Hematologic Malignancies in Pregnancy

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Hematologic malignancies, as a group, represent 25\% of the cancers complicating pregnancy, behind carcinomas of the breast (26\%) and cancer of the uterine cervix (26\%)\cite{1–3}. In women 15 to 24 years of age, however, the most frequent malignant tumor is Hodgkin’s lymphoma (HL)\cite{4}. Like other cancers complicating pregnancy, they are uncommon, with the incidence of HL during gestation reported at 1:1000 to 1:6000, whereas the incidence of leukemia coincident with pregnancy is reported at 1:75,000 to 1:100,000\cite{1–3}. Clearly, no single individual can have sufficient experience with these malignancies to be considered an expert. It is imperative that a multidisciplinary team involving oncologists, pediatric specialists, nurse coordinators, and obstetricians care for patients with hematologic malignancies. The primary role of the obstetrician is to assist in the diagnosis of these disorders and to coordinate the various subspecialty consultations. The obstetrician should also play an integral role in counseling the patient and her family regarding their options and establishing the timing and method of delivery.
This article discusses the three most common categories of hematologic malignancies: (1) HL, (2) non-Hodgkin’s lymphoma (NHL), and (3) leukemia. Case vignettes are used to illustrate the importance of early diagnosis on maternal and fetal prognosis, the effect of the disease on the pregnancy, and the effect of pregnancy on the disease. Finally, the effect of pregnancy on the available treatment options is also discussed.

**Vignette 1: Hodgkin’s lymphoma**

A 25-year-old white woman, G2P1001, presented for her follow-up prenatal visit at 29 weeks without complaints other than an enlarged nontender mass in her right axilla that had been present for the last 2 months. This finding was thought to represent extramammary tissue, and the patient was reassured and scheduled for a follow-up appointment in 3 weeks. At the patient’s follow-up appointment, it was believed that the mass was more enlarged, measuring $3 \times 3$ cm, firm and nontender. There was no history of night sweats, fever, or weight loss, but she did complain of increased pruritus over the last few weeks. She had a history of having mononucleosis, while she was a college student; otherwise, her medical history was unremarkable. Her hemoglobin, hematocrit, leukocyte levels, and platelet count and electrolytes, erythrocyte sedimentation rate, and liver function studies were all normal. Serologies for acute infection with cytomegalovirus, toxoplasmosis, HIV, and her heterophile antibody test were all negative. After referral to a hematologist at 32 weeks, the patient underwent a lymph node biopsy that was histologically classified as HL of nodular sclerosis subtype. Bone marrow biopsy was negative. Chest and abdominal MRI showed some mediastinal enlargement (<10 cm), but no evidence of abdominal paraaortic lymph node enlargement, hepatic or spleen enlargement, or occult bone marrow involvement.

Based on these results the patient was staged as clinical stage 1A and her treatment options were discussed. She and her family elected to delay treatment until after delivery. Antenatal steroids were administered and her labor was induced after fetal lung maturation was confirmed at 35 weeks. Both the patient and infant did well and were discharged home on postpartum day 2. The patient was scheduled for follow-up with oncology for further treatment.

**Hodgkin’s lymphoma**

HL is a disease of young adults with an average age of diagnosis in pregnant and nonpregnant women of 25.5 years [5]. It accounts for 51% of the hematologic malignancies complicating pregnancy and is the fourth most common cancer encountered during gestation [1–3]. HL is a neoplasm that originates in the lymph nodes and seems to spread contiguously from one lymph node group to another. It often presents with painless lymphadenopathy, usually of the
cervical, submaxillary, or axillary nodes. The etiology is uncertain, but is probably multifactorial with both a genetic predisposition (based on studies of familial aggregation) and environmental factors (based on the finding of Epstein-Barr virus DNA) in up to 50% of biopsy specimens [6]. HL is a pathologic diagnosis, characterized by the presence of the clonal malignant Hodgkin cell or multinucleated Reed-Sternberg cell in a background mixture of reactive, inflammatory, and stromal cells (Figs. 1 and 2). Until the mid-late 1990s, the origin of the Reed-Sternberg cell was obscure. It has recently been demonstrated, however, that these cells are of B-cell lineage [7]. These tumors can be subclassified based on their histopathologic characteristics (World Health Organization [WHO] classification), with the most common histologic subtype, nodular sclerosis, also occurring most frequently in pregnancy. In the past, the histologic subtype was believed to have important prognostic significance, with the nodular sclerosis subtype conferring a more favorable prognosis. More recently, however, with advancements in the treatment of HL, the two most important and consistent prognostic factors that have emerged are the stage of disease (modified Ann
Arbor system for staging) and the patient’s age. Patients who are less than 60 years of age and who have limited-stage disease can expect long-term survival rates of at least 90% [8]. The Ann Arbor staging system incorporates the number and location of involved lymph nodes, the presence of extralymphatic extensions, and the presence or absence of B symptoms (unexplained weight loss, recurrent fever >38°C, and recurrent night sweats) into a prognostically valuable system for staging lymphomas [9]. In North America, patients with Ann Arbor stage I to II, the absence of bulky disease (tumor mass <10 cm), and without B symptoms are considered to have early stage disease [10].

