls [198]. Verbal IQ was more affected in children whose mothers had died, highlighting the need for additional support for these children. At 9 years of age cognitive and behavioural outcomes of the children exposed to cancer in utero did not differ from normal population ranges [199]. There was no difference in Full-Scale Intelligence Quotient (FSIQ) with exposure to chemotherapy nor type of chemotherapy. FSIQ continued to be adversely affected by preterm birth, maternal death and was also by maternal education level. A systematic review, published in 2020, of 17 studies exploring the impact of prenatal exposure to chemotherapy found no major consequences on the long term neurodevelopmental outcome of children after prenatal exposure to chemotherapy [200]. Despite the reassurances these studies provide, there remains a paucity of data and more research is needed. [*Evidence level 2+*]

The platinum agent carboplatin is increasingly used as part of chemotherapy regimens for women diagnosed with triple negative breast cancer. Children treated with platinum agents, particularly cisplatin or high doses of carboplatin (more than 1500 mg/m^2) are at risk of ototoxicity [201]. A registry study of childhood hearing loss after in utero exposure to platinum agents identified hearing loss in three of 16 children exposed to cisplatin and one of 13 exposed to carboplatin; 264 children exposed to other chemotherapy drugs experienced no ototoxicity [202]. Of note, the three cisplatin-exposed children passed standard newborn audiometry testing, and diagnosis required auditory brainstem response testing. [*Evidence level 3*]

5 | Future Fertility Considerations

5.1 | Impact of Systemic Therapy for Breast Cancer on Fertility

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women of childbearing potential with a new diagnosis of breast cancer should be counselled, at diagnosis, about the potential impact of systemic therapy on their future fertility	2++	B	Chemotherapy reduces ovarian reserve, whereas endocrine therapy indirectly impairs fertility because of the time on treatment. Women with breast cancer need to make informed decisions about both fertility preservation and systemic therapy choices

In women, germ cells are non-proliferative. Chemotherapy reduces ovarian reserve by destroying the primordial and growing follicles within the ovary, accelerating the aging process. The degree of gonadotoxicity seen is dependent on the type of chemotherapy used, the dose and duration of chemotherapy, and the age and pretreatment fertility of the woman [203]. Quantification of the actual risk to fertility with chemotherapy is difficult; most data come from published studies using surrogate markers, such as amenorrhoea and ovarian reserve assessments, rather than the standard definition of delay in conceiving after 1 year of regular, unprotected intercourse. This makes counselling women about their exact fertility risk with a given regimen extremely challenging. Nevertheless, it is clear that all the standard (neo)adjuvant chemotherapy agents used in breast cancer are known to have an impact on fertility. Alkylating agents, such as cyclophosphamide, are a standard component of most regimens. Cyclophosphamide is one of the most studied agents in relation to fertility and carries a high risk of amenorrhoea, with six cycles of CMF or 5-fluorouracil/

epirubicin/cyclophosphamide (FEC) causing an intermediate risk (20%–80% risk of permanent amenorrhoea in a women aged 30–39), and a lower risk (less than 20%) in women under 30 [203]. Data on the impact of taxanes on fertility are conflicting, although a meta-analysis of studies looking at ovarian function recovery (most frequently by menses recovery) concluded that the addition of taxane to an anthracycline-based regimen adversely affected ovarian function recovery [204]. This is consistent with a study of ovarian reserve, as assessed by anti-Müllerian hormone levels, in 50 premenopausal women undergoing adjuvant chemotherapy for breast cancer in which taxane-containing regimens showed increased gonadotoxicity [205]. [*Evidence level 2–*]

All women who are considering chemotherapy for early breast cancer should be counselled about the possible gonadotoxic risk of that chemotherapy in order to allow them to make informed decisions about their treatment. Options to minimise the impact on fertility by selection of a less gonadotoxic regimen are somewhat limited, as a deviation from a standard anthracycline–taxane regimen would, in general, be associated with a loss of efficacy against the cancer itself. However, as cumulative dose and duration of chemotherapy are both implicated in gonadotoxicity [203], where a six- to eight-cycle regimen is an accepted standard, using six cycles rather than eight may have a lesser impact on fertility [206]. Likewise, for low risk HER2 positive breast cancer, 12 weeks of paclitaxel and trastuzumab is now an acceptable alternative to standard anthracycline–taxane based regimens [207] and appears to result in lower rates of amenorrhoea [208]. [*Evidence level 2–*]

There is limited evidence of the risk of fertility impairment with the use of anti-HER2 therapies. The addition of trastuzumab to a standard anthracycline–taxane based regimen does not appear to increase the rate of treatment-induced amenorrhoea [209, 210]. [*Evidence level 2–*]

Endocrine therapy with tamoxifen does not appear to affect ovarian reserve. Several studies have shown no effect of tamoxifen on anti-Müllerian hormone levels [211–213]. Many premenopausal women on tamoxifen will not menstruate; the mechanism behind this is incompletely understood but may relate to increased plasma oestrogen levels and consequent impact on the hypothalamic–pituitary–ovarian axis [214]. Endocrine therapy is, however, taken for 5–10 years during which time a woman's fertility would be expected to decline. [*Evidence level 2+*]

