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Pregnancy-associated breast cancer

ARTIGO DE REVISÃO NARRATIVA

ÁREA CIENTÍFICA DE GINECOLOGIA

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List of abbreviations

AI: Aromatase Inhibitors

BC: Breast Cancer

BCS: Breast Conservative Surgery

CEUS: Contrast-Enhanced Ultrasound Scan

ELIOT: Electron Beam Intraoperative Radiotherapy

FDA: Food and Drug Administration

HR: Hormone-Receptor

IGF-1: Insulin-Like Growth Factor 1

MRI: Magnetic Resonance Imaging

NCCN: National Comprehensive Cancer Network

PABC: Pregnancy-Associated Breas Cancer

RT: Radiotherapy

SLNB: Sentinel Lymph Node Biopsy

SPIO: Superparamagnetic Iron Oxide

TILS: Tumor-Infiltrating Lymphocytes

Resumo

O cancro da mama (CM) é a causa mais frequente de doença oncológica em mulheres grávidas. O adiar da natalidade para idades mais avançadas tem resultado num aumento da prevalência do cancro da mama associado à gravidez (CMAG). O CAMG é definido como CM diagnosticado durante a gravidez e até 1 ano após o parto, com uma maior incidência de casos diagnosticados no período pós-parto.

O subtipo molecular mais frequente neste grupo de doentes é o triplo-negativo, comparativamente a mulheres não grávidas, com a mesma idade.

A ecografia mamária e a mamografia, com proteção adequada, representam a base do diagnóstico. O tratamento deve, sempre que possível, seguir as mesmas diretrizes que nas mulheres não grávidas, com as devidas especificidades. A cirurgia e a biópsia do gânglio sentinela (BGS) podem ser realizadas durante toda a gravidez. A radioterapia (RT), por sua vez, apenas deve ser considerada em casos de emergências oncológicas, situações em que o risco materno prevalece. A quimioterapia é considerada segura após o primeiro trimestre, mas deve ser interrompida três semanas antes da data prevista do parto ou até às 35 semanas de gestação. A hormonoterapia e tratamentos alvo só podem ser administrados com segurança após o parto.

O CMAG requer um equilíbrio cauteloso entre riscos e benefícios para a mãe e descendência, tornando a sua gestão um desafio clínico que reforça a importância de uma abordagem multidisciplinar em centros altamente qualificados e experientes.

Esta revisão da literatura visa destacar as principais particularidades da gestão do CMAG, no que diz respeito à epidemiologia, biologia, diagnóstico, estadiamento, tratamento e prognóstico.

Palavras-chave: gravidez, pós-parto, cancro da mama, cancro da mama associado à gravidez, amamentação.

Abstract

Breast cancer (BC) is the most common cause of malignancy in pregnant women. The postponement of natality to more advanced ages has been responsible for the increase in the prevalence of pregnancy-associated breast cancer (PABC). PABC is defined as BC diagnosed during pregnancy or in the first year postpartum, with a higher incidence of cases in the postpartum period.

The most frequent molecular subtype is triple-negative, compared to age-matched controls in women without associated pregnancies.

Breast ultrasound and mammography, with proper shielding, represent the cornerstones of diagnosis. Treatment should, whenever it is possible, follow the same guidelines as in non-pregnant women, with specific considerations. Surgery and sentinel lymph node biopsy (SLNB) can be performed during all pregnancy. Radiotherapy (RT) is only selected in case of oncological emergencies when the maternal risk prevails. Chemotherapy is considered safe after the first trimester and should be interrupted three weeks before the expected childbirth or at 35 weeks. Hormonal therapy and molecular target agents can only be safely administered after delivery.

PABC requires a cautious balance of risks and benefits for the mother and the offspring, making its management a clinical challenge that reinforces the multidisciplinary approach in highly qualified and experienced health centers.

This literature review aims to highlight the main particularities of PABC management, regarding epidemiology, biology, diagnosis, staging, treatment, and prognosis.

Keywords: pregnancy, postpartum, breast cancer, pregnancy-associated breast cancer, breastfeeding.

Introduction

Pregnancy-associated breast cancer (PABC) is classically defined as breast cancer (BC) diagnosed during pregnancy or in the first postpartum year, representing the most common malignancy diagnosed during pregnancy. [1–4] Despite being relatively rare, the incidence of PABC is likely to increase over the years due to the tendency of postponing childbearing to later ages. [4,5]

Therefore, even though 80% of breast lesions during pregnancy are benign, PABC should be taken into consideration by healthcare providers every time a breast or an axillary mass persists for more than 2 weeks, so it can be promptly evaluated. [6–8]

The physiological changes of the breast resulting from this period, including immunological suppression, increased vascularization and permeability, and higher density, difficult the clinical and imagiological detection of suspicious masses, which leads to a delay in diagnosis of approximately 1-2 months in PABC patients, compared to non-pregnant women. [4,6,9]

That results in more locally advanced stages with nodal positivity tumors (≥T3, N+) at the time of the diagnosis, which combined with the younger age and the higher prevalence of more aggressive biologic patterns in PABC, poses a challenge in terms of clinical and therapeutic approach, given the goal of ensuring the best maternal outcome without compromising the fetal welfare. [6–8,10]

The diagnosis and treatment of cancer in pregnant women evoke ethical dilemmas that require an early multidisciplinary team-based approach, including surgical oncology, radiation oncology, medical oncology, maternal-fetal medicine, plastic surgery and psychology. [11] To diminish the risk of possible harm to the fetus and to improve and maximize maternal survival, healthcare providers must be aware of the particularities of the diagnosis and multidisciplinary management of these women. [9,12–14]

This article pretends to provide an updated review of BC's current diagnostic and therapeutic challenges during pregnancy and breastfeeding, considering the particularities in these two groups compared to non-pregnant women.

Methods

This work pretends to be a narrative review of the literature available on Pregnancy-Associated Breast Cancer, encompassing epidemiology, biology, diagnosis, staging, treatment, and prognosis. In order to carry out the proposed work, the recommended method consisted of a literature review of the existing medical literature on the subject, covering the last 13 years (between 2009 and 2022).

Literature searches were run in PubMed using the National Cancer Institute (NCI)/National Library of Medicine special topic query for pregnancy-associated breast cancer as a base with additional medical subject heading (MeSH) terms and keywords for relevant topics, such as Gestational Breast Cancer; Postpartum Breast Cancer; Diagnosis; Staging; Radiotherapy; Chemotherapy; Targeted Therapies; Hormonal Therapy; Immediate Breast Reconstruction; Prognosis. The database LactMed and the website of the Food Drugs and Administration were also consulted to assess the safety of specific drugs during pregnancy and breastfeeding that were relevant for this review.

International review articles, clinical meta-analyses, clinical trials, books, and guidelines in English were included. The references lists of the reviewed articles were also used to expand the search.

Approximately 200 published pieces were assessed, and 111 were selected as relevant references for this review. Citations of interest and areas of agreement and disagreement among writers were highlighted, with a preference for the most up-to-date literature.

