MATHEWS

Review Article

Mathews Journal of Case Reports

Gestation Concomitant: Breast Cancer

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ABSTRACT

Pregnant women may be diagnosed with up to 3% of breast malignancies, according to estimates. Clinicians face unique difficulties when treating patients with breast cancer associated with pregnancy. Due to the physiological changes occurring within the breast and the investigational resources available, the diagnosis may be delayed and challenging. Additionally, if a diagnosis has been made and a staging has been performed, treatment options will be impacted by the desire to provide the mother with the best care possible while reducing risks to the foetus. This paper discusses the unique difficulties encountered in the initial diagnosis and treatment of women with pregnancy-associated breast cancer. To provide patients with the finest multidisciplinary care, considerable effort is needed when breast cancer occurs during pregnancy. Although breast cancer during pregnancy appears to be associated with distinct patterns of gene expression, the pathology-based classification remains unaffected. In the second and third trimesters of pregnancy, chemotherapy and surgery are typically safe and well-tolerated by patients. The longer time to diagnosis and the more aggressive nature of breast cancer in young people may be the main causes of the worse prognosis. The balance between the mother's and the child's health must be prioritized.

Keywords: Pregnancy, Breast Cancer, Chemotherapy, Malignancies.

ABBREVIATIONS

ER: Estrogen-Receptor; HER2: Human Epidermal Growth Factor Receptor; MRI: Magnetic Resonance Imaging; BIG: Breast International Group; CT: Computed Tomography.

INTRODUCTION

Breast cancer is the most common malignant tumour in women and the main factor in deaths from cancer among women globally [1]. Although the average age of breast cancer start is 61 years, 1 in 40 women who are diagnosed with the disease are under the age of 40, and breast cancer accounts for 5-7% of all cancer fatalities in these young women.

The physiological changes in the breast that take place during pregnancy may make clinical evaluation more challenging as the pregnancy goes on. Contrary to widespread assumption, performing a mammogram with abdominal shielding while pregnant can be done with little danger [2,3]. A normal two-view mammography of each breast is thought to

Vol No: 09, Issue: 08

Received Date: July 25, 2024

Published Date: September 16, 2024

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Citation: Chandak CS, et al. (2024). Gestation Concomitant: Breast Cancer. Mathews J Case Rep. 9(8):181.

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expose the foetus to only 0.004 Gy of radiation. However, mammography may be challenging to interpret due to the increased breast density found in premenopausal women and the physiological changes within the breast during pregnancy [3]. Mammographic abnormalities are reported in 63–87% of patients with pregnancy-associated breast cancer in small series [4,5]. On the other hand, ultrasound has been proven in two short series to be more sensitive than mammography, making it a straightforward, sensitive replacement for mammography in pregnant and nursing women [4-6]. Therefore, in our opinion, mammography should only occasionally be required in the investigation of breast cancer in a pregnant woman. On the other hand, ultrasound has been proven in two short series to be more sensitive than mammography, making it a straightforward, sensitive replacement for mammography in pregnant and nursing women [4-5,7]. Therefore, in our opinion, mammography should only occasionally be required in the investigation of breast cancer in a pregnant woman. There is a chance that a milk fistula will develop during any interventional operation done on a pregnant woman's breast, and there is also a larger chance of bleeding and infection. By ceasing breastfeeding before the biopsy, taking prophylactic antibiotics, and closely monitoring haemostasis, these risks can be reduced [8].

