

REVIEW ARTICLE

Safety and effectiveness of chemotherapy in pregnant women with breast cancer: A systematic review

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Abstract

Breast cancer during pregnancy presents unique therapeutic challenges, as effective maternal treatment must be balanced against potential risks to fetal and neonatal health. This systematic review aims to evaluate current evidence regarding the safety and effectiveness of chemotherapy during pregnancy in women with breast cancer (BC). This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive literature search was conducted in PubMed, Google Scholar, Scopus, and the Open Inter-university Consortium for Political and Social Research databases. Following the search and selection process, a total of 14 articles met the inclusion criteria. Risk of bias was assessed using design-specific Joanna Briggs Institute critical appraisal tools. The administration of specific chemotherapy regimens, mainly anthracyclines, after the first trimester was generally not associated with an apparent increase in congenital abnormalities or perinatal mortality. However, an increased risk of preterm birth was observed, with a substantial proportion of preterm deliveries being iatrogenic. Furthermore, available comparative evidence did not indicate substantially worse maternal oncological outcomes attributable to pregnancy itself. Taken together, these findings suggest that chemotherapy for BC during pregnancy can be administered with relative safety after the first trimester, within an individualized treatment approach and close collaboration among obstetricians, oncologists, and neonatologists. Nevertheless, further multicenter studies are required to fully elucidate long-term neonatal outcomes.

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Citation: Tsochrinis A, Pappou P, Gourounti K, *et al.* Safety and effectiveness of chemotherapy in pregnant women with breast cancer: A systematic review. *Cancer Plus*.
doi: 10.36922/CP026330050

Received: August 12, 2026

Revised: September 9, 2026

Accepted: September 20, 2026

Published online: October 14, 2026

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Keywords: Pregnancy-associated breast cancer; Antineoplastic agents; Prenatal exposure delayed effects; Maternal-fetal outcome; Congenital abnormalities; Preterm birth; Treatment outcome; Gestational age

1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer among women worldwide and remains one of the main causes of cancer-related deaths in the female population,

accounting for approximately 20.6 million disability-adjusted life years globally in 2019.¹ New cases are expected to increase globally as a result of population aging and global population growth. According to the World Health Organization, approximately 2.3 million women were diagnosed with BC in 2024, and about 694,000 deaths were attributed to the disease.²⁻⁴ BC occurs in all regions of the world and can affect women of any age after puberty, with the risk rising significantly as age increases.²

Breast cancer diagnosed during pregnancy or within the first year after childbirth is defined as pregnancy-associated BC (PABC). Although it is a relatively rare condition, its management is particularly challenging, as it requires careful balance between effective oncological treatment and the safety of the pregnancy.⁵

In pregnant women, the incidence of BC is estimated at approximately 1 in 3,000 to 1 in 10,000 pregnancies, with an increasing trend attributed to delayed childbearing.⁶ Approximately 10% of cases involve women under the age of 40,⁷ while the highest frequency is observed among those aged 32–38 years.⁸

Clinical decision-making in PABC is influenced by gestational age (GA) and tumor biological features, requiring individualized therapeutic strategies to optimize both maternal and fetal outcomes.⁸ Since diagnosis often occurs at an advanced stage and pregnancy can limit or delay therapeutic choices, PABC is considered a highly complex oncologic condition. As a result, the use of chemotherapy during pregnancy has drawn significant research interest, especially regarding its safety and outcomes for both maternal and fetal health.⁹ Despite the growing literature on BC management during pregnancy, evidence regarding chemotherapy exposure remains heterogeneous, particularly with respect to maternal treatment outcomes and fetal and neonatal safety. Therefore, the present systematic review aimed to evaluate the available evidence on the safety and effectiveness of chemotherapy administered during pregnancy in women with BC.

2. Materials and methods

2.1. Purpose and specific objectives

This systematic review aims to address key research questions regarding the safety and effectiveness of chemotherapy during pregnancy in women with BC. Specifically, it examines chemotherapy agents considered safe for use during different pregnancy trimesters, along with the most common maternal and fetal adverse effects. It also assesses the impact of chemotherapy on fetal development, delivery outcomes, and long-term child health. Additionally,

the review evaluates the effectiveness of chemotherapy among pregnant women with BC, compares prognosis and survival outcomes between pregnant and non-pregnant patients, and identifies chemotherapy regimens associated with optimal oncological outcomes during pregnancy.

2.2. Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which provide a structured framework for the transparent reporting of systematic reviews. The PRISMA framework was applied to the identification, screening, eligibility assessment, and final inclusion of studies. The study selection process is presented in the PRISMA flow diagram (**Figure 1**), including the number of records identified, screened, assessed for eligibility, excluded, and ultimately included in the systematic review. A comprehensive literature search was conducted in PubMed, Google Scholar, Scopus, and OpenICPSR databases, using Boolean operators and Medical Subject Headings, including the terms “breast neoplasms,” “breast cancer,” “pregnancy,” “pregnant,” “gestation,” “antenatal,” “chemotherapy,” “adjuvant,” “antineoplastic agents,” “chemotherapy,” “treatment outcome,” “survival,” “therapy response,” “therapeutic efficacy,” “effectiveness,” “complications,” “adverse effects,” “toxicity,” “maternal-fetal outcome,” “comparative study,” “comparison,” and “protocol.” This systematic review protocol was not prospectively registered in the International Prospective Register of Systematic Reviews.

2.3. Inclusion and exclusion criteria

Clearly defined inclusion and exclusion criteria were applied to enhance sample consistency and ensure methodological rigor. This systematic review included primary research studies (clinical studies and comparative observational investigations) published within the last decade (2015–2025) and available in English. Specifically, eligible studies involved pregnant women diagnosed with BC and reported clinical outcomes relevant to chemotherapy exposure and/or the oncological management of BC during pregnancy. Included studies were required to report data on treatment safety, including adverse effects and complications, and/or treatment effectiveness, such as survival outcomes and response to therapy. Comparative studies evaluating different chemotherapy protocols or relevant maternal and pregnancy outcomes were also included.

