Normal Baby Born in Spontaneous Preterm Delivery in Patient with Pregnancy-Associated Breast Cancer: Case Report

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Abstract
Introduction:Breast cancer during pregnancy is rare, with 2.3 to 40 cases per 100,000 women. It is typically defined as cancer diagnosed during pregnancy or within a year post-delivery. While some argue pregnancy accelerates cancer progression, others see no effect or potential protective benefits. Treating pregnant patients requires balancing the mother's cancer stage and fetal health, as surgery and chemotherapy pose risks like teratogenesis or miscarriage. Timing therapy appropriately remains a major challenge.
Case Presentation: A patient, P4A0, presented with spontaneous preterm delivery and a prior history of a total left modified radical mastectomy due to left tubular breast carcinoma (T1aN1M0). She had undergone six cycles of chemotherapy with Cyclophosphamide (876 mg/m²), Epirubicin (80 mg/m²), and 5-Fluorouracil (Lipiforin) (759 mg/m²). Despite receiving chemotherapy, the patient discovered she was pregnant at 33 weeks of gestation. She arrived at the Obstetrics and Gynecology Emergency Department of Prof. Dr. Margono Soekarjo General Hospital during the second stage of labor. A female infant was born, weighing 1950 grams and measuring 44 cm in length, with no detectable congenital anomalies. The patient experienced no complications after delivery and was discharged in stable condition.
Conclusion: The main challenge is deciding when to start chemotherapy in pregnant patients, considering risks like miscarriage and teratogenic effects. More research is needed to develop safe chemotherapy guidelines that balance maternal treatment and fetal health.

Keywords: Breast carcinoma, Chemotherapy, Pregnancy, Teratogenous

Bayi Normal dengan Partus Prematurus Spontan pada Ibu Hamil dengan Kanker Payudara: Sebuah Laporan Kasus

Abstrak
Pendahuluan: Kanker payudara selama kehamilan jarang terjadi, dengan 2,3 hingga 40 kasus per 100.000 wanita. Kondisi ini biasanya didefinisikan sebagai kanker yang didiagnosis selama kehamilan atau dalam satu tahun setelah melahirkan. Beberapa ahli berpendapat bahwa kehamilan dapat mempercepat perkembangan kanker, sementara yang lain berpendapat bahwa kehamilan tidak memiliki pengaruh signifikan atau bahkan memberikan manfaat perlindungan tertentu. Penanganan pasien hamil memerlukan keseimbangan antara stadium kanker ibu dan kesehatan janin, karena operasi dan kemoterapi membawa risiko seperti teratogen atau keguguran. Penentuan waktu terapi yang tepat tetap menjadi tantangan utama.
Presentasi Kasus: Seorang pasien, P4A0, datang dengan persalinan prematur spontan dan riwayat sebelumnya menjalani mastektomi radikal modifikasi total di sisi kiri karena karsinoma payudara tubular kiri (T1aN1M0). Pasien telah menjalani enam siklus kemoterapi dengan Cyclophosphamide (876 mg/m²), Epirubicin (80 mg/m²), dan 5-Fluorouracil (Lipiforin) (759 mg/m²). Meskipun menjalani kemoterapi, pasien baru mengetahui bahwa dirinya hamil pada usia kehamilan 33 minggu. Pasien tiba di IGD Obstetri dan Ginekologi RSUD Prof. Dr. Margono Soekarjo dalam tahap kedua persalinan. Seorang bayi perempuan lahir dengan berat badan 1950 gr dan panjang 44 cm, tanpa kelainan bawaan yang terdeteksi. Pasien tidak mengalami komplikasi setelah persalinan dan dipulangkan dalam kondisi stabil.
Kesimpulan: Tantangan utama adalah menentukan waktu yang tepat untuk memulai kemoterapi pada pasien hamil, dengan mempertimbangkan risiko seperti keguguran dan efek teratogenik. Penelitian lebih lanjut diperlukan untuk mengembangkan pedoman kemoterapi yang aman, yang dapat menyeimbangkan untuk Kesehatan ibu dan janin.