Many common staging tests performed on non-pregnant women include the use of ionising radiation and could pose a risk to the foetus. The effects of ionising radiation exposure during pregnancy will vary depending on the radiation dose, how it is distributed, and the stage of foetal development at the time of exposure [9]. Embryonic mortality may result from radiation exposure during the peri-implantation and early post-implantation period (up to 8 days). The foetus is particularly susceptible to radiation-induced abnormalities during organogenesis (up to 8 weeks), which can happen with exposure to more than 0.05 Gy [10]. Ionising radiation exposure during this time also increases the fetus's risk of intrauterine growth retardation, mental impairment. When the foetus is 8 to 15 weeks old, the risk of severe mental retardation is dose- and age-dependent, with a threshold of 0.06-0.31 Gy and of 0.28 Gy, respectively [11]. Although lengthy follow-up studies would be necessary to determine the actual incidences of these issues, it is theoretically also plausible that irradiation may predispose to sterility and future malignancies in the child. Since the anticipated foetal dosages are within the upper limits mentioned above, chest X-rays are generally considered safe during pregnancy [9]. When clinically necessary, it is reasonable to carry out these procedures while using the proper shielding. The foetus may be exposed to mean doses of 0.0036 and 0.089 Gy, respectively, during computed tomography (CT) scans of the pelvis and liver. Therefore, CT scans are typically avoided in favour of alternate imaging techniques like ultrasonography, which are used to look for metastases. The UK medical devices agency advises against MRI scans during the first trimester until more information is available [12] because there are theoretical dangers to the foetus from exposure to the strong magnetic fields used to create an MRI. Gadolinium, a contrast agent that has been demonstrated to cross the placenta, should also be avoided if at all possible because it is unknown how it would affect a growing foetus [13]. MRI of the skeleton or modified bone scans can be used to detect bone metastases [14]. The hazards to the foetus can be minimised using such staging techniques. However, it is crucial that these investigations only be employed in situations where a favourable outcome would change immediate management.

MEDICAL AND PATHOLOGICAL CHARACTERISTICS

The typical maternal age at the time of a breast cancer diagnosis during pregnancy is 33 to 34 years, according to several case reports. At diagnosis, the gestational age is typically between 17 and 25 weeks [15-17]. The majority of tumours are invasive ductal carcinomas, just like in non-pregnant patients; between 80% and 100% of patients present with tumours of this subtype [18-19]. Between 40% and 84% of patients had poorly differentiated tumours when they are first diagnosed, albeit in a case-control analysis, the rate of these tumours was not higher than that of matched non-pregnant controls. Although some series suggest greater rates of inflammatory tumours in pregnant women than in non-pregnant controls [19], the incidence of inflammatory tumours is likely between 1.5% and 4% [20]. According to earlier research, patients with breast cancer linked to pregnancy frequently have big tumours, lymphovascular invasion, and pathological lymph node involvement (56–67%) [21]. According to studies, pregnant or lactating women may be more likely than matched non-pregnant controls to appear at a later stage [21]. A high prevalence of estrogen-receptor (ER)-negative tumours is a frequent observation in series of patients with pregnancy-associated breast cancer. Between 54% and 80% of breast tumours linked to pregnancy lack the ER gene. Although ER-negative tumours are known to be more prevalent in younger women in general, case-control studies have revealed that pregnant patients experience ER-negative tumours more frequently than age-matched controls. HER2 positive has been identified in 28% to 58% of breast tumours associated with pregnancy using a variety of antibodies and ssscoring systems.These studies' sample sizes are too small to draw any firm conclusions on whether HER2 positive occurs more frequently than in controls who were age-matched [22,23].

Potential mechanisms involved in the pathogenesis of pregnancy-associated breast cancer

Changes in hormonal profile during pregnancy	• Induced onco-genetic processes and increased breast cell proliferation • Increased development of abnormal cells with cancerous biological characteristics
Changes in immune response during pregnancy	• Cellular immunosuppression • A rise in immunological tolerance and a decline in immune regulation • Increased inflammatory reactions linked to breast involution
Breast involution after lactation	• Regression of a fully functionally differentiated mammary gland to its pre-pregnancy state • Extended stromal modelling, adipogenesis, and activation of inflammatory responses are all associated with increased cell death.
Altered gene expression	• Increased expression of genes related to metabolism, aggression, cell cycle regulation, immunological responses, and recurrence • Modified expression of oncogenes, suppressor genes, apoptotic regulators, DNA repair mechanism-related genes, and immune response-related genes

Treatment options

Surgery

In most cases, individuals with breast cancer consider surgery as their first option for therapy. For a small number of surgeries, local anaesthesia may be used, but for the vast majority of patients, general anaesthesia is required. Due to increased blood volume and coagulability, lower lung capacity, sluggish gastric emptying, and supine positional hypotension in pregnant women, general anaesthesia is challenging. An analysis of 5405 procedures on 720000 pregnant women revealed a higher risk of low birth weight children due to both preterm and intrauterine development retardation in pregnant women who underwent surgery [24]. Neonatal mortality also increased, but there was no similar increase in congenital defects or stillbirths. It is impossible to determine if the negative consequences noted were brought on by the operation, the anaesthetic, or the underlying issues that necessitated the procedure. Small case series, however, demonstrate that axillary surgery, mastectomies, and breast conserving surgery can all be carried out successfully without any unanticipated consequences. It is unknown whether sentinel lymph node biopsy is safe for people who are pregnant [23-24].