Studies involving women with BC outside the context of pregnancy were excluded. Moreover, studies focused exclusively on treatment approaches other than chemotherapy, such as radiotherapy or surgery, were not included. In addition, review articles, animal studies,

and in vitro experimental studies were excluded. Finally, studies presenting insufficient or unclear outcome data were excluded from the review.

2.4. Search and study selection results

The initial literature search identified 650 records across the four databases. After removing 128 duplicate records, we performed a preliminary title and abstract assessment, during which we excluded 477 records for not meeting the

predefined eligibility criteria. The remaining 45 records underwent further screening, resulting in the exclusion of 16 records. The full texts of the remaining 29 articles were subsequently assessed for eligibility according to the predefined inclusion and exclusion criteria. Following full-text assessment, 15 articles were excluded because they did not meet the eligibility criteria, and 14 studies were ultimately included in the systematic review. The study selection process is presented in the PRISMA flow diagram (Figure 1).

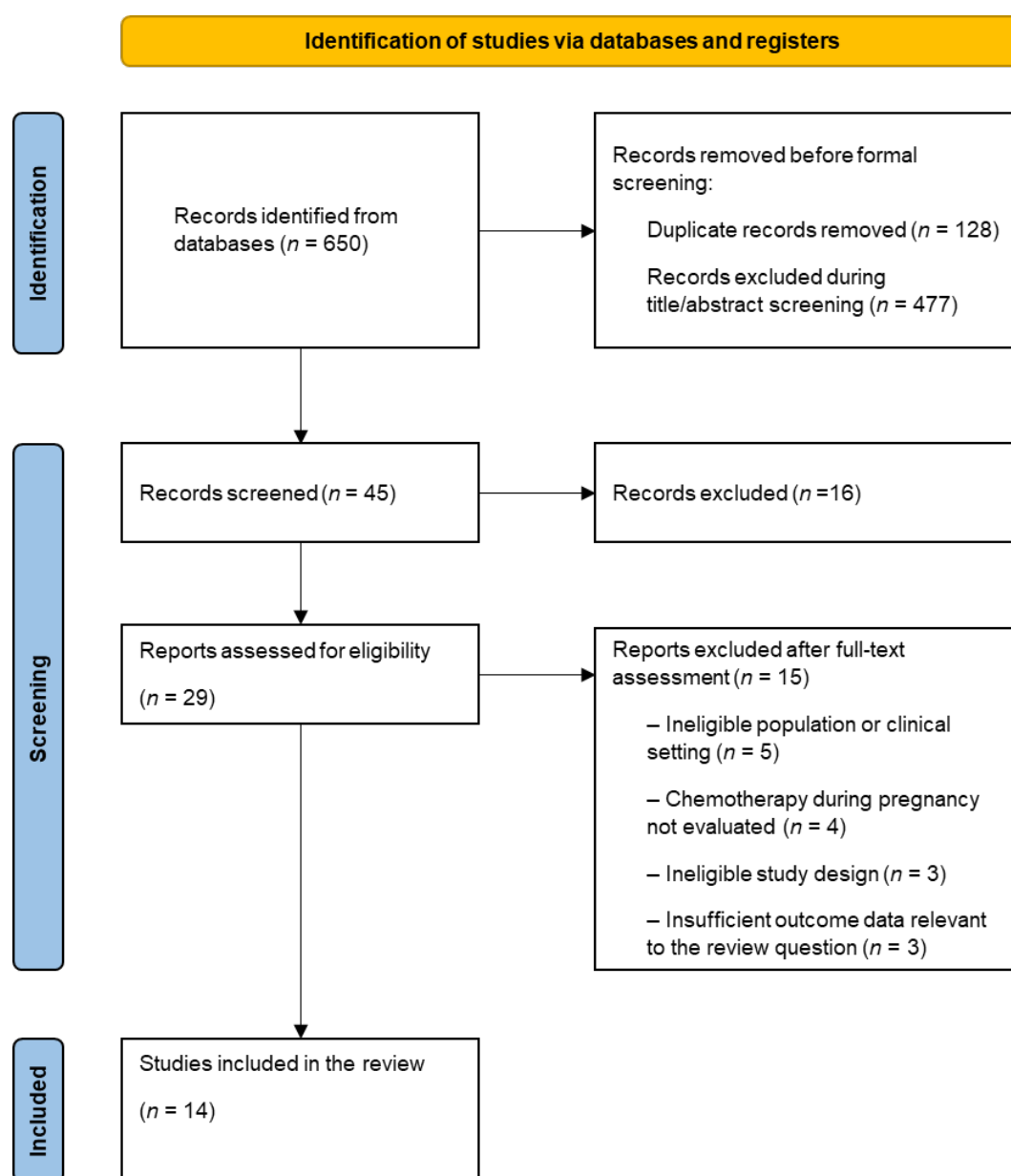


Figure 1. Flow chart of identification, screening, and eligibility of the included studies

3. Results

The available evidence on chemotherapy use during pregnancy primarily comes from studies conducted between 2017 and 2025. Overall, the majority of studies support the administration of chemotherapy during pregnancy when clinically indicated.^{10–22} Most included studies reported favorable maternal and fetal outcomes, even though sample sizes varied widely, ranging from single-case reports to large international cohorts involving up to 1,170 pregnant women. In contrast, one study reported an unfavorable pregnancy outcome following exposure to trastuzumab and pertuzumab during pregnancy.²³ The evidence spans multiple countries and regions, including Europe, Asia, Australia, New Zealand, and the Americas, suggesting consistent findings across diverse populations. A summary of all studies included in the systematic review is presented in [Table 1](#).

