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## **Cancer, Chemotherapy, and Pregnancy**

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In the United States, there are approximately 3500 cases of cancer-complicated pregnancies per year. The most common cancers that occur during pregnancy are cervical, breast, melanoma, thyroid, leukemia, lymphoma and colorectal (Sorosky et al., 1997). In part, the recent increase in cancer-complicated pregnancies may be due to the increased frequency of delayed childbearing. A diagnosis of cancer during pregnancy causes significant conflict for both the physician and the patient when attempting to optimize maternal and fetal well being. The risks and benefits of possible surgery, radiation and chemotherapy and the timing of treatment must be considered. This RISK/NEWSLETTER will present information on the reproductive risks in persons who received cancer treatment prior to pregnancy, the effects of maternal chemotherapy exposure during pregnancy and the pregnancy risks of occupational exposure to chemotherapy. We will not address radiation therapy during pregnancy.

### **PREGNANCY IN CANCER SURVIVORS**

As the survival from childhood and young adult cancers improves, the question about pregnancy outcome subsequent to chemotherapy and/or radiation therapy has become more frequent. Because of the obvious mutagenicity of these agents, there is theoretical concern that prior cancer treatment may alter fertility or increase the risk for birth defects, childhood cancer, chromosome abnormalities (e.g. aneuploidy) and single gene mutations. Most studies, which typically examine outcomes in patients treated between 1960 and the early 1980's, have also considered patient's gender, as male and female gametogenesis are different.

Early studies suggested that the offspring of cancer survivors had an increased risk for low birth weight, perinatal mortality and other adverse outcomes (Green et al., 1982; Li et al., 1987; Byrne et al., 1988; Hawkins and Smith, 1989). These outcomes were more commonly seen in women who received abdominal radiation therapy, and Smith and Hawkins (1989) postulated that these outcomes were related to possible changes in the uterine elasticity or vasculature secondary to radiation therapy.

Many studies have addressed whether birth defects or aneuploidy are increased in offspring of cancer survivors. Nygaard et al. (1991) and Kenney et al. (1996) examined birth outcomes in 48 and 140 offspring of acute lymphoblastic leukemia (ALL) survivors, respectively; neither found an increase in birth defects. More recently, Green et al. (1997) expanded on their earlier studies (1991) to document the outcome of 280 pregnancies to cancer survivors; no increase in birth defects was noted. Finally, Byrne et al. (1987; 1998) found no increase in birth defects, chromosome abnormalities or single gene disorders in 2198 offspring of survivors versus their sibling controls; this was true even when mutagenic and non-mutagenic treatments were considered separately. None of the above studies found

differences in outcomes between male and female cancer survivors.

Finally, studies have examined whether childhood cancer is increased in the offspring of survivors. Mulvihill et al. (1987) examined 2308 offspring of survivors and did not find a significantly increased risk for childhood cancers as compared to sibling controls. Neither Nygaard et al. (1991) nor Green et al. (1997) noted any cases of childhood cancer in 48 and 143 offspring of survivors, respectively. Obviously the presence of a dominantly inherited cancer syndrome within a family can increase the frequency of childhood cancer, and must be considered when providing these risks to family members (Green et al., 1997).

In summary, offspring of cancer survivors do not appear to be at increased risk for birth defects, chromosomal abnormalities or single gene disorders. While the cancer treatment itself does not increase the risk of childhood cancer in offspring, the implications of an inherited cancer syndrome should be addressed in counseling.

### **CHEMOTHERAPY IN PREGNANCY**

Chemotherapeutic agents have been used since the early 1950s (Schardein, 1993). Breast cancer, ovarian cancer, leukemia and lymphomas are commonly treated with chemotherapy (Doll et al., 1988). There are, however, no large prospective studies of chemotherapy use during pregnancy. Physicians must, therefore, rely primarily on case reports and retrospective studies, both subject to confounding factors, when formulating a treatment regimen for the pregnant woman with cancer. Additionally, the physician must consider the gestational age of the pregnancy, the stage of the cancer, and the emotional, religious, social and moral concerns of the individual prospective parents.