Discussion

Epidemiology

Nowadays, there is a steadily rising tendency to plan pregnancy at a later reproductive age, which is reflected in the increased number of pregnant women diagnosed with cancer when compared to the past. [4,6,15]

BC is the most frequently diagnosed cancer during pregnancy, representing 0.2-3.8% of all BC worldwide and 21% of all pregnancy-related malignancies, with a median age at diagnosis of 33 years old. [2,11,16,17]

It is considered a rare and peculiar event, with an incidence of approximately 17.5 to 39.9 per 100,000 births, with fewer BC cases diagnosed during pregnancy (ranging from 3.0 to 7.7) than during the first postpartum year (ranging from 13.8 to 32.2), however, this incidence is expected to increase over the years as pregnancy is delayed. [18]

Proportionally, BC diagnosed during the postpartum period represents 2/3 of all cases of PABC (mainly in the first 6 months following delivery) compared to 1/3 of cases during pregnancy, with an average gestational age of 21 weeks. [6,15,19]

Recently, it has been proposed to differentiate PABC in BC during pregnancy from BC during the postpartum period, which may extend to 5 to 10 years after delivery, since the postpartum period is associated with worse survival rates and a higher risk of metastasis than BC during pregnancy, which can explain the wide range in incidences between these two periods. [20–22]

In a different perspective, some authors continue to defend the classical definition of PABC described above, arguing that physiological changes during pregnancy can mask a suspicious mass that, considering the natural evolution of the tumor, the lesion in situ itself would have been originated during pregnancy but it was only detected during the postpartum period, delaying the diagnosis, what would result as a postpartum diagnosis, even though it was a pregnancy-associated lesion. [22,23]

Pathological features and prognosis

Pregnancy is considered a complex and unique immunological condition. [17,24] The modifications of the mammary gland during pregnancy and lactation, under the hormonal environment during these periods, might theoretically result in a more aggressive biology of BC in these patients. [17,25]

Several studies have shown that PABC seems to be more commonly associated with unfavorable tumor biology, such as, the predominance of triple-negative BC, representing one-third of all of the cases, compared to age-matched controls in patients without associated pregnancies. [10,26–28] Moreover, Amant, *et al.*, in a large cohort study, showed that PABC patients were more commonly diagnosed with stage II BC, grade 3 tumors and lower frequency of hormone receptor (HR) expression and luminal-like phenotype tumors. [29] In addition, BC in pregnant and non-pregnant women are histologically similar, with a predominance of invasive ductal carcinoma. [16,26,30] Moreover, it has been also described a higher proportion of inflammatory BC in PABC. [15] As in non-pregnant women, PABC also metastasizes more frequently to the lungs, liver, brain and bones. [26]

Pathophysiology of PABC is not fully understood, however, some authors postulate that the increased exposure to estrogen, progesterone, and insulin-like growth factor-1 (IGF-1) during pregnancy is associated with the promotion of BC cell proliferation. [31]

Apart from the fact that there is a predominance of triple-negative BC, which in itself is associated with more aggressive behavior due to its high lymph node involvement, metastatic potential, and propensity to relapse, PABC is related to high expression of biomarkers and potentially relevant cancer targets (PD-1/PDL-1, SRC, IGF-1 and Wnt/β-catenin, RANK ligand), and low prevalence of tumor-infiltrating lymphocytes (TILS). [25,32–34] There are also significant differences in gene expression patterns between PABC and non-PABC, with upregulation in PABC of genes involved in cell proliferation, like MKI67, AURKA, BIRC5 and MMP11, and, on the other hand, an under-expression of several tumor suppressors, such as, p63, PTEN and CAV1. [11,26,33,35]

Yet, despite of all of these characteristics associated with a more aggressive phenotype being predominant in PABC patients compared to non-PABC patients, the impact in prognosis is currently controversial.

According to recent meta-analysis, there is an increased risk of death in PABC patients compared with non-pregnant women with BC. [16,36,37] Nonetheless, other studies suggest that there are no significant differences in PABC patients' survival compared to other BC patients with similar tumor characteristics in the same age group. [27,28]

In PABC patients, the tumors with the worst prognosis are observed during the first 6 months postpartum. [27] This highlights the importance of differentiating between BC diagnosed during pregnancy from BC diagnosed during postpartum.

Pregnancy per se does not seems to worsen the prognosis in patients with BC, even though, it is consensual that the modification of breast architecture during pregnancy and lactation can mask the presence of breast masses which results in later diagnosis with more advanced stage tumors and, consequently, poorer prognosis. [15,25,28,38] Indeed, there is a 2.5 times higher risk of advanced stage tumor at the time of diagnosis in PABC compared to non-PABC. [31,39]

Nonetheless, pregnancy is associated with a dual effect on the risk of developing BC. [26] Whereas early age at first pregnancy is a well-established protective factor, this protection is deferred due to a transiently raised risk in the postpartum period for all primigravidae. [26] A recent cohort study showed that a postpartum diagnosis was an independent risk factor for poor prognosis, and its negative impact can be extended to 5 or even 10 years after delivery. [40,41] This fact appears to be supported by the similarities between the pro-inflammatory tumoral microenvironment and the involution of the breast after delivery, associated with massive epithelial cell death, stromal remodeling, and immune cell infiltration. [8,26,42]

This debate on the prognosis of PABC shows the importance of conducting, in the future, long-term prospective cohort studies with larger cohorts, and differentiating between BC diagnosed during pregnancy and BC during postpartum.

Diagnosis and staging

The diagnosis and staging of PABC, as in non-pregnant women, is based on clinical examination, histology and imaging methods, such as, breast ultrasound, mammography, and eventually magnetic resonance imaging (MRI) without contrast agents. [9,43] However, computerized tomography and nuclear imaging are contraindicated during pregnancy. [43]

A suspicious mass that persists for two or more weeks in a pregnant woman should be evaluated as soon as possible, considering that, a 1-month delay in the diagnosis increases the risk of nodal involvement by 0.9%. [38]

Breast ultrasound represents the first-line procedure for the assessment of malignant lesions and image-guided core biopsy in pregnant and breastfeeding women [44,45]. Ultrasound has a higher sensitivity (close to 100%) when compared to mammography (lies between 78-90%) due to the increment in the parenchymal density of the breast during these periods. [43,44] In the case of lactating patients, breastfeed or pump before the procedure is recommended. [46]

According to Jafari Maryam *et al.*, the PABCs were significantly different in orientation and echogenicity with predominantly non-parallel and heterogenous masses (p= 0.02 and p= 0.04, respectively) when compared to non-PABC patients. [6] There were no significant differences as regards shape, margins, or cystic content. Although, PABC patients were chiefly BI-RADS 4c or 5 whereas in non-PABCs the prevalence of 4a-c and 5 was similar (p = 0.008). [6]

Mammography is specially indicated when the ultrasound results are negative or dubious in case of a highly suspicious mass or in case of a solid mass detected. [44] It is also relevant in the detection of malignant microcalcifications and the exclusion of bilateral or multicentric disease. [7] The use of ionizing radiation in pregnant women is still a concern. However, the fetal dose of radiation associated with this method is between 0.001-0.01 mGy which is far inferior to the 50-mGy cutoff below which no known embryotoxicity has been reported. [47,48] In addition, the use of abdominal apron shielding reduces uterine radiation by up to 50%. [49]

The use of breast MRI remains controversial. G. Ray Joel *et al.* concluded that the MRI without contrast agents was safe in all trimesters. [50] However, conforming to the European Society of Urogenital Radiology Guidelines on Contrast Agents, the use of dynamic-contrast-enhanced MRI is contraindicated during pregnancy, even though, it is considered safe during lactation. [51,52]

Equally to non-pregnant women, breast ultrasound-guided biopsy represents the gold standard for the definitive diagnosis of BC due to its accessibility and the absence of ionizing radiation. [53] A core needle biopsy is the preferred technique due to its high sensitivity of around 90% and it should be performed under local anesthesia. [1] Furthermore, fine needle aspiration cytology should be avoided during pregnancy due to the modifications of breast architecture. [1] For this reason, the pathologist should be aware of the patient's condition regarding the fact that the hyperproliferative profile during this period can be misinterpreted as atypia, which can result in false positives. [11] In breastfeeding women, besides the usual risks of bleeding and infection, there is a risk of milk fistula formation so, it is recommended to pump or breastfeed before the procedure and also use a needle as small as possible. [7]