4. Risk of bias

Risk of bias was assessed using design-specific Joanna Briggs Institute (JBI) critical appraisal tools, selected according to the methodological design of each included study. The JBI Critical Appraisal Checklist for Cohort Studies was applied to seven cohort studies, the JBI Critical Appraisal Checklist for Case-Control Studies to three case-control studies, the JBI Critical Appraisal Checklist for Case Series to one case series, and the JBI Critical Appraisal Checklist for Case Reports to three case reports. Each applicable item was rated as “Yes,” “No,” “Unclear,” or “Not applicable” in accordance with the JBI appraisal framework. Numerical summary scores were not calculated, thereby allowing methodological limitations to be evaluated at the individual-item level and according to study design. The appraisal identified methodological concerns primarily related to control of confounding, completeness of follow-up or missing data, and participant selection in some observational studies, while the case reports and case series were additionally limited by the inherent methodological constraints of these study designs. All studies meeting the predefined eligibility criteria were retained in the systematic review, with the findings of the risk-of-bias assessment taken into account when interpreting the overall evidence. The complete design-specific, item-level critical appraisal of all included studies is presented in [Tables 2](#) and [3](#).

Several limitations should be considered when interpreting the findings of this systematic review. Substantial heterogeneity across the included studies, potential publication bias, and the lack of large, randomized controlled trials constitute major limitations of the present systematic review. In addition, long-term follow-up data

on children exposed to chemotherapy during pregnancy remain limited, restricting the ability to fully assess potential developmental and health outcomes.

The heterogeneity and methodological limitations of the available evidence should also be interpreted within the particular clinical context of BC during pregnancy. BC during pregnancy is relatively uncommon, while the conduct of randomized interventional trials involving potentially fetotoxic anticancer therapies raises substantial ethical and practical constraints. Consequently, the available evidence is derived predominantly from observational studies and, given the rarity of the condition, also includes case series and case reports, often involving small and clinically heterogeneous populations. Differences in gestational age at diagnosis and treatment, tumor characteristics, therapeutic regimens, timing and duration of fetal exposure, and reported maternal and neonatal outcomes further limit direct comparisons across studies. These constraints are inherent to research in this vulnerable population and highlight the need for prospective multicenter registries, standardized outcome reporting, and long-term maternal and offspring follow-up. Despite these limitations, the use of predefined eligibility criteria and a design-specific JBI critical appraisal framework strengthened the methodological rigor and transparency of the present systematic review.

5. Discussion

The present systematic review included 14 studies with substantial heterogeneity in study design, population characteristics, sample size, and reporting of pregnancy outcomes. Across the included studies, live births represented the predominant reported pregnancy outcome, although direct aggregation of maternal and pregnancy counts was not considered appropriate because of differences in study populations and outcome denominators. Notably, studies in which chemotherapy was administered during pregnancy reported that the majority of neonates were born alive. The safety of chemotherapy during pregnancy is highlighted by Garofalo *et al.*¹⁰ In their study, 97% of pregnant women diagnosed with cancer delivered live neonates, while only 5% presented with congenital abnormalities, a rate comparable to that of the general population. This observation is consistent with the findings of Amant *et al.*,⁶ who in a multicenter study demonstrated that in utero exposure to chemotherapy, initiated after completion of the first trimester, does not increase the risk of congenital abnormalities or adverse cognitive outcomes in children. Additionally, Van Calsteren *et al.*,²⁴ in a multicenter study of 215 pregnant women with cancer, emphasized the importance of multidisciplinary management and the prevention of iatrogenic prematurity,

Table 1. Summary of studies included in the systematic review

Author	Year	Country	Sample	Results	Conclusion
Garofalo <i>et al.</i> ¹⁰	2017	Italy	The study included 60 pregnancies complicated by maternal cancer (59 singleton and one twin pregnancy), followed over a 15-year period.	- Out of 60 pregnancies, one miscarriage and one intrauterine fetal death at 28 weeks were observed. - Live birth occurred in 97% of cases ($n = 59$). - The rate of congenital abnormalities was 5% ($n = 3$). - Preterm delivery was highly prevalent (83%), and the mean birth weight was 2,098 g, with a mean percentile at the 46th centile; 32% of neonates were classified as SGA. - No significant difference in SGA rates was observed between pregnancies exposed to chemotherapy during gestation and those unexposed (32% in both groups), suggesting that impaired fetal growth is more likely related to the underlying malignancy rather than chemotherapy exposure.	The study supports that chemotherapy administered after 14 weeks of gestation can be delivered with a relatively favorable fetal safety profile, provided that pregnancy is prolonged as close to term as possible and preterm delivery is minimized. It also highlights the importance of multidisciplinary management in specialized centers to optimally balance maternal oncologic treatment with pregnancy continuation.
Ye <i>et al.</i> ¹¹	2017	China	- The study included three pregnant patients (ages 37, 32, and 28) diagnosed with infiltrating ductal carcinoma during the 2nd–3rd trimester. - Immunohistochemical profiles varied: Case 1 and Case 3 had triple-negative tumors (ER-/PR-/HER2-, with Ki-67 values of 10% and 90%, respectively), while Case 2 was ER/PR-positive (ER 30%, PR 40%), HER2 1+, with Ki-67 40%. - All received epirubicin–paclitaxel chemotherapy during pregnancy (5, 1, and 2 cycles, respectively), followed by postpartum surgery and adjuvant therapy as indicated.	- Case 2 developed a single episode of grade III bone marrow suppression (leukopenia with neutropenia), successfully managed with G-CSF. - No hematologic, hepatic, or renal toxicities were observed in Case 1 and Case 3. - Asymptomatic minor electrocardiogram abnormalities were recorded in Case 3, without progression to clinically relevant cardiac disease. - Uterine contractions occurred in all patients, resulting in preterm delivery in Case 2, while requiring magnesium sulfate treatment in Case 3. - No cases of gestational hypertension or preeclampsia were reported. - Common maternal side effects observed in all cases included nausea, alopecia, gastroesophageal reflux, and constipation. - Neonatal outcomes were favorable: the preterm neonate (Case 2) developed transient neonatal jaundice treated with phototherapy, resolving within four days. No congenital anomalies were observed, and postnatal growth and developmental milestones were normal. - At 2-year follow-up, available cardiac and echocardiographic assessments showed normal cardiac function. Follow-up duration was 23 months for Cases 1 and 2 and 13 months for Case 3, with no maternal recurrence or metastatic disease observed.	In conclusion, in these three Chinese cases, chemotherapy administered during the second and third trimesters appeared feasible and well tolerated, with limited maternal and fetal toxicities. The epirubicin–paclitaxel regimen demonstrated acceptable outcomes. However, given the small sample size, larger studies are required to confirm these findings.

