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Chemotherapy during First Trimester Pregnancy Leading to Fetal Malformation: A Case Report with Review of Literature

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Abstract

Pregnancy coexisting with the diagnosis of malignancy is rare. It poses a major management dilemma to the oncologist where adequate oncology outcomes need to be weighed against the fetal well-being. Use of chemotherapy during pregnancy is determined by the type of malignancy, stage, gestational age, chemotherapy agent, and the risk of placental transfer.

A 33-year-old female patient presented with a gradually progressive breast lump. After adequate workup, the patient was diagnosed with infiltrating duct carcinoma left breast (T3N0M1), with liver metastases and triple-negative breast cancer. Subsequently, the patient received detailed counseling about treatment, prognosis, and contraceptive use to avoid conception and was started on palliative chemotherapy with doxorubicin, cyclophosphamide, and docetaxel. Radiology was performed for response assessment after eight cycles of chemotherapy. It demonstrated an accidental pregnancy of 22 weeks and 4 days gestation with major malformations including corpus callosum agenesis with ventriculomegaly, skeletal dysplasia including hypoplastic upper limbs, and absent radius in one arm. The patient underwent medical termination of pregnancy and further oncology treatment as per response and standard treatment guidelines.

Chemotherapy should be strictly avoided for pregnant patients in the first trimester given its teratogenic effects, leading to major fetal malformations. The use of multiple drugs makes it difficult to establish a causal role of a particular chemotherapeutic agent with specific malformation. Adequate anticonception counseling and pregnancy tests should be offered to women diagnosed with cancer who are in the reproductive age group, prior to starting chemotherapy.

Keywords

- pregnancy
- chemotherapy
- fetal malformations
- teratogenic
- corpus-callosum agenesis
- skeletal dysplasia
- case report

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Introduction

Pregnancy-associated cancers are those which are diagnosed during pregnancy or within a year after delivery.[1] The incidence of pregnancy-associated cancer is approximately 1 in 1,000 pregnancies.[2] With increasing maternal childbearing age coupled with onset of cancer in younger population, the incidence of pregnancy-associated cancers is expected to increase.[3] Breast cancer, cervical cancer, lymphoma, ovarian cancer, leukemia, and melanoma are the most frequently occurring cancers in pregnancy.[1,2] Current data on the teratogenic effects of chemotherapy is limited. We present here a case of an accidental pregnancy, conceived while on chemotherapy in a young patient with metastatic breast cancer. We report the teratogenic effects of chemotherapy on the fetus during the first trimester and present some rare fetal malformations like corpus callosum agenesis due to chemotherapy. This case report adds considerable data to the limited evidence available.

Case Report

A 33-year old female patient, presented with a history of painless breast lump for the past 6 months, gradually increasing in size. There were no preexisting comorbidities, the lady was gravida one and para one, had a healthy child who was 6 months old, and was breastfeeding. Patient had last menstrual period 1 week before reporting to the institute. There was no family history of cancer.

On examination, there was a 7×4 cm breast lump in the upper outer quadrant of the right breast, no clinically palpable lymph nodes. Contrast-enhanced computed tomography (CT) of chest and abdomen confirmed the local findings with multiple hypodense lesions in both lobes of the liver. The largest lesion had dimensions of 2.2×2.1 cm in segment VII. The patient was advised positron emission tomography (PET) scan but could not afford it. Biopsy from the breast lump was suggestive of infiltrating duct carcinoma, grade 2, and fine-needle aspiration cytology of liver lesion was suggestive of metastatic carcinoma. The presence of all estrogen receptor (ER), progesterone receptor, and HER2 were negative. Hence, to summarize, we had a 33-year-old female (cT3N0M1), that is, triple-negative breast cancer. The patient and family were explained about the nature and prognosis of the disease. The patient was counseled not to breastfeed the child after the start of chemotherapy. The patient and the spouse were also counseled about the need to use contraception and avoid conceiving till further discussion.

Patient was planned for chemotherapy and received four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2, every 3 weeks) followed by four cycles of docetaxel (75 mg/m^2, every 3 weeks). After completion of eight cycles of chemotherapy with good response at the local tumor site, patient was asked to get an ultrasound (USG) of the abdomen for response assessment for liver lesions.

