

Management of Haematologic Malignancies in Pregnancy

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Abstract

Introduction: Malignancy complicates about 1 in 1000 pregnancies and is the second leading cause of death in women of reproductive age. Commonly diagnosed malignancies during pregnancy include breast cancer, cervical carcinoma, melanoma and lymphoma. Chemotherapy is usually necessary for optimal treatment, especially in patients with leukaemia and lymphoma. Concerns arise regarding the effects of imaging modalities in the pregnant cancer patients and the effects of chemotherapeutic agents on the developing fetus. **Methods:** A Medline search of articles describing haematologic malignancies in pregnant patients was performed. Particular attention was paid to the kind of malignancy, stage of pregnancy, the types and side effects of chemotherapeutic agents used and the outcome of the pregnancy. **Results:** There is no entirely safe cytotoxic drug or timing of exposure for the developing fetus. The administration of chemotherapy during pregnancy will not always produce a poor outcome. A pregnant cancer patient can also be safely and reasonably staged with imaging. Magnetic resonance imaging will most often be the procedure of choice as it does not use ionising radiation. **Conclusions:** The management of each pregnant patient diagnosed with a malignancy has to be highly individualised and involves a multidisciplinary team of medical personnel. The patient and her family need counselling regarding the diagnosis, long-term prognosis, options of termination of pregnancy, choice of chemotherapeutic agents and their effects on the fetus and pregnancy.

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Introduction

Malignancy complicates the course of about 1 in 1000 pregnancies and is the second leading cause of death in women of reproductive age. The most commonly diagnosed malignancies during pregnancy are breast cancer, cervical carcinoma, Hodgkin's lymphoma and melanoma.^{1,2} Patients and their families face emotional trauma and many difficult decisions, requiring the expertise of various specialists. For many patients, chemotherapy will be a necessary component of an optimal treatment regimen, especially for patients with leukaemia and lymphoma. There are no large well-controlled trials of the effects of chemotherapy on the developing fetus. Available information is from anecdotal reports and small series in the medical literature. The National Cancer Institute has begun a registry of pregnancies exposed to chemotherapeutic agents. This is based on voluntary reporting by practitioners and it is hoped that it will increase the information in this area.

Imaging Modalities in the Pregnant Cancer Patient

Various imaging modalities are needed to assess the neoplastic spread of common malignancies in women of reproductive age. Usually, a pregnant cancer patient can be safely and reasonably staged with imaging.

Ionising Radiation

Ionising radiation is used in diagnostic imaging, such as X-rays or computed tomography (CT). Radiation exposure on an embryo or fetus can cause prenatal death, malformations, growth and mental retardation as well as cancer induction. The stage of fetal development at the time of exposure, the total dose and its distribution and modifying factors that may potentiate the radiation effects all have to be taken into consideration in determining the consequences of prenatal exposure to radiation.

Preimplantation (0 to 9 days post-conception) is the time period most sensitive to radiation-induced prenatal death. The period of organogenesis (15 to 50 days post-conception) is the time period most sensitive to radiation-induced malformations. The first trimester (15 to 90 days post-conception) is the time period most sensitive to radiation-induced growth and mental retardation as well as childhood cancer induction.^{3,4} Hence, it is strongly advised that ionising radiation be avoided during the first trimester. However, with modern machines, the amount of radiation delivered during imaging can be many hundred times less than therapeutic radiation. With a radiation dose of less than 5 rads, there is no increased fetal risk of malformation, growth restriction or abortion. Therefore, the benefits of

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imaging may outweigh the potential risks, especially for patients in the third trimester. There are no known adverse effects to the fetus from the use of either ionic or non-ionic, iodinated intravenous contrast media used in CT. The decision to use contrast during pregnancy follows the standard guidelines used for non-pregnant patients. If a reasonably equivalent non-ionising imaging modality can be substituted, then ionising radiation should be avoided.

Non-ionising Radiation

Both ultrasound (US) and magnetic resonance imaging (MRI) create images using non-ionising radiation. However, both can have biologic effects on the fetus. Heating occurs in tissues when they absorb ultrasonic energy. Cavitation or mechanical effects are produced through motion generated by the ultrasonic beam. However, both these effects occur only with power outputs far in excess of available diagnostic ultrasound. Presently, the use of diagnostic ultrasound with standard power levels has not produced confirmed biologic effects.