Pregnancy itself does not seem to affect the stage of the disease at diagnosis, the response to therapy, or the overall survival rate when compared with age- and stage-equivalent nonpregnant controls [11,12]. In addition, pregnancy termination does not seem to improve maternal outcome. Approximately 70% of pregnant patients with HL present with early stage disease (stage I–II) with 8-year survival rates of 83% [4,11]. In the past, staging for HL was both clinical and pathologic, with pathologic staging accomplished by laparotomy. With the use of modern-generation CT and MRI studies, however, and current multiagent chemotherapeutic regimens of doxorubicin, bleomycin, vinblastine, and dacarbazine, the need for staging laparotomy is uncommon [10].

The initial evaluation should include a complete history and physical with careful documentation of B-symptoms. In addition, a thorough documentation of all node-bearing areas should be performed. A complete differential blood count and platelets, an erythrocyte sedimentation rate, tests for liver and renal function, and assays for lactate dehydrogenase and alkaline phosphatase should be obtained. Radiologic studies should include a chest radiograph and an MRI of the chest, abdomen, and pelvis. Although usually negative, bone marrow biopsies are recommended. Fortunately, lymphangiograms, which should be avoided during pregnancy because of potential fetal radiation exposure, are rarely used in the current evaluation of HL patients.

Whether or not HL adversely affects pregnancy is less clear. In the studies performed to date, with some of the reported patients opting to delay treatment until after delivery, there does not seem to be a significant difference in birth weight, mean gestational age, or method of delivery [12,13]. In addition, one study was done of 26 mothers with advanced-stage HL, with treatment started in all three trimesters using combined chemotherapy of doxorubicin, bleomycin, vinblastine, and dacarbazine; mechlorethamine, vincristine, prednisone, and procarbazine; or epirubicin, bleomycin, vinblastine, and dacarbazine. The study found no evidence at long-term follow-up (median age, 18.3 years) of congenital anomalies, hematologic malignancies, or neurodevelopmental abnormalities in any of the individuals exposed to these chemotherapeutic agents in utero [13]. Other studies, however, particularly if treatment is started in the first trimester, have been less optimistic, with fetal anomalies, fetal demise, fetal growth restriction, premature deliveries, and neonatal pancytopenia all reported with various, but not necessarily identical, multiagent chemotherapeutic regimens [14,15].
The treatment for early stage HL has undergone a significant metamorphosis over the last decade. In the past, the mainstay of treatment for early stage HL was external-beam radiation therapy, with the mantle field (axillary, cervical, mediastinal, and pulmonary hilar lymph nodes) used for supradiaphragmatic disease. In the early 1990s, to decrease the relapse rate (40%) with radiation therapy alone, and to avoid the morbidity associated with staging laparotomy and the emerging problem of secondary solid malignancies, the use of combined modality therapy was introduced and later refined [16,17]. Clinical trials of combined modality therapy, involving the use of multiagent chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) plus low-dose involved-field radiotherapy, have produced overall survival rates of 93% [18]. These results have encouraged many experts to recommend, even during pregnancy, that patients with early stage disease be treated with multiagent chemotherapy, preferably doxorubicin, bleomycin, vinblastine, and dacarbazine, with or without involved-field radiotherapy. If involved-field radiotherapy is elected, the study by Woo and coworkers [19] has particular relevance. In this observational study, 11 women with stage IA to IIA nodular sclerosing HL were treated at various gestational ages with mantle irradiation (4000 cGy) doses that far exceed those currently recommended (2800–3200 cGy). Despite these relatively high doses, with proper uterine shielding, the highest estimated fetal dose was 13.6 cGy [19]. Furthermore, none of the infants demonstrated any adverse effects from this exposure. Given that the fetal risks of ionizing radiation are both a gestational age and threshold phenomenon with the risk for congenital malformations, microcephaly, and miscarriage in the first trimester increasing after a dose of 20 cGy, and the threshold dose for mental retardation at 8 to 15 weeks of gestation reported to be 18 cGy, it seems reasonable that treatment in the second and early third trimester for patients with early stage disease should not be altered by the pregnancy [20,21]. In the first trimester, because of concerns for possible adverse fetal effects from multiagent chemotherapy (7%–17%) risk of fetal anomalies, the risk of delaying chemotherapy, progression of maternal disease to a higher stage needs to be balanced with the patient’s desire to avoid potential harm to her fetus. In the third trimester, however, there are few circumstances in which radiation therapy is used before delivery can be accomplished. In this situation antenatal steroids should be administered and delivery accomplished after 32 to 34 weeks gestational age, once fetal lung maturation can be confirmed by amniocentesis. If spontaneous labor ensues after 32 weeks it should be allowed to progress, as long as antenatal steroids have been previously administered, and there are no obstetric indications contradicting spontaneous vaginal delivery [22]. Delivery, if possible, should be timed 2 to 3 weeks after chemotherapy, to avoid the maximum risk of neonatal myelosuppression.

