Children Exposed to Chemotherapy In Utero

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The majority of the information on the effects of in utero exposure to chemotherapy has been derived from retrospective case reports and series. Overviews of the available data have concluded that the timing of chemotherapy exposure (first trimester versus second and third trimesters) as well as the chemotherapeutic agent or agents used affect the risk of spontaneous abortion and miscarriage as well as that of congenital abnormalities. Although there are data from a prospective series of 24 pregnant breast cancer patients treated at the University of Texas M.D. Anderson Cancer Center, there are limited case series in women with hematologic malignancies, with the largest series having 89 pregnancies, that indicate that the fetuses exposed to chemotherapy in utero in the second and third trimesters can be carried to term, be born without evidence of congenital abnormalities, and develop normally. Clearly, ongoing prospective collection of data on the children born to women undergoing therapy for cancer is necessary. [J Natl Cancer Inst Monogr 2005;34:69–71]

The diagnosis of malignancy concurrent with pregnancy is often perceived as putting the health of the mother in conflict with that of the developing fetus. Maternal factors that must be considered in the decision as to how the pregnancy may proceed without significant harm to the mother and fetus include the type of malignancy, its stage or extent at the time of diagnosis, the health of the mother, and the proposed treatment, as well as the woman’s decision to proceed forward with the pregnancy. Fetal factors to be considered include the gestational age of the fetus, the type of uterine malignancy, and the potential risk to the fetus. Clearly, ongoing prospective collection of data on the children born to women undergoing therapy for cancer is necessary. [J Natl Cancer Inst Monogr 2005;34:69–71]

The Food and Drug Administration reviews the available data on a therapeutic agent, both experimental and in vivo, and assigns a pregnancy category (A through D or X) that reflects the safety of the drug for the pregnant woman and her fetus. In cases of known or suspected fetal teratogenesis or if maternal health is in jeopardy, pregnancy termination may be an appropriate medical recommendation. However, a multidisciplinary approach may make it possible to provide the pregnant cancer patient appropriate cancer care while maintaining a successful pregnancy through labor and delivery.

The majority of data on malignancies diagnosed and treated during pregnancy and the subsequent health and well-being of the children exposed to chemotherapy in utero is limited and is primarily based on retrospective case reports and case series. Partridge and Garber have proposed a number of reasons as to why there are limited data on the adverse effects of in utero chemotherapy. The reasons include the low frequency of cancer diagnosed during pregnancy, that pregnant patients with cancer may choose to have an abortion rather than risk the delivery of an infant with congenital malformations, that there are limited data on the detailed examination of infants exposed to chemotherapy in utero for malformations as well as abnormal growth and development, that older data may use agents or combinations of agents or doses not relevant for the current treatment for that malignancy, that concurrent radiation therapy exposure during pregnancy confounds older literature, that there are few reports of systematic or sufficient length of follow-up of the children exposed to chemotherapy in utero, and that there is publication bias in the literature. Thus, the pregnant woman with cancer must be informed of the evidence—or the lack thereof—regarding the long-term consequences of in utero chemotherapy exposure.

Epidemiology of Cancer Diagnosed During Pregnancy

The diagnosis of cancer during pregnancy is an uncommon event. A population-based retrospective review of infant birth and death certificates and maternal and neonatal discharge records in California for the years 1992 through 1997 found the frequency of primary neoplasms diagnosed during pregnancy to be 19 per 100,000 live singleton births. The most frequently documented primary malignant neoplasms associated with delivery were breast cancer (3.7 per 100,000), thyroid cancer (3.3 per 100,000), cervical cancer (1.6 per 100,000), Hodgkin disease (1.0 per 100,000), and ovarian cancer (1.5 per 100,000). The previously estimated frequency of malignancy during pregnancy was 100 in 100,000 deliveries. The lower rate of malignancy complicating pregnancy in the review by Smith et al. may reflect a decreased rate of case ascertainment because the diagnosis of malignancy was dependent on a discharge diagnosis of malignancy.

Timing of Chemotherapy Exposure in Utero

The Food and Drug Administration reviews the available data on a therapeutic agent, both experimental and in vivo, and assigns a pregnancy category (A through D or X) that reflects the safety of the drug for the pregnant woman and her fetus. Many chemotherapeutic agents are Food and Drug Administration pregnancy category D, meaning that there are data on pregnant women indicating potential risk to the fetus. Thus, for the treating oncologist and the patient, a decision needs to be made as to whether the potential risk to the fetus is outweighed by the potential benefit.

There are a number of case reports and case series that have described the successes or failures of a variety of chemotherapeutic agents in the treatment of malignancies in pregnant women. In one of the largest series published to date, Ebert et al. reviewed 217 cases of cytotoxic therapy during pregnancy for a variety of malignant and rheumatologic diagnoses. In their review, 18 newborns had multiple anomalies of differing severities, with two...
additional children having chromosomal abnormalities. Twelve of the 18 mothers had been treated with folic acid, purine, or pyrimidine antagonists, and in 15 cases, cytotoxic therapies were administered along with other drugs during the first trimester. Spontaneous abortions occurred in 15 cases, with the majority of these occurring after methotrexate administration.