Kata kunci: Kanker payudara, Kehamilan, Kemoterapi, Teratogen

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Introduction

Breast cancer typically affects young women, including expectant mothers. The incidence is approximately 1 in 15,000 births out of 11.8 million. Breast cancer during pregnancy is rare, with an occurrence rate of about 2.3 to 40 cases per 100,000 women.[1,2] A family history of breast cancer, particularly with BRCA1 and BRCA2 gene mutations, has been associated with an increased risk of developing malignant breast cancer during pregnancy. Multiple studies have shown that pregnant women carrying BRCA1 or BRCA2 mutations may also have a higher likelihood of experiencing miscarriage.[3] According to Jernström's research, breastfeeding has been shown to provide protection against breast cancer associated with BRCA1 gene mutations but not with BRCA2 gene mutations.[2] Low expression of hormone receptors during pregnancy has been associated with more aggressive subtypes of breast cancer, such as triple-negative and HER2-positive cancers. Various factors related to tumor biology, including mismatch repair deficiency mutational signatures, elevated levels of non-silent mutations, mutations in mucin family genes, increased stromal cell numbers, and high levels of tumor-infiltrating lymphocytes (TILs), have all been linked to pregnancy. These factors may influence the development and progression of breast cancer during pregnancy.[4]

According to multiple genomic studies, pregnancy-associated breast cancer (PABC) has been linked to abnormal expression of several oncogenes (MYC, SRC, FOS), tumor suppressor genes (TP53, PTEN, CAV1), apoptosis regulators (PDCD4, BCL2, BIRC5), transcription regulators (JUN, KLF1, SP110), genes associated with DNA repair mechanisms (SIG20, BRCA1/2, FEN1), as well as factors affecting cell proliferation (AURKA, MK167) and the immunological response (PD-1, PD-L1). These alterations may contribute to the unique characteristics and progression of breast cancer during pregnancy.[5] Breast cancer diagnosed within nine months prior to delivery or up to one year following delivery is referred to as pregnancy-associated breast cancer (PABC).[4,6] Currently, there is no proven treatment specifically for breast cancer during pregnancy. Various therapeutic approaches have been employed to manage pregnancy-associated breast cancer (PABC), considering both fetal development and the severity of the breast cancer.[5] This case report discusses a patient who was undiagnosed with pregnancy while receiving chemotherapy for breast cancer. It explores the selection of the most appropriate treatment options for breast cancer during pregnancy and the potential negative implications or side effects on fetal outcomes.

Case Report

On 4th January 2023, the Obstetrics and Gynecology Emergency Room at Prof. Dr. Margono Soekarjo General Hospital received a 32-year-old woman, G1P0A0, who was 8 months pregnant. She reported experiencing heartburn that had become more frequent and intense over the 12 hours prior to admission. Additionally, she had noted mucus mixed with blood for the past 4 hours and profuse discharge from the birth canal 2 hours before arriving at the hospital. The fluid was colorless and odorless, and the patient did not present with a fever. The mother reported still feeling fetal movements. She mentioned having experienced odorless and non-itchy vaginal discharge for the past week. The patient was diagnosed with breast cancer in April 2022 and subsequently underwent surgery for a left mastectomy, followed by six cycles of chemotherapy consisting of Cyclophosphamide (876 mg/m^2), Epirubicin (80 mg/m^2), and 5-Fluorouracil (Lipiforin) (759 mg/m^2), which she completed in October

2022.

During chemotherapy, the patient experienced irregular menstrual cycles, nausea, and vomiting, which could be attributed to chemotherapy side effects. The patient did not exhibit typical pregnancy symptoms, suggesting a cryptic pregnancy. However, the patient noticed an increasing abdominal size, prompting an ultrasound evaluation. The patient was unaware of her pregnancy until she was 33 weeks along, when a home pregnancy test yielded a positive result, subsequently confirmed by an obstetrics and gynecology specialist. A family history of cancer was noted, specifically involving her grandmother. The patient denied any history of high blood pressure before or during pregnancy, as well as any chronic diseases such as diabetes mellitus, asthma, or heart disease. She has received three doses of the Pfizer COVID-19 vaccine. Due to her complaints, the patient presented to the Obstetrics and Gynecology Emergency Room at Prof. Dr. Margono Soekarjo General Hospital. On May 5, 2022, the patient underwent an ultrasound of the left breast, which indicated the presence of a fibroadenoma at the 12 o'clock and 1-2 o'clock positions. No masses were observed in the right breast tissue, and there was no evidence of bilateral axillary lymphadenopathy. On May 13, 2022, an anatomical pathology examination was performed, revealing that the epithelial tumor tissue had a tubular structure with atypical polymorphous tumor cells, scant cytoplasm, hyperchromatic nuclei, and mitotic figures. This led to the diagnosis of tubular carcinoma of the left mammary gland. Consequently, a modified left radical mastectomy was performed on May 28, 2022. On June 2, 2022, an anatomical pathology examination was conducted on a sample from the axillary lymph nodes. The microscopic analysis showed sinusoids and dilated blood vessels filled with inflammatory cells, lymphocytes, and histiocytes, accompanied by hyperplastic lymphoid follicles, with no signs of malignancy. The conclusion for the axillary lymph nodes was reactive chronic lymphadenitis.

