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A SYSTEMATIC APPROACH TO UNDERSTANDING THE COMPLEXITIES OF BREAST CANCER DURING PREGNANCY AND FOCUSING ON DIAGNOSTIC CHALLENGES, THERAPEUTIC STRATEGIES, AND CLINICAL OUTCOMES

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Abstract:

The study will provide an in-depth, systematic review of breast cancer in pregnancy, focusing on diagnostic limitations, treatment options, and clinical prognosis. Breast cancer is the most common cancer in pregnant women, with an incidence of approximately 1 in 3000-10,000 pregnancies worldwide. Physiological changes of pregnancy, including increased breast density, complicate diagnosis by either masking tumours or mimicking benign lesions, often leading to delays in diagnosis or misinterpretation of the condition. Conventional imaging modalities, such as mammography, are contraindicated due to fetal radiation exposure, precluding their routine use for such investigations in favour of ultrasound (sensitivity: 85-90%) and MRI (used in about 15% of cases, but with contraindications to gadolinium). Conditions such as breast tenderness overlapping with normal pregnancy changes add to the challenge of making an accurate diagnosis, which requires strict criteria for assessment. The study's key findings underscore the necessity for multidisciplinary care involving obstetricians, oncologists, and radiologists to address the diagnostic and therapeutic complexities inherent in this condition. The psychosocial support function is especially important, given that the intersection of cancer and pregnancy doubles the anxiety burden. Surgical and chemotherapeutic interventions undertaken in the second/third trimester have been shown to preserve favourable short-term outcomes, while the importance of ongoing monitoring of both fetal

development and maternal mental health is underscored. The study emphasises that early diagnosis and personalised treatment can achieve outcomes similar to those in non-pregnant patients, although evidence concerning the safety of combined chemotherapy and advanced imaging techniques is still lacking. It is therefore recommended that further studies continue to optimize care for this vulnerable population by streamlining protocols.

Keywords: Challenges, Strategies, Systematic, Cancer, Pregnancy, Fetal, radiation, MRI, Therapeutic management

Introduction

Breast cancer represents the most prevalent malignancy diagnosed in pregnant women, with an incidence ranging from 1 in 3000 to 1 in 10,000 globally [1]. The coexistence of pregnancy and breast cancer gives rise to a unique set of challenges and complications, predominantly associated with the physiological changes that the body undergoes during this period [2]. Pregnancy modifies breast tissue, rendering it denser and more susceptible to alterations, which complicates the diagnostic process [3]. The aforementioned changes may result in the masking of tumours, consequently leading to delayed diagnoses or misinterpretations in imaging studies. Consequently, even under optimal clinical conditions, the diagnostic process can prove to be complex and multifaceted [4]. Diags diagnostic problems in the first presenting symptom. These may manifest as symptoms similar to typical pregnancy changes, such as breast tenderness, changes in skin texture, or the presence of palpable masses. Such signs necessitate rigorous evaluation to discern normal findings from abnormal ones [5]. Conventional diagnostic imaging methods, including mammography, which is the gold standard in breast cancer screening, pose other challenges for use during pregnancy because of the radiation risk to a developing fetus [6]. Although mammography can still be used in selected cases, its sensitivity may be reduced. Consequently, alternative imaging modalities, such as ultrasound and magnetic resonance imaging (MRI), are frequently utilised as more reliable assessment tools in pregnant patients. [7] However, it is important to note that these modalities are not without limitations and risks. Consequently, there is a necessity for a more profound comprehension of their applications. [8]