During the USG, it was revealed that the patient was pregnant. There was a single live intrauterine fetus of 22 weeks and 4 days gestation. There were major malformations including

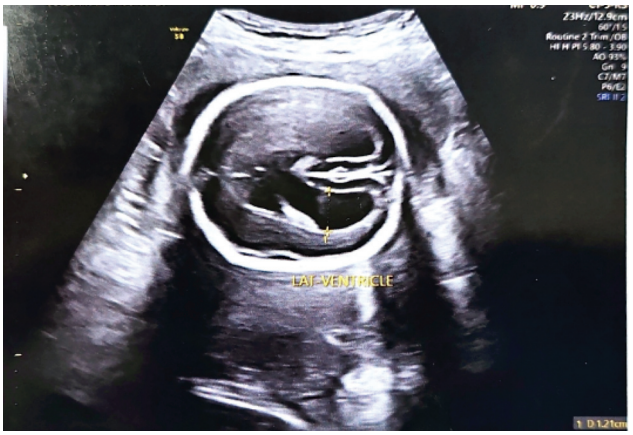

Fig. 1 (Lateral ventricle): Dilatation of lateral ventricle and nonvisualization of cavum septum pellucidum.

corpus callosum agenesis with absent cavum septum pellucidum, parallel lateral ventricles were seen showing communication in their anterior horns, dilatation of the lateral ventricles was seen with atrial diameter of 12 mm (►**Fig. 1**), radius and ulna of left upper limb appeared hypoplastic, and radius of right upper limb appeared absent with hypoplastic ulna (►**Fig. 2**). Patient was informed and counseled about the findings and wanted to discontinue the pregnancy. Patient was referred to the gynecology department for the same and a medical termination of pregnancy was performed immediately. Subsequently, on disease progression, patient was put on second-line chemotherapy with tab capecitabine. The patient has received eight cycles of single-agent capecitabine, has stable disease, 1 month since the last cycle, and is on follow-up at present.

Discussion

Diagnosis of malignancy with pregnancy is a management dilemma. The physicians have to consider the benefits associated with oncology treatment for the patient against the risk of fetal well-being.[4] Treatment has to be individualized based on the type of cancer, stage at presentation, gestational age, and all available treatment options.[2,5] In a study, the

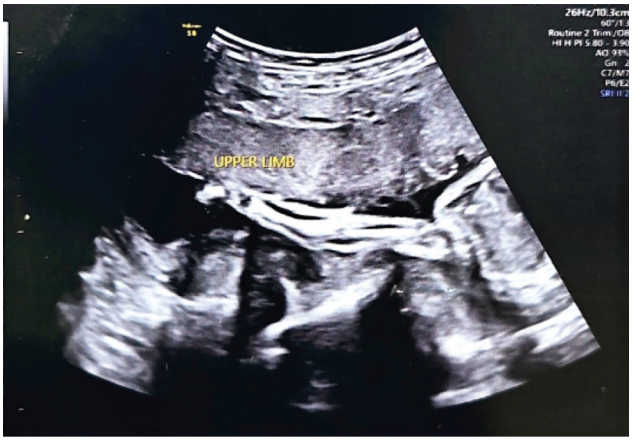

Fig. 2 (Right upper limb): Ulna appears to be hypoplastic with nonvisualization of radius.

median age (range) at diagnosis of cancer during pregnancy was 33 (range: 14–48) years,[6] which is similar to the age of our patient. It is recommended that cancer treatment during pregnancy should be similar to the standard treatment guidelines for nonpregnant patients.[1,2]

Maternal survival has not shown improvement with termination of pregnancy, and is generally not considered unless the malignancy presents in advanced stages or is aggressive in nature where treatment delay is not advisable.[7] In view of the morbidities associated with preterm children, start of oncological treatment after preterm induction of delivery is discouraged.[1,4]

A multidisciplinary approach is required for pregnancy-associated cancers. The team should include radiologists, oncologists (medical, surgical, radiation), hematologists, obstetricians, gynecologists, neonatologists, social workers, and psychologists.[2,4] Informed decisions should be taken by the patient and the family, after being provided with the limited available evidence about the fetal exposure to cancer drugs and other diagnostic and treatment modalities.[2,8]

Nearly 50% of pregnancies are not planned, and exposure to the teratogens has already occurred by the time the pregnancy is confirmed.[9] This is similar to our case where the pregnancy was unplanned and neither the patient nor the physician was aware of the pregnancy during the chemotherapy administration. Hence, women in the fertile age, who are diagnosed with cancer, should undergo counseling about the contraceptive use and to avoid pregnancy,[10] which was comprehensively done in our patient as well.