In the case of MRI, effects occur at the cellular level secondary to exposure to the high static magnetic fields used to generate an image. However, scientific evidence has concluded that no deleterious effects are attributable to static magnetic fields up to 2 Tesla (diagnostic magnets range from 0.1T to 1.5T). Nor are there any adverse effects secondary to tissue heating.

Many magnetic resonance examinations have been performed on pregnant women with no observable adverse effects to the fetus. The potential risk of delayed sequelae is extremely small or non-existent.⁵ The Safety Committee of the Society for Magnetic Resonance Imaging advises that magnetic resonance procedures are indicated during pregnancy when other non-ionising diagnostic imaging methods are inadequate or when the examination will provide information that would otherwise require exposure to ionising radiation.⁶

Gadolinium-based contrast medium used in magnetic resonance is not recommended for use in the pregnant patient. Gadolinium crosses the placenta, is rapidly filtered through the fetal kidneys and is reingested through the amniotic fluid. It should only be used when the potential benefits strongly outweigh the risks.

Imaging for Lymphoma Patients

While both acute and chronic leukaemia have been reported during pregnancy, they generally require less imaging modalities during their management. However, radiologic imaging is still part of the staging procedures for patients with lymphoma.

Staging of a patient with lymphoma traditionally includes chest X-ray and CT scans of the thorax, abdomen and

pelvis. Documentation of lymphadenopathy is essential for staging and planning for possible radiation therapy. In a pregnant patient, a chest X-ray can be performed with negligible exposure to the fetus. MRI can be used as a substitute for CT to minimise exposure of the fetus to ionising radiation. Studies have shown MRI to be at least as comparable to CT in the detection of lymphadenopathy. MRI also has the benefit of being able to evaluate the bone marrow and detect splenic involvement that may not be detectable on CT.

In conclusion, a pregnant cancer patient can be safely and reasonably staged with imaging. MRI will most often be the procedure of choice as it does not use ionising radiation. A chest X-ray, while it involves ionising radiation, will not expose the fetus to significant radiation.

Chemotherapeutic Agents During Pregnancy

Antineoplastic chemotherapy has a definite and beneficial role in treating many malignancies that affect women of childbearing years, particularly leukaemia, lymphoma, breast cancer, ovarian cancer and sarcoma. The benefits and risks of administering treatment must be carefully evaluated on an individual basis.

Antineoplastic drugs act by interfering with cell division and killing rapidly dividing cells. Many cytotoxic drugs are non-specific in their effects and produce varying degrees of deleterious effects in normal tissues. As the fetus is composed of rapidly dividing and differentiating cells, its development can be seriously affected if exposed to these agents.

Drug Metabolism During Pregnancy

The effectiveness of antineoplastic agents can be potentially altered during pregnancy as a result of changes in their metabolism or clearance. The increase in plasma volume during pregnancy can lead to a dilution of the agent in the circulation.⁷ A decrease in albumin concentration results in an increased concentration of free fraction of protein-bound drugs and hence, an increase of pharmacologic effects. The metabolism and elimination of drugs are further affected by the enhanced hepatic function and renal excretion.^{8,9} The absorption and bioavailability of oral medications can also be altered when gastric emptying decreases as the uterus expands. Amniotic fluid can also serve as a pharmacologic third space. This can result in an accumulation of the cytotoxic agent, especially methotrexate, leading to delayed drug clearance and enhanced toxicity.

The placenta may act as a barrier to the passage of antineoplastic drugs from the maternal circulation to the fetus. However, agents with low molecular weight and high lipid solubility are non-ionised, loosely bound to

plasma proteins and may readily cross the placenta into the fetal circulation.^{8,10} The functionally immature fetal liver and kidneys may affect the metabolism and excretion of these drugs in the fetus, thereby producing severe toxicity in the fetus.

All these factors may result in serious teratogenic risks to the fetus. Hence, the changes in pregnancy should be borne in mind when one is prescribing antineoplastic drugs for a pregnant patient.