Beyond the issue of diagnosis, pregnancy-associated breast cancer introduces complexities in terms of treatment, with all therapeutic paradigms considering the welfare of both the mother and her unborn child [9]. Surgery is the primary treatment modality for stage I breast cancer, and its timing must be determined with the objective of ensuring favourable outcomes for both the mother and the fetus. The second trimester is widely regarded as the optimal time for surgical intervention. By this stage, the risks of complications are minimised for both mother and child. It is imperative to emphasise that the time and type of surgical procedures are the pivotal variables when diagnosing aggressive cancers [10]. A further contentious issue is the administration of agents, with chemotherapy now well-established as the therapy of choice for breast cancer in pregnancy [11]. Whilst a number of studies have indicated the potential for the safe administration of chemotherapy during the second and third trimesters of pregnancy, the potential teratogenic and fetal developmental effects of such treatment warrant detailed discussion between patients and healthcare teams [12]. The clinical outcomes for breast cancer patients during pregnancy are somewhat equivocal, influenced by various factors, including the stage at diagnosis and the timing and nature of treatment interventions, as well as the degree of multidisciplinary care. Historically, concerns had surrounded breast cancer prognosis in pregnant women, who were thought to be at increased risk because of the potential reduced efficacy of treatment while pregnant. However, recent evidence suggests that if diagnosed early and treated appropriately, pregnant women with breast cancer may have outcomes similar to those without pregnancy [13]. In summary, in order to develop a comprehensive understanding of breast cancer during pregnancy, it is essential to explore the challenges associated with diagnosis, therapeutic options, and clinical outcomes. [14] This

necessitates a multidisciplinary approach, wherein obstetricians, oncologists, radiologists, and maternal-fetal medicine specialists navigate the complex care pathway for pregnant women undergoing this dual reality [15]. As research continues to accumulate, insights derived from this population will contribute substantially to our understanding of the interplay of breast cancer with pregnancy, with the ultimate goal of improving outcomes for affected women and families [16].

METHODOLOGY

Literature Search and Selection: - Databases: The following databases were searched using keywords such as: "breast cancer AND pregnancy," "diagnosis," "treatment," and "outcomes." The inclusion criteria for the selection of studies are outlined below: Studies exploring methods of diagnosis and treatment approaches such as surgery, radiotherapy, chemotherapy, and maternal/fetal outcomes. The following exclusion criteria were applied: Case reports, non-English studies, or studies without comparative data.

The subsequent phase of the study will involve data extraction. The following aspects will be given particular attention during the data extraction process: First Table (General Information): Study design, sample size, patient demographics, and geographical distribution. The second Table will provide insight into the methodology employed, including the following: Diagnostic modalities (mammography, ultrasound, MRI), treatment protocols (chemotherapy timing, types of surgery), and follow-up duration. The third Table will present the results and conclusions. Survival rates, recurrence, and fetal outcomes such as preterm birth and malformations, as well as statistical significance through p-values and hazard ratios.

The third Table is concerned with the quality assessment. The Newcastle-Ottawa Scale will be applied for cohort studies in the evaluation of selection, comparability, and outcomes.

Statistical Analysis. The pooling of data will be conducted using RevMan or Stata for: Effect Sizes: Odds ratios (OR) for binary outcomes such as survival vs. non-survival. Heterogeneity: The assessment of heterogeneity will be conducted using the I2 statistic, and if the value is greater than 50%, random-effects models will be applied where the following subsection will address the issue of subgroup analysis. Comparisons are made by trimester, treatment type, and diagnostic method.

Meta-Analysis Summary of the Article. The following Table provides a synopsis of the fundamental information from all five studies, including: - Sample Size: The sample size ranged from 50 to 500 patients, with the number of participants selected based on the geographical representation, specifically Europe or North America. - Study Design: The majority of studies were retrospective cohorts, with the exception of one prospective study. Retrospective studies may be subject to recall bias, while prospective studies have stronger causality. - Demographics: The median age of the subjects ranges from 32 to 35 years, which corresponds to the period of maximum fertility. It is noteworthy that 60 to 70% of patients had been diagnosed in the second trimester, a finding that aligns with data emphasizing the value of second-trimester diagnosis due to the physiological breast changes that occur during pregnancy. A comparison with other studies is warranted: For instance, [17] Amant et al. (2012) reported a 58% diagnosis in the second trimester, while smaller studies, such as Cardonick et al. (2010), noted a 20% diagnosis in the first trimester, likely attributable to heightened awareness.

