The treatment of Hodgkin's and non-Hodgkin's lymphoma in pregnancy

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ABSTRACT

Lymphoma is the fourth most frequent malignancy diagnosed during pregnancy, occurring in approximately 1:6000 of deliveries. Its occurrence may increase due to the current trend to postpone pregnancy until later in life and the suggested high incidence of AIDS-related non-Hodgkin's lymphoma in developing countries. The relatively rare occurrence of pregnancy-associated lymphoma precludes the conduction of large, prospective studies to examine diagnostic, management and outcome issues. Chemotherapy and radiotherapy during the first trimester are associated with increased risk of congenital malformations and this risk diminishes as pregnancy advances. In the vast majority of cases, when lymphoma is diagnosed during the first trimester, treatment with a standard chemotherapy regimen, following pregnancy termination should be recommended. In the rare patients at low risk, such as those with stage 1 Hodgkin's lymphoma or indolent non-Hodgkin's lymphoma, therapy can be delayed until the end of the first trimester and of embryogenesis while keeping the patients under close observation. When lymphoma is diagnosed during the second and third trimesters, evidence exists suggesting that full-dose chemotherapy can be administered safely without apparent increased risk of severe adverse fetal outcome.

Key words: lymphoma, pregnancy, chemotherapy, fetus, malformations.

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Cancer is the second leading cause of death during the reproductive years, complicating approximately 1:1000 pregnancies.[1,2] Lymphoma is the fourth most frequent malignancy diagnosed during pregnancy, occurring in approximately 1:6000 deliveries.[1-3] Its occurrence may increase due to the current trend to postpone pregnancy until later in life and the suggested high incidence of AIDS-related non-Hodgkin's lymphoma (NHL) in developing countries.[4,5] The latter continues to be an important medical problem even in the era of highly active antiretroviral therapy (HAART).[5] Hodgkin's lymphoma (HL), whose early peak includes patients from their teens through to 30 years old, thereby covering the prime childbearing years, is the most common type of lymphoma during pregnancy. The incidence of NHL has an age-dependent pattern, with the mean age at diagnosis being 42 years.[2] The diagnosis of lymphoma during pregnancy poses challenges to the woman, her family and the medical team. The relative rarity of pregnancy-associated lymphoma precludes the conduction of large prospective studies to examine diagnostic, management and outcome issues and the literature is largely composed of small retrospective studies and case reports. In this article we critically review the available data, identify controversies and unresolved issues and suggest solutions regarding different aspects of lymphoma diagnosed during pregnancy and lactation.

Design and Methods

We systematically searched the English literature using MEDLINE and Cochrane Controlled Trials Register databases for the years 1976-2006. Combinations of the Medical Subject Headings (MeSH) terms, lymphoma, Hodgkin, radiation and chemotherapy with pregnancy and gestation, only when appearing in the title or abstract of the paper, were used. All titles and abstracts were evaluated; letters and editorials were excluded. The literature search resulted in 2086 articles that were scanned according to inclusion criteria which included studies reporting relevant data regarding the diagnosis and treatment of lymphoma during pregnancy. Overall, 406 articles met our inclusion criteria. References from these articles were scanned as well in order to identify further papers that could have fulfilled the inclusion criteria and contributed to our review.

Diagnosis and staging of pregnancy-associated lymphoma

The diagnosis of lymphoma requires a lymph node biopsy for pathological examination. A lymph node biopsy can safely taken done under local anesthesia during pregnancy without harming the fetus.[2,6] When there are no superficial lymph nodes available for excision, a biopsy under general anesthesia should be performed. Overall, it appears that with modern surgical and anesthetic techniques, elective surgery in a pregnant woman is safe even during the first trimester. The risk of spontaneous abortion is comparable with that of normal miscarriage and there is no significant increase in the risk of maternal death, birth defects or late neurodevelopmental delays.[7] The histological subtypes of HL in pregnancy are the same as in non-pregnant women younger than 40 years, with nodular sclerosis being the most prevalent.[2] It appears that NHL associated with pregnancy often has an aggressive histology, with diffuse large B-cell or peripheral T-cell lymphomas being most common in this context.[8]

