

Hodgkin Lymphoma in Pregnancy: A Case Report

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Introduction

Lymphoma is the fourth most frequently diagnosed malignancy during pregnancy, and the most common type of lymphoma in pregnant women is Hodgkin lymphoma (HL). Although HL has a relatively high incidence in women of reproductive age, HL in pregnancy is still uncommon, corresponding to 3.2% of all patients with HL. HL during pregnancy has a reported incidence ranging from 1 per 1,000 to 1 per 6,000 deliveries.¹

HL is considered one of the most curable forms of cancer, especially if diagnosed and treated early. Unlike other cancers, HL is potentially curable even in late stages. Five-year survival rates for patients diagnosed with HL stages I or II are 90–95%. With advances in treatment, recent studies have indicated that even patients with advanced HL have 5-year survival rates of 90%. Patients who survive for at least 15 years after treatment are more likely to later die from other causes than from HL. Survival rates are lowest for patients who do not respond to first-line therapy and who have signs of disease progression, or those who relapse within a year of treatment.²

During the last decade, it was thought that pregnancy worsened HL prognosis. A case-controlled study of 48 cases of pregnancy-associated HL, however, showed a 20-year survival rate that was similar to that of matched controls. Furthermore, infants born from this cohort of pregnant women did not show worse perinatal outcome. No metastases to the placenta or the fetus were described.³

Although prognosis does not appear to be adversely affected, pregnancy imposes significant limitations on HL management. Exposure of the developing fetus to teratogens should be avoided whenever possible, but delaying treatment may be deleterious to the mother. Chemotherapy

probably can be safely received during the second and third trimesters, but radiotherapy should be avoided late in pregnancy owing to the close proximity of the pregnant uterus to the lower border of the treatment field.⁴ Treatment-related decisions must take into account the clinical presentation, the drug interactions with pregnancy, and the effects of such treatment on fetuses and newborns.

Case Report

A 33-year-old primiparous woman at 16 weeks of gestation was admitted to our hematology department in February 2012 with bilateral inguinal lymphadenopathy. She reported no systemic B symptoms, such as fever, drenching night sweats, or unexplained weight loss of 10% or more, within the last 6 months. Prenatal evaluations and ultrasounds were all normal, demonstrating a single intrauterine pregnancy with appropriate growth for dates and a low aneuploidy risk.

The physical examination evidenced bilateral inguinal lymphadenopathy, with a diameter of 2–3 cm on the left and 4–5 cm on the right. The routine blood test revealed a hemoglobin level of 11.7 g/dL, with a mixed iron pattern, white blood cell count of $11.1 \times 10^9/L$, lymphocyte count of $1.6 \times 10^9/L$, and platelet count of $396 \times 10^9/L$. The erythrocyte sedimentation rate (ESR) and serum lactate dehydrogenase were elevated (120 mm/h and 464 U/L, respectively), while serum albumin was low (33 g/L). The echocardiogram revealed normal left ventricular function, with a 70% ejection fraction at rest.

A lymph node biopsy was performed under local anesthesia. The histologic HL subtype was classic nodular sclerosis with an immunohistochemical pattern of CD30+, CD15+, MUM1+, Bcl2+, EMA (focus)+, PAX5-, ALK-, CD20-, CD79a-, CD3-, CD45ro-, CD10-, and Bcl6-. The proliferation index (Ki-67) was 60%. The bone marrow biopsy was negative for malignant cells, with an immunohistochemical pattern of CD30- and CD15-.

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Radiologic evaluation was performed with magnetic resonance imaging (MRI) using half-acquisition single shot turbo spin echo (HASTE) images with dark blood images to avoid a contrast injection. The head, neck, chest, abdomen, and pelvis were all examined, acquiring axial and coronal slices in T1W and T2W. The evaluation showed no splenomegaly, but presented multiple nodular and focal low-intensity images in the sequences in T2W and short-tau inversion recovery (STIR), and also in T1W. The images did not display the characteristics of liquid, so they may have indicated multifocal splenic involvement of the lymphoma.

Retroperitoneal paraaortic adenopathies were present in the space between the abdominal aorta and the inferior vena cava. There were also numerous images of adenopathic growth in the promontory, iliac, hypogastric, obturator, and inguinal chains. Other findings included a pregnant uterus and minimum amount of free liquid at the minor pelvis. The head, neck, and thorax also were examined and were found to be normal, without ganglionic growth or lymphomatous infiltration.

A new diagnosis of nodular sclerosing HL with clinical stage IIs-A disease was made according to the World Health Organization criteria and the Ann Arbor staging classification, respectively.

The patient's pregnancy was monitored clinically and with ultrasound. The ultrasound examination to detect major fetal structural defects at 18 weeks revealed no detectable congenital anomalies. Fetoplacental biometry and Doppler velocimetry were assessed monthly until the time of delivery: fetal values showed a growth percentile of 30 and fetal echocardiography was normal.