The patient received combination chemotherapy consisting of cyclophosphamide (876 mg/m^2), epirubicin (80 mg/m^2), and 5-Fluorouracil (Lipiforin) (759 mg/m^2). This treatment was administered over six cycles on June 22, July 13, August 3, August 24, September 14, and the final cycle on October 5, 2022. On July 23, 2022, an echocardiography examination was performed, yielding results that indicated normal heart chamber dimensions, good contractility, and an ejection fraction of 59%. The diastolic function was normal, with normokinetic global heart wall movement. Right ventricular contractility, assessed by TAPSE, measured 27 mm. The examination of the aortic heart valves was within normal limits; however, mild mitral regurgitation and mild tricuspid regurgitation were noted, with a maximum pressure gradient (TR max PG) of 26.78 mmHg for the tricuspid valve. The pulmonary valve was also within normal limits. The overall conclusion from the echocardiography examination indicated mild tricuspid regurgitation (TR).

After four cycles of chemotherapy, the patient underwent a follow-up echocardiography examination on August 31, 2022. The results showed normal heart chamber dimensions, good contractility, and an ejection fraction of 59%, consistent with previous findings. Diastolic function remained normal, with normokinetic global heart wall movement. Right ventricular contractility, as measured by TAPSE, was noted to be 23 mm. The aortic heart valve examination was within normal limits, while the mitral valve displayed trivial regurgitation. Mild tricuspid regurgitation was again observed, with a maximum pressure gradient (TR max PG) of 23.09 mmHg, and the pulmonary valve remained

within normal limits. The conclusion from this echocardiography examination was mild tricuspid regurgitation (TR). On 10th November 2022, the patient received the first antenatal care for her pregnancy from an obstetrics and gynecology specialist, during which an ultrasound was performed. The results indicated a single live fetus in the intrauterine space, with a head presentation consistent with 33 weeks of gestation. The measurements recorded included a biparietal diameter (BPD) of 88.2 mm, an abdominal circumference of 263 mm, and a femur length of 66 mm, with an estimated fetal weight of 1900 grams. The placenta was located at the fundus and was graded II-III, while the amniotic fluid volume was adequate. Based on the ultrasonography results, the estimated date of the last menstrual period (LMP) was April 15, 2022, with an estimated due date (EDD) of January 22, 2023.

On November 14, 2022, based on the clinical condition, pregnancy status, and chemotherapy history, the patient was diagnosed with pregnancy-associated breast cancer (PABC) by the Oncology Surgery team. On Wednesday, January 4, 2023, the patient arrived during the second stage of labor. An internal examination revealed that the vulva and vagina were within normal limits, the portio was not palpable, and cervical dilatation was complete. The amniotic fluid

Table 1 Laboratory results for Mrs. R on Thursday January 5, 2023, at 02.29 AM

Item	January 5, 2023	Unit	Normal value
Hemoglobin	12.7	g/dl	10.9-14.9
Hematocrit	39	%	34-45
Leucocyte	13580	/mm3	4790-11340
Thrombocyte	263.000	/uL	216.000-451.000
PT	12.9	second	9.9-11.8
APTT	31.5	second	25-31.3
LDH	252	U/L	<247
SGOT	10	U/L	<31
SGPT	25	U/L	<31
Albumin	4.04	g/dl	3.5-5.2
Random blood glucose	78	mg/dl	80-139
Ureum	18.19	mg/dl	15-40
Creatinine	0.48	mg/dl	0.5-1
Natrium	135	mEq/L	134-145
Kalium	4.1	mEq/L	3.4-4.5
Calcium	9.8	mEq/L	8.6-10.3
Chloride	105	mEq/L	96-108
HbsAg	Non-reactive	-	Non-reactive
Swab antigen	Non-reactive	-	Non-reactive
Urinalysis			
Leukocyte	2-4	/lpb	Negative/lpb
Bacteria	Negative	/lpb	Negative/lpb
Erythrocyte	5+/250	RBC/ul	Negative
Keton	Negative	mg/dl	Negative
Protein	2+/75	mg/dl	Negative