Treatment of pregnant patients with advanced-stage disease is best accomplished with multiagent chemotherapy. Long-term disease-free survival rates of 88% have been observed in advanced-stage patients treated with mechlorethamine, vincristine, prednisone, and procarbazine; doxorubicin, bleomycin, vinblastine, and dacarbazine; or epirubicin, bleomycin, vinblastine, and dacarbazine [13].
There is no evidence that method of delivery should be affected by the presence of HL complicating pregnancy. Pathologic examination of the placenta should be considered because placental metastases, although rare, have been documented [2]. In addition, the patient should be counseled regarding the option of cord blood banking as a source of HLA-compatible stem cells [23,24]. Finally, patients who maintain their fertility after treatment should be advised to avoid pregnancy for at least 2 years, because this is the time of greatest risk for relapse after primary therapy [25].

Vignette 2: non-Hodgkin’s lymphoma

The pregnancy of a 38-year-old woman, G2P1001, had been uneventful until 10 days before admission, when she developed a sore throat, nonproductive cough, vomiting, and a fever. At 27 weeks’ gestational age, she was hospitalized in advanced labor with a cervix dilated to 5 cm and 100% effaced. She had a temperature of 38.8°C, a pulse of 120 bpm, and the fetal heart rate was 160 bpm. No lymphadenopathy was appreciated and her lung fields were believed to be clear. Ultrasound demonstrated an appropriately grown fetus with normal biophysical profile (BPP) and amniotic fluid volume. There were no fetal or placental abnormalities noted. Laboratory data revealed a white blood cell count of 3800/μL, 39% bands, 25% lymphocytes. Her hematocrit was 40% with normal indices; a platelet count was 130,000/μL. Liver functions demonstrated a serum glutamic-oxaloacetic transaminase of 31 U/L and a lactic dehydrogenase of 1697 U/L. Her initial chest radiograph demonstrated a left lower lobe infiltrate and she was started on broad-spectrum parenteral antibiotics.

She progressed rapidly and delivered a 1.214-g girl vaginally, with Apgar scores of 4 and 5. She suffered an immediate postpartum hemorrhage that required manual extraction of the placenta and curettage, and uterotonic to control. The placenta was noted to be friable but was not sent for pathologic investigation. On the evening of her first postpartum day she became tachypneic and her temperature rose to 39°C. Her chest radiograph revealed bilateral pleural effusions. Repeat complete blood count demonstrated a white blood count of 4800/μL; hematocrit of 27%; platelet count of 88,000/μL; prothrombin time 14.8 seconds (control 13 seconds); partial thromboplastin time 63 seconds (control 30 seconds); and a fibrinogen of 103 mg/dL. The patient ultimately required mechanical ventilation for worsening hypoxia and acidosis. Despite aggressive treatment with vasopressors, antibiotics, and blood products, her condition continued to deteriorate and she expired on the fourth postpartum day.

Examination of the patient at necropsy revealed severe pulmonary edema, hepatosplenomegaly but no lymphadenopathy. Microscopic examination of the liver revealed lymphoid infiltrates comprised of mitotically active large lymphoid cells. Cellular infiltrates of similar appearance were present in the uterine myometrium, ovaries, spleen, and the perivascular tissue of the lung. Lymph nodes and bone marrow, however, were not involved. Immunohistochemical
studies of paraffin-imbedded tissue from the liver and myometrium were positive for CD 43 and negative for CD 30, CD 20, and Ki-M1P. These histologic and immunologic features were consistent with a non-Hodgkin’s T-cell lymphoma that would now probably be classified as a hepatosplenic T-cell lymphoma (WHO classification).

The infant’s initial course was unremarkable; however, at 2 months of age she developed respiratory distress and required intubation. An open lung biopsy demonstrated perivascular large mitotically active lymphoid infiltrates, which were cytologically identical to those present in the mother. Immunohistochemistry revealed a cell phenotype identical to that found in the mother’s tissues.

The infant was started on induction chemotherapy with cyclophosphamide, doxorubicin, etoposide, and prednisone. In addition, intrathecal treatment with methotrexate, arabinosylcytosine, and hydrocortisone was initiated. She entered remission and was placed on maintenance chemotherapy for 1 year and has remained in complete remission [5].