All chemotherapeutic agents are potentially teratogenic and mutagenic because they act on rapidly dividing cells. The potential exists for fetal malformations, intrauterine growth restriction, spontaneous abortion, stillbirth or premature delivery when a woman is exposed to chemotherapeutic agents prior to, or during, pregnancy. Possible outcomes depend on the particular treatment, its timing and duration, and the ability of the drug to cross the placenta. Most chemotherapeutic agents do cross the placenta. While the greatest risk for birth defects occurs with first trimester exposure, second and third trimester exposures may result in transient bone marrow suppression, pancytopenia, intrauterine growth restriction (Aviles et al., 1991), low birth weight and prematurity (Zemlickis et al., 1992). It has been suggested that chemotherapy be avoided for three weeks prior to delivery (Sokorsky, 1997), in order to allow the mother to recover from treatment-related bone marrow suppression. In addition, the fetus can better metabolize these agents with the assistance of the maternal system, avoiding the persistence of high levels of drugs in the neonatal circulation.

Most information about chemotherapy in pregnancy is derived from case reports or limited studies of different treatment regimens for pregnant women with specific types of cancer. Case reports are inherently biased towards reporting abnormal outcomes. Reports of outcomes after chemotherapy differ slightly, however, because many of these reports focused primarily on the cancer diagnosis in pregnancy rather than the specific treatment regimen. Also, many of these reports are from the 1960s and 1970s, when lower doses of single agent chemotherapy were commonly used; it is difficult to extrapolate to current doses (Reichman and Green, 1994). Finally, the introduction of combination chemotherapy complicates the assessment of teratogenic risk, because one must also consider the possibility of synergism. Chemotherapy may also be used in combination with radiation therapy, making it difficult to determine which portion of the treatment has teratogenic effects.

In a small number of case control studies, most of which are organized by type of cancer rather than by treatment, the biggest problem is variation in methodology. Specifically, while children exposed in utero to chemotherapy are examined for malformations, these examinations are not standardized, making accurate risk assessment difficult.

## COMMON CHEMOTHERAPEUTIC AGENTS AND THEIR EFFECTS

Chemotherapeutic agents are classified by their mechanism of action corresponding to different stages of the cell cycle. We will discuss common alkylating agents, antimetabolites, vinca alkaloids and anthracycline antibiotics.

### **Alkylating agents:**

The alkylating agents are cell cycle nonspecific (Zemlickis et al., 1996). They work during most cell cycle stages by denaturing DNA and inhibiting cell division and normal biological activity (Hardman et al., 1996).

#### Busulfan (Myleran)

Busulfan is commonly used to treat chronic myeloid leukemia (CML) (Hardman et al., 1996), and may be used either alone or in combination with 6-mercaptopurine, prednisone and radiation therapy (Aviles et al., 1991; Schardein, 1993). There are at least 38 cases in the literature of pregnancies exposed to busulfan (Briggs et al., 1994). Six cases of birth defects have been reported after busulfan exposure during pregnancy; there was no specified pattern to the anomalies. In the first case, a woman was treated with busulfan and 6-mercaptopurine throughout the majority of her pregnancy. The infant had severe growth retardation, cleft palate, microphthalmia, hypoplastic ovaries, bilateral corneal clouding, and poorly developed external genitalia (Diamond et al., 1960). Another infant, exposed throughout the pregnancy developed pyloric stenosis (Gililand and Weinstein, 1983). Two abortuses were reported following busulfan exposures, one with unspecified multiple abnormalities (deRezende et al., 1965) and one with myeloschisis (Abramovici et al., 1978). The remaining two cases cannot be directly correlated to the busulfan exposure either because the exposure occurred later in the pregnancy or the abnormality had a genetic basis (Boros and Reynolds, 1977; Saroux and Lefrancois, 1977). There have been over 30 normal offspring born following in utero exposure to busulfan (Summarized in Nicholson, 1968).