Table 2. Laboratory results for Mrs. R's Baby on Thursday January 5, 2023 at 06.53 AM

Item	January 5th 2023	Unit	Normal Value
Hemoglobin	19.8	g/dl	12.7-18.7
Hematocrit	59	%	42-62
Leucocyte	9870	/mm3	5000-21.000
Thrombocyte	263.000	/uL	217.000-497.000
MCV	12.9	fL	94-150
MCH	31.5	pg	29-45
MCHC	252	g/dl	24-36
Random blood glucose	79	mg/dl	80-139

was clear, and the fetal head was at station 3+, positioned in the right occiput anterior. The patient was encouraged to bear down. At 12:40 AM on January 5, 2023, a baby girl was delivered, weighing 1950 grams, measuring 44 cm in length, with a head circumference of 31 cm and a chest circumference of 31 cm. The infant had an APGAR score of 6/7/8, and no congenital abnormalities were detected. Following the delivery, active management of the third stage of labor was performed, and the placenta was completely delivered at 12:50 AM. The patient was provided with a Copper T-380 IUD contraceptive device, and postpartum observation was conducted for 2 hours. No postpartum complications were noted, and the patient was subsequently moved for further observation in the obstetric ward. The fetal outcome for Mrs. R was the birth of a baby girl on January 5, 2023, at 12:40 AM. At birth, the infant exhibited a pulse rate of 131 beats per minute, a respiratory rate of 41 breaths per minute, a body temperature of 36.7°C, and an oxygen saturation level of 97%. The infant was placed on nasal continuous positive airway pressure (NCPAP) with a positive end-expiratory pressure (PEEP) of 7 mmHg and a fraction of inspired oxygen (FiO2) of 30%. The baby cried vigorously, with mild chest retraction observed. Cyanosis resolved with CPAP oxygen, and the FiO2 was reduced to 25% while maintaining PEEP at 7 mmHg. The infant demonstrated a strong suction reflex with no signs of vomiting, and urination was normal. The baby was monitored in an incubator for 2 days, during which her condition improved. She was diagnosed as a preterm neonate with low birth weight, small for gestational age, following spontaneous birth, and at risk for neonatal infection. The infant was discharged home after 3 days of observation in the perinatology room.

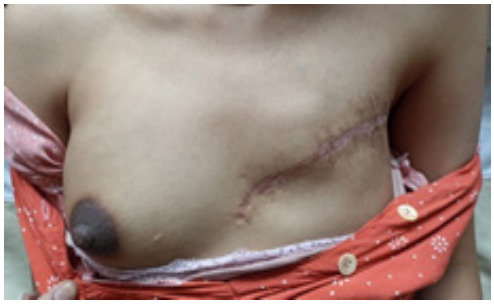

Figure 1 Clinical Picture of Mrs. R (23 yo) Post Left Radical Masmectomy

Figure 2 Clinical picture of Mrs. R's Baby (3 days old)

Discussion

In the current case of Pregnancy-Associated Breast Cancer (PABC), a patient diagnosed with breast cancer during pregnancy underwent chemotherapy. The treatment led to irregular menstruation and other side effects commonly associated with chemotherapy, such as nausea and vomiting that overlapped with the patient's pregnancy sign but were misinterpreted as chemotherapy-related effects.[7,8] It was only when the patient noticed increasing abdominal distention during an ultrasound examination, revealing the pregnancy and confirming a cryptic pregnancy.[9,10] Similar cases reported by Smith et al., in the Journal of Clinical Oncology, describe women with PABC who did not recognize their pregnancy due to the suppression of menstrual cycles and the non-specific symptoms of both conditions.[11] Currently, guidelines for the management of breast cancer in pregnancy (PABC) are still under discussion. In determining treatment, it is essential to consider the staging of breast cancer, which includes factors such as tumor size, high nuclear grade, lymph node involvement, lymphovascular invasion, and hormone receptor-negative status. This is crucial to avoid delaying therapy. Additionally, the selection of chemotherapy drugs must prioritize those that are safe for fetal growth and development while also considering the potential side effects on maternal fertility.[3] Delays in diagnosis, suboptimal staging, and inadequate treatment can significantly worsen the prognosis of breast cancer in pregnancy.[5] When administering chemotherapy regimens, it is important to consider three physiological changes in pregnant women: alterations in glomerular filtration rate (GFR), changes in albumin concentration, and gestational age.[4,5] Several treatment options for pregnancy-associated breast cancer (PABC) include modified or radical mastectomy, chemotherapy, targeted therapy, immunotherapy, radiation therapy, and supportive therapy.[5,12,13]