After the anatomopathological diagnosis, further staging studies should be oriented if advanced disease is suspected. The National Comprehensive Cancer Network (NCCN) Guidelines, recommend that women with clinically local T1-T2 tumors should have a chest x-ray (with appropriate abdominal shielding), liver and renal function evaluations, as well as a complete blood count with differential. [43] In case of clinically node-positive or ≥ T3 tumors, it should be added a liver ultrasound; if a distant disease is highly suspected, it should be considered an MRI of the thoracic and lumbar spine without contrast. [43] The use of radionuclides in bone scans contraindicates this procedure in pregnant women due to the potentially harmful effects on the fetal skeleton. [54] However, in breastfeeding women, the low

excretion of intravenously administered contrast into breast milk does not justify the interruption of breastfeeding for this procedure. [55]

According to the trimester of the diagnosis, the presence of metastases is an important factor in determining the treatment options and the patient's decision to proceed with the pregnancy. [43]

Axillary staging

The SLNB is an important procedure in patients with early-stage, clinically node-negative BC. [56] It reduces the complications subsequent to the axillary lymph node dissection, such as lymphedema, nerve injury or shoulder dysfunction, without interfering with the oncological prognosis. [57]

Although there are a limited number of isolated case reports and small retrospective studies evaluating the use of SLNB in pregnant patients, according to the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine and some authors, namely Han *et al.* and Gropper *et. al.,* the largest single cohort to date about this topic, this procedure is considered safe during pregnancy and lactation. [56,57] Therefore, the decision of undergoing SLNB must be individualized and should be considered in the cases of clinically negative axillae. [43] Nonetheless, breastfeeding should be interrupted for at least 24 hours after the procedure. [58]

In the case of opting for this procedure, it is recommended to use a single-day protocol and perform lymphatic mapping with 99mTc-labeled colloids, with the lowest possible dose. [56,57] The use of blue dye is discouraged due to the 2% risk of anaphylactic reactions, which could be life-threatening. [9,43,59]

Besides the standard techniques already described, there are recent techniques that have been successfully developed, such as fluorescence techniques using indocyanine green, superparamagnetic iron oxide (SPIO) and contrast-enhanced ultrasound scan (CEUS) using microbubbles. [60]

Despite being classified as a pregnancy category C drug by Food and Drug Administration (FDA), indocyanine green has already been used in pregnant women without adverse effects on mother or fetus described. [61] A recent meta-analysis corroborate this fact concluding that ICG is safe during pregnancy. [62] However, physicians should be aware of the hepatic accumulation of this drug in the fetus. [61–63] Indocyanine green should also be used with caution while breastfeeding, especially in the case of newborn or preterm infants. [64]

In opposition, due to the lack of data in humans, SPIO and CEUS using microbubbles are not recommended during pregnancy or breastfeeding. [60,65,66]

Treatment

As in non-pregnant patients with BC, the purpose of PABC treatment is based on local disease control and prevention of systemic spread. [17] That being said, both entities should be managed similarly, with specific considerations for PABC. [67] Nonetheless, considering the simultaneous concern to ensure fetal well-being and to avoid long-term effects in offspring born, the time of diagnosis, more specifically, the trimester of diagnosis, will dictate the timing and course of the treatment (Figure 1). [8,17]

Apart from that, this decision should be individualized, taking into consideration the clinicopathological characteristics, the expected date of delivery, and the patient's intentions. [17] During the first trimester, it should also be discussed about pregnancy termination. [43]

	During pregnancy			Post-partum
	First trimester	Second trimester	Third trimester	
Chemotherapy	⊘	✓	✓	✓
Radiotherapy	⚠	⚠	⚠	✓
Hormonal therapy	⊘	⊘	⊘	✓
Targeted therapies	⊘	⊘	⊘	✓
Surgery	✓	✓	✓	✓

✓ Recommended

⚠ Only recommended in selected cases

⊘ Contraindicated

Figure 1- Treatment options according to the time of diagnosis. Adapted from: Poggio *et al.* 2020 [68].

Systemic Treatment

Chemotherapy

The treatment with antineoplastic drugs represents a major concern in pregnant women and a huge ethical dilemma arises about ensuring the best maternal outcome and the maximal fetal welfare, especially at early gestational stages. [69] For this reason, it is essential to evaluate the safety profile and the therapeutic impact of the anticancer drugs not only to the mother but also to the future new-born. [13]

Theoretically, most anticancer agents can cross the placental barrier by passive diffusion, but this transfer depends not only on the pharmacokinetics of the drug but also on the physiological changes during pregnancy that may cause an impact on the pharmacodynamic properties of these drugs. [70] Most of the anticancer agents have characteristics that favor the transplacental passage, such as highly lipophilia, low-molecular-weight that are not ionized at physiological pH and weakly bound to plasma proteins. [71] Nonetheless, the rise of maternal plasma volume, peaking at 50% in the third trimester, results in a lower distribution volume for water-soluble drugs. [70] Simultaneously, this period is characterized by an increase in renal clearance and liver oxidative metabolism and, consequently, an increased activity of cytochrome P450 isoform 3A4 that, particularly, plays a major role in the metabolism of taxanes, leading to reduced maternal exposure to these types of drugs. [72,73] In addition, the most frequently used drugs, including anthracyclines and taxanes, are substrates of efflux proteins responsible for cancer cell drug resistance mechanisms, which are highly expressed by human trophoblasts and protect the fetus by extruding harmful xenobiotics. [74]

The timing of exposure to anticancer agents influences the severity of intrauterine effects. [75] If it happens in the first weeks after conception, the implantation process may be affected which can lead to miscarriage. [13] Still, if this event doesn't happen and the embryo survives, the fact that the cells at that time are totipotent and undifferentiated may ensure the gestation progress. [76] On the other hand, if the exposure occurs between the second and eighth weeks, the organogenesis period, there is a high risk of embryotoxicity. [76] Consequently, chemotherapy is contraindicated during the first trimester, due to the risk-induced congenital malformations of 14%. [9,75] In case of high-grade or aggressive primary tumors with urgency to initiate the chemotherapy, women must be informed about the possibility of teratogenicity before deciding to carry the pregnancy further. [77]

Conversely, fetal malformation risk in the second and third trimesters is approximately 3%, which is not significantly different from the general population. [67,75] For this reason, chemotherapy is considered safe during the last two trimesters and should be an option as a neoadjuvant approach in patients with operable stage III disease. [59]

Nonetheless, it is important to highlight that this phase is characterized by rapid maturation and growth processes, which can be influenced by the anticancer agents, and may result in intrauterine growth restriction, transient tachypnea of the newborn, and transient neonatal leukopenia. [67,78]

The administration of antineoplastic drugs should be interrupted before 35 weeks of gestation or within 3 weeks of planned childbirth, to reduce the potential hematological toxic effects during delivery. [43,68]

It is recommended to opt for a weekly scheme, with fetal monitoring prior to each cycle, since this approach is associated to lower risk of hematological toxicity and shorter nadir periods. [43,59] .

In a recent case-control study with a total of 129 children, Amant *et. al* [79] concluded that prenatal exposure to chemotherapeutic agents had no clear adverse effects on postnatal growth, neurologic development or cardiac function. Long-term complications, such as behavior alterations, emotional issues and risk for future malignancy are objects for further studies. [67]

Regarding the safety during breastfeeding, antineoplastic agents can amend the normal microbiome of breastmilk which modifies its chemical composition and reduces its production, hindering the breastfeeding process. [80,81]

Considering the standard treatment schemes in early-BC patients, with sequential anthracyclines, such as epirubicin or doxorubicin hydrochloride followed by cyclophosphamide or taxane-based regime, breastfeeding during these treatments is contraindicated. [81,82] There is a high plasma-milk passage of these drugs, especially relevant with alkylating agents such as cyclophosphamide, whose active metabolites are highly toxic to the infant. [64]

It might be possible to breastfeed safely during intermittent therapy with an appropriate period of breastfeeding abstinence depending on the serum half-life of each drug (Table 1). [81] However, in clinical practice, this decision of breastfeeding or not during the treatment should be individualized, since it should take into consideration not only the metabolism and milk transference of each drug but also the patient's kidney and liver function, to ensure the process of elimination of these drugs. [81]

Table 1- Half-lives and breast milk elimination of common chemotherapy agents used for BC.