5.2 | Fertility Preservation After a Diagnosis of Breast Cancer

The likelihood of women achieving a first pregnancy after a diagnosis of breast cancer has improved over the last 20 years but remains approximately 40% lower than those without disease [215]. This is partly explained by chemotherapy-induced gonadotoxicity following treatment with alkylating agents such as cyclophosphamide, and partly because of reduced ovarian reserve in women over 35 years. However it may also be because of the reluctance of women and their clinicians to consider a pregnancy after breast cancer, wrongly believing that pregnancy may adversely affect prognosis. [*Evidence level 2–*]

5.2.1 | Cryopreservation

Recommendation	Evidence level	Strength	Rationale for the recommendation
At diagnosis, the impact of breast cancer diagnosis and its treatment on future fertility should be discussed between the affected woman, their cancer team and the reproductive medicine service who should take into account maternal age, treatment plan, prognosis of the cancer and expected outcome of subsequent fertility treatment	4	GPP	Input from multiple specialists will provide women with information for informed decision making
All women who have not completed their family should, at diagnosis, be offered the opportunity to meet with a reproductive medicine specialist	4	GPP	NICE clinical guideline [CG156] recognises the particular circumstances around a diagnosis of cancer and its effect on fertility (nice.org.uk/guidance/CG156)
Women of reproductive age who are being considered for medical treatment for breast cancer that may cause premature ovarian insufficiency (POI) should be offered oocyte or embryo cryopreservation as appropriate	2+	C	There is substantial evidence outside of oncology that this is the optimal way to maximise future fertility

Cryopreservation of embryos or OOCYTES is established as the best method for preserving female fertility before gonadotoxic chemotherapy [216]. Controlled ovarian stimulation (COS), which is an essential part of in vitro fertilisation (IVF), causes supraphysiological levels of estradiol. Concerns have been raised that COS-induced excess estradiol levels may promote proliferation of breast cancer cells in women with a recent diagnosis of breast cancer. Reassuringly, when COS is carried out with co-administration of an aromatase inhibitor, letrozole, peak estradiol levels are reduced compared with conventional COS protocols without affecting oocyte yield [217]. A meta-analysis of case–control or cohort studies of 1594 women with breast cancer who underwent COS found no detrimental effect on either risk of recurrence (RR 0.58; 95% CI 0.46–73) or mortality (RR 0.54; 95% CI 0.38–0.76) compared with women who did not undergo fertility preservation, even among patients with ER-positive breast cancer. Furthermore, in a non-breast cancer population, a nationwide register-based cohort study, published in 2017, reported no increased incidence of breast cancer in women who received ovarian stimulation as part of assisted reproduction [218]. [*Evidence level 2–*]

Fertility before gonadotoxic treatment can also be preserved by cryopreservation of ovarian tissue [216]. The process is still

being developed, but in general involves laparoscopic removal of an ovary or part of an ovary, cryopreservation until recovery from chemotherapy, then auto-transplantation back into a woman planning pregnancy [216]. Results are promising, with almost two-thirds of cases having restored ovarian function and around 50% resulting in live births [219]. However, the process is still being optimised and is not routinely available on the NHS. [*Evidence level 2–*]

It is vital that women who have not yet completed their family are referred to fertility services at diagnosis by the surgical units, even if the treatment decisions about the need for chemotherapy have not yet been made. COS, even with 'fast start' protocols, will take a couple of weeks [216] and this early referral will minimise delays to starting systemic therapy. A short delay of this extent in starting chemotherapy is not expected to affect outcomes. [*Evidence level 4*]

Comprehensive guidance for fertility specialists and breast cancer teams working to preserve female fertility before chemotherapy can also be found in NICE Clinical Guideline [CG 156] [220] and the European Society of Human Reproduction and Fertility (ESHRE) guideline [221].

5.2.2 | What Is the Role of Gonadotrophin-Releasing Hormone Analogues as Fertility Preservation During Chemotherapy?

Recommendation	Evidence level	Strength	Rationale for the recommendation
Premenopausal women undergoing (neo)adjuvant chemotherapy for breast cancer and who are interested in fertility preservation should be offered temporary ovarian suppression with a gonadotrophin-releasing hormone (GnRH) agonist during their chemotherapy	1–	A	A meta-analysis of randomised trials has shown that GnRH agonists reduce the likelihood of chemotherapy-induced POI. The trials were not however designed to assess pregnancy as a primary endpoint
Fertility preservation with GnRH agonists should commence, where possible, at least 1 week prior to the first dose of chemotherapy and continue for the duration of treatment	1–	A	The majority of trials investigating the use of GnRH agonists as fertility preservation, commenced dosing at least 1 week before chemotherapy
Fertility preservation with GnRH agonists should not be offered as an alternative to oocyte or embryo cryopreservation, but should be offered to all regardless of whether or not they are having oocyte/embryo cryopreservation	4	GPP	Oocyte or embryo cryopreservation remains the most effective option for fertility preservation

