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Cancer Chemotherapy and Pregnancy

This clinical practice guideline has been prepared by the Chemotherapy During Pregnancy Working Group and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Gideon Koren, MD, Toronto ON

Nathalie Carey, BSc, Toronto ON

Robert Gagnon, MD, Montreal QC

Cynthia Maxwell, MD, Toronto ON

Irena Nulman, MD, Toronto ON

Vyta Senikas, MD, Ottawa ON

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Abstract

Objective: To promote careful education, administration, monitoring and restricted distribution when prescribing and dispensing chemotherapeutic and potentially teratogenic medications, as well as to develop clinical recommendations for the use of cancer chemotherapy in pregnant women and women of child-bearing age.

Outcomes: To ensure that women of child-bearing age receiving chemotherapy can be appropriately counselled on the risks of becoming pregnant during treatment, and to provide guidance for health care practitioners treating pregnant women with antineoplastic agents.

Evidence: Published literature was retrieved through searches of PubMed or Medline, CINAHL, and The Cochrane Library in 2011, using appropriate controlled vocabulary (e.g., antineoplastic agents, neoplasms, pregnancy) and key words (e.g., cancer, neoplasms, pregnancy, chemotherapy, antineoplastic agents). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Studies were restricted to those with available English abstracts or text. Searches were updated on a regular basis and incorporated in the guideline to October 2011. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and from national and international medical specialty societies.

Values: The quality of evidence is rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: This guideline highlights the need to prevent pregnancy in women who are being treated for cancer and informs health care professionals treating pregnant women with chemotherapy of the potential risks of the therapy or ameliorated treatment protocols.

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Key Words: Pregnancy prevention, cancer, neoplasms, pregnancy, chemotherapy, antineoplastic agents

SUMMARY STATEMENTS AND RECOMMENDATIONS

Summary Statements

1. As women are postponing child-bearing, more of them are experiencing cancer in pregnancy. (II-2)
2. Chemotherapeutic agents used to combat cancer cross the placenta and may adversely affect embryogenesis by affecting cell division. (II-1)
3. Exposure to such agents after the first trimester of pregnancy has not been associated with increased risk of malformations but is associated with increased risk of stillbirth, intrauterine growth restriction, and fetal toxicities. (II-2)

Recommendations

1. The health care provider should examine the patient's risk of pregnancy and desire to prevent pregnancy during chemotherapy. (I-A)
2. Decisions about the best course of management in pregnancy, including timing of delivery, should balance maternal and fetal risks. Most authorities concur that maternal health and well-being must prevail. (I-A)
3. Women diagnosed with cancer in pregnancy should be optimally managed by a multidisciplinary team that includes oncologists and/or hematologists (depending on the malignancy), perinatologists, family physicians, psychologists, social workers, and spiritual advisors, if sought by the family. (I-A)

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[88]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[88]

INTRODUCTION

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%.[1] A diagnosis of cancer during this stage of life may postpone or complicate child-bearing.

Almost all chemotherapeutic agents are teratogenic in animals. For some drugs only experimental data exist. Women diagnosed with cancer during their child-bearing years should therefore be made aware of the risks associated with the use of cancer chemotherapy in pregnancy. Information must be provided by the woman's health care providers, including the obstetrician, who can engage in an active discussion, answer questions, and provide any additional clarification required.

Research conducted by Santucci et al.[2] suggested that women want their health care providers to initiate discussions regarding the potential teratogenic/reproductive risks of exposure to medications. The following are important principles of effective teratogenic counselling:

1. Timely provision of information
2. Provision of data on all potential effects on a fetus
3. Provision of clear information
4. Repetition of important information
5. Avoidance of assumptions about women's pregnancy intentions
6. Explanation of why health care providers are asking about sexual activity and pregnancy intentions
7. Discussion of consequences for reproductive health.[2]

These discussions are best conducted by multidisciplinary teams that include the woman's family physician, hematologist and/or oncologist, and obstetrician-gynaecologist.

Providing women with detailed and updated information about pregnancy-related risks before they begin chemotherapy is necessary to reduce the risk of fetal exposure. Since nearly one half of pregnancies are unplanned, the use of effective methods of contraception during chemotherapy should be discussed. To date, no cases of fetal exposure to lenalidomide have been reported, highlighting the effectiveness of the RevAid program,[3] and supporting the use of such methods.

ABBREVIATIONS

ABD	doxorubicin, bleomycin, dacarbazine
ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
AVD	doxorubicin, vinblastine, dacarbazine
CNS	central nervous system
FAC	5-fluorouracil, doxorubicin, cyclophosphamide
IUGR	intrauterine growth restriction
MOPP	mechlorethamine, vincristine, procarbazine, prednisone

The occurrence of cancer in pregnancy is a rare and challenging event, complicating up to 0.02% to 0.1% of pregnancies annually.[4,5] Because of the rise in delayed child-bearing, the rates of cancer in pregnancy are expected to rise with the increased incidence of several age-dependent malignancies.[5] The cancers most commonly diagnosed during pregnancy are breast cancer, cervical cancer, thyroid cancer, Hodgkin's lymphoma, and non-Hodgkin's lymphoma.[4]

Although surgery is generally considered safe during pregnancy, there is little information regarding the safety of cytotoxic agents, which are often required in the optimal management of cancer.[4,6] Anticancer drugs aim, through different mechanisms, to arrest cell division and cell growth. By doing so, they pose direct risk to the developing embryo during the first trimester of pregnancy. Knowledge of pregnancy outcomes following cancer treatment has been limited by the low prevalence of cancer during pregnancy, high rates of pregnancy terminations in women with cancer, and the decision not to treat during critical fetal periods. The scarce evidence regarding the fetal safety of maternal chemotherapy during pregnancy is limited to small retrospective studies and case reports that are often underpowered, making their results difficult to interpret and generalize. Additionally, because cytotoxic agents are usually administered in multiple-drug regimens, it is difficult to estimate the potential teratogenic effects of each individual drug.[7] In contrast to this paucity of information, there is a plethora of animal studies showing high rates of teratogenicity for most cancer chemotherapeutics. The main problem in interpreting these experimental data is the substantially higher dose per kg (or m^2) used in the animal experiments, and inability to extrapolate these data to human experience.

Several issues highlight the problems of drug therapy facing pregnant women. An estimated 50% of pregnancies are unplanned, so many women are exposed to teratogens before they realize they are pregnant.[8] Also, women may decline treatment, even for life-threatening conditions, for fear of being exposed to medication that could harm their fetus.[9]

Following a diagnosis of cancer in pregnancy, the pregnant woman, her family, and her medical team are required to make complex treatment decisions, often in the absence of definitive evidence. Without standardized guidelines concerning chemotherapy in pregnant women, a woman may compromise her health or the health of the developing fetus.