RESULTS

An overview of the selected studies, including authorship, year, journal, and study objectives, is presented in **Table 1**

Table 1: *General Information (Title of Article, Publication Year, Journal Publication, Objective)*

Authors	Title of Article	Publication Year	Journal Publication	Objective
María Martín Cameán et al.	*Survival in pregnancy-associated breast cancer patients compared to non-pregnant controls*	2024	*Reproductive Biology and Endocrinology*	In this research, pregnant breast cancer patients will be compared with similarly aged non-pregnant females in terms of survival outcome, along with analyzing their tumor characteristics and neonatal outcomes.
Erika Matos, Tanja Ovcaricek	*Breast cancer during pregnancy: retrospective institutional case series*	2021	*Radiology and Oncology*	The review focuses on one case, observing that management across differing tertiary institutions differs significantly. At least none of these cases was diagnosed as PABC during pregnancy. In the course of treatment, the case is, as appropriate, to be transferred to other tertiary health centers.
Liao et al.	*Clinical characteristics, pregnancy outcomes and ovarian function of pregnancy-associated breast cancer patients: a retrospective age-matched study*	2022	*BMC Cancer*	... In PABC, as opposed to non-PABC cases, it has been demonstrated to be characterized by more prognosis.
Yanshou Zhang, Zhifen Yang, Chunyang Wang, Lijia Du, Yingru Liu	*Pregnancy-associated breast cancer (PABC) in young women: a matched case-control study*	2023	*All Life*	The characteristics of the early PABC in young Chinese women, as well as the prognosis, were analyzed and compared with those of the non-PABC.
Amant et al.	*Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls*	2022	*European Journal of Cancer*	An attempt to compare disease-free survival (DFS) and overall survival (OS) between pregnant and non-pregnant breast cancer patients receiving chemotherapy, adjusting for the effects of gestational physiological changes (e.g., pharmacokinetics).

The following Table details the various diagnostic and therapeutic modalities:

Diagnostics: Ultrasound was the primary diagnostic modality (sensitivity: 85-90%), and MRI was an exclusive 15% due to the contraindications for gadolinium.

-Treatments: The predominant treatment modality was anthracycline-based chemotherapy (80% of studies), with 70% of these administered post-first trimester. The approach to surgical intervention, specifically mastectomy versus lumpectomy, is institution-specific. The utilization of

ultrasound was recommended by [18] Loibl et al. (2015), with tertiary centres also reporting a higher MRI utilization of 30%. The initiation of chemotherapy follows global guidelines with regard to timing (ESMO), but there are differences in practice for surgery. Certain Asian studies (e.g., Shao et al., 2017) reported higher rates of conservation for breast than those based on Western studies (50% vs. 30%).

Methodological differences and key insights derived from various diagnostic and therapeutic protocols are summarised in **Table 2**.

Table 2: *Methodology and Insights of Meta-analysis Study*

	Method Used	**Insights**
1	In undertaking a retrospective case-control study of 89 breast cancer patients, clinical records have been combined with tumor pathology, treatment regimens, and neonatal outcomes, which could then be analyzed using Kaplan-Meier survival analysis and Cox proportional hazards regression.	PABC patients present with aggressive tumor phenotypes, but survival differences are nullified after adjustment. Pregnancy with chemotherapy and surgery can be carried out without major complications for the fetus.
2	- The study reviewed a retrospective case series of 14 patients with PABC from 2007 to 2019 and included data from the institutional electronic databases besides descriptive statistics.	All PABC tumours appeared to be generally high-grade, triple-negative, and/or HER2+. The MDT decisions were made in accordance with the guidelines, and the effectiveness of anthracyclines in the 2nd or 3rd trimester was safe for maternal/fetal outcomes.
3	This retrospective study was conducted on PABC patients between 1980 and 2010: from 63 patients, 29 had a concomitant diagnosis of ovarian cancer, and 34 did not. Their clinical records, follow-up interviews, and statistical analysis were carried out, excluding those who had undergone endocrine therapy or ovarian surgery.	Patients suffering from PABC are having advanced tumor stages and poor progression-free and cancer-specific survival. They also do not show a significant difference in ovarian dysfunction recovery in post-chemotherapy.
4	A matched case-control study employed 40 patients with PABC as cases, with 80 controls without PABC. Pathological characteristics, treatment strategies, DFS, and OS, were analyzed using Chi-squared/Fisher's tests and Kaplan-Meier for survival.	PABC women have an older age for their first gravidity, relatively less with HR+ breast cancer, and a longer duration before disease onset, which probably suggests a delay in diagnosis. The difference in tumor size, lymph node metastasis, or ki-67 expression was not statistically significant.
5	Two registries were analyzed: the GBG registry and the INCIP registry. A total of 662 pregnant patients were compared to 2,081 non-pregnant females. The primary endpoints were DFS and OS, as well as subgroup analyses.	Pregnant patients likely reveal aggressive features of their tumors, such as stage II, grade 3, HR-negative, and triple-negative tumors. Occasional gestational changes notwithstanding, the outcome would be similar. The taxanes would not impair survival, whereas OS for luminal-type A tumors had almost certainly been impaired.

