Appraisal of Chemotherapy Effects on Reproductive Outcome According to Animal Studies and Clinical Data

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Cancer in women or men during reproductive life raises fears and dilemmas regarding the ability to have a healthy child. Chemotherapy and radiotherapy increase genetic defects in germ cells, depending on the agent used and the stage of gamete maturation. No increase in miscarriage or congenital malformation rates is detected among children born years post-cancer treatment. However, when pregnancy occurred shortly after treatment, increased abortion and malformation risk was reported. Until more data are available, monitoring of chromosomal aberrations and birth defects is recommended. Complexity of cancer treatment is significantly amplified in women exposed to chemotherapy during pregnancy due to concerns regarding direct maternal risks caused by treatment and risk to the developing embryo-fetus. The potential teratogenic effect of cancer treatment depends upon the developmental stage of the fetus at exposure and on drugs used. During the first trimester, abortion and malformation rates are increased, while second- and third-trimester chemotherapy may increase the risk of stillbirth, fetal growth restriction, and premature birth. Maternal myelosuppression increases bleeding and infection tendency, which can harm the fetus. A multidisciplinary team alerted to possible consequences of cancer treatment on pregnancy outcome should provide the optimal treatment options for these patients. [J Natl Cancer Inst Monogr 2005;34:21–5]

The desire for parenthood in young patients exposed to cancer treatment is strong and is frequently discussed. Since most childhood cancers are likely to be cured and cancer is not infrequent during women's reproductive lifespan, the number of young adults who desire parenthood following cancer treatment is significantly high *(1)*.

However, major concerns are raised concerning possible adverse effects of cancer treatment on gametes and outcome of future pregnancies. Administration of chemotherapy agents has long been known to have a multitude of short- and long-term adverse effects. They have been shown to be mutagenic to somatic cells, causing gene mutations, chromosomal breaks, rearrangements, and aneuploidy *(2)*. Animal and human studies indicate that chemo- and radiotherapy treatments are mutagenic to germ cells at various stages of maturation. Therefore, the possible risks on the offsprings of cancer-treated individuals are raised and investigated.

Cancer complicates about 0.02%–0.1% of all pregnancies *(3)*, and the incidence is expected to rise with the concomitant

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increasing age of childbearing. When cancer occurs during gestation, it poses a very difficult challenge to the pregnant patient, her relatives, and the medical staff. The benefit of the diagnostic workup and the use of chemotherapy, radiotherapy, and surgery should be weighted carefully against their risk to the unborn child. This often raises conflicts between optimal maternal therapy and fetal well-being.

The possible adverse consequences of cancer treatment on reproductive outcome are related to the chemotherapeutic regimen administered and the time of exposure and can be divided into the following categories (Fig. 1): 1) exposure of gametes to chemotherapy—remote from pregnancy, 2) exposure of gametes to chemotherapy—preconception period, 3) preimplantation and postimplantation of embryos, 4) embryonic or major organogenesis period, 5) fetal period, and 6) treatment adjacent to delivery.

This article presents data collected from both animal experiments and human studies that highlight the possible adverse effects of cancer treatment on reproductive outcome as related to the time of exposure in females.

Exposure of Gametes to Cancer Treatment

Radiotherapy and/or chemotherapy in female cancer patients can cause ovarian damage and may result in ovarian failure or premature menopause. The risk of such damage is related to the patient's age at the time of treatment, her ovarian function prior to administration of chemotherapy, and the treatment protocol *(4)*. Nevertheless, in many cases, conception and pregnancy are feasible after cancer treatment. The quality of such pregnancies and the health of children born to women after cancer treatment are thus a major concern.

Most of the data on the mutagenic effects of specific chemotherapeutic agents come from animal studies. There is less information on the effect of individual drugs in humans, as most reports come from exposures to the multiple-drug regimens administered for common malignancies.

The data collected from animal studies indicate that chemo- and radiotherapy treatments are mutagenic to female germ cells at various stages of maturation.

Alkylating Agents

These agents have been shown to cause significant damage to preovulatory oocytes. We have shown an increase in abortions and fetal malformations in pregnancies resulting from oocytes exposed to cyclophosphamide at different stages of oocyte maturation. Oocytes exposed at the preovulatory stage had the highest abortion rate (56%) compared with 19%–31% for oocytes exposed at earlier stages of maturation. The malformation rate was at least 10 times higher in oocytes exposed at any stage than that for controls (1.2%). The highest malformation rate (33%) was found in oocytes exposed at the earliest stage of maturation. Thereafter, malformation rates decreased gradually as the time interval between cyclophosphamide exposure and ovulation increased (Fig. 2) *(5)*.