PREGNANCY PREVENTION

The detrimental impact of thalidomide worldwide in the late 1950s and early 1960s[1] provides clear evidence of the need for careful education, administration, monitoring and restricted distribution in prescribing and dispensing chemotherapeutic and potentially teratogenic medications. The devastating effects of fetal exposure to teratogenic drugs are not limited to thalidomide: diethylstilbestrol was withdrawn from the Canadian market, and isotretinoin capsules are available only through a company-sponsored pregnancy prevention program.[2,4,5,10]

Beyond awareness and education, the health care professional and the patient must examine the patient's risk of pregnancy, including fertility and/or menopausal status (with consideration of previous chemotherapy and age), frequency or potential of sexual activity with a male partner, and desire to prevent pregnancy.

After completing a pregnancy risk assessment, the patient and health care provider must fully discuss methods of contraception, giving careful consideration to the efficacy and availability of contraceptive options, the patient's previous choices and her motivation to adhere to a contraceptive regimen, the rate of adherence, ease of use, cost, side-effect profile (considering disease state and chemotherapy regimen), and access to emergency contraception.

While a contraceptive plan may be in place, health care providers should check frequently with the patient to assess adherence and satisfaction with the chosen methods. Additional considerations may be necessary for higher risk populations, including teenage patients. This additional support and optimal prevention of fetal exposure to teratogens for all women of child-bearing age can be achieved with the implementation of an effective controlled distribution program such as RevAid.[3]

DEFINING TERATOLOGY

Physiological Background

Teratogenesis is defined as the structural or functional dysgenesis of fetal organs.[11] Broadly, exposures that irreversibly affect the normal growth, structure, or function of a developing embryo or fetus are defined as teratogenic.[12] Known teratogens include environmental factors such as radiation, certain viruses such as rubella, chemicals such as alcohol, and therapeutic drugs such as thalidomide and isotretinoin.[9] Teratogenic effects vary widely in severity and range, and include death (miscarriage or stillbirth), malformations, impaired organ functioning, impaired fertility, and mutagenicity.[8]

Congenital malformations, defined as defects in organ structure or function, occur in 1% to 3% of the general population.[9] Of the major defects, about 25% are of genetic origin and 65% are of unknown etiology.[9] Only 2% to 3% of malformations are believed to be associated with drug treatment.[8]

The teratogenic potential of any drug depends on a variety of factors that include the extent of its placental transfer,

the dose administered, the duration of exposure, the genetic variability in drug metabolism of the mother and the fetus, and the timing of exposure.

Teratogens must reach the fetus in sufficient amounts and during critical time windows to cause adverse fetal effects.[8,9] Most drugs reach the fetus through the maternal bloodstream, and several factors can affect the fetus's exposure to the drug Most molecules with molecular weights smaller than 500 Da easily diffuse across the placenta, whereas large molecules with molecular weights greater than 1000 Da do not easily cross the placental barrier.[8,9] Additionally, factors such as lipid solubility, polarity, maternal and fetal pH, protein binding, and maternal drug metabolism profile can affect the amount of drug reaching the developing fetus.[8,9]

The timing of the exposure is critical, as the effect produced by a teratogen depends on the developmental stage.[8,9]

The all-or-none period

The all-or-none period includes the time from conception until somite formation (on average 8 to 14 days from conception). Insult during this phase typically results in fetal death and miscarriage, or intact survival. Teratogen exposure at this stage may interrupt processes that facilitate implantation, leading to miscarriages. However, if implantation is successful despite teratogen exposure, the fetus is expected to develop normally. This is due to the presence of totipotent cells found in the undifferentiated embryo at this time; these cells enable repair and recovery of damaged tissue. In general, exposure during this period does not cause congenital malformations unless the insult persists beyond this stage.[9]

Organogenesis

The most sensitive period of drug exposure is during *organogenesis,* which occurs roughly 2 to 8 weeks post-conception during the embryonic period.[9] Especially during gastrulation, which occurs 3 to 5 weeks post-conception, tissues are differentiating rapidly, and damage becomes vast and irreparable. Additionally, each organ system has a period of maximum vulnerability. For example, the neural tube, heart, and limbs are affected earlier than the palate and ears. Following organogenesis, the genitals, eyes, CNS, and hematopoietic system continue to be sensitive to teratogenic insult.[8,9]

The fetal phase

The fetal phase, from the end of the embryonic stage to term, is characterized by growth and functional maturation of formed organs and systems. Exposures during this later stage of pregnancy can result in IUGR and low birth weight, and may affect the size or function of several organs.[8,9]

In summary, the teratogenic potential of a drug is dynamic, affected by the timing, the dose, and the molecular properties of the teratogens, and by cumulative exposure.

HISTORICAL PERSPECTIVE

The consequences of thalidomide use in the late 1950s and early 1960s dramatically changed the public perception regarding fetal exposures during pregnancy, leading to fear and resistance against pharmacotherapy, as well as to extensive research in the field. Before this, it was generally believed that the placenta served as a barrier to prevent adverse effects of drugs from reaching the fetus.[8]

Thalidomide, although originally marketed as a safe and effective sedative and anti-emetic for the management of nausea and vomiting in pregnancy, was found to cause malformations at a frequency of 15% to 100%, particularly when taken between 27 and 50 days post-conception.[13,14] Although the rates of malformation for thalidomide were high and followed a characteristic pattern (phocomelia and CNS dysmorphology), its teratogenicity was not suspected for several years. In Canada, 115 children were born with malformations after exposure to the drug.[15] As a result, thalidomide was withdrawn from Canadian markets on March 2, 1962, although some pharmacies continued to have the drug available as late as May 1962.[13,14]

AVOIDING TERATOLOGICAL RISKS

Although the teratological risks of thalidomide are clear, this drug and lenalidomide are currently indicated in treating multiple myeloma. Their effectiveness in treating this disorder suggests there is a need for them. However, their high risk for teratogenicity, combined with the high occurrence of unplanned pregnancies, demands safety measures in their distribution to ensure they are not used during pregnancy.

These requirements led to the establishment of the RevAid program,[3] which carefully and effectively controls the distribution of thalidomide and lenalidomide. Only prescribers registered with the RevAid program are able to prescribe lenalidomide and thalidomide to patients. Physicians registered with RevAid are informed of the risks of these medications, and especially the risks they pose during pregnancy. In registering, the physicians must comply with the requirements of the program, which include an obligation to inform patients considering treatment with these drugs of all the risks and benefits of the drugs and requirements of the RevAid program. All patients and physicians are required to complete a RevAid Patient-Physician agreement form. In addition, only RevAid certified pharmacists may dispense thalidomide or lenalidomide. These specially trained pharmacists must also agree to comply with the requirements of the program.