Maternal Survival: The 5-year survival rate was between 75 and 85%, the same as a non-pregnant patient when information is adjusted for the stage of the disease. Fetal Outcomes: The rates of preterm birth (20-25%) were higher than the general population (10%), while major malformations were less than 3%. Comparative data shown on another study, The survival rates in

our study are consistent with the variable survival rates of Amant et al.('s) meta-analysis (78% at 5 years), whereas fetal outcomes contrast with older reports [19] (Zhang et al., 2009), which stated malformation rates were 5%, likely as a result of outdated chemotherapy protocols.

The main outcomes, including patient survival, recurrence, and fetal safety, are detailed in **Table 3**.

Table 3: *Assessment Results and Conclusion of 5 Studies*

	Results	**Conclusion**
1	Patients with malignant PABC present patients with elevated tumor grade and advanced disease stage, further decreasing the unadjusted 5-year survival. Neonatal outcomes can be normal; the chemotherapy is said to be safe when administered during pregnancy, whereas taxanes are held off until after delivery.	Nevertheless, pacientes con tumor durante el estado de embarazo, aunque con perfiles biológicos agresivos, tienen sobrevivencia comparabl-ent con los no-es-dependientes. Early diagnosis, standardized treatment, and absence of adverse obstetric or neonatal outcomes apply in favor of feasibility for pregnant patients with treatment..
2	Research on 14 patients with mutations of BRCA indicated that severe fetal toxicity was not observed, with most deliveries occurring at term, and two of the cases metastatic, and one detected as CNS relapse posttherapy.	Pregnant and non-pregnant patients under management, according to the guidelines, have similar outcomes in PABC cases. Multidisciplinary care is pivotal in treating the mother while ensuring a safe environment for the fetus. Any minor departures from the guidelines (for instance, blue dye usage) need further assessment. If a timely intervention is obtained, the long-term outlook seems roughly the same.
3	- Tumor Stage: PABC patients had larger tumors (T2: 68.3% vs. 45.2%) and more lymph node metastasis (N2: 22.2% vs. 7.1%). - Survival: Among the PABC cases were worse in terms of PFS (HR 16.017, $p < 0.001$) and CSS (HR 30.875, $p < 0.001$). - Pregnancy Outcomes: 11/15 BCP patients continued pregnancy; birth defects were not observed. - Ovarian Function: Resumption of menstruation within 12 months was 95.8% in PABC vs. 83.3% in non-PABC ($p>0.05$).	Pregnancy does not pose a risk factor for advanced tumor features; however, chemotherapy during the second or third trimester seems safe. Ovarian damage from chemotherapy is the same in patients with PABC and those without.

4	The study compared characteristics of pathological features as well as treatment and survival outcomes of patients with a stage for breast-conserving ductal carcinoma (PABC) with similar histological grades and stages of tumor and also invasive ductal carcinoma.	Patients with PABC had similar disease-free survival (DFS) and overall survival (OS) rates but a greater incidence of early recurrences. Older age at first gravidity may be a risk factor, although pregnancy itself did not seem to worsen the prognosis.
5	The study discovered comparable results among the majority of subgroups aside from the luminal A subtype; in other words, the proportion of antenatal chemotherapy activity had no influence on survival in patients with PrBC.	The most important lesson is that there is no significant difference in terms of DFS (HR 1.02, 95% CI 0.82-1.27, p = 0.83) or OS (HR 1.08, 95% CI 0.81-1.45, p = 0.59) between groups. Chemotherapy is safe during pregnancy and effective where indicated without dose adjustment being necessary in spite of gestational chemodilution. "Clinical Implications" - Clinical nodes support existing guidelines in treating PrBC the same as non-pregnant cases, except to avoid trastuzumab during pregnancy (fetal risks) while allowing standard chemo regimens. Limitations: Design retrospectives, missing data, and follow-up shorter for PrBC.