Non-Hodgkin’s lymphoma

The NHLs are a heterogeneous group of lymphoid malignancies that have their origins in lymphoreticular tissue. They are separated from HL by the absence of Reed-Sternberg cells. NHLs are tumors of either T- or B-cell origin and differ in their presentation, stage at diagnosis, and prognosis. Some follow an indolent course, with small component cells and retention of a follicular architecture, whereas others are aggressive tumors with primitive blasts and loss of the normal nodal structure (Fig. 3). Approximately 88% of NHLs are derived from monoclonal populations of B cells [26]. In pregnancy and patients younger than 35 years of age, however, there seems to be a disproportionate number of T-cell and indeterminate phenotypes [27,28].

Unlike HL, which has its peak incidence in the reproductive years, NHL occurs with a mean age at diagnosis of 42 years. The estimated incidence during

![Fig. 3. Non-Hodgkin diffuse large B-cell lymphoma involving a cervical lymph node, with large pleomorphic lymphoma cells (hematoxylin-eosin, original magnification ×250).](image)
pregnancy is thought to be 0.8 cases per 100,000 women [29]. The exact prevalence of NHL during pregnancy, however, is unknown. In 1993, Hurley and coworkers [30], in a review of the current literature, reported only 103 cases of NHL occurring coincident with pregnancy or the immediate postpartum period. Since that report, however, there have been an additional 35 cases reported in association with pregnancy [31–45].

The etiology for most NHLs is not clearly defined; however, a number of well-defined risk factors have been reported. Viral agents, most notably Epstein-Bar virus, human T-cell lymphotropic virus, hepatitis C virus, and HIV, have all been associated with one or another form of NHL [29,42]. Multiple autoimmune diseases, including Sjögren’s disease, lupus erythematosus, and rheumatoid arthritis, have also been implicated in the development of NHL [29,42].

Immunosuppression, whether primary or iatrogenic, is well established as a risk factor for the development of NHL [43]. This association has tempted some authors to speculate that the reported diminution in cellular immune response associated with pregnancy could adversely affect either the stage at diagnosis or the progression of these neoplasms during pregnancy [44,46]. Others, however, have suggested that the apparent association with more aggressive types of NHL and overall worse prognosis is more a result of a delay in diagnosis or a reluctance to use chemotherapy during gestation, than by pregnancy itself [16, 47,48].

Most patients (66%) present with lymphadenopathy, and only 20% of patients present with B-symptoms (night sweats, weight loss, or fever). Bone marrow involvement is found more frequently in the indolent lymphomas (39%) than with the more aggressive, high-grade, varieties (18%) [49]. Unlike high-grade lymphomas, however, the prognosis does not seem to be altered by the presence of bone marrow involvement with the more indolent types of lymphomas. Patients with T-cell lymphomas present more often with constitutional symptoms, extranodal disease, and have a poorer prognosis than those with B-cell lymphomas [50]. Burkitt’s lymphoma (a B-cell NHL), however, is one of the most aggressive malignancies known and B-symptoms are often present.

The initial approach to the patient with NHL is similar to that used in patients with HL. Most patients are diagnosed based on pathologic findings of a lymph node biopsy. Importantly, however, extranodal involvement is usually widespread by the time the peripheral lymph nodes are involved. For this reason, although an accurate anatomic staging (based on the Ann Arbor staging system) is still important, staging laparotomy is not used. Furthermore, in the nonpregnant population, CT scans of the chest, abdomen, and pelvis have largely replaced lymphangiograms. During pregnancy, MRI, in addition to avoiding radiation exposure to the fetus, provides not only information regarding extranodal involvement, but possible bone marrow involvement. Both gallium and thallium scanning, although of prognostic value, are contraindicated during pregnancy.

The classification systems for the NHLs have changed numerous times over the last 40 years. The most recent system, the WHO classification, incorporates morphologic, genetic, immunophenotypic, and clinical features in organizing
these malignancies [51]. In this classification scheme, NHL are divided into precursor and mature B-cell neoplasms, and precursor and mature T-cell or NK-cell neoplasms. Further refinement is based on cytogenetic studies. This system has been shown clinically to provide a higher degree of diagnostic accuracy and reproducibility than the previous system [42].

Although the stage and most common histoimmunologic types of NHL may be different in pregnancy, their clinical behavior, when properly treated, does not seem to differ significantly from nonpregnant patients. Treatment choices must be based on the stage, classification, and International Prognostic Index. Recent studies in nonpregnant patients have shown that, with aggressive NHL, standard therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone results in 3-year overall survival rates (53%–62%) that are not significantly different than those with other intensive chemotherapeutic regimens (48%–56%) [50,52]. Similar long-term survival rates in pregnancies complicated by NHL and treated with multiagent chemotherapy have been reported [47].