The conditions that must be met for access to thalidomide or lenalidomide are the most stringent for women of child-bearing age. Women must be warned of the potential for birth defects and that, because of the risk to others, they must never share their medication or give blood up to 4 weeks after ceasing to take the medication. To ensure prevention of pregnancy, the RevAid program requires that women use 2 methods of contraception in parallel, starting 4 weeks before they begin taking the medication and continuing until 4 weeks after cessation of therapy. In addition, they must consent to regular pregnancy tests before and during treatment. Two pregnancy tests are given before the first prescriptions; a pregnancy test is done weekly during the first 4 weeks of therapy; and, with regular therapy, pregnancy tests are performed every 4 weeks with both regular or no periods, and every 2 weeks if periods are irregular.

The RevAid program represents a safe, controlled way to provide these useful drugs to people who are not at risk of suffering their negative effects. As many chemotherapeutic agents are potentially teratogenic, and as women of childbearing age often require prompt pharmacological intervention, guidelines like those of the RevAid program are necessary to prevent pregnancy during chemotherapy treatment.

In Canada, a program similar to RevAid outlines the use of isotretinoin.[10] Women are informed of fetal risks, are prescribed 2 contraceptive methods in parallel, and sign a document attesting to compliance. However, unlike the RevAid program, it does not require registration and has no mandatory follow-up. The lack of these measures has resulted in unplanned pregnancies and fetal exposures to this teratogen, highlighting the importance of thorough guidelines outlining the distribution of all teratogenic substances in women of child-bearing age.

Currently, no guidelines exist for the use of chemotherapy in non-pregnant women of child-bearing age. The development of a program similar to RevAid to monitor the distribution of chemotherapeutic agents and follow-up on all women enrolled in the program are needed to ensure pregnancy prevention during chemotherapy treatment.

Additional guidelines are necessary to address the use of chemotherapy when it is indicated during pregnancy. The importance of these guidelines is 2-fold. First, they would give health care providers a conclusive resource on which to base their treatment plans. Second, they would help to dispel common misconceptions patients have about the use of chemotherapy during pregnancy; this will encourage pregnant women to pursue care that ensures the best long-term outcome for themselves and their infants.

CANCER AND PREGNANCY

The diagnosis of cancer during pregnancy poses difficult dilemmas for the pregnant patient, her family, and the medical team. Cancer in pregnancy is rare, complicating up to 0.02% to 0.1% of pregnancies annually.[4,5,16]

The cancers most commonly diagnosed in pregnancy are breast cancer, cervical cancer, thyroid cancer, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. See Table 2 for details on particular cancers during pregnancy.

ANTINEOPLASTIC AGENTS AND PREGNANCY

The main challenge in managing cancer during pregnancy is treating the patient with the optimal anti-cancer regimen without harming the developing fetus. Critically, for the best chance at survival for the mother, chemotherapy cannot always be postponed until the end of the pregnancy, and no current regimen has been confirmed (by studies with sufficient statistical power) safe for use during gestation.

Because of their relatively low molecular weight, most cytotoxic agents cross the placenta and reach the fetus.[17,18] The pharmacology of various anti-cancer drugs may be altered by the normal physiological changes that occur during pregnancy, such as increased plasma volume, enhanced renal and hepatic elimination, and decreased albumin concentration. Dosing similar to that of non-pregnant women of the same weight may lead to under-treatment of pregnant women with cancer.[18] However, it is still not clear whether pregnant women should be treated with different doses of chemotherapy, and no studies have addressed the effectiveness of treatment regimens in pregnancy.

Chemotherapy during the first trimester may increase the risk of spontaneous abortions, fetal death, and major congenital malformations. The teratogenic effects depend on the dosage, time of administration, and cumulative exposure to the chemotherapeutic agent. Fetal malformations reflect the gestational age at exposure, and the most vulnerable period is during weeks 2 to 8, when organogenesis occurs. The eyes, ears, teeth-palate, genitalia, hematopoietic system, and CNS remain vulnerable to chemotherapy beyond organogenesis.[17]

Almost all chemotherapeutic agents are teratogenic in animals. For many chemotherapeutic agents, the risk of teratogenesis in humans is unknown. However, the risk of teratogenesis in humans following cancer treatment appears to be lower than is commonly estimated from animal data because of the proportionately larger doses used in animals First trimester exposure to chemotherapy has been estimated to have a 10% to 20% risk for major malformations. It has been suggested that this risk may decline to about 6%

Table 2. Cancers during pregnancy

Cancer	Frequency in pregnancy	Diagnosis	Staging	Pathology	Prognosis
Bone malignancies	Unknown	• Pain • Joint dysfunction • Pathological fractures	• MRI • Ultrasound • Biopsy	—	• Limited data suggest that pregnancy does not exacerbate tumour growth or affect the patient outcome.
Breast	0.01% to 0.3%	• Often delayed in pregnancy, 9 to 15 months • Ultrasound • Excisional biopsy (palpable mass) • Incisional mass (large mass)	• Clinical examination • Biopsy • Ultrasound or MRI • Stage II/III (65% to 90%)	• Invasive ductal carcinoma (75% to 90%) • Inflammatory breast cancer (1.5% to 4%)	• No differences found in survival between pregnant and non-pregnant women with breast cancer of same nodal status. • However, pregnant women have 2.5-fold higher risk for metastases because of delays in diagnosis.
Cervical	0.0015% to 0.012%	• Papanicolaou smear • Abnormal cytology • Colposcopy	• Clinical examination • Biopsy or cone histology • Ultrasound and MRI • Stage I (79%) • Stage II/III (21%)	• Squamous carcinoma (> 80%) • Adenocarcinoma • Neuroendocrine	• Higher proportion of early stage tumours likely due to increased screening performed routine antenatal care. • No differences in survival of matched pregnant and non-pregnant women.
Hepatocellular carcinoma	Unknown	• Right upper quadrant pain or distention and weight loss.	• Liver sonography • MRI • Fine liver aspiration	—	• Small number of published cases precludes any firm conclusions.
Hodgkin's Lymphoma	0.016% to 0.1%	• Painless lymph node enlargement • Lymph node biopsy	• Physical exam • Blood tests • Bone marrow biopsy • Abdominal ultrasonography or chest X-ray with abdominal shielding • MRI	• Nodular sclerosis most common. • Histological subtypes are the same as in non-pregnant women < 40 years.	• Survival rates found to be similar to that of non-pregnant control matched for age, stage and treatment protocol.
Intracranial tumours	Unknown	• Headache • Nausea and vomiting • Nonspecific symptoms to focal neurologic deficits such as hemiparesis and visual field defects. • Pregnancy can exacerbate neurology with the patient presenting with impending or actual cerebral herniation. • Common symptoms of intracranial pressure can potentially be confused with routine pregnancy-related conditions.	• MRI	—	• Very limited data suggest that pregnancy does not exacerbate tumour growth or affect the outcome of the patients.