#### Chlorambucil (Leukeran)

Chlorambucil is used to treat chronic lymphocytic leukemia (CLL), Hodgkin's disease and non-Hodgkin's lymphoma (Hardman et al., 1996). More recently, it has been used to treat rheumatic disease and systemic lupus erythematosus because of its immunosuppressive properties (Ramsey-Goldman and Schilling, 1997). Four birth defects have been reported following first trimester exposure to chlorambucil. Two fetuses exposed at 5-11 weeks and 7-20 weeks respectively, had kidney and ureter agenesis. A third fetus, exposed at weeks 3-4, had a retinal defect (Rugh and Skaredoff, 1965; Shotten and Monie, 1963; Steege and Caldwell, 1980). Finally, a fetus exposed in the tenth week had a congenital heart defect (Thompson and Conklin, 1983). Several normal pregnancies have been reported after exposure to chlorambucil (summarized in Schardein, 1993; Ramsey-Goldman and Schilling, 1997; Jacobs et al., 1981; David et al., 1993).

#### Cyclophosphamide (Cytosan, Neosar)

Cyclophosphamide is used in the treatment of ALL, CLL, Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, Wilms' tumor, soft-tissue sarcomas, cancers of the breast, ovary, lung, and cervix, (Hardman et al., 1996) and connective tissue disorders such as systemic lupus erythematosus (Clements, 1991). Cyclophosphamide is commonly used in combination chemotherapy regimens (see Combination Chemotherapy Section). Five cases of birth defects have been reported in conjunction with first trimester exposure to cyclophosphamide. The first case, an infant exposed from weeks 4-11, had four toes on each foot, a flattened nasal bridge, palatal grooves, a small skin tag on the anterior mid-abdomen, a slightly hypoplastic middle phalanx of the fifth finger and bilateral inguinal hernia sacs (Greenberg and Tanaka, 1964). In a second case, a woman exposed to cyclophosphamide and

radiation terminated a male fetus with no toes and a single left coronary artery (Toledo et al., 1971). Another first trimester exposure resulted in a growth-retarded infant with imperforate anus and a rectovaginal fistula (Murray et al., 1984). Kirshon et al. (1988) reported exposure on days 15 and 46 in an infant with bilateral radial ray defects, cleft palate, low-set ears and multiple eye anomalies. Reynoso et al. (1987) described an exposed fetus with club hand, esophageal atresia and abnormal inferior vena cava. Additionally, reports exist of neonatal immunosuppression following in utero exposure (Khurshid and Saleem, 1978; Okun et al., 1979, Pizzuto et al., 1980, Zuazu, 1991) and a child who developed papillary thyroid cancer and neuroblastoma (Zemlickis, 1993).

#### Mechlorethamine (Nitrogen Mustard, Mustargen)

Mechlorethamine, used to treat Hodgkin's disease and non-Hodgkin's lymphoma (Hardman et al., 1996), is most commonly used in combination chemotherapy. Two reports of first trimester exposure resulted in infants with birth defects, but the mothers were also exposed to other agents. One child had four toes on each foot, a malformed ear, bowed tibia and cerebral hemorrhage (Garrett, 1974). A second exposed fetus had small malpositioned kidneys (Menutti et al., 1975). A third malformed fetus was described with hydrocephaly and early infant death following first trimester exposure (Zemlickis, 1992). At least 10 other reports document normal pregnancy outcome following in utero exposure to mechlorethamine (summarized in Briggs et al., 1994; Schardein, 1993) with an increased number if combination chemotherapy cases were included.

#### **Antibiotics:**

Antibiotics used in chemotherapy covalently bind to DNA, causing cytotoxicity (Hardman et al., 1996). The most commonly used antibiotics include doxorubicin, mitomycin, catinomycin and bleomycin. The antibiotics are most often used in combination chemotherapy (see section on combination chemotherapy). None of these agents has been associated with an increased risk of birth defects when used during the first trimester (summarized in Schardein, 1993). However, one case of bleomycin exposure in combination with two other drugs, 7 to 10 days before delivery, resulted in transient neonatal leukopenia and neutropenia in a premature infant (Raffles et al., 1989).