In general, women diagnosed in the third trimester and those with early stage disease tend to have a better prognosis. Unfortunately, most pregnant women with NHL have aggressive and advanced-stage disease. Because these women have a poor prognosis, standard chemotherapy should not be delayed. Those women diagnosed in the first trimester and unwilling to accept the potential risk of fetal malformations (6%–20%), should be offered pregnancy termination [48]. After the first trimester, when the risk of fetal malformations with standard multiagent chemotherapy seems negligible, pregnancy termination is not indicated for maternal benefit. Furthermore, although second- and third-trimester exposure to multiagent chemotherapy has been associated with fetal growth restriction and myelosuppression, several recent studies have shown no significant risk of fetal toxicity [13,53].

Another potential risk to the fetus and infant whose mother has NHL is maternal-fetal transmission of malignant cells. In 2002, Walker and coworkers [54], in a review of metastatic disease of the fetus or placenta, found no cases of maternal NHL metastatic to either placenta or fetus. In 1994, however, Hurley and coworkers [30] reported a maternal case of T-cell NHL, with cytologically and immunohistologically identical T-cell lymphoma developing in the infant at 2 months of age. In 1997, Megvarian-Bedoyan and coworkers [41] described a case of anaplastic large cell lymphoma metastatic to the placenta. These same authors, on review of the literature, were able to identify three additional cases of documented placental involvement by metastatic NHL. Overall, since 1992 there have been a total of eight cases of maternal NHL metastatic to the placenta, fetus, or both [30,39–41,55]. In these cases, 62% of the mothers and 25% of the infants died, presumably from complications of disseminated NHL. It has been recommended that pathologic examination of the placenta be undertaken so that appropriate and timely consideration for neonatal follow-up and treatment can be effected [30].

As with HL, cord blood should be collected as a potential source of HLA-compatible progenitor cells, in the event that bone marrow transplant is needed.
Finally, delivery should be timed to minimize the risk of pulmonary immaturity, and the risk of neonatal myelosuppression.

Vignette 3: leukemia

A 15-year-old Hispanic woman, G₁P₀ at 27 weeks’ gestational age, was transported to the university hospital after presenting to a local hospital with right lower extremity pain and new-onset ecchymoses with fairly extensive petechial rash. A complete blood count showed severe anemia (hemoglobin 4.6 g/dL) with thrombocytopenia (platelets of 17,000). The patient had a normal white blood cell count, but the differential was remarkable for 35% blasts on the peripheral smear (Fig. 4). Her electrolytes were normal, as were her coagulation studies. Her serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase were in the normal range as was her lactic dehydrogenase. Her urine analysis, chest radiograph, and level 2 ultrasound were unremarkable. She was transfused with packed red blood cells and platelets before undergoing bone marrow aspiration and biopsy. The morphologic and immunophenotypic findings were consistent with pre-B-cell acute lymphoblastic leukemia (Fig. 5). Cytogenetic studies were sent and later demonstrated hyperdiploidy, with 55 chromosomes, including trisomies 2, 4, 6, 8, 10, 16, 17, 18, 21, and 22. Her initial spinal fluid showed no evidence of blasts. The patient was placed in a high-risk prognostic category based on her age.

The patient and her family were counseled extensively regarding the importance of initiating chemotherapy, despite the potential risks to her fetus from prematurity, intrauterine growth restriction, and a possible increased risk of fetal demise. She was counseled that at this gestational age, there did not seem to be an increased risk of congenital birth defects attributable to the recommended chemotherapy, and that the best data, although limited, did not demonstrate any significant long-term neurologic sequelae attributable solely to chemotherapy. After consultation between the pediatric oncology and maternal-fetal medicine
services, the patient was offered and accepted aggressive induction chemotherapy consisting of vincristine, L-asparaginase, daunomycin, and prednisone. Methylprednisolone and prednisone were chosen over dexamethasone because of the concerns of repeated fetal exposure to dexamethasone and adverse neurologic sequelae. The patient also received central nervous system prophylaxis consisting of intrathecal arabinosylcytosine instead of the usual methotrexate, because of concerns for the potential toxic effect of methotrexate on trophoblastic cells. The decision was also made to maintain the patient at a hemoglobin level greater than 8 g/dL and platelet count greater than 30,000. The patient responded well to her chemotherapy and entered remission after day 8. Serial growth scans and fetal surveillance remained normal. Two weeks after initiating chemotherapy, the patient required insulin for gestational diabetes. At 31 weeks, conveniently the end of induction therapy, the patient developed symptomatic preterm labor with cervical change, and was admitted for magnesium sulfate tocolysis and antenatal corticosteroids. Her labor was successfully thwarted and she was discharged home after 4 days of observation. She developed a urinary tract infection, with methicillin-resistant enterococcus, that was successfully treated and she was placed on nitrofurantoin suppression. One day before scheduled start of consolidation chemotherapy, she developed recurrent preterm labor and it was elected to allow her labor to progress. She delivered a healthy 2086-g boy with Apgar scores of 9 and 9. The newborn showed no signs of myelosuppression and was discharged in good condition at 5 days of age. The mother’s postpartum course was uneventful. She received medroxyprogesterone intramuscularly the day of delivery and was counseled against breast-feeding. She resumed her chemotherapeutic regimen 3 days postpartum.