continued

Table 2. ***Continued***

Cancer	Frequency in pregnancy	Diagnosis	Staging	Pathology	Prognosis
Leukemia	0.001%	• Blood work • Bone marrow biopsy	• Ultrasounds • MRI	• Acute myeloid leukemia • Acute lymphoblastic leukemia • Chronic myeloid leukemia • Chronic lymphocytic leukemia	• Spontaneous abortion, prematurity, IUGR, and death have been associated with maternal leukemia. • Survival rates found to be similar to that of non-pregnant control matched for age, stage and treatment protocol.
Lung	Unknown	• Symptoms such as blood-streaked sputum, persistent cough or change in cough pattern, wheezing, decreased appetite with poor weight gain, along with other loco-regional symptoms are commonly seen. • Delays in diagnosis may occur because of low index of suspicion, tendency to attribute symptoms such as fatigue and dyspnea on the pregnant state and the reluctance to order chest radiography during pregnancy.	• Anteroposterior and lateral chest radiographs. • Ultrasound • MRI • Sputum cytology • Fine needle aspiration biopsy • Bronchoscopy with biopsy • Bronchoalveolar lavage	• Non-small cell lung cancers, in order of most to least frequent: adenocarcinoma, squamous cell, large cell, and bronchoalveolar. • Small cell lung cancer.	• No evidence that pregnancy alters the prognosis of lung cancer. • Maternal outcome for both small cell and non-small cell lung cancer has been poor and is a reflection of the advanced stage at diagnosis.
Malignant melanoma	0.014% to 0.28%	• Changes to the shape or colour of existing moles or any pigmented lesion, or the appearance of a new lump anywhere on the skin.	• Assessment of tumour site. • Ultrasound • Fine needle aspiration biopsy. • Lymphatic mapping with blue dye or radio-labelled tracer injected at tumour site plus sentinel lymph node biopsy. • MRI	• Superficial spreading melanomas most common (41%).	• Malignant melanoma is the most frequent cancer that metastasizes to the placenta or fetus, accounting for 31% of reported cases. • When matched for age, anatomic site and stage, most studies have not demonstrated a difference in survival between pregnant and non-pregnant women.
Non-Hodgkin's Lymphoma	0.016%	• Painless lymph node enlargement • Lymph node biopsy	• Physical exam • Blood tests • Bone marrow biopsy • Abdominal ultrasonography or chest X-ray with abdominal shielding • MRI	• Degrees of severity from indolent to very aggressive. • Histological subtypes in pregnancy appear to be aggressive with diffuse large B-cell or peripheral T-cell lymphomas being the most common.	• Survival rates found to be similar to that of non-pregnant control matched for age, stage and treatment protocol. • There may be a trend toward lower birth weight infants born to mothers who had non-Hodgkin's lymphoma in pregnancy.

continued

Table 2. *Continued*

Cancer	Frequency in pregnancy	Diagnosis	Staging	Pathology	Prognosis
Ovarian	0.002% to 0.008%	• Significant numbers of patients are asymptomatic. • Adnexal masses.	• Pelvic ultrasounds. • MRI	• Vast majority of adnexal masses are benign and are diagnosed at an early stage. • Surface epithelial-stromal tumour (50.6%) • Germ cell tumours (dysgerminomas and malignant teratomas) (39%)	• Survival rates found to be similar to that of non-pregnant control matched for age, stage and treatment protocol.
Thyroid	0.0036% to 0.014%	• New thyroid nodule or enlargement of a pre-existing nodule • Pain in the neck region, hoarseness • Horner's syndrome may be present	• Thyroid function test • Fine needle aspiration biopsy • Ultrasound	• Differentiated thyroid cancer, subtypes papillary and follicular, are most common. • Medullary thyroid cancer accounts for only 5% to 10% of all thyroid cancers.	• Survival rates found to be similar to that of non-pregnant control matched for age, stage and treatment protocol.

when folate antagonists (which are considered the most teratogenic anti-cancer drugs) are excluded.[17,19]

The administration of chemotherapy during the second and third trimesters has not been associated with major congenital malformations but may increase the risk for IUGR, low birth weight, and stillbirth. A review of 376 cases of fetuses exposed to chemotherapy in utero, most after organogenesis, demonstrated 5% fetal death rate and 1% neonatal death rate. Other complications included preterm delivery (5%), IUGR (7%), and transient myelosuppression (4%).[17]

A recent American registry of 152 women exposed to chemotherapy mostly after the first trimester demonstrated only a single case of intrauterine fetal death and a single case of neonatal death.[20] The malformation rate was 3.8%, with a 7.6% risk for IUGR. Only 2 of the 159 live born infants suffered transient myelosuppression. A European study compared the rates of adverse pregnancy outcomes in patients exposed to chemotherapy (117 pregnancies) during the second and third trimesters and in healthy control patients (58 pregnancies).[21] Although the incidences of major and minor malformations had not increased compared with previous reports, the small size of the control group prevents extensive conclusions. The rate of low birth weight was higher in the chemotherapy group (17.9%) than in the control group (8.6%). Most of the infants with low birth weight were born to mothers treated for hematological malignancies.[21]

For cancer diagnosis made late in pregnancy, consideration can be given to delaying initiation of chemotherapy balanced against gestational age and possible delivery before treatment.

The major message is that most fetuses whose exposure is limited to the second and third trimester of pregnancy are born healthy.

Specific Cytotoxic Groups

Alkylating agents

Alkylating agents are commonly used for the treatment of a variety of cancers. These compounds act directly on cell DNA to prevent rapidly replicating cells from reproducing. Their action is not specific to a particular phase of the cell cycle. Cyclophosphamide, dacarbazine, ifosfamide, mechlorethamine, and procarbazine are among those commonly used.[22]