The routine staging process of both NHL and HL requires radiological evaluation usually using chest and abdominal computed tomograpy (CT). Fetal exposure to radiation during most radiographic examinations, including chest X-rays and CT, is much lower than the threshold dose for adverse fetal effects and should not present fetal risk.[9] However, abdominal and pelvic CT are associated with higher fetal radiation exposure of up to 0.02Gy. Such radiation exposure is still below the threshold dose for severe congenital malformation and should not, therefore, harm the fetus.[10] However, in many cases other types of examinations that are not associated with radiation, such as ultrasonography or magnetic resonance imaging (MRI), may provide the desired diagnostic information without measurably increasing the risk of fetal malformations.[11,12] Therefore, abdominal and pelvic CT should be avoided during pregnancy. Recently, positron emission tomograpy (PET) CT has been increasingly used for both staging and treatment follow-up in patients with lymphoma. However, since ^{18}F-FDG can cross the placenta and reach the fetus, it may involve higher radiation exposure than regular CT and its use cannot be recommended during pregnancy.[13] PET CT should be performed after delivery to assess treatment response. Breastfeeding should be discontinued for at least 24 hours since the radioactive ^{18}F-FDG is concentrated both in the breasts and in breast milk.[14]

Since the vast majority of both HL and NHL patients are treated initially with chemotherapy, independently of disease stage, staging of a pregnant patient with lymphoma should be limited and should be based on the history, physical examination, routine blood tests, bone marrow biopsies and chest X-ray with abdominal shielding. Abdominal ultrasonography or MRI can be useful alternaives to CT, which involves ionized radiation.

Treatment of lymphoma: general principles

Chemotherapy during pregnancy

Due to their relatively low molecular weight, most cytotoxic agents cross the human placenta and reach the fetus.[6] When treating pregnant patients with chemotherapy, it is important to consider the physiological changes that occur during pregnancy such as the increased plasma volume and renal clearance of drugs and the third space created by the amniotic fluid.[15] These changes might decrease active drug concentrations compared to those in women of the same weight who are not pregnant.[15] No pharmacokinetic studies have been conducted in pregnant women receiving

chemotherapy in order to understand whether pregnant women should be treated with different doses of chemotherapy.

Almost all chemotherapeutic agents have been documented to be teratogenic in animals and for some drugs only experimental data exist.[15] Chemotherapy during the first trimester may increase the risk of spontaneous abortions, fetal death and major malformations.[16,17] Malformations reflect the gestational age at exposure: the fetus is extremely vulnerable from weeks 2 to 8 of gestation, during which organogenesis occurs.[15] During this period, damage to any developing organ may lead to fetal death or to major malformations. After organogenesis, several organs including the eyes, genitalia, the hematopoietic system and the central vernous system remain vulnerable to chemotherapy.[17] This vulnerability persists throughout pregnancy, However, between the 14th to 16th weeks of gestation the risk of severe malformations or mental retardation is reduced significantly.[15] Overall, the risk of teratogenesis following cancer treatment appears to be lower than is commonly estimated from animal data. First trimester exposure to chemotherapy has been associated with a 10 to 20% risk of major malformations.[6] This risk was found to be lower with exposure to a single agent compared to exposure to combination regimens,[18,19] and when anti-metabolites, which are considered the most teratogenic among the chemotherapeutic drugs, were excluded.[18,19] However, the existing data are derived from pregnant women who were treated with different chemotherapeutic regimens over long periods of time during which the treatment of cancer has changed. Most critically, these evaluations were based on a collection of case reports and there is a well-documented reporting bias whereby malformed infants are more likely to be reported after drug exposure than healthy infants. For details on specific drugs the reader is referred to the CCOPE database (*www.motherisk.org*).

Second and third trimester exposure is not associated with malformations but increases the risk of fetal or neonatal death, intrauterine growth retardation (IUGR), pre-term delivery and low birth weight.[6,17] These complications may be associated with adverse long-term effects such as neurodevelopmental impairment,[20] increased rate of cardiovascular risk factors[21] and renal dysfunction[22] (most typically microalbuminuria). However, these data were based solely on non- chemotherapy causes, and their relevance to fetuses exposed to chemotherapy is not well established. Furthermore, despite these possible complications it seems that the advantage of treatment is clear and that multi-drug regimens can be administered during this period.