**Leukemia**

The leukemias are a heterogeneous group of malignancies that arise from genetically altered, lymphoid or myeloid progenitor cells, located in the bone
marrow. This genetic abnormality results in dysregulated growth and clonal expansion. As first described by Virchow in 1845, these clonal leukemic blasts not only spill into the bloodstream, but also ultimately infiltrate liver, spleen, and other tissues [56,57]. Historically, the leukemias were classified based on their clinical presentation and life expectancy into two basic groups: acute and chronic. With advances in histochemical techniques, however, these malignancies can be further classified, based on morphologic characteristics, as being of myeloid or lymphoid cell origin: acute myeloid leukemia, chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), and chronic lymphoid leukemia (CLL). Current pathologic classification using immunophenotyping and molecular-cytogenetic studies has produced a more complex, but prognostically accurate, classification of the leukemias [58].

In the nonpregnant population, 43% of leukemias are classified as acute, whereas 41% are chronic. In pregnancy, however, most leukemias (90%) are classified as acute [25,59]. Furthermore, 68% are of myeloid cell lineage (61% acute myeloid leukemia, 7% CML), whereas 31% are of lymphoid lineage (28% ALL, 3% CLL) [60].

For most cases of leukemia, the precise causal links have not been established. There are, however, numerous associations between leukemias and various environmental, socioeconomic, infectious, and genetic events. A higher incidence of certain leukemias among monozygotic twins and syndromes with somatic cell aneuploidy (eg, Down syndrome, Patau’s syndrome, and Klinefelter’s syndrome) suggests a genetic etiology. Other syndromes associated with both chromosomal fragility and immune dysregulation, such as Bloom syndrome and x-linked agammaglobulinemia, also demonstrate a higher incidence of leukemia [61–64]. Numerous environmental factors, however, such as radiation exposure, exposure to alkylating agents, and certain viral infections, have been implicated in the etiology of leukemia. Known viral etiologies, including the retrovirus human T-cell lymphoma virus, are thought to play a role in adult T-cell leukemia, and Epstein-Barr virus, a DNA virus associated with mature B-cell ALL [59]. In addition, the human herpes virus-6 has been cited as a possible modulating factor in lymphocytic leukemias [65].

The clinical manifestations of the acute leukemias are nonspecific and many of these symptoms, such as fatigue, weakness, dyspnea, and lack of energy, are common in normal pregnancies. In the acute leukemias, however, they are the clinical manifestations of bone marrow infiltration by the leukemic clonal cells with resulting suppression of normal hematopoiesis. As pancytopenia progresses, however, symptoms of epistaxis, easy bruisability, and recurrent infections should suggest a more precarious etiology. On physical examination, these patients often demonstrate pallor, petechiae, or ecchymoses. Lymphadenopathy and hepatosplenomegaly are uncommon and gingival hyperplasia, caused by leukemic cell infiltration of the gums, and cranial neuropathies may occasionally be present. In the absence of a pulmonary infection, the chest radiograph usually is normal, but may demonstrate mediastinal enlargement, particularly in patients with acute T-cell leukemia.
The diagnosis of an acute leukemia is usually suspected when a peripheral blood smear demonstrates a normocytic, normochromic anemia with a mild to severe thrombocytopenia. Although the white blood cell count is variable, blasts are virtually always present [62]. In acute promyelocytic leukemia there may be evidence of an intravascular coagulopathy, with prolongation of the partial thromboplastin time, the prothrombin time, and depression of fibrinogen, but this is a rare finding in ALL. Lumbar puncture to determine disease status in the central nervous system is recommended, and bone marrow aspiration and biopsy are essential for the diagnosis and morphologic, immunophenotypic, and cytogenetic classification of the patient’s leukemia [62].

Cytogenetic abnormalities have emerged as powerful determinants of patient outcome. They are numerous in type and occur in most leukemias. The Philadelphia chromosome, translocation t (9; 22), occurs more frequently in adult ALL (25%) than in childhood ALL (3%) and is associated with a worse prognosis. The t (12; 21) translocation, seen in approximately 25% of pre-B-cell ALL, confers a favorable prognosis. Age is clearly an important prognosticator with younger patients, especially children, having a better prognosis than adults. Within the pediatric population, age continues to be a significant prognostic factor, with children diagnosed between the ages of 2 and 10 years doing better than children over 10 years at diagnosis, who in turn do better than infants. Clinically, however, the patient’s rate of response to induction chemotherapy and time to normalization of bone marrow findings is one of the most useful indicators of ultimate outcome [62].