Effects of Chemotherapeutic Agents on the Fetus

Implantation of the embryo occurs in the first 2 weeks following conception. Chemotherapy administration during this time is likely to result in spontaneous abortion. The second to eighth week of gestation (first trimester) is the period of organogenesis during which the embryo is most susceptible to the teratogenic effects of drugs. The second and third trimesters are characterised by maturation of tissues and growth. Hence, insults during this period, including therapy and disease-related effects, can cause growth retardation and low birth weight.

The fetal consequences of antineoplastic drugs can be due to drug dosage, fetal gestational age, type and combination of chemotherapy and duration of therapy. Immunosuppression secondary to chemotherapy can result in opportunistic infections that can affect the developing fetus. Nutritional deficiencies from anorexia of chemotherapy can also adversely affect fetal development. Fetal abnormalities that result from chemotherapy during pregnancy can, therefore, result from a multitude of factors.

The adverse effects of chemotherapeutic agents on the embryo or fetus are not well documented and may be related to the timing of exposure during fetal development. First trimester exposure predisposes to spontaneous abortion, congenital malformations and premature births, while second and third trimesters exposure can result in sterility, low birth weight, pancytopenia, delayed mental development and carcinogenesis. Although the teratogenic potential of drugs may be demonstrable in animals, extrapolation to humans may not be reliable.¹¹

Case reports have described both normal and abnormal fetal outcomes following chemotherapy exposure during pregnancy. In general, antimetabolites carry a significant risk to the fetus. First trimester exposure to aminopterin, a folate antagonist, causes a characteristic syndrome of cranial dysostosis, hypertelorism, anomalies of the external ears, micrognathia and cleft palate.¹² However, other antimetabolites are less potent. In a study by Maloney¹³ in which 21 pregnant patients with acute leukaemia were treated with 6-mercaptopurine, there were no teratogenic effects in the surviving children. Nicholson's¹⁴ review of 185 pregnancies showed that less than 8% of infants were

congenitally malformed if the drugs were administered in the first trimester. It was also noted that exposure in the second and third trimesters was not associated with increased risk of congenital malformation but 40% of the exposed infants had low birth weight. A case of trisomy C was reported in an aborted fetus of a patient given cytarabine and thioguanine during her second trimester.¹⁵ There was also another patient with leukaemia treated with cytarabine and idarubicin during her second and third trimesters. The child developed growth retardation but had no permanent sequelae.¹⁶ Hence, it appears that there is no safe drug or timing of exposure to chemotherapy during pregnancy.

Alkylating agents, such as busulfan, chlorambucil, cyclophosphamide and nitrogen mustard, cause an approximately 13% rate of fetal malformation with first trimester exposure but 4% with exposure in second or third trimesters.¹⁷ Bleomycin, doxorubicin and daunorubicin, the antitumour antibiotics, have not been reported to cause adverse fetal outcome.¹⁸ The vinca alkaloids, vinblastine and vincristine, cause fetal malformations in animals but none has been reported in two reports in humans exposed in the first trimester.¹⁹

An infant exposed to antineoplastic agents *in utero* may appear normal at birth but the child should also be reviewed for delayed effects in the cardiac, pulmonary and central nervous systems. The child's fertility may also be affected. The risk of developing malignancy later in life after *in utero* exposure to cytotoxic drugs is feared because of the diethylstilbestrol experience, but there has been no demonstrable association for any agent. Hence, these infants should be on long-term follow-up.

The timing of delivery of the infant and chemotherapy administration is important. Myelosuppression of the mother from chemotherapy, should be avoided during delivery and perinatally to minimise infections and bleeding to the mother. The newborn infant may also be pancytopenic at birth. As many as one third of the exposed infants can be pancytopenic at birth. The placenta can act as a route of elimination of drugs. Administration of chemotherapy close to delivery may lead to accumulation of drugs in the fetus, resulting in prolonged drug exposure and severe toxicity.

Lactating women on chemotherapy should avoid nursing. The secretion of chemotherapy drugs into milk has not been well studied but may occur for some agents.

In summary, there is no entirely safe cytotoxic drug or timing of exposure for the developing fetus. The administration of chemotherapy during pregnancy will not always produce a poor outcome. Therapy should be individualised with consults with the patient and her family, obstetrician, oncologist and the paediatrician.