Chemotherapy Agent	Serum half-life	Recommended interval between drug administration and breastfeeding
Cyclophosphamide	7.5 hours	72 hours
Paclitaxel	13-52 hours	6-10 days
Doxorubicin	24-36 hours	7-10 days
Docetaxel	11 hours	4-5 days
Carboplatin	More than 5 days	Cessation of breastfeeding

Adapted from: Johnson et al. *2020* [81]

Hormonal therapy

Hormonal therapy remains an important cornerstone of hormone-sensitive BC treatment. [83] It is well established its effects on decreasing the mortality in 1/3 and the risk of contralateral tumor in 39% in HR-positive cancer patients. [3]

In premenopausal BC patients, the standard endocrine agent is tamoxifen for 5 to 10 years, depending on the stage. [82,83] Alternatively, in the case of high-risk patients, aromatase inhibitors (AI), such as anastrozole, letrozole, and exemestane, should be considered, associated with ovarian suppression function. [82,83]

The NCCN Guidelines recommend delaying the administration of hormonal therapy until the postpartum period, due to the high risk of harmful effects on the fetus and the lack of well-controlled studies in pregnant women and long-term data on pediatric outcomes. [43,84]

More specifically, tamoxifen causes epithelial changes that resemble the ones caused by diethylstilbestrol or clomiphene citrate, which are known teratogenic agents. [76,84,85]

Although limited, there are reports of vaginal bleeding, miscarriage, congenital abnormalities, such as craniofacial malformations and ambiguous genitalia, and fetal deaths in pregnant women taking tamoxifen. [85,86] Supporting that, Schuurman *et al*. reported an incidence of 12.6% of congenital malformations after tamoxifen exposure against 3.9% in the general population. [87]

Regarding the teratogenicity of AI, the current studies available are limited to experimental models and showed that these agents could trigger toxicity to the embryo/ fetus, even at doses lower than the therapeutic doses used. [68]

More specifically, anastrozole and exemestane seem to be associated with an increase of incidence of abortions; letrozole also showed an increase number of pregnancy losses and an increased risk for congenital malformations affecting the renal and skeletal systems and dead fetus at birth. [88–90]

It is known that tamoxifen and its active metabolites are detectable and accumulative in milk over time, however, there is still no current evidence about the excretion of AI in human milk and long-term adverse effects in breastfed infants [64,88–90]. For this reason, it is recommended to not breastfeed during hormonal treatment [88–91]. More specifically, it is proposed to wait 3 and 1 month, respectively, after the last dose of tamoxifen and exemestane until resuming breastfeeding. [89,91]

Targeted therapies

In the case of HER-2 positive tumors, several anti-HER2 agents, such as trastuzumab, pertuzumab, neratinib and trastuzumab-emtansine have been used in early BC, typically as adjuvant treatment in stage I tumors and as neoadjuvant in more advanced stages. [68,82]

Except for trastuzumab, no data are available on their administration in pregnant or breastfeeding women, and for this reason they are not indicated in the treatment of PABC. [68,76]

Regarding trastuzumab, it should only be administered in the postpartum period, since its use during pregnancy is discouraged. [43] Trastuzumab is associated with a high risk for oligohydramnios or anhydramnios development, which is considered to be caused by the toxic effect of its active substance on fetal renal cells, and for this same reason, a high risk for fetal renal failure. [86,92] These risks seem to be reversible upon discontinuation of the treatment and less significant when administered exclusively during the first trimester or for relatively short periods. [92,93]

Breastfeeding is not recommended during the administration of any of these agents and for 7 months after the last dose. [64]

Local treatment

Radiotherapy

RT plays an important role in BC treatment by increasing disease-free survival and locoregional control. [3] It should be systematically performed after breast conservative surgery (BCS) or after mastectomy in the case of high-risk patients as an adjuvant treatment. [94]

However, according to the NCCN Guidelines, RT is contraindicated during pregnancy and should be postponed until after childbirth. [43] It can only be considered in life-saving situations, like in spinal cord compression syndrome, central nervous system metastases, or superior vena cava syndrome, or to preserve organ function. [9,67]

Exposure to ionizing radiation in the uterus is still a controversial and debatable topic. There is a significant risk of potentially harmful effects involved since it can induce pregnancy loss, congenital malformations (particularly of the central nervous system), growth and mental retardation and mutagenic and carcinogenic effects in the fetus. [47]

Nonetheless, it is a major concern to the physicians because it may adversely affect the maternal outcome, especially if the diagnosis occurs in the first semester, since the risk of recurrence increases as adjuvant treatment is delayed. [95] Corroborating this, Toesca, *et al*., in a meta-analysis of 20 studies, showed that, for each month of delay in starting RT, a 1% risk of local recurrence is added. [96]

The increase of abdominal perimeter with the gestational age reduces the distance between the field's edge and the fetus, which represents the most critical factor that increases the fetal dose of radiation. [97] This can justify why RT for non-pelvic cancers could be considered as an option, by some authors, during the first trimester, when the distance between the uterus from the irradiation field is maximum. [59,75,78] However, it is well known that the period from the pre-implantation until the 15 weeks of gestation is associated with the highest risk of radiation-related embryonic and/or fetal effects. [97]

In case RT is required, it is important to calculate the dose to the fetus before the treatment since it must be taken into consideration when planning RT. [9]

During the irradiation, appropriate abdominopelvic shielding must be used, which can become more difficult as the gravid uterus enlarges. [67] In order to demonstrate the importance of shielding during the procedure, Monte Carlo Simulation demonstrated that the use of the lateral shield together with a 5-cm-thick lead shield, placed over the abdomen of the pregnant woman, led to a reduction of fetal doses by 50.0–70.7%. [98]

The standard radiation dose used in the adjuvant treatment in the whole breast is 50 Gy fractionated in 25 sessions, which results in an exposure of 5–8 mGy per fraction. [43,95,99] On

the other hand, doses under 0.1-0.2 Gy are proved to be associated with no measurable increased risk of fetal damage. [96,100]

That said, it has been estimated that if a dose of 50 Gy is applied to the chest wall, with the proper shielding, the fetus will receive a dose of 0.05-0.15 Gy, which is still under the threshold. [97] However, with the decrease of distance between the field and the fetus throughout the gestation, especially during the second and third trimesters, this dose can be increased to 2 Gy, which exceeds the threshold for potential harm to the fetus, and should therefore be assessed before irradiation. [97]

As an alternative for the external breast RT, electron beam intraoperative radiotherapy (ELIOT) appears to be a good option in the adjuvant treatment in pregnant women, once it can be completed with a single session of irradiation, with an estimated fetal dose of 0.84 mGy (0.004% of the prescribed ELIOT dose), which is still inferior to that of one fraction. [96,99,101] For this reason, ELIOT, with a mobile linear accelerator and shielding apron, is considered safe during the first and second trimesters, and discouraged during the third due to the distance between the uterus and the irradiation's field being minimum. [95,101] However, despite being an attractive option, there are still limitations about the efficacy of ELIOT in young patients with BC, because it may affect local recurrence rates, and this justifies why is currently only recommended in women older than 50 years old. [43,96]