Chronic leukemias complicating pregnancy are rare, reflecting a median age of onset in the sixth decade of life. Most that do occur in pregnancy are myeloid (90%), with only four cases of CLL reported during pregnancy [66]. Only 10% of all CML cases occur during pregnancy. Chromosomal translocations, particularly the reciprocal t (9; 22)(q34; q11) and its bcr-abl fusion gene product, play a central role in the development of CML and are found in 95% of cases. The presenting symptoms of patients with CML are similar to those of acute leukemia; however, the most common sign of CML, occurring in over 90% of cases, is splenomegaly. Symptoms or signs of granulocytopenia or thrombocytopenia are uncommon and usually suggest transformation into the accelerated or blast phase. Elevated white blood cell counts, and anemia, are often seen at diagnosis. The median survival time is 4 years, with blast crisis developing 3 to 4 years after the initial diagnosis [67]. B-cell hematologic malignancies can present as either leukemia (CLL), with lymphocytosis, or as an NHL. It typically has in indolent course and may not require treatment for months to years [57].

Before the institution of modern chemotherapy, the outcome for both adults and children with acute leukemia was grim. Even today, without treatment, the average life expectancy is measured in months and not years. With treatment, however, children with ALL can now anticipate being cured of their disease 80% of the time [68]. The outcome for adults with acute leukemias, although not nearly as optimistic, has also improved with advancements in chemotherapeutic regimens and in supportive care for treatment-induced morbidities. Today,
complete remission can be expected in 70% to 85% of patients, with long-term disease-free survival in 25% to 50% of patients [62].

In the patient with acute leukemia, the primary goal of chemotherapy is the eradication of leukemic clone cells from the bone marrow (less than 5% blasts) and restoration of normal hematopoiesis (granulocyte count ≥1000/μL, platelet count ≥100,000/μL). The secondary goal is the prevention, through the use of multiagent chemotherapeutic regimens, of the emergence of resistant clones, and through the treatment of leukemic cell sanctuaries, the elimination of residual disease. To this end, chemotherapy is divided into several phases: induction, consolidation, and maintenance [62,69].

For acute myeloid leukemia patients less than 60 years of age, remission induction typically includes the use of an anthracycline (daunorubicin or idarubicin) and cytarabine. Those who do not achieve complete remission (30% of younger adults) are candidates for allogenic hematopoietic stem cell transplant. In patients with ALL, the combination of vincristine, anthracycline, steroids, and L-asparaginase often constitutes the standard induction regimen. Newer regimens in adults with ALL, incorporating higher dose intensities, and the addition of cyclophosphamide and cytarabine have produced complete remission rates of 93%, induction mortalities of 8%, and 6-year disease-free survival of 55% [69]. Because the central nervous system is a common sanctuary for lymphocytic leukemic cells, central nervous system prophylaxis is standard therapy for adults and children with ALL. In addition to the previously mentioned chemotherapeutic drugs, patients with acute leukemia often require treatment with a pharmacopeia of other medications used in the treatment and prevention of induction-induced morbidities: allopurinol to reduce the risk of urate nephropathy; cotrimoxazole for *Pneumocystis carinii* prophylaxis; fluconazole to reduce the risk of *Candida albicans* infection; and hematopoietic growth factors (granulocyte colony–stimulating factor) to shorten the period of profound neutropenia. For most of these drugs published human experience is limited [70]. Finally, supportive measures, such as blood and platelet transfusions, and the aggressive diagnosis and treatment of febrile neutropenia, have become critical in minimizing induction morbidity and mortality [62].

The treatment of patients with chronic leukemias is individualized. For those with CLL, who present with lymphocytosis and bone marrow involvement, and for whom median survival is greater than 10 years, immediate treatment may not be required [71]. In those patients for whom treatment is deemed necessary, fludarabine is the usual treatment recommended. For those at risk of complications from thrombocytosis and leukostasis, leukapheresis may be recommended. In patients with chronic-phase CML, who are not candidates for bone marrow transplantation, imatinib is recommended as the first drug of choice [72]. In those who do not respond to imatinib, interferon-α has been shown to improve survival [67,71]. Leukapheresis may be used for the same indications as in CLL.

The incidence of leukemia in pregnancy is unknown, but is estimated to range from 1:75,000 to 1:100,000 pregnancies [73]. Although estrogen has been implicated in leukemic cell proliferation and estrogen receptors have been found
in leukemic cell lines, it does not seem that the course of leukemia is adversely affected by pregnancy [74–77]. Unfortunately, there are no recent large reviews of pregnancy complicated by leukemia incorporating newer drug regimens and advancements in supportive care, with the largest recent series of 17 patients spanning a 37-year period [78]. Despite this, there seems to be a consensus of expert opinion that the outcome of pregnant patients with acute leukemia is adversely affected only when appropriate therapy is withheld for more than a few weeks [77–79]. Reported complete remission in pregnancies complicated by acute leukemia and aggressively treated with chemotherapy does not seem to be substantively different from those in the nonpregnant adult population [25,78,79]. Regardless of gestational age, the immediate induction of remission, as in the nonpregnant population, remains the first objective in the management of the pregnant patient with acute leukemia.