Radiation Therapy (RT) in Pregnancy

In a pregnant patient diagnosed with a malignancy that potentially requires RT, it should first be decided whether appropriate measures are available to bring the pregnancy to term prior to RT. If a delay in treatment to increase fetal maturity compromises maternal prognosis, an alternative management to RT should be considered. The benefits of RT as part of a treatment regimen must be weighed against the potential risk of harm to the patient (mutagenesis, carcinogenesis, acute and delayed tissue damage) and the risk to the developing fetus. Radiation therapy during pregnancy has been associated with a wide variety of congenital anomalies and late toxicities.

The potential effects of RT on the developing fetus depend on the gestational age, absorbed fetal dose-equivalent (fetal dose X radiation weighting factor for typing of RT) and dose rate. The risk periods in humans for RT-induced prenatal or neonatal death, congenital anomalies, severe growth retardation, carcinogenesis, sterility and germ cell mutations have been elicited from the study of Japanese victims of atomic bombs and indirectly from animal experiments.

Information regarding prenatal and neonatal death in human embryos is limited. Studies have shown that therapeutic abortion was induced in the majority of pregnant women who received 360 to 500 cGy to the pelvis.^{20,21} The incidence of congenital anomalies or malformations varies according to genetic and environmental factors. Ionising radiation can be strongly teratogenic when embryos are exposed during organogenesis. The highest risk period for severe mental retardation correlates with the differentiation of the cerebral cortex.²² Irradiation during the first 7 weeks post-conception may cause microcephaly without severe mental retardation. However, irradiation from 8 to 25 weeks post-conception impairs proliferation, differentiation and migration of neurons from their proliferative zones.

Permanent growth retardation, caused by irreversible depletion of cells and expressed as growth retardation persisting into adulthood, is typically seen if doses exceed 50 cGy during the fetal period.²³ During organogenesis, temporary growth retardation is likely with doses as little as 10 cGy²³ to 25 cGy.²² Germ cell mutations are gene or chromosomal alterations within germ cells that may be passed on to future generations. Ionising radiation as a mutagenic agent has been evaluated in animal experiments and in the offspring of atomic bomb survivors. A trend towards higher mutation frequency proportional to dose was noted.

Radiation Therapy for Pregnant Patients with Hodgkin's Disease

Hodgkin's disease is the fourth most common malignancy

diagnosed during pregnancy, occurring in 1 in 5000 pregnancies.²⁴ The stage at presentation and the long-term prognosis of patients diagnosed during pregnancy are similar to those of non-pregnant Hodgkin's patients.²⁰ Therapeutic doses have been delivered via mantle fields to patients in their second and third trimesters of pregnancy.^{23,25} With appropriate abdominal and pelvic shielding, it is possible for most of the fetus to receive less than 10 cGy, a reasonable risk based on current radiobiology data. However, the use of radiotherapy during pregnancy is always controversial and is best avoided if alternative therapeutic options exist.

Leukaemia and Pregnancy

The diagnosis of leukaemia during pregnancy, understandably, creates enormous psychological stresses for the patient and her family. Pregnancy does not alter the prognosis of the leukaemia. Management of both leukaemia and pregnancy becomes very complicated and requires close co-operation between everyone involved. Validated data from which conclusions may be drawn about the management of leukaemia during pregnancy are sparse. The management of both the pregnancy and the leukaemia depends on the stage of pregnancy at which the diagnosis is made and/or the type of leukaemia involved.

Cytotoxic agents for acute leukaemia should generally be avoided during the first trimester, when there is an approximately 17% chance of fetal malformation, particularly with folate antagonists. Induction therapy during the first trimester of pregnancy usually induces abortion.²⁶ Therapeutic abortion prior to induction therapy should be considered in patients with acute myeloid leukaemia diagnosis in the first trimester. If the patient opts to continue with the pregnancy, one should consider postponing chemotherapy till after the first trimester. Measures such as repeated leukopheresis and judicious use of blood and platelets should be considered. Treatment beyond the first trimester is generally safe if appropriate monitoring and obstetric care are available. Treatment of chronic leukaemia can usually be delayed until delivery without compromising maternal health.