A systematic review and meta-analysis of patient-level data of 873 women from five trials demonstrated that the co-administration of GnRH agonist with (neo)adjuvant chemotherapy was significantly associated with a reduced risk of POI and higher pregnancy rates. The POI rate was 14.1% in the GnRH agonist group compared with 30.9% in the control group (OR 0.38; 95% CI 0.26–0.57; $p < 0.001$), with 37 (10.3%) pregnancies in the treated group compared with 20 (5.5%) in the control group (incidence rate ratio 1.83; 95% CI 10.06–3.15; $p = 0.030$) [222]. The studies were not, however, powered to address pregnancy as a primary endpoint; nor were data captured on the participants' intent to become pregnant after treatment. [*Evidence level 2–*]

Importantly, no differences were seen in either disease-free or overall survival with the use of GnRH agonist in either ER+ or ER– disease. Further reassuring data for the safety of this approach in women with ER+ breast cancer come from a retrospective analysis of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), in which the concurrent use of GnRH agonist and chemotherapy had no detrimental effect on disease outcomes [223]. [*Evidence level 1–*]

5.3 | Contraception After a Diagnosis of Breast Cancer

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women undergoing systemic therapy for breast cancer should be advised to use contraception	4	GPP	All systemic therapy for breast cancer is contraindicated prior to conception and in the first trimester because of the risk of fetal anomalies
Women who have a history of breast cancer should be advised to use non-hormonal contraception	4	GPP	Hormonal-based contraception may increase the risk of recurrence, and non-hormonal approaches should be used if at all possible
Women who have a history of breast cancer who require emergency contraception can be offered hormonal contraception	4	GPP	A single dose of hormones is very unlikely to have any effect on breast cancer recurrence

5.3.1 | Hormonal Contraception and the Risk of Breast Cancer

Women who currently or have recently used hormonal contraceptives have been shown to be at increased risk of breast cancer (RR 1.20; 95% CI 1.14–1.26), rising with each year of use [224]. The absolute risk was one extra case of breast cancer for every

7690 women who used hormonal contraception for 1 year. The levonorgestrel intrauterine system is also associated with a higher risk of breast cancer (RR 1.21; 95% CI 1.11–1.33) [224]. [*Evidence level 2++*]

5.3.2 | Contraception After Breast Cancer

Approximately 13% of breast cancer in Europe is in premenopausal women (less than 45 years). Contraceptive counselling should form an important part of the care for premenopausal women with breast cancer [225].

The ideal contraception for women with breast cancer is non-hormonal. Safe options include the copper intrauterine device (IUD) [226]. The risk of infection associated with chemotherapy is not a contraindication to use of the copper IUD [226]. Other contraceptive options include two simultaneous forms of barrier contraceptive, or if future pregnancy is not desired, sterilisation of the woman or her partner. While small studies do not show an increased risk of recurrence with the levonorgestrel intrauterine system [227], there is insufficient evidence to confirm that this device is safe after a previous diagnosis of breast cancer, even in women with an ER– cancer, who may be at risk of a new ER+ cancer. For the rare circumstance where there are no suitable non-hormonal options, input from the women's breast specialist team should be sought prior to use of a progestogen intrauterine device. [*Evidence level 4*]

Emergency hormonal contraception is not contraindicated in women with a history of breast cancer [228].

5.4 | Preimplantation Genetic Diagnosis for Familial Breast Cancer

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women who carry pathogenic genes associated with breast cancer should be offered preimplantation genetic testing for a monogenic disorder (PGT-M) following counselling about the IVF process and likelihood of a successful pregnancy outcome	4	GPP	This is in line with UK Human Fertilisation and Embryology Authority guidance and based on the woman's preference

Women who develop breast cancer during their reproductive years, or who have a family history of breast cancer, are more likely than older women to carry a genetic predisposition to cancer [229]. Pathological gene variants in the autosomal dominant *BRCA1* and *BRCA2* tumour suppressor genes are the most common and well-known genes accounting for approximately 10% of breast cancer in women younger than 39 years [230]. Breast cancer incidences increase rapidly in early adulthood until 30–40 years of age for carriers of *BRCA1* and until 40–50 years for *BRCA2* carriers then remain constant [231]. By 80 years, the cumulative breast cancer risk is 72% (95% CI 65%–79%) for *BRCA1* and 69% (95% CI 61%–77%) for *BRCA2* carriers [231]. For this reason, screening tools have been developed to identify women at risk of inheriting a gene variant associated with breast cancer [229].

Other rarer pathogenic variants have also been identified in families with a high incidence of breast cancer [232, 233]. These include tumour protein 53 (*TP53*), inherited as the Li-Fraumeni syndrome, *PTEN* gene as part of Cowden's syndrome and *PALB2* genes [232, 234]. Improvements in the accuracy and accessibility of gene panel testing now allows a search for these genes in families with a high incidence of breast cancer.

Women who carry breast-cancer associated genes can avoid passing them on to their offspring through PGT-M, previously known as preimplantation genetic diagnosis (PGD). PGT-M involves COS, collection of oocytes and IVF. Despite early concerns, women who carry the *BRCA* gene variants appear to have normal ovarian response to IVF cycles [235]. After a period in culture, a cell is removed from each viable embryo and tested for the putative gene. Only embryos without the gene variant are selected for subsequent embryo transfer. PGT-M is therefore a selection process which on average will result in 50% of autosomal dominant *BRCA* embryos being discarded [216]. Furthermore, less than 40% of these IVF cycles results in a healthy live born baby [236]. [*Evidence level 2–*]

In the UK, most IVF centres offer PGT-M for women with an inherited risk of breast cancer. The Human Fertilisation and Embryology Authority currently support PGT-M for the *BRCA1/2*, *TP53, PTEN* and *PALB2* genes [237].