The patient underwent chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for 6 cycles, every 4 weeks starting from gestation week 18. The antiemetic used was granisetron. Neither significant adverse effects associated with chemotherapy nor adverse fetal effects during pregnancy were observed.

Peripheral lymphadenopathy was resolved after 3 cycles of chemotherapy. The radiologic MRI evaluation showed persistency of the paraaortic and paracaval lymph nodes in the retroperitoneum, but the size was smaller than in the prescan. The lymph nodes in the iliac, hypogastric, and obturator chains also were smaller. The size of the bilateral inguinal lymph nodes was substantially reduced; the few small ones that remained did not exceed 15 mm in diameter. The amniotic sac with the placenta and fetus in its interior was evident.

Chemotherapy was completed after 5 courses (3 weeks prior to delivery), when complete blood counts were normal. Labor was induced with oxytocin at 37 weeks of gestation with continuous fetal heart monitoring control. In a second stage of labor, assistance in delivering

the baby using vacuum extraction was required. A female neonate was born of normal weight (2,750 g) and with a normal Apgar score (8/9), and complete blood counts were within normal limits. The newborn required initial resuscitation steps, but it was not necessary to separate her from her mother after birth. The patient and her infant were monitored in the hospital. A patent foramen ovale with 4 mm of diameter with interatrial right-to-left blood shunting was seen in the newborn at 24 hours after birth. An echocardiogram done 6 months later confirmed a spontaneous closure of this shunt, with normal function of heart. Transfontanelar and abdominal ultrasound scans that were conducted 24 hours after birth to rule out abnormalities in the nervous central system and the abdominopelvic organs showed no abnormalities.

The mother was given a positron emission tomography computed tomography (PET/CT) scan that showed complete remission on day 5 after delivery, when she and her infant were discharged. The patient was advised to not breastfeed.

Four weeks later, she received her sixth cycle of ABVD chemotherapy. At the time of writing this report, 10 months after delivery, the mother is still in complete remission and her infant is healthy.

Discussion

Pregnancy imposes significant limitations on the ability to effectively treat patients with HL. The immediate health of both the mother and child must be considered, as well as the long-term health of the child if exposed to potentially teratogenic drugs or radiation as a fetus. Hence, the decision to initiate therapy with a pregnant patient is usually a difficult one, which may be further complicated by heightened emotions, ethical issues, and religious beliefs.⁴

HL characteristics are the same in pregnant women as in nonpregnant women. The clinical behavior and histologic subtypes of HL in pregnancy are no different from those of nonpregnant women of similar age. From the pathology viewpoint, presentation during pregnancy is also the same. The more frequent histologic type found in a study of 17 women diagnosed with HL at approximately 22 weeks of gestation was classic nodular sclerosing HL, found in 13 patients.⁵

For HL staging, either CT or PET/CT scans of the neck, chest, abdomen, and pelvis are typically requested. CT of abdomen and pelvis could expose the fetus to radiation of at least 0.02 Gy, which is considered potentially teratogenic. However, the HASTE sequence of MRI provides a rapid and comprehensive imaging of the entire chest that has largely replaced conventional MRI, and it obtains a rapid dark-blood images that provide enough information on lymph node size with no measurable radiation risk to the fetus. Therefore, abdominal and

pelvic CT should be avoided during pregnancy. PET/CT should be performed after delivery to assess treatment response. Staging of a pregnant patient with HL should be based on history, physical examination, routine blood tests, and bone marrow biopsies, as well as on MRI or ultrasonography, which can be useful alternatives to CT.^{6,7} There was no adverse birth outcome, with the exception of a temporary patent foramen ovale. This may have been related to exposure to doxorubicin, whose cardiotoxicity has been well described. The chronic cardiotoxicity of this drug has been described in adults as a dose-related effect.⁸ The effect of doxorubicin on the heart of an exposed fetus or neonate is under evaluation because no definitive information is available; 1 review showed no fetal effects after a long-term evaluation of cardiac function in children who received anthracyclines in utero.⁹

On the other hand, previous cohort studies also have found no substantial increased risk of low birth weight, stillbirth, or chromosomal abnormalities, and no chromosomal abnormalities among newborns.^{10,11} In recent cohorts, prematurity or low birth weight may be considered confounding factors.^{12,13}