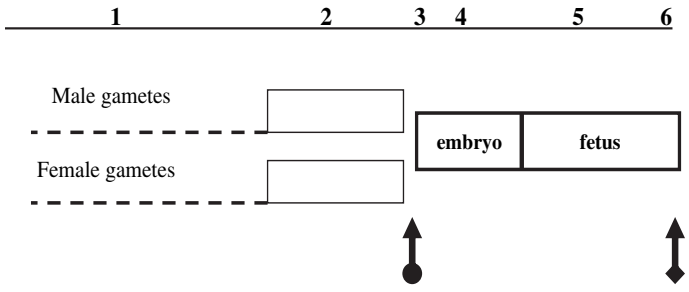


Fig. 1. Possible adverse consequences of cancer treatment on reproductive outcome are related to the chemotherapeutic regiment administered and the time of exposure: **1**) Exposure of gametes to chemotherapy—remote from pregnancy, **2**) exposure of gametes to chemotherapy—preconception period, **3**) preimplantation and postimplantation of embryos, **4**) embryonic or major organogenesis period, **5**) fetal period, and **6**) treatment adjacent to delivery. **Arrow** and **solid circle** = conception; **arrow** and **solid square** = delivery.

Cisplatin and Analogues

These agents are specific inducers of dominant lethal mutations in female mice. These agents cause various different types of chromosomal damage and DNA adducts and result in early embryonic mortality. Mature oocytes exposed to cisplatin prior to ovulation showed marked aneuploidy *(6,7)*.

Plant Alkaloids

When mouse oocytes were exposed to vinblastin prior to the first meiotic division, high levels of aneuploidy were observed *(8)*. Significant meiotic arresting activity following administration of vinblastin resulted in increased frequency of ovulated oocytes arrested in MI phase *(9)*. Damaged oocytes went on to produce malformed fetuses *(10)*.

Antimetabolites

There is insufficient research on the effects of antimetabolites on female germ cells.

Anthracycline Antibiotics

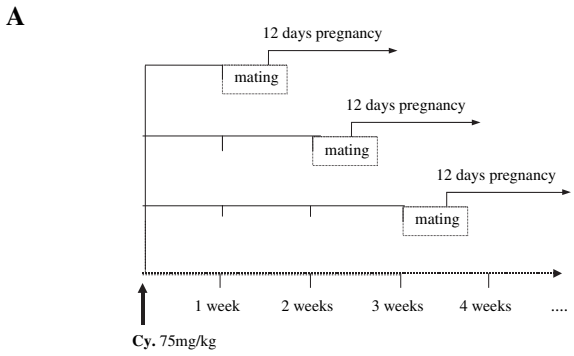
Adriamycin and bleomycin are female-specific mutagens that have both been shown to induce dominant lethal mutations in maturing and preovulatory oocytes of female mice *(7,11)*. Inhibition of topoisomerase II activity results in DNA strand breaks and aberrant chromosomal structure. An animal study demonstrated aneuploidy in mouse oocytes induced by the topoisomerase II inhibitor etoposide *(9)*.

Human Studies (Combination Chemotherapy)

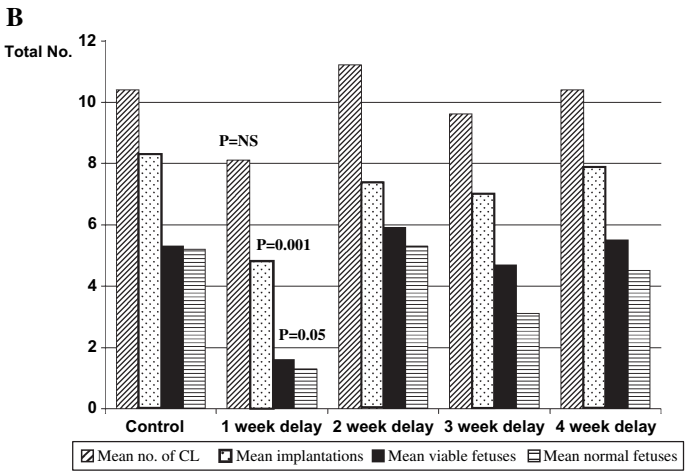
Studies that monitored pregnancies in women exposed to chemotherapy before conception showed that the observed increase in mutations in germ cells (mostly male germ cells) and the alarming results of animal studies do not translate into an increase in the rate of miscarriage or congenital abnormalities compared to the general population *(13–16)*. However, these pregnancies were established long after treatment had ceased. Possible explanations are correction mechanisms that exist within the oocyte or undetected miscarriage due to dominant lethal mutations at a very early stage if fertilization occurs.