Whether *in utero* exposure to anthracyclines is cardiotoxic to the fetus is controversial. While one study of 81 children whose mothers were treated with cytotoxic drugs including anthracyclines showed no myocardial damage in either gestational or post-natal echocardiograms,[23] two case-reports have documented both transient and permanent cardiomyopathy.[24,25] There are no reports regarding fetal pulmonary damage or neurotoxicity associated with treatment with bleomycin or vinca-alkaloids, respectively.

The decision to use chemotherapy during pregnancy should be weighed against the effect of treatment delay on maternal survival. If possible, chemotherapy should be postponed until the end of the first trimester. Of the different types of chemotherapy, alkylating agents may be less teratogenic than antimetabolites.[6] If chemotherapy is required in the first trimester, a therapeutic abortion should be considered by the family. When termination of pregnancy is unacceptable to the patient, a single-agent treatment with anthracycline antibiotics or vinca-alkaloids followed by multi-agent therapy at the end of the first trimester can be considered.

Consideration should be given to postponing delivery for 2-3 weeks following treatment to allow bone marrow recovery. Furthermore, neonates, especially preterm babies, have limited capacity to metabolize and eliminate drugs due to liver and renal immaturity. Delaying delivery after chemotherapy will allow fetal drug elimination via the placenta.[16]

Radiotherapy during pregnancy

When radiotherapy is delivered during pregnancy, the fetal exposure to radiation depends on several factors including the target dose, size of radiation fields and the distance from the edges of the fields to the fetus. Abdominal shielding can further decrease fetal radiation exposure and should be used in all cases. Generally, when conventional doses of radiotherapy are administered, a distance of over 30 cm from the field edges will limit the total exposure of the fetus to only 4-20 cGy. Therefore, radiotherapy may be considered in specific circumstances such as lymphoma confined to the neck or axillary lymph nodes.[9,26] Exposure to 0.1-0.2 Gy of radiation is considered as the threshold dose for severe congenital malformation when given during organogenesis.[27]

Radiation exposure during the second and third trimesters is associated with a carcinogenic effect that may include an increased risk for the development of leukemia and solid tumors within the first decade of life (3-4 cases per 1000 in those exposed to prenatal irradiation compared to 2-3 cases per 1000 in those not exposed).[9] Later in life, this increased risk becomes less pronounced or even ceases to exist.[9] Another concern is the increased risk of neurodevelopmental impairment, including a decrease in the intelligence quotient (IQ) and even severe mental retardation.[27,28] Fetal radiation exposure must be measured individually and a expert medical physicist should be consulted in each case before any treatment decision is taken.

Supportive treatment

Up to 70% of cancer patients may suffer from nausea or emesis following chemotherapy. No association has been found between treatment with metoclopramide, antihistamines or ondansetron-based anti-emetics and congenital malformations in either animal models or humans.[29,30]

Since pregnant women with lymphoma might be treated with antibiotics, especially due to neutropenic fever, their effects on the mother and fetus must be addressed. The fetal safety of penicillins, cephalosporins and erythromycin is well established.[31] Aminoglycosides and metronidazole do not appear to be teratogenic, although the data on these drugs are more limited.[31] Quinolones, which cause arthropathy, and tetracyclines which affect bone and teeth, should be avoided during pregnancy.[2,31] Sulfonamides, like to other folate antagonists, have been associated with neural tube defects and cardiac malformations and should be avoided when possible.[32]

The experience regarding the treatment of chemotherapy-induced cytopenias with granulocyte colony-stimulating factor and erythropoietin is limited. However, so far no teratogenic effects have been reported.[2,33]

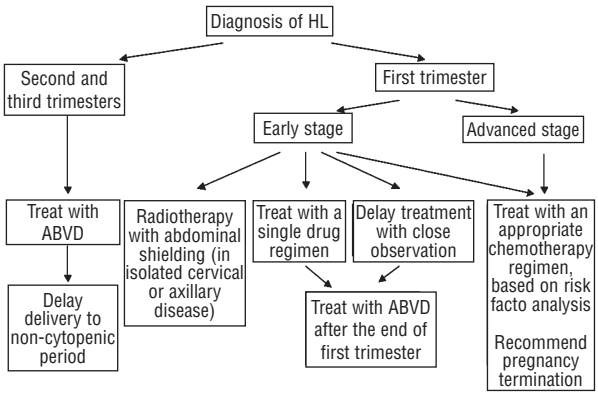

Figure 1. Suggested algorithm for the treatment of pregnancy-associated HL.

