



Original Article

Uses of Chemotherapeutic agents during pregnancy

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Abstract

Chemotherapy services have expanded over recent years. Mothers remain concerned about the safety of their unborn babies while handling hazardous materials. Most chemotherapy drugs are cytotoxic. This means they may be mutagenic, carcinogenic, or teratogenic in nature. How toxic they can be during pregnancy is not absolutely clear. Therefore, handling such drugs may not be 100% safe in pregnancy. Although several chemotherapeutic agents have been proven to be safe for the fetus after the organogenesis period, there is limited information on their use during the first trimester of pregnancy.

Key Word: Pregnancy, Chemotherapy.

Background: The main aim of this paper is to describe the available evidence concerning the short- and long term neonatal impact of chemotherapy given to pregnant women.

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Introduction

The concomitant incidence of cancer and pregnancy is a rare event and is estimated to account for only 1 to 2 cases per 1000 pregnancies. However, the numbers have increased in recent years because of the increase in maternal age at the time of the 1st pregnancy.^[1-3]

In Canada, over 9% of the 1.2 million cancers diagnosed annually in adults are diagnosed in those aged 20 to 44 years, and almost two thirds of these diagnoses are in women. This is likely because of the tendency for sex-specific cancers, such as breast and cervical cancer, to occur at younger ages than other cancers. Demonstrably, breast and cervical cancers are the 2 most common cancers to occur in young women, with rates of 34% and 10%, respectively. Thyroid cancer is the third most common at around 9%^[4].

The diagnosis of cancer in pregnant women causes ethical and therapeutic problems for both the patient and the physician. Most of the problems arise from the treatment options and in particular, from chemotherapy. Pregnant women with cancer tend to abstain from treatment for the fear of fetal damage. Conversely, physicians have to balance embryo and fetal wellbeing with maternal prognosis, taking in account that, even if rarely, vertical transmission of cancer can occur and the child can suffer of the same disease of the mother^[5].

Treatment Guideline:

Cisplatin: Cisplatin should only be given during pregnancy when there are no alternatives and benefit outweighs risk.

Out of five known cases where cisplatin was used during pregnancy, four resulted in normal healthy

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infants. In the fifth case, the mother had been treated with a combination of cisplatin, bleomycin, and etoposide. Both the mother (one week prior to delivery) and the infant (three days after birth) developed neutropenia. Ten days after birth, the infant began losing scalp hair and lanugo. Etoposide was felt to be the causative agent for the neutropenia and alopecia. In one study, cisplatin was administered to male rats before mating. Significant reductions were found in reproductive organ weights, sperm counts, sperm motility, fertility, and levels of testosterone ^[6].

Cyclophosphamide:

The finding of a similar pattern of malformation among eight infants prenatally exposed to CP suggests that CP is a human teratogen. MTX and CA produce similar patterns of malformation in prenatally exposed infants despite very different pharmacologic profiles and metabolism. We speculate that the phenotype is a consequence of apoptosis in certain cells which are susceptible to the effects of the teratogen at specific stages of development. ^[7] Cyclophosphamide has been assigned to pregnancy category D by the FDA. While normal newborns have been delivered to women who were exposed to cyclophosphamide during pregnancy, human data have revealed evidence of embryotoxicity and fetotoxicity. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy. The use of cyclophosphamide during pregnancy is contraindicated ^[8].