The effect of the timing of chemotherapeutic exposure is reiterated in the review by Doll et al. (6). In their review of the literature on pregnancy and cancer, the researchers reported that the incidence of fetal malformations with first-trimester chemotherapy exposure with a variety of agents ranged from 14% to 19%. However, exposure in the second or third trimester was associated with an incidence of fetal malformations of 1.3%. In the general population, the incidence of major congenital malformations has been reported as approximately 3% of all births, whereas the incidence of minor malformation could be as high as 9%, depending on the definition of a minor malformation (7).

Cardonick and Iacobucci (8) have recently published a compilation of their cases as well as of published cases of cancer treated with chemotherapy during pregnancy. In their review of 376 fetuses exposed to chemotherapy in utero, most of the fetuses were exposed after organogenesis. Nine of the 11 reported malformations occurred when chemotherapy was given in the first trimester.

Thus, the use of chemotherapy during the first trimester—the period during which the majority of organogenesis occurs—appears to have the greatest potential for harm to the fetus, and this risk may be increased with the use of particular chemotherapeutic agents. Although there are some malignancies, such as early-stage breast cancer, for which chemotherapeutic exposure may be delayed until the second trimester, there are malignancies, primarily the hematologic, for which chemotherapy must be initiated as soon as possible so as to not jeopardize the health of the mother.

**Transplacental Passage of Chemotherapy**

For a fetus to be exposed to any drug, including chemotherapeutic agents, it must cross the placenta. Drugs that have a low molecular weight and a high lipid solubility, that are nonionized, and that loosely bind to plasma protein are most likely to cross the placenta (9). Most drugs possess some of these characteristics and thus can cross the placenta and enter the fetal circulation (6). The fetal liver is able to metabolize substrates by oxidation, and the fetal kidney may be involved in the elimination of drugs. However, it is possible that a drug excreted into the amniotic fluid may be ingested by the fetus and reabsorbed from the gastrointestinal tract. This mechanism could potentiate the effect of a drug exposure on the fetus if the drugs or their breakdown products are excreted in an active form. The placenta is also a route of drug elimination, as it serves as a mechanism to remove waste products and toxins from the fetus. The placenta itself also has a variety of enzymes, including cytochrome P450, that may aid in the metabolism of drugs that are crossing the placenta (10).

The literature actually documenting the transplacental passage of chemotherapeutic agents is sparse and has focused on exposure to the anthracyclines. There are case reports regarding the detection of anthracyclines in the placenta, umbilical cord, or fetal tissues (11,12). Two reports of fetal exposure to doxorubicin failed to demonstrate this drug in the amniotic fluid, but the placenta and fetal tissues were not examined (13,14).

**Effects of Chemotherapy on Labor and Delivery Outcomes**

The data on the labor and delivery outcomes of women treated with chemotherapy during pregnancy are limited to case series and case–control studies, with the exception of two prospective series of pregnant breast cancer patients (8,15). These studies have reported that the children of women with hematologic and nonhematologic malignancies exposed to chemotherapy in utero tend to be born prematurely (15–20). Although some studies also appear to demonstrate a lower-than-average birth weight, normal birth weights were reported in the large series of the children born to 84 pregnant patients with hematologic malignancies, reported by Aviles and Neri (15–17,20).

Information on labor and delivery outcomes may be limited by the fact that pregnant patients with cancer may deliver at a hospital different from that in which they are receiving systemic therapy for their cancer and by the retrospective nature of most reports.

**Long-Term Effects of In Utero Exposure to Chemotherapy**

The information on the long-term effects of in utero chemotherapeutic exposure is limited. This lack of data is concerning because little is known regarding the theoretical risks of transplacental carcinogenesis, gonadal dysfunction and infertility, impairment of physical or neurologic growth and development, and transplacental mutagenesis of germ-line tissue (1).

The largest and most comprehensive data set on the long-term effects of chemotherapy exposure in utero comes from a series of pregnant women with hematologic malignancies followed by Aviles and Neri (20). A review of the records of the National Medical Center in Mexico identified 89 women diagnosed with hematologic malignancies while pregnant. Five of the women died before any therapy, and the fetuses were lost. The children of the remaining 84 women participated in this study, which examined their physical growth and development, cardiac function, and bone marrow for chromosomal abnormalities. Neurological and psychological evaluations were performed, and school records examined. With a median follow-up of 18.7 years (range, 6–29 years), no cancer or acute leukemia has yet been observed in the cohort of 84 patients or in the 12 second-generation children. Learning and education performance were normal, and no congenital, neurological, or psychological abnormalities were noted. No cytologic abnormalities were seen in the 76 bone marrow samples and eight peripheral blood samples. Despite conflicting case reports as to whether exposure to anthracyclines may cause fetal cardiac dysfunction, no cardiac abnormalities were observed (20–23).

Other studies have reported long-term follow-up of children exposed to chemotherapy in utero, but their follow-up is less complete or less extensive than that of the series by Aviles and Neri (15,16,18,20,23). Clearly, the additional, and preferably prospective, collection of data of children exposed to chemotherapy in utero is warranted. This information will guide the future management of pregnant cancer patients, especially with regard to the use of newer agents. It will also provide parents and their children with information on the short- and long-term complications of exposure to chemotherapy in utero.
REFERENCES