Cyclophosphamide is commonly used for the treatment of breast cancer, ovarian cancer, and non-Hodgkin's lymphoma. Avilés et al.,[23] reported healthy pregnancy outcomes in 11 patients treated during the first trimester with cyclophosphamide-containing protocols.[23] A further 5 reported exposures in the first trimester resulted in several congenital malformations including absent big toes, single coronary artery, imperforate anus, umbilical hernia, cleft palate, multiple eye defects, and esophageal

atresia.[24–28] Included in this, one set of twin infants in which the male twin, born with congenital anomalies, later developed thyroid cancer at age 11 and stage III neuroblastoma at age13.[28] His twin sister was unaffected by the exposure and was developing normally at the time of the study, suggesting differential pharmacogenetic effects on the drug metabolism into the active form of the drug. Cyclophosphamide exposures in the second and third trimester of pregnancy are more frequent. One study examined the outcomes of 61 patients treated for different malignancies during the second and third trimester and found 59 infants were born with no malformations.[21] One infant whose mother was treated also with doxorubicin was born with hip subluxation and another infant who was exposed to the EFC protocol (epirubicin, cisplatin, fluorouracil) was born with rectal atresia. Another 110 patients exposed during the second and third trimesters to an assortment of multi-drug protocols, including cyclophosphamide, resulted in 105 normal births and 5 congenital malformations: 1 intrauterine death with normal autopsy, 1 neonatal death due to autoimmune disorder, 1 infant with IgA deficiency, 1 with pyloric stenosis, and 1 with holoprosencephaly.[20] Intrauterine growth restriction occurred in 7 cases (6%). An additional 81 women who were treated with the FAC regimen for breast cancer during the second to third trimesters demonstrated 3 congenital abnormalities, including 1 case of Down syndrome, 1 infant with ureteral reflux, and another with talipes.[29,30] Finally, 28 patients treated for breast cancer with different cyclophosphamide-containing regimens during the second and third trimesters all had normal deliveries and outcomes.[31] This information suggests that second and third trimester exposure to cyclophosphamide may not increase the risk for adverse effects.

Dacarbazine exposures occur most frequently in pregnancy during administration of ABVD protocols, or in combination MOPP, ABVD or MOPP/AVD protocols. In 19 patients treated for lymphoma with ABVD after the first trimester, 17 healthy infants were born, and 2 with congenital malformations: 1 infant with plagiocephaly, and 1 infant with fourth and fifth syndactyly.[20] In another 12 reports of lymphoma patients treated with ABVD (83.3%), MOPP/ABVD (8.3%), or MOPP/ABD (8.3%) protocols, all resulted in normal deliveries and healthy outcomes.[32] Through this limited information, it appears that exposure to dacarbazine during the later stages of pregnancy is not associated with a specific set of malformations. Use in the first trimester cannot be recommended.

Two case reports of ifosfamide treatment, combined with doxorubicin for Ewing sarcoma in pregnancy were located.[33,34] One exposure occurred during the second trimester and the other in the third trimester. Both pregnancies had normal outcomes. Scarcity of information regarding ifosfamide is a recommendation for using a better-studied alternative.

MOPP treatment, involving exposure to alkylating agents mechlorethamine and procarbazine was reported in 14 patients.[21,32,34,35] One patient treated during the first trimester delivered an infant with hydrocephaly that died 4 hours after birth.[35] A second trimester exposure to MOPP/ABV resulted in bilateral partial syndactyly of second and third digits in the fetus.[21] Twelve exposures to MOPP/ABV or ABVD described by Avilés et al., with an unspecified amount occurring in the first trimester, all resulted in normal outcomes.[32] These data suggest mechlorethamine and procarbazine are not associated with an increased risk in the second and third trimesters.

Platinum compounds

Platinum compounds form DNA adducts that result in DNA crosslinking. DNA crosslinks inhibit replication, transcription, and other nuclear functions. The combination of these events arrests cell proliferation and ultimately tumour growth. Cisplatin and carboplatin are among the most commonly used platinum compounds.

Cisplatin exposure in the second and third trimesters has been frequently described. Four patients who had cervical cancer during pregnancy and who were treated in the second trimester with cisplatin all delivered healthy infants with no congenital malformations.[36–39] Another 3 patients treated for small cell lung carcinoma and 2 treated for ovarian cancer delivered healthy infants after exposures to cisplatin.[40–42] Finally, 6 of 7 infants born to 7 patients exposed to cisplatin in various regimens for different malignancies were healthy. Only 1 infant was born with a congenital malformation, hearing loss that was attributed to genetic factors from the parents.[20] Cisplatin use in the second and third trimesters of pregnancy has not been found to be associated with any pattern or increased risk of adverse fetal effects.

Carboplatin exposure occurred during the second and third trimesters of 5 patients. Four were women with ovarian cancer, all of whom delivered healthy infants. The 1 case of CNS malignancy was the only report of an adverse pregnancy outcome, with a spontaneous abortion of a fetus with gastroschisis, as reported by Cardonick et al.[20]

Although evidence is limited**,** carboplatin exposure in the second and third trimesters does not appear to increase the risk for major malformations.

Antimetabolites

Antimetabolites are small compounds used to treat leukemia, lymphoma, and breast cancer. They act as false substrates during DNA or RNA synthesis, resulting in inhibition of cellular metabolism. This process occurs independently of the phase of the cell cycle. Common examples of chemotherapeutic agents of this drug class are methotrexate, 5-fluorouracil, aminopterin, cytarabine, tioguanine, and mercaptopurine.[22]

Methotrexate exposure during the first trimester of pregnancy has been associated with malformations similar to the aminopterin syndrome, including cranial dysostosis with delayed ossification, hypertelorism, wide nasal bridge, micrognathia, and ear anomalies.[43] In a series of 20 exposures during the first trimester, 7 infants developed this pattern of anomalies.[44–52] In addition, there were 5 cases of miscarriage and 1 case of skeletal abnormalities with ambiguous genitalia. Exposure to methotrexate (together with cyclophosphamide and 5-fluorouracil) in the second and third trimesters in 12 patients did not show the same pattern of malformations: all infants were born healthy.[31] Because of the suspected teratogenicity of methotrexate, it should not be considered a first-line therapy, and should not be used at any stage of pregnancy.

One study reported on 53 exposures to 5-fluorouracil, with 5 occurring in the first trimester.[17] One of these patients spontaneously miscarried, and there were 6 cases of IUGR. The rest of the infants had normal outcomes. A further 12 patients exposed to 5-fluorouracil, along with cyclophosphamide and methotrexate, in the second and third trimesters had normal outcomes.[31] Similarly, 18 patients treated with 5-fluorouracil for breast and colorectal cancers during the second and third trimester all had normal pregnancy outcomes.[20] Hahn et al. reported 3 congenital malformations out of 35 exposures to 5-fluorouracil in an FAC protocol during the second and third trimesters for the treatment of breast cancer.[29] One infant was born with Down syndrome, 1 with clubfoot, and 1 with congenital bilateral ureteral reflux. As these are fairly common congenital abnormalities, the authors compared these rates with expected population frequencies and determined that the chemotherapy may not have been the cause. As an antimetabolite, 5-fluorouracil is not one of the first-line agents recommended, but it has not been associated with any increased risk for malformation in the second and third trimesters.

Capecitabine exposure in 1 patient treated during the first trimester for colorectal cancer resulted in a normal pregnancy with a healthy outcome.[20] Evidence is insufficient for conclusions to be made about the safety of capecitabine.

In 9 patients treated with various regimens including cytosine arabinoside for leukemia, 5 of them during the first trimester, no congenital malformations were reported.[23] Two more patients treated during the second and third trimesters with this antimetabolite for non-Hodgkin's lymphoma and acute myeloid leukemia also had healthy pregnancy outcomes.[20] Although information is limited, there is so far no evidence to indicate that administration of cytosine arabinoside in pregnancy results in fetal malformations.