Operative mastectomy is a definitive treatment option that can be performed during all trimesters of pregnancy with minimal risk to the fetus.[14] Radical mastectomy is a treatment option that must be considered, as epidemiological data indicate that pregnancy-associated breast cancer (PABC) often presents with a high incidence of axillary metastases. When the tumor is detected early, sentinel lymph node biopsy (SLNB) may be considered. While this approach remains controversial, several studies have reported its success and safety.[13,15]

Systemic chemotherapy is contraindicated during the first trimester due to the high risk of fetal malformation.[4] Research indicates that the prevalence of congenital abnormalities associated with chemotherapy administration in the first trimester is 14%. This risk decreases to 11% in the second trimester and further reduces in the third trimester.[13,15] During the first trimester, exposure to cytotoxic agents can disrupt fetal organogenesis, thereby increasing the risk of miscarriage and congenital abnormalities.[5] Several chemotherapy regimens, including trastuzumab, tamoxifen, and other endocrine agents, should be avoided during pregnancy due to their potential for fetal toxicity.[5,6] The teratogenic effects of medications are influenced by several factors, including the duration of exposure, dosage, protein binding, and placental transfer.[16] Anthracyclines, cyclophosphamide, and taxanes are standard adjuvant and neoadjuvant therapies recommended for both non-pregnant women and pregnant women during the second and third trimesters.[14] A retrospective study was conducted on a cohort of 75 pregnant women with breast cancer who were treated in the second and third trimesters using 5-fluorouracil, doxorubicin, and cyclophosphamide. This cohort was compared to a group of non-pregnant women

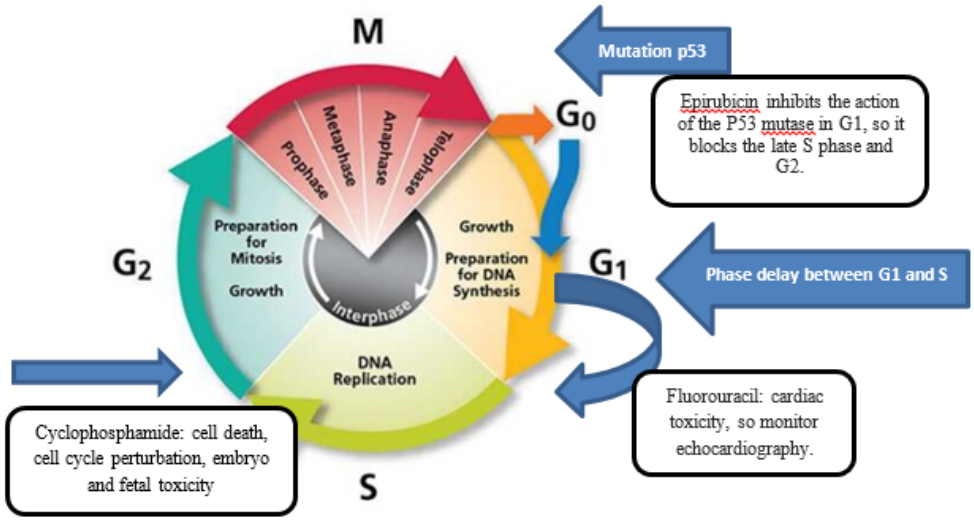

Figure 3 Cycle Cell and Chemotherapy Regimen Interventions of Cyclophosphamide-Epirubicin-5FU[4]

matched by age, cancer stage, and year of diagnosis. The results showed a significant improvement in disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) in pregnant women.[5] Cyclophosphamide is known to be safe for use in pregnant women. However, the potential toxic effects of platinum-based derivatives may lead to the risk of small gestational age.[5] In another study, cyclophosphamide was found to significantly reduce serum levels of anti-Müllerian hormone and inhibin B immediately after chemotherapy in breast cancer patients.[17]