#### **Antimetabolites:**

The antimetabolites are comprised of analogues of folic acid, purines and pyrimidines. Antimetabolites interfere with the function of these components, resulting in deficiencies or substitutions of the above (Hardman et al., 1996).

#### Amnioplerin

Amnioplerin is a folic acid antagonist and abortifacient. A known human teratogen, it is no longer used in cancer treatment. The amnioplerin syndrome is characterized by central nervous system abnormalities, including spina bifida, mental retardation, hydrocephalus and anencephaly. Other abnormalities include synostosis of the lambdoid sutures, partial or absent ossification of bones, micrognathia, high arched palate, short extremities, syndactyly of fingers, absent digits, clubfoot, large anterior and posterior fontanelles, wide depressed bridge of the nose and wide-set eyes. Cardiac abnormalities such as dextrocardia have also been reported (Powell and Ekert, 1971). There are a total of 17 reported cases of malformations following exposure to amnioplerin during the first trimester (summarized in Schardein, 1993). About half of the cases resulted in a liveborn with the remainder resulting in miscarriage or stillbirth.

#### Methotrexate (Amethoplerin)

Methotrexate, closely related to aminoplerin, also acts as a folic acid antagonist and abortifacient (Hardman et al., 1996). Methotrexate is commonly used to treat ALL, cancers of the breast, head, neck

and lungs (Hardman et al., 1996) and rheumatic disease (Songstridey and Furst, 1990). There are four documented cases of malformations consistent with aminopterin syndrome following exposure to methotrexate in utero (Milunsky et al., 1968; Powell and Ekert, 1971; Diniz et al., 1978, Buckley et al., 1997). Additionally, an ultrasound study by Van den Hof et al. (1990) reported 2 out of 14 fetuses exposed to folic acid antagonists during the first trimester had neural tube defects. Severe myelosuppression has been reported in two infants exposed to methotrexate and other chemotherapeutic agents in utero (Tokuda et al., 1994). There have been over 20 reports of normal pregnancies following fetal methotrexate exposure (summarized in Schardein, 1993). Kozlowski et al. (1990) described 10 pregnancies exposed to low-dose weekly methotrexate for rheumatic disease, resulting in 3 spontaneous abortions, 2 elective abortions and 5 normal infants (mean follow-up: 11 years). Donnenfeld et al. (1994) reported three normal infants, two after first trimester in utero exposure to methotrexate and one after exposure during the third trimester.

#### 5-Flourouracil (Adrucil, Efudex, 5-FU)

5-FU is a pyrimidine antagonist that interferes with DNA and RNA synthesis (Hardman et al., 1996). It is commonly used to treat cancer of the breast, colon, stomach, pancreas, ovary, head, neck and bladder (Hardman et al., 1996) and topically to treat human papillomavirus infections (Van Le et al., 1991). There is one case report of a therapeutically aborted fetus exposed to 5-FU from 11-12 weeks gestation. The fetus had bilateral radial aplasia with absent thumbs and fingers (two on one hand and one on the other), hypoplasia of the lungs, aorta, thymus and bile ducts and aplasia of the esophagus, duodenum and ureters (Stevens et al., 1980). Another fetus exposed to 5-FU during the third trimester was structurally normal but had cyanosis and jerking of extremities during the neonatal period (Stadler and Knowles, 1971). A small but healthy neonate was born following a five month exposure to high dose 5-FU during the second and third trimesters (Dreicer and Love, 1991). There have been at least 4 other normal pregnancies reported following in utero exposure to 5-FU (summarized in Schardein, 1993). A study investigating the effects of topical 5-FU noted four normal infants and one infant with 47,XXX (Van Le et al., 1991).