Treatment HL during pregnancy

A decision tree for the treatment of HL in pregnancy is proposed in Figure 1. The current trend in the treatment of HL is to administer of chemotherapy for all stages. However, radiotherapy can still be considered an appropriate treatment for stage 1 HL, especially in pregnant women with isolated involvement of neck or axillary lymph nodes.[26] This is of great clinical significance since HL most commonly presents as supra-diaphragmatic lymphadenopathy.

The most popular chemotherapy regimen for the treatment of HL is ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Among those four drugs dacarbazine is the least investigated. Although there is some evidence suggesting that the ABVD regimen is safe-during pregnancy,[2,15,34,35] the data are limited and based on case-reports and, therefore, ABVD cannot be considered safe when administered during the first trimester. Experience regarding treatment with the MOPP (mechlorethamine, vincristine, procarbazine and prednisone) regimen during pregnancy is even more limited.[36] There are no reports on treatment of pregnant patients with the Stanford V protocol, or with the high dose BEACOPP regimen which has become increasingly popular lately for treating high risk patients.

For women with advanced disease in an early stage of pregnancy, a delay in therapy may adversely affect survival.[37] Therefore, based on risk factor analysis, treatment with an appropriate chemotherapy protocol (ABVD, BEACOPP, etc) should be initiated promptly and a therapeutic abortion should be considered due to the potential teratogenic effects of chemotherapy in the first trimester.

Patients with early stage HL diagnosed in the first trimester can be followed-up at short intervals for signs of disease progression without any treatment until the second trimester. Several experts have suggested treatment with single agent chemotherapy (preferably vinca alkaloids or anthracycline antibiotics) for these low risk patients.[1,2,6,15] Such treatment is considered safe even during the first trimester,[1,2,6,15] however, data regarding its efficacy are lacking. Furthermore, it is not clear whether such treatment may induce chemotherapy resistance. Single agent therapy may be considered as well in patients diagnosed with HL during the first trimester and who reject therapeutic abortion as an option. In any case, at the beginning of the second trimester, adequate treatment with ABVD should be administered promptly.

Based on the available limited data, it seems that patients presenting in the second or third trimesters can be safely treated with chemotherapy similarly to non-pregnant women,[2,6,15,34,35] and therefore full treatment with ABVD may be given.[6,34,35,37-40] Table 1 summarizes the available experience regarding multi-drug chemotherapy regimens for the treatment of HL during the second and third trimesters.

For many years it was believed that pregnancy increases relapse and mortality rates in patients with HL.[37] However, a case-control study of 48 cases of pregnancy-associated HL showed a 20-year survival rate which was similar to that of matched controls.[37] Furthermore, infants born to women with HL during pregnancy did not have a higher risk of prematurity or intrauterine growth retardation.[37] There are no reports of HL metastases to the placenta or the fetus.

Treatment of NHL during pregnancy

A decision tree for the treatment of NHL diagnosed in the first trimester is proposed in Figure 2. We have divided the different types of NHL into three groups (indolent, aggressive and very aggressive lymphomas) according to the WHO classification

Indolent NHL

This group includes follicular lymphomas and chronic lymphocytic leukemia/small lymphocytic lymphomas and is extremely rare during pregnancy. The indolent NHL are characterized by a slow clinical course and since they are not curable with standard chemotherapy, treatment is usually delayed until the patient is symptomatic. Therefore, administration of chemotherapy during the first trimester is usually unnecessary. Most patients can be followed

Table 1. Pregnancy outcome after treatment with different combination chemotherapy regimens for HL.