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Table 1. (Continued)

Author	Year	Country	Sample	Results	Conclusion
de Haan <i>et al.</i> ¹²	2018	International	A total of 1,170 women with primary invasive cancer diagnosed during pregnancy were analyzed across 37 centers in 16 countries. Among them, 779 (≈ 67%) received cancer treatment during pregnancy.	A total of 1,089 singleton pregnancies were analyzed, of which 955 (88%) resulted in live births. Among 887 completed pregnancies, 430 (48%) were preterm. Over time, an increase in live birth rates (RR 1.04, 95% CI 1.01–1.060 and a decrease in iatrogenic preterm deliveries (RR 0.91, 95% CI 0.84–0.98) were observed based on log-binomial regression analysis.	Overall, treatment during pregnancy, particularly chemotherapy, has been increasingly applied over time, with no consistent associations observed with other neonatal complications.
			BC was the most frequent malignancy (<i>n</i> = 462, 39%).	Neonatal exposure to platinum-based chemotherapy was associated with a higher risk of SGA infants (OR 3.12, 95% CI 1.45–6.70), while taxane exposure was associated with increased NICU admission (OR 2.37, 95% CI 1.31–4.28). The risk of NICU admission also varied by cancer type, with higher risk observed in gastrointestinal malignancies (OR 7.13, 95% CI 2.86–17.7) and lower risk in thyroid cancer (OR 0.14, 95% CI 0.02–0.90), compared with BC.	
			Temporal analysis showed an increasing likelihood of receiving treatment during pregnancy every five years (RR 1.10, 95% CI 1.05–1.15), particularly chemotherapy (RR 1.31, 95% CI 1.20–1.43).		
Yildirim and Bahceci ²³	2018	Turkey	The study included one 22-year-old woman diagnosed with metastatic infiltrating ductal breast carcinoma (ER-/PR-, HER2+).	Ultrasound revealed oligohydramnios and absence of the right kidney (renal agenesis). Treatment was discontinued, and the pregnancy was closely monitored. Seven weeks later, fetal growth restriction and anhydramnios were noted, leading to termination of the pregnancy. Autopsy showed mostly normal fetal organs, except for right adrenal hyperplasia, with no renal pathology.	The authors recommend avoiding monoclonal antibodies like trastuzumab and pertuzumab during pregnancy unless delaying treatment seriously endangers maternal survival. Close fetal monitoring and individualized counseling on potential risks and pregnancy options are essential. This report highlights possible severe fetal complications, supporting the recommendation to postpone such therapies until after delivery whenever feasible.
			Initial treatment consisted of docetaxel combined with trastuzumab and pertuzumab according to standard HER2+ protocols. After six cycles, near-complete response was achieved, followed by two additional cycles.		
			During follow-up, pregnancy at 20 weeks was confirmed, and treatment with trastuzumab and pertuzumab was continued temporarily.		

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Table 1. (Continued)

Author	Year	Country	Sample	Results	Conclusion
Gomez-Hidalgo <i>et al.</i> ¹³	2019	Spain	This study retrospectively compared 13 women diagnosed with PABC to a large cohort of 66,265 pregnant women without cancer. The mean age of the PABC group was 34 years, with 77% diagnosed before stage III. The mean GA at delivery was 35 weeks, lower than in the general population. Induced labor and preterm birth were more frequent in the PABC group. Most cancers were invasive, often hormone receptor–positive, with mastectomy and lymph node dissection as standard surgical management. When administered, chemotherapy was mainly given during the third trimester.	- After a median follow-up of 70 ± 8 months, survival among women with PABC was approximately 90%, provided comprehensive oncologic management combined with obstetric care. - Comparison of the single-center series of 13 cases with a larger international INCIP cohort (<i>n</i> = 1,170) highlights that small clinical series provide detailed insights into practice patterns, while broader cohorts strengthen the generalizability of findings. The small series showed increased preterm birth and emphasized the importance of early-stage diagnosis and surgical management during pregnancy. The INCIP cohort confirmed overall trends of improved outcomes, with higher live birth rates, fewer iatrogenic preterm deliveries, but increased neonatal complications when chemotherapy was administered.	Overall, simultaneous diagnosis of cancer and pregnancy can result in satisfactory maternal and neonatal outcomes when appropriate, complementary treatments are selected, and care is coordinated by specialized oncology and obstetric teams.
Lambertini <i>et al.</i> ¹⁴	2019	Belgium	A total of 92 patients with early HER2⁺ BC became pregnant during the trials. 12 were in the “exposed” group, conceiving during or shortly after trastuzumab/lapatinib treatment, and 80 were in the “unexposed” group, conceiving after a safe interval (more than seven days after lapatinib or more than seven months after trastuzumab).	- In the exposed group, 7 of 12 pregnancies (58.3%) were electively terminated. - In the unexposed group, 10 of 80 (12.5%) were induced, and another 10 (12.5%) ended in spontaneous miscarriage. - Among completed pregnancies, no complications occurred during pregnancy or delivery, except for one case of trisomy 21. - DFS rate did not differ significantly between groups (adjusted HR 1.12, 95% CI 0.52–2.42), indicating that conception after cessation of anti-HER2 therapy with recommended intervals does not compromise maternal survival and does not appear to increase fetal risk. - Even in cases of inadvertent exposure to trastuzumab or lapatinib, the few live births showed no apparent complications during pregnancy or at birth.	In summary, the study provides strong evidence that in women with early HER2⁺ breast cancer, pregnancy after completion of trastuzumab and lapatinib therapy does not appear to worsen maternal prognosis or adversely affect fetal outcomes, provided appropriate time intervals are observed, and monitoring is conducted in specialized centers.