One patient treated with gemcitabine for a pancreatic tumour during the second and third trimesters had a normal pregnancy and healthy outcome.[20] A second patient treated for non-small cell lung cancer delivered prematurely, at 28 weeks, but with no congenital malformations.[53]

Anti-tumour antibiotics

Microorganisms produce these cytotoxic agents that interact directly with DNA resulting in anti-cancer activity. The manner in which antibiotics interact with DNA differs considerably between agents.

Bleomycin creates DNA breaks and is commonly used in the ABVD protocol. Cardonick et al.[20] reported on 23 exposures to bleomycin in pregnancy, with varying malignancies and regimens.[20] Twenty of the women were being treated for lymphoma, while the remaining 3 had ovarian cancer. Treatment occurred during the second and third trimesters, and 3 congenital malformations resulted. One infant was born with plagiocephaly and another with fourth and fifth finger syndactyly. A third infant was born with genetic hearing loss, of which his parents were both genetic carriers.[20] Another patient treated with bleomycin (in combination with etoposide and cisplatin) for teratoma during the third trimester had a normal delivery and healthy infant.[42] Bleomycin therapy in the second and third trimesters of pregnancy was not associated with any grouping of malformations.

Topoisomerase inhibitors

Anthracyclines

Anthracyclines commonly used are doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone.

Van Calsteren et al. reported on a number of pregnant patients treated with topoisomerase inhibitors.[18] A total of 36 patients treated for various malignancies with doxorubicin during the second and third trimester were evaluated. One infant, also exposed to cyclophosphamide, was born with hip subluxation. A second infant exposed to FAC regimen was born with doubled cartilage rings in both ears. The rest of the infants (34/36) had normal outcomes. Another 25 patients in this series were exposed to daunorubicin-containing treatments for various malignancies during the second and third trimesters. Two infants had congenital malformations: 1 with bilateral partial syndactyly of second and third digits, and the other with rectal atresia. The remaining 23 outcomes were normal. Cardonick et al. detailed the pregnancy outcomes of 118 patients treated for breast cancer (98) and lymphoma (20) with various topoisomerase inhibitor-containing regimens, all during the second and third trimesters.[20] A total of 5 abnormal outcomes were observed: 1 infant with IgA deficiency, 1 neonatal death due to autoimmune disorder, 1 infant with pyloric stenosis, 1 infant with holoprosencephaly, and 1 intrauterine demise with normal autopsy. In another series of 11 patients treated with doxorubicin together with

cyclophosphamide during the second and third trimesters of pregnancy, all infants had normal outcomes.[31]

Epirubicin exposure was noted in 5 patients concomitant with cyclophosphamide during the second and third trimesters. No congenital malformations were reported.[31]

In 1 case, a patient treated for acute myeloid leukemia was exposed to idarubicin together with all-trans retinoic acid during the first trimester and had a normal pregnancy outcome.[54] A further 9 cases of patients treated for various malignancies during the second and third trimesters, however, resulted in 4 congenital malformations,[32,55–59] including 1 case of transient dilated cardiomyopathy and 2 cases of permanent dilated cardiomyopathy.[55–57] As data on possible effects to the fetal heart are inconclusive, caution should be exercised with respect to the use of idarubicin during pregnancy.

One patient treated for teratoma with mitoxantrone and bleomycin and cisplatin during the third trimester had a normal delivery, and the infant had no congenital malformations.[42]

Plant alkaloids and taxanes

Plant alkaloids and natural products, such as taxanes, may inhibit mitosis or inhibit enzymes needed for reproduction of the cell. These agents are specific to the M phase of the cell. They include paclitaxel, docetaxel, etoposide, vinblastine, and vincristine.[22]

In 19 patients, 2 in the first trimester, exposed to docetaxel for the treatment of breast cancer, 3 congenital malformations were noted.[60] Two infants had cerebral ventriculomegaly; however, in both cases the diagnosis was made before administration of chemotherapy. The only malformation potentially related to cytotoxicity is 1 case of pyloric stenosis in an infant whose mother was exposed to doxorubicin, cyclophosphamide, paclitaxel, and docetaxel. Therefore, the use of docetaxel appears to be safe in the second and third trimesters.

Exposures to paclitaxel in multi-drug therapies for various malignancies in 19 patients resulted in 1 congenital malformation and 1 intrauterine or postnatal demise.[20] Pyloric stenosis was reported in an infant exposed to paclitaxel, docetaxel, cyclophosphamide, and doxorubicin as discussed above. In a patient treated with doxorubicin, vincristine, cyclophosphamide, prednisone, and rituximab for non-Hodgkin's lymphoma, intrauterine fetal demise occurred at 30 weeks. The autopsy results were normal. Twenty-four more cases of exposure to paclitaxel for the treatment of breast cancer in the second and third trimester resulted in 23 healthy outcomes. The 1 congenital malformation was the case of pyloric stenosis following multi-drug exposure reported previously. Finally, 1 patient treated with paclitaxel weekly from 20 weeks' gestation delivered a healthy infant with no congenital malformations.[61] These data suggest that paclitaxel may be compatible with therapy in the second and third trimesters of pregnancy.

Vincristine exposures in 11 patients treated for various cancers during the second and third trimesters resulted in healthy outcomes for 10 infants.[20] As previously noted, 1 infant exposed to vincristine, doxorubicin, cyclophosphamide, prednisone, and rituximab died in utero at 30 weeks, and the autopsy results were normal. These limited exposures suggest that vincristine therapy does not increase risk for malformation during the second and third trimesters.

Of 20 patients treated in the second and third trimesters for Hodgkin's lymphoma and non-Hodgkin's lymphoma with varying vinblastine-containing regimens, 2 had infants with malformations.[20] After in utero exposure to doxorubicin, bleomycin, dacarbazine, and vinblastine throughout second and third trimesters for Hodgkin's lymphoma, there was 1 case of plagiocephaly. Another infant exposed to the same regimen was born with fourth and fifth finger syndactyly. Although evidence to date suggests there is not a significant concern with unique vinblastine treatment in the second and third trimesters, more research is needed.

Etoposide exposure in 6 patients during the second and third trimesters did not appear to cause any congenital malformations.[20,40,42] One infant was born with genetic hearing loss ruled unrelated to exposure to etoposide, cisplatin, and bleomycin. Although there is only limited experience with etoposide, there were no patterns of congenital malformations noted with etoposide exposure in the later stages of pregnancy.

Molecularly targeted agents

Recently, the choice of treatment for the pregnant patient with cancer has become even more complicated because of the increasing use of targeted anti-cancer therapies. The benefit of the targeted agents has been well demonstrated for various malignancies; however, their safety during pregnancy has not been established. Currently, significant experience with exposure during pregnancy is available only for the tyrosine kinase inhibitor, imatinib and the monoclonal antibody, rituximab.