Regarding breastfeeding during RT, there are no absolute contraindications. [46] However, it is recommended to only breastfeed with the untreated breast (in case of unilateral disease) since the skin toxicity from the treatment might be increased with the suckling effect of the baby on the under-treatment side. [64] On the other hand, irradiation itself can cause a reduction or cessation of milk production, but only on the affected breast. [64,102]

Surgery

During pregnancy, several physiologic changes occur that might affect the anesthesia process and should be taken into consideration during all surgeries. [103]

Pregnancy is associated with lower blood pressure levels, which, in addition to the progressive aortocaval compression by the gravid uterus, results in a higher risk of hypotension, which can compromise uteroplacental blood flow. [103] In order to reduce this effect, pregnant patients after 18-20 weeks should be positioned with a 15° left lateral tilt during the surgery. [104] Concerning respiratory alterations, it is known that short-term apneas can quickly cause maternal

hypoxemia; moreover, the intubation process may be hindered by hypervascularization and swelling of the upper airways. [103] There is also a higher risk of gastric content aspiration due to the reduced gastric barrier pressure and lower esophageal sphincter tone, and for this reason, acid aspiration prophylaxis should be considered in all patients from 16 weeks gestation. [104] Thromboprophylaxis should also be considered due to the hypercoagulable state related to pregnancy. [104] In the case of a combination of surgery and therapy with tamoxifen, this drug should be interrupted for several days and up to 2 weeks after surgery due to the increased risk of venous thromboembolism in this group of patients. [105]

Surgical procedures and the related use of anesthetics in pregnant women are considered safe, based on robust evidence, and have been widely used during pregnancy with a good safety record, without teratogenic effects described. [9,19,104] However, it is prudent to administer the lowest effective concentrations in standard doses, during limited exposures of less than 3 hours in duration. [106]

Furthermore, surgery during pregnancy is not associated with a higher risk of maternal death or birth defects. [9] However, there is a slightly elevated risk of 1-2% pregnancy loss, especially during the first trimester, and a 1.5-2 times higher risk of preterm labor, more significant in the last trimester. [9] As a result, if surgery is performed at 25 weeks or later, it should be done at a facility with neonatal and obstetrical specialists in case of premature delivery of a viable fetus. [43,106] Cardiotocography should be performed in the pre and postoperative period and, if it is possible, also during the procedure to ensure fetal welfare. [106]

The second trimester represents the safest period to perform a surgery, since the organogenesis process is already concluded and the risk of premature delivery is lower than in the third trimester. [107] However, surgery can be safely performed during all trimesters and, for this reason, when indicated, it should not be delayed by the woman's condition. [103]

As mentioned above, RT plays a crucial role in the adjuvant treatment after BC surgery, however, its use during pregnancy is not recommended. [43] Raphael *et al*. concluded that BC survival outcomes appear to be inferior when adjuvant RT is delayed for periods longer than 12 weeks. [108] This is particularly important in early-stage BC patients, in whom BCS is considered the preferred surgical approach and, additionally, it is related to better cosmetic outcomes, which are highly valued by younger women. [81,109]

During the later second and third trimesters, RT can be safely delayed to the postpartum period so that BCS can be performed, without having a significant impact on the recurrence rate or survival compared to total mastectomy. [110] On the contrary, it is not possible to perform RT within the recommended time interval after surgery in the first or beginning of second

trimesters, since this time would still overlap with pregnancy and, for this reason, total mastectomy is the technique that should be used in these cases. [19,110]

In cases where total mastectomy is unavoidable, breast reconstruction is usually preferred by women. [117] Most surgeons decide to not perform immediate reconstruction to reduce the surgical risk associated with additional operative time, at the expense of aesthetic results. [109,111]

Breast changes associated with pregnancy make immediate definitive implant placement and contralateral reshaping impractical [96]. However, tissue expanders represent a good alternative as they do not seem to be associated with significant time increments to surgery and consequent anesthesia when compared with conventional mastectomy (adding around 20-30 minutes) and do not appear to be associated with a significant risk of obstetrical complications or have a negative impact on the outcomes of RT post-mastectomy [12,111].

Conclusions

Even though PABC is a rare condition, this entity is expected to become more prevalent with women's increased tendency to delay childbearing. It is a unique clinical situation that demands a cautious balance between ensuring the best maternal outcome and simultaneously guaranteeing the safety of the offspring.

Early identification of BC represents a challenge in terms of clinical management during pregnancy and the postpartum period. The physiological changes related to these periods can mask an underlying tumor. For this reason, healthcare providers must be aware of the growth of this complex condition so they can provide an early diagnosis and intervention in order to reduce morbidity and mortality in this group of patients. A multidisciplinary approach and close monitoring by a differentiated team in a high-risk obstetrical unit are essential for the proper management of this situation. This team should include surgical oncology, radiation oncology, medical oncology, maternal-fetal medicine, plastic surgery, and psychology specialists.

Concerning the diagnosis, non-ionizing and non-contrast agents' procedures should be privileged to minimize breast and fetal radiation exposure, and they should only be performed if they interfere with the therapeutic approach.

It is essential to choose the treatment that maximizes the chance of the best cancer outcome while minimizing fetal risk. Surgery and SLNB can be safely performed during all trimesters and should not be postponed if indicated. In case mastectomy is performed, immediate breast reconstruction with tissue expanders appears to be safe during pregnancy and even in the case of patients who have undergone RT post-mastectomy, the outcomes are satisfactory. Chemotherapy is not recommended during the first trimester and for this reason pregnancy termination should be taken into consideration if postponing systemic therapy worsens the prognosis. RT, hormonal therapy and targeted therapies should only be safely administered after delivery, except for RT as a life-saving treatment in case of oncological emergencies.

The current discrepant results in this field, more evident in the pathophysiology and prognosis of PABC, enforce the need for future research to re-evaluate and clarify the definition of PABC. Although it is ethically and clinically challenging to conduct studies in this patients group and to assess long-term effects on the offspring, the implementation of prospective and randomized control trials in the future is crucial for the best management of these patients.

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References

1. Amant F, Deckers S, van Calsteren K, Loibl S, Halaska M, Brepoels L, et al. Breast cancer in pregnancy: Recommendations of an international consensus meeting. Eur J Cancer. 2010;46(18):3158–68.
2. Zubor P, Kubatka P, Kapustova I, Miloseva L, Dankova Z, Gondova A, et al. Current approaches in the clinical management of pregnancy-associated breast cancer—pros and cons. Vol. 9, EPMA Journal. Springer International Publishing; 2018. p. 257–70.
3. C. Parker C, Damodaran S, I. Bland K, K. Hunt K. The Breast. In: Brunicardi FC, K. Andersen D, R. Billiar T, L. Dunn D, G. Hunter J, B. Matthews J, et al., editors. Schwartz's principles of surgery. 11th ed. New York: McGraw-Hill Education; 2019. p. 541–612.
4. Boere I, Lok C, Poortmans P, Koppert L, Painter R, vd Heuvel-Eibrink MM, et al. Breast cancer during pregnancy: epidemiology, phenotypes, presentation during pregnancy and therapeutic modalities. Vol. 82, Best Practice and Research: Clinical Obstetrics and Gynaecology. Bailliere Tindall Ltd; 2022. p. 46–59.
5. Ramesh P, Srikumar S, Mahendran V, Nair SS, Radhamany K. Pregnancy-Associated Breast Cancer: A Realistic Approach. Journal of Obstetrics and Gynecology of India. 2019 Dec 1;69(6):514–9.
6. Jafari M, Abbasvandi F, Nazeri E, Olfatbakhsh A, Kaviani A, Esmaeili R. Ultrasound features of pregnancy-associated breast cancer: A retrospective observational analysis. Cancer Med. 2022;
7. Kieturakis AJ, Wahab RA, Vijapura C, Mahoney MC. Current recommendations for breast imaging of the pregnant and lactating patient. Vol. 216, American Journal of Roentgenology. American Roentgen Ray Society; 2021. p. 1462–75.
8. Schad A, Slostad J, Rao R. Gestational breast cancer: Current challenges in staging and treatment of breast cancer. BMJ Case Rep. 2020 Nov 3;13(11).
9. Hepner A, Negrini D, Hase EA, Exman P, Testa L, Trinconi AF, et al. Cancer During Pregnancy: The Oncologist Overview. World J Oncol. 2019;10(1):28–34.
10. Sajjadi E, Venetis K, Noale M, Azim HA, Blundo C, Bonizzi G, et al. Breast Cancer during Pregnancy as a Special Type of Early-Onset Breast Cancer: Analysis of the Tumor Immune Microenvironment and Risk Profiles. Cells. 2022 Aug 1;11(15).
11. Paris I, di Giorgio D, Carbognin L, Corrado G, Garganese G, Franceschini G, et al. Pregnancy-Associated Breast Cancer: A Multidisciplinary Approach. Vol. 21, Clinical Breast Cancer. Elsevier Inc.; 2021. p. e120–7.