Assisted Reproduction in Cancer Patients

To overcome future female sterility, some centers offer in vitro fertilization (IVF) and embryo cryopreservation to patients following first-line chemotherapy before administration of



	Time post treatment						
	1 week	2 weeks	3 weeks	4 weeks	6 weeks	9 weeks	12 weeks
Antral							
Large growing follicles	+						
Small growing follicles	+/-	+/-					
Primary follicles		+	+/-				
Primordial follicles			+	+	+	+	+



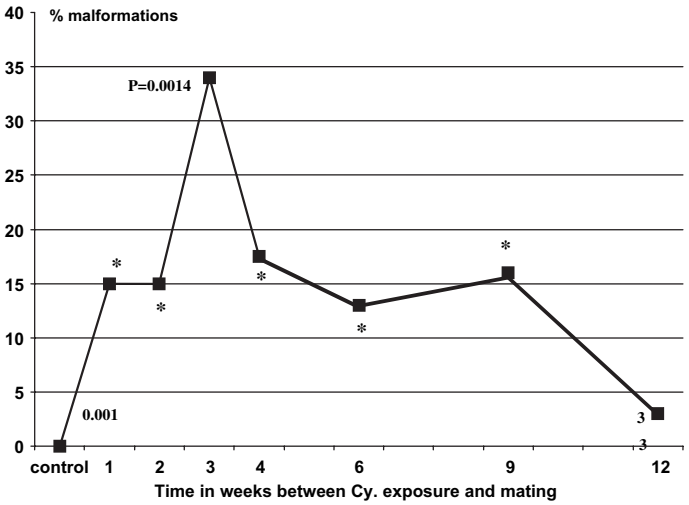


Fig. 2. Animal study aimed to determine reproductive performance, fetal viability, and teratogenicity in female mice exposed to cyclophosphamide (*Cp)* in relation to the stage of follicle development at the time of exposure [from Meirow et.al. *(5)* with permission]. **A**) Diagrammatic representation of methods: Groups of mice were mated at weekly intervals following exposure Cy. (75 mg/kg of body weight). Oocytes, which contributed to the pregnancies, would have been at the stages indicated in this figure at the time of exposure. **B**) Comparison of the mean numbers (for each female) of corpora lutea (CL), implantations (viable fetuses and resorption sites), viable fetuses, and normal (not malformed) fetuses seen in the females which became pregnant 1–4 weeks after treatment with Cy, as well as controls. *P* value indicates the significance of the results compared with controls. **C**) Incidence of malformations in the fetuses of mice mated at different time intervals (1–12 weeks) following injection with Cy (***** indicates $P<0.05$).

sterilizing treatment. However, the full span of follicle growth from the primordial to Graafian stage is on the order of 6 months *(17)*. When growing follicles are exposed to chemotherapy and then subsequently stimulated and fertilized, the possibility of adverse pregnancy outcomes must be considered because these embryos are formed shortly following exposure to cytotoxic agents. In these cases, we cannot rely upon the reassuring studies presented. Therefore, several key questions should be investigated in the near future. Are there more adverse outcomes in pregnancies shortly after exposure to cytotoxic agents? Do they carry increased genetic risk? If so, what is the safe period between cessation of treatment and oocyte retrieval for IVF? Clearly, pregnancy outcomes of all these patients should be monitored and, until more data are available, fetuses and neonates should be screened for chromosomal aberrations and birth defects and patients should be made aware of the lack of information *(18)*.

Cancer During Pregnancy

The use of chemotherapy, radiotherapy, and surgery in the treatment of pregnant cancer patients should be weighed carefully against the risk to the unborn child. This often raises conflicts between optimal maternal therapy and fetal well-being. The incidence of specific malignant neoplasms in pregnant women parallels that of nongravid women of reproductive age *(19)*. The most frequent malignant neoplasms associated with pregnancy are cervical and breast cancer, malignant melanoma, and Hodgkin lymphoma *(20)*.

Effect of Cytotoxic Therapy on the Developing Fetus

Since most cytotoxic agents used today reach the fetus in significant concentrations after maternal administration and these agents are known to be mutagenic to somatic cells, significant concerns have been raised regarding the adverse effects of these treatments on fetuses exposed in utero. As with gamete exposure, most of the existing data on the mutagenic effects of chemotherapeutic agents come from animal studies. There is very little information on the effect of individual drugs in humans, as most reports arise from exposures to multiple agents administrated in combination for common malignancies.