Combination chemotherapy has been used since the mid-1970s and cytarabine and an anthracycline regimen have been established as the most efficacious in the initial treatment of acute leukaemia. Subsequently, improved antiemetics, antibiotics and hematopoietic growth factors have made treatment safe and more tolerable. Blood products usage has decreased mortality from bleeding complications. Besides chemotherapeutic agents, any of the "supportive" drugs may have had an adverse effect on fetal outcome but none has been studied independently of chemotherapy.

Fetal Effects of Antileukaemic Agents

Some of the fetal effects of antileukaemic agents have been mentioned earlier in this article under the section on “Effects of Chemotherapeutic Agents on the Fetus”. With the exception of folate antagonists, teratogenesis cannot be accurately attributed to a single agent as chemotherapy frequently involves a combination of agents together with antiemetics, antibiotics, antifungals, antivirals and blood products in a neutropenic, thrombocytopenic pregnant host.

Acute Leukaemias

Cytarabine and an anthracycline combination regimen have been most efficacious in the frontline treatment of acute leukaemia. It is difficult to definitively assess the teratogenicity of cytarabine. Few reports of cytarabine as a single agent or with an anthracycline exist in pregnant women. Wagner et al²⁷ treated a patient with acute lymphocytic leukaemia who was on maintenance treatment with cytarabine when she conceived. Her infant had malformed right hand and bilateral femur, tibia-fibula and foot defects. Her three cytarabine cycles probably coincided with normal limb bud development. Caligiuri and Mayer²⁸ noted 30 leukaemic patients treated with cytarabine as a single or combination agent. Eighteen of these patients gave birth to normal offspring and 5 had elective abortions.

The anthracyclines have been evaluated in combination when used in pregnant leukaemic patients. In a report by Turchi and Villasis,¹⁸ there was no malformations among 20 acute leukaemia patients treated during pregnancy. There was 1 maternal/fetal death, 1 therapeutic abortion, 1 spontaneous abortion and 4 neonatal problems that resolved.

Catanzanite and Ferguson²⁹ reviewed records regarding pregnancy and acute leukaemia from 1972 to 1982 in the English, French and German literature. Thirty-nine fetuses were exposed to chemotherapy during gestation, ranging from conception to the third trimester. Seven acute lymphoblastic leukaemia (ALL) and 24 acute myelogenous leukaemia (AML) patients received induction chemotherapy during their pregnancy; 8 patients conceived while on maintenance. Twelve infants were premature and 20 were delivered at term. There were 3 therapeutic abortions, 2 perinatal deaths and 2 intrauterine deaths.

Before the advent of all-trans retinoic acid (ATRA), acute promyelocytic leukaemia (APL) was treated with chemotherapy alone. ATRA brought unknown risks to pregnant APL patients. In a report by Hoffman et al,³⁰ 3 patients received ATRA between gestational weeks 30 and 32. They delivered 4 normal but premature neonates. One patient was diagnosed with relapsed APL in the first trimester and was treated with ATRA. Her infant was premature but healthy at 15 months of age.

All the cases illustrate that it is difficult to incriminate a certain chemotherapeutic agent. Many factors such as the leukaemia itself, combination chemotherapeutic agents, antiemetics, analgesics, antibiotics, antivirals and antifungals can contribute to the production of malformations and adverse pregnancy outcomes.

Chronic Leukaemias

Chronic leukaemias often do not require immediate treatment, unlike acute leukaemias. Hence, many pregnancies can be completed without additional complications by delaying the initiation of treatment. However, in chronic myelogenous leukaemia (CML), symptoms or signs of hyperleukocytosis or hyperviscosity will require urgent treatment. Leukopheresis or splenectomy may be used without teratogenic consequences. Hydroxyurea usage during pregnancy has been documented in a few cases. Most of these patients conceived while on treatment and their fetuses were exposed throughout gestation without adverse effects.

Interferon alpha (IFN α) may be required during gestation. Baer et al³¹ reported 2 CML patients receiving IFN α at conception and the other at 2 months' gestation. Both pregnancies were uncomplicated and healthy offspring were delivered at term. Another patient had been on IFN α for approximately 2 years when she conceived. She continued therapy and delivered a normal term infant.³² Other pregnant CML patients had also received IFN α at different stages of gestation with no adverse fetal effects.