Clear indications for treatment include: local symptoms due to progressive or bulky nodal disease; compromised organ function due to progressive or bulky disease; symptomatic infradiaphragmatic disease; high-risk criteria (elevated serum lactate dehydrogenase and ESR, and low serum albumin); presence of systemic B symptoms; presence of symptomatic extranodal disease, such as effusions; cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia, thrombocytopenia, or hypersplenism; and prolonged disease tempo.¹⁴ When lymphoma is diagnosed during the second or third trimester, evidence suggests that full-dose chemotherapy can be administered safely with no apparent increased risk of severe adverse fetal outcome. Avoiding chemotherapy if possible during the first trimester of pregnancy is generally recommended, as is postponing radiotherapy until after delivery. Significant exposure to cytotoxic agents during the first 4 weeks of gestation may result in spontaneous abortion. The risk of birth defects increases if exposure occurs in gestation weeks 5–12, when organogenesis takes place. Organogenesis is complete by gestation week 12, except for the brain and gonads. Exposure to these drugs during the second or third trimester is not associated with teratogenic effects, but may result in intrauterine growth retardation, prematurity, and stillbirth. Thus, close monitoring of fetal well-being throughout pregnancy is mandatory.⁴

A comprehensive literature review has concluded that ABVD is a regimen of choice (grade 1C recommendation) if multi-agent chemotherapy is to be used. ABVD appears to be safe for fetal development when used during the second or third trimester. An extensive literature review was conducted

in 2008 for the American Society of Hematology Education Program. This review assessed papers published from 1950 to 2008 that appeared in the MEDLINE database. After excluding those articles that did not meet the research criteria, 8 case reports, 9 case series, and 2 case-control studies remained for analysis. The case reports highlighted the outcome of pregnant women who underwent chemotherapy in relation to the evolution of the disease and the newborn's well-being. Of all the case reports, only one reported malformation. In this case, the mother was treated only with oral cyclophosphamide during all 3 trimesters of pregnancy and the newborn had syndactyly.¹⁵

The treatment approach should be individualized in accordance with the gestation period, disease stage and localization, and progression of symptoms and signs. If patients have aggressive disease with systemic B symptoms or symptomatic subdiaphragmatic disease, are in an advanced clinical HL stage, or have high-risk criteria, chemotherapy should commence in accordance with the ABVD protocol. A follow-up of high-risk pregnancies should be done with a specialized obstetrician.¹⁴

The current trend in the treatment of HL is to administer chemotherapy for all stages.⁷ However, radiotherapy can still be considered an appropriate treatment for stage I HL, especially in pregnant women with isolated involvement of the neck or axillary lymph nodes. This is of great clinical significance because HL most commonly presents as supradiaphragmatic lymphadenopathy.¹⁶

For patients with advanced disease in an early stage of pregnancy, a delay in therapy may adversely affect survival. Therefore, based on risk factor analysis, chemotherapy with ABVD should be initiated promptly and a therapeutic abortion should be considered owing 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, and given no treatment until the second trimester. If treatment is needed during the first trimester, pregnancy termination should be considered before initiation of standard therapy with ABVD.¹⁷ Several experts have suggested treatment with single-agent chemotherapy (vinca alkaloids or anthracycline antibiotics) for these low-risk patients. Such treatment is considered safe even during the first trimester,¹ but 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. Radiotherapy with abdominal shielding can be considered in cases of cervical disease or localized axillary spread.^{6,16}

Based on the available data, it appears that patients presenting in the second or third trimester can be safely treated with chemotherapy similarly to nonpregnant women, and therefore full treatment with ABVD may be given.⁷ For high-risk cases, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) should be considered. In progressing cases, pregnancy termination should be considered in order to treat the patient as a nonpregnant woman.¹⁷ Because chemotherapy is associated with transient bone marrow depression, delivery should be planned accordingly. Women should not give birth within 3 weeks of chemotherapy, but delivery should take place when maternal blood counts are optimal. Neonatal cytopenia has been noted after exposure to chemotherapy; thus, blood counts should be monitored in newborns. Mothers receiving chemotherapy are advised to not breastfeed during treatment, as these agents administered at therapeutic doses reach significant levels in breast milk.⁴

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 antiemetics and congenital malformations in either animal models or humans.^{18,19}

The experience regarding the treatment of chemotherapy-induced cytopenias with granulocyte colony-stimulating factor and erythropoietin is limited. However, no teratogenic effects have been reported thus far.²⁰

Our patient presented with subdiaphragmatic disease with 4 involved areas and other high-risk criteria (elevated serum lactate dehydrogenase and ESR, and low serum albumin). She showed no systemic B symptoms. We outline a successful practical HL management approach during the second trimester of pregnancy.