Most of the presenting signs and symptoms, of pregnancy, like fatigue, breast changes, anemia, nausea, vomiting, amenorrhea, etc., may mimic chemotherapy-induced toxicity, which leads to delay in diagnosis of pregnancy during chemotherapy, similar to our patient. As a result of these, diagnosis of cancer in pregnancy or pregnancy in cancer becomes challenging.[2,10] The pregnancy-associated increase in breast density makes breast examination more difficult, leading to further delays in detection. Breast cancers in pregnancy are usually poorly differentiated, 50 to 72% are ER negative and 30% cases are HER2 positive.[9]

Following are the modalities and treatments used to detect and treat pregnancies, respectively, in a pregnant patient with breast cancer.

Diagnostic Imaging

Ionizing imaging for diagnostic purposes should be avoided to limit the fetal dose of radiation to less than 100 mGy.[11] Nonionizing imaging like USG and magnetic resonance imaging are considered safe, but contrast medium gadolinium should be avoided as it may cross the placenta. 18-Fluorodeoxyglucose-PET/CT is associated with approximately 50 mGy radiation exposure to the fetus and is hence not recommended. Mammography of the breast can be done with required shielding.[12]

Surgery

Though surgery can be safely performed in all periods of pregnancy, but to reduce the risks of abortion, early second trimester is the preferred time for surgery. Major surgeries in the abdomen or pelvis are more commonly associated with preterm delivery and fetal distress, secondary to enlarged uterus and increased blood supply.[2,4,7] Laparoscopic interventions during pregnancy are considered safe when time for surgery can be reduced to 90 to 120 minutes while simultaneously maintaining a low intra-abdominal pressure (10–13 mm Hg).[7]

For patients with breast cancer, mastectomy is preferred, and breast conservative surgery can be considered, if adjuvant radiation can be given after the delivery of the baby. Sentinel lymph node biopsy can be performed, if required, but should be avoided in patients with < 30 weeks of gestation. Blue dye is contraindicated during pregnancy while Tc-99 is considered relatively safe.[4,13]

Radiation Therapy

Pelvic irradiation is absolutely contraindicated during pregnancy. Nonpelvic radiotherapy can be delivered in the first trimester, since the uterus is away from the irradiation field.[14] Radiation during pregnancy should be delivered with the aim to not exceed the total cumulative fetal dose of 100 mGy. Individualized abdominal shielding can be used to meet the radiation constraints.[15]

Physiology of Pregnancy and Transplacental Transfer of Chemotherapy Drugs

Physiological changes during pregnancy in the liver, kidney, and gastrointestinal tract influence the pharmacokinetics, metabolism, and excretion of anticancer drugs, which might decrease their efficacy.[9,10] Additionally, there is an increase in the blood volume and water content of the body, which leads to dilution of the drugs.[16]

Chemotherapy drugs are transferred across the placenta by passive diffusion. Majority of anticancer drugs are of low molecular weight (< 400 kDa), uncharged, and easily cross the placenta.[17] However, despite this, the fetus usually tolerates the chemotherapy drugs well due to change in the maternal pharmacokinetics.[9,10] Besides, the physiological changes during pregnancy, some placental transporters like multidrug-resistant proteins further reduce the drug concentrations in the fetal blood.[17]

Chemotherapy Administration

Chemotherapeutic drugs are considered to be teratogenic to the fetus. The risk to the fetus is determined by the gestational age during chemotherapy administration, chemotherapy agent used, dose of the drug, and the transplacental passage of the drug.[17] Chemotherapy administered during the early embryogenesis in the periconceptional period can lead to miscarriage. First trimester is the period of organogenesis, chemotherapy administered during this period can lead to major congenital malformations with risk of miscarriage and fetal death. For this reason, chemotherapy is contraindicated before 12 weeks of pregnancy.[1,6] The most commonly reported fetal malformations affect the limbs, palate, heart, neural tube, eyes, ears, and craniofacial structures.[6,9,18] This is similar to our patient where substantial cranial and limb abnormalities were diagnosed. Both single-

agent and multiagent chemotherapy increase the risk of fetal malformations by 7 to 17% and 25%, respectively.[6]