Radiation Treatment

The foetus is exposed to a significant risk of harm because the radiation doses used in cancer therapy are far higher than those used in diagnostic radiography. It could be possible to irradiate specific portions of the mother without considerably irradiating the foetus by carefully evaluating the foetal dose. Foetal dose exposure during adjuvant breast irradiation may be as low as 0.036-0.038 Gy when finished by the sixth week of pregnancy [25], but exposure may rise noticeably later in pregnancy as the foetus comes closer to the radiation field [26]. Adjuvant breast radiation is typically postponed until after delivery since these exposures could still pose a risk to the developing foetus. Unfortunately, maternal outcome may be impacted by delivery delays of adjuvant radiation longer than 8 weeks in women not undergoing systemic therapy [27]. This issue will need to be explored with the patient in these cases. However, in practise, the necessity to postpone adjuvant radiotherapy until after delivery is rarely a problem because adjuvant chemotherapy is frequently provided in the interim due to the young age of the patients and high incidence of unfavorable prognostic characteristics.

Chemotherapy

Maternal effects of chemotherapy

The pharmacokinetics and pharmacodynamics of chemotherapy in the mother may be affected by the physiological changes seen during pregnancy. Hepatic metabolism, renal plasma flow, and plasma protein binding

are all altered in pregnant women, which may have an impact on medication clearance [28]. Additionally, the amniotic fluid might function as a pharmacological third space, delaying the clearance of medications like methotrexate. These side effects make it challenging to determine the right amount to provide and may raise the risk of foetal and maternal toxicity.

Fetal effects of chemotherapy

Because of the cytotoxic chemotherapy's effects on microtubule function and nucleic acid synthesis, as well as the fetus's high rate of cell division, it is likely to be especially vulnerable to the side effects of chemotherapy. All medications have the ability to cross the placenta, but how much depends largely on the physical and chemical characteristics of the substance. Due to their widespread distribution in tissues and bodily fluids, methotrexate and 5-fluorouracil appear to have the potential to reach the amniotic fluid [29-31]. In contrast, doxorubicin was not found in amniotic fluid taken 4 and 16 hours after the drug was administered to a pregnant woman who was 20 weeks along in one research [32]. Additionally, in vitro perfusion investigations employing term placentas have only detected very modest levels of epirubicin transplacental transfer [33]. Little is known about the transplacental transfer of taxanes. P-glycoprotein is expressed in the human placenta, and its presence may limit the exposure of the foetus to a number of antineoplastic drugs, including paclitaxel [34].

Effect in First trimester

There is a high risk of spontaneous abortion when chemotherapy is administered during the first few weeks of pregnancy. The foetus continues to be at risk of spontaneous abortion for the remainder of the first trimester, and chemotherapy exposure also increases the chance of foetal abnormalities. When chemotherapy is administered during the first trimester, the risk of foetal abnormalities is estimated to be up to 17%. Combination therapies and the administration of chemotherapy together with radiotherapy are thought to raise this risk. Antimetabolites and alkylating agents are more likely to be linked to miscarriage and abnormalities than other agents in terms of their potential teratogenicity. Chemotherapy during the first trimester of pregnancy is typically avoided due to the severe hazards it poses to the foetus [34,35].