Research by Loibl et al. involving 197 women with pregnancy-associated breast cancer (PABC) found that administering a combination regimen of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) after 24 weeks of gestational age resulted in obstetric complications in 17% of cases, congenital malformations in 4%, and spontaneous abortion or stillbirth in 1%. The average delivery occurred at 37 weeks of gestation.[5,18] Administering epirubicin (35 mg/m²) to women at 20 weeks of gestation as an adjuvant therapy for breast cancer shows that epirubicin levels are nearly undetectable in fetal circulation.[16] A systematic review of the use of platinum salts indicates that cisplatin has a lower level of toxicity compared to other platinum-based agents.[5,16]

Endocrine therapy is contraindicated in pregnant women. Animal studies have shown that tamoxifen can cause teratogenic effects on the genitourinary tract, leading to major malformations such as ambiguous genitalia and oculoauriculovertebral dysplasia in 18% of cases. It may also result in minor malformations, including preauricular skin tags and severe hypermetropia, in 3% of cases.[5] Tamoxifen has a complex action mechanism that includes estrogenic effects on tissues such as the endometrium and anti-estrogenic activities in the breast. Women undergoing tamoxifen therapy should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcoma, as well as potential side effects such as irregular vaginal bleeding and vaginal discharge.[19]

Trastuzumab, an IgG monoclonal antibody that targets the HER2 oncogene, and tamoxifen, a selective estrogen receptor modulator, have been associated with a 53% decrease in amniotic fluid volume, leading to

oligohydramnios. This condition increases the risk of premature labor, morbidity, and mortality in the fetus, making this regimen contraindicated for use in pregnant women.[4,14] Targeted therapy and immunotherapy can lead to teratogenic effects, including malformations due to angiogenesis inhibition, as well as miscarriage, bone damage, and impaired fetal growth. These treatments may disrupt the normal development of the placenta and fetus.[20]

The administration of chemotherapy during the second and third trimesters is associated with an increased risk of intrauterine growth restriction (IUGR) and low birth weight, as well as a higher incidence of preterm labor.[20] Administering early adjuvant chemotherapy within three weeks before surgery has been shown to improve outcomes for patients with hormone receptor-negative tumors. If chemotherapy is administered during pregnancy, routine fetal monitoring through morphometric ultrasound and umbilical artery Doppler evaluations is essential. Furthermore, if chemotherapy must be given at a gestational age of less than 12 weeks from the last menstrual period (LMP), termination of the pregnancy should be considered.[5,15,16] Premature labor is defined as labor that occurs before 37 weeks of pregnancy. Early premature labor is characterized by delivery at less than 32 weeks of gestation, while late premature labor occurs between 32 and 36 weeks. Either early or late premature labor carries a high risk of complications, including unstable body temperature, respiratory distress, apnea, hypoglycemia, seizures, jaundice, digestive problems, and periventricular leukomalacia, often requiring intensive care.[5,14] Delivery is recommended within three weeks of the last administration of chemotherapy to minimize the risk of neonatal immunosuppression. This timeframe allows the placenta to metabolize and excrete the chemotherapy agents from the fetus effectively.[21,22] In patients with