Chronic lymphocytic leukaemia (CLL) is rare in reproductive age women. Only 1 case has been described.³³ This patient was not treated because of the indolent course of the disease.

Conclusion

The development, response to treatment, duration of response and overall survival of acute leukaemia have not been shown to be affected by pregnancy.^{28,29} Acute leukaemia is fatal if untreated, with an overall survival duration of weeks to 3 months. Patients require therapy for disease control almost immediately upon diagnosis to increase chances of a complete remission or possible cure.

Treatment for early stages of chronic leukaemia is not always indicated. Cytoreduction can be achieved with leukopheresis and haematologic parameters can be maintained till delivery before institution of therapy.

Lymphoma and Pregnancy

Lymphoma, including Hodgkin's disease and non-Hodgkin's lymphoma, is the fourth most frequent cancer diagnosis among pregnant women.³⁴ The incidence rates of Hodgkin's disease and non-Hodgkin's lymphoma among women of childbearing ages are similar: 2 to 6 per 100,000

for Hodgkin's disease and 1 to 8 per 100,000 for non-Hodgkin's lymphoma. However, the peak incidence of Hodgkin's disease occurs at approximately 20 years of age, while the incidence of non-Hodgkin's lymphoma increases with age. The incidence of non-Hodgkin's lymphoma has also increased. Hence, the co-incident occurrence of both non-Hodgkin's lymphoma and pregnancy is likely to increase.

Hodgkin's Disease

Hodgkin's disease has no biologic effect on pregnancy and pregnancy has no biologic effect on the course of Hodgkin's disease. Barry et al³⁵ described a series of 84 pregnant women in whom pregnancy had no influence on the lymphoma outcome—response rate and median duration of survival were identical to non-pregnant patients with the same disease. There was also no difference in survival among women who had a therapeutic abortion compared to women who did not.

Ebert et al³⁶ described 24 cases of pregnant women with Hodgkin's disease who received chemotherapy between 1983 and 1995. Two women received MOPP (mechlorethamine, vincristine, procarbazine and prednisone) or MOPP without mechlorethamine and 1 had cyclophosphamide plus radiation therapy during the first trimester. All had therapeutic abortions and all 3 fetuses had multiple anomalies. One mother received single-agent cyclophosphamide in the first trimester and the infant was born with multiple anomalies. Another woman was given vinblastine, vincristine and procarbazine at 25 weeks of gestation. The infant was born with atrial septum defect and died 2 days after delivery. In contrast, 15 other women received COPP (cyclophosphamide, vincristine, procarbazine and prednisone), MOPP, ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or MOPP/ABVD beginning in the first, second and third trimester. All 15 infants were normal.

Management of a pregnant patient with Hodgkin's disease must be individualised and involves a multidisciplinary team. The patient and her family should be counselled about the risks and benefits to both mother and fetus of the diagnostic and therapeutic alternatives. The staging evaluation includes a history, physical examination, laboratory tests, chest X-ray with abdominal shielding, bone marrow biopsies and/or lumbar puncture. Ultrasound can be used to identify disease in the abdomen or pelvis. MRI (without contrast) of the chest, abdomen and pelvis is safe. CT is contraindicated.

Several authors have published treatment recommendations. For most patients with early-stage disease, chemotherapy followed by radiation therapy may be at least as, if not more, effective than radiation therapy

alone.³⁷⁻⁴⁰ For advanced stage disease, combination chemotherapy (with or without adjuvant radiation therapy) is standard treatment and ABVD is considered the standard combination chemotherapy regimen in the United States.⁴¹ Pohlman and Macklis⁴² recommended the following treatment guidelines. Patients who are diagnosed in the first trimester of pregnancy may be observed until the second trimester or an indication to initiate treatment. Therapeutic abortion should be advised for patients who require initiation of treatment during the first trimester, usually for B symptoms, bulky or advanced stage disease or rapid progression. If abortion is not an option, single-agent vinblastine should be used until the second trimester or until significant disease progression. ABVD (without dacarbazine) during the first trimester and standard ABVD subsequently is the recommended combination therapy. Patients who present in the second or third trimester should be closely observed and the fetus delivered when it is considered viable. ABVD is the recommended chemotherapy if treatment is warranted. Postchemotherapy which involved field radiation therapy may be withheld till after delivery. Mantle radiotherapy with extensive abdominal blocking may be an acceptable alternative in some situations.