Effect in Second and third trimesters

Due to the fact that organogenesis is finished and foetal abnormalities are therefore unlikely to occur, chemotherapy has been used more frequently in the second and third trimesters. The M.D. Anderson Cancer Center's future series is the only one [35]. In this trial, 24 breast cancer patients, both primary and recurrent, received treatment with doxorubicin 50 mg/m2 as a continuous infusion over 72 hours, cyclophosphamide 500 mg/m2 on day 1, and bolus 5-fluorouracil 500 mg/m2 on days 1 and 4, all given every 3–4 weeks. There were no maternal or foetal fatalities, nor were there any discernible congenital abnormalities. There were no deaths or congenital deformities when chemotherapy was administered after the first trimester in a retrospective cohort of 28 pregnant patients treated with chemotherapy for breast cancer at London teaching hospitals. Nine children in the London series had pre-term deliveries (under 37 weeks gestation), one of which was caused by a spontaneous commencement of labour and the other eight by medical intervention. Pregnant women who undergo chemotherapy have previously been documented to experience spontaneous labour as well as other pregnancy issues such pre-eclampsia [36]. It is unknown, therefore, whether these consequences are more common than they would be in a healthy population and how much chemotherapy contributes to the effects of the underlying illness. Neonatal recipients of chemotherapy have also been reported to experience transient leukopenias. Chemotherapy should be avoided for at least three weeks prior to birth to ensure that maternal blood counts are adequate. Myelosuppression that occurs around the time of delivery may increase the risk of sepsis and haemorrhage for both mother and baby [36]. On the basis of the available information, it is challenging to evaluate the relative toxicities of various drugs. Anthracycline-based therapy was used to treat all of the patients in the M.D. Anderson series and 16 of the patients. It indicates that these medicines can be given to women safely during the second and third trimesters with regard to peri-partum problems and immediate foetal outcome [37]. Similarly came at same result after reviewing the records of 160 patients who had taken anthracyclines while pregnant. However, it also appears that alternative cytotoxic substances could be used in the second and third trimesters. Three patients in the second and third trimesters received vinorelbine combined with 5-fluorouracil without any immediate foetal or maternal problems [38]. Although paclitaxel has been demonstrated in animal trials to be toxic to the foetus, it has been used in conjunction with cisplatin from 28 weeks of pregnancy and with epirubicin from 14 weeks with no unforeseen consequences for either the mother or the foetus [39,40]. However, the one report of its use to treat metastatic breast cancer between the 23rd and 32rd weeks of pregnancy showed no specific issues [41]. Docetaxel is also hazardous to the foetus in animal trials. However, there were no particular problems noted in the one case of its use to treat metastatic breast cancer between the 23rd and 32nd weeks of pregnancy [41]. In animal studies, docetaxel is also harmful to the foetus.

Long-term effects of chemotherapy exposure

The M.D. Anderson Cancer Center prospective study, the French National Survey and the London hospitals series suggest that in the short-term chemotherapy can be safely administered to women within the second and third trimesters of pregnancy [41]. Whilst this is true for the pre-partum and immediate peri-partum periods, little is known about the long-term effects on the fetus of in utero chemotherapy exposure. One could postulate that fetal exposure to chemotherapy may lead to gonadal damage and later problems with fertility, germ cell damage, and higher rates of malignancy and teratogenicity in subsequent generations. Similar to how damage to the central nervous system or the heart may not cause physical or neurological disability until later in life. Actually, there aren't many studies that show how long-term monitoring of kids exposed to chemotherapy in pregnancy has gone. A cohort of 84 infants delivered to moms who received combination chemotherapy during pregnancy for haematological malignancies [42]. At the time of the assessment, the children's ages ranged from 6 to 29 years (median 18.7), and 12 second-generation children were included in the study. All children showed normal physical, neurological, and psychological development, and there were no reports of cancers among this cohort. While reports like this are encouraging, more comprehensive prospective studies, like the ones started by the German Breast Group [43] and most recently expanded by the Breast International Group (BIG 2-03), are required to offer details on the aftereffects of treatment.

Growth factor

When using dose-dense chemotherapy, growth factors are occasionally required for hemological support; anecdotal studies describe the use of granulocyte colony-stimulating factor during pregnancy without any immediate problems [44].

Targeted therapy

Trastuzumab treatment may be taken into consideration because studies have indicated that HER2-positive tumours are present in pregnant women at relatively high rates [44]. However, placental transfer of the monoclonal antibody trastuzumab has been noted in animal investigations, and HER2 expression is also high in embryonic tissues, suggesting a function in embryonic development (personal communication from Roche Pharmaceuticals, Welwyn Garden City, UK). Therefore, it is not currently advised to use trastuzumab while pregnant.

Endocrine therapy

Tamoxifen, a selective ER modulator, has been shown in animal experiments to have teratogenic potential [45]. Ten foetal abnomalies, including two craniofacial deformities, were found in data from 50 pregnancies in which the mother received tamoxifen [46]. Numerous other uncommon foetal anomalies have also been reported, such as ambiguous genitalia and Goldenhar's syndrome (oculoauriculovertebral dysplasia) [47,48]. As a result, tamoxifen use is typically postponed until after delivery, mechanism given in Figure 1.