6 | What Are the Considerations for Subsequent Pregnancies After a Diagnosis of Breast Cancer?

6.1 | Impact of Pregnancy on Breast Cancer Survival

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women with a history of early breast cancer who wish to become pregnant should be advised that pregnancy does not increase their risk of breast cancer recurrence	2++	B	It is important that women make informed decisions about their choices

There have been concerns that in women with a history of breast cancer, even after all adjuvant therapies had been completed, any future pregnancy could lead to an increased risk of recurrence. However, this concern has not been borne out by data. A meta-analysis of 14 studies [238] involving 1244 cases of women who became pregnant after a diagnosis of breast cancer, compared with 18 145 controls matched for a breast cancer diagnosis and who did not become pregnant, reported that the women who became pregnant had a 41% reduced risk of death compared with those women who did not (RR 0.59; 90% CI 0.50–0.70). The survival advantage may in part be attributable to selection bias, i.e., a 'healthy mother effect', whereby women well enough to attempt pregnancy are a self-selecting group. The meta-analysis does, nevertheless, provide reassuring data that pregnancy after early breast cancer is a reasonable choice. [*Evidence level 2++*]

A more recent study aimed to assess the impact of pregnancy on breast cancer survival by ER status. In this multicentre retrospective cohort study, 333 women with a pregnancy after a breast cancer diagnosis were matched with 874 non-pregnant controls. After a median follow-up of 7.2 years no difference in overall survival was seen in the ER+ (HR 0.84, 95% CI 0.60–1.18; $p = 0.32$) or ER– (HR 0.57, 95% CI 0.36–0.90 $p = 0.01$) cohorts [239]. The termination of pregnancy rate in this [239], and other studies [240, 241], was high (at approximately 30%), which may reflect clinicians' and women's concerns of a detrimental effect of pregnancy on breast cancer survival—concerns which are not borne out by the published data. [*Evidence 2+*]

6.2 | Timing of Subsequent Pregnancies After a Diagnosis of Breast Cancer

The optimal timing of pregnancy after breast cancer remains uncertain. Two studies have shown a non-significant increased risk of recurrence across 60 pregnancies within 6 months [240] and 12 months [241] after diagnosis. Data from the meta-analysis of 14 studies investigating pregnancy after breast cancer found that pregnancy within 6–24 months after diagnosis or beyond showed no reduction in survival with a pregnancy [238]. Similar results were seen in a more recent cohort study of 7553 women diagnosed between 2003 and 2014, in which 196 women with pregnancy 6 months or more after diagnosis had a 5-year actuarial survival rate of 96.7% (95% CI 94.1%–99.3%) versus 87.5% (95% CI 86.5%–88.4%) for women with no pregnancy (age-adjusted hazard ratio 0.22; 95% CI 0.01–0.49; $p < 0.01$) [242]. Taken as a whole, these studies suggest that timing of a pregnancy after breast cancer does not impact on breast cancer outcome. [*Evidence level 2+*]

Other considerations pertinent to pregnancy after breast cancer include the woman's age and ovarian reserve, their risk of recurrence and their personal circumstances and wishes. For woman who have been treated with systemic therapy there may be drug-related safety issues that necessitate delays in pregnancy because of concerns about fetal harm. Women should discontinue tamoxifen 2 months prior to conception. This is based on four half-lives of the drug, the standard approach to guide timing of conception after exposure to a toxic drug after which time the drug is considered eliminated [243]. Women should not conceive while receiving chemotherapy. Manufacturers also advise a delay of variable intervals of between 6 and 12 months after chemotherapy dosing before conception. The data on which this guidance is based are uncertain. For women who have an unplanned pregnancy within a year after completion of chemotherapy, there is no evidence that developmental harm to the embryo will occur. MABs, such as trastuzumab, have slow clearance with sustained post-dosing systemic exposure. The manufacturers recommend women avoid a pregnancy for 7 months after the final dose of an anti-HER2 MAB; although as discussed in Section 4.2.3.3, inadvertent short duration exposure in pregnancy is unlikely to be harmful. Women with TNBC treated in the adjuvant setting with pembrolizumab should avoid a pregnancy for at least 4 months after the last treatment dose [244]. Prior exposure to the bisphosphonate, zoledronic acid, is not a reason to advise against a subsequent pregnancy, but UKTIS advise that where exposure to bisphosphonates has occurred, either prior to or during pregnancy, monitoring of fetal growth, skeletal development and neonatal calcium levels may be warranted. [*Evidence level 4*]

6.3 | Interruption of Endocrine and Other Targeted Therapy

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women planning a pregnancy who are taking adjuvant tamoxifen must discontinue treatment at least 2 months before attempting to conceive	4	GPP	This time is recommended by the manufacturers for adequate washout of tamoxifen and its active metabolites
Any woman receiving endocrine or other targeted therapy and planning a pregnancy should be referred to their oncologist for a discussion regarding their proposed treatment break	4	GPP	The reduction in risk of breast cancer recurrence from endocrine therapy is individual to the woman, dependent on the primary tumour characteristics. Therefore, their oncologist is best placed to have a discussion regarding the potential loss of treatment efficacy arising from a break in treatment