Just as in the nonpregnant patient, supportive care is also critical. Maintenance goals should include a platelet count of ≥30,000/μL, or ≥50,000/μL in the presence of bleeding or at the time of delivery to allow for regional anesthesia [80]. The maternal hemoglobin should be maintained above the lower (±2 SD) limits of 9.8 mg/dL, because the risk of perinatal complications (preterm labor, intrauterine growth restriction, and fetal demise) increase progressively as the hemoglobin declines [81].

When deciding on chemotherapeutic options, the physiologic adaptations of pregnancy need to be taken into consideration. Pregnancy is known to be a thrombogenic state, with the risk of thromboembolism six times higher than in the nonpregnant individual. L-Asparaginase, derived from either Escherichia coli or Erwinia crysanthemi, significantly decreases the levels of certain thrombosis inhibitors (eg, antithrombin III) and in children and adults with ALL has been associated with a significant risk of thromboembolism [82–85] The use of this agent in pregnancy complicated by ALL should be approached with caution. Pregnancy is also a state of increased insulin resistance. It is not surprising that the concomitant use of high doses of glucocorticoids may exacerbate what is otherwise a mild degree of carbohydrate intolerance. In addition to the effect of steroids on maternal glucose homeostasis, the type of steroid used may also be important in terms of potential adverse fetal effects. Most chemotherapeutic protocols prefer dexamethasone because of its improved central nervous system penetration. Neonatal data, however, have demonstrated a threefold increased risk of leukomalacia and neurodevelopmental abnormalities in infants exposed to repeated doses of dexamethasone for induction of fetal lung maturity [86].

The management of the chronic leukemias in pregnancy is not well defined because of the paucity of cases reported. Maternal and fetal outcomes are generally excellent, with maternal and fetal survival rates of 96% and 84%, respectively [87]. Therapy is generally aimed at controlling splenomegaly, leukocytosis, and constitutional symptoms. Interferon-α, which does not seem to cross the placental barrier to any appreciable degree, has been used in at least 10 cases of CML complicating pregnancy without adverse maternal effects, with only one case of transient neonatal thrombocytopenia [67,88]. Of the four cases of CLL
complicating pregnancy, only one patient required treatment with anything other than antibiotic and blood transfusions for symptomatic anemia. She was treated with leukapheresis three times, starting in the second trimester and neither she nor her baby suffered any ill effects [66].

The effects of acute leukemia on pregnancy have not been recently studied. From the available literature, it seems that acute leukemia and or its treatment may have a detrimental effect on pregnancy outcome. Premature births occur either iatrogenically or spontaneously in over 50% of cases. Stillbirths have been reported in from 7% to 17% of cases and intrauterine growth restriction in approximately 8% of infants [17,23,25,28]. Furthermore, neonatal deaths from neutropenia and cardiomyopathy have also been reported [23,89]. The risk for adverse outcome is greatest for those diagnosed in the first trimester, but can occur in any trimester [23,77,78]. The risk of teratogenicity seems to be confined to the first 12 weeks of gestation, with folate antagonists and alkylating agents posing the greatest risk [90]. Whether methotrexate, the chemotherapeutic agent preferred for trophoblastic disease, poses a greater risk for adverse fetal outcome (excluding fetal anomalies) in the second or third trimester is neither substantiated nor refuted by the currently available literature [23,90]. What is clear from the literature, however, is that delaying appropriate chemotherapy for more than a few weeks at any time other than the latter part of the third trimester is associated with excessive fetal mortality (29%) [25,60,78].

Both NHL and leukemia metastatic to the fetus or placenta have been documented, albeit rarely. As a group, however, leukemia and lymphoma account for 19% of the malignancies metastatic to the products of conception and 50% of those metastatic to the fetus [2,54]. The placenta should always be sent for histopathologic evaluation. Because patients often require prolonged maintenance therapy, and because they are at significant risk of recurrence even if complete remission occurs, they should be provided with effective and reliable contraception. In addition, although the data on most of the agents used for chemotherapy and breast-feeding are scarce, patients should be instructed to avoid breast-feeding during chemotherapy.

**Summary**

Hematologic malignancies occurring during pregnancy are fortunately uncommon. When they do collide, their inherent and diametrically opposed natures, life-giving and life-threatening, create fear and anxiety for the patient, her family, and all of those who are charged with her care. It is imperative that physicians and health care providers approach these patients and their families with compassion, empathy, and most importantly the knowledge and expertise necessary to optimize the outcome for both mother and baby. Inherent conflicts between maternal and fetal well-being must be dealt with in an honest and nonjudgmental fashion. Finally, frequent communication and a spirit of teamwork between the
various specialists involved in her care go far in alleviating the patient’s fears and ensuring a favorable outcome.

References