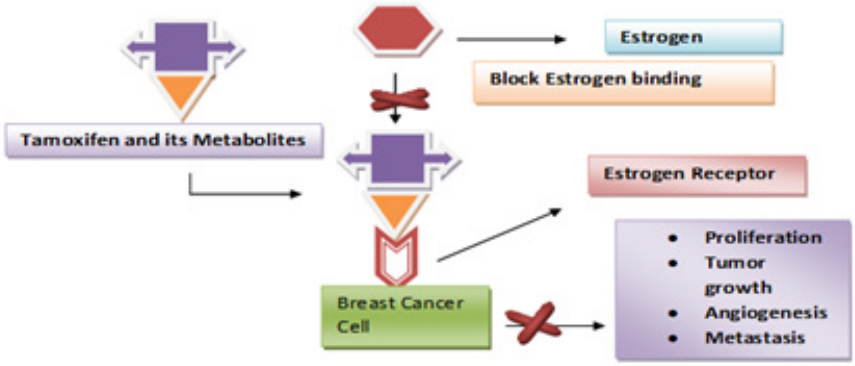

Figure 1. Tamoxifen mechanism for breast cancer.

Termination of pregnancy

Pregnant women with breast cancer who are given the opportunity to terminate their pregnancies do so occasionally. This choice was previously advocated due to the notion that pregnancy's hormonal changes encouraged the development of breast cancer. Historical studies have not shown a significant decrease in the rate of relapse or an improvement in survival with pregnancy termination, but it's possible that any potential benefit from termination was hidden by the propensity of women with poorer prognoses to choose it or by the prevalence of hormone receptor-negative tumours. It may still be reasonable to discuss termination if the fetus is likely to be exposed to significant risk of harm by potentially curative treatment given to the mother. In

addition, some women with metastatic or high-risk cancer may not want to carry on with the pregnancy. Patients and their relatives must be provided with adequate counseling in order that they can make an informed rational decision in these very difficult circumstances [48,49].

Prognosis of pregnancy-associated breast cancer

Pregnancy-associated breast cancer has long been regarded as having a poor prognosis, with the earliest reports describing 5-year survival rates of <20%. However, in a more recent study overall survival of patients with stage II and III disease was found to be 75% (at a median of 40 months), suggesting that with modern multimodality therapy outcome may not be as poor as was previously thought . The previously observed poor prognosis was thought to be partly explained by a tendency for pregnant patients to present at a more advanced stage than non-pregnant women, possibly reflecting delay in diagnosis. However, late stage at diagnosis may not be the only explanation for the poor prognosis observed; it has been proposed that pregnancy itself may be an independent predictor of worse survival. Many of the earlier studies that documented poor survival rates unsuccessful to adjust for age, stage, pathological features, treatment effect and other established prognostic variables. Where case–control studies have been carried out, most suggest little difference in survival between pregnancy-associated and non-pregnancy associated breast cancer [50].

CONCLUSION

The growing incidence of breast cancer at younger ages and the need for a comprehensive approach to managing pregnant women diagnosed with breast cancer are important considerations. These women require careful attention to their individual needs and the potential risks to their unborn child. Currently, there is limited information available on the long-term risks associated with surgery, radiation, and systemic anticancer therapies. The stage of pregnancy can greatly impact management, with serious concerns for fetal harm, particularly during the first trimester, and limited options for investigations and treatments. However, recent findings on the short-term safety of surgery and chemotherapy administered during the second and third trimesters are reassuring. It is crucial to ensure the best possible outcome for both mother and child that a multidisciplinary team, including breast surgeons, medical and clinical oncologists, obstetricians, neonatologists, and specialized nursing staff, makes the management decisions.

AUTHOR CONTRIBUTION

CSC, KPG and JPA Conceived the idea, designed, wrote, and edited the review.

ACKNOWLEDGMENTS

Authors are thankful to Dr. Rajendra Gode College Pharmacy, Malkapur, for providing adequate facilities and unqualified support to carry out this review.

CONFLICT OF INTEREST

There are no conflicts of interest.

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