The largest report regarding exposure to imatinib during pregnancy included 180 pregnant women with chronic myeloid leukemia. Outcome data were available for 125 patients.[62] Congenital malformations were identified in 12 infants, 3 of whom had strikingly similar complex malformations (a combination of omphalocele with severe renal and skeletal malformations) that are clearly cause for concern. All congenital malformations were associated with first trimester exposure to imatinib. It appears that although most pregnancies exposed to imatinib are likely to have a successful outcome, this exposure may result in serious fetal

malformations. These concerns suggest that imatinib should not be administered during the first trimester.[62,63]

Rituximab is an anti-CD20 monoclonal B-cell antibody indicated mainly for diffuse large B cell and follicular non-Hodgkin's lymphomas. Recently it has been also administered to patients with several autoimmune diseases. A 2011 report described 231 pregnancies associated with maternal rituximab exposure.[64] Most cases were confounded by the concomitant use of potentially teratogenic medications (most commonly methotrexate). Of the 153 pregnancies with outcome data, 90 resulted in live births. First trimester miscarriages were reported in 33 (21%) cases, and 28 pregnancies were electively terminated. Twenty-two infants were born prematurely, and there was 1 neonatal death. Eleven neonates had hematological abnormalities without corresponding infections. Two congenital malformations were identified: 1 case of talipes, and 1 of cardiac malformation (a combination of ventricular septal defect, persistent foramen ovale, and persistent ductus arteriosus). The limited experience to date suggests that the administration of rituximab may be considered safe during the second and third trimesters.

TREATMENT GUIDELINES

Patients with a slowly growing cancer diagnosed during the first trimester may be followed at short intervals for signs of disease progression without treatment until the second trimester. However, when aggressive, advanced, or progressive disease is diagnosed in the first trimester, a delay in therapy may adversely affect maternal survival.[3,63–67] Therefore, treatment with appropriate, often combination, chemotherapy should be given promptly. However, this should be accompanied by detailed counselling to ensure that the woman and her family understand the potential teratogenic effects of chemotherapy in the first trimester. In specific cases, the treatment with single-agent chemotherapy (preferably a vinca alkaloid or an anthracycline) during the first trimester followed by conventional multi-agent therapy at the beginning of the second trimester may be considered. Such therapeutic approaches appear to be safe; however, data regarding their efficacy for the maternal cancer is lacking. Most multi-drug protocols may be administered during the second and third trimesters without an apparent increase in the risk for severe malformations. Regimens based on a combination of cyclophosphamide and an anthracycline administered to women with breast cancer or lymphoma have been most commonly used during pregnancy, and their administration after the end of the first trimester found to be safe. Weekly fractionated-dose chemotherapy may be preferred to allow ease of pregnancy monitoring, and interruption of treatment if necessary.[6]

Treatment during the second and third trimesters does not carry a risk for morphological congenital malformation; however, infants may be born earlier than expected and small for gestational age, and some of the agents used in treatment are neurotoxins, which may theoretically affect brain development. The timing of delivery should be planned to avoid myelosuppression, but no long-term developmental sequelae have been reported. If possible, delivery should be postponed for 2 to 3 weeks following anti-cancer treatment to allow bone marrow recovery.[4,69] Furthermore, neonates, especially preterm infants, have limited capacity to metabolize and eliminate drugs because of liver and renal immaturity. The delay of delivery after chemotherapy will allow fetal drug excretion by the placenta.

POSTPARTUM CARE

Breastfeeding

As a rule, women using cancer chemotherapeutic agents after delivery should not be breastfeeding as neither short-term nor long-term safety has been established. Exceptions include azathioprine, with which repeated measures failed to show accumulation in milk.

If the lactating mother requires drug therapy, safety of breastfed infants is a concern because almost all drugs the mother ingests are excreted into milk. Of many factors that determine magnitude of drug excretion into milk, plasma protein binding, ionization characteristics and lipophilicity of drug are the most important.[70]

Recently, expression and function of carrier-mediated drug transport in the mammary gland have been elucidated. For example, the lactating mammary gland highly expresses breast cancer resistant protein (BCRP: ABCG2), which carries its substrates from maternal circulation into milk. Initially, its role as a toxin transporter was perplexing as it appeared to actively contaminate mother's milk. However, it was later shown that breast cancer resistant protein in the mammary gland is a major vitamin B2 transporter.[71] Some organic cation transporters carry both xenobiotics and nutrients, and mammary gland drug transporters have a nutrient carrier function that is taken over by maternal xenobiotics. In addition to the above mentioned attributes of drugs, such as protein binding and ionization characteristics, transporter affinity as a substrate is another important factor for defining milk excretion of drugs.[70]

Risk assessment of drug therapy, including cancer chemotherapy, during lactation must consider several factors that are distinct from those of pregnancy. First, average levels of drug exposure in the infant are usually an order of magnitude lower in lactation-mediated exposure than in transplacental exposure. Second, the mother has an option to discontinue, or temporarily interrupt, breastfeeding if the risk is perceived to be high. Third, cancer chemotherapy schedules may allow breastfeeding women to store their

own milk for near-future use. In addition, women with cancer who are being treated with chemotherapy may perceive the importance of breastfeeding and the risks associated with it differently from women who are taking non-cancer related medications.

Published clinical studies on excretion of cancer chemotherapy agents into milk, and resultant infant plasma levels, are very limited. Breastfeeding-related information is available for the following chemotherapeutic agents in cancer treatment, but levels of evidence are not high enough to make firm recommendations.

Cisplatin

There are 3 published case reports on use of cisplatin in lactating women with cancer.[72–74] At various post-dose time points, plasma cisplatin concentrations were measured as platinum. The maternal plasma levels ranged from 0.8 mg/mL to about 3 mg/mL when measured and expressed as plasma platinum levels, but the maternal plasma ratio varied widely from nearly zero (milk levels were below the detection limit of platinum) to 1.1. Cisplatin pharmacokinetic studies in non-lactating patients indicate that average plasma platinum concentrations after 100 mg/m^2 dosing (a high therapeutic dose) are about 3.91 ± 1.41 mg/mL.[75] Assuming maternal plasma ratio to be the reported highest (1.1), the infant would receive 4.3 mg/kg/day of platinum. Taken together, evidence of cisplatin safety/toxicity in breastfeeding is weak. Because of the relatively long half-life of cisplatin, most experts recommend discontinuation of breastfeeding, but emerging data on benefits of breastfeeding and lack of clear toxicity data may require revisiting the current recommendation.