Report description	*No. of cases*	*Outcome of pregnancy*	*Ref.*
Patients with HL treated with combination therapy (four treated with ABVD, two treated with MOPP)	6	Five cases treated in second trimester - normal pregnancy outcome one case treated with MOPP during first trimester -hydrocephalus	37
Long-term follow-up of children exposed to combination therapy for HL (all three trimesters)	19	No congenital neurological or psychological abnormalities were observed. Learning and educational performances were normal	35
Combination of vinblastine, cyclophosphamide and prednisone (third trimester)	1	Normal pregnancy outcome	38
Combination of cytarabine, etoposide and cisplatin (third trimester)	1	The newborn had severe but transient anemia. No congenital malformations	39
Combination of cyclophosphamide and vinblastine (second trimester)	1	Normal pregnancy outcome	40

closely without therapy until delivery or until signs of disease progression develop. When treatment is indicated during the first trimester, single therapy with rituximab may be considered.

Several therapeutic options are available for indolent NHL. The CVP (cyclophosphamide, vincristine and prednisone) regimen, which is actually CHOP (cyclophamide, doxorubicin, vincristine and prednisone) without doxorubicin should be at least equally safe. The use of fludarabine for treating young patients with indolent lymphoma has been gaining popularity lately. There are no reports regarding treatment with fludarabine during pregnancy; however since anti-metabolites tend to be more teratogenic than other anti-cancer drugs, its use during pregnancy should be avoided if possible. The very rare patients with stage 1 indolent lymphoma isolated to neck or axillary lymph nodes may be treated with local radiotherapy. The use of radio-labeled monoclonal antibodies is contraindicated during pregnancy due to the high fetal radiation exposure.[2]

Among the various indolent NHL, gastric mucosa-associated lymphoid tissue (MALT) lymphoma is considered a separate entity due to its well-recognized association with *Helicobacter pylori* infection and the relatively high remission rates after eradication of the bacterium. As for all other indolent lymphomas, treatment during the first trimester is usually not mandatory. However, since *H. pylori* eradication (with the most popular regimen being the combination of amoxicillin, clarithromycin and a proton pump inhibitor for 2 weeks) does not include chemotherapeutic agents and is not known to be associated with fetal malformation it can be safely administered during pregnancy.[31,41]

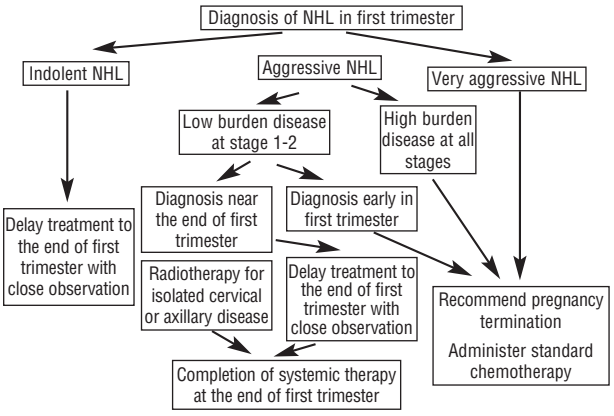

Figure 2. Suggested algorithm for the treatment of NHL diagnosed in the first trimester.

Aggressive NHL

This group includes large B-cell lymphomas, mantle cell lymphoma, mature T-cell and NK-cell neoplasms, and represents the majority of NHL cases diagnosed during gestation. Because of the aggressive course of these lymphomas during pregnancy, except for the rare patient with localized disease, most patients should be treated promptly with intensive combination chemotherapy. The CHOP regimen, usually in combination with rituximab, has been commonly used for treating patients with aggressive NHL, especially diffuse large B-cell lymphoma. Evidence regarding the fetal safety of CHOP for the treatment of NHL diagnosed during the first trimester of pregnancy is extremely limited. The existing data, based mainly on case reports, have shown no increase in the risk of severe fetal malformation in the few cases in which CHOP was given in the first trimester.[2,15,35,42] However, further studies are needed to evaluate the safety of CHOP during the first trimester, and, as in all other cases in which multi-drug regimens are used, therapeutic abortion should be strongly considered. Table 2 summarizes the available data regarding the treatment of aggressive NHL with different multi-drug chemotherapy regimens in the second and third trimesters. The majority of these regimens are based on a combination of an alkylating agent and an anthracycline, with CHOP being the most common regimen. The existing data suggest that treatment with CHOP during the second and third trimesters may be administered safely without adverse fetal outcomes.[2,35,38,39,42-54] These relatively limited data are further supported by data arriving from the treatment of pregnant patients with non-hematologic malignancies such as breast cancer, who were treated with regimens that share major similarities with CHOP. Two reports on a total of 53 pregnant patients with breast cancer who were treated with cyclophosphamide and doxorubicin with or without 5-fluorouracil during the second and third trimesters, documented no congenital anomalies or growth restriction in the women's offspring.[15,55]