Women with an ER+ cancer are recommended adjuvant endocrine therapy for at least 5 years, but for up to 10 years in women at higher risk. Five years of adjuvant tamoxifen reduces the risk of death from ER+ breast cancer by 30% [245], with similar gains seen from an additional 5 years of therapy [246]. Tamoxifen does not appear to have a direct effect on fertility [247], but during the 5–10 years of therapy a woman's ovarian reserve may fall off substantially owing to natural aging. The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) study is collating outcomes from women who have received adjuvant endocrine therapy for 18–24 months and who choose to interrupt that therapy in order to conceive [248]. The first results from this study showed that recurrence rates for women who temporarily interrupted their

endocrine therapy to become pregnant were similar to a matched control cohort, with a 3-year incidence of breast cancer events 8.9% in the treatment-interruption group (95% CI 6.3%–11.6%) compared with 9.2% in the control cohort [249]. Follow-up of the study participants will continue. Women on endocrine therapy who wish to conceive should be given the opportunity to discuss the individual gains from their therapy, using tools such as Predict (breast.predict.cam). Given the established safety of long durations of endocrine therapy, making up any years of therapy missed after a pregnancy attempt is a reasonable approach, although there are no data to suggest this will be of equivalent efficacy to continuous therapy. In addition, an assessment of their fertility and advice on the needs for assisted reproduction can be helpful prior to interrupting endocrine therapy. This planning may enable women wishing to conceive to interrupt their endocrine therapy for as short a time as possible. [*Evidence level 2++*]

The PARP inhibitor, olaparib, is indicated as an adjuvant treatment for women with a high risk early breast cancer and a germline *BRCA1/2* mutation [250]. It is taken orally for 12 months after completion of chemotherapy and radiotherapy. Abemaciclib, a selective inhibitor of CDKs 4 and 6, is indicated as an adjuvant treatment for women with high risk ER+ HER2 negative early breast cancer and is taken for 2 years after completion of chemotherapy and radiotherapy [251]. Olaparib needs to be interrupted for 6 months prior to conception [252], and abemaciclib (which is also taken in conjunction with endocrine therapy) for 3 weeks [253]. Women considering stopping either drug should have a discussion with their oncologists about the implications of stopping treatment prior to any pregnancy attempt. [*Evidence level 4*]

6.4 | Assisted Reproduction After Treatment for Breast Cancer

UK and international guidelines recommend fertility preservation at diagnosis prior to starting anti-cancer therapy for all women who have not completed their family. Despite these guidelines, there are little safety data on the use of assisted reproductive technologies (ART) following anti-cancer treatment completion. Four small studies, each with 20–39 women, two with matched-controls [254, 255] and two with unmatched controls [256, 257] have been published to date. None of the studies showed any detrimental effect on breast cancer recurrences in the women undergoing ART after completion of treatment for breast cancer. [*Evidence level 2–*]

6.5 | What Is the Optimal Care in Pregnancy Following Treatment for Breast Cancer?

Recommendation	Evidence level	Strength	Rationale for recommendation
Pregnant women who have been treated for breast cancer can be reassured that pregnancy will not adversely affect their disease-free survival	1+	B	Evidence from mainly retrospective case series shows that pregnancy following a diagnosis of breast cancer does not reduce overall or disease-free survival
Pregnant women who have had chemotherapy for breast cancer should have additional fetal growth scans from 28 weeks (and thereafter according to clinical need) to identify an increased risk of FGR	2	B	Women who have received chemotherapy have an increased risk of small-for-gestational-age babies
Women who had treatment-related left ventricular dysfunction (LVD) are at risk of heart failure during pregnancy and should be referred for cardiology assessment pre-pregnancy, or as soon as possible during pregnancy	2	B	Approximately 30% of women who have chemotherapy-induced cardiotoxicity develop peripartum heart failure
Women with no history of treatment-related LVD are at low risk of pregnancy-related heart failure and should be offered an echocardiogram to assess left ventricular function	4	GPP	Women with subclinical heart failure are at risk of becoming symptomatic from 26^{+0} weeks of gestation, when cardiac output is maximum

Breast cancer survivors are less likely to have a subsequent pregnancy compared with the general population (RR 0.40; 95% CI 0.32–0.49) [258]. This may be a consequence of breast cancer being diagnosed relatively late in a woman's reproductive life, gonadotoxic chemotherapy, and prolonged endocrine treatment for those with hormone receptor positive disease. Furthermore, clinicians and their patients may believe that pregnancy adversely affects breast cancer outcomes. This is not the case [242, 258]. A systematic review and meta-analysis of 11 studies that included 63 968 women with breast cancer, of whom 3387 (5.3%) became pregnant, showed no detrimental effect of pregnancy on either disease-free or overall survival [258]. [*Evidence level 2++*]