Conclusion

Lymphoma is a rare diagnosis in pregnancy. Immunohistochemical markers provide prognostic stratification, and—together with other clinical factors—can outline the risk profile for certain groups of patients more accurately; this may have a critical impact on therapeutic decisions. Therefore, immunohistochemical evaluations should be considered in all cases.¹⁴

Given the relative rarity of pregnancy-associated lymphoma, there is a critical need for multicenter cooperation and a central registry to collect data on a large number of

cases and their follow-up. Such an action would facilitate epidemiologic studies and patient follow-up, and would enable physicians to more accurately assess the safety of different anticancer treatments during pregnancy. It would also enable clinicians to predict which pregnant patients with lymphoma can safely accommodate postponed treatment, and which should be treated without delay.^{7,19}

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Commentary

Hodgkin Lymphoma in Pregnancy: Achieving the Best Outcome for Both Mother and Infant

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Hodgkin lymphoma (HL) occurs in a bimodal age distribution, with a peak in young adults and a peak in older age. The incidence of HL in the United States is 9,220 new cases per year, of which 4,220 are in women. Given that incidence peaks in the reproductive years, it is not surprising that 3% of women diagnosed with HL are pregnant.¹

Sanchez and colleagues present a case of a 33-year-old woman who was diagnosed with stage IIA classical HL during the second trimester of an intrauterine pregnancy. Because of the timing of diagnosis, most of the treatment was delivered during pregnancy. The outcome was good in both mother and infant.

Treating HL in a pregnant woman often presents diagnostic and therapeutic challenges to hematologists, as they must decide on the most beneficial course of action for both patient and infant. HL in pregnancy requires an interdisciplinary approach to the patient that involves medical oncology, maternal-fetal medicine, and pediatrics.

The first challenge is staging the pregnant patient. Staging of HL in the nonpregnant patient involves the use of positron emission tomography/computed tomography (PET/CT). Exposure of the fetus to less than 5 rads (0.05 Gy) is not associated with fetal congenital anomalies, growth restriction, intellectual disabilities, or miscarriage.² However, 1–2 rads (0.01–0.02 Gy) of exposure may increase the risk of childhood cancer in the developing fetus by a factor of 1.5 to 2, although this finding is controversial.^{2,3} Fetal radiation exposure during nonabdominal CT scan is minimal. For example, a chest CT scan without the use of an abdominal shield exposes the fetus to 30 mrad (0.0003 Gy), far less than what could pose a safety risk to the fetus. Although a single anteroposterior

chest radiograph with the use of an abdominal shield can be used for staging of the chest in HL, we recommend the use of chest CT with an abdominal shield, taking into consideration the radiation figures mentioned previously. Although the safety of using PET/CT in pregnancy has not been extensively studied, the exposure to the uterus using normal standard levels of isotope is 370–740 mrad (0.0037–0.0074 Gy). This is still well below the threshold of 5 rads (0.05 Gy), but the use of PET/CT in pregnancy is contraindicated because of the lack of studies.⁴

The second challenge faced is choice and timing of HL treatment. Currently, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is considered standard of care for classical HL because it has been demonstrated to have similar efficacy as mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), but with less toxicity.⁵ ABVD also appears to be safe to the fetus in the second and third trimesters of pregnancy, and is the recommended therapy in early-stage HL.⁶ On the other hand, for patients with unfavorable HL (stage IIB, III, or IV, or an International Prognostic Score of ≥ 3), dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) is advocated as the standard of care. However, since the difference between ABVD and dose-escalated BEACOPP in this high-risk population can be salvaged with a high-dose salvage regimen, we will recommend the use of ABVD even in this circumstance, because the toxicity of dose-escalated BEACOPP might compromise the infant.⁷

Treatment with chemotherapy in the first trimester remains controversial; some studies show that 33% of fetuses exposed in the first trimester are born with congenital abnormalities.⁸ Those patients with low-risk clinical circumstances (ie, slowly growing disease, disease above the diaphragm, diagnosis late in pregnancy) can have therapy delayed until after delivery without affecting long-term survival. To prevent delivery at a time where fetal myelosuppression would occur, chemotherapy should not be given within 3 weeks of scheduled delivery or after 35 weeks of gestation. This delay allows for fetal myelosuppression from chemotherapy to resolve and for the placenta to excrete any remaining drugs from the fetus.⁹

HL is a highly curable malignancy. The 10-year survival figures for HL are close to or exceed 90% in all age groups up to age 45 years.¹⁰ These figures are not affected if standard chemotherapeutic regimens for HL are administered during the second and third trimester.¹¹ Long-term studies on children exposed to standard chemotherapy regimens for HL in utero have not shown increased rates of congenital anomalies, differences in birth weight or school performance, or increased rates of neurologic or psychologic problems. The children also did not have an increased rate of secondary malignancies.¹² Standard treatment for low-risk

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HL in the second or third trimester with ABVD is associated with favorable maternal and fetal outcomes.¹¹ Management of high-risk HL in pregnancy is less well described, but we advocate for use of ABVD in this population, along with a planned high-dose salvage regimen that includes autologous stem cell transplantation. Treatment within the first trimester of pregnancy remains controversial.

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