In patients with refractory or relapsed Hodgkin's disease, MOPP and MOPP-like regimens have documented efficacy in and limited adverse effect on the fetus if administered after the first trimester. For most patients who fail initial chemotherapy, high-dose therapy with autologous blood stem cell transplantation is the treatment of choice.

Non-Hodgkin's Lymphoma

Pregnant women with non-Hodgkin's lymphoma usually present with an aggressive histologic subtype and advanced disease.⁴³ This could be due to the biology of lymphoma in young women of childbearing age or to a delay in diagnosis. There is also an unexpectedly high incidence of breast, uterine, cervical and ovarian involvement among pregnant women. This could be attributed to the increased blood flow to these organs during pregnancy.^{44,45}

The effect of non-Hodgkin's lymphoma on pregnancy and vice versa is not clear. Some authors noted relatively stable disease during pregnancy followed by rapid progression after delivery, while others have noted pregnancy has no influence on the course or response rate to treatment of non-Hodgkin's lymphoma. Women who were diagnosed during the third trimester of pregnancy appeared to have a better outcome than those diagnosed in the first or second trimester. Those with early-stage disease tended to have a better outcome than those with advanced stage disease.

Few recommendations exist for patients with non-

Hodgkin's lymphoma during pregnancy. Dhedin and Coiffier⁴⁶ suggested that low-grade lymphoma might be delayed until after delivery. They felt that patients with an aggressive lymphoma during the first trimester should get a therapeutic abortion and immediate chemotherapy. During the second and third trimester of pregnancy, full doses of a multidrug regimen appropriate to the patient's specific lymphoma should be given.

Pohlman and Macklis⁴² recommended that patients with indolent or low-grade lymphoma who are asymptomatic, have a relatively normal full blood count and do not have impending organ compromise may be safely observed till delivery or significant disease progression. However, patients with aggressive histologic subtypes have poor outcome and their treatment should not be compromised. Women diagnosed during the first trimester and those unwilling to accept any potential therapy-related adverse fetal outcome should have a therapeutic abortion. All other patients should be treated immediately with standard therapy.

Most patients with non-Hodgkin's lymphoma have diffuse large B-cell or peripheral T-cell lymphoma. The standard treatment is 3 to 8 cycles of CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) chemotherapy followed by involved field radiation for localised disease and 6 to 8 cycles of CHOP chemotherapy for those with advanced disease.^{47,48} Pohlman and Macklis recommended that patients diagnosed in the first trimester should have a therapeutic abortion and those diagnosed in second or third trimester receive CHOP chemotherapy. Radiation therapy may be delayed until after delivery for women with localised disease who have completed 3 to 8 cycles of CHOP chemotherapy.

No data is available for women who relapse during pregnancy. Standard therapy consists of 2 or more cycles of salvage chemotherapy followed by high dose therapy and autologous or allogeneic haematopoietic cell transplantation. Relapsed non-Hodgkin's lymphoma is more aggressive than at diagnosis, hence, there should be no delay in treatment. The effect on the fetus of standard salvage chemotherapy regimens is largely unknown.

Coincident pregnancy and lymphoma is rare but most of these women can be cured (especially patients with Hodgkin's disease) and potentially become pregnant again. The management of these patients requires a multidisciplinary approach, with discussion of issues with the patient, her family and the managing physicians of various disciplines.

Conclusions

At least 1 of every 1000 pregnant women will be diagnosed with cancer. The diagnosis of cancer during pregnancy is

both a medical and a psychosocial crisis. Medical personnel from various disciplines, especially the oncologist, radiotherapist and psychiatrist, need to counsel the patient and her family with regards to the diagnosis, long-term prognosis, options of termination of pregnancy, choice of chemotherapeutic agents and their effects on the fetus and pregnancy. Psychological issues which need to be dealt with include coping with abortion decisions, worry about effects of chemotherapy on the fetus and pregnancy and subsequent growth of the child. Indeed, it will be a challenge to manage such a patient.

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