Chemotherapy administered in the second and third trimester of pregnancy can lead to intrauterine growth reduction (IUGR), prematurity, low birth weight, and stillbirth, but is generally not associated with increased risk of fetal malformations.[6,10] Irrespective of the physiological changes in pregnancy, chemotherapy doses are calculated using the weight of the mother during the particular period of pregnancy.[13,16] After the first trimester, several chemotherapy agents including taxanes, platinums, doxorubicin, cyclophosphamide etoposide, and bleomycin are considered to be relatively safe for administration.[9,10]

In a study, when chemotherapy was administered before and after the first trimester, it was associated with a 21.7 and 3.0% rate of major congenital malformations, respectively. The rate of minor malformations was comparable, irrespective of the gestational age of chemotherapy administration. In the same study, 58.6% women who received chemotherapy before 12 weeks of gestation were not even aware that they were pregnant.[6] This is similar to our case where the patient was not aware of the pregnancy and chemotherapy during the first trimester lead to major malformations in the fetus.

Teratogenicity of Chemotherapy Drugs

The risks of fetal malformations associated with individual chemotherapy agents are difficult to interpret due to the use of multiple drugs, including supportive molecules during chemotherapy administration. Patients with pregnancy-associated cancers should be adequately counseled about risk to fetus associated with chemotherapy administration.[4,19]

Anthracyclines

Anthracyclines have a low passage across the placenta due to their high molecular weight. Doxorubicin use is associated with reduced intrauterine growth, prematurity, and reversible fetal cardiotoxicity.[10,20]

Data on use of anthracyclines from a study shows that of the 25 cases exposed to doxorubicin, during the first trimester, three limb malformations occurred in fetuses. However, one of these mothers also received radiation with anthracycline and another received cytarabine with radiation.[20] Similar to above data, our patient who received doxorubicin also presented with limb malformations.

Taxanes

Based on the available data, taxanes are considered to be safe when administered after the first trimester of pregnancy. However, patients with breast cancer who are pregnant and need to be administered paclitaxel, weekly regimens should be used after the first trimester.[13]

Cyclophosphamide

In the first trimester of pregnancy, cyclophosphamide administration is associated with cyclophosphamide embryopathy. This includes a pattern of birth defects including growth deficiency, developmental delay, hydrocephaly, blepharophimosis, craniosynostosis, abnormal ears, flat nasal bridge, distal limb defects, oligodactyly, etc.[21] In the second and third trimester of pregnancy, cyclophosphamide is associated with a risk of IUGR, microcephaly, and neonatal pancytopenia, though congenital malformations are not reported.[6] This is similar to our patient who had limb defects with use of cyclophosphamide.

In a case of twins, reported in the literature, where cyclophosphamide was administered through the entire duration of pregnancy, one of the twins, the boy, had congenital anomalies including IUGR, esophageal atresia, right arm deformity, and abnormal inferior vena cava. Subsequently, the boy developed thyroid cancer and neuroblastoma at 11 and 14 years of age, respectively. However, the twin girl, who had similar exposure as the boy, had no abnormalities.[22]

HER2-Directed Therapy

Monoclonal antibodies (mAbs) are considered to be safe for administration during the first trimester as they are mostly immunoglobulin G, which are actively transported across the placenta after the first trimester. HER2 is expressed in the kidneys of the fetus and also plays a role in organogenesis. Trastuzumab, the mAb directed against HER2-positive cancer cells, when administered in the second and third trimester is associated with oligohydramnios, anhydramnios, and neonatal respiratory failure.[23]

A meta-analysis[24] reported that 73% of patients who received trastuzumab during the second or third trimester of pregnancy reported oligohydramnios/anhydramnios during pregnancy, while patients in whom trastuzumab was given during the first trimester had healthy babies at birth.