(Cont'd...)

Table 1. (Continued)

Author	Year	Country	Sample	Results	Conclusion
Safi <i>et al.</i> ¹⁵	2019	Australia and New Zealand	A total of 24 births (≥ 400 g or ≥ 20 weeks gestation) were identified in women diagnosed with BC during the first or second trimester. Of these, 18 fetuses were exposed to chemotherapy in utero. Chemotherapy was initiated at a mean GA of 20 weeks and continued for approximately 10 weeks.	- Comparison of 18 chemotherapy-exposed and six unexposed neonates showed that exposed infants were born significantly earlier (mean GA ~35.7 vs. ~38.8 weeks, $p = 0.002$), with 12 preterm births primarily due to induced labor or cesarean section. - No neonatal deaths or congenital abnormalities occurred, and no stillbirths or postnatal deaths were reported. - Despite preterm delivery, no severe perinatal complications were observed beyond iatrogenic intervention. - In specific cases, neonates exposed to tamoxifen or trastuzumab required transient respiratory support (some with continuous positive airway pressure), but none required prolonged NICU admission or had lasting morbidity. - Although tamoxifen is contraindicated during pregnancy, the two exposed infants had no congenital abnormalities. - Trastuzumab exposure is often associated with fetal complications such as reduced amniotic fluid; however, in the present study, only one infant was exposed, without apparent adverse outcomes.	- Anthracycline and cyclophosphamide administration appears safe after 12 weeks of gestation, while experience with other agents such as taxanes or anthracyclines combined with trastuzumab remains limited and requires caution. - Overall, PABC treated with chemotherapy after the first trimester results in a high rate of iatrogenic preterm birth but does not significantly increase the risk of congenital abnormalities or neonatal mortality.
			The article reports a single case of a patient diagnosed with recurrent BC during pregnancy, who was exposed to tamoxifen and trastuzumab during the first and second trimester, followed by docetaxel during the second and third trimester.	No fetal abnormalities or pregnancy complications were observed.	This single case suggests that immediate adverse outcomes may not always occur, highlighting the need for systematic case reporting, careful monitoring, and further studies to establish evidence-based guidelines for managing HER2⁺ BC during pregnancy.
			- The study included 102 women: 51 with HER2⁺ PABC and 51 age-matched non-pregnant women with HER2⁺ BC. - Diagnosis in the PABC group occurred during various trimesters of pregnancy or within the first year postpartum. - Treatment followed standard protocols, including surgery, chemotherapy, HER2-targeted therapy, and radiotherapy when indicated.	- HER2⁺ PABC patients showed significantly lower recurrence-free survival (RFS) compared to non-pregnant HER2⁺ patients ($p = 0.008$). - OS did not differ significantly between groups ($p = 0.25$). - Timing of diagnosis within pregnancy (1st vs. 2nd/3rd trimester) did not significantly affect relapse-free survival or OS.	The study indicates that HER2⁺ PABC is associated with worse RFS compared to non-pregnant patients with similar disease, while OS does not differ significantly, likely reflecting the effectiveness of contemporary therapies and the importance of proper clinical management.

(Cont'd...)

Table 1. (Continued)

Author	Year	Country	Sample	Results	Conclusion
Del Gobbo <i>et al.</i> ¹⁸	2020	Italy	23 placentas from women with invasive ductal BC who received 2–6 cycles of chemotherapy after 16 weeks of gestation (mainly anthracyclines and cyclophosphamide), compared with 23 gestational age-matched normal placentas.	Histological evaluation of the 23 placentas showed non-specific vascular changes suggesting hypoxia and accelerated maturation.	The study confirms that chemotherapy during the second or third trimester of pregnancy may be associated with minor placental histological changes, but these do not appear to have immediate clinical impact on the neonate.
			Tumors were predominantly Grade 3 (19/23).	Specifically, 20/23 (86 %) exhibited Tenney–Parker syncytial knotting, fibrous perivillous deposits, villous hypoplasia, or focal chorangiogenesis.	
			No cases of gestational hypertension or preeclampsia were reported.	Similar changes were observed in 83% of control placentas, with no statistically significant differences between groups.	
			Neonatal birth weights were appropriate for gestational age, with no neonatal deaths or congenital abnormalities.	- These findings indicate that chemotherapy during the second and third trimester does not induce unique or severe placental lesions beyond those seen in normal pregnancies. - Clinically, all neonates had appropriate birth weight, and no neonatal deaths or congenital abnormalities were reported.	
Zhang <i>et al.</i> ¹⁹	2021	China	41 women with PABC were included (22 diagnosed during pregnancy, 19 within one year postpartum), each matched with one non-PABC control.	Median DFS for the PABC group was 29.0 months (95 % CI 6.5–51.5) vs. 40.9 months (95 % CI 22.8–58.8) for the non-PABC group, with no statistically significant difference ($p = 0.167$).	This study indicates that PABC may exhibit certain adverse biological features, such as higher rates of PR and triple-negative tumors. However, after matching for key factors (age, stage, year of diagnosis), OS does not differ significantly from non-pregnant patients, suggesting that with appropriate management, PABC does not inherently worsen long-term maternal outcomes.
			- Most tumor characteristics (histologic type, grade, size, nodal involvement) were similar between groups, but PABC tumors more frequently lacked progesterone receptor expression (PR-) and were more often triple-negative compared to non-PABC tumors (56.1% vs. 31.7% for PR-, and 24.4% vs. 4.9% for triple-negative) ($p = 0.045$ and $p = 0.026$, respectively). HER2 positivity was similar (~31.7%) in both groups - Chemotherapy (mainly anthracyclines, occasionally taxanes) was given in the 2nd–3rd trimester with close maternal-fetal monitoring. Surgery was performed as needed, while radiotherapy and hormonal therapy were postponed postpartum. Early cesarean delivery was planned in some cases to continue maternal treatment.	- Median OS was 82.8 months (95 % CI 39.3–126.5) for PABC and 80.1 months (95 % CI 56.7–103.6) for non-PABC ($p = 0.131$). - Moreover, when the PABC group was divided into subgroups (diagnosis during pregnancy [pregnancy] and diagnosis within the first year postpartum [postpartum]), there was a trend toward slightly worse prognosis for postpartum-diagnosed tumors, with lower DFS and OS; however, due to the small subgroup sizes, these differences were not statistically significant. - Overall, after matching for age, stage, and year of diagnosis, PABC patients did not exhibit significantly worse outcomes compared to non-PABC patients, despite more adverse tumor biology (higher rates of PR- and triple-negative tumors).	