#### Cytarabine (Cytosar, AraC, Cytosine arabinoside)

Cytarabine is a pyrimidine antagonist that impairs nucleic acid synthesis (Hardman et al., 1996). It is used in the treatment of AML and ALL (Hardman et al., 1996). There are two case reports of birth defects associated with cytarabine exposure during pregnancy. Wagner et al. (1980) reported an infant exposed to cytarabine early in pregnancy with bilateral microtia, atresia of the external auditory canals and abnormalities in three of four limbs. The second case involved a woman treated with cytarabine and thiogaunine who delivered an infant with distal limb defects including the thumbs and two digits on each foot (Schafer, 1981). Pancytopenia and low birth weight was observed in one infant exposed to cytarabine and several other chemotherapeutic drugs during the first trimester (Pizzuto et al., 1980). There are at least 15 case reports of normal infants and fetuses following in utero exposure to cytarabine, with increased numbers if combination chemotherapy cases were added (summarized in Schardein, 1993; Caligiuri and Mayer, 1989; Schafer, 1981; Taylor and Blom, 1980; Newcomb et al., 1978, Lilleyman et al., 1977).

#### Azathioprine (Imuran)

Azathioprine is a purine antagonist that metabolizes to 6-mercaptopurine (Hardman et al., 1996). It is most commonly used to treat leukemias, lupus, rheumatoid arthritis (Dameshek and Schwartz, 1960), inflammatory bowel disease (Present et al., 1989) and as an anti-rejection medication following transplantation (McKendry, 1991). There are three reports of birth defects associated with in utero exposure to azathioprine. One infant was born with unilateral polydactyly (Williamson and Karp, 1981). The second case was an infant with pulmonic stenosis who was not exposed during the first

trimester (Nishimura and Tanimura, 1976). The final case, also exposed in the second trimester, described an infant with an atrial septal defect (Burluson et al., 1983). Because of the inconsistent nature of these anomalies it is unlikely that azathioprine use during pregnancy increases the risk for birth defects above the general population risk. Intrauterine growth retardation has been noted after in utero exposure to azathioprine, primarily in pregnancies of renal transplantation patients; the underlying disease may have contributed to this observation (Davidson and Lindheimer, 1982; Marushak et al., 1986). In a study by Cararach et al. (1993) examining the outcomes of 103 pregnancies in renal transplantation patients, 90% were exposed to azathioprine during gestation and no increase in birth defects were noted. No congenital anomalies were observed in 20 infants born to mothers treated with azathioprine during pregnancy following heart transplantation (Haagsma et al., 1989; Baxi and Rho, 1993; Wagoner et al., 1994). In addition, 14 normal infants were reported following first trimester exposure to azathioprine to treat inflammatory bowel disease (Alstead et al., 1990).

### **Vinca Alkaloids:**

Vinka alkaloids inhibit spindle formation by binding to tubulin and preventing cell division during the M phase of cell division (Sorosky et al., 1997).

#### **Vinblastine (Velban)**

Vinblastine is commonly used in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma and breast cancer. Of 10 case reports of fetuses exposed to vinblastine, there were no reported abnormalities (summarized in Schardein, 1993; Schapira and Chudley, 1983). There are two case reports of adverse outcomes following first trimester exposure: one spontaneous abortion and one infant with hydrocephalus (Schilsky et al., 1980). Vinblastine has been used in conjunction with other chemotherapeutic agents; reports of birth defects exist but these have been attributed to other agents.

#### **Vincristine (Oncovin)**

Vincristine is used to treat ALL, AML, Wilms' tumor, Hodgkin's disease and non-Hodgkin's lymphoma (Hardman et al., 1996). Vincristine is also very commonly used in combination with other chemotherapeutics. No congenital malformations were noted in 14 infants born to mothers treated with only vincristine (summarized in Schardein, 1993). There have been at least 2 case reports of complications following exposure to vincristine in conjunction with other chemotherapeutic agents; it is possible that these complications were related to the other drugs (summarized in Gililand and Weinstein, 1983).

### **COMBINATION CHEMOTHERAPY**

There are several combinations of chemotherapy that are commonly used to treat various types of cancer. The information is summarized below; overall, there does not appear to be an increased risk of birth defects associated with any particular combination therapy. Doll et al. (1989) noted that the rate of fetal malformation when more than one chemotherapeutic agent was used was similar to the rate observed with monotherapy.