Pregnancy outcomes following a diagnosis of breast cancer are generally good. A meta-analysis of nine studies that included almost 5 million women, of whom 3240 became pregnant after a diagnosis of breast cancer, showed a greater risk of small-for-gestational-age (OR 1.16; 95% CI 1.01–1.33), low birthweight (OR 1.50; 95% CI 1.31–1.73) and preterm birth (OR 1.45; 95% CI 1.11–1.88) following a diagnosis of breast cancer [258]. These adverse pregnancy outcomes were more common among women who had received chemotherapy. Following a diagnosis of breast cancer, women were also more likely to have a caesarean birth (OR 1.14; 95% CI 1.04–1.25), but adverse pregnancy outcomes including risk of miscarriage, fetal anomaly, pre-eclampsia and peripartum haemorrhage were similar to those of women without previous breast cancer [258]. [*Evidence level 2–*]

Women who have had breast cancer treated with anthracyclines (e.g., epirubicin, doxorubicin) have an increased risk of cardiotoxicity with LVD, which increases further if followed by HER2-directed therapy (e.g., trastuzumab, pertuzumab and trastuzumab-ADCs) [259–261]. However, chemotherapy-induced cardiotoxicity in women younger than 50 years of age is rare. This is because of a low incidence of pre-existing hypertension, diabetes, smoking and hyperlipidaemia [259–261]. Anthracycline-induced cardiotoxicity is also dose-dependent and unlikely to develop in those who receive low dose doxorubicin (less than 200 mg/m^2) [259–261]. If it does manifest, almost all cases of cardiotoxicity present within 12 months of treatment [260]. It is these women who are at high risk of developing pregnancy-related heart failure. In one study, 4/13 women who developed chemotherapy-induced cardiotoxicity went on to develop pregnancy-related heart failure, whereas all women who did not develop cardiotoxicity following chemotherapy (65/65) remained free of gestational cardiac problems [262]. An attenuated gestational increase in cardiac output may also explain the increased risk of FGR and peripartum heart failure following chemotherapy [258, 263, 264]. [*Evidence level 3*]

Women who receive radiotherapy for treatment of breast cancer have a dose-dependent increased risk of ischaemic heart disease that increases over the subsequent 20 years [265]. Ischaemic heart disease is rare in pregnant women [266] and despite an aging maternal population, there have been no reports of acute myocardial infarction during pregnancy following left-sided breast radiotherapy.

6.6 | Breastfeeding During and After Treatment for Breast Cancer

Recommendation	Evidence level	Strength	Rationale for the recommendation
Women taking tamoxifen should be advised not to breastfeed	3	D	Preclinical studies show harmful effects of tamoxifen on urogenital tract development. Clinically significant levels of tamoxifen are present in human breast milk
Women receiving chemotherapy should be advised not to breastfeed	2+	B	Chemotherapy drugs can be measured in breast milk and could be harmful to the infant
Women can continue to breastfeed following breast surgery and adjuvant irradiation if they wish to do so	4	D	Lactation from the untreated breast will be unaffected. Milk production and delivery from the treated breast may be attenuated
Prevention and suppression of lactation can be achieved by administration of oral cabergoline	1+	A	Cabergoline provides rapid, safe inhibition of lactation by decreasing prolactin production

The literature on caring for women with breast cancer who are pregnant or who are lactating is sparse as these women are frequently excluded from clinical trials, and women are commonly advised to interrupt lactation while on cytotoxic drugs. The importance of breastfeeding in emotional bonding between the woman and infant, and in the infant's cognitive and health development is well-established [267].

6.6.1 | Transfer of Therapeutic Drugs Into Breast Milk

A number of breast cancer drugs will pass into breast milk and therefore be transferred to the newborn baby during breastfeeding. Excretion of drugs into milk will depend on a number of factors such as lipid solubility, molecular size and degree of protein binding. However, the most important factor influencing this transfer is the maternal plasma level [268, 269]. Involutionary changes seen within breast glandular tissue during the first week and also at cessation of breastfeeding, result in larger gaps between alveolar breast cells permitting greater transfer of medicines from mother to child during lactation [269, 270].

6.6.1.1 | Tamoxifen. Tamoxifen is a selective oestrogen receptor modulator and is part of the standard of care for treatment of premenopausal women with ER+ breast cancer [271]. Women with PABC will be advised to take tamoxifen for 5–10 years depending on tumour histology and local MDT recommendations.

Two studies from the 1970s indicated that tamoxifen may inhibit lactation in the puerperium [272, 273].

Tamoxifen can be found in human breast milk within 1 day of starting treatment and levels rise until 3 weeks [274]. Similar results are noted for the active metabolites of tamoxifen. As the plasma steady state is not achieved in the woman for 28 days [275], it is possible that levels in breast milk will continue to rise beyond 3 weeks. Preclinical studies have shown harmful effects of tamoxifen administered in the neonatal period on urogenital tract development [276]. As clinically significant levels of tamoxifen and its active metabolites are present in human milk [274], it is not advisable for women with PrBC to breastfeed while taking tamoxifen. [*Evidence level 3*]

6.6.1.2 | Chemotherapeutic Agents. Traditionally, women on cytotoxic drugs have been counselled not to breastfeed because of concerns that these agents could be injurious to the infant and manufacturers in general recommend breastfeeding should cease for the duration of therapy. In many instances there are little data on which to offer evidence-based advice, but small studies have demonstrated that many of the commonly-used chemotherapeutic drugs are excreted into breast milk. Regarding commonly-used drugs, no information of breast milk drug levels are available for either epirubicin or docetaxel. Twice-daily monitoring of milk samples post-chemotherapy for B cell lymphoma found cyclophosphamide levels fell to low levels 1 week after dosing, but toxic metabolites were still present at 21 days post dosing [277]. A similar study with carboplatin found the drug still measurable in breast milk 316 hours post dosing [278], and while, in theory, it might be possible to breastfeed intermittently during chemotherapy, in

practice the duration of abstinence for chemotherapy drugs is unknown. The US National Institutes of Health Drugs and Lactation Database (LactMed) [279] is an evidence-based resource that provides up-to-date information to guide clinicians about prescribing medicines, including chemotherapy, for women who are lactating.