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Table 1. (Continued)

Author	Year	Country	Sample	Results	Conclusion
Sella <i>et al.</i> ²⁰	2022	International	A total of 139 pregnancies with PABC were analyzed, of which 82 (59.0 %) received chemotherapy during pregnancy. Among these, 26 (31.7 %) received at least one regimen containing taxanes, and 18 (22.0 %) received G-CSF support. The overall use of chemotherapy, as well as the incorporation of taxanes and G-CSF, increased progressively over the study period.	- Among pregnancies resulting in live singleton births (<i>n</i> = 123), those exposed to chemotherapy during pregnancy were equally likely to reach full term compared with those not receiving chemotherapy (59.5 % vs. 63.6 %, <i>p</i> = 0.85). - In treated women, detailed analyses of combined maternal and fetal complications showed no statistically significant increase in risk associated with taxane use (OR 1.24, 95 % CI 0.27–5.72) or G-CSF support (OR 2.11, 95 % CI 0.48–9.22).	The researchers conclude that the gradually increasing, yet carefully managed, use of taxanes and/or G-CSF during pregnancy was not associated with adverse short-term maternal or fetal outcomes in this cohort.
Valente <i>et al.</i> ²¹	2022	Brazil	- The study included a young woman with a family history of BC diagnosed with invasive ductal carcinoma of the right breast at nine weeks of gestation. - Upon confirmation of the diagnosis and considering the stage of pregnancy, neoadjuvant chemotherapy with a doxorubicin and cyclophosphamide regimen was initiated, followed by mastectomy, aiming to minimize recurrence risk while managing the disease during pregnancy.	- After completion of chemotherapy and surgery, the patient showed signs of left ventricular overload, likely due to doxorubicin cardiotoxicity, but responded to management. - Following delivery, trastuzumab was initiated, but the patient developed a hypersensitivity reaction requiring discontinuation of treatment.	This case illustrates that aggressive HER2+ BC can be managed during pregnancy with chemotherapy and potential future HER2-targeted therapy, without compromising the pregnancy, provided careful monitoring and management of cardiac complications are in place.
Johnson <i>et al.</i> ²²	2025	USA	- The study analyzed 143 cases of PABC and 285 age- and stage-matched non-pregnant BC patients, with a median follow-up of 11.4 years. - DFS, progression-free survival, and OS were assessed using Kaplan–Meier curves and a Cox proportional hazards model.	- In PABC patients, median DFS and OS were not reached during follow-up, whereas in non-pregnant patients, median DFS and OS were 5.6 and 19.3 years, respectively (<i>p</i> = 0.0001 for DFS, <i>p</i> = 0.0262 for OS). - Median <i>p</i> was 24.1 years in the PABC group vs. 8.4 years in the non-pregnant group (<i>p</i> = 0.0008). - Multivariate Cox analyses showed that non-pregnant patients had a higher recurrence risk (HR 1.91, 95% CI 1.33–2.76, <i>p</i> = 0.0005), a higher risk of progression or death (HR 1.68, 95% CI 1.19–2.39, <i>p</i> = 0.0035), and reduced OS (HR 1.52, 95% CI 1.01–2.29, <i>p</i> = 0.0442) compared to PABC patients.	These findings suggest that women with BC who receive chemotherapy during pregnancy, when managed according to established treatment protocols, can achieve survival outcomes at least equivalent—and potentially superior—to those of non-pregnant patients.

Abbreviations: BC: Breast cancer; CI: Confidence interval; DFS: Disease-free survival; ER: Estrogen receptor; GA: Gestational age; G-CSF: Granulocyte colony-stimulating factor; HER: Human epidermal growth factor; INCIP: International Network on Cancer, Infertility, and Pregnancy; NICU: Neonatal intensive care unit; OR: Odds ratio; OS: Overall survival; PABC: Pregnancy-associated breast cancer; PR: Progesterone receptor; RFS: Recurrence-free survival; RR: Relative risk; SGA: Small for gestational age.