The potential teratogenic effect of cancer treatment during pregnancy depends upon the developmental stage of the fetus at exposure. These developmental stages can be divided into the preimplantation and early postimplantation period, the embryonic period or period of major organogenesis (third- to eighth-week postconception), and the fetal period (ninth completed gestational week to term) *(21)*. During the early postimplantation-predifferentiation period, the conceptus is mostly resistant to teratogenic insult *(22)*. Any embryonic damage during the first four weeks of gestation most likely leads to the death of the conceptus *(23)*. Although organogenesis is mostly complete by the eighth week of gestation, closure of the palate and the development of the definite kidney (metanephros) continue through the end of the tenth week. By the tenth week of gestation (postconception), organogenesis is complete with the exception of the central nervous system and the gonads. During organogenesis, damage to any developing organs most likely leads to major malformations. Exposure to cytotoxic agents during the second and third trimester is not associated with teratogenic effects but may result in intrauterine growth retardation, prematurity, and stillbirth *(24,25)*. Disturbance of fetal development later in gestation may have more subtle effects that are manifest only later in development. In particular, impairment of neurologic maturation may not be apparent at delivery and is manifest only early in life *(26)*.

In humans, the risk of teratogenesis following cancer treatment appears to be significantly lower than is commonly appreciated. The incidence of major malformations in fetuses exposed to chemotherapy during the first trimester is estimated to be 10%–20% *(27)*. Malformations were reported in all organ systems with no discernible pattern. A review of 139 cases (82 articles) of women exposed to chemotherapy during the first trimester of pregnancy reported a total of 24 (17%) infants born with malformations after single-agent exposure and 25% after combination-agent exposure *(28,29)*. While antimetabolites have been associated with birth defects more frequently than any other agents, the reported incidence of fetal malformations declined to only 6% following first-trimester single-agent exposures when folate antagonists were not included. In 1985, the National Cancer Institute started a registry for in utero exposure to chemotherapeutic agents. Out of the first 210 children monitored, there were 29 abnormal outcomes and 27 of these 29 resulted from first-trimester exposure *(27)*.

Alkylating agents are apparently less teratogenic than antimetabolites. Vinca alkaloids are potent teratogens in animals, although most cases of human exposure resulted in normal infants *(29)*. The use of doxorubicin in 160 pregnant women showed that fetal outcome was frequently normal *(30)*, although patients who received therapy during the first trimester or doses exceeding 70 mg/m^2 were more prone to complications including fetal demise. It was also suggested that doxorubicin might induce cardiomyopathy, which may have a prominent effect on both maternal and fetal circulation. Although no fetal cardiotoxicity was reported, an echogecardographic evaluation of these fetuses (in utero) was recommended *(31)*.

The risk of fetal anomalies after administration of chemotherapy in the second and third trimester has not been shown to be higher than the background rate. However, these cases may be associated with a greater risk of various obstetric complications. Based on these studies, it is recommend that, when treatment cannot be delayed and is administered in the first trimester, termination of the pregnancy should be considered. Furthermore, whenever possible, chemotherapy should be delayed to the second trimester to reduce the risk of fetal anomalies *(20)*.

The central nervous system continues to develop after the first trimester and is thus sensitive to teratogenic insult during the entire period of gestation. Thus, delayed effects of in utero exposure to chemotherapeutic agents that may result in intellectual and neurologic dysfunction were evaluated. It is known that exposure after the first trimester does not cause anatomical defects. However, there is little data on long-term development and cognitive function following in utero exposure to maternal cancer treatment. Results of neurodevelopmental studies as well as school performance and intelligence testing of children indicated that all the parameters obtained for children exposed to chemotherapy in utero were comparable with control values *(16,17)*. Children born to mothers exposed to chemotherapy in utero displayed normal growth and development according to height and weight developmental tables. Moreover, the risk of developing childhood malignancies was not shown to be different from that for the general population. *(27,32–35)*.

Chemotherapy during the second and third trimesters may increase the risks of stillbirth, fetal growth restriction, premature birth, and maternal and fetal myelosupression. Therefore, a routine and frequent fetal monitoring protocol should be implemented for these patients. Furthermore, routine ultrasonographic evaluation may aid in detecting the early stages of intrauterine growth restriction indicating the need for induced delivery. When indicated, the need for preterm delivery is supported by neonatal care units results that report a highly favorable outcome in preterm neonates delivered at 32 weeks' gestation. *(36)*

When chemotherapy is administrated to pregnant patients close to the time of delivery, important effects of chemotherapy treatments should be considered in order to prevent maternal complications or possible adverse fetal outcome. Delivery after administration of cytotoxic agents that cause anemia and severe thrombocytopenia should be carefully planned *(15,26,37,38)*. Bone marrow suppression also results in an increased tendency toward viral infections such as herpes, cytomegalovirus, and human papilloma virus, which can affect the newborn during pregnancy or at the time of delivery. Chemotherapy-induced maternal organ toxicity may, in addition to having serious adverse effects on the mother, also interfere with normal fetal development and necessitate termination of pregnancy or urgent premature delivery. Thus, the decision regarding delivery should be discussed in a multidisciplinary forum involving the obstetricians, neonatologists, and oncologists *(15,37)*.

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