Empirically, chemotherapy is unlikely to have an effect on milk production and if lactation is maintained during treatment by use of breast pumps, breastfeeding could commence several weeks after treatment completion [280]. [*Evidence level 2+*]

6.6.1.3 | Monoclonal Antibodies. MABs, such as trastuzumab and pertuzumab, are large protein molecules and it is likely only small amounts will transfer into breast milk, with partial destruction in the infant's gastrointestinal tract. While drug exposure from a woman receiving MAB therapy to a breastfeeding infant may well be minimal, there are no data on which to base useful advice [281]. The manufacturers advise breastfeeding should discontinue during therapy and for 7 months after the last dose. [*Evidence level 4*]

6.6.1.4 | Diagnostic Imaging by PET-CT. The International Atomic Energy Agency advise that small amounts of ^{18}F-fluorodeoxyglucose is excreted in breast milk [67]. Therefore, if the scan is needed urgently, as in women with PrBC, then it is advisable to collect milk before the scan in order to provide a feed after the scan. Breast milk should be collected and discarded for 2 hours after the scan following which normal breastfeeding may resume [70]. [*Evidence level 4*]

6.6.2 | Lactation Following Breast Conserving Surgery and Irradiation

There is very little literature examining the effect of breast conserving surgery itself on the ability of women to breastfeed following birth. Almost all publications assess the combined effect of breast conserving surgery and adjuvant radiotherapy. Intuitively, it would be clear to most clinicians and women that surgery which excises or disrupts the subareolar lactiferous ducts/sinuses nipple will potentially impair or negate the ability of the woman to breastfeed from that breast. There are some case reports indicating that circumareolar surgery can prevent breastfeeding [282]. Further clues can be obtained from examination of reduction mammoplasty techniques—those which maintain the subareolar paranchyma result in the highest rates of successful postsurgical breastfeeding [283]. Therefore, breast conserving surgery to remove cancers near or at the nipple is more likely to impair breastfeeding from that breast, whereas excision of tumours more distant from the nipple areolar complex is less likely to cause an effect.

The probability of a previously irradiated breast being able to produce milk depends to a large degree on the delivered radiation dose [284]. Breast conserving surgery followed by adjuvant breast irradiation may induce anatomical distortion, which can limit nipple extension and inhibit latching of the infant to initiate lactation [282]. Additionally, breast irradiation invokes histopathological changes within the breast glandular tissue that can disrupt the production and flow of milk from breast alveolar cells to the nipple [284]. Studies examining small numbers of women showed that following radiotherapy, around 80% experienced diminished breast enlargement in the irradiated breast during pregnancy, with reduced postnatal milk production seen in approximately half of the women [285–287]. Normal lactation was seen in the untreated breast in almost all cases [286]; and women should be reassured that adequate nutrition for their baby can be provided by feeding from one breast alone. [*Evidence level 4*]

Breastfeeding after breast cancer treatment was evaluated as a secondary endpoint of the POSITIVE trial, which investigated the impact of interrupting adjuvant endocrine therapy in order to attempt a pregnancy [248,249]. Of 317 patients who gave birth, 196 (62%) women breastfed from the contralateral breast in all but two patients; only 38 (12%) breastfed from both breasts. The median duration of breastfeeding was 4.4 months [288]. [*Evidence level 2++*]

6.6.3 | Inhibition of Lactation

Cabergoline is a synthetic dopamine D2 agonist, acting on the anterior pituitary gland to decrease synthesis and release of prolactin and hence inhibit lactation. A dose of 1 mg of cabergoline given orally on the first day postpartum inhibits lactation within 1 day [289]. Where breastfeeding has already commenced, milk production can be stopped by oral administration of 250 micrograms cabergoline 12-hourly for 2 days [289, 290]. Adverse effects include dizziness, headaches and nausea, which occur mainly in the first 3 days after intake, but the treatment is generally well-tolerated by the majority of women [289]. [*Evidence level 1+*]

7 | Recommendations for Future Research

- Data on the management on breast cancer in pregnancy and subsequent paediatric outcomes are sparse. To facilitate future research, a national database of all women with a diagnosis of breast cancer in pregnancy, to include details of their management and outcomes, should be established as a priority. This database can feed into aligned international projects. The database should clearly discriminate between women with breast cancers diagnosed during pregnancy (PrBC) and women diagnosed with breast cancer in the 5 years post pregnancy (PPBC).
- A prospective audit of radiotherapy decision making in women with PrBC (including those with metastatic disease). This will feed into a research project examining safe and effective radiotherapy administration in these women.
- The role of proton-beam therapy in women with breast cancer is not established, but may have dosimetric advantages for women who could benefit from radiotherapy during pregnancy. This topic may require a multinational study to achieve a conclusion.
- In young women with a previous history of breast cancer, the optimal ART to achieve a pregnancy has not been established. Research into this field could produce valuable results for women wishing to commence a family.