Cyclophosphamide

Three case reports of use of cyclophosphamide during breastfeeding exist; however, there are no quantitative data on cyclophosphamide levels in milk.[76–78] In one case, a woman with leukemia received weekly intravenous doses of cyclophosphamide 800 mg and vincristine 2 mg over a 6-week period, in addition to prednisolone (30 mg/day). Her 4-month-old infant was breastfed during this treatment cycle and found to be neutropenic at the end of the treatment, but returned to normal after breastfeeding was discontinued.[76] Another patient with Burkitt lymphoma received daily cyclophosphamide 6 mg/kg intravenously. At 23 days of life, her infant developed neutropenia and thrombocytopenia over a 3-day period. The limited information from these reports suggests that cyclophosphamide is not compatible with breastfeeding.[77]

Doxorubicin

In milk samples of a woman receiving doxorubicin 70 mg/m^2 (an intravenous dose of 90 mg), the drug and its active metabolite, doxorubicinol, were detected. The peak milk concentrations of doxorubicin and doxorubicinol were 128 mg/L (0.24 mM) and 111 mg/L (0.20 mM), respectively, 24 hours after the dose.[72] Anthracyclines may not be absorbed orally, and the dose to the infant, based on the peak levels, may be in the low range of 2% of the weight-adjusted dose. However, safety data are too scant to make a firm recommendation at this point.

A 28-year-old woman with acute promyelocytic leukemia received chemotherapy during pregnancy and breastfeeding.[79] After first consolidation therapy, she delivered healthy baby at 34 weeks' gestation. After delivery she received second consolidation therapy. Then she was treated with intravenous etoposide (80 mg/m^2/day: days 1 to 5) and other drugs including mitoxantrone (6 mg/m^2/day: days 1 to 3) and cytarabine (170 mg/m^2/day: days 1 to 5) as third consolidation therapy. The post-infusion peak milk concentrations of etoposide ranged from 580 mg/L to 800 mg/L, which quickly declined and became undetectable in 24 hours. Breastfeeding was resumed 3 weeks after the end of the therapy without incident.

In the same woman described above, mitoxantrone milk concentration reached 120 mg/mL immediately after the third dose. Mitoxantrone milk concentrations decreased to about 20 mg/mL by 7 days after the last (third) dose, and remained at that level 4 weeks after the last dose.[79]

After maternal oral doses of imatinib (400 mg/day), milk concentrations are approximately in the range of 0.5 mg/mL to 3.2 mg/mL. Its active metabolite is also in a similar range of concentrations (1 mg/mL to 2.5 mg/mL). One infant was breastfed during the maternal imatinib treatment without incident.[80–83]

Methotrexate

A 25-year-old woman with choriocarcinoma received methotrexate 22.5 mg orally (15 mg/m^2/day). Peak methotrexate concentrations in milk samples were 2.6 ng/mL on 2 different dosing occasions.[84] In the case of a woman who received a single dose of 65 mg of methotrexate intramuscularly (50 mg/m^2) for ectopic pregnancy, 6 milk samples taken over the following 24-hour period did not show detectable levels of the drug.[85]

Studies on excretion of cancer chemotherapeutic agents into human milk are scarce, but accumulating evidence is overwhelmingly supportive of the tangible benefit of human milk for many aspects of infant development. Given the nature of the maternal diseases in question, risk-benefit assessment of breastfeeding during maternal chemotherapy needs to be carefully individualized.

Follow-Up

While treating pregnant women during the second and third trimesters, it is important to bear in mind that the CNS is still developing and that treatment can have long-term

side effects on the child's development. Long-term follow-up data on children born to mothers treated for leukemia during pregnancy have been published.[32] The children's psychological, physical, and neurological development were reported as normal. The grandchildren of exposed pregnant women were also followed up in the same study. Even those children had normal neurological and psychological development. No congenital malformations were reported. One review included 111 children born to women treated during pregnancy, who were followed for up to 19 years. All the children had normal neurological development.[86]

Another concern is the possibility of secondary malignancies in exposed children. Avilés and Neri followed 84 children to a median age of 18 years: no secondary malignancies and no fertility issues were reported.[32] Yet, in a case of twin exposure to cyclophosphamide, 1 infant developed 2 different cancers (neuroblastoma and thyroid) over his lifetime.[28]

To date, there is no other large-scale follow-up. A recent registry reported on well-being of infants born to treated mothers, but the follow-up period is only a few years.[20]

Ongoing observation is underway to provide a full and detailed report in the coming years.

At birth, the placenta should be examined for invasion of malignant cells. Any infant with placental involvement should be considered high risk and subsequently monitored. Cardonick et al. recommend follow-up every 6 months for at least 2 years, with a focus on the primary malignancy. A physical examination, blood chemistry, and chest X-ray may also be of value.[20]

ETHICAL CONSIDERATIONS

When considering the treatment of cancer during pregnancy with chemotherapeutic agents, it is important to balance maternal and fetal interests Decisions about the management of cancer in pregnancy should be made individually for each patient after careful consideration of cancer type, cancer stage, gestational age, maternal and fetal risks, and possible treatment alternatives.

Termination of pregnancy may be indicated but will not be acceptable in all cases for social and sometimes religious reasons. Furthermore, most evidence does not suggest increased maternal survival following therapeutic abortion.[87]

If the patient desires the pregnancy, and termination is not an option, the decision to start chemotherapy during pregnancy should be weighed against the potential impact on maternal survival.[17] Physicians should discuss the situation with the pregnant patient and her family, providing all the information available regarding the malignancy, possible treatment alternatives, and both maternal and fetal risks.[17] A multidisciplinary team, which includes the family physician, hematologist and/or oncologist, obstetrician, social worker, psychologist, and in some cases religious advisors, should be assembled whenever possible to optimize the physical and mental well-being of the woman, her baby, and her family.

SUMMARY STATEMENTS AND RECOMMENDATIONS

Summary Statements

1. As women are postponing child-bearing, more of them are experiencing cancer in pregnancy. (II-2)
2. Chemotherapeutic agents used to combat cancer cross the placenta and may adversely affect embryogenesis by affecting cell division. (II-1)
3. Exposure to such agents after the first trimester of pregnancy has not been associated with increased risk of malformations but is associated with increased risk of stillbirth, intrauterine growth restriction, and fetal toxicities. (II-2)

Recommendations

1. The health care provider should examine the patient's risk of pregnancy and desire to prevent pregnancy during chemotherapy. (I-A)
2. Decisions about the best course of management in pregnancy, including timing of delivery, should balance maternal and fetal risks. Most authorities concur that maternal health and well-being must prevail. (I-A)
3. Women diagnosed with cancer in pregnancy should be optimally managed by a multidisciplinary team that includes oncologists and/or hematologists (depending on the malignancy), perinatologists, family physicians, psychologists, social workers, and spiritual advisors, if sought by the family. (I-A)

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