12. Caragacianu DL, Mayer EL, Chun YS, Caterson S, Bellon JR, Wong JS, et al. Immediate breast reconstruction following mastectomy in pregnant women with breast cancer. J Surg Oncol. 2016 Aug 1;114(2):140–3.
13. Esposito S, Tenconi R, Preti V, Groppali E, Principi N. Chemotherapy against cancer during pregnancy: A systematic review on neonatal outcomes. Medicine (United States). 2016;95(38).
14. Koutras A, Ntounis T, Fasoulakis Z, Papalios T, Pittokopitou S, Prokopakis I, et al. Cancer Treatment and Immunotherapy during Pregnancy. Vol. 14, Pharmaceutics. MDPI; 2022.
15. Ruiz R, Herrero C, Strasser-Weippl K, Touya D, st. Louis J, Bukowski A, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review. Vol. 35, Breast. Churchill Livingstone; 2017. p. 136–41.
16. Wang B, Yang Y, Jiang Z, Zhao J, Mao Y, Liu J, et al. Clinicopathological characteristics, diagnosis, and prognosis of pregnancy-associated breast cancer. Thorac Cancer. 2019 May 1;10(5):1060–8.
17. Zhang M, Zhou J, Wang L. Breast cancer and pregnancy: Why special considerations prior to treatment are needed in multidisciplinary care. Vol. 15, BioScience Trends. International Advancement Center for Medicine and Health Research Co., Ltd.; 2021. p. 276–82.
18. Johansson AL v., Stensheim H. Epidemiology of Pregnancy-Associated Breast Cancer. In 2020. p. 75–9.
19. Liberale V, Tripodi E, Ottino L, Biglia N. Surgery on breast cancer in pregnancy. Vol. 8, Translational Cancer Research. AME Publishing Company; 2019. p. S493–502.
20. Amant F, Lefrère H, Borges VF, Cardonick E, Lambertini M, Loibl S, et al. The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Vol. 22, The Lancet Oncology. Lancet Publishing Group; 2021. p. 753–4.
21. Lefrère H, Lenaerts L, Borges VF, Schedin P, Neven P, Amant F. Postpartum breast cancer: Mechanisms underlying its worse prognosis, treatment implications, and fertility preservation. Vol. 31, International Journal of Gynecological Cancer. BMJ Publishing Group; 2021. p. 412–22.
22. Buré LA, Azoulay L, Benjamin A, Abenhaim HA. Pregnancy-Associated Breast Cancer: A Review for the Obstetrical Care Provider. Journal of Obstetrics and Gynaecology Canada. 2011;33(4):330–7.
23. Ives A, Saunders C. Breast cancer associated with a concurrent or subsequent pregnancy. Vol. 5, Expert Review of Obstetrics and Gynecology. 2010. p. 357–69.

24. Mor G, Cardenas I. The Immune System in Pregnancy: A Unique Complexity. Vol. 63, American Journal of Reproductive Immunology. 2010. p. 425–33.
25. Peccatori FA, Lambertini M, Scarfone G, del Pup L, Codacci-Pisanelli G. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. Vol. 15, Cancer Biology and Medicine. Cancer Biology and Medicine; 2018. p. 6–13.
26. Allouch S, Gupta I, Malik S, al Farsi HF, Vranic S, al Moustafa AE. Breast Cancer During Pregnancy: A Marked Propensity to Triple-Negative Phenotype. Vol. 10, Frontiers in Oncology. Frontiers Media S.A.; 2020.
27. Johansson ALV, Andersson TML, Hsieh CC, Jirström K, Cnattingius S, Fredriksson I, et al. Tumor characteristics and prognosis in women with pregnancy-associated breast cancer. Int J Cancer. 2018 Apr 1;142(7):1343–54.
28. Puchar A, Despierres M, Boudy AS, Selleret L, Gligorov J, Richard S, et al. Prognosis of triple-negative breast cancer associated with pregnancy: A propensity score-matched analysis from the French CALG (Cancer Associé à la Grossesse) network. Breast. 2022 Feb 1;61:168–74.
29. Amant F, Nekljudova V, Maggen C, Seither F, Neven P, Cardonick EH, et al. Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer. 2022 Jul 1;170:54–63.
30. Bae SY, Jung SP, Jung ES, Park SM, Lee SK, Yu JH, et al. Clinical Characteristics and Prognosis of Pregnancy-Associated Breast Cancer: Poor Survival of Luminal B Subtype. Oncology (Switzerland). 2018 Aug 1;95(3):163–9.
31. Lyons TR, Schedin PJ, Borges VF. Pregnancy and breast cancer: When they collide. J Mammary Gland Biol Neoplasia. 2009;14(2):87–98.
32. Yin L, Duan JJ, Bian XW, Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. Vol. 22, Breast Cancer Research. BioMed Central Ltd; 2020.
33. Azim HA, Peccatori FA, Brohée S, Branstetter D, Loi S, Viale G, et al. RANK-ligand (RANKL) expression in young breast cancer patients and during pregnancy. Breast Cancer Research. 2015 Feb 21;17(1).
34. Azim HA, Vingiani A, Peccatori F, Viale G, Loi S, Pruneri G. Tumour infiltrating lymphocytes (TILs) in breast cancer during pregnancy. Breast. 2015 Jun 1;24(3):290–3.
35. Harvell DME, Kim J, O'Brien J, Tan AC, Borges VF, Schedin P, et al. Genomic Signatures of Pregnancy-Associated Breast Cancer Epithelia and Stroma and their Regulation by Estrogens and Progesterone. Horm Cancer. 2013 Jun 1;4(3):140–53.

36. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016 Nov 1;160(2):347–60.

37. Shao C, Yu Z, Xiao J, Liu L, Hong F, Zhang Y, et al. Prognosis of pregnancy-associated breast cancer: A meta-analysis. BMC Cancer. 2020 Aug 10;20(1).

38. Doğer E, Çalişkan E, Mallmann P. Pregnancy associated breast cancer and pregnancy after breast cancer treatment. Vol. 12, Journal of the Turkish German Gynecology Association. AVES; 2011. p. 247–55.

39. Maggen C, Wolters VERA, Cardonick E, Fumagalli M, Halaska MJ, Lok CAR, et al. Pregnancy and Cancer: the INCIP Project. Curr Oncol Rep. 2020 Feb 5;22(2):17.

40. Zhang Z, Bassale S, Jindal S, Fraser A, Guinto E, Anderson W, et al. Young-Onset Breast Cancer Outcomes by Time since Recent Childbirth in Utah. JAMA Netw Open. 2022 Oct 14;5(10):E2236763.