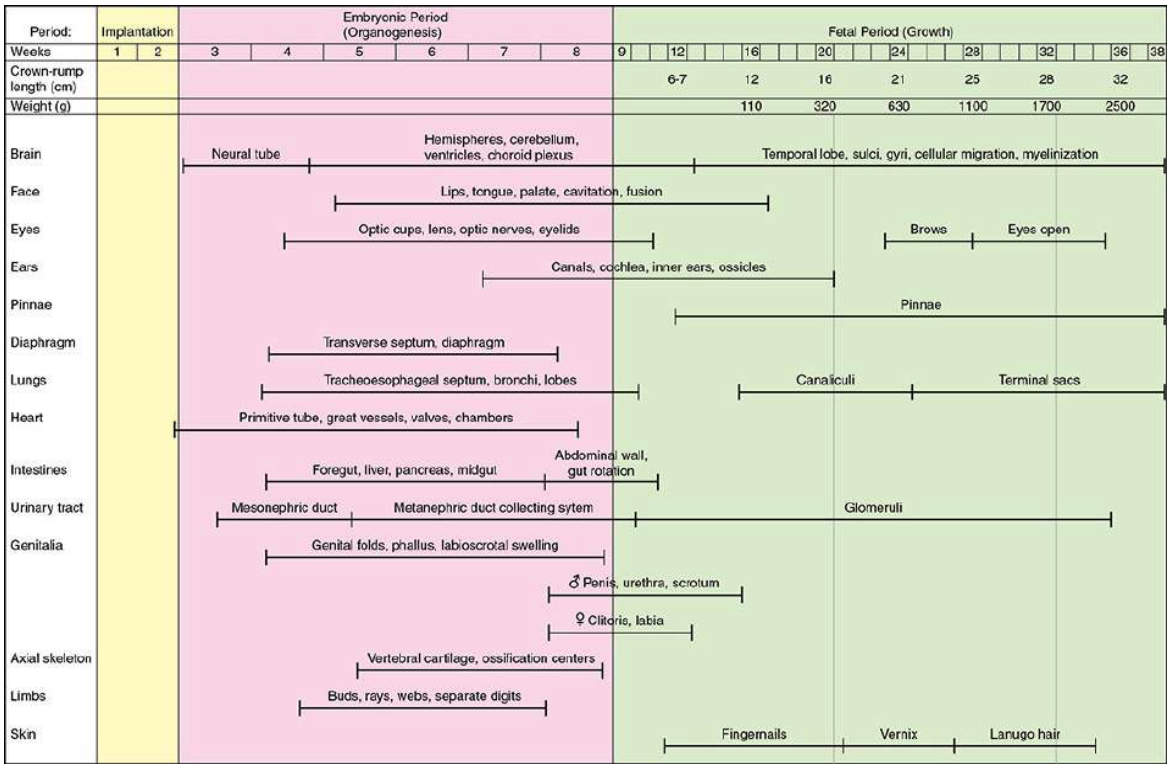

Figure 4 Embryofetal Development Based on Gestational Age[2]

pregnancy-associated breast cancer (PABC) undergoing chemotherapy, there is no indication for a cesarean section unless there are specific obstetric reasons.[14]

For optimal management of patients with pregnancy-associated breast cancer (PABC) undergoing chemotherapy with doxorubicin or epirubicin regimens, it is recommended that echocardiography be performed. This assessment helps detect the risk of left ventricular dysfunction or cardiomyopathy by evaluating the left ventricular ejection fraction or fractional shortening.[4] The impact of reproductive age is a key concern due to chemotherapy-induced gonadotoxicity, which can lead to permanent amenorrhea (the absence of menstruation), loss of germ cells, temporary amenorrhea, irregular menstrual cycles, and subfertility. Alkylating agents, such as cyclophosphamide, are well-known for their gonadotoxic effects. In particular, regimens that include cyclophosphamide, methotrexate, and 5-fluorouracil are associated with a higher incidence of amenorrhea compared to anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide. Recent studies indicate that taxanes have lower gonadotoxic effects.[4,22] Taxanes are substrates of P-glycoprotein, which is expressed in the maternal compartment of the placenta. P-glycoprotein plays a crucial role in protecting the fetus from xenobiotics and reducing the risk of transplacental transfer. In a review of 40 pregnant women treated with taxanes, there were no reports of intrauterine fetal death (IUFD) or congenital abnormalities. Additionally, taxanes are metabolized by cytochrome P450, whose activity increases by 50-100% during the third trimester. This increase results in a shorter half-life and enhanced clearance of the drugs, which helps reduce their toxicity profile during pregnancy.[13]

Conclusion

Pregnancy-associated breast cancer (PABC) is a diagnosis that is rarely encountered in clinical practice, leading to ongoing debate about its management. Several treatment modalities are recommended for PABC. These include radical operative management or modified mastectomy, both of which can be performed during any trimester of pregnancy. Chemotherapy regimens are recommended for administration during the second and third trimesters, as treatment during the first trimester may interfere with fetal growth and development. Targeted therapy and immunotherapy are considered teratogenic and should be administered only after childbirth, particularly when the mother is not exclusively breastfeeding, as these drugs may be excreted in breast milk. Additionally, supportive therapies can be considered to mitigate the side effects associated with chemotherapy. The primary goal in managing PABC is to determine the safest approach for both the mother and the fetus. If termination of the pregnancy is considered, careful consideration of all factors is essential.

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Conflict of Interest

The author confirms that the content of this case report has no conflict of interest.

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