Table 2. Design-specific critical appraisal of the included studies using Joanna Briggs Institute (JBI) tools

Study	Study design	JBI tool	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Garofalo <i>et al.</i> ¹⁰	Cohort	JBI cohort	Y	Y	Y	Y	U	Y	Y	Y	U	N/A	Y
Ye <i>et al.</i> ¹¹	Case series	JBI case series	U	Y	Y	U	U	Y	Y	Y	U	N/A	–
de Haan <i>et al.</i> ¹²	Cohort	JBI cohort	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y
Yildirim and Bahceci ²³	Case report	JBI case report	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–
Gomez-Hidalgo <i>et al.</i> ¹³	Case-control	JBI case-control	N	N	Y	Y	Y	Y	N	Y	Y	Y	–
Lambertini <i>et al.</i> ¹⁴	Cohort	JBI cohort	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y
Safi <i>et al.</i> ¹⁵	Cohort	JBI cohort	Y	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y
Berwart <i>et al.</i> ¹⁶	Case report	JBI case report	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–
Boudy <i>et al.</i> ¹⁷	Cohort	JBI cohort	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y
Del Gobbo <i>et al.</i> ¹⁸	Case-control	JBI case-control	Y	Y	Y	Y	Y	U	N	Y	Y	Y	–
Zhang <i>et al.</i> ¹⁹	Matched case-control	JBI case-control	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	–
Sella <i>et al.</i> ²⁰	Cohort	JBI cohort	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Valente <i>et al.</i> ²¹	Case report	JBI case report	Y	Y	Y	Y	Y	Y	Y	Y	–	–	–
Johnson <i>et al.</i> ²²	Matched cohort	JBI cohort	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y

Notes: Y: Yes; N: No; U: Unclear; N/A: Not applicable; –: Item not included in the corresponding JBI checklist.

Table 3. Joanna Briggs Institute (JBI) checklist

JBI category	Checklist
JBI cohort	Q1. Were the two groups similar and recruited from the same population?
	Q2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
	Q3. Was the exposure measured in a valid and reliable way?
	Q4. Were confounding factors identified?
	Q5. Were strategies to deal with confounding factors stated?
	Q6. Were the groups/participants free of the outcome at the start of the study?
	Q7. Were the outcomes measured in a valid and reliable way?
	Q8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
	Q9. Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored?
	Q10. Were strategies to address incomplete follow-up utilized?
	Q11. Was appropriate statistical analysis used?

(Cont'd...)

Table 2. (Continued)

JBI category	Checklist
JBI case-control	Q1. Were the groups comparable other than the presence of disease in cases or absence of disease in controls?
	Q2. Were cases and controls matched appropriately?
	Q3. Were the same criteria used for identification of cases and controls?
	Q4. Was exposure measured in a standard, valid, and reliable way?
	Q5. Was exposure measured in the same way for cases and controls?
	Q6. Were confounding factors identified?
	Q7. Were strategies to deal with confounding factors stated?
	Q8. Were outcomes assessed in a standard, valid, and reliable way for cases and controls?
	Q9. Was the exposure period of interest long enough to be meaningful?
	Q10. Was appropriate statistical analysis used?
JBI case series	Q1. Were there clear criteria for inclusion in the case series?
	Q2. Was the condition measured in a standard, reliable way for all participants?
	Q3. Were valid methods used for identification of the condition for all participants?
	Q4. Did the case series have consecutive inclusion of participants?
	Q5. Did the case series have complete inclusion of participants?
	Q6. Was there clear reporting of the demographics of the participants?
	Q7. Was there clear reporting of clinical information of the participants?
	Q8. Were the outcomes or follow-up results clearly reported?
	Q9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
	Q10. Was statistical analysis appropriate?
JBI case report	Q1. Were the patient's demographic characteristics clearly described?
	Q2. Was the patient's history clearly described and presented as a timeline?
	Q3. Was the current clinical condition of the patient on presentation clearly described?
	Q4. Were diagnostic tests or assessment methods and results clearly described?
	Q5. Was the intervention or treatment procedure clearly described?
	Q6. Was the post-intervention clinical condition clearly described?
	Q7. Were adverse events or unanticipated events identified and described?
	Q8. Does the case report provide takeaway lessons?

particularly given the increased rates of preterm labor and small-for-gestational-age infants observed among pregnancies exposed to cytotoxic treatment.

A recurrent finding across the reviewed studies is the high incidence of preterm delivery among women treated for BC during pregnancy. In the study by Garofalo *et al.*,¹⁰ the rate of preterm delivery was notably high (83%), while congenital malformations occurred in only 5% of cases, comparable to the general population. Although this pattern is largely expected, it underscores the fact that delivery is frequently iatrogenically induced to allow the initiation or continuation of maternal oncologic treatment. Similar rates were reported in the International Network on Cancer, Infertility, and Pregnancy registry study by De Haan *et al.*,¹² where 48% of births occurred before 37 weeks of gestation. Low birth weight and the need for intensive neonatal support frequently accompany these outcomes. However, these outcomes appear to be primarily related to prematurity itself rather than to direct exposure to chemotherapy.

The study by Gomez-Hidalgo *et al.*¹³ provides further insights into maternal outcomes, showing that although labor induction and preterm delivery are more frequent than in healthy pregnancies, there is no statistically significant difference in maternal overall survival (OS). This reinforces the evidence that oncologic interventions can be safely implemented during pregnancy and provides evidence against the belief that pregnancy negatively impacts maternal outcomes. Johnson *et al.*²² similarly confirmed that, under appropriate therapeutic conditions, the prognosis of pregnant women with BC is comparable to that of non-pregnant patients, providing evidence against the conventional assumption that treatment requires delay or pregnancy termination. Consistent conclusions were also reported by Zhang *et al.*¹⁹

In the French Cancer Associé à La Grossesse network study on women with human epidermal growth factor 2-positive PABC, a slightly lower disease-free survival rate was observed compared to non-pregnant patients.¹⁷ This finding is likely related to limitations in the use of certain chemotherapy agents, such as trastuzumab, which are contraindicated during pregnancy. However, a review by Lambertini *et al.*¹⁴ indicates that pregnancy after completion of therapy for human epidermal growth factor 2-positive BC is not associated with an increased risk of recurrence. This distinction underscores the importance of the timing of pregnancy in relation to the initiation and completion of treatment as a critical factor in maternal outcomes.