TABLE 1 | Possible topics that could be considered for audit.

Topic	Rationale	Measure	Target
The time to first breast clinic review for pregnant women following presentation to medical care with a breast lump compared with age-matched non-pregnant women	Pregnant women with breast symptoms should be seen within the same treatment target times as non-pregnant women	NHS England Faster diagnostic pathways: implementing a timed breast cancer diagnostic pathway: guidance for local health and social care systems	100%
The incidence of haematoma and of lactational fistulae following core biopsy in pregnant and lactating women	The incidence of these complications in pregnant women is unknown, and because of this there is misconception that core biopsies in pregnant/lactating women lead to complications	Pregnant women undergoing this diagnostic intervention should have the following outcomes recorded in the medical notes: • no complication • post biopsy haematoma • post biopsy lactational fistula • both complications	100%
Operative choices of pregnant women versus age-matched non-pregnant women corrected for tumour size and preoperative axillary status	• The surgical choices of pregnant women are poorly recorded • Women may be undergoing mastectomy unnecessarily	Women undergoing breast cancer surgery while pregnant should have their breast surgery and the gestational age at this breast surgery recorded	100% Rates of mastectomy and breast conserving surgery can then be compared with non-pregnant counterparts using the matched criteria
Wound complications following mastectomy and wide local excision in women with PABC and PPBC	Wound complication rates in women with PABC and PPBC are poorly recorded	Pregnant women undergoing breast surgery should have wound complications (as defined by National Mastectomy and Breast Reconstruction Audit [291] and Jonczyk et al. [292]) recorded in the medical notes	100% Wound complication rates can then be compared with non-pregnant counterparts
Incidence of perioperative deep vein thrombosis following breast surgery in pregnant women	Women with PABC and PPBC should receive thromboprophylaxis in accordance with RCOG Green-top Guideline No. 37a [80]	Percentage of women with PABC and PPBC who are diagnosed with thromboembolic disease perioperatively	Incidence rate of $<0.5\%$
Dosing of chemotherapy	Women are being underdosed and thus undertreated	Dosing of chemotherapy should be based on the woman's actual weight, not pre-pregnancy weight. The woman should be reweighed and doses recalculated at each cycle of treatment	100%

- Examination of psychological outcome measures in women with PrBC and PPBC (compared with age-matched controls) could provide information important in the holistic management of this group of women.
- Any database should ideally link maternal exposure to cancer to paediatric data to gain information on long term outcomes following in utero exposure to cancer.

8 | Auditable Topics

Audit of current practice, benchmarked against the above guidance, can provide a valuable lever for change and improvement. Possible topics that could be considered for audit are shown in Table 1.

9 | Useful Links

RCOG patient information Pregnancy and breast cancer

Mummy's Star

Breast Cancer Now

Cancer Research UK

Macmillan Cancer Support

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This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
Dr A Armstrong, Manchester; Mr A Gandhi MBChB, MD, FRCS, Manchester; Ms S Frank, Manchester; Professor D Williams FRCOG, London and Dr S Nimalasena, London.
Acknowledgements
The guideline was reviewed and ratified by the Executive Committee of the Association of Breast Surgery.
The following individuals and organisations submitted comments at peer review:
Dr. A Banerjee FRCP, London; Mr. M Benjamin, Kemptown; British Association of Perinatal Medicine; Dr. M El-Zibdeh FRCOG, Amman, Jordan; H Flint MRPharmS, Liverpool; Dr. C Ovadia, MRCOG, London; K Sampat, MRCOG, Dartford; and Dr. LI Stirrat, MRCOG, Edinburgh.
Committee lead reviewers were: Dr. A Campbell FRCOG, Edinburgh;[1] Miss L Knight MRCOG, Devon;[1] Dr. SJ Pierce MRCOG, Leeds;[2] Mr. A McKelvey MRCOG, Norwich;[3] Dr. A El-Ghobashy MRCOG, Wolverhampton;[4] Dr. M Annappa, FRCOG, Lincolnshire;[5] Dr. N Potdar, Leicester.[6]
[1]from June 2024; [2]until June 2023; [3]until May 2024; [4]until February 2020; [5]until June 2024; [6]until May 2024.
The Co-Chairs of the Guidelines Committee were: Dr. A Campbell FRCOG, Edinburgh;[1] Miss L Knight MRCOG, Devon;[1] Dr. N Potdar FRCOG, Leicester;[2] Mr. A McKelvey MRCOG, Norwich;[2] Dr. MA Ledingham MRCOG, Glasgow;[3] and Dr. B Magowan FRCOG, Melrose.[4]
[1]from June 2024; [2]until May 2024; [3]until December 2021; [4]until June 2021.
The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Appendix A

Explanation of Grades and Evidence Levels

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1−	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points

GPP	Recommended best practice based on the clinical experience of the guideline development group[a]

[a] On the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by GPP. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.