Only a few cases of rituximab administration during

pregnancy have been reported, most of them for the treatment of non-malignant disorders such as different autoimmune diseases.[56-58] In these reports the administration of rituximab in pregnancy, including during the first trimester, was not associated with an increased risk of adverse fetal outcome. A recent report of a 35-year old pregnant woman, treated with rituximab and CHOP therapy early during pregnancy, described transient complete fetal B-cell depletion associated with high rituximab cord blood concentrations.[59] However, B-cell recovery was fast, showing a regular immunophenotype without loss of CD20 antigen, no functional deficits and adequate vaccination IgG titers. Based on this very limited experience it seems that the combination of CHOP with rituximab may be considered safe for treating diffuse large B-cell lymphoma during the second and third trimesters of pregnancy.

Patients diagnosed near the end of the first trimester may be considered for more conservative management. Treatment options in these patients include localized radiation therapy for limited cervical disease or close observation until the end of the first trimester followed by completion of adequate therapy.[42] However, this option should be limited to patients with stage 1-2 NHL with low volume disease, especially with a normal level of lactate dehydrogenase and low Ki-67expression on biopsy. Patients in early stage NHL but with high burden disease should not be candidates for this conservative option and should be treated with full dose chemotherapy soon after pregnancy termination.

Very aggressive NHL

This group includes precursor (B or T) lymphoblastic leukemia/lymphoma and Burkitt's lymphoma. Although these lymphomas have been reported to have a more rapid and fatal course during pregnancy, it appears that patients with this unfavorable outcome were probably not optimally treated with high intensity chemotherapy.[2,42] Due to the aggressive course and poor prognosis of aggressive lymphomas, treatment of those cases should be initiated immediately after diagnosis even during the first trimester. The pregnant patient must be informed about the high teratogenic risk and pregnancy termination should be strongly recommended. Many chemotherapeutic regimens for very aggressive lymphoma include high dose methotrexate which, among the currently used anti-cancer drugs, poses the greatest risk to the developing fetus when administered during the first trimester. Based on the very limited available data, it seems that treatment with methotrexate during the second and third trimesters is not teratogenic but can cause severe fetal myelosuppression.[2,35] Whether conventional chemotherapy for Burkitt's and lymphoblastic lymphomas, including high dose methotrexate, can be safely administered during the second and third trimesters has not been determined yet.

As mentioned above, pregnancy-associated NHL tends to exhibit more aggressive histology. However, when adequate combination chemotherapy is given, the survival rates of pregnant patients with NHL are similar to those of non-pregnant controls matched for grade.[2,8] The incidence of spontaneous abortions and prematurity does not appear to be affected by pregnancy-associated NHL.[38] However, there may be a trend toward a lower mean birth weight in babies born to mothers who had NHL.[8] Placental involvement in pregnancy-associated NHL is extremely rare but several case-reports including one case of dissemination to the fetus have been reported.[2,60]

Table 2. Pregnancy outcome after treatment with different combination chemotherapy regimens for aggressive NHL.

Report description	*No. of cases*	*Pregnancy outcome*	*Ref.*
Patients with NHL treated with CHOP (all in second and third trimesters)	4	Normal pregnancy outcome	42
Long-term follow-up of children exposed to different combination chemotherapy protocols (all containing an alkylating agent and an anthracycline) for NHL (all three trimesters)	33	No congenital neurological or psychological abnormalities were observed. Learning and educational performances were normal	35
Case reports of patients treated for NHL with combination chemotherapy protocols (all containing an alkylating agent and an anthracycline) atthe second and third trimesters	10	One case of stillbirth No congenital malformations	39, 43-51
Treatment with bleomycin, vinblastine, cyclophosphamide and prednisone (second and third trimesters)	3	Normal pregnancy outcome	52,53
Treatment with etoposide and cisplatin (second trimester)	1	Stillbirth at week 25	38
Treatment with cyclophosphamide vincristine, prednisone and rituximab (second trimester)	1	Normal pregnancy outcome	54