The study by Safi *et al.*,¹⁵ based on the Australian Maternal Outcomes Surveillance System registry,

reported highly favorable obstetric and neonatal outcomes in pregnant women who received chemotherapy. No congenital abnormalities were observed, further supporting the safety of anthracycline-based therapy during the second and third trimesters. Importantly, these neonates exhibited normal developmental progress during follow-up. Similarly, in the study by Ye *et al.*,¹¹ neonates experienced jaundice, which was promptly managed, highlighting generally positive neonatal outcomes even in the context of in utero chemotherapy exposure.

Importantly, treatment-related findings should be interpreted according to therapeutic class, distinguishing conventional cytotoxic chemotherapy, including anthracyclines and taxanes, from targeted and endocrine therapies. A single case report described exposure to trastuzumab and tamoxifen during pregnancy without apparent complications.¹⁶ However, isolated favorable outcomes cannot establish the safety of these agents during pregnancy, and trastuzumab has been associated with oligohydramnios and remains contraindicated during pregnancy.²⁵ Further evidence is therefore required to define the pregnancy-related safety of non-cytotoxic systemic therapies.

The findings of the present systematic review should also be interpreted in the context of previous and more recent evidence syntheses and clinical guidelines. An earlier systematic review by Monteiro *et al.*²⁶ specifically evaluated chemotherapy use during pregnancy in women with BC, based on evidence published between 2001 and 2012, and concluded that anthracycline-based regimens could be administered after the first trimester, while evidence regarding taxanes remained limited. Subsequent reviews by Bajpai *et al.*²⁷ and Mumtaz *et al.*²⁸ addressed BC during pregnancy within the broader context of diagnosis, multidisciplinary management, and clinical outcomes. More recently, Zhang *et al.*²⁹ focused specifically on taxane chemotherapy, highlighting the growing but still limited evidence regarding its use during pregnancy and the need for further data on fetal safety and long-term outcomes. Current clinical guidance, including the Royal College of Obstetricians and Gynecologists Green-top Guideline on pregnancy and BC, further emphasizes trimester-dependent treatment planning and careful consideration of maternal and fetal risks and benefits.⁵ Against this evolving evidence base, the present systematic review provides an updated and focused synthesis of primary clinical evidence concerning chemotherapy exposure in women with BC during pregnancy, integrating maternal treatment outcomes with fetal and neonatal safety outcomes.

Future research may also explore strategies aimed at reducing treatment-related systemic exposure and toxicity

during pregnancy. Emerging approaches include tumor-targeted microbial platforms and locoregional or stimulus-responsive drug-delivery systems, although their potential application in PABC remains investigational and requires rigorous maternal and fetal safety evaluation.^{30–32} In parallel, maternal microbiome alterations have been implicated in the pathophysiology of spontaneous preterm birth, but their potential interaction with anticancer treatment and pregnancy outcomes remains unclear.³³ Emerging deep-learning approaches may additionally improve BC prognostic assessment and treatment-response prediction, although their specific clinical utility in PABC remains to be established.³⁴

In conclusion, the findings of the present systematic review support that pregnancy does not necessarily preclude active oncological treatment, provided that such treatment is carefully planned, delivered in specialized centers, and based on a multidisciplinary approach. Maternal oncological care can coexist with fetal protection when guided by evidence-based, individualized therapeutic strategies.

Future challenges include the consolidation of the existing evidence through larger population-based studies, as well as the continual updating of clinical practice guidelines, as reflected in the recent ASCO recommendations for cancer management during pregnancy.³⁵

6. Conclusion

The systematic review highlights crucial aspects of BC management in pregnancy, emphasizing that individualized, evidence-based treatment may allow continuation of pregnancy while balancing maternal oncological needs and fetal safety. Neonatal survival, congenital abnormalities, preterm birth, and maternal prognosis represent outcomes evaluated in the available literature.

The findings of the systematic review support the relative fetal safety of anthracycline-based chemotherapy administered after the first trimester, while the available evidence regarding taxanes, although increasingly reassuring, remains more limited. Across the included studies, most reported neonatal outcomes were favorable, with live births predominating and congenital abnormality rates generally comparable to those expected in the general population. Although preterm, often iatrogenic, births required care from the neonatal intensive care unit, preterm birth remained an important adverse outcome and was associated with increased need for neonatal care. Additionally, available evidence suggests that pregnancy itself does not necessarily confer a worse

maternal prognosis, although interpretation is limited by the observational nature and heterogeneity of the available studies.

Although current data support the relative safety of chemotherapy during pregnancy, study heterogeneity, differences in therapeutic exposure, and limited long-term follow-up of exposed offspring restrict the generalizability of conclusions. These gaps underscore the need for expanded multicenter registries with comprehensive maternal and child follow-up, including neuropsychological assessments to evaluate cognitive development, school performance, and psychosocial well-being.

Future research should also examine the experiences of women diagnosed with cancer during pregnancy, considering the psychological, social, and familial impacts on treatment adherence, mother–infant bonding, and overall quality of life. Additionally, efforts should focus on developing pregnancy-compatible therapies and predictive biomarkers to optimize treatment response and minimize complications. Altogether, these strategies aim to ensure comprehensive psychosocial support alongside safe and effective medical care.

In summary, the available evidence indicates that pregnancy should not be considered an automatic contraindication to active anticancer treatment. Appropriate patient counseling, multidisciplinary management, and trimester-specific, evidence-based treatment planning are essential to optimize maternal outcomes while minimizing fetal and neonatal risks.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: All authors

Data curation: All authors

Writing—original draft: All authors

Writing—review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data supporting the findings of this study are available from the corresponding author upon reasonable request. All data extracted and analyzed during the systematic review are derived from previously published studies cited within the article.

Further disclosure

During the revision of this manuscript, ChatGPT (GPT-5.6 Sol; OpenAI) was used solely to assist with language editing and to improve the clarity and readability of selected passages. All AI-assisted content was critically reviewed, verified, and edited by the authors. The authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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