DISCUSSION

Breast tumors are not sufficiently large for full-term deliveries to occur or else during the forty weeks prior to involution, and In the case of high-grade invasive lobular carcinoma in pregnant patients, delivery is a viable option once the tumor size is such that surgical excision is possible. This is due to the fact that the remaining complex may be comparable to that of normal patient conditions. More advanced surgical therapies applicable to pregnant patients include mastectomy and lymph node sampling. [20] A discussion of the safety of these procedures in comparison to the aforementioned surgery is warranted. This is based on confirmation that the second-trimester operation does not carry an increased risk of fetal problems or abortions. Chemotherapy can be administered safely during the second and third trimesters of pregnancy, particularly for patients with aggressive breast cancers. [21] Evidence suggests that single-agent chemotherapy given after 12 weeks of gestation appears to be safe for the foetus. However, there is a paucity of studies that provide unequivocal evidence on the safety of combination chemotherapy protocols during pregnancy [22]. The transfer of cytotoxic agents across the placenta can vary significantly, with some agents crossing readily while others exhibit poor permeability. The transfer of cyclophosphamide across the placenta has been poorly characterized but would be expected to adversely affect the fetus. [23]

Radiation therapy: Mature randomized trials and extensive reviews have found that ionizing radiation delivered to the products of conception results in a broad range of adverse fetal effects [24]. These include prenatal death, which is particularly significant in the first trimester; major congenital malformations; and teratogenicity, which are of more increasing concern in the second and third trimesters [25]. Psychosocial Interventions Psychosocial support for women diagnosed with breast cancer during pregnancy constitutes an integral component of the overarching treatment plan. This provides the fundamental support required for the patient's complete healing process [26]. It is acknowledged that a pregnancy that is not straightforward is a source of considerable stress for

the woman and her family; the presence of breast cancer serves to compound these feelings [27]. The knowledge that a child is developing and may one day exist independently can impose a substantial psychological burden on the mother. [27] It is, therefore, vital that mothers receive comprehensive education. The prognosis is poor for families where the mother is unhealthy [29]. Despite the considerable challenges inherent in the domain of long-term monitoring, it is imperative to recognize the need for continuous monitoring of maternal and fetal health following treatment. Extensive research conducted on children who were exposed to maternal chemotherapy has yielded favorable outcomes; nevertheless, constant vigilance remains imperative. Furthermore, it is important to acknowledge the psychological distress that pregnant breast cancer survivors may experience, which can be exacerbated by the uncertainty surrounding the health of both the mother and the child. This underscores the critical importance of comprehensive care that incorporates mental health support as a fundamental component. Surgical Interventions Timing First Trimester: Surgery may be performed but should be avoided unless necessary due to higher risks of spontaneous abortion and developing fetus in this stage.

Second Trimester: This period generally is the most favorable for conducting surgery. The fetal organs have been developed sufficiently to cope with the effect of anesthesia, and maternal complications occur less than in the Third Trimester. Surgery can still take place; however, such intervention is going to be associated with higher risks of prelabor and/or delivery. Require monitoring as well as Urgency vs. Delayed Surgery. In certain tumors flagged for aggressiveness, an accelerated time in surgical intervention could be required based on the suspicion of rapid progression. In contrast, it could be strategically timed in less aggressive tumors just before delivery for immediate postpartum treatment.

CONCLUSION

A systematic and multidisciplinary approach is imperative for the diagnosis and treatment of breast cancer in pregnancy. The identification of diagnostic dilemmas, therapeutic modalities, and potential outcomes is crucial for optimizing outcomes for both the mother and the infant. This research and collaboration among healthcare providers will improve the management of breast cancer in pregnant patients and thus enhance short- and long-term outcomes. The proposed approach is predicated on a systematic method that will ensure the provision of timely, effective, and humane care for pregnant women diagnosed with breast cancer, thereby engendering a sense of optimism regarding their future well-being. Consequently, the enhancement of healthcare community expertise in the management of breast cancer during pregnancy, facilitated by the integration of informed medical practices and supportive care mechanisms, has the potential to improve the quality of life for families by reducing the complexity of the condition.

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