Long-term effect of the treatment of lymphoma

The fact that the central nervous system continues to develop throughout gestation has raised concerns regarding long-term neurodevelopmental outcome of children exposed *in utero* to chemotherapy for the treatment of lymphoma. Other concerns are childhood malignancy and long-term fertility. Information regarding these issues is limited due to the difficulties in long-term follow-up and the relative rarity of such cases. A long-term (up to age 6-29, average 18.7 years) follow-up of 84 children born to mothers with hematologic malignancies, including 26 patients with HL and 29 patients with NHL, reported normal physical, neurological and psychological development.[35] This study partially addressed the issue of reproduction in that all offspring showed normal sexual development and 12 of them had become parents to normally developed children. Finally, the offsprings' risk of developing childhood cancer was no higher than that in the general population. This report was supported by a review sum-

marizing 111 cases of children born to mothers treated with chemotherapy during pregnancy.[61] These children, who were followed-up for different periods of time (1 to 19 years) had normal late neurodevelopment based on formal developmental and cognitive tests. In summary, the available data regarding the late effects of chemotherapy on children's neurodevelopment are limited and most reports used a retrospective design in order to recruit a sufficient number of cases. However, the general impression based on the available data is that chemotherapy does not have a major impact on later neurodevelopment.

Breastfeeding and chemotherapy

Experience regarding chemotherapy during lactation is limited and based on case-reports. The concentrations of different chemotherapeutic agents in breast milk vary. However, dose-dependent as well as dose-independent effects of these drugs cannot be ruled out. Although it is unclear how much toxicity can be attributed to these drugs during lactation, most authorities consider cancer chemotherapy to be incompatible with breastfeeding.[2]

Ethical considerations

Pregnancy-associated lymphoma raises complex ethical dilemmas. The fact that an optimal anti-lymphoma treatment may be associated with adverse fetal outcome including severe malformations or death raises a potential maternal-fetal conflict. This dilemma is further complicated by the disparity between available data regarding different aspects of pregnancy-associated lymphoma and the dramatic decisions that need to be taken. Therefore, decisions about treatment of lymphoma diagnosed during gestation should be case-specific. It is most important that the attending physician provides the pregnant patient and her family with all the available information regarding the disease and its prognosis, possible treatment alternatives and maternal and fetal risks. Every decision should be made together with the patient after careful consideration of both risks and benefits. In many cases, such as low-grade NHL or early stage HL, there are options to postpone treatment until fetal maturity is achieved without altering maternal prognosis. However, when there is a clear risk to the mother, her safety must supercede fetal risk and an appropriate multi-drug regimen should be administered promptly.

Future perspectives

The teratogenic effects of chemotherapy are usually studied in animal models. However, the doses of chemotherapy used in humans are often lower than the minimum teratogenic doses applied in animals, making it difficult to extrapolate data from animals to humans. Recently, there has been a growing interest in studying the effect of different drugs, including chemotherapeutic agents, on the placenta.[62-64] For example, the adverse effects of 6-mercaptopurine on the placenta have been documented with inhibition of both migration and proliferation of trophoblast cells in first-trimester human placental explants.[62] Furthermore, placental perfusion studies can provide valuable information regarding both transfer and biotransformation of different drugs in the human placenta.[65-67] To date, these studies have been used with drugs not usually prescribed for cancer treatment. However, they can serve as a model for the assessment of placental transfer and effect of cancer chemotherapy and thus add important information regarding fetal safety. Finally, due to the relative rarity of pregnancy-associated lymphoma, there are only few medical centers or physicians that have gained expertise in this area. There is a critical need for multicenter cooperation and a central registry to collect data on a large number of cases of pregnancy-associated lymphoma and their follow-up. This would facilitate better conduction of epidemiologic studies and follow-up, and would enable physicians to assess more accurately the safety of the different anti-cancer treatments during pregnancy. It would also enable a prediction of those pregnant patients with lymphoma for whom postponement of treatment can be safely considered and those with a worse prognosis for whom therapy cannot be delayed.

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