Safety of other HER2-targeted therapies, like pertuzumab, ado-trastuzumab emtansine, etc., during pregnancy is not well known due to limitations in the availability of data. Based on the availability of the current data, the use of HER2-targeted therapies is not recommended during pregnancy, irrespective of the gestation period.[13]

Endocrine Therapy

Hormonal therapies, like tamoxifen and aromatase inhibitors, are not recommended to be used during pregnancy.[13,25] Use of tamoxifen during pregnancy is associated with birth defects, including Goldenhar syndrome (oculoauriculovertebral dysplasia), ambiguous genitalia, and Pierre–Robin sequence (triad of small mandible, cleft palate, and glossoptosis).[2] Hence, use of hormone therapy should be deferred until the delivery.[13]

Supportive Medicines

Metoclopramide is the commonly used drug for emesis during pregnancy, irrespective of the gestational period. Ondansetron is recommended to be used only during the second and third trimester as its use in the first trimester is associated with congenital malformations.[26] Betamethasone or dexamethasone easily pass through the placenta, to the fetus, and are hence substituted by methylprednisolone, prednisolone, or hydrocortisone for use as premedication.[4,13]

Evidence is limited about the safety of use of granulocyte colony-stimulating factor including pegylated formulations in pregnancy. Generally, its use in pregnancy is not

associated with increased risk of congenital malformations.[27] Hence, when required growth factors can be used during pregnancy under close fetal monitoring.[13]

Delivery and Breast Feeding

In oncology patients with pregnancy, the aim is to deliver the baby after 37 weeks with an ideal gap of 3 weeks between the last cycle of chemotherapy and delivery. This time period of 3 weeks allows time for the placenta to metabolize the fetal chemotherapy, which is more effective than neonatal hepatic and/or renal drug clearance and helps in the recovery from myelosuppression.

Preterm delivery is avoided to prevent the consequences of prematurity like neurodevelopmental defects.[28] Vaginal delivery is the routine procedure while caesarean section is limited for regular obstetric indications or presence of pelvic tumors. Placental metastases can be ruled out by detailed histological examination of the placenta.[2,7]

The most common chemotherapy drugs that pass into breast milk are cyclophosphamide, cyclosporine, doxorubicin, and methotrexate. If nursing is desired, a gap of 3 weeks is recommended since the last chemotherapy cycle.[29] Breastfeeding is not recommended for patients on chemotherapy or endocrine therapy.[4,13]

Patients with cancer having a history of chemotherapy report reduced milk production due to lobular atrophy, while breast cancer patients with breast conservative surgery also have decreased milk production from the affected breast.[29,30] Breast engorgement secondary to breast feeding may lead to difficulty in diagnostic and therapeutic procedures in breast cancer patients.[29]

Strengths and Limitations

The strength of the approach to this case was that the patient and her spouse were adequately counseled not to breastfeed their infant while on chemotherapy and to avoid conceiving till further discussion. The last menstrual period date was recorded as being 1 week before administration of chemotherapy. However, the limitations include that the incidental pregnancy was missed both by the clinician and the patient. The complaints of amenorrhea, nausea, vomiting, and fatigue were thought to be only associated with the administration of chemotherapy and managed symptomatically. Urine pregnancy test was missed being performed prior to initiation of chemotherapy. The patient and the family did not consent for fetal autopsy, which was not done henceforth.

Future Perspectives

In future, institutional protocols should be made to manage oncology patients in the reproductive age group with a urine pregnancy test being compulsorily performed before starting chemotherapy, adequate counseling about future conception, fertility preservation, breastfeeding, and psychological support should be undertaken.

Conclusion

Pregnancy during treatment of malignancy is rare and a diagnostic dilemma for the treating oncologists. Aim is to deliver an oncology treatment as similar to that for a nonpregnant patient while prioritizing the fetal well-being. Chemotherapy during first trimester is contraindicated in view of the definitive teratogenic effects. Young patients with malignancy should be adequately counseled to avoid conception while on chemotherapy.

Authors' Contributions

The manuscript has been read and approved by the authors and all have contributed to it.

Patient's Consent

Written consent was taken from the patient to share the clinical details and USG images.

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Conflict of Interest

None declared.

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