CHOP= cyclophosphamide, doxorubicin, vincristine, prednisolone

CHOP-Bleo= same as above, plus bleomycin

COPP= cyclophosphamide, vincristine, prednisone, procarbazine

COP-Bleo= cyclophosphamide, vincristine, prednisone, bleomycin

CEOP-Bleo= cyclophosphamide, epidoxorubicin, vincristine, prednisone, bleomycin

DATOP= daunorubicin, arabinosylcytosine, thioguanine, vincristine, prednisone

ABVD= adriamycin, bleomycin, vinblastine, decarbazine

AVTEP= doxorubicin, vincristine, teniposide, cyclophosphamide, prednisone

MOPP= mechlorethamine, vincristine, procarbazine, prednisone

### **Combination Chemotherapy Treatment and Pregnancy Outcomes Treatment Follow Up Reference**

CHOP All normal Ward 1989, Aviles 1991, Zuazu et al 1991

CHOP-Bleo All normal Aviles, 1991

COPP 1 normal, 1 EAB Ward 1989, Zuazu et al. 1991

COP-Bleo Normal Ward 1989

CEOP-Bleo All normal Aviles 1991

DATOP 3 normal, 2 SAB(nml) Zuazu et al. 1991

ABVD All normal Aviles 1991

AVTEP Normal Ward 1989

MOPP 11 Normal, 1 SAB Ward 1989, Aviles 1991, Zuazu et al 1991

### **COUNSELING ISSUES**

Following a cancer diagnosis early in pregnancy, a patient must cope with the shock of the diagnosis, her own mortality, and potential fears about the future of her unborn child. Regardless of treatment, it is important to assess the patient's support system and make referrals when appropriate. Because cancer during pregnancy is relatively uncommon, it may be difficult to find anyone who has a similar experience. The National Cancer Information Service (1-800-4-CANCER) may be of assistance.

Both patient and physician must weigh the risks and benefits of delaying treatment until after the first trimester versus the prognosis of the cancer. If treatment cannot be delayed, termination of pregnancy may be an option for some women. Chorionic villus sampling and amniocentesis are not useful in detecting teratogenic effects of chemotherapeutic agents because there is no increased risk of chromosome abnormalities related to treatment. Targeted ultrasound may detect certain structural anomalies associated with first trimester exposure to chemotherapeutics.

### **OCCUPATIONAL EXPOSURE TO CHEMOTHERAPEUTIC AGENTS**

Information on the reproductive effects of workplace exposure to chemotherapeutic agents is limited. A study by Selevan et al. (1985) observed an increased risk of fetal loss in nurses exposed to cyclophosphamide, doxorubicin and vincristine. However, because most nurses reported handling more than one agent, the individual effects of each drug could not be assessed. deWerk et al.. (1983), investigated the potential risks of inhaling chemotherapeutic agents. Most surveyed facilities had inadequate ventilation and did not use universal precautions when handling the medications. The authors found that 5-FU and cyclophosphamide could linger in the air and potentially be inhaled and systemically absorbed. Since there is little information regarding risks associated with occupational exposure to chemotherapeutics, it is prudent to minimize exposure in the pregnant worker. Ideally this means total avoidance, but other ways to decrease exposure include working in a hood, and using gloves, mask and other protective clothing.

### **SUMMARY**

Most data suggests that cancer survivors are not at increased reproductive risk for offspring with structural malformations, aneuploidy or childhood cancers. While there are reports that provide specific risk estimates after first trimester exposure to chemotherapeutic agents (e.g. Schardein, 1993), the paucity of human data and the reporting biases inherent in case reports make the accuracy of these estimates suspect. Case reports of malformations and normal outcomes have been published. Studies of

combination chemotherapy do not suggest an increased risk as compared to monotherapy. In any case of cancer diagnosed during pregnancy, the risks and benefits of starting versus delaying treatment must be weighed. In those women where treatment is initiated in the first trimester, targeted ultrasound may be useful in detecting structural abnormalities. It has been recommended that chemotherapy be ceased three weeks prior to delivery in order to minimize neonatal complications.

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