Methotrexate:

In study sample included 324 MTX-exposed pregnancies (188 exposed post-conception, 136 exposed pre-conception), 459 disease-matched comparison women, and 1,107 comparison women without autoimmune diseases. In the post-conception cohort, the cumulative incidence of spontaneous abortion was 42.5% (95% confidence interval [95% CI] 29.2-58.7), which was significantly higher than the incidence of spontaneous abortion in either comparison group. The risk of major birth defects (7 of 106 [6.6%])

was elevated compared to both the cohort of women without autoimmune diseases (29 of 1,001 [2.9%]) (adjusted odds ratio [OR] 3.1 [95% CI 1.03-9.5]) and the disease-matched cohort (14 of 393 [3.6%]) (adjusted OR 1.8 [95% CI 0.6-5.7]). None of the malformations were clearly consistent with MTX embryopathy. Neither the cumulative incidence of spontaneous abortion (14.4% [95% CI 8.0-25.3]) nor the risk of major birth defects (4 of 114 [3.5%]) was increased in the pre-conception cohort. Elective termination rates were increased in both of the MTX-exposed cohorts. There were no other significant differences among groups in other study end points ^[9].

Doxorubicin:

Cardiotoxicity is a recognized complication of anthracycline drugs given as part of chemotherapy; however, the pre- and postnatal cardiac effects of in utero exposure are not well documented. In this report we present a case of gestational breast cancer with initiation of four cycles of doxorubicin/cyclophosphamide chemotherapy after modified radical mastectomy and axilla dissection during the early second trimester. Serial echocardiographic measurements of the ventricular shortening fraction and biometry of the ventricular cavities were performed. Allowing for the individual variability of these values in the fetus no myocardial dysfunction was observed. The literature was reviewed in an attempt to delineate the possible role of prenatal echocardiography in the diagnosis of doxorubicin-induced cardiotoxicity in the fetus ^[10].

Trastuzumab:

The management of breast cancer during pregnancy is a complex clinical issue because of the potential risks to the fetus posed by cancer treatment clashing with the potential risks to the mother from delayed cancer treatment.

Trastuzumab is a monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2) protein. The HER2 protein is a member of the epidermal growth factor receptor family. When the HER2 protein is overexpressed, it causes increased cell growth and proliferation leading to a more aggressive breast cancer.

Treatment with trastuzumab has been shown to improve outcomes in the treatment of HER2-positive breast cancer. This drug is listed as a category-B drug by the United States Food and Drug Administration. There is no similar classification system in Canada^[11].

Docetaxel:

Two patients with breast cancer received docetaxel-containing chemotherapy as adjuvant or neoadjuvant therapy during pregnancy. The first pregnant patient began neoadjuvant therapy with doxorubicin/cyclophosphamide at 14 weeks of gestation. After 4 cycles of doxorubicin/cyclophosphamide and surgery, she received adjuvant docetaxel for 4 cycles. The second patient began neoadjuvant therapy with doxorubicin/docetaxel at 14 weeks of gestation and received 6 cycles. The fetus of the first patient had hydrocephalus on ultrasound at 17 weeks of gestation (before docetaxel therapy) that persisted on serial follow-up ultrasounds and spontaneously regressed over several months after delivery. No fetal malformations were detected in the second fetus. These 2 cases add to the existing data on the use of taxanes during pregnancy. Although the data are limited with case reports, pregnant patients with cancer can be treated with chemotherapy including taxanes during the second and third trimesters without significant risks to the fetus. Taxanes should not be excluded, if indicated, in pregnant patients with cancer^[12].

Conclusion:

Around one in 2,000 pregnancies is affected by cancer, a rate that is increasing by 2.5 per cent a year as women have children later in life. The number of chemotherapy cycles received during pregnancy did not appear to affect the babies' birth weight, leading the authors to suggest that the lower birth weight is not clinically meaningful. Most doctors agree that chemotherapy should be given only after the first trimester (the first 12 to 14 weeks). This is because the baby's organs are developing rapidly during the first trimester. Doctors also don't give chemotherapy near the delivery date. In most cases, the last dose is given about 8 weeks before the delivery date (32 to 33 weeks into the pregnancy). This is because

chemotherapy can lower white blood cell counts (neutropenia), which can increase the risk of infection in the mother and the baby around the time of delivery. Anthracycline chemotherapy regimens are more commonly used when chemotherapy is needed during pregnancy. Taxane chemotherapy regimens aren't commonly used during pregnancy.

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