41. Gou Q, Liu Z, Xie Y, Deng Y, Ma J, Li J, et al. Systematic evaluation of tumor microenvironment and construction of a machine learning model to predict prognosis and immunotherapy efficacy in triple-negative breast cancer based on data mining and sequencing validation. Front Pharmacol. 2022 Sep 26;13.

42. Jindal S, Gao D, Bell P, Albrektsen G, Edgerton SM, Ambrosone CB, et al. Postpartum breast involution reveals regression of secretory lobules mediated by tissue-remodeling. Breast Cancer Research. 2014 Mar 28;16(2).

43. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022. JNCCN Journal of the National Comprehensive Cancer Network. 2022 Jun 1;20(6):691–722.

44. Vashi R, Hooley R, Butler R, Geisel J, Philpotts L. Breast imaging of the pregnant and lactating patient: Imaging modalities and pregnancy-associated breast cancer. Vol. 200, American Journal of Roentgenology. American Roentgen Ray Society; 2013. p. 321–8.

45. Jha P, Põder L, Glanc P, Patel-Lippmann K, McGettigan M, Moshiri M, et al. Imaging Cancer in Pregnancy. Radiographics. 2022 Sep 1;42(5):1494–513.

46. Johnson HM, Mitchell KB. Breastfeeding and Breast Cancer: Managing Lactation in Survivors and Women with a New Diagnosis. Ann Surg Oncol. 2019 Oct 1;26(10):3032–9.

47. Kumar R DJO. Radiation Effects On The Fetus. Treasure Island (FL): StatPearls Publishing. 2022.

48. American College of Obstetricians and Gynecologists. Guidelines for Diagnostic Imaging During Pregnancy and Lactation. Committee Opinion No. 723. Vol. 130. 2017. p. 210–6.
49. ACR practice guideline for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation.
50. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA - Journal of the American Medical Association. 2016 Sep 6;316(9):952–61.
51. Nissan N, Bauer E, Moss Massasa EE, Sklair-Levy M. Breast MRI during pregnancy and lactation: clinical challenges and technical advances. Vol. 13, Insights into Imaging. Springer Science and Business Media Deutschland GmbH; 2022.
52. ESUR Contrast Media Safety Committee. ESUR guidelines on Contrast Agents. 2018. p. 29.
53. Perez F, Bragg A, Whitman G. Pregnancy associated breast cancer. J Clin Imaging Sci. 2021;11.
54. Zanotti-Fregonara P. Pregnancy should not rule out 18FDG PET/CT for women with cancer. Vol. 379, The Lancet. Elsevier B.V.; 2012. p. 1948.
55. Mitchell KB, Fleming MM, Anderson PO, Giesbrandt JG, Young M, Noble L, et al. ABM Clinical Protocol #30: Radiology and Nuclear Medicine Studies in Lactating Women. Breastfeeding Medicine. 2019 Jun 1;14(5):290–4.
56. Gropper AB, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. Ann Surg Oncol. 2014;21(8):2506–11.
57. Han SN, Amant F, Cardonick EH, Loibl S, Peccatori FA, Gheysens O, et al. Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. Breast Cancer Res Treat. 2018 Apr 1;168(2):551–7.
58. Giammarile F, Alazraki N, Aarsvold JN, Audisio RA, Glass E, Grant SF, et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging. 2013 Dec 1;40(12):1932–47.
59. Peccatori FA, Azim JA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013;24(SUPPL.6).
60. Ferrucci M, Franceschini G, Douek M. New techniques for sentinel node biopsy in breast cancer. Vol. 7, Translational Cancer Research. AME Publishing Company; 2018. p. S405–17.

61. Papadia A, Mohr S, Imboden S, Lanz S, Bolla D, Mueller MD. Laparoscopic Indocyanine Green Sentinel Lymph Node Mapping in Pregnant Cervical Cancer Patients. J Minim Invasive Gynecol. 2016 Feb 1;23(2):270–3.

62. Thongvitokomarn S, Polchai N. Indocyanine green fluorescence versus blue dye or radioisotope regarding detection rate of sentinel lymph node biopsy and nodes removed in breast cancer: A systematic review and meta-analysis. Vol. 21, Asian Pacific Journal of Cancer Prevention. Asian Pacific Organization for Cancer Prevention; 2020. p. 1187–95.

63. Wang X, Zhang Y, Yang H, Xu Y. Maternal–fetal transfer of indocyanine green: a systematic review. Journal of Maternal-Fetal and Neonatal Medicine. Taylor and Francis Ltd.; 2021.

64. Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501922/.

65. Wáng YXJ, Idée JM. A comprehensive literatures update of clinical researches of superparamagnetic resonance iron oxide nanoparticles for magnetic resonance imaging. Vol. 7, Quantitative Imaging in Medicine and Surgery. AME Publishing Company; 2017. p. 88–122.

66. Endomagnetics, Inc. Magtrace (MagtraceTM and Sentimag® Magnetic Localization System). U.S. Food and Drug Administration Website https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160053B.pdf. Revised July 2018. Accessed January 2023. [Internet]. Available from: www.fda.gov/medwatch.

67. Labriola, RN, MSN, FNP-C B. Treatment of Pregnancy-Associated Breast Cancer. J Adv Pract Oncol [Internet]. 2019 Oct 1;10(7). Available from: https://www.advancedpractitioner.com/issues/volume-10,-number-7-(sepoct-2019)/treatment-of-pregnancy-associated-breast-cancer.aspx

68. Poggio F, Tagliamento M, Pirrone C, Soldato D, Conte B, Molinelli C, et al. Update on the management of breast cancer during pregnancy. Vol. 12, Cancers. MDPI AG; 2020. p. 1–17.

69. Alpuim Costa D, Nobre JG, de Almeida SB, Ferreira MH, Gonçalves I, Braga S, et al. Cancer During Pregnancy: How to Handle the Bioethical Dilemmas?—A Scoping Review With Paradigmatic Cases-Based Analysis. Vol. 10, Frontiers in Oncology. Frontiers Media S.A.; 2020.

70. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Vol. 5 APR, Frontiers in Pharmacology. Frontiers Media SA; 2014.

71. Triarico S, Rivetti S, Capozza MA, Romano A, Maurizi P, Mastrangelo S, et al. Transplacental Passage and Fetal Effects of Antineoplastic Treatment during Pregnancy. Vol. 14, Cancers. MDPI; 2022.
72. van Eijk M, Boosman RJ, Schinkel AH, Huitema ADR, Beijnen JH. Cytochrome P450 3A4, 3A5, and 2C8 expression in breast, prostate, lung, endometrial, and ovarian tumors: relevance for resistance to taxanes. Vol. 84, Cancer Chemotherapy and Pharmacology. Springer Verlag; 2019. p. 487–99.
73. Isoherranen N, Thummel KE. Drug metabolism and transport during pregnancy: How does drug disposition change during pregnancy and what are the mechanisms that cause such changes? Vol. 41, Drug Metabolism and Disposition. 2013. p. 256–62.
74. del Gobbo A, Scarfone G, Peccatori FA, Villa A, Ossola W, Ercoli G, et al. Chemotherapy for breast cancer during pregnancy induces vascular alterations and impaired development of placental villi: A preliminary histopathological study. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2020 Jul 1;250:155–61.
75. Lambertini M. E-Learning: Cancer Management During Pregnancy. Genova; 2021.
76. Alfasi A, Ben-Aharon I. Breast cancer during pregnancy—current paradigms, paths to explore. Vol. 11, Cancers. MDPI AG; 2019.
77. Yu HHY, Cheung PSY, Leung RCY, Leung TN, Kwan WH. Current management of pregnancy-associated breast cancer. Vol. 23, Hong Kong Medical Journal. Hong Kong Academy of Medicine Press; 2017. p. 387–94.
78. Wolters V, Heimovaara J, Maggen C, Cardonick E, Boere I, Lenaerts L, et al. Management of pregnancy in women with cancer. Vol. 31, International Journal of Gynecological Cancer. BMJ Publishing Group; 2021. p. 314–22.
79. Lejarraga HA. Pediatric outcome after maternal cancer diagnosed during pregnancy. Vol. 114, Archivos Argentinos de Pediatria. Sociedad Argentina de Pediatria; 2016. p. e121–2.
80. Stopenski S, Aslam A, Zhang X, Cardonick E. After Chemotherapy Treatment for Maternal Cancer during Pregnancy, Is Breastfeeding Possible? Breastfeeding Medicine. 2017 Mar 1;12(2):91–7.
81. Johnson HM, Mitchell KB. ABM Clinical Protocol #34: Breast Cancer and Breastfeeding. Breastfeeding Medicine. 2020 Jul 1;15(7):429–34.
82. Society for Medical Oncology E. Early Breast Cancer ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.

83. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Annals of Oncology. 2021 Oct 1;32(10):1216–35.

84. Buonomo B, Brunello A, Noli S, Miglietta L, del Mastro L, Lambertini M, et al. Tamoxifen Exposure during Pregnancy: A Systematic Review and Three More Cases. Vol. 15, Breast Care. S. Karger AG; 2020. p. 148–56.

85. Braems G, Denys H, de Wever O, Cocquyt V, van den Broecke R. Use of Tamoxifen Before and During Pregnancy. Available from: http://dx.doi.org/10.1634/theoncolo-

86. Shlensky V, Hallmeyer S, Juarez L, Parilla B. Management of Breast Cancer during Pregnancy: Are We Compliant with Current Guidelines? American Journal of Perinatology Reports. 2017 Jan;07(01):e39–43.

87. Schuurman TN, Witteveen PO, van der Wall E, Passier JLM, Huitema ADR, Amant F, et al. Tamoxifen and pregnancy: an absolute contraindication? Vol. 175, Breast Cancer Research and Treatment. Springer New York LLC; 2019. p. 17–25.

88. Astrazeneca Pharmaceuticals. Arimidex (anastrozole). U.S. Food and Drug Administration Website https://www.accessdata.fda.gov/drusatfda_docs/label/2011/020541s026l l.pdf. Accessed December, 2022. [Internet]. Available from: www.fda.gov/medwatch

89. Pfizer Inc. Aromasine (exemastene). U.S. Food and Drug Administration Website https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020753s020lbl.pdf. Revised May 2018. Accessed December 2022. [Internet]. Available from: www.fda.gov/medwatch.

90. Novartis Pharmaceuticals Corporation. Femara (letrozole). U.S. Food and Drug Administration Website https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020753s020lbl.pdfhttps://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s027lbl.pdf. Revised January 2014. Accessed December 2022. [Internet]. Available from: www.fda.gov/medwatch.

91. Midatech Pharma US Inc. Soltamox (tamoxifen). U.S. Food and Drug Administration Website https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021807s005lbl.pdf. Revised May 2018. Accessed December 2022. [Internet]. Available from: www.fda.gov/medwatch.

92. Goller SS, Markert UR, Fröhlich K. Trastuzumab in the Treatment of Pregnant Breast Cancer Patients – an Overview of the Literature. Geburtshilfe Frauenheilkd. 2019 Jun 14;79(06):618–25.

93. Andrikopoulou A, Apostolidou K, Chatzinikolaou S, Bletsa G, Zografos E, Dimopoulos MA, et al. Trastuzumab administration during pregnancy: un update. BMC Cancer. 2021 Dec 1;21(1).

94. Hennequin C, Belkacémi Y, Bourgier C, Cowen D, Cutuli B, Fourquet A, et al. Radiotherapy of breast cancer. Cancer/Radiothérapie. 2022 Feb;26(1–2):221–30.

95. Galimberti V, Ciocca M, Leonardi MC, Zanagnolo V, Paola B, Manuela S, et al. Is electron beam intraoperative radiotherapy (ELIOT) safe in pregnant women with early breast cancer? in vivo dosimetry to assess fetal dose. Ann Surg Oncol. 2009 Jan;16(1):100–5.

96. Toesca A, Gentilini O, Peccatori F, Azim HA, Amant F. Locoregional treatment of breast cancer during pregnancy. Vol. 11, Gynecological Surgery. Springer Verlag; 2014. p. 279–84.

97. Michalet M, Dejean C, Schick U, Durdux C, Fourquet A, Kirova Y. Radiotherapy and pregnancy. Cancer/Radiotherapie. 2022 Feb 1;26(1–2):417–23.

98. Mazonakis M, Tzedakis A, Damilakis J. Monte Carlo Simulation of Radiotherapy for Breast Cancer in Pregnant Patients: How to Reduce the Radiation Dose and Risks to Fetus? Radiat Prot Dosimetry. 2016 Sep 9;

99. Leonardi M, Cecconi A, Luraschi R, Rondi E, Cattani F, Lazzari R, et al. Electron Beam Intraoperative Radiotherapy (ELIOT) in Pregnant Women with Breast Cancer: From in Vivo Dosimetry to Clinical Practice. Breast Care. 2017 Dec 1;12(6):396–400.

100. CDC. Radiation and Pregnancy: Information for Clinicians [Internet]. 2019. Available from: http://www.icrp.org/publication.asp?id=ICRP%20Publication%2084

101. Basta P, Bak A, Roszkowski K. Cancer treatment in pregnant women. Vol. 19, Wspolczesna Onkologia. Termedia Publishing House Ltd.; 2015. p. 354–60.

102. Leal SC, Stuart SR, Carvalho HDA. Breast irradiation and lactation: A review. Vol. 13, Expert Review of Anticancer Therapy. 2013. p. 159–64.

103. Eskandari A, Alipour S. Aspects of anesthesia for breast surgery during pregnancy. In: Advances in Experimental Medicine and Biology. Springer; 2020. p. 107–14.

104. Upadya M, Saneesh PJ. Anaesthesia for non-obstetric surgery during pregnancy. Vol. 60, Indian Journal of Anaesthesia. Indian Society of Anaesthetists; 2016. p. 234–41.

105. Heery, APRN, AOCNS, CBCN M, Corbett, RPh, PharmD P, Zelkowitz, MD R. Precautions for Patients Taking Tamoxifen. J Adv Pract Oncol. 2018 Feb 1;9(1).

106. ACOG COMMITTEE OPINION Number 775 [Internet]. 2019. Available from: www.acog.org/More-Info/

107. Yu JH, Kim MJ, Cho H, Liu HJ, Han SJ, Ahn TG. Breast diseases during pregnancy and lactation. Obstet Gynecol Sci. 2013;56(3):143.

108. Raphael MJ, Saskin R, Singh S. Association between waiting time for radiotherapy after surgery for early-stage breast cancer and survival outcomes in Ontario: A population-based outcomes study. Current Oncology. 2020;27(2):e216–21.

109. Chirappapha P, Thaweepworadej P, Ngamphaiboon N, Sukprasert M, Sukarayothin T, Leesombatpaiboon M. Breast reconstruction in pregnancy: a case report of multidisciplinary team approach in immediate autologous flap reconstruction for pregnancy-associated breast cancer. Clin Case Rep. 2017 Sep;5(9):1450–3.

110. Zagouri F, Psaltopoulou T, Dimitrakakis C, Bartsch R, Dimopoulos MA. Challenges in managing breast cancer during pregnancy. Vol. 5, Journal of Thoracic Disease. 2013.

111. Lohsiriwat V, Peccatori FA, Martella S, Azim HA, Sarno MA, Galimberti V, et al. Immediate breast reconstruction with expander in pregnant breast cancer patients. Breast. 2013;22(5):657–60.